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CASE REPORT / OLGU SUNUMU

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EDITORIAL / EDİTÖRYAL

From Data to Consciousness: Artificial Intelligence and the Future of Medicine

Every era seeks to understand itself. Yet some are compelled not only to understand, but to redefine themselves. In such moments, philosophy takes the lead—asking the questions that science can not yet formulate and technology can not yet answer.
Artificial intelligence is more than the sum of algorithms. It is a new way of perceiving—discovering hidden patterns, unveiling unseen connections, and extending human intuition beyond its natural boundaries. In this transformation, knowledge ceases to be mere accumulation; it becomes movement, a continuous flow.
For medicine, this shift is profound. A symptom may no longer be only the shadow of a disease but the language of an entire system. A patient's behavior may provide more than personal context; it may reveal signals of collective health patterns. Clinical data, from the tracings of an electrocardiogram to the vast layers of epidemiological records, is no longer just archival memory—it is becoming a predictive voice.
Public health, diagnostics, and personalized medicine are already being reshaped. Artificial intelligence can discern what the human eye overlooks, model what the human brain cannot compute, and anticipate what traditional analysis cannot foresee. The implications reach from bedside decisions to global health preparedness, urging us to reconsider how knowledge is generated and applied in clinical care. This transformation also compels us to confront questions of ethics, transparency, and responsibility, ensuring that these tools serve medicine and humanity with accountability.
Now humanity must face the intelligence it has created with its own hands. How will we converse with a mind that does not merely process but thinks? How will we govern this partnership responsibly, ensuring that its power serves patients, communities, and societies at large?
And, more importantly: Are we prepared to share the role of primary thinker on Earth?
Because today, patterns are not only visible.
Patterns are thinking.
Artificial intelligence is the thinking face of data.
And this emerging consciousness whispers to us the most powerful question of all time:
for this dialogue between humanity and artificial intelligence, are you ready?

"This editorial marks our first reflection on artificial intelligence in medicine, opening a dialogue we aim to deepen in future issues.

Assoc. Prof. Murat Altuntaş
Editor-in-chief

ORIGINAL RESEARCH

Bagcilar Med Bull 2025;10(3):209-216
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Pediatricians' Knowledge, Attitudes and Practices Regarding Childhood Eye Diseases

Pediyatri Uzmanlarının Çocukluk Çağı Göz Hastalıklarına İlişkin Bilgi, Tutum ve Uygulamaları

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Abstract

Objective: Pediatricians' knowledge, attitudes, and practices regarding the etiology of eye diseases play a critical role in the early diagnosis of these conditions and in referring patients to ophthalmologists when necessary. The aim of this study is to evaluate pediatricians' knowledge, attitudes, and behaviors related to childhood ocular disorders.

Method: In our study, we used a descriptive cross-sectional study design to assess the knowledge, attitudes, and practices of pediatricians in our country regarding childhood ocular disorders. The survey was conducted online via Google forms and distributed to participants through WhatsApp and e-mail. The questionnaire consisted of two sections: One addressing demographic information and the other evaluating pediatricians' knowledge, attitudes, and practices related to childhood ocular diseases.

Results: A total of 110 pediatricians participated in our study. Of the participants, 84.5% reported performing eye examinations in children, but only 16.7% conducted routine eye exams during every child visit. All participants reported assessing the light reflex during eye exams. Nearly all participants were able to identify the risk factors for retinopathy of prematurity. The majority of pediatricians (99.1%) stated they would immediately refer a child with suspected glaucoma to an ophthalmologist. Regarding leukocoria, most participants identified retinoblastoma (89.8%) and cataracts (85.2%) as the primary causes of this condition. Almost all pediatricians (98.2%) indicated they would immediately refer a child with suspected leukocoria to an ophthalmologist. Only 63.2% of participants acknowledged that refractive errors could contribute to strabismus. A large proportion of pediatricians (82.6%), concerned about

Öz

Amaç: Pediyatri uzmanlarının göz hastalıklarının etiyolojisi hakkında sahip oldukları bilgi, tutum ve uygulamalar, bu hastalıkların erken teşhisi ve gerektiğinde hastaların göz hekimine yönlendirilmesi açısından kritik bir rol oynamaktadır. Bu çalışmanın amacı, bu hekimlerin çocukluk dönemi göz hastalıklarına ilişkin bilgi, tutum ve davranışlarını değerlendirmektir.

Yöntem: Çalışmamızda, ülkemizdeki pediyatri uzmanlarının çocukluk dönemi oküler hastalıklarına ilişkin bilgi, tutum ve uygulamalarını değerlendiren tanımlayıcı bir kesitsel çalışma tasarımı kullanılmıştır. Anket, Google forms üzerinden çevrimiçi olarak gerçekleştirilmiş ve katılımcılara WhatsApp ile e-posta yoluyla dağıtılmıştır. Anket, demografik bilgiler ve pediyatri uzmanlarının çocukluk dönemi göz hastalıklarına yönelik bilgi, tutum ve uygulamalarını içeren iki bölümden oluşmaktadır.

Bulgular: Çalışmamıza toplamda 110 pediyatri uzmanı katılmıştır. Katılımcıların %84,5'i çocuklarda göz muayenesi yaptıklarını belirtirken, yalnızca %16,7'si her çocuk ziyareti sırasında rutin göz muayenesi gerçekleştirdiğini ifade etmiştir. Tüm katılımcılar, göz muayenesi sırasında ışık refleksini değerlendirdiklerini bildirmiştir. Prematüre retinopatisi ile ilgili risk faktörlerini tanımlama konusunda katılımcıların neredeyse tamamı başarılı olmuştur. Şüpheli glokom tespit edilen bir çocuğu hemen bir göz doktoruna yönlendireceğini belirten pediyatri uzman oranı %99,1'dir. Lökokori konusunda, katılımcıların çoğunluğu retinoblastoma (%89,8) ve kataraktı (%85,2) bu durumun başlıca nedenleri olarak tanımlamıştır. Şüpheli lökokori tespit edilen bir çocuğu hemen bir göz doktoruna yönlendireceklerini belirten pediyatri uzman oranı %98,2'dir. Katılımcıların yalnızca %63,2'si, kırılma kusurlarının şaşılığa katkıda bulunabileceğini kabul etmiştir. Ambliyopi (%88,1) ve merkezi nedenler

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Abstract

amblyopia (88.1%) and central causes (77.1%), stated they would promptly refer children with strabismus to an ophthalmologist.

Conclusion: Although pediatricians' overall knowledge and attitudes are satisfactory, there are significant gaps in the understanding of certain eye diseases. It is crucial to enhance pediatricians' knowledge of eye disorders through comprehensive ophthalmology training and workshops during residency. Furthermore, pediatricians should be encouraged to perform detailed eye exams, and collaboration between ophthalmology and pediatrics should be strengthened.

Keywords: Childhood blindness, eye disorders, knowledge, leukocoria, pediatrics, red eye disease

Öz

(%77,1) konusunda endişeli olan pediyatri uzmanlarının büyük bir kısmı, şaşılık tespit edilen çocukları hemen bir göz doktoruna yönlendireceklerini ifade etmiştir (%82,6).

Sonuç: Pediyatri uzmanlarının genel bilgi ve tutumları tatmin edici olmakla birlikte, bazı göz hastalıklarının anlaşılmasında belirgin eksiklikler mevcuttur. Pediyatri uzmanlarının göz hastalıklarına dair bilgi seviyelerinin, uzmanlık eğitimi sırasında kapsamlı oftalmoloji eğitimleri ve atölye çalışmaları ile güçlendirilmesi önemlidir. Ayrıca, pediyatri uzmanlarının ayrıntılı göz muayenesi yapma konusunda teşvik edilmesi ve oftalmoloji ile pediatri arasındaki iş birliğinin güçlendirilmesi gerekmektedir.

Anahtar kelimeler: Bilgi, çocukluk çağı körlüğü, göz hastalıkları, kırmızı göz hastalığı, lökokori, pediyatri

Introduction

Early disease detection and treatment as well as avoiding permanent vision issues, depend on a thorough assessment of eye conditions in children (1,2). The World Health Organization reports that at least 2.2 billion individuals globally have blindness or visual impairment, with 1 billion cases being preventable (3). Visual impairments adversely impact all aspects of children's development, including physical, cognitive, social and emotional growth (4-6).

The examination of the visual system begins in the newborn period, and all routine check-ups for the baby include an eye health screening (7). The American Academy of Pediatrics recommends that pediatricians evaluate the eye health of babies in routine check-ups beginning at birth: External examination of the eyes and adnexa, vision examination, red reflex test, pupil examination, and eye movements should all be evaluated based on the developmental stage (8). Again, the guidelines underline that visual acuity should be measured beginning at the age of three (9). This would allow for the detection and treatment of illnesses such as congenital cataracts, congenital glaucoma, retinoblastoma, and strabismus, which can cause severe vision loss in early childhood (10).

The pediatrician's knowledge, attitude and practice regarding the causes of eye problems are critical in detecting them early and referring patients to an ophthalmologist when necessary. Several studies have found gaps in doctors' knowledge, attitudes, and practices regarding childhood eye disorders (11,12). A research published last year in Turkey found that the majority of pediatricians want to improve their knowledge and practice in the diagnosis and treatment of visual issues (7). Our study aimed to assess pediatricians' knowledge, attitudes and behaviors towards childhood ocular disorders.

Materials and Methods

In our study, we used a descriptive cross-sectional study design to evaluate the knowledge, attitudes, and practices of pediatricians in our country regarding childhood ocular diseases. The study design and questionnaire were prepared based on a preliminary study on reality (2). A pre-test was performed to assess the survey's functionality, understandability, and ability to be completed within a suitable time frame. This pre-test was administered to a group of ten participants who were not part of the study's target population, and were therefore eliminated. The open online survey was created with Google forms software, and it was sent to the participants' mobile telephones via WhatsApp and mail links. The survey covered all pediatricians, including assistant physicians, specialists, and academic staff, from all parts of our country. Random sampling was used to distribute the survey. This study was approved by the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee with the decision numbered 010.99/20 on February 28, 2024. The study was conducted in accordance with the Declaration of Helsinki.

The study questionnaire had 38 questions divided into two sections. The first section questioned the demographic characteristics of the participants: Age, gender, region, duration of work in pediatrics, whether they received training in ophthalmology, etc. The second section included knowledge, attitudes, and practices of pediatricians regarding important childhood eye pathologies such as visual acuity issues, painful red eye, neonatal conjunctivitis, leukocoria, strabismus, congenital glaucoma, and retinopathy of prematurity (ROP), etc. The study was conducted on a voluntary basis, and a total of 110 participants who signed an informed consent form completed the survey. Participants were assured that data

confidentiality would be maintained and the research team collected, analyzed, and securely stored the data.

Statistical Analysis

The data were compiled and organized using the Microsoft Excel database. Descriptive data were presented in terms of percentages and frequencies %, (n) and Jamovi version 2.3.18 statistical software was employed for statistical analyses. In addition to descriptive statistics, further calculations were performed to understand the distribution of variables and detailed data cleaning procedures were conducted to ensure data reliability and validity. Moreover, qualitative data obtained during and after the survey administration were conceptualized to address the research questions, systematically coded and organized under specific categories.

Results

This study included 110 pediatricians (75 females, 35 males). In all participants, a total of 18.3% (n=20) were working in state hospitals, 54.1% (n=59) in education and research hospitals, 13.8% (n=15) in university hospitals, 10.1% (n=11) in private hospitals and 3.7% (n=4) in private clinics. The average clinical experience of the pediatricians in this study was 12.06±6.12 years. Among them, 22.2% (n=24) had 0-5 years of experience, 22.2% (n=24) had 5-10 years of experience, 24.1% (n=26) had 10-15 years of experience, 13.9% (n=15) had 15-20 years of experience, and 17.6% (n=19) had more than 20 years of clinical experience. To gain insights into the participants' attitudes towards routine eye examinations, we administered a set of eight questions.

The majority of respondents (84.5%) reported that they conduct routine eye exams; however, only a small number reported having participated in a rotation at an ophthalmology clinic (9.1%) or having attended an ophthalmology conference (6.5%). The predominant reason cited for not performing eye examinations was insufficient knowledge. The majority also reported that they perform eye examinations for all newborns and during routine child visits (72.7% and 80.9%, respectively) (Table 1).

To assess the participants' knowledge regarding visual acuity, we posed five questions. The majority (85.5%) expressed awareness of the signs associated with diminished visual acuity, and most of them (81.7%) believed that it could be treated. A small number (40.0%) indicated that contact lenses could also be used in treatment. However, 60% of pediatricians were unfamiliar with the World Health Organization's definition of blindness. The majority of participants (97.3%) identified conjunctivitis as the cause of painful red eyes. Furthermore, most respondents (40%) indicated that they would initiate treatment and refer the patient to an ophthalmologist on the third day based on the response to treatment. The most commonly prescribed medication (90%) was an antibiotic (Table 2).

Table 1. Routine eye examination approaches of the pediatricians

Variable	% n
Participated in an ophthalmology congress	6.5% (n=7)
Had a rotation in an ophthalmology clinic?	9.1% (n=10)
Perform eye examination	84.5% (n=83)
Eye examination frequency	
In all examinations	16.7% (n=18)
Only after birth	17.6% (n=19)
If the parents, ask to do so	8.3% (n=9)
If I see an eye issue	57.4% (n=62)
Which examinations do you perform? (Multiple answers)	
Pupil light reflex	98.2% (n=118)
Ocular motility	37.2% (n=41)
Fundus examination	13.6% (n=15)
Visual acuity	20.9% (n=23)
The prominent reason not to perform eye examination?	
Not enough time	23.6% (n=26)
Not enough knowledge	41.8% (n=46)
No device	25.5% (n=28)
Children do not cooperate	6.3% (n=7)
Not my area	8.2% (n=9)
When should an ophthalmologist see the children? (Multiple answers)	
All newborns	72.7% (n=80)
Routine well-child visits	80.9% (n=89)
No need if there is no symptom	3.6% (n=4)
An eye examination should be performed before 3 years old	99.1% (n=109)

Table 2. Knowledge of pediatricians about visual acuity and painful red eye

Variable	% n
Dou you know the signs of impaired visual acuity?	85.5% (n=94)
Which are the signs of impaired acuity? (multiple answers)	
Impaired school success	86.4% (n=95)
Nystagmus	26.4% (n=29)
Too much blinking	82.7% (n=91)
Eye squinting/rubbing	82.7% (n=91)
Torticollis	73.6% (n=81)
Eye deviation	54.5% (n=60)
Could visual acuity be treated in children?	
Yes,	81.7% (n=89)
No	18.2% (n=20)
How could visual acuity be fixed? (multiple answers)	
Surgery	54.5% (n=60)
Eyeglasses	80.0% (n=88)
Contact lens	40.0% (n=44)
What is the WHO blindness definition?	
No idea	60% (n=66)
Visual acuity <3/60	20% (n=22)
Visual acuity between 3/60-6/60	14.5% (n=16)
No sense of light	5.4% (n=6)
The causes of painful red eye (multiple answers)	
Conjunctivitis	97.3% (n=107)
Corneal trauma/abrasion	90.9% (n=100)
Allergic	78.2% (n=86)
Uveitis	75.5% (n=82)
Glaucoma	30.9% (n=34)
Strabismus	1.8% (n=2)
How do you manage a patient with painful red eyes?	
Prescribe eye drops, follow-up for 3 days than refer to an ophthalmologist	40% (n=44)
Both prescribe eye drops and refer to an ophthalmologist	30% (n=33)
Refer to an emergency ophthalmologist	30% (n=33)
What do you prescribe for a painful red eye? (multiple answers)	
Antibiotic drops	90.0% (n=99)
Steroid drops	30% (n=33)
Anti-histaminic drops	50.9% (n=56)
Artificial eye drops	71.8% (n=79)

WHO: World Health Organization

In the section of the questionnaire presented in Table 3, questions focused on specific pediatric eye disorders, including neonatal conjunctivitis, leukocoria, congenital glaucoma, and ROP. A significant majority (98.2%) recognized the urgency of leukocoria, with retinoblastoma cited as the most common cause; however, approximately 41.8% of pediatricians incorrectly identified glaucoma as a potential cause.

Regarding strabismus, 8.2% of participants mistakenly identified large nasal roots and 14.5% misattributed congenital eyelid anomalies as false causes of strabismus. Furthermore, 39.1% of pediatricians indicated spontaneous resolution as a treatment option, despite its lack of relevance in the management of strabismus (Table 4).

Discussion

To protect children's healthy visual development, physicians must have a thorough understanding of childhood eye illnesses and be able to spot early indications of these diseases. However, it is well known that many pediatricians are either unaware of eye disorders or are unable to implement eye health care procedures. Because eye illnesses are usually asymptomatic in childhood, children have difficulty communicating their concerns, making early diagnosis and intervention difficult and potentially delaying access to required health treatments. This study will assess pediatricians' knowledge, attitudes, and behaviors in addressing childhood eye disorders.

In this study, 85.5% of the participants reported that they were aware of the symptoms that can arise when children's

Table 3. Knowledge of pediatricians about childhood eye diseases

Variable	% n
Which agent do you prefer in neonatal conjunctivitis?	
Erythromycin drops	14.0% (n=15)
Gentamicin drops	61.7% (n=66)
Any antibiotic drops	15.0% (n=16)
Chloramphenicol drops	1.9% (n=2)
Artificial eye drops	7.5% (n=8)
Which is one of the reasons that causes leukocoria? (multiple answers)	
Cataract	83.6% (n=92)
Glaucoma	41.8% (n=46)
Retinoblastoma	88.2% (n=97)
Severe retinal diseases	38.2% (n=42)
Toxocariasis	23.6% (n=26)
How do you manage a patient with leukocoria?	
I urgently refer to an ophthalmologist	85.5% (n=94)
Order a cranial imaging	12.7% (n=14)
I follow-up, refer to an ophthalmologist if it doesn't get better	1.8 % (n=2)
When do you refer a patient with leukocoria to an ophthalmologist?	
Urgently	98.2% (n=108)
No idea	1.8% (n=2)
Which are one of the signs of congenital glaucoma? (multiple answers)	
Corneal haze	63.6% (n=70)
Wide cornea	46.4% (n=51)
Leukocoria	46.4% (n= 51)
Tearful eyes	20.0% (n=22)
Red painful eye	36.4% (n=40)
How do you manage a child with congenital glaucoma?	
Urgently refer to an ophthalmologist	99.1% (n=106)
Prescribe eye drops	0.9% (n=1)
Which are one of the risk factors for retinopathy of prematurity? (multiple answers)	
Gestational week at birth <32 weeks	92.7% (n=102)
Birth weight <1500 grams	93.6% (n=103)
Concomitant comorbidities	69.1% (n=76)
Prolonged mechanical ventilation	88.2% (n=97)
When do you refer a patient to an ophthalmologist for prematurity retinopathy?	
Postnatal 4-6 weeks or at post conceptual 32nd week	89.6% (n=95)
Immediate after birth	5.7% (n=6)
After discharging from intensive care unit	4.7% (n=5)

visual acuity declines. However, only 63.2% of the physicians stated that refractive defects play a role in strabismus. In the study by Ababneh et al. (2), 70.8% of the participants classified refractive errors as one of the primary causes of strabismus. The participants in our study performed below expectations. Early identification of refractive problems is crucial for avoiding consequences like amblyopia and strabismus.

According to the guidelines, children's visual acuity should be examined as early as age three (9,13). The American Association for Pediatric Ophthalmology and Strabismus recommends that children have at least one vision screening before beginning kindergarten (14). In our study, all physicians, except one, answered "yes" to the question "Should an eye examination be performed at least once before the toddler phase? (before age 3)". The majority of participants (84.5%) indicated that they examined children's eyes, but only 16.7% claimed that they did so at every assessment. 57.4% of physicians said they only performed eye exams when they observed an issue. During eye examinations, all physicians in our study tested the light reflex, 38% evaluated ocular mobility, and 21.3% assessed visual acuity. Insufficient training, a lack of proper equipment, and time constraints are the most common causes for not completing eye tests. In a study conducted by Ababneh et al. (2) in Northern Jordan, 66.7% of participants inspected their children's eyes, but just 10.4% did so at each health visit. Another study conducted in Ghana discovered that 87.8% of physicians examined children's eyes at all, with 59.3% doing so only when the family reported an eye problem, and 26.4% at every routine examination (15). In a study of 262 physicians in Turkey, over half of the participants reported that they only perform eye exams when they see an eye problem, whereas 27.9% undertake standard eye exams at every child visit. According to this survey, the pupillary response test was the most commonly

Table 4. Knowledge of pediatricians about strabismus in children

Variable	% n
Which could be a finding in a patient with strabismus? (multiple answers)	
Eye deviation	95.4% (n=105)
Abnormal face position while focusing an object	77.3% (n=85)
Abnormal head position while focusing an object	73.6% (n=81)
Large nasal root	8.2% (n=9)
Congenital eyelid malformation (epicanthic folds)	14.5% (n=16)
What should be suggested in a patient with strabismus? (multiple answers)	
Amblyopia	87.3% (n=96)
Vision impairment	65.4% (n=72)
Concomitant neurologic disorder	73.6% (n=81)
Impairment in eye structures (cornea, retina, lens)	60.9% (n=67)
No idea	4.5% (n=5)
How do you manage a child with strabismus?	
Urgently refer to an ophthalmologist	82.6% (n=90)
Order a cranial imaging	11% (n=12)
I follow-up, refer to an ophthalmologist if it doesn't get better	6.4% (n=7)
Which could be used for strabismus treatment? (multiple answers)	
Eyeglasses	84.5% (n=93)
Surgery	77.3% (n=85)
Spontaneous resolution	39.1% (n=43)
No idea	8.2% (n=9)

used test. Furthermore, it was mentioned that factors such as the large number of patients, lack of time, and absence of visual acuity tables in Turkey are among the main reasons why physicians do not perform routine eye examinations (7). Our study, similar to other studies, found that the majority of participants were not familiar with the World Health Organization's definition of blindness (6,7).

In our study, physicians indicated corneal traumatic abrasion (91.8%), uveitis (82%), and glaucoma (30.9%) as the most common causes of painful red eyes. Although conjunctivitis is typically a mild illness, 97.3% of participants incorrectly answered that it can cause painful red eye. These findings are comparable to those of previous investigations (2,12). Furthermore, 40% of physicians chose to initiate treatment and follow-up for three days, while 30% said they would choose to initiate treatment, and the remaining 30% would refer the patient to an ophthalmologist right away. In Hersi et al.'s (12) study, 51.5% of physicians immediately referred the patient to an ophthalmologist, 12.8% preferred to start therapy with eye drops and refer immediately, and 28.4% preferred to refer if there was no improvement within three days (2). In our survey, 92.5% of physicians chose antibiotic drops as their preferred treatment, 73.8% preferred artificial tears, and 52.3% chose antihistamine drops. These findings imply that pediatricians' expertise in red eye may influence their treatment techniques (16). Studies have emphasized that physicians with higher knowledge levels consider eye examination part of their responsibilities in red eye cases, whereas lack of knowledge is associated with increased antibiotic prescriptions (16,17). In cases of neonatal conjunctivitis, physicians' approaches include 13.8% referring the patient to an ophthalmologist right away, 36.7% referring the patient to an ophthalmologist if no improvement is detected, and 48.6% giving therapy with eye drops. Gentamicin (61.7%), unidentified antibiotics (15%), erythromycin (14%), artificial tears (7.5%), and chloramphenicol (1.9%) were the most frequently used eye drops in this case.

In our study, 89.8% of physicians cited retinoblastoma, and 85.2% cited cataract as potential causes of leukocoria. The majority of participants were aware that leukocoria could be life- or vision-threatening, and 98.2% said they would immediately refer patients with leukocoria to an ophthalmologist. However, 42.6% of individuals wrongly indicated glaucoma as a cause of leukocoria. In the Silva et al. (18) study, 54% (n=49) of participants were unaware that retinoblastoma, ROP, and exudative retinal illness may produce leukocoria. In another Brazilian study conducted by Manica et al. (19), only 37% of participants correctly recognized retinoblastoma. Yılmaz Tuğan et al. (7) found that 94.8% of pediatricians thought leukocoria was caused by retinoblastoma, 84.3% thought it was caused by cataracts, and 97.2% said they would immediately refer patients with leukocoria to an ophthalmologist.

In our study, the majority of physicians identified real strabismus symptoms as squinting (95.5%), aberrant facial position (80%), and abnormal head position (73.6%). Some doctors were unable to differentiate bogus strabismus symptoms, such as nasal root width (8.2%), and epicanthal

fold (14.5%). Participants responded that they would immediately refer their children to an ophthalmologist (82.6%) because they were concerned that strabismus could lead to amblyopia (88.1%) or originate from a central source (77.1%). In accordance with these findings. Hersi et al. (12) found that strabismus can cause amblyopia (83.1%) and can arise from a central source (51.4%). Furthermore, 79.1% of physicians preferred to refer to an ophthalmologist promptly in this instance. Again, in the study performed by Hersi et al. (12), pseudosquint, which is often mistaken for strabismus, was evaluated as strabismus by the physician at a rate of 5%; whereas in the study conducted by Ababneh et al. (2), this rate was stated as 4.2%.

ROP is a disorder that arises in preterm infants as a result of inadequate vascular development of the embryonic retina, which can cause blindness or severe visual loss. Infants weighing 1500 grams or who are ≤32 weeks of gestation should undergo a ROP assessment within the first month of life, at the latest (20). 99.1% of physicians in our study identified a history of birth before 32 weeks of gestation, 94.5% a birth weight less than 1500 grams, and 89% a prolonged duration of artificial ventilation as risk factors for ROP. Ababneh et al. (2) found that 98% of participants recognized risk factors in a similar fashion. A study conducted in India reported that 42.2% of pediatricians had limited knowledge about ROP, while another study in Saudi Arabia found that nearly half of the physicians had limited knowledge about this condition (21,22). In one study by Akkawi et al. (23), only 41.4% of participants knew when to report a child with ROP, whereas in another, 36.5% did (12). In our survey, 89.6% of doctors agreed that a child should be referred to an ophthalmologist for ROP monitoring between 4-6 weeks after birth or at 32 weeks gestational age. In our study, the rate of recognizing congenital glaucoma symptoms was low, which is consistent with other studies. While symptoms such as cloudy cornea (65.4%), large cornea (47.7%), and watery eyes (32.7%) were partially known to the medical community, most physicians (99.1%) stated that they quickly referred children with congenital glaucoma to an ophthalmologist (2,12).

The recommended periodic intervals for vision screening in school-aged children vary among professional organizations. According to the Bright Futures guidelines, annual vision screening is recommended for children aged 3 to 6 years. Additionally, screenings are advised at ages 8, 10, 12, 15, and 18, while risk-based assessments are recommended for other age groups (24). These periodic screenings play a crucial role in the early detection of visual impairments, contributing to improved academic performance and overall quality of life in school-aged children.

In our country, the National Vision Screening Program primarily includes vision screenings for newborns, 1-year-olds, 3-year-olds, and first-grade students (25). However, there is no routine national vision screening program for children aged 8 and above. Undiagnosed vision problems in early childhood can lead to a decline in academic performance, delays in motor skill development, and difficulties in social adaptation in later years. Therefore, implementing routine vision screenings at regular intervals for school-aged children would enhance early diagnosis and treatment processes, ultimately contributing to their healthy development.

Study Limitations

The limitations of our study include the lack of sufficient similar research with which to compare our findings, as well as the risk of false-positive results due to the use of closed-ended questions. Additionally, the limited number of pediatricians participating in the survey is another constraint.

Conclusion

In conclusion, it was found that the participating physicians' knowledge and attitudes about pediatric ophthalmology were generally adequate, but they had limited understanding of some disorders. It is critical to expand efforts to improve pediatricians' knowledge of ophthalmology. Workshops and more extensive ophthalmology teaching during residency training should help to support these initiatives. Furthermore, pediatricians should be encouraged to conduct comprehensive eye exams, and collaboration between the ophthalmology and pediatrics fields should be promoted.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee with the decision numbered 010.99/20 on February 28, 2024. The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: The study was conducted on a voluntary basis, and a total of 110 participants who signed an informed consent form completed the survey.

Footnotes

Authorship Contributions

Concept: U.K., M.T.K., F.Ç., F.Ö., B.Y., Y.A., Design: U.K., M.T.K., F.Ç., F.Ö., B.Y., Y.A., Data Collection or Processing: U.K., M.T.K., F.Ç., F.Ö., D.G., Y.A., Analysis or Interpretation: M.T.K., F.M., D.G., B.Y., Y.A., Literature Search: U.K., M.T.K., F.Ç., F.Ö., D.G., B.Y., Y.A., Writing: U.K., M.T.K., D.G., Y.A.

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References

1. Gilbert C, Bowman R, Malik AN. The epidemiology of blindness in children: changing priorities. Community Eye Health. 2017;30(100):74-77.
2. Ababneh LT, Khriesat W, Dalu SA, Hanania RJ, Ababneh BF, Amer NAB, et al. Knowledge of and attitude to eye disorders among pediatricians in North Jordan. Ann Med Surg (Lond) 2021;67:102430.
3. World Health Organization; Blindness and vision impairment: WHO Factsheet. World Heal Organ 2021;11.
4. Tadić V, Pring L, Dale N. Attentional processes in young children with congenital visual impairment. Br J Dev Psychol. 2009;27(Pt 2):311-330.
5. Modest JR, Majzoub KM, Moore B, Bhambhani V, McLaughlin SR, Vernacchio L. Implementation of ınstrument-based vision screening for preschool-age children in primary care. Pediatrics. 2017;140(1):e20163745.
6. Regassa TT, Daba KT, Fabian ID, Mengasha AA. Knowledge, attitude and practice of Ethiopian pediatricians concerning childhood eye diseases. BMC Ophthalmol 2021;21(1):91.
7. Yılmaz Tuğan B, Sönmez HE, Yüksel N. Knowledge, attitude, and practice toward eye disorders among pediatricians in Turkey. Pediatrician. 2023;213:58.
8. Donahue SP, Baker CN; Committee on Practice and Ambulatory Medicine, American Academy of Pediatrics; Section on Ophthalmology, American Academy of Pediatrics; American Association of Certified Orthoptists; American Association for Pediatric Ophthalmology and Strabismus; American Academy of Ophthalmology. Procedures for the evaluation of the visual system by pediatricians. Pediatrics. 2016;137.
9. Atowa UC, Wajuihian SO, Hansraj R. A review of paediatric vision screening protocols and guidelines. Int J Ophthalmol. 2019;12(7):1194-1201.
10. Balmer A, Munier F. Differential diagnosis of leukocoria and strabismus, first presenting signs of retinoblastoma. Clin Ophthalmol. 2007;1(4):431-439.
11. Marcinak JF, Yount SC. Evaluation of vision screening practices of Illinois pediatricians. Clin Pediatr (Phila). 1995;34(7):353-357.
12. Hersi RM, Naaman NK, Alghamdi AM, Alnahdi WA, Bukhari ZM, Almarzouki HS. Knowledge and attitude toward eye disorders in children among pediatricians and family physicians: a survey study. BMC Ophthalmol. 2023;23(1):90.
13. American Optometric Association. Evidence-based clinical practice guideline: comprehensive pediatric eye and vision examination. Optometric Clinical Practice. 2020;2(2):7.
14. Donahue SP, Arthur B, Neely DE, Arnold RW, Silbert D, Ruben JB, et al. Guidelines for automated preschool vision screening: a 10-year, evidence-based update. J AAPOS. 2013;17(1):4-8.
15. Bonsaana GB, Yakubu RC, Wanyama PS, Nuertey BD. Knowledge, attitudes and practices of paediatricians on the management of childhood eye diseases in Ghana. Postgraduate Medical Journal of Ghana. 2023;12(2):92-100.
16. Mostovoy D, Bunin A, Eyni Y, Ben Natan M. Pediatricians' knowledge, attitude and practice on treating children with red eye disease. BMC Ophthalmol. 2023;23(1):65.
17. Cronau H, Kankanala RR, Mauger T. Diagnosis and management of red eye in primary care. Am Fam Physician. 2010;81(2):137-144.
18. Silva JFL, Foschini RS, Paula JS, Silva MJL. Evaluation of pediatricians and neonatologists knowledge about ocular disorders in childhood. Residência Pediátrica. 2023;13(4).
19. Manica MB, Corrêa ZMS, Marcon ÍM, Telichevesky N, Loch LF. O que os pediatras conhecem sobre afecções oculares na criança? [What do pediatricians know about children's eye diseases?] Arq Bras Oftalmol. 2003;66:489-492.
20. Wilkinson AR, Haines L, Head K, Fielder AR. UK retinopathy of prematurity guideline. Early Hum Dev 2008;84(2):71-74.
21. Sathiamohanraj SR, Shah PK, Senthilkumar D, Narendran V, Kalpana N. Awareness of retinopathy of prematurity among pediatricians in a tier two city of South India. Oman J Ophthalmol. 2011;4(2):77-80.
22. Hadlaq AA, AL-Muqbil A, Al-Ali A, Al-Rashidi I, Iqbal Z. Knowledge, attitude, and practice study about retinopathy of prematurity among pediatricians in Al-Qassim region, Saudi Srabia. IJMDC. 2021;5(6):1290-1295.
23. Akkawi MT, Qaddumi JAS, Issa HRM, Yaseen LJK. Awareness of retinopathy of prematurity among pediatricians in West Bank, Palestine: a descriptive study. BMC Ophthalmol 2018;18(1):195.
24. Committee on Practice and Ambulatory Medicine, Bright Futures Periodicity Schedule Workgroup. 2021 recommendations for preventive pediatric health care. Pediatrics. 2021;147:e2020049776.
25. Çevik İ, Çakmak H, Çelik Ö, Okyay P. Lifelong eye health: "vision 2020: the right to sight". ESTÜDAM Halk Sağlığı Dergisi. 2021;6(3):310-321.

ORIGINAL RESEARCH

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Serum Leptin as a Diagnostic Biomarker in Preeclampsia: A Prospective Controlled Study

Preeklampside Serum Leptin Seviyelerinin Tanısal Potansiyeli: Prospektif Bir Çalışma

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Abstract

Objective: To compare serum leptin levels in preeclamptic pregnant women with those in healthy (normotensive) pregnant women and evaluate the potential of leptin as a diagnostic marker for preeclampsia.

Methods: This prospective study included 37 preeclamptic pregnant women and 37 healthy (normotensive) controls. Serum leptin concentrations were determined through the enzyme-linked immunosorbent assay method. Additionally, sociodemographic, clinical, and laboratory parameters were assessed. Receiver operating characteristic (ROC) curve analysis was performed to evaluate diagnostic performance.

Results: Mean serum leptin levels were significantly higher in the preeclampsia group (26.6±10.9 ng/mL) compared to the control group (10.8±5.3 ng/mL) ($p<0.05$). The area under the ROC curve was calculated as 0.928. A leptin threshold of 12.86 ng/mL yielded a sensitivity of 95% and a specificity of 70%, while a threshold of 15.36 ng/mL yielded 92% sensitivity and 79% specificity. Analysis of covariance confirmed that the differences in leptin levels remained statistically significant after adjusting for body mass index.

Conclusion: Serum leptin levels are significantly elevated in preeclamptic pregnancies, supporting its potential as a diagnostic biomarker. Further large-scale studies are needed to validate these findings and to investigate the mechanistic role of leptin in the pathogenesis of preeclampsia.

Keywords: Biomarker, hypertension, leptin, preeclampsia, pregnancy

Öz

Amaç: Preeklamptik gebelerde serum leptin düzeylerini sağlıklı (normotansif) gebelerle karşılaştırmak ve leptinin preeklampsi tanısındaki potansiyelini değerlendirmek.

Yöntem: Bu prospektif çalışmaya 37 preeklamptik gebe ile 37 sağlıklı (normotansif) gebe dahil edilmiştir. Serum leptin düzeyleri enzim bağlantılı immünosorbent analiz yöntemiyle ölçülmüştür. Demografik, klinik ve laboratuvar verileri toplanmış ve tanısal doğruluk alıcı çalışma karakteristiği (ROC) eğrisi analizi ile değerlendirilmiştir.

Bulgular: Serum leptin düzeyleri preeklampsi grubunda (26,6±10,9 ng/mL), kontrol grubuna (10,8±5,3 ng/mL) kıyasla anlamlı derecede yüksek bulunmuştur ($p<0,05$). ROC eğrisi altında kalan alan 0,928 olarak hesaplanmıştır. 12,86 ng/mL eşik değeri %95 duyarlılık ve %70 özgüllük sağlarken, 15,36 ng/mL eşiği %92 duyarlılık ve %79 özgüllük sağlamıştır. Vücut kitle indeksi farklarının etkisini kontrol etmek amacıyla yapılan kovaryans analizi, leptin düzeylerindeki farkların bağımsız olarak anlamlı olduğunu göstermiştir.

Sonuç: Preeklamptik gebeliklerde serum leptin düzeylerinin anlamlı şekilde yüksek bulunması, leptinin tanısal bir biyobelirteç olarak potansiyelini desteklemektedir. Bu bulguların daha büyük örneklemli çalışmalarla doğrulanması ve leptinin preeklampsi patogenezindeki rolünün aydınlatılması gerekmektedir.

Anahtar kelimeler: Biyobelirteç, gebelik, hipertansiyon, leptin, preeklampsi

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Introduction

Preeclampsia (PE) is a multifactorial and complex condition unique to pregnancy, defined by the emergence of hypertension and proteinuria after 20 weeks of gestation (1). Globally, it impacts 2-8% of pregnancies, representing a significant contributor to maternal and fetal morbidity and mortality (2). The pathophysiology of PE involves a combination of maternal and placental factors, including abnormal placental development, immune dysregulation, and systemic endothelial dysfunction (3).

Leptin, a 16 kDa protein produced mainly by adipocytes, plays an important role in regulating energy balance and reproductive functions (4). During pregnancy, leptin is also produced by the placenta, with levels rising substantially as gestation progresses (5). In the context of PE, placental hypoxia and ischemia are believed to enhance leptin production, potentially contributing to the disease's pathogenesis (6). Preeclamptic pregnancies are associated with markedly increased leptin levels, indicating a possible relationship between leptin dysregulation and the pathogenesis of PE (7). However, the precise role of leptin in PE and its utility as a predictive biomarker remain areas for further investigation. This study aims to provide additional evidence for the potential utility of leptin as a diagnostic marker in PE.

Materials and Methods

Study Design and Participants

This prospective study was conducted at Okmeydanı Health Research and Training Center, now known as University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital. A total of 74 pregnant women participated, including 37 women diagnosed with PE and 37 normotensive controls. Ethical approval was granted by the Clinical Research Ethics Committee of Okmeydanı Health Research Center, and written informed consent was obtained from all participants. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (date: 27/01/2020, no: 48670771-514.10/15).

Inclusion and Exclusion Criteria

Participants were included if they were between 18 and 44 years old, had a singleton pregnancy, and were either diagnosed with PE according to the American College of Obstetricians and Gynecologists criteria or had an uncomplicated pregnancy for the control group (8). Exclusion criteria included multiple pregnancies, chronic hypertension, diabetes, thyroid disorders, and other systemic diseases.

Data Collection

Demographic data, obstetric history, and clinical measurements were collected from all participants. Blood pressure was measured using standardized techniques (9). Venous blood samples for leptin measurement were collected after an overnight fast at the time of hospital admission for delivery. Demographic and clinical characteristics were recorded for all participants.

Laboratory Analysis

Serum leptin levels were measured using the enzyme-linked immunosorbent assay method. Blood samples were collected, processed, and stored according to standardized protocols. The leptin assay was conducted in accordance with the manufacturer's instructions.

Statistical Analysis

Data were analyzed using SPSS version 25.0. Descriptive statistics, including mean and standard deviation, were used to summarize continuous variables, while frequencies and percentages were used for categorical variables. The Student's t-test and Mann-Whitney U test were employed to compare continuous variables, and chi-square or Fisher's exact tests were used for categorical variables. A p-value of less than 0.05 was considered statistically significant.

To account for differences in body mass index (BMI) between the preeclamptic and normotensive groups, an analysis of covariance (ANCOVA) was performed. This allowed for the adjustment of leptin levels by controlling BMI, providing a clearer comparison between the groups. Additionally, the diagnostic performance of serum leptin levels was evaluated using receiver operating characteristic (ROC) curve analysis.

Results

Participant Characteristics

The study included 74 pregnant women 37 diagnosed with PE and 37 normotensive controls. Table 1 presents the demographic and clinical characteristics of the participants. The two groups showed no significant differences in terms of age, gravida, or parity. The mean gestational age at the time of blood sampling was 36.5±2.6 weeks (median 37) in the PE group, whereas it was 39.5±1.1 weeks (median 39) in the control group, showing a statistically significant difference ($p<0.001$). However , the preeclamptic group had a significantly higher BMI compared to the control group ($p<0.05$).

Leptin Levels

Serum leptin levels were markedly elevated in the preeclamptic group, with a mean value of 26.6±10.9 ng/mL, compared to 10.8±5.3 ng/mL in the control group ($p<0.05$) (Table 2).

Diagnostic Performance

ROC curve analysis revealed an area under the curve (AUC) of 0.928 (95% confidence interval: 0.873-0.983, $p<0.001$), demonstrating excellent diagnostic accuracy for serum leptin levels. A threshold of 12.86 ng/mL provided 95% sensitivity and 70% specificity, while a higher threshold of 15.36 ng/mL yielded 92% sensitivity and 79% specificity (Table 3). Figure 1 illustrates the ROC curve.

BMI-adjusted Leptin Analysis

To evaluate the influence of BMI on serum leptin levels, an ANCOVA was conducted. The analysis revealed a statistically significant variation in leptin levels between preeclamptic and control groups after adjusting for BMI [$F(1, 71)=79.658$, $p<0.05$). Moreover, BMI itself exhibited a notable impact on leptin concentrations [$F(1, 71)=8.987$, $p=0.004$, partial eta squared=0.112]. These findings underscore the significant disparities in leptin levels between preeclamptic and normotensive pregnancies, regardless of BMI adjustments (Table 4).

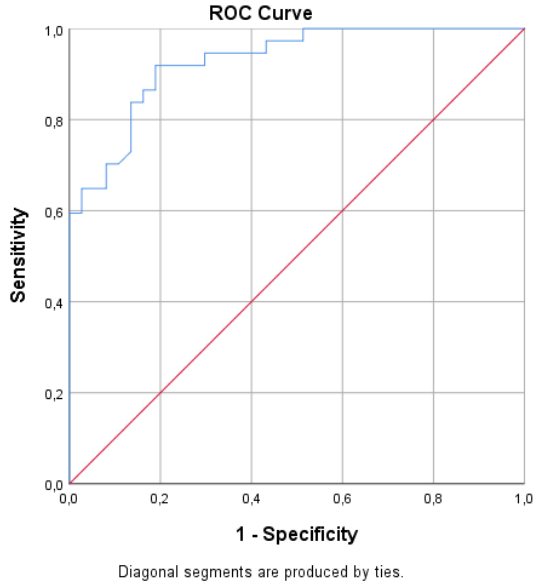

Figure 1. Receiver operating characteristic (ROC) curve for serum leptin levels

ROC curve for serum leptin levels in predicting preeclampsia. The area under the curve was 0.928 (95% confidence interval: 0.873-0.983, $p<0.001$). An optimal cut-off value of 12.86 ng/mL yielded 95% sensitivity and 70% specificity, while a higher threshold of 15.36 ng/mL provided 92% sensitivity and 79% specificity

Table 1. Demographic and clinical characteristics of the participants

Characteristic	Preeclamptic group (n=37)	Control group (n=37)	p-value
Age (years)	27.5±4.9	26.9±5.5	0.594
BMI (kg/m^2)	27.1±3.8	29.8±4.8	0.009
Gravida	2.8±1.4	2.4±1.3	0.462
Parity	1.1±1	0.9±1	0.444
Systolic BP (mmHg)	166.5±18.6	113.8±11.3	0.000
Diastolic BP (mmHg)	104.3±11.7	71.1±7.7	0.000

BMI: Body mass index, BP: Blood pressure

Table 2. Leptin levels

Group	Mean leptin levels (ng/mL)	Standard deviation	p-value
Preeclamptic (n=37)	26.6	10.9	0.000
Control (n=37)	10.8	5.3	0.000

Table 3. Diagnostic performance of leptin levels

Cut-off value (ng/mL)	Sensitivity (%)	Specificity (%)	AUC
12.86	95	70	0.928
15.36	92	79	0.928

AUC: Area under the curve

Table 4. ANCOVA results for BMI-adjusted leptin levels

Tests of between-subjects effects

Dependent variable: Leptin

Source	Type III sum of squares	df	Mean square	F	Sig.	Partial eta squared	Noncent. parameter	Observed power[b]
Corrected model	5253.959[a]	2	2626.980	39.881	0.000	0.529	79.762	1.000
Intercept	0.015	1	0.015	0.000	0.988	0.000	0.000	0.050
BMI	592.009	1	592.009	8.987	0.004	0.112	8.987	0.841
Preeclampsia status 1 PE/0 control	5247.115	1	5247.115	79.658	0.000	0.529	79.658	1.000
Error	4676.798	71	65.870					
Total	35771.807	74						
Corrected total	9930.757	73						

[a]: R squared =0.529 (adjusted R squared =0.516), [b]: Computed using alpha =0.05, ANCOVA: Analysis of covariance, BMI: Body mass index

Discussion

PE continues to rank among the primary contributors to maternal and perinatal morbidity and mortality. While its etiology and pathogenesis remain incompletely elucidated, current evidence suggests a multifactorial origin involving maternal and placental components, such as impaired placental development and endothelial dysfunction. This study highlights the significance, as a potential predictive marker for PE, of leptin, a hormone predominantly secreted by adipose tissue and additionally produced by the placenta during pregnancy.

Multiple studies have demonstrated the potential of serum leptin levels as a biomarker for early-onset PE. Taylor et al. (10) demonstrated in a large nested case-control study that serum leptin concentrations measured between 9 and 26 weeks of gestation were significantly elevated in women who later developed PE, independent of BMI and other confounders. Similarly, Hao et al. (11) conducted a longitudinal cohort study and found that leptin levels were consistently higher from the first trimester onwards in women who subsequently developed PE, surpassing traditional markers such as s soluble FMS-like tyrosine kinase receptor-1 and placental growth factor in early detection (10).

Beyond its role as a metabolic hormone, leptin is increasingly recognized as a pro-inflammatory cytokine-like mediator. It has been shown to stimulate the production of inflammatory cytokines, including interleukin-6 and tumor necrosis factor-alpha, which contribute to endothelial dysfunction, systemic inflammation, and abnormal placental development-key elements in the pathogenesis of PE. This mechanistic link may explain why leptin levels are elevated in preeclamptic pregnancies and supports the hypothesis that leptin actively participates in the disease process, rather than serving solely as a biomarker of adiposity or metabolic disturbance. Leptin's involvement in metabolic dysregulation and physiological imbalances during pregnancy underscores its pivotal role in the onset and progression of PE (12).

Our findings further support the potential role of leptin in PE pathogenesis, possibly via its influence on placental dysfunction and inflammatory pathways. This supports the hypothesis that leptin may act as a critical factor in the development of PE through its involvement in placental function and systemic inflammation (13). The ROC curve analysis in our study indicated a substantial AUC, confirming leptin's predictive value for PE at various cut-off points.

Other studies have reported consistent findings, further highlighting the significance of leptin in the pathophysiology of PE. Additionally, alterations in leptin dynamics and cellular metabolic pathways are believed to play a fundamental role in the mechanisms underlying hypertensive disorders in pregnancy, including PE (14).

Wang et al. (15) used an integrative approach combining bioinformatics tools with clinical sample analysis to identify leptin as a potential biomarker for PE. Their findings suggest that elevated leptin expression is strongly linked to PE and holds promise as both a diagnostic indicator and a therapeutic target (15).

Furthermore, a detailed review by Veiga et al. (16) confirmed that inflammatory markers, including leptin, are elevated in women with PE, reinforcing the potential of leptin as a biomarker for this condition.

Our findings on the diagnostic performance of serum leptin in PE are consistent with previous studies. El Shahat et al. (17) reported a cut-off value of 13.7 ng/mL for the diagnosis of PE with 91% sensitivity and 100% specificity, and a cut-off value of 22.5 ng/mL to predict severe cases, again with high diagnostic accuracy (AUC ~0.90). Similarly, Rao et al. (18) identified a threshold of 23.3 ng/mL, achieving 90% sensitivity and 88.3% specificity. Compared to previous studies, our study demonstrated a slightly lower diagnostic threshold (12.86 ng/mL) with higher sensitivity (95%) and acceptable specificity (70%), and an AUC of 0.928, indicating excellent discrimination. These findings suggest that serum leptin offers robust diagnostic utility across different populations and methodologies, reinforcing its value as a biomarker for PE.

Study Limitations

A notable strength of this study lies in its prospective design, enabling a precise evaluation of leptin levels in connection with PE. Furthermore, this research stands out as one of the few that accounts for BMI in the analysis of leptin levels, offering a more detailed understanding of its role in PE, independent of adiposity.

Nevertheless, this study has certain limitations. The relatively small sample size may restrict the generalizability of the results. Additionally, the research did not investigate longitudinal variations in leptin levels across different stages of pregnancy, which could offer deeper insights into the temporal dynamics of leptin's relationship with the onset of PE.

Moreover, it is noteworthy that the control group in our study exhibited a higher BMI compared to the PE group, which contrasts with existing literature, where higher BMI is typically associated with PE risk. This unexpected finding might be attributed to specific demographic or lifestyle characteristics of the study population and requires cautious interpretation.

Furthermore, the gestational age at the time of blood sampling was significantly lower in the PE group (median 37 weeks) compared to the control group (median 39 weeks). Given that serum leptin levels are known to increase with advancing gestational age, this discrepancy may have influenced the observed leptin concentrations and represents an additional limitation of our study.

Implications for Future Research

The results of this study suggest that serum leptin levels, especially when adjusted for BMI, may serve as a potential biomarker. Future investigations should prioritize large-scale, multicenter studies to confirm these findings. Moreover, research aimed at elucidating the mechanistic pathways by which leptin influences the pathogenesis of PE is strongly recommended.

Conclusion

PE remains a major obstetric challenge with complex and multifactorial pathophysiology that is yet to be fully elucidated. Among various biomarkers under investigation, leptin has emerged as a candidate involved in several key pathological pathways including placental dysfunction and systemic inflammation. In our study, significantly elevated serum leptin levels in preeclamptic pregnancies support its potential role in disease prediction.

Moving forward, our findings underscore the need for large-scale, multicenter studies to validate leptin's diagnostic performance across diverse populations. Future research should also focus on integrating leptin with other biochemical and clinical markers to develop robust predictive models for the early identification and risk stratification of PE.

Ethics

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (date: 27/01/2020, no: 48670771-514.10/15).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.İ.T., B.C., H.C.U., S.G., Concept: M.İ.T., E.A., Y.D.Y.K., V.M., Design: E.A., B.C., S.G., V.M., Data Collection or Processing: M.İ.T., B.C., S.G., V.M., Analysis or Interpretation: E.A., H.C.U., V.M., Literature Search: M.İ.T., E.A., Y.D.Y.K., S.G., Writing: M.İ.T., B.C., H.C.U., Y.D.Y.K., V.M.

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References

1. Başol E, Özdemir S. The analysis of serum calcium and urine calcium/creatinine ratio in diagnosis of preeclampsia. Bagcilar Med Bull. 2023;8(1):62-67.
2. Özalp M, Yaman H, Demir Ö, Aytekin Garip S, Aran T, Osmanağaoğlu MA. The role of maternal serum catestatin in the evaluation of preeclampsia and fetal cardiac functions. Turk J Obstet Gynecol. 2021;18(4):272-278.
3. Tomimatsu T, Mimura K, Matsuzaki S, Endo M, Kumasawa K, Kimura T. Preeclampsia: maternal systemic vascular disorder caused by generalized endothelial dysfunction due to placental antiangiogenic factors. Int J Mol Sci. 2019;20(17):4246.
4. Barrios-Correa AA, Estrada JA, Contreras I. Leptin signaling in the control of metabolism and appetite: lessons from animal models. J Mol Neurosci. 2018;66(3):390-402.
5. de Knegt VE, Hedley PL, Kanters JK, Thagaard IN, Krebs L, Christiansen M, et al. The role of leptin in fetal growth during pre-eclampsia. Int J Mol Sci. 2021;22(9):4569.
6. Mise H, Sagawa N, Matsumoto T, Yura S, Nanno H, Itoh H, et al. Augmented placental production of leptin in preeclampsia: possible involvement of placental hypoxia. J Clin Endocrinol Metab. 1998;83(9):3225-3229.
7. Miehle K, Stepan H, Fasshauer M. Leptin, adiponectin and other adipokines in gestational diabetes mellitus and pre-eclampsia. Clin Endocrinol (Oxf). 2012;76(1):2-11.
8. Gestational hypertension and preeclampsia: ACOG Practice Bulletin, number 222. Obstet Gynecol. 2020;135(6):e237-e260.
9. Stergiou GS, Palatini P, Parati G, O'Brien E, Januszewicz A, Lurbe E, et al. 2021 European Society of Hypertension practice guidelines for office and out-of-office blood pressure measurement. J Hypertens. 2021;39(7):1293-1302.
10. Taylor BD, Ness RB, Olsen J, Hougaard DM, Skogstrand K, Roberts JM, et al. Serum leptin measured in early pregnancy is higher in women with preeclampsia compared with normotensive pregnant women. Hypertension. 2015;65(3):594-599.
11. Hao S, You J, Chen L, Zhao H, Huang Y, Zheng L, et al. Changes in pregnancy-related serum biomarkers early in gestation are associated with later development of preeclampsia. PLoS One. 2020;15(3):e0230000.
12. Harish R, Reshma D, AshakiranS, Shetty VV. The Role of leptin in preeclampsia: insights into pathogenesis and potential therapeutic implications. Current Progress in Medicine and Medical Research. 2023;3:10-42.
13. Peltokorpi A, Irina L, Liisa V, Risto K. Preconceptual leptin levels in gestational diabetes and hypertensive pregnancy. Hypertens Pregnancy. 2022;41(1):70-77.
14. Nonn O, Fischer C, Geisberger S, El-Heliebi A, Kroneis T, Forstner D, et al. Maternal angiotensin increases placental leptin in early gestation via an alternative renin-angiotensin system pathway: suggesting a link to preeclampsia. Hypertension. 2021;77(5):1723-1736.
15. Wang Y, Bai X, Guo X, Gao X, Chen Y, Li H, et al. Bioinformatics analysis combined with clinical sample screening reveals that leptin may be a biomarker of preeclampsia. Front Physiol. 2023;13:1031950.
16. Veiga ECA, Korkes HA, Salomão KB, Cavalli RC. Association of LEPTIN and other inflammatory markers with preeclampsia: a systematic review. Front Pharmacol. 2022;13:966400.
17. El Shahat AM, Ahmed AB, Ahmed MR, Mohamed HS. Maternal serum leptin as a marker of preeclampsia. Arch Gynecol Obstet. 2013;288(6):1317-1322.
18. Rao S, Kumari A, Sharma M, Kabi BC. Predicting maternal serum adiponectin and leptin level as biomarkers of pre-eclampsia: a prospective study. J Obstet Gynaecol India. 2021;71(1):58-65.

ORIGINAL RESEARCH

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Evaluation of ChatGPT's Performance in Making-decision of Dialysis in Acute Kidney Injury

Akut Böbrek Hasarında Diyaliz Kararı Almada ChatGPT Performansının Değerlendirilmesi

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Abstract

Objective: Artificial intelligence chatbots have begun to be widely used in medicine. We aimed to evaluate the performance of ChatGPT in identifying patients in need of dialysis.

Method: A total of 100 patients who presented with acute kidney injury and were treated either with dialysis or without dialysis at the internal medicine clinic were retrospectively reviewed. Patient histories were created, consisting of demographic data, physical examination, and some laboratory tests. These patient histories were input into ChatGPT, and we requested a clinical evaluation along with recommendations categorizing them as low, medium, or high risk for dialysis treatment. The responses from ChatGPT were compared with the actual dialysis status of the patients. Additionally, ChatGPT responses were evaluated and scored by two nephrologists who were unaware of the dialysis status.

Results: The sensitivity of ChatGPT in recommending patients' need for dialysis was calculated as 94%, 97%, and 97% for ChatGPT 1, 2, and 3 answers, respectively. Specificity for ChatGPT responses 1, 2, and 3 was calculated as 81%, 76%, and 78%, respectively (p<0.001). The mean clinical evaluation scores were 4.71±0.4 and 4.67±0.4, and treatment recommendation scores were 4.45±0.7 and 4.39±0.7 for nephrologist 1 and nephrologist 2 (p=0.002) (p<0.001).

Conclusion: ChatGPT can be used as a decision support tool to identify patients who may need dialysis. Nevertheless, healthcare professionals should remain part of the decision-making process at present.

Keywords: Acute kidney injury, artificial intelligence, ChatGPT, dialysis

Öz

Amaç: Yapay zeka sohbet botları tıpta yaygın olarak kullanılmaya başlanmıştır. Çalışmamızda, ChatGPT'nin diyaliz ihtiyacı olan hastaları belirlemedeki performansını değerlendirmeyi amaçladık.

Yöntem: Akut böbrek hasarı nedeniyle dahiliye kliniğine başvuran ve diyalizle veya diyalizsiz tedavi edilen toplam 100 hasta retrospektif olarak incelendi. Hastaların demografik verileri, fizik muayene bulguları ve bazı laboratuvar testlerini içeren hasta öyküleri oluşturuldu. Bu hasta öyküleri ChatGPT'ye girilerek hastalar için klinik bir değerlendirme yapılması ve diyaliz tedavisi gerekliliğine göre düşük, orta veya yüksek risk kategorilerine ayrılması istendi. ChatGPT'nin yanıtları, hastaların gerçek diyaliz durumlarıyla karşılaştırıldı. Ayrıca ChatGPT'nin yanıtları, diyaliz gereksiniminden habersiz olan iki nefrolog tarafından değerlendirilerek puanlandı.

Bulgular: ChatGPT'nin hastaların diyaliz ihtiyacını belirlemedeki duyarlılığı, ChatGPT 1, 2 ve 3 yanıtları için sırasıyla %94, %97 ve %97 olarak hesaplandı. Spesifiklik ise ChatGPT 1, 2 ve 3 yanıtları için sırasıyla %81, %76 ve %78 olarak belirlendi (p<0,001). Klinik değerlendirme puan ortalamaları nefrolog 1 ve nefrolog 2 için sırasıyla 4,71±0,4 ve 4,67±0,4 olarak hesaplandı. Tedavi önerisi puan ortalamaları ise sırasıyla 4,45±0,7 ve 4,39±0,7 olarak bulundu (p=0,002 ve p<0,001).

Sonuç: ChatGPT, diyaliz ihtiyacı olabilecek hastaları belirlemede bir karar destek aracı olarak kullanılabilir. Bununla birlikte, sağlık profesyonellerinin karar verme sürecinde belirleyici bir rol oynamaya devam etmesi gerekmektedir.

Anahtar kelimeler: Akut böbrek hasarı, ChatGPT, diyaliz, yapay zeka

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Introduction

Acute kidney injury (AKI) is defined as a syndrome characterized by impairment in kidney function resulting from a pathophysiological process caused by various etiologies. Estimates of AKI prevalence vary widely, ranging from less than 1% to as high as 66% (1). The primary causes of AKI include post-surgical or diagnostic interventions, sepsis, volume depletion, exposure to toxins, pregnancy-related complications, and iatrogenic factors (2,3). In AKI, impaired electrolyte balance and accumulation of waste products can induce a systemic inflammatory response and affect distant organs.

Uremic encephalopathy, pericarditis, life-threatening hyperkalemia, refractory acidosis, and hypervolemia causing end-organ complications are some indications for immediate dialysis (4). In some patients, dialysis treatment should be planned urgently to prevent complications such as permanent nephron loss. However, given the growing workload of clinicians and the challenges faced by healthcare systems in many countries, implementing systems that assist with patient treatment decisions may make a significant contribution.

Chat generative pretrained transformer (ChatGPT) is an artificial intelligence chatbot specializing in conversation. ChatGPT was first introduced into daily practice in late 2022. In a short period, it started being used in numerous areas of life, spanning from economics to education, and from engineering to medicine. Recently, numerous studies have demonstrated ChatGPT's ability in medical research (5-7). In this study, we aimed to evaluate the decision-making ability of ChatGPT in determining the need for dialysis in patients presenting to the hospital with AKI.

Materials and Methods

We conducted a retrospective review of 100 consecutive patients who presented with AKI at the internal medicine clinic between January 2023 and May 2023. Demographic features, dialysis status, blood gas analysis, creatinine levels, hypervolemia, and uremic symptoms were retrospectively recorded for each patient. The study protocol was approved by the Local Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital and conducted in accordance with the Declaration of Helsinki (approval no: 2024.03.226, date: 22.04.2024). Patients diagnosed with chronic kidney disease (CKD), those with a history of dialysis, and those who may require intensive care were excluded from the study.

In the present study, the free version of ChatGPT 4, as of June 2024, was utilized to assess patient data. Before asking ChatGPT patient-related clinical questions, all personal browser data was cleared to prevent bias. New accounts were created. An entry was created for each patient that summarized the patient's demographic characteristics and clinic. We asked ChatGPT to evaluate the patients' need for dialysis. The exact question to ChatGPT was "Hi, can I give you a patient story, where AKI is detected, and can you predict the risk stage as high, moderate, or low for immediate dialysis?". Then, we entered patient information during the application (within a few hours), including age, gender, comorbidities, blood pressure, volume status (such as hypervolemia), uremic symptom status, urine output (in cc/h), blood gas analysis and levels of urea and creatinine. For example, "a 68-year-old woman has diabetes mellitus, hypertension, and asthma. Blood pressure: 122/155 mmHg, pericardial effusion (+), pleural effusion (+), nausea (+), vomiting (+), urine output: 83 cc/h. In venous blood gas, pH=7.37 HCO_3=17, lactate=1, potassium=4.7 creatinie=8.3, urea=214".

All prompts were formulated in English. ChatGPT answered the questions for each patient with a clinical evaluation and a risk stratification as high, moderate, and low. To account for variability, ChatGPT was queried weekly for three weeks, yielding three responses per patient (1 day, 7 day, 14 day). Thus, ChatGPT's answers were labeled as 1, 2, and 3.

We evaluated the compatibility between these three ChatGPT's answers. Additionally, the study evaluated whether patients identified by ChatGPT as high-risk, for the need for emergency dialysis, actually received dialysis in real life.

ChatGPT answers were also evaluated by two experienced nephrologists. Two nephrologists independently evaluated ChatGPT responses in separate settings. The nephrologists scored the ChatGPT answers based on clinical evaluation and treatment recommendations. The nephrologists used a 5-point Likert scale for assessment. The meaning of points was (1) Strongly Disagree; (2) Disagree; (3) Neither Agree nor Disagree; (4) Agree; (5) Strongly Agree. The agreement between nephrologists' scores was also evaluated. Nephrologists were blinded to patients' actual dialysis status during the evaluation of ChatGPT responses.

Since the nephrologists in the study are the clinicians, we did not find it necessary to directly compare ChatGPT's predictions with the independent predictions made by nephrologists.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc, Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation. Cohen's kappa test was utilized to assess the agreement between the ChatGPT answers 1, 2, and 3. Similarly, the agreement of the nephrologists was evaluated with Cohen's kappa test. The relationship between patients recommended as high risk by ChatGPT and those who actually received dialysis was evaluated using the chi-squared test. A p-value of <0.05 was considered statistically significant.

Results

A total of 100 patients with AKI were included in the study. General information of patients with AKI was presented in Table 1. The mean age of the patients was 68.07±16.3 years. Out of the patients, 44 were male and 56 were female.

Immediate dialysis treatment was administered to 36 of the patients presenting with AKI. On the other hand, 64 patients received medical treatment without dialysis. Out of 100 patients, 26 exhibited signs of hypervolemia, and 28 patients experienced uremic symptoms. The mean creatinine level was 5.4±3.5 mg/dL. The mean hospitalisation time was 13.7±9.9 days. All patients were discharged in stable condition following their treatment. In the blood gas analysis, the mean pH level was 7.2±0.09, and the mean HCO_3 level was 18.7±6.4 mEq/L. The mean lactate level was 38.1±8.4 mg/dL.

Table 1. General information of acute kidney injury patients

	n=100 Acute kidney injury patients
Age (mean ± SD)	68.07±16.3
Gender (male/female)	44/56
Urea (mean ± SD) (mg/dL)	164.8±78.5
Creatinine (mean ± SD) (mg/dL)	5.4±3.5
Hypervolemia sign* (yes/no)	26/74
Uremic symptom# (yes/no)	28/72
Immediate dialysis (yes/no)	36/64
Hospitalization (mean ± SD) (day)	13.7±9.9
Blood gas analysis	
pH (mean ± SD)	7.2±0.09
HCO_3 (mean ± SD) (mEq/L)	18.7±6.4
Lactate (mean ± SD)	38.1±8.4

pH: Potential of hydrogen, HCO_3: Bicarbonate, SD: Standard deviation, *: Pleural effusion or pericardial effusion or pretibial edema, #: Nausea or vomiting or encephalopathy

According to Cohen's kappa test, the pairwise consistency between ChatGPT answer 1 and 2, ChatGPT answer 2 and 3, and ChatGPT answer 1 and 3 was all statistically significant (p<0.001). The relationship between ChatGPT treatment recommendation and dialysis status is presented in Table 2. Based on all ChatGPT results, there was a statistically significant association between patients predicted to be at high risk for dialysis and patients who actually received dialysis (for all ChatGPT answers p<0.001).

The results of nephrologists' evaluation of ChatGPT answers are presented in Figure 1. The mean clinical evaluation scores were 4.71±0.4 and 4.67±0.4 for nephrologist 1 and nephrologist 2 (p=0.002, respectively). The mean treatment recommendation scores were 4.45±0.7 and 4.39±0.7 for nephrologist 1 and nephrologist 2 (p<0.001) (respectively). The consistency of nephrologists was statistically significant for both clinical evaluation and treatment recommendation.

The sensitivity of the artificial intelligence chatbot in recommending patients' need for dialysis was calculated as 94%, 97%, and 97% for ChatGPT answers 1, 2, and 3,

Table 2. The relationship between ChatGPT treatment recommendation and dialysis status

		Dialysis (+) n=36	Dialysis (-) n=64	p-value
ChatGPT answer 1	High risk	34	12	<0.001
	Non-high risk	2	52	
ChatGPT answer 2	High risk	35	15	<0.001
	Non-high risk	1	49	
ChatGPT answer 3	High risk	35	14	<0.001
	Non-high risk	1	50	

ChatGPT: Chat generative pre-trained transformer

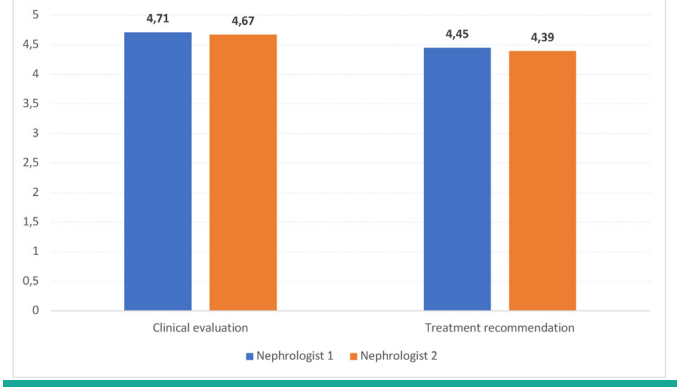

Figure 1. Rating of the performance of ChatGPT in two categories by the two reviewers: Clinical evaluation and treatment recommendation

ChatGPT: Chat generative pre-trained transformer

respectively. The specificity was calculated as 81%, 76%, and 78% for ChatGPT answers 1, 2, and 3, respectively.

Discussion

The present study revealed that ChatGPT has high sensitivity in suggesting patients' need for dialysis. Additionally, accuracy rates were verified by two independent nephrologists.

In recent years, artificial intelligence technology has been increasingly utilized in medicine (8). However, there are many questions regarding the reliability and efficacy of this new technology in medicine. In the field of medicine, ongoing research is focused on the use of AI in various areas including medical counselling, diagnosis, screening, surgery, patient management, and documentation (6,9). In our study, we evaluated the performance of ChatGPT in making decisions regarding the need for dialysis in patients. To the best of our knowledge, this is the first study assessing ChatGPT for this purpose.

AKI is a complex disease that can be apparent with various symptoms and signs, sometimes causing disruptions in multiple organ systems. Clinicians commonly use clinical semiology when evaluating the symptoms, signs, and clinical history of patients with conditions like AKI. However, our study demonstrated that if the relevant clinical findings and laboratory values of a patient with AKI are known, an artificial intelligence chatbot can determine the need for dialysis with up to a 97% accuracy rate.

On the other hand, using ChatGPT is not always optimal and straightforward. How healthcare professionals will use the chatbot is also an important consideration. When we ask ChatGPT about a patient's clinical details and treatment suggestions, it provides general recommendations and emphasizes the importance of seeking professional medical help. In this regard, as researchers gain a better understanding of how chatbot models like ChatGPT respond, they will learn how to formulate their future questions more effectively. We developed a question pattern through iterative trials to elicit correct answers and conducted the study using it. As stated in the methodology section, the question framework begins with the patient's age, sex, and comorbidities. The sentence is incomplete and lacks a subject and main verb to convey a complete thought. The effectiveness of this question framework model in decision-making processes for other nephrological diseases will be determined by future studies.

It is known that some questions asked of ChatGPT remain unanswered or may give incorrect answers (10). Similarly, in the study of Morath et al. (11), ChatGPT provided incorrect or incomplete answers to most of the 50 questions regarding drug information. These studies indicate that ChatGPT's performance may not be suitable for every medical topic at the present time. Therefore, due to the possibility of ChatGPT's responses being incorrect or inconsistent, we repeated the same clinical data and questions on the first day, on day 7, and on day 14, and requested treatment recommendations and patient evaluations from ChatGPT. The consistency and high accuracy rate of ChatGPT responses in this study showed that ChatGPT does not exhibit these limitations in making dialysis decisions.

The accuracy of information in healthcare services is critically important because errors or inaccuracies can lead to serious and irreversible consequences. A rigorous human review process, as well as human involvement at any stage of the workflow, can be crucial to the ChatGPT decision process. Although our study demonstrates that ChatGPT effectively manages the cases with high sensitivity and specificity, we believe that blindly relying on ChatGPT recommendations may entail clinical risks. However, in cases where access to a nephrologist is limited, initial guidance on treatment can be provided, and necessary cases can be shared with the nephrologist. Thus, the workload of nephrologists can be reduced. There is a lack of studies in the literature evaluating the decision-making capability of ChatGPT in nephrological diseases. In our previous study, we demonstrated that ChatGPT provided highly accurate answers to CKD-related questions aimed at informing patients (12). Nevertheless, further studies are needed in this area related to other nephrological diseases.

ChatGPT's training is based on large datasets of text sourced from the Internet. Therefore, as the size of chatbot models increases and they are trained on larger datasets, they have the potential to provide more accurate and detailed answers to the questions asked. Specialized chatbots tailored for specific healthcare purposes can be researched and developed, such as an AKI chatbot or a thyroid disease chatbot.

To reduce the possibility of bias in the datasets on which the model is trained, we cleared the browsers, created new users, input data into ChatGPT, and then queried the patient clinics. Nevertheless, reducing this potential bias to zero may be nearly impossible. After accumulating data, we believe that more comprehensive studies involving machine learning will improve the results.

Study Limitations

Our study has identified certain limitations associated with ChatGPT, particularly related to patient privacy and the risk of information misuse. Therefore, meticulous data storage and access management are crucial aspects that require strict regulation and oversight (13). Another limitation of the study is the potential bias arising from its retrospective nature. Although the inclusion of only 100 patients limits the statistical power and generalizability of the findings, we believe it is sufficient for this preliminary study. Healthcare professionals must be aware of ChatGPT's limitations to use it effectively and responsibly.

Conclusion

ChatGPT can serve as a decision-support tool to assist in identifying patients who may require dialysis. Additionally, software can be integrated into Hospital Health Information Management Systems to assist healthcare professionals in the initial management of patients with AKI. Although artificial intelligence cannot yet replace clinical judgment in dialysis decisions, its potential for future integration appears promising. Prospective studies with larger sample sizes are needed to strengthen the validity of these findings.

Information: A preprint version of our article is available on Research Square.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital and conducted in accordance with the Declaration of Helsinki (approval no: 2024.03.226, date: 22.04.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.C., F.P., M.K., Z.K., Concept: B.C., E.D.K., Design: B.C., M.K., Z.K., Data Collection or Processing: B.C., E.D.K., F.P., Z.K., Analysis or Interpretation: B.C., F.P., M.K., Literature Search: B.C., E.D.K., Writing: B.C.

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References

1. Hoste EAJ, Kellum JA, Selby NM, Zarbock A, Palevsky PM, Bagshaw SM, et al. Global epidemiology and outcomes of acute kidney injury. Nat Rev Nephrol. 2018;14(10):607-625.
2. Jha V, Parameswaran S. Community-acquired acute kidney injury in tropical countries. Nat Rev Nephrol. 2013;9(5):278-290.
3. Olowu WA, Niang A, Osafo C, Ashuntantang G, Arogundade FA, Porter J, et al. Outcomes of acute kidney injury in children and adults in sub-Saharan Africa: a systematic review. Lancet Glob Heal. 2016;4(4):e242-e250.
4. Murdeshwar H, Anjum F. Hemodialysis. [Accessed on: 2023 Apr 27] [Internet]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563296/%0A
5. Zhou Z. Evaluation of ChatGPT's capabilities in medical report generation. Cureus. 2023;15(4):e37589.
6. Sorin V, Klang E, Sklair-Levy M, Cohen I, Zippel DB, Balint Lahat N, et al. Large language model (ChatGPT) as a support tool for breast tumor board. NPJ Breast Cancer. 2023;9(1):44.
7. Sievert M, Conrad O, Mueller SK, Rupp R, Balk M, Richter D, et al. Risk stratification of thyroid nodules: assessing the suitability of ChatGPT for text-based analysis. Am J Otolaryngol - Head Neck Med Surg. 2024;45(2):104144.
8. Wen Z, Huang H. The potential for artificial intelligence in healthcare. J Commer Biotechnol. 2022;27(4):217-224.
9. Del Vecchio D, Stein MJ, Dayan E, Marte J, Theodorou S. Nanotechnology and artificial intelligence: an emerging paradigm for postoperative patient care. Aesthetic Surg J. 2023;43(7):748-757.
10. Mediboina A, Badam RK, Chodavarapu S. Assessing the accuracy of information on medication abortion: a comparative analysis of ChatGPT and Google Bard AI. Cureus. 2024;16(1):e51544.
11. Morath B, Chiriac U, Jaszkowski E, Deiß C, Nürnberg H, Hörth K, et al. Performance and risks of ChatGPT used in drug information: an exploratory real-world analysis. Eur J Hosp Pharm. 2024;31(6):491-497.
12. Can B, Kahvecioğlu ED, Palıt F, Cebeci E, Küçük M, Karaali Z. Assessing the performance of chat generative pretrained transformer (ChatGPT) in answering chronic kidney disease-related questions. Ther Apher Dial. 2024;1-6.
13. Cascella M, Montomoli J, Bellini V, Bignami E. Evaluating the feasibility of ChatGPT in healthcare: an analysis of multiple clinical and research scenarios. J Med Syst. 2023;47(1):33.

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The Impact of Systemic Inflammation and Electrolyte Imbalance on Electrocardiogram Parameters in Acute Pancreatitis: A Clinical Research Article

Akut Pankreatitte Sistemik Enflamasyon ve Elektrolit Dengesizliğinin Elektrokardiyogram Parametreleri Üzerindeki Etkisi: Klinik Bir Araştırma Makalesi

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Abstract

Objective: Acute pancreatitis (AP) frequently results in hospitalization and is associated with substantial morbidity and mortality, and may lead to various complications, including electrocardiographic (ECG) abnormalities. Cardiovascular manifestations in AP are often underrecognized, despite their potential clinical significance. We aimed to analyze ECG changes in patients with AP and examine their associations with systemic inflammatory response and electrolyte imbalances.

Method: We retrospectively reviewed data from 89 patients with a diagnosis of AP and 49 healthy controls. ECG parameters and laboratory data were analyzed. Comparative statistical analyses were performed to assess differences in ECG findings and laboratory results between the AP and control groups.

Results: Patients with AP demonstrated significant prolongation of P_{max}, P dispersion, P wave peak time in lead D2, and V1, QT_{max}, QTc_{max}, and Tp-e intervals compared to controls. These ECG alterations were associated with lower serum potassium and calcium levels in the AP group. Inflammatory markers, particularly C-reactive protein, were significantly

Öz

Amaç: Akut pankreatit (AP), önemli morbidite ve mortaliteye yol açabilen, sık görülen bir hastaneye yatış nedenidir ve elektrokardiyografik (EKG) değişiklikler dahil olmak üzere çeşitli komplikasyonlara neden olabilir. AP'de kardiyovasküler bulgular, klinik olarak anlamlı olabilmelerine rağmen sıklıkla göz ardı edilmektedir. Bu çalışmanın amacı, AP'li hastalarda EKG değişikliklerini değerlendirmek ve bu değişikliklerin sistemik enflamatuvar yanıt ve elektrolit dengesizlikleriyle ilişkisini incelemektir.

Yöntem: Bu retrospektif çalışmada AP tanısı almış 89 hasta ile 49 sağlıklı kontrol grubu değerlendirildi. EKG parametreleri ve laboratuvar verileri analiz edildi. AP grubu ile kontrol grubu arasındaki EKG bulguları ve laboratuvar sonuçlarındaki farkları değerlendirmek için karşılaştırmalı istatistiksel analizler yapıldı.

Bulgular: AP'li hastalarda, kontrol grubuna kıyasla P_{maks}, P dispersiyonu, D2 ve V1 derivasyonlarında P dalga pik zamanı, QT_{maks}, QTc_{maks} ve Tp-e aralıklarında anlamlı uzamalar saptandı. Bu EKG değişiklikleri, AP grubunda düşük serum potasyum ve kalsiyum düzeyleri ile ilişkiliydi. Enflamatuvar belirteçlerden özellikle C-reaktif protein düzeyleri anlamlı

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Abstract

elevated and showed a positive correlation with ECG abnormalities. Multivariate analysis revealed that P_{max} and QTc_{max} durations remained prolonged significantly and independently in the AP group.

Conclusion: ECG monitoring should be considered in patients with AP, as ECG changes may reflect underlying systemic inflammation and electrolyte disturbances, which could have prognostic value.

Keywords: Acute pancreatitis, ECG parameters, electrolyte imbalance, inflammation

Öz

şekilde yüksekti ve EKG anormallikleriyle pozitif korelasyon gösterdi. Çok değişkenli analizde, P_{maks} ve QTc_{maks} sürelerinin AP grubunda anlamlı ve bağımsız şekilde uzamış olduğu görüldü.

Sonuç: AP'li hastalarda EKG izlem dikkate alınmalıdır; çünkü EKG değişiklikleri altta yatan sistemik enflamasyonu ve elektrolit bozukluklarını yansıtabilir ve prognostik değer taşıyabilir.

Anahtar kelimeler: Akut pankreatit, EKG parametreleri, elektrolit inbalansı, enflamasyon

Introduction

Pancreatitis accounts for a significant portion of hospital admissions for gastrointestinal diseases in the United States, and due to its high morbidity and mortality rates, it represents a major healthcare concern; it also imposes a substantial socioeconomic burden (1).

In patients presenting to the emergency department with abdominal pain, acute pancreatitis (AP) holds substantial percentage of cases. A thorough medical history, a well-conducted physical examination, along with laboratory findings and imaging results, is generally sufficient for diagnosis. The diagnosis of pancreatitis requires at least two out of three diagnostic criteria: Increased pancreatic enzyme levels, typical abdominal pain, and imaging findings supportive of the diagnosis (2).

To grasp the concept of pancreatitis, it is crucial to explore its fundamental pathophysiological processes. Over time, considerable progress has been made in elucidating the molecular mechanisms of acute pancreatitis. Studies have demonstrated how calcium (Ca) contributes to acinar cell injury and death, particularly by triggering Ca influx pathways and causing mitochondrial membrane disruption. Furthermore, the beneficial effects of the unfolded protein response and autophagy in alleviating prolonged endoplasmic reticulum stress, apoptosis, and necrosis have been clearly established. The significant role of unsaturated fatty acids in triggering pancreatic organ failure has also been extensively investigated (3).

AP is caused by numerous etiological factors. The primary causes include gallstones, ethanol consumption, hypertriglyceridemia, medications, endoscopic retrograde cholangiopancreatography, trauma, hypercalcemia, viral infections, tumors, anatomical variations, cardiac bypass surgery, scorpion stings, and organophosphate poisoning (4).

AP can affect multiple organ systems, with the extent of involvement largely depending on the severity of inflammation. Cardiovascular changes in AP are often overlooked but can present with life-threatening complications. Several studies have explored the mechanisms by which pancreatitis affects the cardiovascular system. It was predicted that severe hypotension in AP could reduce coronary artery perfusion, thereby precipitating myocardial ischemia (5). In addition, vagal reflexes triggered by parasympathetic stimulation increase the secretion of proteolytic enzymes from the pancreas, which are believed to directly contribute to myocardial and cardiac damage (6,7). It was shown that certain electrolyte imbalances observed in pancreatitis could trigger ischemic changes on the electrocardiographic (ECG) (8). Myocardial injury may occur in patients with AP, irrespective of the disease's severity. In some cases, pancreatitis can mimic the clinical manifestations of acute coronary syndrome, despite the absence of significant coronary artery obstruction (9). AP patients presenting to the emergency department might exhibit atrial extrasystole, bradycardia, T wave and/or ST segment changes, intraventricular conduction abnormalities, left anterior hemiblock, complete left bundle branch block, incomplete right bundle branch block, and first-degree atrioventricular block (10). Moreover, there is a significant association between atrial fibrillation (AF) and AP. In patients with AF, the risk of developing AP is 1.5 times that of those without AF (11). Furthermore, the occurrence of AF in patients with AP has been associated with unfavorable clinical outcomes (12). In addition to AF, a case report was presented in which a patient with AP developed ventricular extrasystoles and ventricular tachycardia (13). Given the clinically meaningful association between AP and cardiac arrhythmias, both in terms of potential causality and prognostic implications, the evaluation of ECG parameters to predict arrhythmias holds considerable importance. Such an approach may contribute to more accurate

risk stratification and improved patient management, ultimately enhancing clinical outcomes.

Given the growing evidence of cardiovascular involvement in AP and the potential prognostic implications of ECG changes, this research aimed to comprehensively investigate alterations in specific ECG parameters at the time of hospital admission in patients with AP compared to healthy controls. Furthermore, the study sought to evaluate whether these parameters, particularly P wave indices, QT and QTc intervals, and ventricular repolarization markers, could serve as indicators of arrhythmic risk in this patient population, thereby contributing to improved risk stratification and early clinical management strategies.

Materials and Methods

A total of 89 patients diagnosed with acute pancreatitis between January 2023 and January 2024 and admitted to the Department of Internal Medicine of University of Health Sciences Turkey, İstanbul Training and Research Hospital were included in our retrospective study. Medical records, including complete blood count (CBC) and biochemical data, were obtained from the hospital's electronic health information system. ECG parameters were derived from measurements taken from ECG recordings obtained at the time of hospital admission. The CBC, biochemical, and ECG data from these patients were then compared to those of a control group made up of 49 healthy individuals of similar age. The control subjects had no documented history of cardiovascular disease, chronic systemic illness, or the use of medications known to influence ECG parameters or laboratory findings. The inclusion criteria were being over 18 years old and being admitted to the internal medicine department with a diagnosis of AP. Exclusion criteria included having type 1 or type 2 diabetes, end-stage renal disease, liver cirrhosis, a background of bypass surgery or operative treatment for heart valve disorders, recent ST-elevation myocardial infarction, newly diagnosed heart failure with reduced ejection fraction, atrial or ventricular arrhythmias, and bundle branch block detected on ECG. Electrolyte imbalance was not excluded, as it is a common component of the natural course of AP. Any observed ECG changes could, at least in part, be attributed to electrolyte disturbances secondary to the underlying disease process.

The Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital granted approval for this study (approval no: 15, date: 05.07.2024). Written informed consent was obtained from all participants prior to their inclusion in the study. All study procedures complied with the ethical standards of the 1964 Helsinki Declaration and its later amendments.

ECG Evaluation

Upon admission to the hospital, every patient underwent a standard 12-lead ECG, performed at a paper speed of 25 mm/s with signal amplitude standardized to 10 mm per millivolt. The durations of the P wave at its longest and shortest were recorded, and P wave dispersion was determined by subtracting the shortest duration from the longest. The amplitude of the P wave in lead DI was measured in millivolts. We defined the P wave peak time (PWPT) as the time from the start of the P wave to its peak, measured in leads DII and VI. For cases with a biphasic P wave morphology, the PWPT was calculated as the time between the initiation of the P wave and its maximal downward deflection. The P wave morphology in lead V1 was categorized as positive, negative, or biphasic. Adjustment of the QT interval was performed according to Bazett's correction method. The lead displaying the highest T wave amplitude was used to measure R-R intervals, as well as the maximum and minimum QT intervals. The termination of the T wave was determined by locating the intersection between the isoelectric line and the tangent drawn along its steepest descending slope. QT and QTc dispersions were calculated by subtracting the shortest QT measurement from the longest. The JTp interval was described as the interval from the start of the J wave to the peak of the T wave, and the Tpe interval as the interval from the peak of the T wave to its endpoint (Figure 1). Amplitude and time interval measurements on the ECG recordings were performed using the EP Calipers software (EP Studios, London, UK). PWPT was assessed by two independent observers who were unaware of the patients' clinical data.

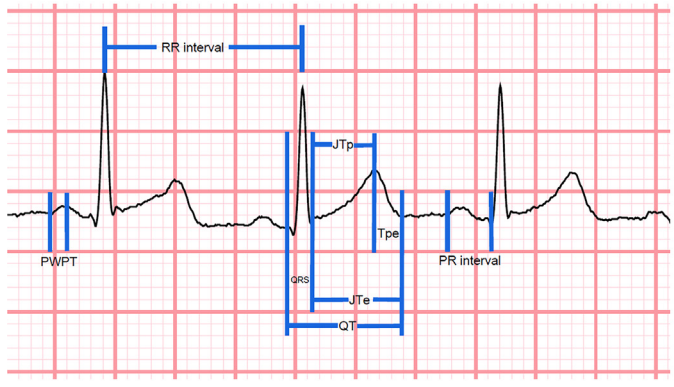

Figure 1. Image related to ECG measurements
ECG: Electrocardiographic, PWPT: P wave peak time, JTp: J to T peak

The inter-observer reliability for PWPT measurements was high, with a Pearson correlation coefficient of 0.88 ($p<0.001$).

Statistical Analysis

Findings were summarized using descriptive statistics, including mean, standard deviation, median, minimum, maximum, frequency, and percentage values. Normality of the variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Parametric tests (Independent samples t-test) were conducted for variables with normal distributions, while non-parametric methods (Mann-Whitney U test) were utilized for variables without normal distributions. Qualitative independent variables were assessed through the chi-square test. Logistic regression models, both univariate and multivariate, were applied to assess the magnitude of the effect. Statistical analyses were performed with SPSS software (version 27.0).

Results

The study included 138 participants, comprising 89 patients with AP and 49 healthy controls. The overall mean age was 49.5±9.7 years, 49±9.8 years in the pancreatitis group and 50.5±9.5 years in the control group. Among the study participants, 61.6% (n=85) were male and 38.4% (n=53) were female. In the pancreatitis group, 67.4% (n=60) were male and 32.6% (n=29) were female.

When examining the etiology of the 89 pancreatitis patients, 28.3% (n=39) were found to have idiopathic pancreatitis, 14.5% (n=20) had pancreatitis secondary to hypertriglyceridemia, 13% (n=18) had biliary pancreatitis, 5.8% (n=8) had alcoholic pancreatitis, 2.2% (n=3) had drug-induced pancreatitis, and 0.7% (n=1) had pancreatitis of infectious origin.

The laboratory parameters of 89 pancreatitis patients and 49 healthy controls at hospital admission are collectively presented in Table 1. Table 2 presents the results of collective measurements obtained from the ECG' s of all patients.

Table 3 presents the laboratory parameters of the pancreatitis patients and the control group. Age and gender distributions were comparable between the control and case groups, with no statistically significant differences observed ($p>0.05$). In the case group amylase, lipase, aspartate aminotransferase, alanine aminotransferase, C-reactive protein (CRP), and white blood cell (WBC) levels were significantly increased compared to the control group ($p<0.05$). Conversely, potassium (K) and Ca levels were significantly decreased in the case group than in the control group ($p<0.05$) (Table 3).

Table 4 presents the ECG parameters of the pancreatitis patients and the control group together. In the case group, P_{max}, P dispersion, PWPT-D2, and PWPT-V1 values were significantly higher ($p<0.05$) compared to the control group. The biphasic P wave in lead V1 was significantly lower ($p<0.05$) in the case group compared to the control group. Furthermore, the control and case groups showed no statistically significant differences in minimum and mean QT intervals ($p>0.05$). However, the maximum and QT dispersion values were significantly higher ($p<0.05$) in the case group compared to the control group. Similarly, there were no significant differences ($p>0.05$) in minimum or mean QTc values between the groups, but maximum QTc and QTc dispersion values were significantly higher ($p<0.05$) in the case group. In the case group, Tp-e, Tp-e/QT_{mean}, Tp-e/QTc_{mean}, and Tp-e/JTp values were significantly higher ($p<0.05$) compared to the control group (Table 4).

In the univariate model, significant ($p<0.05$) effectiveness of amylase, K, Ca, CRP, WBC, P_{max}, P dispersion, PWPT-D2, PWPT-V1, P wave morphology in lead V1, QT_{max}, QT dispersion, QTc_{max}, QTc dispersion, Tp-e interval, Tp-e/QT_{mean}, Tp-e/QTc_{mean}, Tp-e/JTp values, was observed in distinguishing between control and case group patients. In the multivariate model, a significantindependent ($p<0.05$) association of amylase, WBC, P_{max}, and QTc_{max} values was observed in the distinction between control and case group patients (Table 5).

Discussion

In our study evaluating the ECG changes in patients admitted to the hospital with AP, the main ECG changes we observed were prolongation of P_{max}, P dispersion, PWPT-D2, PWPT-V1, QT_{max}, QT dispersion, QTc_{max}, and QTc dispersion. Also, Tp-e, Tp-e/QT_{mean}, Tp-e/QTc_{mean}, and Tp-e/JTp values were found to be prolonged in patients with pancreatitis. Moreover, the biphasic P wave in lead V1 was markedly lower in pancreatitis patients than in the control group. In the multivariate analysis, P_{max} and QTc_{max} durations were found to be significantly and independently longer in patients with AP.

In the present study, the maximum duration of the P wave (P_{max}), which corresponds to atrial depolarization in the ECG, was found to be prolonged in patients with pancreatitis. A possible mechanism may involve P_{max} prolongation. Firstly, AP is an acute inflammatory disease that begins in the pancreas but is significantly influenced by systemic inflammatory mediators. The importance of

inflammatory mediators in the morbidity and mortality of the disease is substantial (14). Lazzerini et al. (15) conducted a study investigating the effects of inflammation on atrial electrical remodeling; it was found that the P_{max} duration was associated with levels of inflammatory mediators, leading to the conclusion that the pro-inflammatory process may prolong P_{max} duration. This result is consistent with our study. The second possible mechanism may be related to alterations in electrolyte levels. Severi et al. (16) explored the relationship between electrolyte levels and P wave durations in patients undergoing haemodialysis. They identified an inverse relationship between K levels and P wave durations. It was shown that after hemodialysis, K levels decreased while P wave durations increased (16). In our study, K levels in the AP group were likely to be lower as compared to the control group. This mechanism can be another factor contributing to the prolonged P_{max} period in our patients with AP. Other possible myocardial involvement mechanisms are immune-mediated myocyte damage, disruptions in myocardial microcirculation, and autonomic dysfunction, in AP (9). As a result of the factors outlined above, atrial electrophysiology may be altered, causing a prolongation of the P wave.

Another statistically significant ECG change in our study was the prolongation of QTc duration. The QT interval on the ECG reflects the time required for ventricular depolarization and repolarization, corresponding to the duration of the cardiac action potential (17). Since the QT

Table 1. Classification of all patients in the study

		Min-max	Median	Mean ± SD/n-%	
Age (years)		19.0-78.0	50.0	49.5±9.7	
Gender	Male			85	61.6%
	Female			53	38.4%
Pancreatitis etiology	Idiopathic			39	28.3%
	Hypertriglyceridemia			20	14.5%
	Biliary			18	13.0%
	Alcoholic			8	5.8%
	Drug related			3	2.2%
	Infection			1	0.7%
Control group				49	35.5%
Glucose (mg/dL)		73.0-156.0	94.0	99.9±19.1	
HbA1c (%)		4.3-6.4	5.6	5.6±0.4	
Amylase (U/L)		26.0-3909.0	145.7	479.1±766.6	
Lipase (U/L)		12.0-8472.6	261.8	926.6±1523.6	
AST (U/L)		10.0-604.0	23.0	51.3±83.9	
ALT (U/L)		10.0-421.0	23.0	43.1±61.8	
Urea (mg/dL)		11.0-67.1	29.0	29.1±9.4	
Creatinine (mg/dL)		0.41-1.5	0.8	0.8±0.2	
GFR (mL/min/1.73 m^2)		13.4-134.3	98.0	95.9±18.1	
Na (mmol/L)		122.0-148.0	139.0	138.4±4.1	
K (mmol/L)		3.21-5.5	4.2	4.2±0.4	
Mg (mg/dL)		1.0-3.6	2.0	2.0±0.3	
Albumin (g/L)		3.9-56.1	44.0	42.8±7.0	
Ca (mg/dL)		7.8-10.6	9.4	9.3±0.6	
CRP (mg/L)		0.3-412.0	6.6	36.3±68.6	
WBC (10^9/L)		4.9-31.3	9.0	10.1±4.3	
Hb (g/dL)		8.9-18.2	14.0	13.9±1.8	
PLT (10^9/L)		79.0-448.0	256.5	260.6±78.5	

Values are presented as minimum, maximum, medain, mean ± standard deviation and number (%)
SD: Standard deviation, HbA1c: Glycated haemoglobin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, e-GFR: Estimated glomerular filtration rate, Na: Sodium, K: Potassium, Mg: Magnesium, Ca: Calcium, CRP: C-reactive protein, WBC: White blood cell, Hb: Hemoglobin

Table 2. ECG characteristics of all patients in the study

		Min-max	Median	Mean ± SD/n-%	
P_{max} (ms)		57.3-164.8	102.9	104.9±16.3	
P_{min} (ms)		26.3-85.0	56.9	58.2±12.3	
P_{disper} (ms)		13.4-100.8	43.9	46.9±17.8	
P wave D1 amplitude time (mm)		0.70-3.08	1.30	1.40±0.42	
PR interval (ms)		70.6-280.5	142.6	143.9±26.0	
PWPT in lead DII (ms)		17.3-77.9	52.1	50.3±13.0	
PWPT in lead V1 (ms)		13.5-65.5	31.6	32.0±9.4	
P-wave morphology in lead V1	Positive			45	32.6%
	Negative			63	45.7%
	Biphasic			30	21.7%
QRS duration (ms)		62.0-196.0	84.0	85.8±14.2	
Heart rate (/min)		46.0-126.0	79.0	79.9±13.9	
P axis (o)		-4.0-89.0	55.0	51.5±18.6	
R axis (o)		-63.0-101.0	28.0	28.1±30.9	
T axis (o)		-27.0-200.0	43.5	44.2±27.1	
QT_{min} interval (ms)		175.9-428.6	325.4	325.8±37.6	
QT_{max} interval (ms)		317.7-490.8	382.0	383.4±32.4	
QT_{mean} interval (ms)		265.2-459.7	352.5	357.4±39.7	
QT_{disper} interval (ms)		6.6-214.4	52.0	57.6±33.2	
QTc_{min} interval (ms)		204.0-483.0	376.5	372.4±39.3	
QTc_{max} interval (ms)		346.0-546.0	436.0	438.3±32.0	
QTc_{mean} interval (ms)		298.5-514.5	407.0	408.2±43.4	
Qtc_{disper} interval (ms)		9.0-252.0	58.0	66.0±38.6	
Tp-e interval (ms)		34.8-124.0	64.4	65.6±15.4	
JTp interval (ms)		116.1-294.2	197.8	201.0±31.0	
JTe interval (ms)		154.0-388.5	267.0	266.7±35.0	
Tp-e/QT_{mean} (ms)		0.09-0.36	0.18	0.18±0.04	
Tp-e/QTc_{mean} (ms)		0.07-0.35	0.15	0.16±0.04	
Tp-e/JTp (ms)		0.15-0.72	0.31	0.33±0.10	
RR interval (ms)		446.9-1301.0	765.2	778.8±145.8	

Values are presented as minimum, maximum, medain, mean ± standard deviation and number (%). SD: Standard deviation, disper: Dispersion, PWPT: P wave peak time, QTc: Corrected QT, Tp-e: Tpeak-Tend interval, JTp: J to T peak, JTe: J to T end

duration varies with heart rate, the QT value measured on the ECG needs to be corrected to obtain the QTc. Various formulas have been developed for this purpose (18). The compelling evidence of relationship between QTc and ventricular arrhythmias establish QTc as a highly significant parameter (19,20). While the exact mechanism of QTc max prolongation in AP patients remains unclear, several potential pathophysiological processes are suggested. One mechanism may be the systemic inflammatory response caused by AP. Because it has been shown that there is a relationship between active inflammation, pro-inflammatory cytokine levels, and QTc duration in different clinical scenarios, such as myocarditis, inflammatory bowel disease, and rheumatoid arthritis (21-24), these associations warrant further investigation. Since AP is a clinical condition that generates a strong inflammatory response, the prolongation of QTc_{max} duration in our study may have been secondary to the inflammatory process. Consistent with our findings, Ates et al. (25) observed that patients with acute biliary pancreatitis had a significantly prolonged QTc_{max} compared to healthy controls. Another possible scenario for the prolongation of QTc_{max} durations in the AP

Table 3. Comparison of control group and case group

		Control group (n=49)			Case group (n=89)			p
		Mean ± SD/n-%		Median	Mean ± SD/n-%		Median	
Age (years)		50.5±9.5		50.0	49.0±9.8		50.0	0.782[m]
Gender	Male	25	51.0%		60	67.4%		0.058[X²]
	Female	24	49.0%		29	32.6%		
Glucose (mg/dL)		96.2±14.3		92	101.9±21.1		96.0	0.076[m]
HbA1C (%)		5.60±0.3		5.5	5.6±0.4		5.6	0.594[m]
Amylase (U/L)		65.7±18.6		67.0	706.7±875.9		260.1	**0.000**[m]
Lipase (U/L)		38.2±13.6		38.0	1415.8±1712.5		644.7	**0.000**[m]
AST (U/L)		23.2±7.4		22.0	67.0±101.2		23.4	**0.000**[m]
ALT (U/L)		24.1±14.3		22.0	53.8±74.4		22.0	**0.000**[m]
Urea (mg/dL)		29.4±8.5		29.0	28.9±9.9		29.0	0.78[m]
Creatinine (mg/dL)		0.8±0.14		0.8	0.83±0.20		0.80	0.304[m]
GFR (mL/min/1.73 m²)		93.3±15.3		95.0	97.4±19.4		100.9	0.090[m]
Na (mmol/L)		139.4±2.7		139.0	137.9±4.7		139.0	0.198[m]
K (mmol/L)		4.41±0.41		4.47	4.13±0.44		4.13	**0.001**[m]
Mg (mg/dL)		1.96±0.15		1.98	1.95±0.34		1.98	0.593[m]
Albumine (g/L)		42.1±8.5		44.0	43.1±6.1		43.9	0.727[m]
Ca (mg/dL)		9.6±0.5		9.6	9.2±0.6		9.2	**0.001**[t]
CRP (mg/L)		3.6±1.6		4.0	54.3±80.0		22.1	**0.000**[m]
WBC (10^9/L)		7.4±1.5		7.2	11.6±4.5		10.9	**0.000**[m]
Hb (g/dL)		13.7±1.5		13.4	14.0±1.9		14.1	0.342[t]
PLT (10^9/L)		277.0±69.1		261.0	251.5±82.2		254.0	0.105[m]

[t]: Independent sample t-test, [m]: Mann-Whitney U test, X^2: Chi-square test
Values are presented as mean ± standard deviation, median and number (%).
SD: Standard deviation, HbA1c: Glycated haemoglobin, AST: Aspartate aminotransferase, ALT: Alanine transaminase, e-GFR: Estimated glomerular filtration rate, Na: Sodium, K: Potassium, Mg: Magnesium, Ca: Calcium, CRP: C-reactive protein, WBC: White blood cell, Hb: Hemoglobin

group could be related to Ca and K levels, which in the AP group tended to be lower than those in the healthy control group. Pickham et al. (26) showed that hypocalcemia and hypokalemia were predictors of QT prolongation in acutely ill patients. One more potential mechanism that could lead to the prolongation of QTc is the use of certain medications. Pain management constitutes a fundamental component of AP treatment. Non-steroidal anti-inflammatory drugs or opioids used for this purpose can cause QTc prolongation (27).

To summarize, ECG changes can be observed in patients with AP. In some cases, these changes may even include ST-segment elevation or mimic the presentation of acute coronary syndrome. ECG changes are not exclusively caused by AP; they can also be observed in a variety of other clinical conditions (28-31).

Table 4. Comparison of ECG features of the control group and the case group

		Control group (n=49)			Case group (n=89)			p
		Mean ± SD/n-%		Median	Mean ± SD/n-%		Median	
P_{max} (ms)		93.8±13.7		93.8	110.9±14.3		109.3	**0.000**[m]
P_{min} (ms)		57.6±11.8		56.7	58.5±12.6		56.9	0.676[t]
P_{disper} (ms)		36.3±12.4		38.3	52.6±17.7		49.1	**0.000**[m]
P wave D1 amplitude time (mm)		1.32±0.25		1.30	1.44±0.49		1.30	0.461[m]
PR interval (ms)		140.2±21.0		142.0	146.0±28.3		146.0	0.171[m]
PWPT in lead DII (ms)		47.4±12.2		48.0	52.0±13.2		53.1	**0.045**[t]
PWPT in lead V1 (ms)		28.3±8.5		28.4	34.1±9.2		33.0	**0.001**[m]
P-wave morphology in lead V1	Positive	15	30.6%		30	33.7%		**0.001**[X^2]
	Negative	15	30.6%		48	53.9%		
	Biphasic	19	38.8%		11	12.4%		
QRS duration (ms)		83.2±9.9		82.0	87.2±16.0		84.0	0.152[m]
Heart rate (/min)		78.7±13.0		78.0	80.6±14.4		79.0	0.460[t]
P axis (o)		51.1±18.2		55.0	51.7±18.9		54.5	0.704[m]
R axis (o)		25.1±25.1		22.0	29.7±33.7		30.0	0.406[t]
T axis (o)		44.1±18.8		44.0	44.3±30.8		43.0	0.613[m]
QT								
QT_{min} interval (ms)		331.0±24.8		326.6	323.0±42.9		324.6	0.426[m]
QT_{max} interval (ms)		373.1±25.1		376.7	389.1±34.6		383.6	**0.017**[m]
QT_{mean} interval (ms)		358.6±48.9		348.6	356.7±34.0		353.8	0.786[t]
QT_{disper} interval (ms)		42.1±17.3		42.0	66.1±36.7		56.0	**0.000**[m]
QTC								
QTc_{min} interval (ms)		375.3±23.6		376.0	370.8±45.8		377.0	0.897[m]
QTc_{max} interval (ms)		422.9±20.9		418.0	446.8±33.9		447.0	**0.000**[m]
QTc_{mean} interval (ms)		407.0±56.9		402.0	408.8±34.1		410.5	0.060[m]
Qtc_{disper} interval (ms)		47.6±19.3		49.0	76.1±42.7		64.0	**0.000**[m]
Tp-e interval (ms)		59.5±11.5		59.1	68.9±16.3		66.6	**0.000**[t]
JTp interval (ms)		200.5±23.7		198.4	201.3±34.5		197.2	0.864[t]
JTe interval (ms)		260.0±25.3		258.5	270.4±39.0		268.8	0.094[t]
$Tp\text{-}e/QT_{mean}$ (ms)		0.17±0.03		0.16	0.19±0.05		0.19	**0.000**[m]
$Tp\text{-}e/QTc_{mean}$ (ms)		0.15±0.03		0.15	0.17±0.04		0.17	**0.001**[m]
Tp-e/JTp (ms)		0.30±0.07		0.29	0.35±0.10		0.33	**0.003**[m]
RR interval (ms)		789.7±126.4		803.1	772.8±155.8		758.6	0.366[m]

[t]: Independent sample t-test, [m]: Mann-Whitney U test, X^2: Chi-square test
Values are presented as minimum, maximum, median, mean ± standard deviation and number (%).
SD: Standard deviation, disper: Dispersion, PWPT: P wave peak time, QTc: Corrected QT, Tp-e: Tpeak-Tend interval, JTp: J to T peak, JTe: J to T end, ECG: Electrocardiographic

Table 5. Univariate and multivariate analysis of biochemistry values and ECG findings

	Univariate model			Multivariate model		
	OR	95% CI	p	OR	95% CI	p
Amylase (U/L)	1.072	1.037-1.107	**0.000**	1.117	1.020-1.222	**0.017**
Lipase (U/L)	2.756	0.000->100	0.900			
K (mmol/L)	0.440	0.215-0.900	**0.025**			
Ca (mg/dL)	0.333	0.170-0.650	**0.001**			
CRP (mg/L)	1.362	1.154-1.608	**0.000**			
WBC (10^9/L)	1.744	1.406-2.164	**0.000**	2.627	1.077-6.408	**0.034**
P_{max} (ms)	1.122	1.074-1.173	**0.000**	1.105	1.005-1.215	**0.040**
P_{disper} (ms)	1.078	1.044-1.114	**0.000**			
PWPT in lead DII (ms)	1.028	1.000-1.057	**0.048**			
PWPT in lead V1 (ms)	1.085	1.035-1.137	**0.001**			
P-wave morphology in lead V1	0.569	0.347-0.931	**0.025**			
QT_{max} interval (ms)	1.018	1.005-1.031	**0.007**			
QT_{disper} interval (ms)	1.049	1.025-1.074	**0.000**			
QTc_{max} interval (ms)	1.030	1.015-1.046	**0.000**	1.098	1.006-1.199	**0.037**
Qtc_{disper} interval (ms)	1.047	1.024-1.070	**0.000**			
Tp-e interval (ms)	1.048	1.019-1.078	**0.001**			
Tp-e/QT_{mean} (ms)	>100	450.230->100	**0.002**			
Tp-e/QTc_{mean} (ms)	>100	361.366->100	**0.002**			
Tp-e/JTp (ms)	>100	7.736->100	**0.005**			

Logistic regression (forward LR)
OR: Odds ratio, CI: Confidence interval, K: Potassium, Ca: Calcium, CRP: C-reactive protein, WBC: White blood cell, disper: Dispersion, PWPT: P wave peak time, QTc: Corrected QT, Tp-e: Tpeak-Tend interval, JTp: J to T peak, ECG: Electrocardiographic

Conclusion

In conclusion, significant changes in ECG parameters may be observed in patients with AP. Various factors, such as the cardiac effects of the systemic inflammatory response, fluctuations in electrolyte levels, and the medications used, can contribute to these ECG changes.

Ethics

Ethics Committee Approval: The Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital granted approval for this study (approval no: 15, date: 05.07.2024).

Informed Consent: Informed consent was obtained from each participant in compliance with applicable ethical regulations.

Footnotes

Authorship Contributions

Concept: V.C.Ç., A.Ö., E.A., F.A., B.B., Design: V.C.Ç., A.Ö., E.A., F.A., M.A., F.N.T., B.B., Data Collection or Processing: V.C.Ç., M.A., F.N.T., Y.G., Analysis or Interpretation: V.C.Ç., A.Ö., E.A., M.A., Y.G., Literature Search: V.C.Ç., A.Ö., E.A., F.A., M.A., F.N.T., Y.G., B.B., Writing: V.C.Ç., E.A.

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References

1. Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. Gastroenterology. 2019;156(1):254-272.e11. Erratum in: Gastroenterology. 2019;156(6):1936.
2. Tenner S, Baillie J, DeWitt J, Vege SS; American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108(9):1400-1415; 1416. Erratum in: Am J Gastroenterol. 2014;109(2):302.
3. Lee PJ, Papachristou GI. New insights into acute pancreatitis. Nat Rev Gastroenterol Hepatol. 2019;16(8):479-496.
4. Szatmary P, Grammatikopoulos T, Cai W, Huang W, Mukherjee R, Halloran C, et al. Acute pancreatitis: diagnosis and treatment. Drugs. 2022;82(12):1251-1276.

5. Vasantha Kumar A, Mohan Reddy G, Anirudh Kumar A. Acute pancreatitis complicated by acute myocardial infarction – a rare association. Indian Heart J. 2013;65(4):474-477.

6. Lieberman JS, Taylor A, Wright IS. The effect of intravenous trypsin administration on the electrocardiogram of the rabbit. Circulation. 1954;10(3):338-342.

7. Kellner A, Robertson T. Selective necrosis of cardiac and skeletal muscle induced experimentally by means of proteolytic enzyme solutions given intravenously. J Exp Med. 1954;99(4):387-404.

8. Rubio-Tapia A, García-Leiva J, Asensio-Lafuente E, Robles-Díaz G, Vargas-Voracková F. Electrocardiographic abnormalities in patients with acute pancreatitis. J Clin Gastroenterol. 2005;39(9):815-818.

9. Luo Y, Li Z, Ge P, Guo H, Li L, Zhang G, et al. Comprehensive mechanism, novel markers and multidisciplinary treatment of severe acute pancreatitis-associated cardiac injury - a narrative review. J Inflamm Res. 2021;14:3145-3169. Erratum in: J Inflamm Res. 2021;14:6669-6670.

10. Pezzilli R, Barakat B, Billi P, Bertaccini B. Electrocardiographic abnormalities in acute pancreatitis. Eur J Emerg Med. 1999;6(1):27-29.

11. Lai SW, Lin CL, Liao KF. Atrial fibrillation associated with acute pancreatitis: a retrospective cohort study in Taiwan. J Hepatobiliary Pancreat Sci. 2016;23(4):242-247.

12. Jamal S, Khan MZ, Kichloo A, Edigin E, Bailey B, Aljadah M, et al. The effect of atrial fibrillation on inpatient outcomes of patients with acute pancreatitis: a two-year national inpatient sample database study. J Innov Card Rhythm Manag. 2020;11(12):4338-4344.

13. Uvelin A, Hajduković D, Vrsajkov V, Kolak R, Lazukić A, Vicković S, et al. A case of recurrent arrhythmia in an acute pancreatitis patient--pathophysiological explanation using shortage of 'repolarization reserve'. Acta Clin Croat. 2013;52(4):515-522.

14. Papachristou GI, Whitcomb DC. Inflammatory markers of disease severity in acute pancreatitis. Clin Lab Med. 2005;25(1):17-37.

15. Lazzerini PE, Laghi-Pasini F, Acampa M, Srivastava U, Bertolozzi I, Giabbani B, et al. Systemic inflammation rapidly induces reversible atrial electrical remodeling: the role of interleukin-6–mediated changes in connexin expression. J Am Heart Assoc. 2019;8(16):e011006.

16. Severi S, Pogliani D, Fantini G, Fabbrini P, Viganò MR, Galbiati E, et al. Alterations of atrial electrophysiology induced by electrolyte variations: combined computational and P-wave analysis. Europace. 2010;12(6):842-849.

17. Grant AO. Cardiac ion channels. Circ Arrhythm Electrophysiol. 2009;2(2):185-194.

18. Which QT correction formulae to use for QT monitoring? J Am Heart Assoc. 2018;7(16):e004252. Erratum for: J Am Heart Assoc. 2016;5(6):e003264.

19. Roden DM. Keep the QT interval: it is a reliable predictor of ventricular arrhythmias. Heart Rhythm. 2008;5(8):1213-1215.

20. Chávez-González E, Rodríguez-Jiménez AE, Ferrer-Rodríguez CJ, Donoiu I. Ventricular arrhythmias are associated with increased QT interval and QRS dispersion in patients with ST-elevation myocardial infarction. Rev Port Cardiol. 2022;41(5):395-404. English, Portuguese.

21. Lazzerini PE, Laghi-Pasini F, Bertolozzi I, Morozzi G, Lorenzini S, Simpatico A, et al. Systemic inflammation as a novel QT-prolonging risk factor in patients with torsades de pointes. Heart. 2017;103(22):1821-1829.

22. Viscido A, Capannolo A, Petroni R, Stefanelli G, Zerboni G, De Martinis M, et al. Association between corrected QT interval and C-reactive protein in patients with inflammatory bowel diseases. Medicina (Kaunas). 2020;56(8):382.

23. Hung Y, Lin WH, Lin CS, Cheng SM, Tsai TN, Yang SP, et al. The prognostic role of QTc interval in acute myocarditis. Acta Cardiol Sin. 2016;32(2):223-230.

24. Adlan AM, Panoulas VF, Smith JP, Fisher JP, Kitas GD. Association between corrected QT interval and inflammatory cytokines in rheumatoid arthritis. J Rheumatol. 2015;42(3):421-428.

25. Ates F, Kosar F, Aksoy Y, Yldrm B, Sahin I, Hilmioglu F. QT interval analysis in patients with acute biliary pancreatitis. Pancreas. 2005;31(3):238-241.

26. Pickham D, Helfenbein E, Shinn JA, Chan G, Funk M, Weinacker A, et al. High prevalence of corrected QT interval prolongation in acutely ill patients is associated with mortality: results of the QT in practice (QTIP) study. Crit Care Med. 2012;40(2):394-399.

27. Klivinyi C, Bornemann-Cimenti H. Pain medication and long QT syndrome. Korean J Pain. 2018;31(1):3-9.

28. Khan U, Petrechko O, Sagheer S, Majeed H, Zaidi SH, Wasty N, et al. Acute pancreatitis and myocardial infarction: a narrative review. Cardiology. 2023;148(1):1-11.

29. Kumar N, Waheed S, Siddiqui A, Tamiz A. Necrotizing acute pancreatitis with electrocardiogram changes masquerading acute coronary syndrome. Oxf Med Case Reports. 2023;2023(6):omad055.

30. Hsieh YL, Wu SH, Liu CY, Lin WC, Chen MJ, Chang CW. Acute pancreatitis presented with diffuse ST-segment elevation: a case report and literature review. Medicine (Baltimore). 2024;103(7):e37245.

31. Alsancak Y, Çölkesen F. Electrocardiographic alterations in patients with common variable immune deficiency. Istanbul Med J. 2020;21(2):109-114.

ORIGINAL RESEARCH

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The Impact of Health Literacy of Primary Caregivers of Hemiplegic Patients on Functional Level and Mobility

İnmeli Hastaların Primer Bakım Verenlerinin Sağlık Okuryazarlığının Fonksiyonel Düzey ve Mobilite Üzerindeki Etkisi

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Abstract

Objective: Although rehabilitation patients make significant progress during the rehabilitation period, many of them face long-term physical, functional, and cognitive disabilities upon discharge. Patients' primary caregivers also play an important role during this process. The aim of this study was to investigate the relationship between primary caregivers' health literacy and hemiplegic patients' functional status and mobility.

Method: This cross-sectional study included hemiplegic patients aged 18-75 who were attending Başkent University, Department of Physiotherapy and Undergoing Rehabilitation. Patients in the acute phase (first 3 months) with uncontrolled systemic disease or psychiatric disease, aphasia, recurrent stroke, impaired swallowing, or psychiatric disease that may prevent them from answering the questions, or more than one neurologic disease were excluded from the study. Demographic information of all participants was recorded. Patients were evaluated with the functional impairment measurement, and patients' primary caregivers were evaluated with the Turkish health literacy scale-32. The effect of primary caregivers' health literacy on hemiplegic patients' function and mobility was statistically analyzed. A p-value <0.05 is considered statistically significant.

Results: A total of 107 patients and their primary caregivers were analyzed: 59 male patients, 48 female patients, 45 male caregivers, and 62 female caregivers. The average patient age was 52.23±22.92 years, and caregivers' average age was 49.40±14.72 years. Among patients, 62.6% had ischemic and 37.4% had hemorrhagic cerebrovascular disease. The mean disease duration was 71.78±36.32 months. The health literacy of primary caregivers was found to be correlated with the functional

Öz

Amaç: Rehabilitasyon hastaları önemli ilerlemeler kaydetmelerine rağmen taburcu olduktan sonra fonksiyonel ve bilişsel engellerle karşı karşıya kalabilmektedir. Primer bakım veren de bu süreçte önemli bir rol oynamaktadır. Bu çalışmanın amacı hemipleji hastalarının primer bakım verenlerinin sağlık okuryazarlığı ile hemiplejik hastaların fonksiyonel durumu ve mobilitesi arasındaki ilişkiyi araştırmaktır.

Yöntem: Kesitsel bir çalışmadır. Çalışmaya Başkent Üniversitesi Fiziksel Tıp ve Rehabilitasyon Polikliniği'ne hemipleji tanısıyla başvuran ve aktif rehabilitasyon programına alınan 18-75 yaşları arasındaki hastalar dahil edildi. Akut dönemdeki (ilk 3 ay içinde bulunan), afazisi, rekürren hemipleji öyküsü, yutma güçlüğü, kontrol edilemeyen sistemik hastalığı veya sorulara cevap verilmesini engelleyecek psikiyatrik hastalığı veya birden fazla nörolojik hastalığı olan hastalar çalışma dışı bırakıldı. Tüm katılımcıların demografik bilgileri kaydedildi. Hastaların fonksiyonel düzeyleri fonksiyonel bağımsızlık ölçümüyle, hastaların primer bakım verenlerinin sağlık okuryazarlık düzeyleri ise Türkçe sağlık okuryazarlığı ölçeği-32 ile değerlendirildi. Hemipleji hastalarının primer bakım verenlerin sağlık okuryazarlığının bu hastalarının fonksiyonel düzeyi, mobilitesi ve kognitif düzeyi üzerindeki etkisi istatistiksel olarak analiz edildi. P<0,05 olması istatistiksel olarak anlamlı olarak kabul edildi.

Bulgular: Toplamda 107 hemiplejik hasta ve primer bakım vereni analiz edildi. Hastaların 48'i kadın, 59'u erkekti. Primer bakım verenlerinin 62'si kadın, 45'i erkekti. Hastaların yaş ortalaması 52,23±22,92, primer bakım verenlerin yaş ortalaması 49,40±14,72 idi. Hastaların %62,6'sında iskemik nedenli serebrovasküler hastalık, %37,4'ünde ise hemorajik nedenli serebrovasküler hastalık tanısı mevcuttu. Ortalama hastalık süresi 71,78±36,32 ay olarak saptandı. Primer bakım verenlerin sağlık

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Abstract

impairment measurement scores (p<0.05). Additionally, it was found that health literacy was correlated with both motor and cognitive subscores of functional impairment measurement (p<0.05). It was determined that the health literacy of primary caregivers predicted the functional independence score and its subparameters (p<0.05).

Conclusion: These findings suggest that the health literacy of primary caregivers of hemiplegic patients was correlated with patients' motor and cognitive outcomes. Primary caregivers' health literacy level may affect these patients' functional outcomes.

Keywords: Cerebrovascular disease, health literacy, hemiplegia, rehabilitation

Öz

okuryazarlığının fonksiyonel bağımsızlık ölçümü puanları ile ilişkili olduğu tespit edildi (p<0,05). Ayrıca sağlık okuryazarlığın fonksiyonel bağımsızlık ölçümünün hem motor hem de bilişsel alt puanlarıyla ilişkili olduğu belirlendi (p<0,05). Sağlık okuryazarlık oranının Fonksiyonel bağımsızlık puanı ve alt parametrelerini yordadığı (p<0,05) tespit edildi.

Sonuç: Bu bulgular, hemiplejik hastaların primer bakım verenlerinin sağlık okuryazarlığının hastaların fonksiyonel motor aktivite ve kognitif fonksiyon düzeyi ile ilişkili olduğunu göstermektedir. Primer bakım verenlerin sağlık okuryazarlığı düzeyi bu hastaların fonksiyonel düzeylerini etkileyebilir.

Anahtar kelimeler: Hemipleji, rehabilitasyon, sağlık okuryazarlığı, serebrovasküler hastalık

Introduction

Stroke is characterized by the sudden interruption or significant reduction of blood flow to the brain. Less frequently, it may result from the rupture of a cerebral blood vessel, leading to hemorrhaging either within the brain tissue itself or in the surrounding membranes, a condition referred to as a cerebral hemorrhage (1). Given that distinct regions of the brain are responsible for specific bodily functions, the area directly affected by the stroke, along with adjacent tissues, typically experiences impairment (2). Depending on the site of damage, individuals may suffer from deficits in speech, motor strength, coordination, balance, vision, or memory. While some patients achieve complete recovery, others may endure long-term disabilities (3).

Recovery outcomes vary significantly among individuals. Some patients fully recover, while others continue to have lasting impairments. These sequelae depend largely on the location and extent of cerebral damage. Common post-stroke complications include cognitive deficits (such as memory and attention problems), language and communication disorders, emotional disturbances like depression, and impairments in balance, gait, and fine motor control (4). Consequently, thorough evaluation of cognitive status, mobility, and overall functional capacity is crucial in this patient population. Functional recovery largely depends on the patient's overall health and medical condition (5).

Health literacy refers to an individual's capacity to acquire, comprehend, and effectively utilize health-related information to make informed decisions and adhere to medical recommendations. Although many individuals demonstrate notable improvements during inpatient rehabilitation, the majority of stroke survivors continue to experience persistent physical, functional, and cognitive impairments following discharge (6).

Proficient literacy skills are essential for adults to navigate daily life effectively. Research indicates that limited literacy can hinder an individual's ability to interact efficiently with the healthcare system, potentially leading to adverse health outcomes. Inadequate health literacy remains a prevalent concern and has been linked to diminished access to health information; worsening health conditions; poor utilization and understanding of preventive services; increased risk of medication errors; higher healthcare expenditures; and elevated rates of hospital admissions. Furthermore, low health literacy has been associated with increased mortality, reduced self-efficacy, and insufficient knowledge and self-management capabilities in relation to chronic diseases (7). This study aims to examine the impact of health literacy among primary caregivers of hemiplegic patients on the patients' functional status, cognitive functions, and mobility outcomes.

Materials and Methods

It is a cross-sectional study. Approval was obtained from the Başkent University Non-Interventional Clinical Research Ethics Committee (approval number: E-94603339-604.01-458957, date: 06.05.2025). The research was conducted according to the rules of the Helsinki Declaration. A consent form was obtained from all participants.

Sampling, Patient Selection, and Randomization

The required sample size was calculated using the G*Power 3.1.9.4 software. For the multiple linear regression model, the parameters were set as a medium effect size (f^2=0.15), 95% statistical power (1-β=0.95), and a significance level of 5% (α=0.05). The analysis accounted for two tested independent variables and five predictor variables. The

results indicated that a minimum of 107 participants were necessary to detect a statistically significant effect within the model.

Patients aged 18 to 65 years, diagnosed with hemiplegia, who sought treatment at the Başkent University Physical Medicine and Rehabilitation Clinic, and the primary caregiver neighbor, who was an unpaid and informal caregiver, were enrolled in the study following their informed consent. The study excluded patients in the acute phase (within the initial 3 months), patients with aphasia, recurrent stroke, impaired swallowing, unmanaged systemic diseases that might affect results, patients with psychiatric conditions limiting their capacity to answer, and patients diagnosed with multiple neurological disorders.

Evaluation of the Patients

All patients and primary caregivers had an interview with a physiatrist who had more than ten years of experience in neurologic rehabilitation. All participants were reviewed by the same specialist. Demographic information of the patients and their primary caregivers, including age, gender, educational attainment, occupation, type of cerebrovascular disease, and disease duration, was collected and documented. Patients were assessed using the functional independence scale, while their relatives completed the health literacy-32 scale.

The Turkish health literacy scale-32 (TSOY-32) is a psychometrically validated instrument designed to accurately assess the health literacy levels of adults in Turkey. Comprising 32 items, the scale evaluates health literacy across four fundamental domains: access, comprehension, appraisal, and decision-making/ implementation. Items are primarily rated on a Likert-type scale, with higher scores reflecting more advanced abilities in obtaining, understanding, interpreting, and applying health information in everyday life (8).

The functional independence measure (FIM) is a widely utilized instrument in rehabilitation that assesses individuals' levels of independence in activities of daily living. The scale comprises 18 items divided into two primary domains: motor (physical) and cognitive. It evaluates fundamental functions such as eating, personal hygiene, toileting, mobility, communication, and social interaction. Each item is scored on a scale from 1 (complete dependence) to 7 (complete independence), yielding a total score ranging from 18 to 126, with higher scores indicating greater independence. The FIM is a validated and reliable tool commonly employed to monitor functional progress and to inform care planning for patients recovering from stroke, spinal cord injuries, orthopedic surgeries, and chronic illnesses (9).

The study aimed to examine the influence of the primary caregivers' health literacy on the patients' functional status and mobility.

Statistical Analysis

Statistical analyses were conducted using SPSS version 25.0. Descriptive statistics for categorical variables were expressed as frequencies and percentages. The Shapiro-Wilk test was employed to assess the normality of numerical variables. For variables demonstrating a normal distribution, descriptive statistics were presented as mean ± standard deviation, whereas variables not conforming to normality were summarized using median (minimum-maximum) values. Since the data did not satisfy parametric assumptions, Spearman correlation was used to examine links between health literacy, functional level, and mobility. Linear regression helped identify risk factors affecting function and mobility. For all hypothesis tests, the Type I error rate was set at α=0.05, and p-values less than 0.05 were considered statistically significant.

Results

A total of 107 patients and their primary caregivers were included in the analysis. Among the patients, 59 were male and 48 were female, while the primary caregivers comprised 45 males and 62 females. The mean age of the patients was 52.23±22.92 years, and the mean age of the primary caregivers was 49.40±14.72 years. Of the patients, 62.6% were diagnosed with ischemic cerebrovascular disease, whereas 37.4% had hemorrhagic cerebrovascular disease. The mean duration of illness was 71.78±36.32 months. The demographic characteristics of patients and primary caregivers are presented in Table 1. As there was no normal distribution among values, median and min-max values, of the functional independence scale and TSOY-32 were given in Table 2.

A statistically significant positive correlation was found between the health literacy levels of primary caregivers and the FIM total scores (r_s=0.324, p=0.001). Furthermore, health literacy was significantly correlated with both the motor (r_s=0.262, p=0.006) and cognitive (r_s=0.278, p=0.004) subscales of the FIM. However, these correlations were revealed as weak. Accordingly, variation in health literacy accounted for approximately 10% of the variance in the total FIM score, 6% of the variance in motor function, and

Table 1. Demographic properties of participants

Patients' gender	n (%)
Female	48 (44.9)
Male	59 (55.1)
Patients' age (years) (mean ± std deviation)	52.23±22.92
Disease duration (months) (mean ± std deviation)	71.78±36.32
Disease etiology	
Ischemic	67 (62.6)
Hemorrhagic	40 (37.4)
Primary caregivers' gender	
Female	62 (57.9)
Male	45 (42.1)
Primary caregivers' age (years) (mean ± std deviation)	49.40±14.72
Primary caregivers' education	
Illiterate	3 (2.8)
Primary school	28 (26.2)
Secondary school	9 (8.4)
High school	30 (28.0)
University	37 (34.6)
Primary caregivers' occupation	
Unemployed	52 (48.6)
Lecturer	7 (6.5)
Health professional	5 (4.7)
Desk worker	3 (2.8)
Worker	40 (37.4)

Table 2. Median and range (min-max) values of functional independence scale and Turkish health literacy scale-32

Functional independence scale (min-max)	84 (18-126)
Motor function (min-max)	68 (13-91)
Cognitive function (min-max)	29 (5-35)
Turkish health literacy scale-32 (min-max)	57 (32-139)

Functional independence scale is scored ranging from 18 to 126 with subscales of motor function (13 to 91) and cognitive function (5 to 35). Turkish health literacy scale-32 is scored ranging from 32 to 160

7% of the variance in cognitive function. Although these associations were statistically significant, the effect sizes indicate that the strength of the relationships was weak.

The predictive influence of primary caregivers' health literacy on FIM scores, including motor and cognition subscores, was assessed using simple linear regression analysis. The results demonstrated that the health literacy level of primary caregivers significantly predicts FIM total scores (F=12.277, p=0.001). Health literacy levels of primary caregivers explain 10% of the variance (R-squared=0.105). A one-point increase in health literacy corresponds to a 0.353 unit rise in FIM scores [95% confidence interval (CI): 86.010 to 114.350]. Additionally, the health literacy level of primary caregivers significantly predicts the motor subscore (F=7.734, p=0.006). Health literacy levels of primary caregivers explain 6.9% of the variance (R-squared=0.069). A one-point increase in health literacy corresponds to a 0.247 unit rise in motor subscores. Ensure that the 95% confidence interval (63.925 to 88.852) is correctly paired with the relevant figure in your data presentation. The health literacy level of primary caregivers significantly predicts cognitive subscore (F=8.766, p=0.004). Health literacy levels of primary caregivers explain 7.7% of the variance (R-squared=0.077). A one-point increase in health literacy corresponds to a 0.091 unit rise in cognitive subscore [95% CI: (review needed for accuracy)]. The predictive power of the TSOY-32 on functional, motor, and cognitive scores is presented in Table 3.

Discussion

In the current study, a significant positive relationship was identified between the health literacy of primary caregivers

Table 3. The predictive power of the Turkish health literacy scale-32 on functional, motor and cognitive scores

	Unstandardized coefficients		Standardized coefficients	t	p	95.0% CI
	B	SE	β			
Constant	100.180	7.146		14.018	0.001	86.010 to 114.350
FIM[μ]	-0.353	0.101	-0.324	-3.504	0.001*	-0.554
Durbin-Watson =1.753 F=12.277 p=0.001* R=0.324 R^2=0.105 Adjusted R^2=0.096						
Constant	76.388	6.286		12.153	0.001	63.925 to 88.852
Motor function[μ]	-0.247	0.089	-0.262	-2.781	0.006*	-0.423
Durbin-Watson =1.677 F=7.734 p=0.006* R=0.262 R^2=0.069 Adjusted R^2=0.060						
Constant	31.656	2.166		14.612	0.000	27.361 to 35.952
Cognitive function[μ]	-0.091	0.031	-0.278	-2.961	0.004*	-0.151
Durbin-Watson =1.788 F=8.766 p=0.004* R=0.278 R^2=0.077 Adjusted R^2=0.068						

CI: Confidence interval, SE: Standard error, β: Standardized regression coefficient, FIM: Functional independence measure, [μ]: Lineer regression analysis, *: p<0.05 statistically significant

and the total scores on the FIM. Additionally, the health literacy of primary caregivers showed a notable association with the motor and cognitive components of the FIM. Nonetheless, these associations were found to be relatively weak. It was found that primary caregivers' health literacy was predictive of the total FIM score and its motor and cognitive subscales.

Health literacy is a person's ability to understand, evaluate, and use health information to manage their own well-being. It involves basic skills needed to navigate healthcare, make informed decisions, and lead a healthy lifestyle. This includes understanding medical information, accessing care, and choosing actions that prevent or manage illness (10). Proficient health literacy improves health, helps prevent disease, and makes healthcare work better. On the other hand, low health literacy can lead to a misunderstanding of medical information, difficulty following treatment regimens, and poor health choices. This lack of health literacy can cause serious problems like missed treatments, miscommunication, spread of false information, delayed care, higher costs, and poor self-care (11).

For hemiplegic patients, health literacy is crucial because it affects their quality of life, treatment adherence, complication prevention, and independence. Low health literacy can slow recovery, extend rehabilitation, and increase the risk of problems (12-16). Health literacy is vital not just for patients but also for their primary caregivers, who play a key role in care. Caregivers' understanding of health information affects the patient's recovery by ensuring correct treatment, timely emergency response, ongoing care, clear communication with doctors, emotional support, and avoidance of misinformation. For hemiplegic patients, caregivers' health literacy directly impacts care quality, treatment follow-through, and the patient's quality of life. Since hemiplegic patients often need help with medication, therapy, nutrition, and daily tasks, caregivers with good health literacy make fewer mistakes and better support recovery and monitoring (12-15).

Başaran and Doğan (12) studied 50 hemiplegic patients using the Turkish version of the European health literacy scale. They evaluated patients' conditions with the Brunnstrom stages and Nottingham health profile, and measured pain using the numeric rating scale. Results showed that health literacy had a strong impact on the quality of life, especially energy, emotional well-being, sleep, and physical activity, but no clear link with functional status (12). In the current study, there was a weak correlation between caregivers' health literacy and patients' functional scores.

Hahn et al. (13) studied people with hemiplegia, spinal cord injury, and traumatic brain injury, assessing cognitive function, literacy, and patient-reported outcomes over two days. They found strong links between functional literacy, health literacy, and cognitive function (13). The current study supports this, showing a correlation between caregivers' health literacy and the cognitive subscale.

Kolunsağ and Ardıç (14) conducted a study using interviews with home healthcare caregivers and assessed their performance using the Lawton daily living scale and the adult health literacy scale. They found that caregivers' health literacy was linked to education, job status, and income, with education being the strongest predictor. Understanding caregivers' health knowledge gaps and educational needs can help improve care quality and patient well-being (14). Both their study and the current one found a connection between caregivers' health literacy and patient functional outcomes.

Tony et al. (15) studied 50 hemiplegic patients and their family caregivers at home. Caregivers' knowledge about hemiplegia was measured with a 29-item open-ended questionnaire, and patient function was assessed using the barthel index. Half the caregivers had moderate knowledge, but 78.6% showed incorrect care practices. Caregivers' education and job were linked to their knowledge, but no connection was found between knowledge and patient function (15). Unlike the methodology employed by Tony et al. (15), this study used the validated TSOY-32 questionnaire instead of open-ended questions. Meanwhile, Hess Engström et al. (16) argued that health literacy is not a burden for caregivers. Everyone agrees that health literacy shouldn't be a burden. This study found a positive link between caregivers' health literacy and patients' FIM scores, suggesting, that improving health literacy can help outcomes.

Levasseur and Carrier (17) highlighted that improving patients' health literacy is key to better rehabilitation outcomes. Blázquez-González et al. (18) showed in a randomized trial that virtual reality can boost health literacy in stroke patients. Smith and Magnani (19) emphasized the important role of technology and digital health literacy in increasing patient knowledge. Cook and Pompon (20) offered recommendations on health literacy and communication for stroke recovery.

Study Limitations

Unlike Tony et al. (15), who used open-ended questions, this study's main strength is using the validated TSOY-32. It also focuses solely on hemiplegic patients, unlike broader studies by Hahn et al. (13) and Kolunsağ and Ardıç (14). The main limitations are the lack of objective tests beyond the FIM, a single-center design, and a small sample size. Although caregivers' health literacy shows some correlation with functional, motor, and cognitive outcomes, this link is weak. Larger, multicenter studies using technology are needed to confirm these findings and apply them in healthcare.

Conclusion

These findings indicate that the health literacy of primary caregivers of hemiplegic patients is associated with the patients' motor and cognitive outcomes. The level of health literacy among primary caregivers may influence the functional recovery of these patients. A statistically significant positive correlation was observed between caregivers' health literacy and the total scores on the FIM, including both its motor and cognitive subscales. Nevertheless, the strength of these correlations was found to be weak. Health literacy proved to be a predictor for the overall FIM score as well as its motor and cognitive sections, while age did not serve as a predictor.

Ethics

Ethics Committee Approval: The study approved by Başkent University Non-Interventional Clinical Research Ethics Committee (approval number: E-94603339-604.01-458957, date: 06.05.2025).

Informed Consent: The consent forms were obtained from all participants and primary caregivers.

Footnotes

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References

1. Feigin VL, Brainin M, Norrving B, Martins SO, Pandian J, Lindsay P, F et al. World Stroke Organization: global stroke fact sheet 2025. Int J Stroke. 2025;20(2):132-144.
2. Ortiz de Mendivil A, Alcalá-Galiano A, Ochoa M, Salvador E, Millán JM. Brainstem stroke: anatomy, clinical and radiological findings. Semin Ultrasound CT MR. 2013;34(2):131-141.
3. Guzik A, Bushnell C. Stroke epidemiology and risk factor management. Continuum (Minneap Minn). 2017;23(1, Cerebrovascular Disease):15-39.
4. Tater P, Pandey S. Post-stroke movement disorders: clinical spectrum, pathogenesis, and management. Neurol India. 2021;69(2):272-283.
5. Toman NG, Grande AW, Low WC. Neural repair in stroke. Cell Transplant. 2019;28(9-10):1123-1126.
6. Liu C, Wang D, Liu C, Jiang J, Wang X, Chen H, et al. What is the meaning of health literacy? A systematic review and qualitative synthesis. Fam Med Community Health. 2020;8(2):e000351.
7. Nutbeam D, Lloyd JE. Understanding and responding to health literacy as a social determinant of health. Annu Rev Public Health. 2021;42:159-173.
8. Bulun MA, Çepni S, Ermez Y. Turkish sign language adaptation of the Turkish health literacy scale-32. J Deaf Stud Deaf Educ. 2022;27(4):443-452.
9. Dodds TA, Martin DP, Stolov WC, Deyo RA. A validation of the functional independence measurement and its performance among rehabilitation inpatients. Arch Phys Med Rehabil. 1993;74(5):531-536.
10. Parnell TA, Stichler JF, Barton AJ, Loan LA, Boyle DK, Allen PE. A concept analysis of health literacy. Nurs Forum. 2019;54(3):315-327.
11. Hersh L, Salzman B, Snyderman D. Health literacy in primary care practice. Am Fam Physician. 2015;92(2):118-124.
12. Başaran PÖ, Doğan AG. Evaluation of the health literacy in patients with stroke and relationship between health literacy and functional status on quality of life in patients with stroke. J Health Sci Med. 2024;7(1):32-38.
13. Hahn EA, Magasi SR, Carlozzi NE, Tulsky DS, Wong A, Garcia SF, et al. Health and functional literacy in physical rehabilitation patients. Health Lit Res Pract. 2017;1(2):e71-e85.
14. Kolunsağ S, Ardıç A. Health literacy of caregivers. Home Healthc Now. 2023;41(5):277-281.
15. Tony MI, Ragheb SG, Ibrahim WK. Caregivers' awareness regarding hemiplegia among adults. 2018.
16. Hess Engström A, Lindblom S, Flink M, Söderberg S, von Koch L, Ytterberg C. Stroke survivors' health literacy is not associated with caregiver burden: a cross-sectional study. Sci Rep. 2025;15(1):4720.
17. Levasseur M, Carrier A. Do rehabilitation professionals need to consider their clients' health literacy for effective practice? Clin Rehabil. 2010;24(8):756-765.
18. Blázquez-González P, Mirón-González R, Lendínez-Mesa A, Arroyo MTC, Mancebo-Salas N. Luengo-González R, et al. Efficacy of virtual reality on health literacy in patients with stroke: randomized pilot clinical trial. Revista Científica de la Sociedad de Enfermería Neurológica (English ed.), 2025;61:100161.
19. Smith B, Magnani JW. New technologies, new disparities: the intersection of electronic health and digital health literacy. Int J Cardiol. 2019;292:280-282.
20. Cook CV, Pompon RH. Lessons on health literacy and communication in post-stroke rehabilitation:: a primer and proposal. Dela J Public Health. 2023;9(3):44-49.

ORIGINAL RESEARCH

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Metformin Therapy Preserves Superoxide Dismutase and Glutathione Peroxidase, and Minimizes the Enlargement of Ascendant Aorta in the Newly Diagnosed Type 2 Diabetes Patients

Metformin Tedavisi: Yeni Tanı Konmuş Tip 2 Diyabet Hastalarında Süperoksit Dismutaz ve Glutatyon Peroksidazı Korur ve Asendan Aort Genişlemesini En Aza İndirir

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Abstract

Objective: To examine the levels of antioxidants including glutathione peroxidase (GPx), superoxide dismutase (SOD) and total antioxidant capacity (TAC), and to compare the effects of oral antidiabetics and insulin therapy on antioxidant molecules and echocardiographic measurements in patients with newly diagnosed type 2 diabetes mellitus (T2DM).

Method: Eighty-one newly diagnosed (diagnosed in the last 4 weeks) T2DM patients were divided into 3 groups according antidiabetic regimen (group 1: Receiving metformin only and HbA1c <8.5, group 2: Receiving metformin plus vildagliptin and HbA1c between 8.5-10 and group 3: Receiving metformin plus vildagliptin plus premixed insulin and HbA1c >10). The serum levels of GPx, SOD, TAC and echocardiographic measurements including ejection fraction (EF), left ventricular end diastolic thickness (LVEDT) and ascendant aorta diameter (AAD) of the patients were examined at the first visit and at the 6th month of the study.

Öz

Amaç: Yeni tanı konmuş tip 2 diabetes mellitus (T2DM) hastalarında glutatyon peroksidaz (GPx), süperoksit dismutaz (SOD) ve total antioksidan kapasite (TAK) gibi antioksidanların düzeylerini incelemek ve oral antidiyabetikler ile insülin tedavisinin antioksidan moleküller ve ekokardiyografik ölçümler üzerindeki etkilerini karşılaştırmaktır.

Yöntem: Yeni tanı konmuş (son 4 hafta içinde tanı konmuş) T2DM 81 hasta antidiyabetik rejime göre 3 gruba ayrılmıştır (grup 1: Sadece metformin alan ve HbA1c <8,5, grup 2: Metformin artı vildagliptin alan ve HbA1c 8.5-10 arasında ve grup 3: Metformin artı vildagliptin artı premiks insülin alan ve HbA1c >10). Hastaların serum GPx, SOD, TAK düzeyleri ve ejeksiyon fraksiyonu (EF), sol ventrikül diyastol sonu kalınlığı (LVEDT) ve asendan aort çapı (AAD) gibi ekokardiyografik ölçümleri ilk vizitte ve çalışmanın 6. ayında incelenmiştir.

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***One of the authors of this article (A.E.A.) is a member of the Editorial Board of this journal. He was completely blinded to the peer review process of the article.**

Abstract

Results: While there was no statistically significant difference between the baseline and the 6th month averages of SOD, GPx and TAC values in 3 groups, the reduction in the mean SOD, GPx and TAC levels throughout the study period were significant in the groups, except group 1. The echocardiographic measurements of the groups were similar but the mean increase in the AAD was significant in all groups, with the lowest enlargement in aortic diameter was also in metformin only group. The changes in EF and LVEDT throughout the study period were non-significant. The correlation between SOD and AAD in the group 1 was significant.

Conclusion: Metformin therapy preserves the levels of SOD and GPx in the newly diagnosed diabetic patients, and the enlargement in the AAD is minimized by single metformin therapy compared to other combinations. Echocardiography parameters revealed that ascendant aorta diameter is a reliable and early marker of cardiovascular complications of DM.

Keywords: Ascendant aorta diameter, glutathione peroxidase, metformin, superoxide dismutase, total antioxidant capacity

Öz

Bulgular: SOD, GPx ve TAC değerlerinin başlangıç ve 6. ay ortalamaları arasında 3 grupta istatistiksel olarak anlamlı bir fark bulunmazken, çalışma süresi boyunca ortalama SOD, GPx ve TAC seviyelerindeki azalma grup 1 hariç tüm gruplarda anlamlıydı. Grupların ekokardiyografik ölçümleri benzerdi ancak AAD'deki ortalama artış tüm gruplarda anlamlıydı ve aort çapındaki en düşük genişleme de sadece metformin grubundaydı. Çalışma süresi boyunca EF ve LVEDT'deki değişiklikler anlamlı değildi. Grup 1'de SOD ve AAD arasındaki korelasyon anlamlı bulunmuştur.

Sonuç: Metformin tedavisi, yeni tanı konmuş diyabet hastalarında SOD ve GPx seviyelerini korumakta ve AAD'deki genişleme, diğer kombinasyonlara kıyasla tekli metformin tedavisi ile en aza indirilmektedir. Ekokardiyografi parametreleri, asendan aort çapının DM'nin kardiyovasküler komplikasyonlarının güvenilir ve erken bir belirteci olduğunu ortaya koymuştur.

Anahtar kelimeler: Asendan aort çapı, glutatyon peroksidaz, metformin, süperoksit dismutaz, total antioksidan kapasite

Introduction

The frequency of type 2 diabetes mellitus (T2DM) has been rising alarmingly. According to the Turkey Diabetes, Hypertension, Obesity and Endocrinological Disease Prevalence (TURDEP)-1 Study, the rate of T2DM in the Turkish population was 7% in 1998, almost doubling to 13.7% in the TURDEP-2 study in 2010 (1). Diabetes is recognized as comparable to coronary artery disease, presenting an elevated risk of cardiovascular mortality relative to non-diabetics, with cardiovascular complications being the primary causes of death and morbidity (2,3).

Among different pathogenetic mechanisms, oxidative stress plays a vital role in the development of atherosclerosis and the subsequent emergence of micro and macrovascular complications of T2DM (4,5). Oxidative stress is defined as the impairment of the oxidative balance as a result of the increase in reactive oxygen species (ROS) production during cellular metabolism or insufficiency in antioxidant mechanisms detoxifying ROS, which eventually results in the oxidization of carbohydrates, lipids, proteins, deoxyribonucleic acid and damage on cellular membranes (6,7). Antioxidants with enzymatic activity are capable of neutralizing ROS. Superoxide dismutase (SOD) is an enzymatic antioxidant which removes superoxide anions from tissues (8). Glutathione peroxidase (GPx) is another antioxidant that reverses the oxidation of sulfhydryl groups (9). On the other hand, total antioxidant capacity (TAC) is defined as the combined ability of antioxidant enzymes ranging from classical enzymes like SOD, GPX, and catalases to ancillary enzymes like oxidoreductases and conjugate enzymes (10,11).

This study aimed to assess the impact of various antidiabetic regimens on antioxidant molecule levels and echocardiographic indicators in newly diagnosed T2DM patients with differing HbA1c values at the initial visit and six months post-diagnosis. The secondary objective was to examine the impact of antidiabetic therapy combinations on blood concentrations of SOD, GPx, and TAC, as well as echocardiographic parameters at the initial diagnosis and after 6 months.

Materials and Methods

Study Design and Participants

Eighty-one patients diagnosed with T2DM in the last 4 weeks at the Internal Medicine Outpatient Service of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, İstanbul, between 1 February 2017 and 15 February 2018, were enrolled in the study. Diagnosis of T2DM was based on the criteria of 2017 American Diabetes Association guidelines and the guidelines of the Turkish Society of Endocrinology and Metabolism. The participants' antidiabetic medications (metformin only, metformin plus vildagliptin, and metformin plus vildagliptin plus premixed insulin) were recorded after examining medical recordings and/or interviews with the patient. We classified the patients according to the antidiabetic regimen and HbA1c value

(group 1: Receiving metformin only and Hba1c <8.5, group 2: Receiving metformin plus vildagliptin and HbA1c between 8.5-10, and group 3: Receiving metformin plus vildagliptin plus premixed insulin and HbA1c >10). The groups were age, gender, and body mass index (BMI) matched. The patients with hypertension, ischemic heart disease, stroke, thyroidal dysfunction, autoimmune disorders, chronic liver disease, chronic kidney disease, smokers, or the patients receiving any other medication were excluded. The study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (approval number: 2016-507, date: 27.12.2016). Entire patients gave written informed consent. Demographic data of participants were collected from patients themselves or family members.

Clinical and Laboratory Assessments

Patients aged >18 years without a comorbidity underwent a detailed physical examination. The demographic characteristics, including age, gender, and BMI were recorded. Blood samples were collected after an 8-hour fasting period. Biochemical analysis including glucose, urea creatinine, uric acid, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase, calcium, sodium, potassium, total protein, albumin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, thyroid-stimulating hormone (TSH), and free thyroxine was performed by using photometric method in Siemens Advia 1800 device. Blood samples for analyzing SOD, GPx, and TAC were obtained at the first and second visits and preserved at -80 °C. All blood samples were centrifugated for 5 minutes at 2000 turn before analysis.

Antioxidant Enzyme Measurements

ELISA method with the commercially available kits was used to analyze SOD, GPx, and TAC after dissolving the portions of the serum samples on the same day as instructed by the company [Abbkine kit (Wuhan China) as follows; human SOD KTE62765, Abbkine, INC Bldg 1, No.35, Optical Valley Ave, Wuhan, China]. The SODELISA Kit employs a two-site sandwich ELISA to quantitate SOD in samples (Human SOD Elisa Kit). An antibody specific to SOD has been pre-coated onto a microplate. Standards and samples are pipetted into the wells, and any SOD present is bound by the immobilized antibody. After removing any unbound substances, HRP-Conjugate Human SOD detection antibody is added to the wells. Following a wash to remove any unbound HRP reagent, a Chromogen solution is added to the wells, and color develops in proportion to the amount of SOD bound in the initial step. This inhibition activity of SOD is measured by the colorimetric method at OD 450 nm.

The analysis of GPx (Human GSH-PX Elisa KiT, KTE62766 Abbkine, INC Bldg 1, No.35, Optical Valley Ave, Wuhan, China) was done by mixing 0.2 mL of 0.8 Mm EDTA, 0.2 mL of reduced glutathione and 0.4 mL of phosphate buffer (pH 7.0) at 37.8 °C for 10 minutes and centrifugated at 2000 rpm. After adding disodium hydrogen phosphate, the activity of GPx was read photometrically at 420 nm and expressed as nanomoles of glutathione oxidized per minute per milligram.

For the TAC analysis (Human TAC Elisa KiT, KTE62767 Abbkine, INC Bldg 1, No.35, Optical Valley Ave, Wuhan, China), plasma samples were collected by centrifugation for 1.5 minutes at 2000 rpm. DPPT was dissolved in methanol (200 mL 80%) and centrifugated to obtain the supernatant. The absorbance of TAC was measured after the reaction between the supernatant and DPPH solution at 517 nm.

Additional Clinical Measurements

Urine analysis was done using the spectrophotometric method on the Siemens Advia 1800 device. The height and weight of participants were measured in the Tanita Body Composition Analyzer (Tanita Corporation of America, Illinois, USA). BMI was calculated as weight/height (kg/m^2). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or receiving any antihypertensive agent. Urine albumin excretion rate exceeding 20 µg/min (30 mg/day), in the absence of uncontrolled hypertension or urinary tract infection, was defined as microalbuminuria.

Echocardiographic Examination

An echocardiographic examination was performed by the same cardiologist at the Cardiology Department of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital. All cases were examined by iE33 echocardiography system to detect LV end-diastolic dimension, left atrial diameter, left ventricular (LV) posterior wall thickness in diastole, interventricular septum thickness in diastole, LV ejection fraction (LVEF). The echocardiographic examination included measurements of LV end-diastolic thickness and ascending aorta diameter (AAD). LV mass was calculated according to the American Society of Echocardiography formula. Body surface area (BSA) was calculated as [(height(cm) x weight (kg)/3600)]

1/2, and LV mass index was calculated by dividing LV mass into the BSA. LV hypertrophy was defined as LV mass index >115 g/m^2 (for men) and >95 g/m^2 (for women).

Statistical Analysis

Data were analyzed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). Data distribution was assessed using Shapiro-Wilk test before applying parametric tests. Parametric tests were applied for normally distributed data, while non-parametric tests were used for data that did not meet normality assumptions. All data is expressed as the mean ± standard deviation. Categorical variables were compared using chi-square test. For normally distributed continuous variables, One-Way ANOVA was used for between-group comparisons and paired t-test for within-group comparisons. For non-normally distributed data, Kruskal-Wallis test was used for between-group comparisons and Wilcoxon signed-rank test for within-group comparisons. Correlations were assessed using Pearson correlation for normally distributed data and Spearman's rank correlation for non-normally distributed data. A p-value <0.05 was considered to be statistically significant.

Results

The mean ages of the three groups participating in the study were 51.83±11.71, 53.01±9.83, and 49.63±12.06 years, respectively, and there was no significant difference between the groups. Similarly, BMI values were also similar between groups. There was no statistically significant difference between the groups in terms of gender distribution. Significant weight loss was observed in all groups during the follow-up period (Table 1).

The HbA1c measurements from biochemical tests verified the correct patient distribution based on the established criteria because group 1 started with HbA1c levels at 8.1±0.4% while group 2 began at 9.2±0.5% and group 3 started at 11.8±1.2%. All three groups achieved substantial HbA1c reductions during their follow-up period (p=0.0001 for all groups). The initial glucose measurements in group 1 exceeded those of the other two groups because HbA1c levels directly correlated with these measurements. The baseline measurements of creatinine, urea, LDL cholesterol and triglycerides showed no significant differences between the groups but all groups demonstrated a significant decrease in LDL cholesterol levels during follow-up.

The metformin group demonstrated the most substantial rise in HDL cholesterol levels among all groups (p=0.0001). The liver enzyme values of ALT and AST together with thyroid function tests TSH and free T4 remained constant throughout the study period with no differences between groups (Table 2). The initial measurements of SOD, GPx and TAC antioxidant molecules showed no significant differences between the groups.

However, during follow-up, while no decrease in SOD and GPx levels was observed in the group receiving only metformin, a significant decrease in these parameters was detected in the other two groups. A significant decrease in TAC levels was observed in all three groups during follow-up (Table 3).

In terms of echocardiographic measurements, the ejection fraction and LV end-diastolic thickness values of the groups were similar, and no changes in these parameters were observed during the follow-up period. In the measurements of the aortic outflow tract diameter, there was no difference between the groups at baseline, but a significant increase in the aortic outflow tract diameter occurred in all three groups during the follow-up period. This increase was observed at least in the group receiving metformin alone (Table 4).

Table 1. Demographic characteristics of groups

	Metformin group n=30	Metformin+sOAD group n=32	Metformin+sOAD+insulin group n=19	p
Age	51.83±11.71	53±9.83	49.63±12.06	0.579*
Gender				0.230†
Male	13 (43.33%)	17 (53.13%)	13 (68.42%)	
Female	17 (56.67%)	15 (46.88%)	6 (31.58%)	
BMI				
1st visit	34.13±5.87	32.92±4.77	31.49±5.1	0.238*
2nd visit	31.89±4.88	30.91±4.74	29.75±4.54	0.310*
p	0.0001‡	0.0001‡	0.041‡	

*: One-Way ANOVA, †: Chi-square test, ‡: Paired t-test, sOAD: Second oral antidiabetic (vildagliptin), BMI: Body mass index

Table 2. Biochemical and hormonal parameters of the groups

	Metformin group n=30	Metformin+sOAD group n=32	Metformin+sOAD+insulin group n=19	p
HbA1c (%)				
1st visit	8.1±0.4	9.2±0.5	11.8±1.2	0.0001§
2nd visit	6.8±0.3	7.5±0.4	8.7±0.8	0.0001§
p	0.0001‡	0.0001‡	0.0001‡	
Glucose				
1st visit	131.96±30.73	174.58±73.12	295.74±90.94	0.0001§
2nd visit	118.33±23.66	152.54±53.33	120.63±21.64	0.001§
p	0.031‡	0.884‡	0.0001‡	
Creatinine				
1st visit	0.88±0.59	0.83±0.16	0.80±0.2	0.58*
2nd visit	0.82±0.18	0.79±0.12	0.79±0.23	0.195*
p	0.490‡	0.530‡	0.327‡	
Urea				
1st visit	35.42±37.35	30.27±7.35	30.42±8.5	0.645§
2nd visit	31.12±9.56	31.93±6.53	31.03±9.5	0.907*
p	0.512¶	0.277‡	0.765‡	
LDL				
1st visit	127.29±30.86	134.59±28.48	133.47±28.14	0.591*
2nd visit	117.14±28.61	121.47±35.78	102.41±31.63	0.124*
p	0.042‡	0.015‡	0.005‡	
Triglyceride				
1st visit	203.57±146.71	218.09±126.66	347.46±407.61	0.081§
2nd visit	182.21±166.79	225.01±209.73	171.11±81.82	0.473§
p	0.122¶	0.833¶	0.082¶	
HDL				
1st visit	42.7±13.53	44.27±11.16	38.5±8.34	0.228*
2nd visit	52.01±11.96	48.38±14.34	47.1±14.29	0.400*
p	0.0001‡	0.079‡	0.002‡	
Total cholesterol				
1st visit	207.46±33.85	220.16±33.58	227±47.41	0.176*
2nd visit	201.99±33.47	212.57±38.61	182.39±34.56	0.058*
p	0.301‡	0.295‡	0.001‡	
ALT				
1st visit	27.67±18.93	22.91±11.24	28.74±22.77	0.421§
2nd visit	23.26±11.99	20.43±7.55	29.33±23.43	0.103§
p	0.086¶	0.235¶	0.930¶	
AST				
1st visit	23.29±9.9	21.26±11.26	21.16±18.94	0.789§
2nd visit	21.67±6.44	18.69±4.3	23.02±10.46	0.073§
p	0.346¶	0.210¶	0.706¶	
TSH				
1st visit	2.04±1.37	2.82±2.7	2.46±0.97	0.297§
2nd visit	2.36±1.34	2.72±1.89	2.34±1.19	0.584§
p	0.197¶	0.661¶	0.546¶	
fT4				
1st visit	1.15±0.28	1.06±0.24	1.22±0.18	0.068*
2nd visit	1.25±0.27	1.2±0.2	1.18±0.2	0.491*
p	0.056‡	0.002‡	0.479‡	

*: One-Way ANOVA, ‡: Paired t-test, §: Kruskal-Wallis test, ¶: Wilcoxon test, sOAD: Second oral antidiabetic (vildagliptin), LDL: Low-density lipoprotein, HDL: High-density lipoprotein, ALT: Alanine transaminase, AST: Aspartate transaminase, fT4: Free thyroxine, TSH: Thyroid-stimulating hormone

Table 3. The serum levels of antioxidant molecules of groups

		Metformin group n=0	Metformin+sOAD group n=32	Metformin+sOAD+insulin group n=19	p§
SOD	1st visit	36.3±64.12	87.94±150.7	54.79±105.16	0.221
	2nd visit	32.92±69.12	55.44±105.78	22.07±23.16	0.370
	p	0.304¶	0.005¶	0.008¶	
GPx	1st visit	5.22±12.57	9.68±18.59	5.17±10.66	0.501
	2nd visit	4.27±9.69	4.94±10.22	2.61±2.71	0.661
	p	0.600¶	0.008¶	0.007¶	
TAC	1st visit	1.57±2.34	3.28±5.18	1.99±3.33	0.492
	2nd visit	0.81±1.49	0.95±1.76	0.54±0.59	0.656
	p	0.0001¶	0.0001¶	0.0001¶	

§: Kruskal-Wallis test, ¶: Wilcoxon test, SOD: Superoxide dismutase, sOAD: Second oral antidiabetic, TAC: Total antioxidant capacity

Table 4. The echocardiographic measurements of the groups

		Metformin group n=30	Metformin+sOAD group n=32	Metformin+sOAD+insulin group n=19	p*
EF (%)	1st visit	60.77±2.43	60.78±1.85	61.05±2.09	0.884
	2nd visit	59.77±2.4	60.41±1.32	60.11±0.46	0.338
	p	0.114‡	0.385‡	0.077‡	
LVEDT	1st visit	4.27±0.48	4.32±0.56	4.29±0.46	0.941
	2nd visit	4.35±0.66	4.37±0.5	4.43±0.61	0.893
	p	0.328‡	0.601‡	0.457‡	
AAD	1st visit	3.17±0.43	3.18±0.31	3.31±0.26	0.331
	2nd visit	3.29±0.45	3.42±0.31	3.47±0.31	0.210
	p	0.019‡	0.0001‡	0.004‡	

*: One-Way ANOVA, ‡: Paired t-test, sOAD: Second oral antidiabetic, LVEDT: Left ventricular end-diastolic thickness, AAD: Ascending aorta diameter, EF: Ejection fraction

According to the results of the correlation analysis, a positive correlation was found between SOD level and aortic outflow tract diameter in the group receiving metformin alone. No significant relationship was found between other antioxidant parameters and echocardiographic indices. No significant correlation was found between biochemical variables, hemogram parameters, thyroid function tests, and antioxidant parameters (Table 5).

Discussion

This investigation revealed that patients with varying glycemic management exhibit comparable antioxidant enzyme levels in the early stages of T2DM; however, the metformin-only therapy strategy emerged as the most favorable alternative, maintaining stable SOD and GPx levels throughout the study duration. All groups showed significant weight loss, but patients receiving an insulin-based regimen had the lowest reduction. Another important finding in our study was that, while all groups experienced an increase in the AAD, the metformin-only group had the least significant increase in the AAD.

Oxidative stress has more severe and destructive effects in both blood and tissue levels in diabetic patients compared to healthy people as a result of the increase of free radicals, especially the oxygen radicals, auto-oxidation of glucose, a shift in redox balances, insufficient activities of antioxidant enzymes such as SOD dismutase, GPx , absence of reduced glutathione, and decrease of tissue concentrations of antioxidants that eventually resulted with the formation and the progression of atherosclerosis (17,18). Kimura et al. (19) showed a linear relationship between SOD activity and the severity of micro and macrovascular diabetic complications, and the authors concluded that serum SOD activity reflects diabetic vascular damage. Gómez-Marcos et al. (20) conducted a study on 307 individuals, including 54 diabetic and hypertensive patients, 16 non-hypertensive diabetic patients, 185 non-diabetic hypertensive patients, and 52 non-hypertensive and non-diabetic healthy

Table 5. The correlation of echocardiographic measurements and antioxidant molecules

		Metformin group			Metformin+sOAD group			Metformin+sOAD+insulin group		
		SOD	GPx	TAC	SOD	GPx	TAC	SOD	GPx	TAC
EF	r	0.166	0.073	0.121	-0.054	-0.03	-0.064	-0.108	-0.142	-0.131
	p	0.381*	0.702*	0.525*	0.769*	0.87*	0.73*	0.659*	0.562*	0.594*
LVEDT	r	-0.242	-0.229	-0.136	0.031	0.003	0.015	0.27	0.22	0.314
	p	0.198†	0.224*	0.473*	0.865*	0.985*	0.936*	0.264†	0.366*	0.191†
AAD	r	**0.387**	0.197	-0.212	-0.027	-0.117	-0.027	0.257	0.282	0.228
	p	**0.034***	0.296*	0.261†	0.882*	0.523*	0.883*	0.288†	0.242*	0.349†

*: Pearson Correlation test; †: Spearman's rank correlation test, sOAD: Second oral antidiabetic, LVEDT: Left ventricular end-diastolic thickness, AAD: Ascending aorta diameter, EF: Ejection fraction, GPx: Glutathione peroxidase, SOD: Superoxide dismutase

individuals, continued for 24 months. They determined a reverse correlation between SOD level and macrovascular complications like carotid intima-media thickness (CIMT) and ambulatory arterial stiffness index (20).

The study design included patients with various HbA1c levels to match real-world clinical practice where treatment decisions depend on glycemic control. The observed differences in antioxidant enzyme preservation could be influenced by baseline disease severity instead of treatment effects alone. The patients who received metformin monotherapy showed better initial blood sugar control with HbA1c levels below 8.5% compared to those who needed combination therapy with HbA1c between 8.5-10% or insulin addition with HbA1c above 10%. The formation of advanced glycation end-products and polyol pathway activation through hyperglycemia leads to oxidative stress according to previous research (21). The scientific literature shows that patients with higher HbA1c levels at baseline tend to have reduced antioxidant capacity because their existing oxidative damage limits their response to antioxidant-preserving treatments (22). The better results in our study might be due to lower baseline oxidative stress levels instead of superior therapeutic effects of metformin monotherapy.

Conflicting findings exist about antioxidant levels in diabetic versus non-diabetic individuals. Markedly reduced levels of antioxidants were observed in conjunction with similar levels of antioxidants disparity was attributed to ethnicity and gender (23,24). It was shown that female gender and African origin positively influence these antioxidants. Another conflict in the literature was observed about the relationship between glycemic regulation and antioxidant enzyme levels (25,26). Similar to our results, Wong et al. (27) found similar SOD and GPx levels between patients with varying glucose control. However, Doddigarla et al. (28) determined an inverse association between HbA1c and SOD and decreased SOD levels among diabetic patients with high HbA1c. Authors emphasized that high antioxidant levels in patients with poor glycemic control are a compensatory response against enhanced oxidative stress burden.

Some researchers examined the role of antidiabetic medications on the serum levels of antioxidants. They demonstrated that rats receiving metformin showed no reduction in heart SOD activity compared to other groups that did not receive metformin in an experimental study (29). Altınkaynak (30) divided 50 diabetic patients into two groups according to their antidiabetic therapy: The metformin-only group and the thiazolidinedione-only group. They determined an increase in the SOD and GPx levels in both groups; however, the rise was significant only in the metformin group. Similarly, Hatipoğlu (31) compared the effects of metformin+DPP4 inhibitor (sitagliptin) combination with metformin plus basal insulin (insulin glargine) on the serum levels of TAC and pointed out significantly higher TAC levels in the former group. In sepsis-induced oxidative stress, SOD and GPx levels of rats remained normal by administration of metformin, but, similar to our study, TAC levels decreased significantly (32). Dogan Turacli et al. (33) proved that metformin enhances SOD and GPx activity in the diabetic population. However, the same positive effect was not seen in the TAC. Some authors raised concerns about the shortcomings of the TAC assay and strictly discouraged the use of hydroxyl radicals as the oxidant because of the molecule's high and non-specific reactivity, resulting in discrepancies in the literature (34). On the other hand, Zhang et al. (35) showed that SOD level is decreased in patients receiving premixed insülin and improved by switching to basal insulin.

The study revealed substantial weight loss in all treatment groups with the metformin-only group achieving the greatest reduction in BMI at 2.24 kg/m² compared to the

insulin-containing regimen with a mean BMI decrease of 1.74 kg/m². Weight reduction leads to better oxidative stress markers and cardiovascular parameters regardless of blood sugar control according to Scioli et al. (36). The study of overweight and obese young adults showed that BMI reductions directly correlated with decreased aortic stiffness measurements but heart rate and C-reactive protein reductions explained the improvements in peripheral arterial stiffness (37). The different weight loss amounts between groups might have protected antioxidant enzyme levels in the metformin group. The better cardiovascular outcomes can be attributed to metformin's weight-neutral or weight-reducing properties compared to insulin's weight gain potential. The study design limitation prevents us from directly evaluating how weight changes affect antioxidant parameters through correlation analysis.

Regarding echocardiographic indices, the only significant change was observed in the ascendant aorta diameter throughout the timescale in our study. The diameter of the ascendant aorta reflects atherosclerosis in the short term and is considered a predictor of aortic aneurysms (16). Several studies mentioned that the diabetic population had smaller arterial diameter and lower frequency of aortic dilatation (38). In contrast, Miao et al. (39) concluded that diabetes induces aortic oxidative stress and increases the aortic wall-thickness and proximal aorta diameter, which can be suppressed by zinc supplementation via antioxidant pathways. Static and dynamic changes in the ascending aorta are the earliest manifestation of vascular aging, and aortic diameter has an important impact on pulse wave velocity and is the most prominent predictor of aortic rupture (40). Jensen et al. (41) concluded that subtle changes occur before the LVEF is impaired and LV mass increases.

The study revealed an interesting positive relationship between SOD levels and AAD that only appeared in the metformin group (r=0.387, p=0.034). The relationship did not exist in patients who received combination therapy or insulin. The unique correlation pattern between metformin-treated patients suggests they have a distinct compensatory response. The research by Buczyńska et al. (42) demonstrates that metformin protects blood cells and vascular endothelial cells from oxidative damage through NADPH oxidase inhibition and SOD upregulation which strengthens cellular resistance to oxidative stress. The research by Buczyńska et al. (42) demonstrates that metformin activates AMPK-dependent pathways which both protect and potentially boost endogenous antioxidant responses when cells experience stress. The lack of this correlation in other treatment groups suggests an impaired adaptive response which could stem from insulin's pro-oxidant effects or the more severe baseline oxidative stress in these patients. The findings confirm that metformin protects blood vessels by maintaining oxidative stress response mechanisms instead of basic antioxidant functions.

Considering the effects of metformin on the cardiovascular system, Kaya et al. (43) determined an improvement in the elastic properties of the aorta by adding metformin to oral contraceptives in women with PCOS. Bjornstad et al. (44) showed that metformin improved both static (intima-media thickness) and dynamic (ascending aorta pulse wave velocity) properties of the aorta in the diabetic population. Dallak et al. (45) demonstrated a protective effect of metformin on type 2-induced aortapathy by suppressing OS. In an experimental animal study, Sena et al. (46) showed that metformin restored endothelial vasodilatation of the aorta via inhibition of OS. In a study from Australia, metformin improved vascular smooth muscle function, and the reducing with metformin vascular adverse lesions in type 1 diabetes mellitus study showed that metformin therapy reduces maximal CIMT (47,48).

Gordin et al. (49) discovered that insulin exposure impairs aortic and brachial pulse wave velocity and enhances arterial stiffness, which is probably related to the mitogenic effect of hormones. Insulin receptors are found on angiogenic structures in human atherosclerotic plaques, and both short and long-acting insulin compounds stimulate angiogenesis (50). Improvement of oxidative stress and microcirculatory damage was significantly better with metformin compared to insulin monotherapy (51). Lloyd et al. (52) showed that insulin administration increased glucose and pyruvate oxidation. Intensification of metformin-based antidiabetic therapy with insulin is associated with a higher risk of cardiovascular disease (53,54). On the other hand, some authors mentioned that insulin infusion may decrease atherosclerosis by improving inflammation in the short term in animal studies (55). However, there is still a lack of available data on the long-term effects of different insulin types on endothelial functions in human studies.

Study Limitations

There are some limitations of our study. First, the number of cases in our study was relatively low due to our strict exclusion criteria. Many patients were excluded from the study due to irregular follow-ups or comorbidities such

as hypertension, heart failure, autoimmune disorder, chronic renal or liver disease, thyroid dysfunction, and prolactinoma. The second limitation may be the shorter follow-up time. We believe that longer follow-ups will impact the significance of our results. This study was performed on the Turkish population, and therefore, it may not be correct to generalize the results of our study to other populations since there may be effects of environmental factors such as diet or lifestyle as well as genetic factors. Planning a study that considers the dietary habits and physical activities of individuals in the future may help produce more meaningful results.

Conclusion

The research demonstrated that metformin monotherapy achieved the best results because it maintained stable SOD levels (p=0.304) and GPx levels (p=0.600) without significant decline while other treatment combinations led to substantial decreases in both antioxidant enzymes. The aortic diameter growth was most limited in patients who received metformin therapy among all treatment groups. The research demonstrates that metformin provides better protection to the antioxidant system than insulin-based regimens thus making it a potential treatment for preventing macrovascular complications in early-stage type 2 diabetes. The baseline glycemic control differences between groups should be taken into account because patients on metformin monotherapy started with less severe disease.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (approval number: 2016-507, date: 27.12.2016).

Informed Consent: Entire patients gave written informed consent. Demographic data of participants were collected from patients themselves or family members.

Footnotes

The abstract of the study was presented at the 20th Congress of Internal Medicine, Antalya, Turkey in 2018.

Authorship Contributions

Surgical and Medical Practices: S.Y., E.G., A.E.A., Concept: S.Y., Z.S.İ., H.S., M.Y., Ö.S., E.G., F.B., A.E.A., N.G., Design: S.Y., E.B.K., S.P.G., N.G., A.E.A., Data Collection or Processing: S.Y., R.Ç., Z.S.İ., E.B.K., H.S., M.Y., Ö.S., E.G., F.B., Analysis or Interpretation: S.Y., R.Ç., S.P.G., N.G., A.E., Literature Search: S.Y., R.Ç., Z.S.İ., H.S., M.Y., Ö.S., E.G., F.B., N.G., A.E.A., Writing: S.Y., Z.S.İ., E.B.K., S.P.G., A.E.A.

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References

1. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, et al; TURDEP-II Study Group. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol. 2013 b;28(2):169-180.
2. Vasan RS, Enserro DM, Xanthakis V, Beiser AS, Seshadri S. Temporal trends in the remaining lifetime risk of cardiovascular disease among middle-aged adults across 6 decades: the Framingham study. Circulation. 2022;145(17):1324-1338.
3. Heller GV. Evaluation of the patient with diabetes mellitus and suspected coronary artery disease. Am J Med. 2005;118(Suppl 2):9S-14S.
4. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993;16(2):434-444.
5. Newsholme P, Cruzat VF, Keane KN, Carlessi R, de Bittencourt PI Jr. Molecular mechanisms of ROS production and oxidative stress in diabetes. Biochem J. 2016;473(24):4527-4550.
6. Kosova F, Altan N, Sepici A, Engin A, Kocamanoglu N. Thyroid hormones-mediated effects of insulin on antioxidant enzymes from diabetic rat hearts. Bratisl Lek Listy. 2013;114(4):183-188.
7. Asmat U, Abad K, Ismail K. Diabetes mellitus and oxidative stress-A concise review. Saudi Pharm J. 2016;24(5):547-553.
8. Scott LJ. Teriflunomide: a review in relapsing-remitting multiple sclerosis. Drugs. 2019;79(8):875-886.
9. Margis R, Dunand C, Teixeira FK, Margis-Pinheiro M. Glutathione peroxidase family - an evolutionary overview. FEBS J. 2008;275(15):3959-3970.
10. Parohan M, Anjom-Shoae J, Nasiri M, Khodadost M, Khatibi SR, Sadeghi O. Dietary total antioxidant capacity and mortality from all causes, cardiovascular disease and cancer: a systematic review and dose–response meta-analysis of prospective cohort studies. Eur J Nutr. 2019;58(6):2175-2189.
11. Helmut S. Total antioxidant capacity: appraisal of a concept. J Nutr. 2007;137(6):1493-1495.
12. Fang ZY, Schull-Meade R, Downey M, Prins J, Marwick TH. Determinants of subclinical diabetic heart disease. Diabetologia. 2005;48:394-402.
13. Hickson SS, Butlin M, Graves M IB, Taviani V, Avolio AP, McEniery CM, et al. The relationship of age with regional aortic stiffness and diameter. JACC Cardiovasc Imaging. 2010;3(12):1247-1255.
14. Nelson AJ, Worthley MI, Cameron JD. Regional differences in aortic geometry pathologic or compensatory? JACC Cardiovasc Imaging. 2011;4(5):562-563; author reply 563-564.

15. Günay Ş, Güllülü NS. Yaşlılarda aort anevrizmalarına yaklaşım [Approach to aortic aneurysms in the elderly]. Turk Kardiyol Dern Ars. 2017;45(Suppl 5):93-95. Turkish.

16. Clerc OF, Fuchs TA, Stehli J, Benz DC, Gräni C, Messerli M, et al. Non-invasive screening for coronary artery disease in asymptomatic diabetic patients: a systematic review and meta-analysis of randomised controlled trials. Eur Heart J Cardiovasc Imaging. 2018;19(8):838-846.

17. Singh H, Singh R, Singh A, Singh H, Singh G, Kaur S, et al. Role of oxidative stress in diabetes-induced complications and their management with antioxidants. Arch Physiol Biochem. 2024;130(6):616-641.

18. Hamamcıoğlu AC. The role of oxidative stres and antioxidants in diabetes. Turk J Diab Obes. 2017;1:7-13.

19. Kimura F, Hasegawa G, Obayashi H, Adachi T, Hara H, Ohta M, et al. Serum extracellular superoxide dismutase in patients with type 2 diabetes: relationship to the development of micro- and macrovascular complications. Diabetes Care. 2003;26(4):1246-1250.

20. Gómez-Marcos MA, Blázquez-Medela AM, Gamella-Pozuelo L, Recio-Rodriguez JI, García-Ortiz L, Martínez-Salgado C. Serum superoxide dismutase is associated with vascular structure and function in hypertensive and diabetic patients. Oxid Med Cell Longev. 2016;2016:9124676.

21. González P, Lozano P, Ros G, Solano F. Hyperglycemia and oxidative stress: an integral, updated and critical overview of their metabolic interconnections. Int J Mol Sci. 2023;24(11):9352.

22. Pieme CA, Tatangmo JA, Simo G, Biapa Nya PC, Ama Moor VJ, Moukette Moukette B, et al. Relationship between hyperglycemia, antioxidant capacity and some enzymatic and non-enzymatic antioxidants in African patients with type 2 diabetes. BMC Res Notes. 2017;10(1):141.

23. Memisoğullari R, Taysi S, Bakan E, Capoglu I. Antioxidant status and lipid peroxidation in type II diabetes mellitus. Cell Biochem Funct. 2003;21(3):291-296.

24. Nobar M, Pour A, Nobar M, Beig F, Mirhashemi S. Total antioxidant capacity, süperoxide dismutase and glutathion peroxidase in diabetic patients. Medical Journal of Islamic Academy of Sciences. 1999;12(4):109-114.

25. Kumawat M, Sharma TK, Singh I, Singh N, Ghalaut VS, Vardey SK, et al. Antioxidant enzymes and lipid peroxidation in type 2 diabetes mellitus patients with and without nephropathy. N Am J Med Sci. 2013 5(3):213-219.

26. Rani AJ, Mythili SV. Study on total antioxidant status in relation to oxidative stress in type 2 diabetes mellitus. J Clin Diagn Res. 2014;8(3):108-110.

27. Wong FN, Chua KH, Tan JAMA, Wong CM, Kuppusamy UR. Glycaemic control in type 2 diabetic patients with chronic kidney disease: the impacts on enzymatic antioxidants and soluble RAGE. PeerJ. 2018;6:e4421.

28. Doddigarla Z, Parwez I, Ahmad J. Correlation of serum chromium, zinc, magnesium and SOD levels with HbA1c in type 2 diabetes: a cross sectional analysis. Diabetes Metab Syndr. 2016;10(1 Suppl 1):S126-S129.

29. Karam HM, Radwan RR. Metformin modulates cardiac endothelial dysfunction, oxidative stress and inflammation in irradiated rats: a new perspective of an antidiabetic drug. Clin Exp Pharmacol Physiol. 2019;46(12):1124-1132.

30. Altınkaynak SE. Tip 2 diabetes mellitus'lu hastalarda rosiglitazon veya metformin tedavisinin leptin, total antioksidan kapasite, süperoksit dismutaz, paraoksonaz ve lipid peroksidasyonu üzerindeki etkisinin incelenmesi. Gazi Üniversitesi Sağlık Bilimleri Enstitüsü Biyokimya Ana Bilim Dalı, Ankara, 2009.

31. Hatipoğlu H. The effects of metformin+insülin glargine and metformin+sitagliptin therapies on oxidative stres, antioxidants, paraoxonase, aryl esterase in patients with type 2 diabetes mellitus. Internal Medicine Speciality Thesis. Internal Medicine Department of Medical School of Harran University, Şanlıurfa, Turkey, 2010.

32. Ghavimi H, Sheidaei S, Vaez H, Zolali E, Asgharian P, Hamishehkar H. Metformin-attenuated sepsis-induced oxidative damages: a novel role for metformin. Iran J Basic Med Sci. 2018;21(5):469-475.

33. Dogan Turacli I, Candar T, Yuksel EB, Kalay S, Oguz AK, Demirtas S. Potential effects of metformin in DNA BER system based on oxidative status in type 2 diabetes. Biochimie. 2018;154:62-68.

34. Bartosz G. Non-enzymatic antioxidant capacity assays: Limitations of use in biomedicine. Free Radic Res. 2010;44(7):711-720.

35. Zhang Y, Xie YJ, Meng DD, Zhang HH, Chen H, Liu E. Clinical study of treatment switching from premixed insulin to basal insulin combined with oral hypoglycemic drugs in patients with type 2 diabetes. Diabetol Metab Syndr. 2014;6(1):37.

36. Scioli MG, Storti G, D'Amico F, Rodríguez Guzmán R, Centofanti F, Doldo E, et al. Oxidative stress and new pathogenetic mechanisms in endothelial dysfunction: potential diagnostic biomarkers and therapeutic targets. J Clin Med. 2020;9(6):1995.

37. Cooper JN, Buchanich JM, Youk A, Brooks MM, Barinas-Mitchell E, Conroy MB, et al. Reductions in arterial stiffness with weight loss in overweight and obese young adults: potential mechanisms. Atherosclerosis. 2012;223(2):485-490.

38. Vlachopoulos C, Alexopoulos N, Stefanadis C. Diabetes mellitus and aorta: does size matter? Cardiology. 2009;112(2):135-137.

39. Miao X, Wang Y, Sun J, Sun W, Tan Y, Cai L, et al. Zinc protects against diabetes-induced pathogenic changes in the aorta: roles of metallothionein and nuclear factor (erythroid-derived 2)-like 2. Cardiovasc Diabetol. 2013;12:54.

40. Redheuil A, Yu WC, Wu CO, Mousseaux E, de Cesare A, Yan R, et al. Reduced ascending aortic strain and distensibility: earliest manifestations of vascular aging in humans. Hypertension. 2010;55(2):319-326.

41. Jensen MT, Fung K, Aung N, Sanghvi MM, Chadalavada S, Paiva JM, et al. Changes in cardiac morphology and function in individuals with diabetes mellitus: the UK biobank cardiovascular magnetic resonance substudy. Circ Cardiovasc Imaging. 2019;12(9):e009476.

42. Buczyńska A, Sidorkiewicz I, Krętowski AJ, Adamska A. Examining the clinical relevance of metformin as an antioxidant intervention. Front Pharmacol. 2024;15:1330797.

43. Kaya MG, Calapkorur B, Karaca Z, Yildirim S, Celik A, Akpek M, et al. The effects of treatment with drospirenone/ethinyl oestradiol alone or in combination with metformin on elastic properties of aorta in women with polycystic ovary syndrome. Clin Endocrinol (Oxf). 2012;77(6):885-892.

44. Bjornstad P, Schäfer M, Truong U, Cree-Green M, Pyle L, Baumgartner A, et al. Metformin improves insulin sensitivity and vascular health in youth with type 1 diabetes mellitus. Circulation. 2018;138(25):2895-2907.

45. Dallak M, Haidara MA, Bin-Jaliah I, Eid RA, Amin SN, Abdel Latif NS, et al. Metformin suppresses aortic ultrastrucural damage and hypertension induced by diabetes: a potential role of advanced glycation end products. Ultrastruct Pathol. 2019;43(4-5):190-198.

46. Sena CM, Matafome P, Louro T, Nunes E, Fernandes R, Seiça RM. Metformin restores endothelial function in aorta of diabetic rats. Br J Pharmacol. 2011;163(2):424-437.

47. Anderson JJA, Couper JJ, Giles LC, Leggett CE, Gent R, Coppin B, et al. Effect of metformin on vascular function in children with type 1 diabetes: a 12-month randomized controlled trial. J Clin Endocrinol Metab. 2017;102(12):4448-4456.

48. Petrie JR, Chaturvedi N, Ford I, Brouwers MCGJ, Greenlaw N, Tillin T, et al; REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2017;5(8):597-609. Erratum in: Lancet Diabetes Endocrinol. 2017;5(8):e5. Erratum in: Lancet Diabetes Endocrinol. 2017;5(11):e7.

49. Gordin D, Saraheimo M, Tuomikangas J, Soro-Paavonen A, Forsblom C, Paavonen K, et al. Insulin exposure mitigates the increase of arterial stiffness in patients with type 2 diabetes and albuminuria: an exploratory analysis. Acta Diabetol. 2019;56(11):1169-1175.

50. Fu J, Yu MG, Li Q, Park K, King GL. Insulin's actions on vascular tissues: physiological effects and pathophysiological contributions to vascular complications of diabetes. Mol Metab. 2021;52:101236.

51. Silvares RR, Pereira EN, Flores EE, Estato V, Reis PA, Silva IJ, et al. Combined therapy with metformin and insulin attenuates systemic and hepatic alterations in a model of high-fat diet-/streptozotocin-induced diabetes. Int J Exp Pathol. 2016;97(3):266-277.

52. Lloyd S, Brocks C, Chatham JC. Differential modulation of glucose, lactate, and pyruvate oxidation by insulin and dichloroacetate in the rat heart. Am J Physiol Heart Circ Physiol. 2003;285(1):H163-H172.

53. Mannucci E, Targher G, Nreu B, Pintaudi B, Candido R, Giaccari A, et al; SID-AMD Joint Panel for Italian Guidelines on Treatment of Type 2 Diabetes. Effects of insulin on cardiovascular events and all-cause mortality in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2022;32(6):1353-1360.

54. Schernthaner G, Brand K, Bailey CJ. Metformin and the heart: Update on mechanisms of cardiovascular protection with special reference to comorbid type 2 diabetes and heart failure. Metabolism. 2022;130:155160.

55. Park K, Li Q, Evcimen ND, Rask-Madsen C, Maeda Y, Maddaloni E, et al. Exogenous insulin infusion can decrease atherosclerosis in diabetic rodents by improving lipids, inflammation, and endothelial function. Arterioscler Thromb Vasc Biol. 2018;38(1):92-101.

ORIGINAL RESEARCH

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Evaluation of the Efficacy of Tocilizumab in Cytokine Release Syndrome in Patients with COVID-19 (SARS-CoV-2) Pneumonia Followed in the Intensive Care Unit

Yoğun Bakım Ünitesinde Takip Edilen COVID-19 (SARS-CoV-2) Pnömonili Hastalarda Sitokin Release Sendromunda Tociluzimab Kullanımının Etkinliğinin Değerlendirilmesi

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Abstract

Objective: The global severe acute respiratory syndrome-coronavirus-2 pandemic, which emerged in 2019, has resulted in severe complications in approximately 5% of infected individuals, leading to mortality due to respiratory failure, shock, or multiple organ dysfunction. Mortality is primarily attributed to excessive hyperinflammatory response-induced alveolar damage, which subsequently progresses to severe acute respiratory distress syndrome. Tocilizumab, a monoclonal antibody targeting the interleukin-6 receptor, has been utilized in the management of cytokine release syndrome (CRS) and is hypothesized to mitigate alveolar hyperinflammation, thereby reducing disease severity.

Method: This retrospective study analyzed 76 patients diagnosed with coronavirus disease-2019 (COVID-19) pneumonia and developing CRS in the intensive care unit. The patients were divided into two groups: 39 patients who received tocilizumab (Group T) and 37 patients who did not receive tocilizumab (Group C). The primary objective of the study was to assess the effect of tocilizumab on the PaO_2/FiO_2 ratio in critically ill COVID-19 pneumonia patients requiring mechanical ventilatory support. The secondary objective was to evaluate changes in inflammatory and

Öz

Amaç: 2019 yılında tüm dünyada ortaya çıkan şiddetli akut solunum yolu sendromu-koronavirüs-2'ye bağlı pandemi sonrası enfekte bireylerin %5'inde solunum yetmezliği, şok veya multiorgan yetmezliğine bağlı mortalite geliştiği bilinmektedir. Mortalite, çoğunlukla aşırı hiperenflamatuvar yanıta bağlı alveoler hasar ve ardından gelişen ciddi akut solunum sıkıntısı sendromu tablosuna bağlı olarak gelişmektedir. Tocilizumab sitokin salınım sendromunda (CRS) kullanılan bir monoklonal antikordur. Alveoler hiperenflamasyonu azaltarak hastalığın şiddetini azalttığı düşünülmektedir.

Yöntem: Bu çalışmada, yoğun bakım ünitesinde 18-80 yaş arası koronavirüs hastalığı-2019 (COVID-19) pnömonisi tanısı almış hastalar retrospektif olarak incelendi. CRS gelişen toplam 76 hasta çalışmaya dahil edildi; 39 hasta tocilizumab uygulanan Grup T, 37 hasta ise tocilizumabın temin edilemediği dönemin kayıtlarından elde edilen kontrol grubu (Grup C) olmak üzere iki gruba ayrıldı. Bu çalışmanın primer amacı yoğun bakımda mekanik ventilatör desteği altında takip edilen COVID-19 pnömonili, CRS gelişen bireylerde interlökin-6 reseptör blokörü tocilizumabın kullanımının PaO_2/FiO_2 oranı üzerine olan etkisini

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Abstract

coagulation biomarkers between the groups at different time points during intensive care follow-up.

Results: Patients who received tocilizumab demonstrated a significant improvement in the PaO_2/FiO_2 ratio on the seventh day of follow-up. In addition, C-reactive protein (CRP) levels showed a statistically significant reduction on the third and seventh days, while fibrinogen levels significantly decreased on the seventh day. A notable increase in lymphocyte count was also observed on the seventh day.

Conclusion: In critically ill COVID-19 pneumonia patients requiring mechanical ventilatory support, tocilizumab administration was found to be beneficial in attenuating alveolar damage and oxygenation impairment associated with CRS. The significant improvement in the PaO_2/FiO_2 ratio, along with favorable changes in inflammatory and coagulation biomarkers such as CRP, fibrinogen, and lymphocyte count, suggests that tocilizumab may play a therapeutic role in the management of severe COVID-19 cases.

Keywords: COVID-19 pneumonia, cytokine release syndrome, cytokine storm, SARS-CoV-2, tocilizumab

Öz

değerlendirmektir. Sekonder amacı ise, yoğun bakım takibinin 1., 3., 7., 14. ve 28. günlerinde gruplar arasında CRP, fibrinojen ve lenfosit sayısı biyobelirteçlerini karşılaştırmaktır.

Bulgular: Tocilizumab uygulanan hastalarda, 7. günde PaO_2/FiO_2 oranında anlamlı iyileşme; 3. ve 7. günlerde CRP değerlerinde anlamlı düşüş, 7. günde fibrinojen değerlerinde anlamlı düşüş olduğu ve 7. günde lenfosit sayısında anlamlı yükselme olduğu görüldü.

Sonuç: Yoğun bakımda mekanik ventilatör desteği gerektiren şiddetli COVID-19 pnömonili hastalarda, tocilizumab uygulamasının CRS'nin yol açtığı alveoler hasar ve oksijenasyon bozukluğunu düzeltmede yararlı olduğu görülmüştür. PaO_2/FiO_2 oranında anlamlı iyileşmeyle beraber; CRP, fibrinojen, lenfosit sayısı gibi mortalite ile ilişkili biyobelirteçlerin de olumlu yönde değiştiği görüldü.

Anahtar kelimeler: COVID-19 pnömoni, SARS-CoV-2, sitokin fırtınası, sitokin salınım sendromu, tocilizumab

Introduction

The pandemic caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which emerged in December 2019, has led to serious health problems worldwide. Although most individuals infected with SARS-CoV-2 exhibit mild symptoms, approximately 14% of cases progress to severe disease, while 5% develop respiratory failure, shock, or multiorgan failure-related mortality (1).

Difficulties in controlling viral infections and the emergence of mutant viruses continue to pose significant health challenges for millions of people. In most cases, the host immune system effectively activates both innate and adaptive responses, leading to the release of interferons (IFN-α, IFN-β, IFN-γ) and other cytokines, thereby facilitating viral clearance and tissue repair to control the infection (2,3). However, in severe coronavirus disease-2019 (COVID-19) cases, an abnormal host immune response leads to a cytokine storm characterized by the induction of interleukin (IL)-1β, IL-2, IL-6, tumor necrosis factor-α, monocyte chemoattractant protein 1, as well as CD4+ and CD8+ T-cells, and natural killer T-cells (4-7).

In severe COVID-19 patients, cytokine release syndrome (CRS), also referred to as COVID-19 related cytokine storm, is characterized by an excessive and dysregulated immune response. According to modified Temple criteria, CRS can be identified by worsening respiratory symptoms along with typical bilateral lung infiltrates on imaging, elevated inflammatory markers such as C-reactive protein (CRP >4.6 mg/dL) and ferritin (> 250 ng/mL), and a marked increase in IL-6 ≥10 times the upper limit of normal, confirmed on two separate occasions. Furthermore, alternative laboratory-based diagnostic criteria for CRS include ferritin levels exceeding 2000 ng/mL in combination with at least one additional elevated inflammatory marker (e.g., CRP, IL-6, D-dimer), or the presence of abnormalities in at least four inflammatory markers. These combined clinical and laboratory findings support the diagnosis of CRS associated with severe COVID-19 infection (8-10).

The release of IL-6 and IL-1 accelerates the recruitment of neutrophils and cytotoxic-cells to affected tissues, while the production of reactive oxygen species and leukotrienes contributes to acute lung injury and multiple organ damage in severe cases (2). Elevated IL-6 serum levels have been associated with COVID-19 disease severity, SARS-CoV-2 RNA levels, and poorer prognosis (11). In this context, early detection of cytokine storm and identification of immune dysregulation before progression to acute respiratory distress syndrome (ARDS) are crucial in reducing the need for mechanical ventilation. Experience with macrophage activation syndrome and CRS suggests that early interventions in the course of the disease may prevent irreversible tissue damage (12).

Excessive IL-6 production during infections and tissue injury activates the complement and coagulation systems, leading to vascular leakage (13). Additionally, IL-6 activation is considered a key factor in the progression of COVID-19 pneumonia to ARDS and hyperinflammation

(14). Pathological analyses of patients who succumbed to SARS-CoV-2 infection have revealed elevated levels of proinflammatory cytokines (2,7). This phenomenon is believed to contribute to mortality in severe COVID-19 cases by impairing gas exchange due to increased alveolar exudates. In COVID-19 pneumonia, CRS-induced hyperinflammation has been associated with poor prognosis and mortality, as evidenced by elevated IL-6, CRP, ferritin, fibrinogen, D-dimer, lymphopenia, LDH, and renal/liver dysfunction (15,16).

Given the central role of IL-6 in the cytokine storm associated with COVID-19, the humanized monoclonal antibody tocilizumab, which targets the IL-6 receptor, has been utilized to treat patients developing cytokine storm. If left untreated, cytokine storm can progress to respiratory failure, cardiovascular collapse, multiple organ dysfunction, and death.

The aim of this study is to evaluate the effect of tocilizumab on the PaO_2/FiO_2 ratio in patients with COVID-19 pneumonia receiving mechanical ventilatory support in the intensive care unit (ICU), thereby contributing to the advancement of treatment strategies for COVID-19. Additionally, the study aims to assess the clinical and laboratory parameters as well as the impact of IL-6 receptor blockade with tocilizumab on mortality in patients who develop CRS.

Materials and Methods

This study aimed to retrospectively evaluate patients aged 18-80 years who were followed in the ICU between March 23, 2020, and June 1, 2020. The patients had either a confirmed SARS-CoV-2 infection detected by real-time-polymerase chain reaction (RT-PCR) or were PCR-negative but diagnosed with COVID-19 pneumonia based on radiological and clinical findings. They subsequently developed CRS. During this period, 37 patients who developed a cytokine storm but could not receive cilizumab due to its unavailability were compared with 39 patients who received tocilizumab after its procurement by the hospital.

This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital on June 2, 2020 (approval no: 95). Written informed consent was obtained from all patients or their legal representatives before the administration of tocilizumab. This study was conducted in accordance with the Helsinki Declaration.

Patients included in the study were those who were in the ICU within the first 24 hours of follow-up and were experiencing worsening respiratory distress and persistent hypoxia. These patients were receiving invasive or non-invasive mechanical ventilatory support, had peripheral oxygen saturation <94% or a PaO_2/FiO_2 ratio <200 mmHg, with and bilateral pulmonary infiltrations detected on chest radiography. Patients also exhibited elevated levels of inflammatory and coagulation markers, including CRP (mg/L), ferritin (ng/mL), D-dimer (µg/mL), fibrinogen (mg/dL), and lactate dehydrogenase (LDH) (U/L). They had lymphopenia, negative procalcitonin levels, and no signs of secondary infection. Based on these positive laboratory parameters, clinical findings, and radiological evidence, patients diagnosed with CRS were included in the study.

Patients with severe heart failure, advanced chronic obstructive pulmonary disease (COPD), suspected or confirmed pregnancy or secondary bacterial infections, tuberculosis diagnosis or suspicion, gastrointestinal perforation, hematological malignancy, or neutropenia were excluded from the study. Additionally, patients with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding three times the upper laboratory reference limit and those who died within the first 24 hours of ICU admission were not included.

Demographic information, including age, gender, and comorbidities as well as data on invasive or non-invasive mechanical ventilation (NIV) cytokine storm-related inflammatory markers (ferritin, D-dimer, fibrinogen, CRP, AST, ALT, LDH, platelet count, lymphocyte count, and leukocyte count), and oxygenation status (PaO_2/FiO_2 ratio) was retrospectively recorded in an electronic database. These parameters were documented on ICU admission, which was considered day 1, and subsequently on days 3, 7, 14, and 28.

All treatments were administered in accordance with the guidelines of the Turkish Ministry of Health's Scientific Advisory Board. Patients received favipiravir 400 mg twice daily for five days, 400 mg subcutaneous low molecular weight heparin twice daily, and 400 mg of hydroxychloroquine daily. In patients developing cytokine storm, dexamethasone 6 mg was administered intravenously for five days, followed by gradual dose tapering. In cases where procalcitonin levels were elevated later in the ICU stay, the infectious diseases department was consulted, and antimicrobial therapy with piperacillin-tazobactam or meropenem/vancomycin was initiated as needed. Supportive care measures, including high-flow nasal oxygen (HFNO) therapy with a non-rebreather mask,

delivering oxygen at a flow rate of 30-60 L/min and an adjustable inspiratory oxygen fraction to maintain targeted oxygen saturation, non-invasive or invasive mechanical ventilation (IMV), inotropic support, and renal replacement therapy, were provided based on clinical indications.

Tocilizumab became available in the hospital on April 10, 2020, and was administered intravenously to eligible patients. The dose was determined as 8 mg/kg of body weight, with a maximum dose of 800 mg. A second dose of 8 mg/kg was administered 24 hours later if deemed clinically necessary. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug were designated as Group C.

For all patients, CRP, D-dimer, ferritin, fibrinogen, lymphocyte count, leukocyte count, platelet count, AST, ALT, LDH, and PaO_2/FiO_2 values were recorded on ICU admission (day 1) and subsequently on days 3, 7, 14, and 28. The primary objective of this study was to compare changes in the PaO_2/FiO_2 ratio between groups with and without tocilizumab administration, assessing the efficacy of tocilizumab in improving oxygenation by controlling cytokine storm in COVID-19 patients. The secondary objective was to evaluate changes in inflammatory and coagulation biomarkers, including CRP, ferritin, D-dimer, fibrinogen, lymphocyte count, leukocyte count, platelet count, AST, ALT, and LDH, at specific time points during intensive care follow-up on days 1, 3, 7, 14, and 28.

Statistical Analysis

Data analysis was performed using SPSS (version 17.0 for Windows; IBM, Armonk, NY, USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Parametric tests (Student's t-test) were used for normally distributed data, while non-parametric tests (Mann-Whitney U test) were applied for non-normally distributed data. Repeated measurements within groups were analyzed using Repeated Measures ANOVA with Bonferroni post-hoc correction or the Friedman test. Categorical variables were analyzed using the chi-square test. Results were presented as mean ± standard deviation, and a p-value <0.05 was considered statistically significant.

Results

During this period, a total of 318 patients were admitted to the ICU. CRS was suspected in 109 patients. Among these, 33 patients who died within the first 24 hours of ICU admission were excluded from the study. A total of 76 patients who developed CRS were included and analyzed. Of these, 39 patients received tocilizumab (Group T), while 37 patients formed the control group (Group C), which corresponds to the period when tocilizumab was not available.

The demographic characteristics of the patients, including age and gender, are presented in Table 1, with no significant differences observed between the groups. However, comorbidities such as diabetes mellitus, hypertension, COPD, hypothyroidism, and coronary artery disease were found to be more prevalent in the control group (Group C).

Regarding ventilatory support among ICU-admitted patients, in Group T, 16 out of 39 patients received HFNO in combination with NIV, and 26 patients required IMV. In the control group (Group C, n=37), 11 patients received HFNO + NIV, and 23 patients were treated with IMV.

No statistically significant difference was observed in 28-day mortality between the groups (p=0.063).

Regarding inflammatory markers, CRP, mg/L levels were significantly lower in patients who received tocilizumab (Group T) on days 3 and 7, compared to the control group. Due to high mortality rates, statistical analysis could not be performed for days 14 and 28 (Table 2).

No significant difference was found in D-dimer (µg/L) levels between the groups across different time points (Table 3).

When comparing ferritin (ng/mL) levels, a significant difference was observed between the groups on day 3 (Table 3). Fibrinogen (mg/dL) levels showed a statistically significant difference between the groups on days 1 and 7, while intragroup analyses revealed significant changes over time in both groups (Table 3).

In hemogram evaluations, lymphocyte count ($\times 10^3/\mu L$) was significantly higher in Group T on day 7 (Table 4). No significant difference was detected between the groups in white blood cell (white blood cell, $\times 10^3/\mu L$) counts on days 1, 3, and 7 (Table 4). However, platelet count ($\times 10^3/\mu L$) was significantly higher in Group T on days 1 and 3 (Table 4).

Regarding liver enzymes, AST (U/L) and ALT (U/L) levels were significantly higher in Group T on day 7 (Table 5). Additionally, LDH, U/L levels were significantly higher in Group T on days 1 and 3 (Table 5).

When comparing the PaO_2/FiO_2 ratio, used to assess oxygenation, a statistically significant difference was observed between the groups on day 7. In repeated intragroup measurements, the PaO_2/FiO_2 ratio in Group T on day 7 was significantly higher than on days 1 and 3 (Table 6).

Table 1. Comparison of demographic data between groups

	Group T n=39	Group C n=37	p
Age	60.51±11	64.30±10	0.1
Gender (M/F)	29/10	22/15	0.17
Comorbidity (present/absent)	22/17	31/6	**0.009**
Mortality (deceased/discharged)	17/22	24/13	0.063
HFNO/non-invasive mechanical ventilation	16 (41%)	11 (29.7%)	0.30
Invasive mechanical ventilation	23 (59%)	26 (70.3%)	

Values are presented as mean ± standard deviation for continuous variables and as number (percentage) for categorical variables. Between-group comparisons were performed using Student's t-test for continuous variables and the chi-square test for categorical variables. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug but received standard therapy were designated as Group C. HFNO: High flow nazal oxygen. p-value <0.05 was considered statistically significant

Table 2. Comparison of CRP levels between groups

	Group T	Group C	p
CRP day 1	201.17±91.17	188.31±154.87	0.659
CRP day 3	122.95±91.57	208.14±133.05	**0.002**
CRP day 7	34.12±40.64	204.46±144.69	**<0.001**
p (ANOVA)	**<0.001**	0.662	

Values are presented as mean ± standard deviation. Between-group comparisons at each time point were performed using Student's t-test. Repeated measurements within groups were analyzed using repeated measures ANOVA with Bonferroni post-hoc correction. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug and received standard therapy were designated as Group C. CRP: C-reactive protein. The normal range of CRP is <5 mg/L. A p-value <0.05 was considered statistically significant

Table 3. Comparison of D-dimer, ferritin, and fibrinogen levels between groups on days 1, 3, and 7

	Group T	Group C	p
D-dimer day 1	5451.19±16009.52	6778.86±20436.26	0.753
D-dimer day 3	7625.90±19024.20	5034.30±6256.34	0.433
D-dimer day 7	5723.38±9349.69	5728.78±6506.83	0.998
Ferritin day 1	1043.96±864.43	724.02±1632.52	0.287
Ferritin day 3	971.71±696.12	526.23±431.34	**0.001**
Ferritin day 7	821.09±1316.29	590.76±570.25	0.330
Fibrinogen day 1	454.87±116.70	350.97±94.52	**<0.001**
Fibrinogen day 3	380.08±95.09	412.86±97.00	0.141
Fibrinogen day 7	275.92±79.72	451.22±129.92	**<0.001**

Values are presented as mean ± standard deviation. Between-group comparisons at each time point were performed using Student's t-test. Repeated measurements within groups were analyzed using repeated measures ANOVA with Bonferroni post-hoc correction. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug and received standard therapy were designated as Group C. Ranges of the normal values of the parameters (D-dimer <500 µg/L, fibrinogen: 200-400 mg/dL). A p-value <0.05 was considered statistically significant

Table 4. Comparison of lymphocyte, leukocyte, and platelet levels between groups on days 1, 3, and 7

	Group T	Group C	p
Lymphocyte: day 1	866.92±408.20	905.95±585.25	0.736
Lymphocyte: day 3	800.51±440.01	788.65±462.14	0.909
Lymphocyte: day 7	1304.97±886.78	818.11±570.69	**0.006**
Leukocyte day 1	12421.51±15876.93	10326.22±5336.06	0.448
Leukocyte day 3	13025.67±23712.04	10554.59±6268.03	0.541
Leukocyte day 7	11817.18±6323.41	12464.32±6363.09	0.658
Platelet day 1	307051.28±143657.11	207432.43±83616.69	**<0.001**
Platelet day 3	340102.56±143884.62	226081.08±81576.61	**<0.001**
Platelet day 7	304461.54±133274.51	261513.51±85491.59	0.101

Values are presented as mean ± standard deviation. Between-group comparisons at each time point were performed using Student's t-test. Repeated measurements within groups were analyzed using repeated measures ANOVA with Bonferroni post-hoc correction. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug and received standard therapy were designated as Group C. Ranges of the normal values for the parameters are: leukocytes: 4.4000-12.000/µL; lymphocytes: 1.500-5.000/µL; platelets: 150.000-400.000/L. A p-value <0.05 was considered statistically significant

Table 5. Comparison of AST, ALT, and LDH levels between groups on days 1, 3, and 7

	Group T	Group C	p
AST day 1	99.51±256.89	56.43±65.45	0.326
AST day 3	146.77±586.91	43.54±23.93	0.289
AST day 7	79.13±70.12	43.84±21.88	**0.005**
ALT day 1	58.87±84.80	40.16±48.12	0.244
ALT day 3	81.44±199.41	31.65±27.44	0.137
ALT day 7	95.00±76.34	32.57±21.16	**<0.001**
LDH day 1	593.92±197.16	436.11±211.96	**0.001**
LDH day 3	623.82±272.10	448.78±237.97	**0.004**
LDH day 7	550.41±189.97	507.22±311.40	0.465

Values are presented as mean ± standard deviation. Between-group comparisons at each time point were performed using Student's t-test. Repeated measurements within groups were analyzed using repeated measures ANOVA with Bonferroni post-hoc correction. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug and received standard therapy were designated as Group C. Ranges of the normal values of the parameters are AST <50 U/L, ALT <50 U/L, LDH <250 U/L. A p-value <0.05 was considered statistically significant.
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

Table 6. Comparison of P/F ratios between groups on days 1, 3, and 7

	Group T	Group C	p
P/F day 1	137.74±71.09	170.49±92.27	0.086
P/F day 3	171.05±67.82	170.67±78.76	0.982
P/F day 7	223.05±90.83	170.59±86.70	**0.012**
p (ANOVA)	**<0.001**	1.000	

Values are presented as mean ± standard deviation. Between-group comparisons at each time point were performed using Student's t-test. Repeated measurements within groups were analyzed using repeated measures ANOVA with Bonferroni post-hoc correction. Patients who received tocilizumab were classified as Group T, while those who did not receive the drug and received standard therapy were designated as Group C. P/F (PaO_2/FiO_2 ratio), PaO_2 (arterial oxygen pressure in mmHg), and FiO_2 (fraction of inspired oxygen). A p-value <0.05 was considered statistically significant

Discussion

In patients diagnosed with SARS-CoV-2 pneumonia and monitored in the ICU with severe hypoxia, the addition of tocilizumab to standard treatment in cases of CRS, was associated with a significant improvement in the PaO_2/FiO_2 ratio, a notable reduction in acute-phase reactants such as CRP and fibrinogen, and an increase in lymphocyte count compared to patients who received only standard treatment.

The primary cause of mortality in COVID-19 pneumonia is severe respiratory failure due to ARDS (17). Therefore, early identification of CRS through biomarkers and initiation of treatment before the progression of alveolar damage are crucial. The low survival rates in patients requiring mechanical ventilatory support highlight the necessity of early diagnosis and treatment strategies.

IL-6, a multifunctional inflammatory mediator, is believed to contribute to ARDS and interstitial pneumonia observed in severe COVID-19 cases. Blocking the IL-6 receptor is hypothesized to disrupt this cascade, thereby mitigating cytokine storm and preventing disease progression (17-22).

Patients with PCR-negative results who developed cytokine storm, were also included in the study for the diagnosis of COVID-19. Clinical, laboratory, and radiological data were evaluated comprehensively. Although RT-PCR testing is considered the gold standard for COVID-19 diagnosis, the literature reports a false-negative rate ranging from 30% to 70%. Therefore, patients with negative PCR results but clinical symptoms and laboratory findings consistent with COVID-19 (e.g., elevated IL-6, CRP, ferritin, D-dimer) were evaluated in terms of potential CRS. Indeed, a large cohort study conducted at Mount Sinai demonstrated that PCR-negative patients with clinical features compatible with COVID-19 exhibited elevated levels of proinflammatory cytokines and were at risk of developing CRS. These findings indicate that a negative PCR result does not rule out significant immune dysregulation, and that this patient group should also be carefully evaluated for hyperinflammation (23).

In this study, among 39 patients with severe COVID-19 pneumonia and persistent hypoxia who received tocilizumab in addition to standard treatment, 17 (43.6%) died. In the group receiving standard treatment alone, 24 out of 37 patients (70.6%) died. Although the standard treatment group had a higher prevalence of comorbidities, there was no significant difference in the mean age between the two groups. The higher mortality rate in the standard

treatment group may have been influenced by the greater burden of comorbidities. However, in the tocilizumab group, a rapid response and improvement in PaO_2/FiO_2 ratios were observed following treatment. Additionally, acute-phase reactants such as CRP, fibrinogen, and ferritin showed a decline starting from day 3. A significant increase in lymphocyte count was also detected in the tocilizumab group. Due to the unavailability of IL-6 test kits at the hospital where the study was conducted, IL-6 levels could not be measured in the patients, and therefore monitoring could not be used in the diagnosis of CRS.

A total of 56.4% (n=22) of the patients in the tocilizumab group, were discharged from the ICU to the ward, while in the standard treatment group (Group C), only 35% (n=13) were transferred from the ICU to the ward. These findings suggest that tocilizumab plays an active role in the management of CRS in COVID-19 pneumonia.

In the tocilizumab-treated patients, the PaO_2/FiO_2 ratio increased from 137 on day 1 to 223 on day 7. In contrast, no significant change was observed in the standard treatment group. This improvement was attributed to the reduction of cytokines responsible for alveolar exudate accumulation and alveolar damage, following tocilizumab administration. These findings suggest that tocilizumab treatment should be initiated in patients suspected of CRS before significant alveolar damage and exudate formation occur.

A meta-analysis of 3.377 patients with COVID-19 pneumonia demonstrated that IL-10, IL-6, and ferritin levels correlated with disease severity (18). The same study also reported that patients with severe or fatal disease exhibited thrombocytopenia and lymphopenia, along with atypical higher lymphocyte counts when compared to those with moderate disease who eventually recovered (8). Our study findings were consistent with those reported in that meta-analysis.

Mehta et al. (8) emphasized the importance of using inflammatory biomarkers such as erythrocyte sedimentation rate, decreased platelet count, and elevated ferritin levels to identify patients who might benefit from immunomodulatory therapies, including IL-6 inhibitors unlike that study, our findings revealed higher platelet counts. We believe that early identification of disease severity and progression through biomarkers can help guide early treatment strategies (15,16).

Capra et al. (24), in their retrospective study, reported, similarly to our study, that early administration of low-dose tocilizumab reduced hyperinflammation in the lungs and improved survival. However, unlike our study, they administered tocilizumab at an earlier stage. Their mortality rates were significantly lower than ours. In patients admitted to the ICU, inflammatory markers and coagulation parameters were at extremely high levels. Clinically, patients with severe respiratory distress were admitted to intensive care for monitoring. We believe that closer monitoring of patients in the earlier stages of their ICU stay for CRS could lead to better outcomes. In parallel with their findings, we also suggest that tocilizumab should be administered in the early stages and initiating treatment before the need for mechanical ventilation, following an increasing trend in acute-phase reactants, worsening respiratory distress, or a decrease in the PaO_2/FiO_2 ratio, could yield better results.

In recent years, several new drugs and supportive treatment approaches have been developed for the management of COVID-19; however, the effective treatment of severe cases—particularly those involving cytokine storm and associated ARDS—remains a significant clinical challenge. Complementary therapies such as traditional Chinese medicine have been reported to exert modulatory effects on cytokine release and may help prevent the progression to ARDS. Nevertheless, the current evidence in this area is still limited. Therefore, there is a need for more comprehensive, well-designed, and controlled clinical studies to evaluate the efficacy and safety of therapeutic strategies targeting severe hyperinflammatory responses related to COVID-19 (25-27).

Study Limitations

This study has several limitations. A more balanced distribution of comorbidities between the groups could have allowed for a more accurate analysis. The number of patients included was relatively small. Due to high mortality rates, analyses could not be performed on days 14 and 28. A larger study population could provide more meaningful results regarding mortality and other outcomes.

Conclusion

We believe that the use of tocilizumab in COVID-19 pneumonia has a positive impact on the clinical course of the disease. However, we consider it crucial to initiate treatment at an earlier stage, before the need for mechanical ventilatory support arises.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of University

of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital on June 2, 2020 (approval no: 95).

Informed Consent: Written informed consent was obtained from all patients or their legal representatives before tocilizumab administration.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M., Concept: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M., Design: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M., Data Collection or Processing: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M., Analysis or Interpretation: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M., Literature Search: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M., Writing: S.Ş., F.Ö., M.T., Ü.A.T., D.G.M.

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References

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA. 2020;324(8):782-793.
2. Vardhana SA, Wolchok JD. The many faces of the anti-COVID immune response. J Exp Med. 2020;217(6):e20200678.
3. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6):363-374.
4. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620-2629.
5. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71(15):762-768.
6. Nazerian Y, Ghasemi M, Yassaghi Y, Nazerian A, Hashemi SM. Role of SARS-CoV-2-induced cytokine storm in multi-organ failure: molecular pathways and potential therapeutic options. Int Immunopharmacol. 2022;113(Pt B):109428.
7. Zanza C, Romenskaya T, Manetti AC, Franceschi F, La Russa R, Bertozzi G, et al. Cytokine storm in COVID-19: immunopathogenesis and therapy. Medicina (Kaunas). 2022;58(2):144.
8. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034.
9. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368(6490):473-474.
10. Caricchio R, Gallucci M, Dass C, Zhang X, Gallucci S, Fleece D, et al; Temple University COVID-19 Research Group. Preliminary predictive criteria for COVID-19 cytokine storm. Ann Rheum Dis. 2021;80(1):88-95.
11. Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, et al. Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically Ill patients with coronavirus disease 2019. Clin Infect Dis. 2020;71(8):1937-1942.
12. Henderson LA, Canna SW, Schulert GS, Volpi S, Lee PY, Kernan KF, et al. On the alert for cytokine storm: immunopathology in COVID-19. Arthritis Rheumatol. 2020;72(7):1059-1063.
13. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy. 2016;8(8):959-970.
14. Lipworth B, Chan R, Lipworth S, RuiWen Kuo C. Weathering the cytokine storm in susceptible patients with severe SARS-CoV-2 infection. J Allergy Clin Immunol Pract. 2020;8(6):1798-1801.
15. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020;58(7):1021-1028.
16. Genç Moralar D, Turkmen AÜ, Gökçenoğlu H, Alcı N. Factors affecting mortality in COVID-19 patients in intensive care. Ulus Travma Acil Cerrahi Derg. 2022;28(9):1229-1237.
17. Hiti L, Markovič T, Lainscak M, Farkaš Lainščak J, Pal E, Mlinarič-Raščan I. The immunopathogenesis of a cytokine storm: the key mechanisms underlying severe COVID-19. Cytokine Growth Factor Rev. 2025;82:1-17.
18. Buonaguro FM, Puzanov I, Ascierto PA. Anti-IL6R role in treatment of COVID-19-related ARDS. J Transl Med. 2020;18(1):165.
19. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? J Transl Med. 2020;18(1):164.
20. Favalli EG, Caporali R. GM-CSF in the treatment of COVID-19: a new conductor in the pathogenesis of cytokine storm? Lancet Rheumatol. 2020;2(8):e448-e449.
21. King A, Vail A, O'Leary C, Hannan C, Brough D, Patel H, et al. Anakinra in COVID-19: important considerations for clinical trials. Lancet Rheumatol. 2020;2(7):e379-e381.
22. Monteleone G, Sarzi-Puttini PC, Ardizzone S. Preventing COVID-19-induced pneumonia with anticytokine therapy. Lancet Rheumatol. 2020;2(5):e255-e256.
23. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020;26(10):1636-1643.

24. Capra R, De Rossi N, Mattioli F, Romanelli G, Scarpazza C, Sormani MP, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med. 2020;76:31-35.

25. Yu Q, Zhou X, Kapini R, Arsecularatne A, Song W, Li C, et al. Cytokine storm in COVID-19: insight into pathological mechanisms and therapeutic benefits of chinese herbal medicines. Medicines 2024;11(7):14.

26. Yang L, Wang Z. Bench-to-bedside: innovation of small molecule anti-SARS-CoV-2 drugs in China. Eur J Med Chem. 2023;257:115503.

27. Tong L, Ma Z, Zhou Y, Yang S, Yang Y, Luo J, et al. Combination of Chinese herbal medicine and conventional western medicine for coronavirus disease 2019: a systematic review and meta-analysis. Front Med (Lausanne). 2023;10:1175827.

ORIGINAL RESEARCH

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Predictive Value of Naples Prognostic Score and CONUT Scores for Contrast-induced Acute Kidney Injury After Percutaneous Coronary Intervention in Acute Coronary Syndrome

Perkütan Koroner Girişim Uygulanan Akut Koroner Sendrom Hastalarında Kontrast İlişkili Akut Böbrek Hasarının Öngörülmesinde Naples ve CONUT Skorlarının Prediktif Değeri

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Abstract

Objective: Contrast-induced acute kidney injury (CI-AKI) is a significant complication in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). This study evaluates the predictive value of the Naples prognostic score (NPS) and controlling nutritional status (CONUT) score for CI-AKI risk.

Method: The data of 520 ACS patients who underwent PCI between January 2019 and December 2022 were retrospectively analyzed. Patients were stratified by NPS and CONUT scores, based on blood markers including serum albumin, cholesterol, and inflammatory cell counts. CI-AKI was defined as an acute post-contrast renal function decline. Logistic regression and ROC analyses assessed the predictive value of NPS and CONUT scores.

Results: CI-AKI occurred in 142 (27.3%) patients. Higher NPS and CONUT scores were significantly associated with increased CI-AKI risk (p<0.001). Multivariate analysis identified NPS and CONUT as independent predictors of CI-AKI (odds ratio: 0.060, p=0.002; odds ratio: 0.442, p=0.008). ROC analysis showed high predictive accuracy (AUC: 0.950 for NPS; AUC: 0.930 for CONUT).

Conclusion: NPS and CONUT scores effectively predict CI-AKI risk in ACS patients undergoing PCI. Their routine use may enhance risk stratification and preventive strategies.

Keywords: Acute coronary syndrome, contrast-associated acute kidney injury, CONUT score, Naples prognostic score, percutaneous coronary intervention

Öz

Amaç: Kontrast maddeye bağlı akut böbrek hasarı (CI-AKI), perkütan koroner girişim (PKG) uygulanan akut koroner sendrom (AKS) hastalarında önemli bir komplikasyondur. Bu çalışma, CI-AKI riskini öngörmede Naples prognostik skoru (NPS) ve beslenme durumunun kontrolü (CONUT) skorlarının prediktif değerini değerlendirmeyi amaçlamaktadır.

Yöntem: Ocak 2019-Aralık 2022 tarihleri arasında, PKG uygulanan 520 AKS hastasının verileri retrospektif olarak analiz edilmiştir. Hastalar, serum albümin, kolesterol ve enflamatuvar hücre sayımlarına dayalı olarak NPS ve CONUT skorlarına göre sınıflandırılmıştır. CI-AKI, kontrast sonrası böbrek fonksiyonlarında akut bozulma olarak tanımlanmıştır. Lojistik regresyon ve ROC analizleri ile NPS ve CONUT skorlarının prediktif değerleri değerlendirilmiştir.

Bulgular: CI-AKI, 142 hastada (%27,3) gelişmiştir. Yüksek NPS ve CONUT skorları, CI-AKI riskinde anlamlı artış ile ilişkili bulunmuştur (p<0,001). Çok değişkenli analizde, NPS ve CONUT skorları CI-AKI için bağımsız prediktörler olarak belirlenmiştir (olasılık oranı: 0,060, p=0,002; olasılık oranı 0,442, p=0,008). ROC analizi, yüksek prediktif doğruluk göstermiştir (NPS için AUC: 0,950; CONUT için AUC: 0,930).

Sonuç: NPS ve CONUT skorları, PKG uygulanan AKS hastalarında CI-AKI riskini etkili şekilde öngörebilmektedir. Bu skorların rutin kullanımı, risk sınıflandırması ve önleyici stratejilerin geliştirilmesine katkı sağlayabilir.

Anahtar kelimeler: Akut koroner sendrom, CONUT skoru, kontrast ilişkili akut böbrek hasarı, Naples prognostik skoru, perkütan koroner girişim

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Introduction

Contrast-induced acute kidney injury (CI-AKI) is characterized by a rapid decline in renal function that manifests subsequent to the administration of contrast media during diagnostic or interventional procedures (1). This pathological condition poses a considerable clinical obstacle, particularly in individuals diagnosed with acute coronary syndrome (ACS) who are subjected to percutaneous coronary intervention (PCI) (2). The incidence of CI-AKI results in prolonged hospitalization, increased healthcare costs, and correlates with heightened risks of morbidity and mortality (3,4). Conventional risk determinants for CI-AKI include pre-existing renal dysfunction, diabetes mellitus, and administration of substantial quantities of contrast agents (5-7). Preliminary evaluation of risk in individuals with ACS undergoing PCI has significant clinical relevance.

Inadequate or unbalanced nutrition, classified as malnutrition, has been correlated with unfavorable prognoses in conditions such as heart failure (HF), ACS, and various malignancies (8-10). Malnutrition and systemic inflammation are interrelated, and elevated inflammatory biomarkers are frequently observed during nutritional deficiency (11). Systemic inflammation is associated with increased concentrations of circulating biomarkers, including interleukin-6 (IL-6), C-reactive protein, and tumor necrosis factor-alpha (TNF-α) (12). Moreover, previous research has validated the relationship between inflammation-associated parameters and CI-AKI (13,14).

The Naples prognostic score (NPS) and controlling nutritional status (CONUT) scores were initially established as pivotal prognostic instruments for individuals diagnosed with malignancies; however, they have also been demonstrated to correlate with adverse outcomes in patients presenting with ACS and HF (15,16). Both scoring systems can be readily computed utilizing various biomarkers, including serum albumin concentration, total cholesterol levels, lymphocyte enumeration, neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR), which collectively reflect the inflammatory and nutritional status of the patient (17).

This study aimed to determine whether NPS and CONUT scores independently predict CI-AKI in ACS patients undergoing PCI. By incorporating inflammatory and nutritional assessments, the goal was to enhance early risk stratification. Our findings suggest that higher scores are associated with increased CI-AKI risk and may support individualized prevention strategies in clinical care.

Materials and Methods

Study Design and Population

A retrospective cohort study was conducted between January 2019 and December 2022. A total of 584 patients diagnosed with ACS and treated with PCI using contrast media were assessed. Individuals aged ≥18 years with a confirmed diagnosis of ACS who received contrast agents during PCI were included (18). Patients with epidermal growth factor receptor (eGFR) <30 mL/min/1.73 m², infectious diseases, active malignancy, cardiogenic shock, or pregnancy were excluded. Renal disease was defined as chronic kidney disease stage 4 or higher, corresponding to an eGFR <30 mL/min/1.73 m². In addition, 64 patients were excluded because of incomplete data (n=16), renal disease (n=17), cardiogenic shock (n=12), systemic infection (n=9), hepatic disorders (n=5), or malignancy (n=5), resulting in a final cohort of 520 patients (Figure 1).

This article contains human participants, so Institutional Review Board approval was required for this research article and was obtained from the İstanbul Medipol Mega Hospital's Local Ethical Committee (E-10840098-202.3.02-6647, date: 24.10.2024, number: 986).

Data Collection

Venous blood specimens were obtained prior to PCI at the time of admission by using conventional methods. Hematological parameters were measured within 30 minutes using an automated hematology system (BC-6800 Plus, Mindray, Shenzhen, China). The NLR and LMR were computed based on these indicators, whereas the established scoring framework derived the NPS (Table 1). The subjects were categorized into three separate cohorts predicated on their NPS: Group 0 (NPS score of 0), group 1 (NPS score of 1-2), and group 2 (NPS score of 3-4). The CONUT score, representative of nutritional status, was computed utilizing the serum albumin concentration, total cholesterol level, and lymphocyte enumeration (spanning from 0 to 12). CONUT scores categorized as 0-1, 2-4, and ≥5 correspond to normal nutritional status (group 0), mild nutritional deficiency (group 1), and moderate-to-severe malnutrition (group 2), respectively (19).

Procedures

All patients received dual antiplatelet therapy consisting of aspirin (300 mg loading dose, followed by 100 mg daily), combined with either prasugrel (60 mg loading, 10 mg maintenance), ticagrelor (180 mg loading, 90 mg twice daily), or clopidogrel (600 mg loading, 75 mg maintenance). An intravenous dose of 5,000 IU of

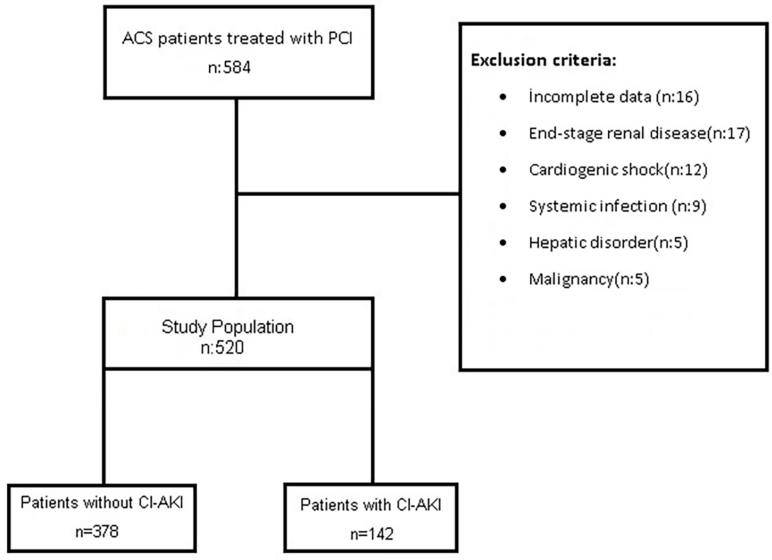

Figure 1. Flowchart illustrating the study process for evaluating the predictive value of the NPS and CONUT score for CI-AKI in ACS patients undergoing PCI

NPS: Naples prognostic score, CONUT: Controlling nutritional status, PCI: Percutaneous coronary intervention, CI-AKI: Contrast-induced acute kidney injury, ACS: Acute coronary syndrome

Table 1. Baseline characteristics of patients with and without CI-AKI

	Patients without CI-AKI n=378	Patients with CI-AKI n=142	p
Age (years)	58.54±11.5	62.09±13.4	0.003
Body mass index (kg/m^2)	27.3±3.5	27.8±3.4	0.158
Gender (female/male)	85/293	32/110	0.991
Systolic BP (mmHg)	131.08±17.73	127.03±17.79	0.048
Diastolic BP (mmHg)	79.07±12.27	77.58±12.32	0.295
Heart rate (bpm)	82.2±12.3	82.3±12.9	0.972
Smoking, n (%)	177 (46.8%)	49 (34.5%)	0.017
Diabetes, n (%)	163 (43.1%)	65 (45.8%)	0.587
Hypertension, n (%)	190 (50.3%)	90 (63.4%)	0.008
Hyperlipidemia, n (%)	87 (23%)	23 (16.2%)	0.09
Family history, n (%)	40 (10.6%)	9 (6.3%)	0.14
Previous ACS, n (%)	24 (6.3%)	15 (10.6%)	0.104
Previous stroke, n (%)	7 (1.9%)	5 (3.5%)	0.259
Peripheral artery disease, n (%)	6 (1.6%)	4 (2.8%)	0.363
ACS type (NSTE-ACS/STE-ACS)	174/204	57/85	0.228
No reflow after PCI n (%)	11 (2.9%)	12 (8.5%)	0.006
Mutivessel disease n (%)	154 (40.7%)	64 (45.1%)	0.373
LV ejection fraction (%)	45.8±8.5	43.6±9.4	0.012
Contrast volume (mL)	182.2±85.5	203.3±89.3	0.032
Duration of procedure (min)	38.8±16.1	42.5±15.5	0.044
Total stent length (mm)	29.9±14.3	30.1±14.2	0.866
Number of stents	1.34±0.56	1.39±0.6	0.406
In hospital ACEI or ARB use (n, %)	359 (95%)	113 (79.6%)	<0.001
In hospital statin use (n, %)	371 (98.1%)	139 (97.9%)	0.501

BP: Blood pressure, BPM: Beat per minute, ACS: Acute coronary syndrome, NSTE: Non-ST elevation, STE: ST elevation, PCI: Percutaneous coronary intervention, LV: Left ventricular, ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin receptor blockers, CVA: Cerebrovascular accident, CI-AKI: Contrast-induced acute kidney injury

unfractionated heparin was administered in line with European clinical guidelines (18). In addition, patients were initiated on beta-blockers, ACE inhibitors, and high-intensity statin therapy unless contraindications were present, consistent with international recommendations. Upon admission, two-dimensional echocardiography was performed as part of the routine cardiovascular assessment. PCI procedures were carried out via femoral or radial artery access using 6-7 Fr sheaths under standard interventional protocols.

Statistical Analysis

All statistical methodologies were executed utilizing IBM SPSS Statistics software (version 21.0; SPSS Inc., Chicago, IL, USA). The normal distribution of continuous variables was analyzed using the Shapiro-Wilk test. Data demonstrating a normal distribution were articulated as mean ± standard deviation, whereas non-normally distributed variables were outlined as median values along with interquartile ranges (IQR, 25^{th}-75^{th} percentiles). Between-group discrepancies were scrutinized employing either the independent samples t-test or Mann-Whitney U test, contingent upon data distribution. Categorical data were delineated as frequencies (percentages) and compared utilizing Pearson's chi-square test or Fisher's exact test when deemed appropriate. The discriminatory efficacy of NPS and CONUT scores for forecasting CI-AKI was examined through receiver operating characteristic (ROC) curve analysis, with area under the curve (AUC) values computed distinctly for each. To ascertain independent predictors of CI-AKI, multivariable logistic regression analysis was executed employing a stepwise backward elimination methodology. Findings were expressed as odds ratios (OR) accompanied by 95% confidence intervals (CI). A p-value <0.05 (two-tailed) was adjudged statistically significant.

Results

A cohort of 520 patients was included in the investigation, of whom 142 (27.3%) manifested CI-AKI after PCI. Baseline characteristics showed CI-AKI patients were older (62.1 vs. 58.5 years, p=0.003), had more hypertension (63.4% vs. 50.3%, p=0.008), and had lower left ventricular ejection fraction(43.6% vs. 45.8%, p=0.012). Significant differences were also noted in systolic blood pressure (127.0 vs. 131.1 mmHg, p=0.048) and contrast volume used (203.3 vs. 182.2 mL, p=0.032) (Table 1). CI-AKI patients exhibited lower hemoglobin (13.2 vs. 14.2 g/dL, p<0.001) and lymphocyte counts (1.7 vs. 2.4, p<0.001), along with higher white blood cell (11.9 vs. 10.8, p=0.004) and neutrophil counts (9.4 vs. 7.6, p<0.001). Baseline creatinine levels were elevated (0.99 vs. 0.85 mg/dL, p<0.001), while total cholesterol (154.4 vs. 194.3 mg/dL, p<0.001) and LDL cholesterol (95.9 vs. 112.9 mg/dL, p<0.001) were lower. There was a significant difference in NPS and CONUT scores between patients with and without CI-AKI. In the NPS, 94.4% of the patients with CI-AKI were in group 2, compared to only 8.7% of those without CI-AKI (p<0.001). Similarly, 38% of patients with CI-AKI had moderate-to-severe CONUT scores, while only 0.3% of those without CI-AKI were in this category (p<0.001) (Table 2).

Independent determinants of CI-AKI were determined using multivariate logistic regression analysis. Age was significant, with older patients showing a higher risk (OR: 0.832; 95% CI: 0.712-0.972; p=0.021), likely due to declining renal function with age. Baseline creatinine (OR: 0.001; 95% CI: 0.000-0.855; p=0.045) and lower GFR (OR: 0.868; 95% CI: 0.787-0.957; p=0.005) also emerged as significant predictors, emphasizing the role of renal function. A higher NPS significantly increased the risk of CI-AKI (OR: 0.060, 95% CI: 0.010-0.344, p=0.002). CONUT score similarly predicted CI-AKI (OR: 0.442; 95% CI: 0.242-0.805, p=0.008) (Table 3).

ROC analysis demonstrated excellent predictive accuracy for NPS (AUC: 0.950; 95% CI: 0.927-0.972) and CONUT scores (AUC: 0.930; 95% CI: 0.902-0.956), highlighting their utility in stratifying the risk of CI-AKI. These findings support their potential use in clinical decision-making (Figure 2).

Discussion

This investigation elucidated that NPS and CONUT indices serve as autonomous prognosticators of CI-AKI in individuals undergoing PCI following ACS. Our results underscore the pivotal significance of nutritional and inflammatory conditions in renal outcomes among these individuals, indicating that nutritional deficiency and systemic inflammation markedly elevate the likelihood of CI-AKI.

Prior examinations have illustrated that undernutrition constitutes a considerable risk determinant for unfavorable outcomes in individuals with cardiovascular ailments, particularly in subjects subjected to invasive procedures, such as PCI (20-22). Undernutrition has been correlated with deteriorated outcomes, encompassing CI-AKI, especially in individuals undergoing PCI (23). The CONUT score has been consistently correlated with elevated

Table 2. Laboratory variables of patients with and without CI-AKI

	Patients without CI-AKI n=378	Patients with CI-AKI n=142	p
Hemoglobin (g/dL)	14.2±1.8	13.2±2.5	<0.001
White blood cell count	10.8±3.4	11.9±4.6	0.004
Platelet count (10^9/L)	263.6±72.7	265.6±86.8	0.791
Neutrophils (10^9/L)	7.6±3.3	9.4±4.48	<0.001
Lymphocyte (10^9/L)	2.4±1.06	1.7±0.88	<0.001
Monocyte (10^9/L)	0.68±0.36	0.72±0.44	0.266
Baseline creatinine (mg/dL)	0.85±0.23	0.99±0.51	<0.001
Total cholesterol (mg/dL)	194.3±41	154.4±38	<0.001
LDL cholesterol (mg/dL)	112.9±39	95.9±35	<0.001
HDL cholesterol (mg/dL)	38.9±10.3	38.5±12.6	0.704
Triglyceride (mg/dL)	182.95±103	157.03±80	0.01
Glucose (mg/dL)	158.9±77.1	175.6±88.7	0.036
Hemoglobin A1c (%)	7.3±2.4	7.85±2.4	0.144
NPS	1.52±0.87	3.46±0.67	<0.001
NPS group 0	54 (14.3%)	0 (0%)	
NPS group 1	291 (77.0%)	8 (5.6%)	
NPS group 2	33 (8.7%)	134 (94.4%)	
CONUT score	0.65±0.96	3.82±1.88	<0.001
CONUT group 0	314 (83.1%)	14 (9.9%)	
CONUT group 1	63 (16.7%)	74 (52.1%)	
CONUT group 2	1 (0.3%)	54 (38%)	

LDL: Low density lipoprotein, HDL: High density lipoprotein, NPS: Naples prognostic score, CONUT: Controlling nutritional status, CI-AKI: Contrast-induced acute kidney injury

Table 3. Multivariate logistic regression analysis to determine the independent predictors of CI-AKI

Variable	p	Odds ratio	95% CI	
			Lower	Upper
Age	0.021	1.202	1.028	1.404
Systolic BP	0.527	0.981	0.924	1.041
Smoking	0.873	0.869	0.155	4.886
Hypertension	0.550	1.986	0.209	18.859
Hyperlipidemia	0.606	0.576	0.071	4.694
Final TIMI 3 flow	0.878	0.551	0.005	11.25
LVEF	0.920	0.994	0.891	1.110
Contrast volume	0.459	1.005	0.992	1.018
Duration of procedure	0.280	1.036	0.972	1.105
Hemoglobin	0.136	0.665	0.388	1.138
WBC count	0.750	1.044	0.800	1.364
LDL cholesterol	0.710	0.995	0.969	1.021
Triglyceride	0.540	0.997	0.986	1.007
Glucose	0.541	1.004	0.992	1.016
C-reactive protein	0.826	1.002	0.985	1.020
eGFR	0.005	0.868	0.787	0.957
Creatinine	0.045	14.84	1.170	188.30
NPS	0.002	16.692	2.909	95.778
CONUT score	0.008	2.265	1.243	4.126

BP: Blood pressure, TIMI: Thrombolysis in myocardial infarction, LVEF: Left ventricular ejection fraction, WBC: White blood cell, LDL: Low density lipoprotein, eGFR: Estimated glomerular filtration rate, NPS: Naples prognostic score, CONUT: Controlling nutritional status, CI-AKI: Contrast-induced acute kidney injury, CI: Confidence interval

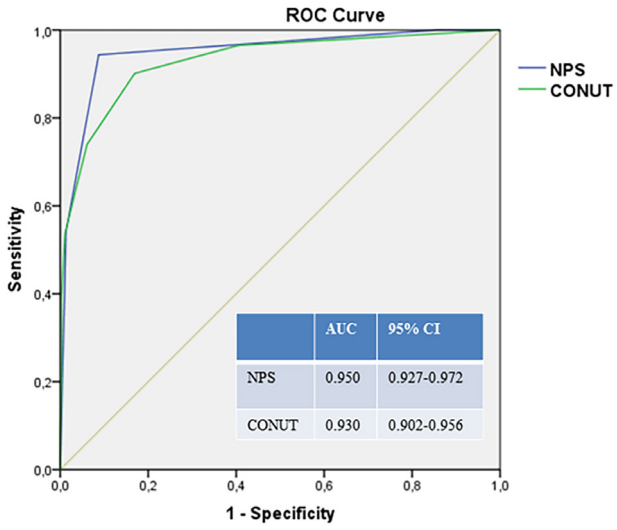

Figure 2. ROC curve analysis to determine predictive value of NPS and CONUT score for occurrence of CI-AKI

NPS: Naples prognostic score, CONUT: Controlling nutritional status, CI-AKI: Contrast-induced acute kidney injury, CI: Confidence interval, ROC: Receiver operating characteristic, AUC: Area under the curve

mortality and poorer clinical outcomes in patients with ACS. Our investigation corroborates these observations by demonstrating that individuals with heightened CONUT scores are at a markedly increased risk of developing CI-AKI. The underlying mechanisms may include reduced albumin levels, which lower oncotic pressure and compromise renal perfusion, and decreased lymphocyte counts, which reflect a weakened immune response and a state of systemic inflammation (1,23,24). The exact mechanism linking CONUT score to CI-AKI development is not yet fully understood; however, its individual components have been consistently associated with kidney damage. Among these, serum albumin, the highest component in the CONUT score, plays a vital role. Research has suggested that diminished serum albumin concentration functions as a notable prognostic marker for both acute renal impairment and mortality subsequent to cardiac interventions. A comprehensive meta-analysis elucidated that decreased albumin levels independently forecasted adverse outcomes in individuals undergoing cardiac surgical procedures or coronary interventions (25). Another investigation fortified its predictive significance by demonstrating that patients undergoing PCI who developed CI-AKI exhibited significantly lower serum albumin concentrations compared to those who did not (26).

Although elevated cholesterol levels have historically been identified as a significant cardiovascular risk determinant within the broader population, diminished cholesterol concentrations in individuals exhibiting renal impairment have been correlated with unfavorable clinical outcomes (27). One study showed that survival rates in AKI patients were significantly better in those with cholesterol levels above 150 mg/dL than in those with cholesterol levels below (28). Supplementary investigations have demonstrated that consistently diminished total cholesterol concentrations are significantly correlated with inferior survival prognoses in individuals suffering from chronic renal impairment (29). Another noteworthy facet of the CONUT score, the lymphocyte enumeration, serves as a parameter of immune functionality and systemic inflammation, which are crucial in the etiology of CI-AKI. Empirical research has demonstrated that diminished lymphocyte counts correlate with unfavorable prognosis in individuals diagnosed with coronary artery disease (30). Moreover, an elevated NLR, signifying an intensified inflammatory response, has been associated with an augmented risk of CI-AKI in individuals undergoing PCI (31). These findings suggest that the CONUT score not only encompasses nutritional deficiencies, but also represents the magnitude of the inflammatory load, thereby establishing it as a pivotal instrument for the early detection of patients predisposed to CI-AKI.

Inflammatory reactions and heightened prothrombotic states are fundamentally implicated in the pathogenesis of CI-AKI. Biomarkers that signify these inflammatory reactions may be pivotal for the detection of CI-AKI. The pathogenesis of CI-AKI is markedly linked with inflammatory mechanisms, featuring pro-inflammatory cytokines, including IL-6 and TNF-α, which are acknowledged as factors contributing to the exacerbation of renal endothelial dysfunction and impairment of renal autoregulation (32,33). Many studies have demonstrated a substantial correlation between inflammatory processes and AKI.

NPS is a novel scoring system designed to simultaneously evaluate inflammation and malnutrition. Initially introduced by Galizia et al. (34), it has been widely employed in assessing cancer prognosis, including gastric and esophageal squamous cell carcinoma. For example, a 2021 study demonstrated that NPS could independently predict survival in patients undergoing surgery for gastric cancer (35). Similarly, this scoring system has also been validated as an independent prognostic indicator in individuals undergoing surgical treatment for esophageal squamous cell carcinoma (36).

In cardiology, NPS has been recognized as a reliable indicator of in-hospital mortality in individuals with HF and has been linked to unfavorable outcomes in various chronic conditions (15). Among its components, NLR has been notably associated with long-term clinical endpoints such as infarct size, mortality, and prognosis in ACS (37). Additionally, NLR has demonstrated predictive value for CI-AKI in ACS patients undergoing PCI. Likewise, LMR has been identified as an independent predictor of CI-AKI in this population (38).

Unlike the CONUT score, which primarily assesses nutritional status, NPS comprehensively evaluates the inflammatory process. In accordance with preceding investigations, our results elucidated that individuals with elevated NPS values, signifying a heightened inflammatory load, are at a considerably increased susceptibility to CI-AKI. Elevated concentrations of inflammatory indicators have persistently been associated with poorer renal outcomes in subjects undergoing PCI, underscoring the pivotal role of inflammation in the pathogenesis of CI-AKI (39).

Our study highlights that nutritional and inflammatory markers independently predict CI-AKI risk and traditional factors, such as age, diabetes, and baseline renal function (40). While these conventional factors remain relevant, our findings suggest that incorporating nutritional and inflammatory assessments could provide more comprehensive risk stratification. Patients identified as high-risk based on NPS or CONUT scores could benefit from targeted preventive strategies such as aggressive hydration, minimizing contrast exposure, or nutritional interventions. Recent investigations have examined the capacity of preprocedural dietary assistance in diminishing the prevalence of CI-AKI, yielding encouraging outcomes.

In our cohort, the overall elevated HbA1c and glucose levels likely reflect the high prevalence of diabetes mellitus and the occurrence of acute stress hyperglycemia in patients presenting with ACS. Although mean glucose levels were significantly higher in the CI-AKI group in univariate analysis, they were not identified as independent predictors in multivariate logistic regression analysis. Stress hyperglycemia represents a neuroendocrine and inflammatory response to acute illness, leading to increased catecholamine and cortisol release, insulin resistance, and enhanced oxidative stress. These mechanisms may contribute to renal microvascular injury and functional impairment, thereby increasing susceptibility to CI-AKI regardless of baseline glycemic status (41).

Furthermore, amalgamating the NPS and CONUT indices into standard clinical praxis presents pragmatic benefits. Both indices are comparatively straightforward to compute utilizing routine hematological assessments and can be effortlessly integrated into extant risk prognostication frameworks. This would enable medical practitioners to discern patients at heightened risk with greater efficacy and execute prompt interventions to alleviate the likelihood of CI-AKI. The incorporation of these indices into established risk frameworks, such as the Mehran risk score, could further augment the precision of CI-AKI forecasting and refine clinical decision-making.

Study Limitations

Notwithstanding the advantages of our examination, which encompassed a relatively considerable sample size and the application of multivariate analysis to alleviate the impact of confounding variables, it is crucial to acknowledge several constraints. Primarily, the retrospective framework of the inquiry obstructs the capacity to establish causal connections between malnutrition, inflammation, and CI-AKI. Prospective studies are vital to authenticate these observations and to evaluate the efficacy of interventions aimed at enhancing nutritional status and diminishing inflammation. Furthermore, our study was restricted to a unique institution, which might limit the external validity of the outcomes to a heterogeneous population. Subsequent inquiries should strive to replicate these results in a more comprehensive multicenter framework.

Conclusion

In this study, evaluating the predictive power of NPS and CONUT scores in predicting the development of contrast nephropathy in patients with ACS undergoing PCI is a clinically important contribution. These scores offer a novel approach to risk stratification by incorporating nutritional and inflammatory statuses, which are increasingly recognized as important determinants of clinical outcomes. The routine use of these scores may guide preventive strategies and improve patient outcomes. Prospective studies are needed to confirm these results and to assess whether nutritional or anti-inflammatory strategies can help reduce the risk of CI-AKI.

Ethics

Ethics Committee Approval: Institutional Review Board approval was required for this research article and was obtained from the İstanbul Medipol Mega Hospital's Local Ethical Committee (E-10840098-202.3.02-6647, date: 24.10.2024, number: 986).

Informed Consent: The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.B., Concept: Ö.B., A.K., Design: Ö.B., Data Collection or Processing: Ö.B., A.K., Analysis or Interpretation: A.K., Literature Search: Ö.B., A.K., Writing: Ö.B.

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References

1. Tehrani S, Laing C, Yellon DM, Hausenloy DJ. Contrast-induced acute kidney injury following PCI. Eur J Clin Invest. 2013;43(5):483-490.
2. Xie W, Liang X, Lin Z, Liu M, Ling Z. Latest clinical evidence about effect of acetylcysteine on preventing contrast-induced nephropathy in patients undergoing angiography: a meta-analysis. Angiology. 2021;72(2):105-121.
3. He H, Chen XR, Chen YQ, Niu TS, Liao YM. Prevalence and predictors of contrast-induced nephropathy (CIN) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI): a meta-analysis. J Interv Cardiol. 2019;2019:2750173.
4. Azzalini L, Spagnoli V, Ly HQ. Contrast-induced nephropathy: from pathophysiology to preventive strategies. Can J Cardiol. 2016;32(2):247-255.
5. Goldenberg I, Matetzky S. Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies. CMAJ. 2005;172(11):1461-7141. Erratum in: CMAJ. 2005;173(10):1210.
6. Fan PC, Chen TH, Lee CC, Tsai TY, Chen YC, Chang CH. ADVANCIS score predicts acute kidney injury after percutaneous coronary intervention for acute coronary syndrome. Int J Med Sci. 2018;15(5):528-535.
7. McCullough PA, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, et al; CIN Consensus Working Panel. Risk prediction of contrast-induced nephropathy. Am J Cardiol. 2006;98(6A):27K-36K.
8. Yang Z, Qiao Y, Wang D, Yan G, Tang C. Association between inflammatory biomarkers and contrast-induced acute kidney injury in ACS patients undergoing percutaneous coronary intervention: a cross-sectional study. Angiology. 2024;75(9):831-840.
9. Li C, Xu L, Guan C, Zhao L, Luo C, Zhou B, et al. Malnutrition screening and acute kidney injury in hospitalised patients: a retrospective study over a 5-year period from China. Br J Nutr. 2020;123(3):337-346.
10. Goldfarb M, Lauck S, Webb JG, Asgar AW, Perrault LP, Piazza N, et al. Malnutrition and mortality in frail and non-frail older adults undergoing aortic valve replacement. Circulation. 2018;138(20):2202-2211.
11. Xiang X, Zhu X, Zhang L. Association of malnutrition with risk of acute kidney injury: a systematic review and meta-analysis. Int J Clin Pract. 2023;2023:9910718.
12. Dai L, Golembiewska E, Lindholm B, Stenvinkel P. End-stage renal disease, inflammation and cardiovascular outcomes. Contrib Nephrol. 2017;191:32-43.
13. Kurtul A, Gok M, Esenboga K. Prognostic nutritional index predicts contrast-associated acute kidney injury in patients with ST-segment elevation myocardial infarction. Acta Cardiol Sin. 2021;37(5):496-503.
14. Jiang H, Li D, Xu T, Chen Z, Shan Y, Zhao L, et al. Systemic immune-inflammation index predicts contrast-induced acute kidney injury in patients undergoing coronary angiography: a cross-sectional study. Front Med (Lausanne). 2022;9:841601.
15. Kılıç O, Suygun H, Mustu M, Ozpamuk Karadeniz F, Ozer SF, Senol H, et al. Is the Naples prognostic score useful for predicting heart failure mortality. Kardiologiia. 2023;63(3):61-65.
16. Saygi M, Tanalp AC, Tezen O, Pay L, Dogan R, Uzman O, et al. The prognostic importance of the Naples prognostic score for in-hospital mortality in patients with ST-segment elevation myocardial infarction. Coron Artery Dis. 2024;35(1):31-37.
17. Yang Q, Chen T, Yao Z, Zhang X. Prognostic value of pre-treatment Naples prognostic score (NPS) in patients with osteosarcoma. World J Surg Oncol. 2020;18(1):24.
18. Correction to: 2023 ESC Guidelines for the management of acute coronary syndromes: developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J. 2024;45(13):1145.
19. Takahashi T, Watanabe T, Otaki Y, Kato S, Tamura H, Nishiyama S, et al. Prognostic significance of the controlling nutritional (CONUT) score in patients with acute coronary syndrome. Heart Vessels. 2021;36(8):1109-1116.
20. Wada H, Dohi T, Miyauchi K, Jun S, Endo H, Doi S, et al. Relationship between the prognostic nutritional index and long-term clinical outcomes in patients with stable coronary artery disease. J Cardiol. 2018;72(2):155-161.
21. Weisbord SD, Palevsky PM, Kaufman JS, Wu H, Androsenko M, Ferguson RE, et al; PRESERVE Trial Investigators. Contrast-associated acute kidney injury and serious adverse outcomes following angiography. J Am Coll Cardiol. 2020;75(11):1311-1320.
22. Arero G, Arero AG, Mohammed SH, Vasheghani-Farahani A. Prognostic potential of the controlling nutritional status (CONUT) score in predicting all-cause mortality and major adverse cardiovascular events in patients with coronary artery disease: a meta-analysis. Front Nutr. 2022;9:850641.
23. Chen L, Huang Z, Li W, He Y, Liang J, Lu J, et al. Malnutrition and the risk for contrast-induced acute kidney injury in patients with coronary artery disease. Int Urol Nephrol. 2022;54(2):429-435.
24. Wei X, Chen H, You Z, Yang J, He H, He C, et al. Nutritional status and risk of contrast-associated acute kidney injury in elderly patients undergoing percutaneous coronary intervention. Clin Exp Nephrol. 2021;25(9):953-962.

25. Wiedermann CJ, Wiedermann W, Joannidis M. Causal relationship between hypoalbuminemia and acute kidney injury. World J Nephrol. 2017;6(4):176-187.

26. Murat SN, Kurtul A, Yarlioglues M. Impact of serum albumin levels on contrast-induced acute kidney injury in patients with acute coronary syndromes treated with percutaneous coronary intervention. Angiology. 2015;66(8):732-737.

27. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-188. Erratum in: Eur Heart J. 2020;41(44):4255.

28. Obialo CI, Okonofua EC, Nzerue MC, Tayade AS, Riley LJ. Role of hypoalbuminemia and hypocholesterolemia as copredictors of mortality in acute renal failure. Kidney Int. 1999;56(3):1058-1063.

29. Park CH, Kang EW, Park JT, Han SH, Yoo TH, Kang SW, et al. Association of serum lipid levels over time with survival in incident peritoneal dialysis patients. J Clin Lipidol. 2017;11(4):945-954.e3.

30. Bian C, Wu Y, Shi Y, Xu G, Wang J, Xiang M, et al. Predictive value of the relative lymphocyte count in coronary heart disease. Heart Vessels. 2010;25(6):469-473.

31. Zorlu C, Koseoglu C. Comparison of the relationship between inflammatory markers and contrast-induced nephropathy in patients with acute coronary syndrome after coronary angiography. Angiology. 2020;71(3):249-255.

32. Bansal S, Patel RN. Pathophysiology of contrast-induced acute kidney injury. Interv Cardiol Clin. 2020;9(3):293-298.

33. Akcay A, Nguyen Q, Edelstein CL. Mediators of inflammation in acute kidney injury. Mediators Inflamm. 2009;2009:137072.

34. Galizia G, Lieto E, Auricchio A, Cardella F, Mabilia A, Podzemny V, et al. Naples prognostic score, based on nutritional and inflammatory status, is an independent predictor of long-term outcome in patients undergoing surgery for colorectal cancer. Dis Colon Rectum. 2017;60(12):1273-1284.

35. Xiong J, Hu H, Kang W, Liu H, Ma F, Ma S, et al. Prognostic impact of preoperative Naples prognostic score in gastric cancer patients undergoing surgery. Front Surg. 2021;8:617744.

36. Feng JF, Zhao JM, Chen S, Chen QX. Naples prognostic score: a novel prognostic score in predicting cancer-specific survival in patients with resected esophageal squamous cell carcinoma. Front Oncol. 2021;11:652537.

37. Arfsten H, Cho A, Prausmüller S, Spinka G, Novak J, Goliasch G, et al. Inflammation-based scores as a common tool for prognostic assessment in heart failure or cancer. Front Cardiovasc Med. 2021;8:725903.

38. Zhou Z, Liang M, Wu H, Huang S, Weng R, Hou J, et al. Preoperative lymphocyte-to-monocyte ratio as a prognostic predictor of long-term mortality in cardiac surgery patients: a propensity score matching analysis. Front Cardiovasc Med. 2021;8:639890.

39. Karauzum I, Karauzum K, Acar B, Hanci K, Bildirici HIU, Kilic T, et al. Predictive value of lymphocyte-to-monocyte ratio in patients with contrast-induced nephropathy after percutaneous coronary intervention for acute coronary syndrome. J Transl Int Med. 2021;9(2):123-130.

40. Chandiramani R, Cao D, Nicolas J, Mehran R. Contrast-induced acute kidney injury. Cardiovasc Interv Ther. 2020;35(3):209-217.

41. Heyman SN, Rosenberger C, Rosen S, Khamaisi M. Why is diabetes mellitus a risk factor for contrast-induced nephropathy? Biomed Res Int. 2013;2013:123589.

ORIGINAL RESEARCH

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Quality of Life Outcomes in Lower Extremity Lymphedema After Manual Lymphatic Drainage Therapy

Manuel Lenfatik Drenaj Terapisi Sonrasi Alt Ekstremite Lenfödeminde Yaşam Kalitesi Sonuçları

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Abstract

Objective: Lymphedema is a complex condition, and there is limited evidence regarding the impact of lower extremity lymphedema on patients' health and quality of life (QoL). This study aims to evaluate the QoL in individuals diagnosed with secondary lymphedema affecting the lower limbs.

Method: This cross-sectional study collected data from outpatient and inpatient lymphedema management units. Assessments included lymphedema quality of life (LQoL), body mass index (BMI), characteristics of secondary lymphedema and demographic details. LQoL scores were recorded both before and after 20 sessions of manual lymphatic drainage (MLD) therapy.

Results: A total of 67 patients diagnosed with secondary lower-extremity lymphedema were included in the study. Lymphedema severity was evaluated through circumferential measurements, with nearly all participants exhibiting moderate to severe swelling. The majority of the participants (79.1%) were female, while 14 were male. The patients' ages ranged from 34 to 83 years, with a mean age of 58.67±10.97 years. The mean BMI was calculated as 34.41±7.13. The mean LQoL score before treatment was 2.53±0.63. A paired samples t-test demonstrated a statistically significant improvement in LQoL scores after MLD therapy ($p=0.035$), confirming its effectiveness. Furthermore, a significant correlation was identified between BMI and LQoL ($r=0.291$, $p<0.021$, Pearson correlation test).

Öz

Amaç: Lenfödem, özellikle alt ekstremitelerde görüldüğünde hastaların yaşam kalitesini (QoL) olumsuz etkileyen karmaşık bir hastalıktır. Ancak, bu durumun QoL üzerindeki etkilerine dair sınırlı sayıda çalışma bulunmaktadır. Bu çalışmanın amacı, alt ekstremitelerde sekonder lenfödem tanısı konmuş bireylerde QoL'yi değerlendirmektir.

Yöntem: Bu çalışmada, alt ekstremite sekonder lenfödemi tanısı almış ve ayakta ya da yatarak tedavi gören hastalardan, lenfödem yönetim birimlerinde veriler toplanmıştır. Katılımcıların demografik özellikleri, lenfödemin klinik parametreleri ve beden kitle indeksleri (BKİ) kaydedilmiştir. Yaşam kalitesini değerlendirmek için lenfödem yaşam kalitesi (LQoL) ölçeği kullanılmış olup, LQoL skorları 20 seanslık MLD tedavisi öncesi ve sonrası olmak üzere iki farklı dönemde ölçülmüştür. Bu sayede, MLD tedavisinin yaşam kalitesi üzerindeki etkileri karşılaştırmalı olarak analiz edilmiştir.

Bulgular: Sekonder alt ekstremite lenfödemi tanısı konmuş toplam 67 hasta çalışmaya dahil edilmiştir. Lenfödem şiddeti, çevresel ölçümlerle değerlendirilmiş ve katılımcıların büyük çoğunluğunda orta ile ileri derecede şişlik tespit edilmiştir. Çalışmaya katılanların %79,1'i kadın, geri kalan 14'ü ise erkektir. Hastaların yaş aralığı 34 ile 83 yıl arasında değişmekte olup, ortalama yaş 58,67±10,97 yıl olarak hesaplanmıştır. Ortalama BKİ ise 34,41±7,13 olarak bulunmuştur. Tedavi öncesinde ortalama LQoL skoru 2,53±0,63 olarak ölçülmüştür. Eşleştirilmiş örneklem t-testi sonuçları, MLD tedavisi sonrasında LQoL skorlarında istatistiksel

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Abstract

Conclusion: This study highlights a significant association between BMI and QoL in patients with secondary lower-extremity lymphedema. MLD was found to be an effective therapeutic approach.

Keywords: Lymphatic, lymphedema, phlebolymphedema, quality of life

Öz

olarak anlamlı bir iyileşme olduğunu göstermiştir (p=0,035) ve bu durum tedavinin etkinliğini desteklemektedir. Ayrıca, BKİ ile LQoL skorları arasında Pearson korelasyon testi ile anlamlı bir pozitif ilişki saptanmıştır (r=0,291, p<0,021).

Sonuç: Bu çalışma, sekonder alt ekstremite lenfödemi olan hastalarda BKİ ile yaşam kalitesi arasında anlamlı bir ilişki olduğunu ortaya koymaktadır. MLD ise etkili bir tedavi yöntemi olarak bulunmuştur.

Anahtar kelimeler: Flebolenfödem, lenfatik, lenfödem, yaşam kalitesi

Introduction

Chronic lymphedema is a condition characterized by inflammatory and lymphostatic changes affecting the interstitial space and lymphatic drainage. It occurs due to mechanical restrictions in the lymphatic system, including lymphatic collectors, trunks, or lymph nodes, rather than congenital or acquired structural damage (1). Lymphedema manifests with a variety of symptoms and clinical features. The most frequently reported complaints include pain, itching, a sensation of heaviness, fatigue, skin changes, and recurrent infections (2). Although lymphedema causes physical and psychological problems and impairs quality of life (QoL), it is underrecognized and undertreated. The diagnosis of lymphedema is clinical and depends on a detailed history and thorough physical examination. In addition, quantitative measurements of functional disability and QoL and the psychological context of the disease (anxiety, depression, sleep disturbances, fear of cancer recurrence and sexuality issues) need to be addressed (3). As lymphedema progresses into a chronic and often irreversible condition, it necessitates continuous care and management, often incorporating psychosocial support. The ongoing requirement for therapy does not imply inadequate treatment but rather reflects the chronic nature of the disease, where outcomes may still be suboptimal. Patient adherence to treatment regimens plays a crucial role in achieving better clinical results. Early diagnosis and intervention are associated with improved treatment efficacy and potential cost reductions through conservative management strategies, including the use of compression garments, self-care education (covering aspects such as skin hygiene, weight management, and anatomy), self-administered or caregiver-assisted manual lymphatic drainage (MLD), psychosocial support, and physical activity. Additionally, timely identification of the condition may facilitate the use of advanced surgical interventions, such as lymphatic-venous shunting, in appropriate cases, potentially reducing the need for lifelong treatment (1). Although studies have shown that MLD therapy is an effective treatment for patients with lymphedema, there is a limited number of studies in the literature examining changes in QoL before and after treatment. This study aims to evaluate the clinical impact of lymphedema, which significantly reduces QoL, and to assess the improvement in QoL following MLD therapy.

Materials and Methods

Patients diagnosed with lymphoedema and followed up at the outpatient clinics of University of Health Sciences Turkey, İstanbul Physical Therapy and Rehabilitation Training and Research Hospital, were included in this study. Ethical approval for the study was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Physical Therapy and Rehabilitation Training and Research Hospital on 02.07.2024 with protocol number 2024-39. Pre- and post-treatment data from 67 patients were obtained from both outpatient and inpatient lymphedema management centers. Recorded variables included lymphedema quality of life (LYMQoL), body mass index (BMI), lymphedema characteristics, disease stage, and demographic data. The severity and presence of lymphedema were assessed through circumferential measurements of the lower extremities. Specifically, measurements were taken at the level of the metatarsophalangeal joint, the narrowest point above the ankle malleolus, and at distances of 10, 20, and 30 cm proximal to the lateral malleolus. Patients underwent 20 sessions of MLD therapy performed by trained therapists. Following the completion of treatment, all measurements were repeated to evaluate post-treatment changes. All patients suffered from lower extremity lymphedema (LEL). Patients with lipedema, venous insufficiency, lower extremity edema due to systemic disease, ulcer or infection were excluded. All patients had received MLD

and compression and exercise therapy. The LYMQoL is a disease-specific health-related quality of life (HRQoL) assessment tool designed to evaluate function, appearance, symptoms, and mood in individuals with lymphedema. It comprises 22 items, each scored on a four-point Likert scale: 1= Not at all, 2= A little, 3= Fairly, 4= A lot. The total score for each domain is derived by summing the item scores and dividing by the total number of items answered. The overall LYMQoL score ranges from 1 to 4, with higher scores indicating a poorer QoL. The scale was originally developed by Keeley et al. (4) in 2010 to assess QoL in individuals with lymphedema. The Turkish adaptation and validation of the scale were conducted by Borman et al. (5). The validated version consists of 21 items categorized into function, appearance, symptoms, and mood, each rated from 1 to 4, where higher scores indicate better QoL.

Statistical Analysis

The normality of the data was analyzed using the Shapiro-Wilk test. Quantitative data were summarized as mean and standard deviation values, while categorical variables were presented as percentages. The relationship between dependent variables was evaluated using the paired sample t-test, and correlations between variables were assessed with the Pearson correlation test. P-value ≤0.05 was considered statistically significant. Statistical analyses were performed using SPSS 21.0 software.

Results

The study included 67 patients with LEL. The presence and severity of lymphedema were evaluated by circumferential measurement and clinical examination. 66.7% of the patients had bilateral lymphedema, 23.3% right and 10% left LEL. Lymphedema developed after gynecologic malignancy in 38% of the patients. The other patients suffered from lymphedema as a result of primary or infection, fracture and surgery. We did not group our patients according to the presence of malignancy. 83.58% of the patients were staged as stage 2 and 16.42% as stage 3 lymphedema. 79.1% of the participants were female. The ages of the patients ranged between 34-83 years. The mean age was 58.67±10.97 years. The mean BMI was 34.40±7.13. 60% of the patients complained of pain and 80% complained of fullness (Table 1).

LQoL was 2.53±0.63 before treatment and 2.31±0.66 after treatment. When the LQoL scores of all patients with LEL were compared with the paired sample test, the p-value was 0.035 and the difference between the LQoL scores before and after manual lymph massage was statistically significant (Table 2).

There was a statistically significant correlation between BMI and LQoL scores before treatment (r=0.291, p<0.021 Pearson correlation test) (Table 3).

Discussion

In this study, MLD therapy was found to be an effective treatment in improving QoL in patients with LEL. Additionally, a weak but statistically significant correlation was observed between BMI and QoL scores. While most lymphedema research has primarily focused on upper extremity lymphedema in breast cancer patients, studies on LEL remain limited despite its frequent occurrence, particularly among individuals with gynecologic cancers. By evaluating QoL outcomes in patients with LEL, our study addresses an important gap in the existing literature.

Table 1. Descriptive data

		Mean ± SD/(%)
Age		58.67±10.97
Gender	Male	(20.9%)
	Female	(79.1%)
BMI		34.40±7.13
Stage	2	(83.58%)
	3	(16.42%)
Extremity	Bilateral	(66.7%)
	Right	(23.3%)
	Left	(10%)
Pain		(60%)
Fullness		(80%)

BMI: Body mass index, SD: Standard deviation

Table 2. Comparison of LYMQOL scores before and after treatment

	Mean ± SD	p-value	%95 confidence interval
LYMQOL before	2.53±0.63	0.035[t]	0.016-0.427
LYMQOL after	2.32±0.67		

LYMQOL: Lymphedema quality of life, SD: Standard deviation, T: Paired samples t-test

Table 3. Correlation between BMI and LYMQOL before treatment

LYMQOL before		
	r	**p-value**
BMI	0.291*	0.021[p]

LYMQOL: Lymphedema quality of life, BMI: Body mass index. [p]: Pearson correlation test *: Correlation is significant at the 0.05 level (2-tailed)

In patients with lymphedema, disturbances in body image often contribute to diminished self-esteem, heightened anxiety regarding disease progression, and impaired extremity function, all of which adversely affect overall QoL. In cases of LEL, these symptoms tend to be more pronounced, and QoL is reported to be significantly lower compared to upper extremity involvement. The deterioration in QoL has been closely associated with the reduction in lower limb functional capacity (6,7). Moffatt et al. (8) screened 823 patients and found that lymphedema incidence increases with age, with a higher prevalence among women. Furthermore, it has been reported that 80% of affected individuals experience work productivity loss, and their QoL is significantly lower than normal. Lymphedema has also been recognized as an important public health concern due to its impact on morbidity and social participation. In the study by Greene and Meskell (9), 77% of the participants were female, while another study reported the proportion of females as 71% (10). In an epidemiological study conducted by Grigorean et al. (11), it was confirmed that lymphedema is more frequently observed in females. Similarly, in our study, 79.1% of the patients were female, supporting the observation that lymphedema is more prevalent among women.

In this study, MLD, compression therapy, and therapeutic exercises were administered to all patients as part of a standardized conservative treatment protocol. These interventions have well-established efficacy. A weak but statistically significant association was observed between BMI and QoL scores before the application of the treatment protocol. Furthermore, a significant improvement was noted in QoL scores following the treatment. In a study investigating the effectiveness of compression therapy in patients with LEL, it was shown that the group receiving compression had better physical functioning after 12 months compared to those who did not. However, no significant differences were observed between the two groups in terms of emotional, cognitive, and social functioning, or symptoms such as pain, constipation, diarrhea, dyspnea, loss of appetite, and insomnia (12). Stolldorf et al. (7) conducted a study involving 213 patients with lymphedema to examine the impact of LEL symptoms on QoL. The study utilized the lymphedema symptom intensity and distress questionnaire-leg alongside an open-ended qualitative question. The findings revealed that a significant proportion of participants experienced psychological and physical symptoms, including depression (65.9%), anxiety about appearance (81.9%), negative body image perception (67.8%), fatigue (75.7%), weakness during leisure activities (65%), and reduced physical activity (69.5%). These factors collectively contributed to a substantial decline in the QoL among individuals with LEL (7). Additionally, studies have identified skin quality as a key determinant in the reduction of QoL among patients with LEL. Proper skin care and cellulitis prevention have been suggested as essential strategies to enhance QoL in these individuals (13).

A study conducted in Bangladesh reported that the QoL of women with LEL, including their mental health, was adversely affected. Participants complained of limited access to healthcare services, the belief that the disease could not be effectively treated, and negative perceptions within society (14). Another study, which included 122 participants receiving MLD at vascular and wellness clinics in Ireland, aimed to assess the effects of chronic LEL on patients' QoL. The results indicated that a majority of participants reported physical difficulties such as limb heaviness (74%), weakness (44%), pain (38%), walking difficulties (53%), standing impairments (51%), and difficulty bending (45%). Furthermore, 76% of patients expressed concerns about poor body image, while 59% reported challenges in finding properly fitting shoes due to edema. Additionally, 55% experienced reduced socialization, and emotional symptoms such as irritability (42%), anxiety (41%), and tension (40%) were commonly observed. These findings emphasize that chronic LEL contributes to significant physical, psychological, and social burdens, ultimately leading to a reduced QoL (9). Schulz et al. (15) administered the LYMQoL questionnaire and demonstrated that patients with LEL experience significantly lower QoL compared to those with UEL. In the systematic review published in 2022, the impact of LEL on the HRQoL and the methodologies used to evaluate HRQoL and compliance with the HRQoL dimensions recommended by the World Health Organization (WHO) were examined. Although LYMQoL is the most widely used questionnaire, studies that include all the elements recommended by WHO have not yet been conducted (16). Therefore, despite the need for a universal, disease-specific methodology to ensure that HRQoL data accurately reflect the impact of the disease, such an approach is still lacking.

Bowman et al. (17) demonstrated that the complex interaction between the QoL, anxiety, depression and psychosocial well-being of LEL patients and supportive care emphasizes the importance of a multidisciplinary approach and services that provide psychosocial support. In another study, it was observed that exercise programs, both with and without resistance, led to improvements in QoL in LEL patients compared to pre-treatment

levels (18). Angst et al. (19) found evidence that patients with LEL benefited significantly from a comprehensive inpatient rehabilitation program and achieved HRQoL levels equal to or higher than expected when compared with general population norms, thus strengthening the recommendation of multidisciplinary inpatient rehabilitation. In this study, LYMQoL, the most commonly used scale, was also employed, and post-treatment findings revealed a significant improvement in scores. This indicates the positive impact of therapeutic interventions on the QoL of individuals with LEL.

Study Limitations

This study has several limitations that should be considered when interpreting the results. First, the retrospective design restricted the available data to information recorded in patient files. As a result, some important variables, such as circumferential measurements and BMI before and after MLD, were not consistently documented and could not be analyzed. Although information regarding the underlying cause of lymphedema (malignant vs. non-malignant) was available, subgroup analyses were not performed due to the limited sample size, to avoid underpowered and potentially misleading results. The relatively small sample size also limits the generalizability and statistical robustness of our findings. While a statistically significant correlation between BMI and LYMQoL scores was observed, the correlation was weak. Therefore, these findings should be interpreted with caution. Additionally, potential confounding factors, such as the stage of lymphedema or the type of underlying pathology, could not be fully accounted for in the analysis. Although all circumferential measurements were performed by a single experienced specialist, eliminating interrater variability, interrater reliability could not be evaluated. Furthermore, minimal detectable change and minimal clinically important difference values specific to the LYMQoL for LEL are not clearly established in the literature, limiting the interpretation of the clinical significance of the changes observed.

Despite these limitations, our study has several strengths. Unlike most studies that primarily focus on upper extremity lymphedema following breast cancer, our research provides valuable insights into QoL changes in patients with LEL after MLD treatment, an area with limited existing research. Additionally, all circumferential measurements were conducted by the same specialist using standardized methods, ensuring consistency and reducing measurement bias.

Conclusion

In conclusion, this study highlights the impact of secondary lower-extremity lymphedema on patients' QoL and reveals a weak but statistically significant correlation between BMI and QoL. The findings support the effectiveness of MLD in improving QoL among affected individuals. Given the limited number of studies focusing specifically on lower-extremity lymphedema, our research contributes valuable insights to a relatively underexplored area. Although lymphedema is often managed within oncology or vascular specialties, the growing field of lymphology underscores the importance of interdisciplinary collaboration and specialized care. Many patients continue to face unmet clinical, psychological, and rehabilitative needs. Future prospective studies with larger sample sizes and objective evaluation tools are warranted to further refine treatment approaches and improve outcomes in this patient population.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Physical Therapy and Rehabilitation Training and Research Hospital on 02.07.2024 with protocol number 2024-39.

Informed Consent: Written İnformed consent was obtained from all subjects involved in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.E., N.K., C.M.C., E.K., Concept: S.E., B.Ş.A., N.P., D.B., Design: S.E., B.Ş.A., N.K., N.P., D.B., E.K., Data Collection or Processing: S.E., N.K., C.M.C., Analysis or Interpretation: S.E., B.Ş.A., N.K., N.P., D.B., Literature Search: B.Ş.A., N.K., C.M.C., Writing: S.E., B.Ş.A., N.K., E.K.

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References

1. Executive Committee of the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2023 consensus document of The International Society of Lymphology. Lymphology. 2023;56(4):133-151.
2. Schiltz D, Eibl D, Mueller K, Biermann N, Prantl L, Taeger CD. Therapist versus machine-immediate effects of manual versus

mechanical lymphatic drainage in patients with secondary lymphedema. J Clin Med. 2024;13(5):1277.

3. Borman P. Lymphedema diagnosis, treatment, and follow-up from the view point of physical medicine and rehabilitation specialists. Turk J Phys Med Rehabil. 2018;64(3):179-197.
4. Keeley V, Crooks S, Locke J, Veigas D, Riches K, Hilliam R. A quality of life measure for limb lymphoedema (LYMQOL). J Lymphoedema. 2010;5(1):26-37.
5. Borman P, Yaman A, Denizli M, Karahan S. The reliability and validity of lymphedema quality of life questionnaire-leg in Turkish patients with lower limb lymphedema. Lymphat Res Biol. 2020;18(1):42-48.
6. Kalemikerakis I, Evaggelakou A, Kavga A, Vastardi M, Konstantinidis T, Govina O. Diagnosis, treatment and quality of life in patients with cancer-related lymphedema. J BUON. 2021;26(5):1735-1741.
7. Stolldorf DP, Dietrich MS, Ridner SH. Symptom frequency, intensity, and distress in patients with lower limb lymphedema. Lymphat Res Biol. 2016;14(2):78-87.
8. Moffatt CJ, Franks PJ, Doherty DC, Williams AF, Badger C, Jeffs E, et al. Lymphoedema: an underestimated health problem. QJM. 2003;96(10):731-738.
9. Greene A, Meskell P. The impact of lower limb chronic oedema on patients' quality of life. Int Wound J. 2017;14(3):561-568.
10. Franks PJ, Moffatt CJ, Doherty DC, Williams AF, Jeffs E, Mortimer PS. Assessment of health-related quality of life in patients with lymphedema of the lower limb. Wound Repair Regen. 2006;14(2):110-118.
11. Grigorean A, Voci D, Farmakis IT, Hobohm L, Keller K, Kucher N, et al. Prevalence of lymphedema using large data sets: an epidemiological analysis in the United States and in Italy. Lymphology. 2023;56(4):178-187.
12. Kurpiewska-Pieniążek J, Ochałek K, Grądalski T, Szuba A. Efficacy of compression stockings in prophylaxis of lower limb lymphedema in women undergoing treatment for gynecological malignancies: a prospective randomized study. Cancers (Basel). 2025;17(15):2530.
13. Eidenberger M. Patient-reported outcome measures with secondary lower limb lymphedemas: a systematic review. J Adv Pract Oncol. 2021;12(2):174-187.
14. Koly KN, Saba J, Nessa Z, Luba FR, Hossain I, Aktaruzzaman MM, et al. Social and healthcare-seeking experiences of people affected with lymphedema in Bangladesh. PLoS Negl Trop Dis. 2025;19(8):e0013384.
15. Schulz T, Lee Warg M, Kurow O, Langer S, Nuwayhid R. The burden of lymphedema on quality of life. Vasa. 2025;54(2):124-132.
16. Chima C, Murray B, Moore Z, Costello M, George S. Health-related quality of life and assessment in patients with lower limb lymphoedema: a systematic review. J Wound Care. 2022;31(8):690-699.
17. Bowman C, Oberoi D, Radke L, Francis GJ, Carlson LE. Living with leg lymphedema: developing a novel model of quality lymphedema care for cancer survivors. J Cancer Surviv. 2021;15(1):140-150.
18. Hsu YY, Lin CF, Liang PC, Nguyen TTB, Hsu KF. Effects of resistance exercise on reducing the risk of lower-limb lymphedema after gynecological cancer surgery. Asia Pac J Oncol Nurs. 2025;12:100756.
19. Angst F, Benz T, Lehmann S, Sándor PS, Wagner S. Effects of inpatient rehabilitation in leg lymphedema: a naturalistic prospective cohort study with intra-individual control of effects. Arch Phys Med Rehabil. 2023;104(12):2035-2042.

ORIGINAL RESEARCH

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Second-trimester Hemogram-derived Inflammatory Markers for the Prediction and Severity Stratification of SGA Fetuses Based on Doppler and Birthweight Percentiles

İkinci Trimester Hemogram Türevli Enflamatuvar Belirteçlerin Doppler ve Doğum Ağırlığı Persentillerine Dayalı Olarak SGA Fetüslerinin Öngörülmesi ve Şiddet Sınıflandırmasındaki Rolü

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Abstract

Objective: This study aimed to evaluate the predictive value of second-trimester maternal hemogram parameters in identifying small for gestational age (SGA) fetuses and assessing the severity of SGA based on umbilical artery Doppler (UAD) findings and birthweight percentiles.

Method: A total of 150 singleton pregnancies were retrospectively analyzed and divided into three groups: SGA with abnormal UAD, SGA with normal UAD, and non-SGA controls. Maternal white blood cell (WBC) count, neutrophil count, lymphocyte count, platelet count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were compared among groups. SGA cases were further stratified into ≤3rd percentile (high risk) and 4th-10th percentile (lower risk) subgroups based on birthweight percentiles, categorizing them as high-risk and low-risk SGA.

Results: Maternal WBC and neutrophil counts were significantly higher in SGA pregnancies compared to non-SGA controls ($p<0.05$). The highest WBC and neutrophil levels were observed in the SGA group with abnormal UAD and in fetuses ≤3rd percentile. No significant differences were found in lymphocyte count, platelet count, NLR, or PLR across groups. A strong association was noted between elevated maternal WBC and markers of SGA severity, including lower gestational age at delivery, reduced birthweight, and abnormal Doppler findings.

Öz

Amaç: Bu çalışma, ikinci trimesterdeki maternal hemogram parametrelerinin, gestasyonel yaşa göre küçük (SGA) fetüslerin tanımlanmasında ve umbilikal arter Doppler (UAD) bulguları ile doğum ağırlığı persentillerine göre SGA şiddetinin değerlendirilmesindeki öngörücü değerini araştırmayı amaçlamıştır.

Yöntem: Toplam 150 tekil gebelik retrospektif olarak analiz edildi ve üç gruba ayrıldı: anormal UAD bulgularına sahip SGA, normal UAD bulgularına sahip SGA ve SGA olmayan kontrol grubu. Gruplar arasında maternal beyaz kan hücresi (WBC) sayısı, nötrofil sayısı, lenfosit sayısı, trombosit sayısı, nötrofil/lenfosit oranı (NLR) ve trombosit/lenfosit oranı (PLR) karşılaştırıldı. SGA olguları ayrıca doğum ağırlığı persentillerine göre ≤3. persentil (yüksek riskli) ve 4-10. persentil (daha düşük riskli) olmak üzere iki alt gruba ayrıldı.

Bulgular: SGA gebeliklerinde maternal WBC ve nötrofil sayıları, SGA olmayan kontrol grubuna kıyasla anlamlı derecede yüksekti ($p<0,05$). En yüksek WBC ve nötrofil düzeyleri, anormal UAD bulgularına sahip SGA grubunda ve ≤3. persentildeki fetüslerde gözlendi. Lenfosit sayısı, trombosit sayısı, NLR ve PLR açısından gruplar arasında anlamlı fark saptanmadı. Artmış maternal WBC düzeyleri ile daha düşük doğum haftası, azalmış doğum ağırlığı ve anormal Doppler bulguları gibi SGA şiddet göstergeleri arasında güçlü bir ilişki gözlemlendi.

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Abstract

Conclusion: Second-trimester maternal WBC and neutrophil counts may serve as useful non-invasive markers for both identifying SGA and evaluating its severity. These routinely available parameters could support early risk stratification and management in clinical practice.

Keywords: Blood cell count, Doppler ultrasonography, intrauterine growth restriction, placental insufficiency, small for gestational age, umbilical artery

Öz

Sonuç: İkinci trimesterde ölçülen maternal WBC ve nötrofil sayıları, SGA fetüslerin belirlenmesinde ve şiddetlerinin değerlendirilmesinde faydalı, non-invaziv belirteçler olarak kullanılabilir. Rutin olarak erişilebilen bu parametreler, klinik uygulamada erken risk sınıflaması ve yönetimi açısından destekleyici olabilir.

Anahtar kelimeler: Doppler ultrasonografi, fetal büyüme geriliği, gebelik haftasına göre küçük bebek, kan hücresi sayımı, plasental yetmezlik, umbilikal arterler

Introduction

Small for gestational age (SGA) refers to a condition in which a fetus fails to achieve its genetically expected growth by the time of birth. Together with intrauterine growth restriction (IUGR), SGA is associated with adverse perinatal outcomes affecting both the mother and the newborn (1,2). By definition, SGA is characterized by a birth weight below the 10th percentile for gestational age (1).

Fetal growth restriction (FGR) increases the risk of early neonatal complications such as low birth weight, the need for neonatal intensive care, and perinatal mortality. In addition, it has been linked to long-term health problems, including obesity, neurodevelopmental disorders, cardiovascular diseases, and type 2 diabetes later in life (3-5). These complications may emerge during the neonatal period and often persist into later stages of life (2). The severity of FGR has been shown to correlate inversely with estimated fetal weight; that is, lower fetal weight is typically associated with more profound placental dysfunction and a worse perinatal prognosis (6).

The development of SGA and IUGR is attributed to various maternal and fetal factors, including fetal chromosomal abnormalities, structural anomalies, and maternal infections (1). Notably, increased resistance and abnormal findings in the umbilical artery Doppler are indicative of more severe FGR and are associated with poorer perinatal outcomes. Such Doppler abnormalities reflect impaired placental perfusion, which further contributes to adverse neonatal prognosis (7).

Recent studies have increasingly emphasized a strong association between FGR and inflammation, indicating that inflammatory mechanisms may be central to the initiation and progression of FGR (8,9). Inflammatory states may activate immune responses that impair placental function and hinder nutrient exchange, thereby contributing to FGR (10). Such impairment can result in compromised fetal development, posing serious risks to both immediate and long-term neonatal health.

Previous studies have indicated that elevated levels of first and second trimester maternal serum inflammatory markers—such as neutrophil count, white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR)—may serve as significant and predictive biomarkers of impaired intrauterine growth (11-15).

The primary objective of this study was to evaluate the predictive value of second trimester maternal serum inflammatory markers—including WBC count, neutrophil count, lymphocyte count, platelet count, NLR, and PLR—for identifying SGA fetuses; the secondary objective was to investigate the utility of these markers in predicting the severity of SGA based on umbilical artery Doppler findings and birthweight percentiles.

Materials and Methods

This retrospective observational case-control study included a total of 150 pregnant women who were followed at the Perinatology Outpatient Clinic of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital between January 2024 and December 2024.The participants were categorized into three groups based on fetal growth status and umbilical artery Doppler findings. Fetuses with an estimated fetal weight below the 10th percentile on ultrasonographic evaluation were diagnosed with SGA.

Group 1 consisted of 50 pregnant women carrying fetuses diagnosed with SGA accompanied by abnormal umbilical artery Doppler findings, such as an increased resistance index. These cases were considered high-risk SGA pregnancies.

Group 2 included 50 pregnant women carrying fetuses diagnosed with SGA but with normal umbilical artery

Doppler findings, and were therefore considered to have lower-risk SGA pregnancies.

Group 3 served as a control group and consisted of 50 randomly selected pregnant women with appropriately grown fetuses and normal Doppler findings, representing healthy pregnancies. In the control group, all patients delivered at ≥37 weeks of gestation without obstetric or neonatal complications.

All participants had hemogram parameters measured during the second trimester (between 14-28 weeks of gestation). The maternal complete blood count (CBC) values analyzed included WBC count, neutrophil count, lymphocyte count, platelet count, NLR, and PLR. CBC analyses were performed using the Sysmex XN-1000 automated hematology analyzer (Sysmex Corporation, Kobe, Japan). These parameters were assessed to investigate their potential predictive value in identifying IUGR fetuses.

Additionally, within the SGA group (Groups 1 and 2), further stratification was performed based on birth weight percentiles. Fetuses born below the 3rd percentile were defined as higher-risk SGA, whereas those between the 3rd and 10th percentiles were considered lower-risk SGA. The predictive performance of the hemogram parameters for both the identification and risk stratification of SGA was statistically analyzed.

Pregnancies complicated by multiple gestations, congenital anomalies, pre-existing maternal chronic illnesses (e.g., diabetes mellitus, hypertension, autoimmune diseases), or incomplete medical records were excluded from the study.

The study protocol, procedures, and ethical conduct were reviewed and approved by the Local Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: KAEK/12.02.2025.41, date: 04.03.2025). All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Because of the retrospective nature of the study, written informed consent was not required from participants.

Selection and Description of the Participants

This study included 150 pregnant women followed at our tertiary care center. Inclusion criteria were singleton pregnancies between 14-28 weeks of gestation with complete medical and ultrasonographic data, including second trimester hemogram results and umbilical artery Doppler findings. Participants were selected to reflect a spectrum of fetal growth status: High-risk SGA, low-risk SGA, and normal fetal growth.

Exclusion criteria were as follows: Multiple gestations, fetal congenital or chromosomal anomalies, known maternal infections, use of medications influencing hematological parameters, maternal hematologic disorders, and chronic maternal conditions such as diabetes mellitus, hypertension, or autoimmune diseases. Cases with incomplete or missing medical records were also excluded.

The study population was not restricted by maternal age, ethnicity, or parity; however, all participants were selected from the same geographical region and healthcare facility to ensure consistency in clinical protocols and data acquisition. The rationale for this selection was to minimize confounding factors related to clinical variability and to reflect a representative sample of patients typically seen in tertiary obstetric care.

Statistical Analysis

All statistical analyses were conducted using R software (version 4.4.2). The Shapiro-Wilk test was used to assess the normality of continuous variables. Normally distributed variables are presented as mean ± standard deviation, and non-normally distributed variables as median and interquartile range (IQR). Categorical variables are expressed as counts and percentages.

Group comparisons for categorical variables were performed using Fisher's exact test or the chi-square test, as appropriate. For continuous variables, the Wilcoxon Rank-Sum test was used for two-group comparisons, and the Kruskal-Wallis test was applied for comparisons across more than two groups. A p-value of <0.05 was considered statistically significant.

Results

A total of 150 pregnant women were included and categorized into three groups based on fetal growth and umbilical artery Doppler findings. Hematologic and perinatal outcomes were compared between groups to assess the predictive value of maternal second-trimester hemogram parameters for SGA fetuses and SGA severity.

Comparison of SGA and Non-SGA Groups

Patients with SGA fetuses (Groups 1 and 2) demonstrated significantly higher maternal neutrophil counts [7,970.00/µL (IQR: 6,380.00-10,390.00)] compared to the non-SGA control group [6,970.00/µL (IQR: 6,230.00-8,440.00]; p=0.021)]. Similarly, WBC counts were significantly elevated

in the SGA group [11,765.00/µL (IQR: 9,500.00-13,240.00)] compared to controls [9,965.00/µL (IQR: 8,740.00-11,540.00); p=0.004]. There were no statistically significant differences in lymphocyte count, platelet count, NLR, or PLR between groups (p>0.05 for all) (Table 1).

Comparison of Non-SGA, SGA with Abnormal UAD and SGA with Normal UAD Groups

A significant difference in gestational age at delivery was observed across the three groups (p<0.001). Pregnancies complicated by SGA with abnormal UAD had the earliest deliveries [29.71 weeks (IQR: 27.93-32.29)] compared to SGA with normal UAD [37.00 weeks (IQR: 36.00-37.14)] and non-SGA pregnancies [39.00 weeks (IQR: 38.57-40.00)]. Birthweights were lowest in the abnormal UAD group [855.00 g (IQR: 635.00-1,190.00)] compared to the normal UAD group [2,330.00 g (IQR: 1,965.00-2,450.00)] and the non-SGA group [3,425.00 g (IQR: 3,140.00-3,630.00); p<0.001].

Similarly, WBC counts were highest among patients with SGA and abnormal UAD [12,430.00/µL (IQR: 10,750.00-14,835.00)], followed by those with normal UAD [10,075.00/µL (IQR: 9,030.00-12,625.00)] and non-SGA pregnancies [9,965.00/µL (IQR: 8,740.00-11,540.00); p<0.001]. Neutrophil counts were also significantly different among groups (p=0.012), while lymphocyte counts, platelet counts, NLR, and PLR did not show significant differences (p>0.05) (Table 2).

Comparison Based on Birthweight Percentiles Among SGA Fetuses

Further stratification of SGA fetuses by birthweight percentiles revealed that those born at ≤3rd percentile had significantly lower gestational age at birth [32.36 weeks (IQR: 29.29-35.29)] compared to those between the 4th-10th percentile [37.00 weeks (IQR: 36.86-37.14); p<0.001]. Birthweights were also significantly lower in the ≤3rd percentile group [1,095.00 g (IQR: 715.00-1,630.00)] compared to the 4th-10th percentile group [2,390.00 g (IQR: 2,340.00–2,470.00); p<0.001]. Maternal WBC counts were significantly higher in the ≤3rd percentile group [12,110.00/µL (IQR: 9,720.00-13,390.00)] compared to the 4th-10th percentile group [9,760.00/µL (IQR: 8,800.00-12,500.00); p=0.021]. No significant differences were observed in other hematological parameters (Table 3).

Discussion

The pathophysiological basis of SGA is multifactorial, with increasing attention directed toward the potential role of inflammation in placental dysfunction and suboptimal fetal growth. Although the association between inflammation and FGR has been hypothesized—particularly due to

Table 1. This table presents a comparison of patients with and without SGA based on the parameters listed below, along with the corresponding p-values

Variable	Group 3 n=50[1]	Group 1+2 n=100[1]	p-value[2]
Age	30.00 (25.00-35.00)	28.00 (24.00-31.00)	0.067
Birthweek	39.00 (38.57-40.00)	35.00 (30.00-37.00)	**<0.001**
Birthweight	3,425.00 (3,140.00-3,630.00)	1,625.00 (880.00-2,360.00)	**<0.001**
Lymphocyte	2,005.00 (1,750.00-2,450.00)	2,080.00 (1,715.00-2,600.00)	0.4
Neutrophil	6,970.00 (6,230.00-8,440.00)	7,970.00 (6,380.00-10,390.00)	**0.021**
Platelets	227,000.00 (184,000.00-268,000.00)	233,000.00 (196,500.00-270,000.00)	0.6
WBC	9,965.00 (8,740.00-11,540.00)	11,765.00 (9,500.00-13,240.00)	**0.004**
NLR	3.60 (2.97-4.29)	3.65 (2.84-4.87)	0.5
PLR	109.08 (95.60-136.73)	114.44 (81.49-138.15)	0.7
UAD	0 (NA%)	40 (40%)	-
Birthweight percentile			**<0.001**
≤3	0 (0%)	66 (66%)	
4-10	0 (0%)	27 (27%)	
11-90	48 (96%)	7 (7.0%)	
>90	2 (4.0%)	0 (0%)	

[1]: Median (Q1-Q3); n (%), [2]: Wilcoxon Rank-Sum test; Fisher's exact test, -: Cannot be obtained, SGA: Small for gestational age, UAD: Umbilical artery Doppler, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.
Maternal neutrophil and WBC counts were significantly higher in the SGA group compared to the non-SGA group (p=0.021 and p=0.004, respectively). No significant differences were observed in lymphocyte count, platelet count, NLR, or PLR between the groups (p>0.05)

Table 2. Comparison of non-SGA, SGA with normal UAD, and SGA with abnormal UAD

Variable	Non-SGA n=50[1]	SGA + Normal UAD n=60[1]	SGA + Abnormal UAD n=40[1]	p-value[2]
Age	30.00 (25.00-35.00)	27.00 (24.00-30.50)	29.00 (24.00-32.50)	0.10
Birthweek	39.00 (38.57-40.00)	37.00 (36.00-37.14)	29.71 (27.93-32.29)	**<0.001**
Birthweight	3,425.00 (3,140.00-3,630.00)	2,330.00 (1,965.00-2,450.00)	855.00 (635.00-1,190.00)	**<0.001**
Lymphocyte	2,005.00 (1,750.00-2,450.00)	1,980.00 (1,660.00-2,355.00)	2,320.00 (1,755.00-2,975.00)	0.079
Neutrophil	6,970.00 (6,230.00-8,440.00)	7,280.00 (6,365.00-9,815.00)	9,070.00 (6,590.00-11,105.00)	**0.012**
Platelets	227,000.00 (184,000.00-268,000.00)	235,000.00 (201,500.00-267,500.00)	229,000.00 (189,000.00-279,500.00)	0.9
WBC	9,965.00 (8,740.00-11,540.00)	10,075.00 (9,030.00-12,625.00)	12,430.00 (10,750.00-14,835.00)	**<0.001**
NLR	3.60 (2.97-4.29)	3.69 (3.09-4.73)	3.57 (2.48-5.44)	0.6
PLR	109.08 (95.60-136.73)	123.75 (95.10-142.47)	94.81 (75.57-129.42)	0.10
Birthweight percentile				**<0.001**
≤3	0 (0%)	27 (45%)	39 (98%)	
4-10	0 (0%)	26 (43%)	1 (2.5%)	
11-90	48 (96%)	7 (12%)	0 (0%)	
>90	2 (4.0%)	0 (0%)	0 (0%)	

[1]: Median (Q1-Q3); n (%), [2]: Kruskal-Wallis Rank-Sum test; Fisher's exact test, SGA: Small for gestational age, UAD: Umbilical artery Doppler, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.
Gestational age at delivery and birthweight differed significantly among the three groups, with the earliest deliveries and lowest birthweights observed in the SGA with abnormal UAD group (p<0.001). WBC and neutrophil counts were also significantly higher in this group (p<0.001 and p=0.012, respectively). No significant differences were found in lymphocyte count, platelet count, NLR, or PLR (p>0.05)

Table 3. Comparison of SGA patients with birthweight <3rd vs. 4th-10th percentile

Variable	BW=4-10 n=27[1]	BW≤3 n=66[1]	p-value[2]
Age	26.00 (23.00-29.00)	29.00 (25.00-32.00)	**0.038**
Birthweek	37.00 (36.86-37.14)	32.36 (29.29-35.29)	**<0.001**
Birthweight	2,390.00 (2,340.00-2,470.00)	1,095.00 (715.00-1,630.00)	**<0.001**
Lymphocyte	1,870.00 (1,650.00-2,600.00)	2,235.00 (1,760.00-2,840.00)	0.3
Neutrophil	6,900.00 (6,220.00-9,660.00)	8,570.00 (6,710.00-10,880.00)	0.086
Platelets	231,000.00 (189,000.00-270,000.00)	237,500.00 (195,000.00-271,000.00)	0.8
WBC	9,760.00 (8,800.00-12,500.00)	12,110.00 (9,720.00-13,390.00)	**0.021**
NLR	3.56 (3.13-4.35)	3.67 (2.54-4.98)	>0.9
PLR	127.48 (80.43-135.76)	110.51 (80.13-136.57)	0.4
UAD			<0.001
	1 (3.7%)	39 (59%)	
	26 (96.3%)	27 (41.0%)	
Birthweight percentile			**<0.001**
≤3	0 (0%)	66 (100%)	
4-10	27 (100%)	0 (0%)	
11-90	0 (0%)	0 (0%)	
>90	0 (0%)	0 (0%)	

[1]: Median (Q1-Q3); n (%), [2]: Wilcoxon Rank-Sum test; Fisher's exact test; Pearson's chi-squared test, SGA: Small for gestational age, BW: Birthweight, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, UAD: Umbilical artery Doppler, SGA fetuses with birthweights at or below the 3rd percentile had significantly lower gestational age at delivery and birthweight compared to those between the 4th-10th percentile (p<0.001 for both). Maternal WBC counts were also significantly higher in the ≤3rd percentile group (p=0.021). No significant differences were found in other hematologic parameters

impaired placental function and nutrient exchange—this mechanism has yet to be fully substantiated with definitive causal evidence.

Previous studies have highlighted the association between systemic inflammation and FGR. Elevated maternal inflammatory markers have been implicated in placental dysfunction, which is a key pathophysiological mechanism underlying SGA (14,15). Consistent with these findings, our study showed significantly higher maternal WBC and neutrophil counts in the SGA group compared to controls. These results align with the findings of Kırmızı et al. (11), who also reported higher WBC counts in pregnancies complicated by FGR.

When SGA pregnancies were further stratified by UAD results, our study revealed that those with abnormal UAD—representing higher-risk SGA—had the earliest gestational age at delivery and the lowest birthweights. This group (Group 1) also exhibited the highest WBC and neutrophil levels, supporting the hypothesis that inflammation may be more pronounced in severe cases of SGA. These findings are in agreement with prior research indicating that elevated WBC levels are linked not only to the presence of SGA but also to the extent of placental insufficiency (16).

Additionally, subgroup analysis based on birthweight percentiles revealed that fetuses below the 3rd percentile had significantly earlier gestational ages at delivery and lower birthweights compared to those between the 4th and 10th percentiles. Notably, WBC counts were significantly higher in the ≤3rd percentile group. The high rate of abnormal UAD findings (59%) in this subgroup, compared to only 3.7% in the 4th-10th percentile group, further emphasizes the clinical value of WBC as a potential marker for severe SGA.

Importantly, in contrast to several previous studies in the literature (13-15), this study did not find a significant association between other hematologic parameters—such as lymphocyte count, platelet count, NLR, and PLR—and the presence or severity of SGA. These findings suggest that while WBC and neutrophil counts may have predictive value, the broader range of hemogram parameters may have limited diagnostic utility in this context. Further large-scale studies are warranted to determine whether these markers could contribute meaningfully to SGA prediction.

As in the present study, various previous investigations have assessed the predictive ability of different maternal serum hemogram parameters for identifying SGA (17,18). However, to the best of our knowledge, this is the first study to comprehensively evaluate multiple second-trimester hemogram parameters specifically for predicting the severity of SGA. Taken together, these findings suggest that routine, non-invasive parameters such as CBC-derived inflammatory markers may hold clinical promise in the early identification of high-risk SGA cases. This could be particularly beneficial in settings with limited access to advanced diagnostic tools. However, prospective, large-scale studies are warranted to validate their utility in broader clinical practice.

Study Limitations

Limitations of our study include its retrospective design and single-center setting, which may limit the generalizability of the findings. Future prospective studies with larger cohorts are warranted to validate our findings and to explore the potential integration of these biomarkers into SGA screening protocols.

Conclusion

In conclusion, maternal WBC and neutrophil counts in the second trimester appear to be promising non-invasive markers for predicting SGA and identifying its severity. These parameters, readily available through routine antenatal care, may enhance current screening strategies when combined with fetal biometric and Doppler assessments.

Ethics

Ethics Committee Approval: The study protocol, procedures, and ethical conduct were reviewed and approved by the Local Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: KAEK/12.02.2025.41, date: 04.03.2025).

Informed Consent: The retrospective nature of the study, written informed consent was not required from participants.

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Footnotes

Authorship Contributions

Concept: Z.K.Y., E.S., Design: Z.K.Y., E.S., Data Collection or Processing: E.S., Analysis or Interpretation: Z.K.Y., Literature Search: Z.K.Y., E.S., Writing: Z.K.Y., E.S.

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References

1. Pylipow M, Spector LG, Puumala SE, Boys C, Cohen J, Georgieff MK. Early postnatal weight gain, intellectual performance, and body mass index at 7 years of age in term infants with intrauterine growth restriction. J Pediatr. 2009;154(2):201-206.
2. Lee AC, Kozuki N, Cousens S, Stevens GA, Blencowe H, Silveira MF, et al. Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21st standard: analysis of CHERG datasets. BMJ. 2017;358:j3677. Erratum in: BMJ. 2017;358:j4229.
3. Sankilampi U, Hannila ML, Saari A, Gissler M, Dunkel L. New population-based references for birth weight, length, and head circumference in singletons and twins from 23 to 43 gestation weeks. Ann Med. 2013;45(5-6):446-454.
4. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48(3):333-339.
5. Dudley NJ. A systematic review of the ultrasound estimation of fetal weight. Ultrasound Obstet Gynecol. 2005;25(1):80-89.
6. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal Diagn Ther. 2014;36(2):86-98.
7. Baschat AA. Fetal growth restriction - from observation to intervention. J Perinat Med. 2010;38(3):239-246.
8. Sauder MW, Lee SE, Schulze KJ, Christian P, Wu LSF, Khatry SK, et al. Inflammation throughout pregnancy and fetal growth restriction in rural Nepal. Epidemiol Infect. 2019;147:e258.
9. Lee AC, Cherkerzian S, Tofail F, Folger LV, Ahmed S, Rahman S, et al. Perinatal inflammation, fetal growth restriction, and long-term neurodevelopmental impairment in Bangladesh. Pediatr Res. 2024;96(7):1777-1787.
10. Goldstein JA, Gallagher K, Beck C, Kumar R, Gernand AD. Maternal-fetal inflammation in the placenta and the developmental origins of health and disease. Front Immunol. 2020;11:531543.
11. Kırmızı DA, Baser E, Onat T, Caltekin MD, Kara M, Yalvac ES. Can inflammatory hematological parameters be a guide to late-onset fetal growth restriction? Z Geburtshilfe Neonatol. 2020;224(5):262-268.
12. Seyhanli Z, Bayraktar B, Karabay G, Filiz AA, Bucak M, Agaoglu RT, et al. Can maternal inflammatory and nutritional status, evaluated by the hemoglobin, albumin, lymphocyte, and platelet (HALP) score and the prognostic nutritional index (PNI) in the first trimester, predict late-onset fetal growth restriction? BMC Pregnancy Childbirth. 2024;24(1):620.
13. Tolunay HE, Eroğlu H, Varlı EN, Akşar M, Şahin D, Yücel A. Evaluation of first-trimester neutrophil-lymphocyte ratio and platelet-lymphocyte ratio values in pregnancies complicated by intrauterine growth retardation. Turk J Obstet Gynecol. 2020;17(2):98-101.
14. Aktemur G, Çakır BT, Karabay G, Filiz AA, Seyhanlı Z, Sucu ST, et al. Second-trimester inflammatory markers in predicting fetal growth restriction: a retrospective analysis. Am J Reprod Immunol. 2025;93(1):e70047.
15. Levy O, Pariente G, Rotem R, Yohai D, Weintraub AY. Early predictors of small-for-gestational-age neonates using non-invasive, low-cost, and readily available hematological markers. Int J Gynaecol Obstet. 2020;150(3):340-345.
16. Conde-Agudelo A, Villar J, Lindheimer M. Maternal infection and risk of preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol. 2008;198(1):7-22.
17. Challis JR, Lockwood CJ, Myatt L, Norman JE, Strauss JF 3rd, Petraglia F. Inflammation and pregnancy. Reprod Sci. 2009;16(2):206-215.
18. Zhang Y, Qian Y, Liu C, Fan X, Li X, Song Y, et al. Association between white blood cell count and adverse pregnancy outcomes: a retrospective cohort study from a tertiary hospital in China. BMJ Open. 2023;13(11):e07263.

ORIGINAL RESEARCH

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Evaluation of Inflammatory Biomarkers in Patients with Ovarian Torsion Presenting to the Emergency Department

Acil Servise Başvuran Over Torsiyon Hastalarda Enflamatuvar Biyobelirteçlerin Değerlendirilmesi

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Abstract

Objective: Ovarian torsion (OT), a gynecological emergency caused by ovarian rotation around its vascular pedicle, threatens ovarian viability and demands urgent surgery. Diagnostic delays increase ovarian loss risks. This study evaluated the prognostic value of the CALLY index [C-reactive protein (CRP) × lymphocyte count/albumin], a composite biomarker reflecting inflammation and nutrition, in predicting ovarian necrosis and oophorectomy need in OT patients.

Method: This retrospective cohort included 58 surgically confirmed OT cases (2019-2023). Demographics, clinical/laboratory data (CRP, complete blood count , albumin), and surgical outcomes were analyzed. The CALLY index was calculated preoperatively. Patients were stratified by surgical outcomes: Ovarian conservation (OC, n=36) or necrosis requiring oophorectomy [Oophorectomy/Necrosis (ON), n=22].

Results: The median CALLY index was significantly higher in the ON group (3.85 vs. 0.95, p<0.001). ROC analysis showed excellent diagnostic accuracy for necrosis prediction (area under the curve =0.902; 95% confidence interval: 0.825-0.978), with optimal cut-off =2.05 (sensitivity =86.4%, specificity =83.3%).

Conclusion: The preoperative CALLY index is a simple, cost-effective tool to assess ovarian viability in OT, enhancing clinical/radiological

Öz

Amaç: Over torsiyonu (OT), overin vasküler pedikül etrafında dönmesiyle oluşan, over canlılığını tehdit eden ve acil cerrahi gerektiren jinekolojik bir acil durumdur. Tanıdaki gecikmeler over kaybı riskini artırır. Bu çalışma, sistemik enflamasyon ve beslenme durumunu yansıtan kompozit bir biyobelirteç olan CALLY indeksinin [C-reaktif protein (CRP) × lenfosit sayısı)/albümin], OT hastalarında over nekrozu ve ooforektomi gereksinimini öngörmedeki prognostik değerini değerlendirmeyi amaçlamıştır.

Yöntem: Bu retrospektif kohort çalışmasına, 2019-2023 arasında cerrahi olarak doğrulanmış 58 OT olgusu dahil edildi. Demografik veriler, klinik/laboratuvar bulguları (CRP, tam kan sayımı, albümin) ve cerrahi sonuçlar analiz edildi. CALLY indeksi preoperatif olarak hesaplandı. Hastalar cerrahi sonuçlara göre iki gruba ayrıldı: Over koruyucu cerrahi (OK, n=36) veya nekroz nedeniyle ooforektomi gerekenler [ooferektomi/nekroz (ON), n=22)].

Bulgular: ON grubunda medyan CALLY indeksi OK grubuna göre anlamlı derecede yüksekti (3,85 vs. 0,95, p<0,001). ROC analizi, nekrozu öngörmede mükemmel tanısal doğruluk gösterdi (eğri altında kalan alan=0,902; %95 güven aralığı: 0,825-0,978), optimal kesim değeri =2,05 (duyarlılık =%86,4, özgüllük= %83,3).

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Abstract

evaluations. Elevated values correlate strongly with necrosis risk, aiding surgical decisions. Larger multicenter studies are needed to validate its integration into routine OT management.

Keywords: Albumin, CALLY index, C-reactive protein, lymphocyte, ovarian torsion, prognosis

Öz

Sonuç: Preoperatif CALLY indeksi, OT'de over canlılığını değerlendirmek için mevcut klinik/radyolojik yöntemleri tamamlayan basit ve düşük maliyetli bir araçtır. Yüksek değerler nekroz riski ile güçlü ilişkilidir ve cerrahi kararları destekler. Rutin OT yönetimine entegrasyonu için geniş ölçekli, çok merkezli çalışmalarla doğrulanması gereklidir.

Anahtar kelimeler: Albümin, CALLY indeksi, C-reaktif protein, lenfosit, over torsiyonu, prognoz

Introduction

Ovarian torsion (OT) is a critical acute abdominal condition in gynecological practice, resulting from axial rotation of the ovary around its vascular pedicle, severely compromising ovarian perfusion and requiring urgent surgical intervention (1,2). This mechanical obstruction initially leads to ovarian congestion and edema due to impaired venous and lymphatic drainage. As the condition progresses, disruption of arterial blood flow may result in ischemia, hemorrhagic infarction, and ultimately irreversible tissue necrosis (3). OT accounts for approximately 2.7% to 7.4% of all gynecological emergencies and can occur at any age. However, it is more prevalent in women of reproductive age, particularly in the presence of predisposing factors such as benign cysts (e.g., dermoid cysts, serous cystadenomas), neoplasms, or pregnancy, which increase ovarian mobility and volume (4). Delays in diagnosis and treatment not only lead to ovarian loss, long-term complications (e.g., reduced fertility potential, premature menopause), but also impose a significant socio-economic burden due to diagnostic uncertainties, increased imaging costs, and potential unnecessary or delayed surgeries (5). Thus, early and accurate diagnostic approaches, coupled with timely surgical strategies, are critical to preserving ovarian viability, maintaining fertility prospects, and minimizing patient morbidity.

The clinical diagnosis of OT has historically been challenging due to variable and non-specific symptoms. While advancements in imaging—particularly transvaginal ultrasonography (USG) and Doppler USG—have improved preoperative diagnostic accuracy (6), their performance is not infallible. In early-stage, partial, or intermittent torsion, the presence of Doppler flow can be misleading, contributing to diagnostic delays (7).

These diagnostic dilemmas and the irreversible consequences of delayed intervention have spurred the search for reliable, rapid, and cost-effective biomarkers to predict OT severity, viability, and outcomes. The pathophysiology of OT involves ischemia-reperfusion injury and a complex inflammatory cascade (8). Individual biomarkers like C-reactive protein (CRP), albumin, and lymphocyte count, while reflective of systemic inflammation, may lack sufficient prognostic power when assessed in isolation (9). This study hypothesizes that the CALLY index [CRP (mg/L) × absolute lymphocyte count (ALC) (10^9/L)/albumin (g/L)], integrating CRP, ALC, and albumin, offers superior prognostic performance compared to individual biomarkers in predicting ovarian necrosis and oophorectomy requirements in OT patients. Our specific aim is to investigate the association between preoperative CALLY index and ovarian viability in surgically confirmed OT cases, evaluating its potential role in clinical decision-making.

Materials and Methods

Study Design and Patient Population

This retrospective cohort study analyzed the medical records of patients diagnosed with OT between January 2019 and December 2023 at the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Emergency Medicine Clinic, who were subsequently referred to gynecology for consultation. The study was conducted in accordance with the ethical principles of the Helsinki Declaration and approved by the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Local Ethics Committee (approval no: E-48670771-514.99-272287936, date: March 24, 2025, meeting no: 126). Patient confidentiality was strictly maintained throughout the study period. Although patient data were anonymized, written informed consent was obtained from all participants for the use of their data.

Inclusion criteria were defined as follows: Surgical confirmation of OT via laparoscopic or laparotomic

intervention; availability of complete preoperative laboratory parameters [CRP, complete blood count including white blood cell count (WBC), lymphocyte percentage (LYM%), and calculated (ALC)], and serum albumin] obtained within the first 24 hours of admission (typically during emergency department evaluation or early hospitalization); age ≥18 years; and surgical reports explicitly documenting ovarian viability (e.g., "normal vascularization post-detorsion", "viable ovary") or necrosis (e.g., "necrotic appearance", "blackened ovarian tissue", "no perfusion observed") alongside the surgical procedure performed (detorsion, cystectomy, oophorectomy, salpingo-oophorectomy).

Exclusion criteria comprised: Known or suspected ovarian malignancy or systemic malignancy history; active systemic autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis) or chronic inflammatory disease (e.g., active inflammatory bowel disease); concurrent severe infection (e.g., sepsis, severe pneumonia, generalized peritonitis) or major trauma potentially confounding inflammatory parameters; long-term immunosuppressive therapy (e.g., high-dose systemic corticosteroids, biologic agents); severe decompensated liver or renal failure (conditions directly affecting albumin and CRP levels); irreparable deficiencies in medical records regarding key variables (CRP, albumin, blood count, surgical findings); and cases of isolated fallopian tube torsion or paraovarian/paratubal cyst torsion without ovarian involvement.

Data Collection Protocol and Variable Definitions

Patient demographic data, obstetric history, presenting symptoms, symptom duration, known comorbidities, preoperative laboratory values, radiological findings (USG, Doppler USG, computed tomography/magnetic resonance imaging when applicable), and surgical details (date of surgery, torsion localization, degree of torsion, macroscopic ovarian appearance, surgical procedure performed) were extracted from the hospital's Panates system using a standardized data collection form. ALC was calculated precisely using the formula: ALC (10^9/L) = [WBC (10^9/L)×LYM%]/100, derived from the complete blood count parameters (13,14). The CALLY index was individually computed for each patient using the formula CALLY index = [CRP (mg/L) × ALC (10^9/L)]/albumin (g/L). To ensure unit standardization, albumin values recorded in g/dL (e.g., 3.8 g/dL) were converted to g/L (e.g., 38 g/L). This meticulous standardization and data extraction process was critical for accurate and consistent CALLY index calculations (10).

Sample Size and Power Analysis

As this study was retrospective and exploratory, no prospective sample size calculation was performed initially. However, based on the observed area under the curve (AUC) value (0.902) for the CALLY index and the effect size between groups, a post-hoc estimation suggested that a future prospective study testing a similar hypothesis would require approximately 40 patients per group (80 total) to detect a comparable difference with 80% statistical power and a 5% Type I error rate. This projection serves as preliminary guidance for methodological planning in larger-scale studies (11).

Outcome Measures and Grouping

The primary outcome measure was defined as the intraoperative confirmation of ovarian necrosis, documented in surgical notes using descriptors such as "necrotic", "absent/inadequate perfusion", or "blackened appearance", or the subsequent requirement for oophorectomy/salpingo-oophorectomy (when ovary-sparing surgery was not feasible) (12). Patients were stratified into two groups based on this outcome: Group 1 [ovarian conservation surgery (OCS)]: Patients who underwent detorsion and/or cystectomy with preserved ovarian viability (13); Group 2 [oophorectomy/necrosis (ON)]: Patients requiring oophorectomy or salpingo-oophorectomy due to ovarian necrosis (14).

Statistical Analysis

Analyses were conducted utilizing IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA). Continuous variables were evaluated for normality via the Kolmogorov-Smirnov or Shapiro-Wilk tests. Variables conforming to a normal distribution were summarized as mean ± standard deviation (SD), whereas non-parametric data were described as median [interquartile range (IQR)]. Categorical variables were expressed as frequency counts (n) and proportions (%). For intergroup comparisons (OCS vs. ON), parametric data were analyzed using Student's t-test, while non-parametric data were assessed with the Mann-Whitney U test. Categorical variables were compared via the chi-square test or Fisher's exact test for small sample sizes.

Associations between the CALLY index and laboratory markers (CRP, albumin, ALC, WBC) were examined using Spearman's rank correlation (15). Diagnostic performance of the CALLY index and other biomarkers in differentiating ovarian necrosis was evaluated through receiver operating characteristic (ROC) curve analysis. AUC values and 95% confidence intervals (CI) were calculated (16). Optimal

cut-off thresholds were identified by maximizing Youden's index (sensitivity + specificity - 1), with corresponding sensitivity, specificity, positive predictive values, and negative predictive values derived. Statistical significance was defined as two-sided p-values <0.05.

Results

The analysis included 58 eligible participants during the research period. Participants had a mean age of 30.2 years. Conservative ovarian surgery (Group 1: OCS) was applied to 36 cases (62.1%), whereas ovarian necrosis (Group 2: ON) necessitated oophorectomy or salpingo-oophorectomy in 22 cases (37.9%).

Group Comparisons

The ON group exhibited a statistically significant longer median symptom duration compared to the OCS group [36 hours (IQR: 24-48) vs. 18 hours (IQR: 12-24), p<0.001]. Absence of blood flow on preoperative Doppler USG was more frequently reported in the ON group (68.2% vs. 27.8%, p=0.003). Preoperative leukocyte count was significantly higher in the ON group [14.8×10^9/L (IQR: 12.1-17.5) vs. 10.3×10^9/L (IQR: 8.2-13.1)], p=0.002) (Table 1).

Comparison of the CALLY Index and Other Inflammatory Markers Between Groups

The median CALLY index was statistically significantly higher in the ON group (3.85, IQR: 2.10-7.50) compared to the OCS group (0.95, IQR: 0.45-1.75) (p<0.001). Median CRP levels were significantly elevated in the ON group (95.6 mg/L vs. 22.5 mg/L in OCS, p<0.001), while median albumin levels were significantly lower in the ON group (34.8 g/L vs. 41.5 g/L in OCS, p=0.003). No statistically significant difference was observed in median ALC between groups (p=0.120) (Table 2).

Diagnostic Performance of Biomarkers in Predicting Ovarian Necrosis

The diagnostic performance of the CALLY index, CRP, albumin, and ALC in predicting ovarian necrosis was evaluated using ROC curve analysis. The CALLY index demonstrated the highest diagnostic accuracy among the evaluated biomarkers, with an AUC =0.902 (95% CI: 0.825-0.978). At the optimal cut-off value of 2.05 for the CALLY index, sensitivity was 86.4% and specificity was 83.3% (Table 3).

Correlation Analysis Between Biomarkers

Spearman's correlation analysis revealed a strong positive correlation between the CALLY index and CRP (r=0.78, p<0.001), a moderate negative correlation with albumin (r=-0.62, p<0.001), and a moderate positive correlation with WBC (r=0.51, p<0.001). No statistically significant correlation was observed between the CALLY index and ALC (r=0.15, p=0.250). These findings suggest that the CALLY index is primarily influenced by CRP and albumin levels and, to a lesser extent, by WBC, integrating the

Table 1. Demographic and clinical characteristics of patients

Characteristic	Group 1 (OCS)	Group 2 (ON)	p-value
Age (years, mean ± SD)	29.8±6.9	34.1±8.2	**0.045***
Gravida (median, IQR)	1 (0-2)	1 (0-3)	0.380
Parity (median, IQR)	0 (0-1)	0 (0-1)	0.450
Symptom duration (hours, median, IQR)	16 (8-30)	48 (24-80)	**<0.001**
Preoperative cyst/mass on USG, n (%)	39 (92.8%)	25 (96.2%)	0.750
Absent Doppler flow on preoperative USG, n (%)	10 (23.8%)	19 (73.1%)	**<0.001**
Leukocyte count (WBC, ×10^9/L, median, IQR)	11.2 (8.9-13.8)	15.5 (12.1-20.5)	**<0.001**

OCS: Ovarian conservation surgery, ON: Oophorectomy/necrosis, USG: Ultrasonography, SD: Standard deviation, WBC: White blood cell count, IQR: Interquartile range, *: p-value approaching 0.05 may indicate a trend but does not demonstrate strong statistical significance

Table 2. Comparison of preoperative inflammatory and nutritional markers between groups (patients with calculable CALLY index, median, IQR)

Parameter	Group 1 (OCS)	Group 2 (ON)	p-value
CRP (mg/L)	15.5-52.0	125.0 (70.0-210.0)	**<0.001**
Albumin (g/L)	40.1 (38.0-42.5)	33.5 (30.5-37.0)	**0.001**
ALC (×10^9/L)	1.75 (1.2-2.4)	1.30 (0.75-1.9)	0.075
CALLY index	1.22 (0.60-2.10)	4.85 (2.90-9.50)	**<0.001**

OCS: Ovarian conservation surgery, ON: Oophorectomy/necrosis, CRP: C-reactive protein, ALC: Absolute lymphocyte count, IQR: Interquartile range

Table 3 ROC analysis results of the CALLY index and other biomarkers in predicting ovarian necrosis

Biomarker	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p-value
CALLY index	0.915	0.810-0.980	≥2.30	84.6	86.4	84.6	86.4	**<0.001**
CRP (mg/L)	0.870	0.750-0.950	≥60.0	76.9	81.8	76.9	81.8	**<0.001**
Albumin (g/L)	0.805	0.650-0.920	<36.5	69.2	77.3	70.0	76.5	**0.003**
ALC ($\times 10^9$/L)	0.630	0.450-0.790	<1.25	61.5	59.1	54.2	65.9	0.150
WBC ($\times 10^9$/L)	0.780	0.630-0.895	>13.5	69.2	72.7	65.4	76.2	**0.008**

AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, CRP: C-reactive protein, ALC: Absolute lymphocyte count, WBC: White blood cell count, ROC: Receiver operating characteristic

inflammatory and nutritional status reflected by these parameters.

Discussion

OT is a critical gynecological pathology requiring urgent diagnosis and surgical intervention, as compromised blood flow threatens tissue viability and may lead to fertility loss, particularly in women of reproductive age. Diagnostic delays or misinterpretations can result in ovarian necrosis and subsequent oophorectomy, with profound consequences for patients (17). In this study, we retrospectively investigated the prognostic value of the CALLY index—an easily calculable composite biomarker reflecting systemic inflammation and nutritional status—in predicting ovarian necrosis and the need for oophorectomy in OT patients. Our key finding is that the preoperative CALLY index was significantly higher in patients with ovarian necrosis requiring oophorectomy (ON group) compared to those who underwent (OCS group), demonstrating high diagnostic accuracy (AUC =0.902) for predicting necrosis (18). These results suggest that the CALLY index could serve as a potential adjunctive tool for risk stratification and optimizing surgical decision-making in OT cases (18).

The higher AUC value of the CALLY index (0.902) compared to standalone CRP (0.845) and albumin (0.712) underscores its integrative prognostic utility and supports the superiority of composite biomarkers in multifactorial pathologies like OT (19).

Clinical Implications, Interpretative Challenges, Role in Differential Diagnosis, and Outlier Considerations

The presence of outlier cases highlights that the CALLY index is not a standalone diagnostic test but a complementary resource in clinical decision-making, particularly in scenarios of diagnostic uncertainty (20). Interpretation must account for factors such as torsion duration, severity, and the patient's physiological response.

Strengths and Limitations of the Study

Another potential limitation of our study lies in the challenges of data standardization due to heterogeneous documentation (e.g., notes entered by different clinicians at varying timepoints) and variable laboratory parameters. Notably, the lack of routine albumin measurement for all patients at admission may have restricted the number of cases with calculable CALLY indices, thereby limiting the statistical power of the analysis.

Future Perspectives and Innovative Research Directions

To solidify the prognostic role of the CALLY index in OT and establish its clinical utility, future research should incorporate innovative approaches. First, our findings must be validated through large-scale, multicenter, prospective studies. Second, integrating the CALLY index into a composite "OT severity score" alongside clinical and radiological parameters warrants investigation. Third, the relationship between serial CALLY index changes and ovarian viability recovery post-detorsion should be explored. Finally, translational studies could assess the CALLY index as a biomarker for evaluating therapeutic agents aimed at mitigating reperfusion injury.

Clinical Implications

In clinical practice, the CALLY index, when integrated with existing clinical and radiological findings during the initial evaluation of patients suspected of OT, may provide valuable, objective, and complementary input for risk stratification and decision-making regarding the urgency and timing of surgical intervention. Clinicians may interpret the CALLY index as a "red flag" system, adopting more vigilant monitoring and proactive surgical approaches for patients with elevated index values. Its cost-effectiveness and ease of application enhance its potential for widespread adoption across diverse healthcare settings.

Study Limitations

Given the limitations of this study—including its retrospective design and single-center nature—there is an urgent need for large-scale, multicenter, prospective validation studies and detailed analyses in diverse patient subgroups to establish the definitive role and optimal utilization strategies of the CALLY index in OT management. Future research should focus on developing sophisticated prognostic models incorporating the CALLY index, integrating this biomarker into clinical decision support systems, and advancing evidence-based strategies to enhance patient care quality and outcomes in time-sensitive, fertility-threatening emergencies like OT. The ultimate goal remains minimizing ovarian loss and preserving long-term health and reproductive potential through informed, timely decisions in OT management.

Conclusion

This retrospective study robustly demonstrates that the preoperative CALLY index holds significant prognostic potential for predicting ovarian necrosis and subsequent oophorectomy in OT patients, with superior diagnostic accuracy compared to individual inflammatory biomarkers. Elevated CALLY index values may reflect a heightened systemic inflammatory response and increased ischemic risk, serving as a critical warning sign of reduced ovarian salvageability. These findings underscore its role as a key factor in optimizing surgical decision-making.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical principles of the Helsinki Declaration and approved by the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Local Ethics Committee (approval no: E-48670771-514.99-272287936, date: March 24, 2025, meeting no: 126).

Informed Consent: Although patient data were anonymized, written informed consent was obtained from all participants for the use of their data.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.S., M.İ.T., A.K., Concept: N.U., M.Y., Design: N.U., N.Y., A.K., Data Collection or Processing: A.S., M.Y., A.K., Analysis or Interpretation: M.İ.T., N.U., N.Y., Literature Search: M.İ.T., M.Y., N.Y., Writing: A.S., M.İ.T., A.K.

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References

1. Baron SL, Mathai JK. Ovarian torsion. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. [Updated 2023 Jul 17]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560675/
2. Tabbara F, Hariri M, Hitti E. Ovarian torsion: a retrospective case series at a tertiary care center emergency department. PLoS One. 2024;19(3):e0297690.
3. Kuo CH, Martingano DJ, Singh P. Pelvic congestion syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. [Updated 2025 Jan 19]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560790/
4. Birbas E, Kanavos T, Gkrozou F, Skentou C, Daniilidis A, Vatopoulou A. Ovarian masses in children and adolescents: a review of the literature with emphasis on the diagnostic approach. Children (Basel). 2023;10(7):1114.
5. Torrealday S, Kodaman P, Pal L. Premature ovarian insufficiency - an update on recent advances in understanding and management. F1000Res. 2017;6:2069.
6. Jebessa Kumsa M, Wubeshet Haile Z. The role of ultrasound in women's health. London: IntechOpen; 2024.
7. Grunau GL, Harris A, Buckley J, Todd NJ. Diagnosis of ovarian torsion: is it time to forget about Doppler? J Obstet Gynaecol Can. 2018;40(7):871-875.
8. Toprak V, Deveci E. Expression of VEGF in fallopian tubes in ovarian ischemia-reperfusion. Med Rec Int Med J. 2023;5(2):337-341.
9. Katkat F, Kalyoncuoglu M, Karahan S. The predictive ability of the C-reactive protein to albumin ratio as a mortality predictor in hospitalized severe SARS-CoV-2 infected patients with cardiovascular diseases. Med Bull Haseki. 2022;60(2):152-160.
10. Zhang J, Lin Y, Zeng J, Luo G, Liao P, Chen Q, et al. The C-reactive protein (CRP)-albumin-lymphocyte (CALLY) index exhibits an L-shaped association with all-cause mortality in rheumatoid arthritis patients: a retrospective cohort study. BMC Rheumatol. 2025;9(1):47.
11. Brooks G, An Q, Li Y, Johanson G. For post hoc's sake: determining sample size for Tukey multiple comparisons in 4-group ANOVA. Gen Linear Model J. 2023;47:1-14.
12. Novoa M, Friedman J, Mayrink M. Ovarian torsion: can we save the ovary? Arch Gynecol Obstet. 2021;304(1):191-195.
13. Wright JD, Jorge S, Tergas AI, Hou JY, Burke WM, Huang Y, et al. Utilization and outcomes of ovarian conservation in premenopausal women with endometrial cancer. Obstet Gynecol. 2016;127(1):101-108.
14. Doshi N, Kanani D, Garber L, Ramaraju RH, Al-Kunani AS. Ischemic gangrene requiring right salpingo-oophorectomy in a patient with ovarian cyst torsion and a history of bilateral ovarian cysts: a case report. Cureus. 2025;17(5):e83595.

15. Liu Y, Wei Y. Association between the CALLY index, vitamin D, and asthma: insights from NHANES. Front Allergy. 2025;6:1557677.

16. Akdoğan O, Yücel KB, Yazıcı O, Özet A, Özdemir N. Assessment of the CALLY index, a novel immunonutrivite marker, in perioperatively treated gastric cancer patients. Gazi Med J. 2025;36(1):85-90.

17. Tielli A, Scala A, Alison M, Vo Chieu VD, Farkas N, Titomanlio L, et al. Ovarian torsion: diagnosis, surgery, and fertility preservation in the pediatric population. Eur J Pediatr. 2022;181(4):1405-1411.

18. Feng J, Wang L, Yang X, Chen Q. Clinical significance of preoperative CALLY index for prognostication in patients with esophageal squamous cell carcinoma undergoing surgery. Sci Rep. 2024;14(1):713.

19. Fu S, Chen Z, Wu H. Association between CRP-albumin-lymphocyte (CALLY) index and asthma-COPD overlap: analysis of NHANES 2015-2018 data. BMC Pulm Med. 2025;25(1):257.

20. Sarıdaş A, Çetinkaya R. The prognostic value of the CALLY index in sepsis: a composite biomarker reflecting inflammation, nutrition, and immunity. Diagnostics (Basel). 2025;15(8):1026.

ORIGINAL RESEARCH

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Examining the Relationship Between Cognitive Insight and Treatment Adherence in Psychiatric Patients

Psikiyatri Hastalarında Bilişsel İçgörü ile Tedavi Uyumu Arasındaki İlişkinin İncelenmesi

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Abstract

Objective: The study aimed to investigate the relationship between cognitive insight and treatment adherence among psychiatric patients.

Method: This descriptive, cross-sectional, and correlational study was conducted between February and April 2023 with 140 psychiatric patients in a public hospital in İstanbul. Data were collected using a personal ınformation form, the Morisky medication adherence scale, and the Beck cognitive insight scale. Statistical analyses, including confirmatory factor analysis and structural equation modeling, were performed using SPSS 25.0 and AMOS 24.0.

Results: The expressing oneself subdimension of cognitive insight had a statistically significant positive effect on treatment adherence (β=0.259; p<0.001), indicating that patients with higher expressive ability showed greater adherence. Conversely, the self-confidence subdimension did not have a significant impact (β=0.050; p>0.05). The model explained 10.5% of the variance in treatment adherence.

Conclusion: The ability to express oneself, an important subdimension of cognitive insight, is a significant predictor of treatment adherence in psychiatric patients. Enhancing expressive abilities may improve therapeutic engagement and adherence. However, self-confidence alone does not appear to directly influence adherence in this clinical context. These findings highlight the importance of incorporating insight-focused interventions into psychiatric care.

Keywords: Cognitive insight, psychiatric inpatients, self-confidence, self-reflectiveness, treatment adherence

Öz

Amaç: Çalışmanın amacı, psikiyatri hastalarında bilişsel içgörü ile tedaviye uyum arasındaki ilişkiyi incelemektir.

Yöntem: Tanımlayıcı, kesitsel ve ilişki arayıcı tasarıma sahip bu çalışma, Şubat-Nisan 2023 tarihleri arasında İstanbul'daki bir kamu hastanesindeki 140 psikiyatri hastası ile gerçekleştirilmiştir. Veriler, kişisel bilgi formu, Morisky ilaç uyumu ölçeği ve Beck bilişsel içgörü ölçeği kullanılarak toplanmıştır. İstatistiksel analizlerde SPSS 25.0 ve AMOS 24.0 programları aracılığıyla doğrulayıcı faktör analizi ve yapısal eşitlik modellemesi uygulanmıştır.

Bulgular: Bilişsel içgörünün kendini ifade etme alt boyutu, tedavi uyumu üzerinde istatistiksel olarak anlamlı ve pozitif bir etkiye sahiptir (β=0,259; p<0,001). Bu durum, ifade yetisi yüksek olan hastaların daha yüksek düzeyde tedavi uyumu gösterdiğini ortaya koymaktadır. Buna karşılık, kendine güven alt boyutunun tedavi uyumu üzerinde anlamlı bir etkisi bulunmamıştır (β=0,050; p>0,05). Kurulan model, tedavi uyumundaki varyansın %10,5'ini açıklamaktadır.

Sonuç: Bilişsel içgörünün önemli bir alt boyutu olan kendini ifade etme yetisi, psikiyatri hastalarında tedavi uyumunun anlamlı bir yordayıcısıdır. Bu yetinin güçlendirilmesi, terapötik katılımı ve tedaviye uyumu artırabilir. Ancak, klinik bağlamda yalnızca kendine güvenin doğrudan bir etkisi gözlenmemiştir. Bu bulgular, psikiyatrik bakım süreçlerine içgörü odaklı müdahalelerin dahil edilmesinin önemini vurgulamaktadır.

Anahtar kelimeler: Bilişsel içgörü, kendine güven, öz yansıtma, psikiyatri hastaları, tedavi uyumu

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Introduction

Treatment adherence (TA) is a vital factor that directly impacts the progression of illness in psychiatric patients. It significantly influences treatment outcomes, quality of life, and the effectiveness of healthcare interventions provided to the patient. Non-adherence may result in higher hospitalization rates, increased symptom severity, and even a greater risk of suicide (1,2). According to the World Health Organization (3), failure to stick to treatment in severe mental disorders such as bipolar disorder and schizophrenia substantially raises mortality, morbidity, and hospital readmission rates. TA in psychiatric patients has important implications not only for individuals but also for healthcare systems and society at large. Recognizing the impact of non-adherence across these domains promotes the development of strategies to improve adherence and, consequently, outcomes at multiple levels. For individuals, sticking to psychiatric medications is essential for effectively managing mental health conditions. Studies show that non-adherence is common, with nearly half of psychiatric patients not taking their medications as prescribed (4,5). This non-adherence can worsen symptoms, aggravate psychiatric conditions, and heighten the risk of hospitalization and crises (1). Contributing factors include a lack of insight into one's illness, negative attitudes toward treatment, and poor communication with healthcare providers (6). From a healthcare system perspective, treatment non-adherence increases the burden on hospitals and mental health services. Poor adherence frequently leads to more visits to emergency departments and psychiatric wards, boosting healthcare utilization and incurring substantial costs (1,7). Moreover, ineffective management of psychiatric disorders due to non-adherence can cause repeated hospital stays and system instability, complicating mental health service delivery (8). On a societal level, the effects of TA in psychiatric patients are significant. Non-adherence not only affects individual health outcomes but also creates broader societal issues, such as higher unemployment, involvement of mentally ill individuals in the criminal justice system, and increased societal costs linked to untreated mental health conditions (7,8). Patients with psychiatric disorders who do not adhere to treatment might also engage in behaviors that endanger public safety and health. For example, untreated mental illness is linked to higher rates of aggression or self-harm, which can pose risks to both the individual and others (9). Cognitive insight plays an important role in motivating patients to follow their treatment plans. Research indicates that patients with greater insight into their mental health are more likely to recognize the need for medication, which directly relates to better recovery outcomes (10,11). Cognitive insight refers to a person's metacognitive capacity to critically evaluate and reappraise their own distorted beliefs and misinterpretations, and to remain receptive to corrective feedback (12). It encompasses two main components: self-reflectiveness, which reflects openness to re-evaluating one's beliefs, and self-certainty, which refers to overconfidence in one's interpretations. Higher levels of cognitive insight have been linked to increased recognition of illness, stronger motivation to engage in treatment, and improved adherence outcomes (11). Understanding their illness often strongly influences adherence behavior. Conversely, poor insight into psychiatric symptoms tends to decrease motivation for treatment, leading to non-adherence (13). For instance, roughly 50% of patients with schizophrenia show poor insight, which is associated with lower medication adherence and worse recovery and treatment results (13). Cognitive insight involves a person's ability to recognize and correct distorted thoughts and beliefs. It encompasses broader metacognitive skills, including awareness and evaluation of one's own thinking processes (14). For psychiatric patients especially those with schizophrenia or bipolar disorder cognitive insight is key to understanding the need for treatment. Without this insight, patients often deny their illness, resulting in lower adherence to medication and treatment plans (15,16). Although previous studies have looked at the relationship between insight and TA in psychiatric groups, the concept of cognitive insight, characterized by self-reflectiveness and self-certainty, has received limited attention in this area. Self-reflectiveness refers to the individual's capacity to question their own beliefs, consider alternative explanations, and remain open to feedback. For example, patients with higher self-reflectiveness may recognize that their symptoms such as unusual thoughts or perceptual experiences could be part of a mental health condition, leading them to seek clarification from healthcare providers and adhere more closely to treatment (17,18). In contrast, self-certainty reflects a high level of confidence in the accuracy of one's beliefs and interpretations, which may lead to resistance toward contradictory information and treatment recommendations (12). Although general clinical insight has been extensively studied in relation to TA, fewer studies have specifically addressed these two cognitive insight dimensions, particularly in bipolar disorder populations (19). Most research has focused on clinical insight or general symptom awareness, often relying on cross-sectional correlations without

exploring underlying mechanisms or the direction of the relationship. Although several studies have investigated the association between clinical insight and TA (19,20), most have conceptualized insight in broad terms, such as general symptom recognition or awareness of illness, and have predominantly relied on cross-sectional designs. This approach limits understanding of the temporal sequence and underlying mechanisms linking insight to adherence. Furthermore, relatively few studies have examined the specific cognitive insight dimensions self-reflectiveness and self-certainty as predictors of adherence, particularly in bipolar disorder populations (21). Addressing this gap is crucial for identifying targeted therapeutic strategies that can enhance adherence through improvements in these specific cognitive processes. Moreover, studies involving inpatient psychiatric populations, particularly those diagnosed with bipolar disorder, are rare, despite the importance of adherence in this group. Additionally, there is a notable lack of research using advanced statistical methods such as structural equation modeling (SEM) to investigate how aspects of cognitive insight might predict adherence behaviors through both direct and indirect routes. Although the study was open to all psychiatric patients meeting the criteria, all participants admitted during data collection happened to have bipolar disorder. This homogeneity reflects the patient profile of the hospital at that time rather than an initial focus on bipolar disorder inpatients.

The study aimed to investigate the relationship between cognitive insight and TA among psychiatric patients.

Materials and Methods

Study Design and Setting

This descriptive, cross-sectional, and correlational study was conducted from February 20 to April 27, 2023, at the psychiatry clinic of a public hospital, the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, in İstanbul, Turkey.

Study Population and Sampling

The study population consisted of all psychiatric patients aged 18 years and older who received care in the aforementioned hospital during the study period (n=200). The final sample included 140 patients, selected through purposive sampling based on inclusion and exclusion criteria and voluntary participation.

The sample size was estimated using G*Power 3.1 software. A priori power analysis for a two-tailed correlation test was conducted using a medium effect size (r=0.30), an α level of 0.05, and a power of 0.80, resulting in a minimum required sample of 84 participants. This estimation was based on Cohen's (22) guidelines. The final sample of 140 participants exceeded this minimum, enhancing statistical validity.

Inclusion and Exclusion Criteria

Inclusion criteria for the study were being 18 years of age or older, providing voluntary participation, having a psychiatric disorder diagnosed according to diagnostic and statistical manual of mental disorders-5, receiving oral or parenteral antipsychotic treatment, and having at least six months since diagnosis. Exclusion criteria were having significant visual or auditory impairments, a history of traumatic brain injury or central nervous system infection, or a substance use disorder within the past two months.

Research Hypotheses

H_1: The "expressing oneself" (EO) subdimension of cognitive insight has a positive and statistically significant effect on TA.

H_2: The "self-confidence" (SC) subdimension of cognitive insight has a positive and statistically significant effect on TA.

Data Collection Tools

Data were collected using the following instruments:

1. Personal information form: Created by the researcher based on literature, this form includes 8 items that assess demographic and clinical characteristics such as age, gender, diagnosis, family psychiatric history, and medication responsibility (21).

2. Morisky medication adherence scale (MMAS-4): A 4-item scale developed by Morisky et al. (23) to measure adherence using "yes/no" responses. Adherence is classified as good, moderate, or poor. The scale's Turkish version was utilized, with reported internal consistency (Cronbach's α=0.61). The Turkish adaptation and psychometric assessment for use in individuals with bipolar disorder was performed by Bahar et al. (24), showing satisfactory validity and reliability.

3. Beck Cognitive Insight Scale (BCIS): A 15-item self-report tool developed by Beck et al. (25) to assess cognitive insight through two subscales: Self-reflectiveness and self-certainty. A composite score is created by subtracting self-certainty from self-reflectiveness. The Turkish version and psychometric validation were carried out by Aslan et al. (26).

Data Collection Procedure

Participants were recruited by the researcher during routine ward visits. After obtaining informed consent, the questionnaires were administered face-to-face in a quiet and private setting. The researcher remained present to ensure that questions were understood and answered appropriately.

Statistical Analysis

Data obtained from 140 participants were analyzed using IBM SPSS Statistics version 25.0 and AMOS version 24.0. Descriptive statistics including mean, standard deviation, frequency, and percentage distributions were used to summarize the demographic and clinical characteristics of the sample. Prior to model testing, the normality of data distribution was assessed using Skewness and Kurtosis coefficients. All variables exhibited values within the acceptable range (-1.5 to +1.5), indicating normal distribution. Accordingly, the maximum likelihood (ML) method was selected for parameter estimation in SEM.

A two-tailed significance level of $p<0.05$ was considered statistically significant for all analyses.

Ethical Considerations

The study was approved by the Ethics Committee of İstanbul Arel University, İstanbul, Turkey (approval date: 10 February 2023; approval no: 2023/03). The research was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. All participants were informed about the purpose, procedures, and voluntary nature of the study, and signed informed consent was obtained. Anonymity and confidentiality were ensured throughout the research process. Data were securely stored and used exclusively for research purposes.

Results

The mean age of the participants was 31.47±7.12 years. Of the total sample, 66.4% (n=93) were female, and 66.4% (n=93) were single. High school graduation was the most common educational level (42.9%, n=60), and 71.4% (n=100) lived in a nuclear family structure. Regarding living arrangements, 51.4% (n=72) lived with parents and siblings. All participants (100%, n=140) were diagnosed with bipolar disorder, and 69.3% (n=97) reported regular medication use. The majority (71.4%, n=100) reported no family history of mental illness. According to the categorical distribution of the medication adherence scale, 47.6% (n=67) demonstrated high adherence, 23.6% (n=33) moderate adherence, and 28.6% (n=40) low adherence.

Confirmatory Factor Analysis (CFA)

Cognitive Insight Scale

The BCIS, consisting of 15 items and two subscales (self-reflectiveness and self-certainty), was subjected to CFA to evaluate construct validity. All item factor loadings were above 0.50, ranging between 0.54 and 0.80, indicating no item removal was required (Figure 1).

Medication Adherence Scale

The MMAS-4, composed of 4 items and a unidimensional structure, was also evaluated using CFA. All factor loadings exceeded 0.50, ranging from 0.52 to 0.86 (Figure 2).

Convergent Validity, Discriminant Validity, and Normality Analysis of the Scale Subdimensions

Composite reliability (CR) values are calculated based on the factor loadings obtained from CFA. A CR value of 0.70 or higher (CR ≥0.70) indicates that the condition for CR has been met. Convergent validity is indicated by the average variance extracted (AVE). For convergent validity to be confirmed, AVE should be at least 0.50 (AVE ≥0.50). However, if CR is above 0.70 for all dimensions, an AVE value of 0.40 or higher is also considered acceptable. To establish discriminant validity, the square root of the AVE for each construct (√AVE), presented in parentheses on the diagonal in Table 1, must be greater than the inter-construct correlation values in the same row and column.

Table 1 presents the reliability and validity values of the scales used in the study. All scales and their subdimensions demonstrated adequate internal consistency (Cronbach's alpha ≥0.70) and met the thresholds for CR and convergent validity. The discriminant validity results confirmed that each construct measured distinct concepts. These results indicate that the instruments were psychometrically sound and suitable for examining the relationship between cognitive insight and TA in the present study.

Normality values of the variables are presented in Table 2. Prior to testing the structural model, the normality of the subdimensions' distribution was assessed through Skewness and Kurtosis coefficients. The values for all variables were found to lie within the acceptable range of -1.5 to +1.5, suggesting that the data followed a normal distribution. Consequently, the ML estimation method was considered suitable for parameter estimation within the model.

Path Analysis of the Structural Equation Model Using Observed Values

In the proposed research model, the effects of the subdimensions of the cognitive insight scale—EO and SC—on the TA score were examined.

In the path analysis model using observed variables, the model fit indices indicated that the model was statistically significant. The chi-square value (χ^2) was 215.55 with 146 degrees of freedom, resulting in a χ^2/df ratio of 1.476, which falls within the acceptable threshold (less than 3), suggesting a good model fit. Furthermore, additional fit indices reinforced the adequacy of the model: The goodness-of-fit index was calculated as 0.920, and the comparative fit index was 0.953—both exceeding the commonly accepted threshold of 0.90, indicating good fit. The standardized root mean square residual was 0.071, and the root mean square error of approximation was 0.059, both within acceptable limits, confirming that the structural model fits the data well (Figure 3).

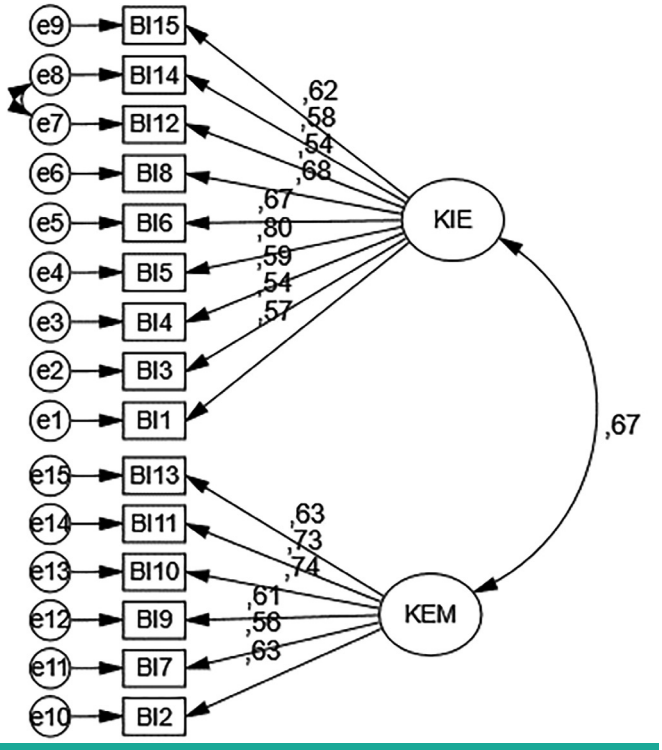

Figure 1. Confirmatory factor analysis structure of the cognitive insight scale

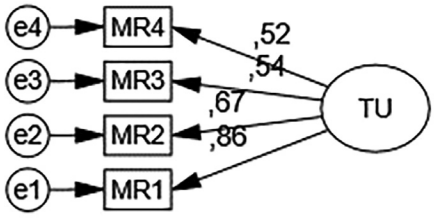

Figure 2. Confirmatory factor analysis structure of the treatment adherence scale

Regression results are presented in Table 3. The following findings were obtained from the model examining the effects of the cognitive insight scale subdimensions on TA:

The EO subdimension had a positive and statistically significant effect on TA (β=0.259; $p<0.05$). This indicates that an increase in EO scores leads to higher levels of TA.

The SC subdimension had a positive but non-significant effect on TA (β=0.050; $p>0.05$), suggesting no statistically meaningful relationship between SC and TA.

The model explained 10.5% of the variance in TA through the EO subdimension (R^2=0.105).

Discussion

This study investigated the effect of cognitive insight—specifically its subdimensions, EO and SC on TA in psychiatric patients diagnosed with bipolar disorder. The findings revealed that only the EO dimension significantly predicted adherence, whereas the SC dimension did not show a meaningful effect.

In psychiatric patients, the way individuals express themselves directly impacts their awareness of the illness, emotional regulation, and social interaction, thereby significantly influencing TA. Expression style helps individuals make sense of their inner experiences (emotions, thoughts, fears) and communicate them to others. As a subcomponent of cognitive insight, the ability to express oneself plays a crucial role in TA. This interaction is influenced by various factors such as communication skills, emotional expression, and the ability to understand and articulate mental health issues. Being able to effectively express emotions and thoughts is essential for establishing a therapeutic alliance between patients and healthcare providers. When patients can communicate their concerns and experiences clearly, healthcare providers gain a better understanding of their perspectives and can develop personalized treatment plans (27). Open communication also helps reduce stigma and encourages TA (28).

Patients who are better at expressing themselves are more likely to cooperate with treatment. Conversely, a lack

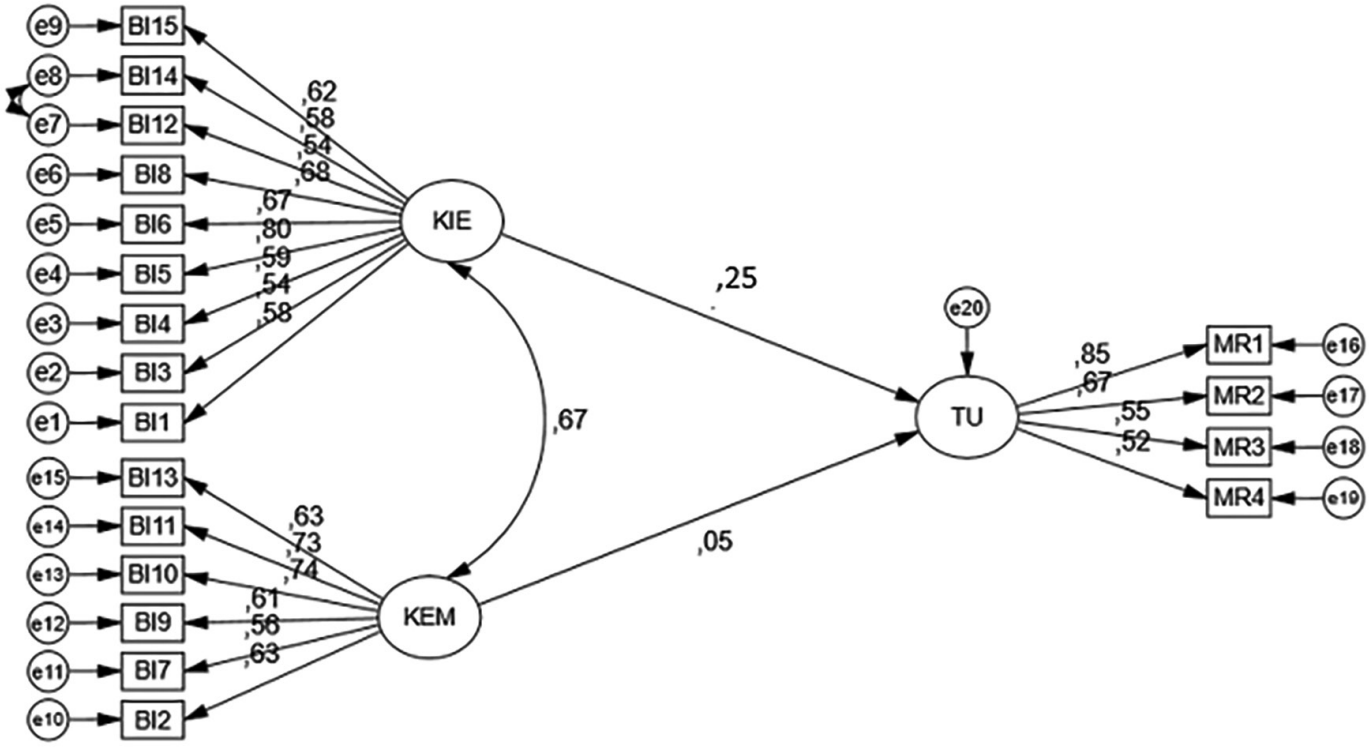

Figure 3. Structural regression model path analysis with observed variables

Table 1. Convergent and discriminant validity values calculated from standardized factor loadings

Dimension	M	SD	EO	SC	TA
EO	2.68	1.08	(0.719)		
SC	2.95	1.20	0.577**	(0.713)	
TA)	1.68	1.18	0.218**	0.015	(0.707)
CA			0.814	0.828	0.737
CR			0.833	0.819	0.713
AVE			0.518	0.509	0.500

**: p<0.01, M: Mean, SD: Standard deviation, EO: Expressing oneself, SC: Self-confidence, TA: Treatment adherence, CA: Cronbach's alpha, CR: Composite reliability, AVE: Average variance extracted

Table 2. Normality analysis of variables in the structural model

Variable	n	Skewness	Kurtosis
Expressing oneself	140	-0.241	-0.889
Self-confidence	140	0.056	-1.090
Treatment adherence	140	-0.874	0.563

Table 3. Significance test of regression coefficients in the model

Independent variable		Dependent variable	Coefficient (B)	Standardized coefficient (β)	Z	p	Hypothesis
EO	→	TA	0.201	0.259	3.868	0.00001***	Accepted
SC	→	TA	0.015	0.05	0.168	0.345	Rejected

***: p<0.001, EO: Expressing oneself, SC: Self-confidence, R^2=0.105

of insight, including difficulties in expressing emotions and thoughts about their condition and treatment, can negatively affect adherence (28). The inability to recognize and articulate personal experiences related to mental health challenges may hinder engagement in treatment. Interventions aimed at increasing insight and enhancing patients' expressive abilities can promote adherence (20). Coping strategies also impact patients' expression styles and adherence. Patients with ineffective coping mechanisms may avoid confronting mental health issues, struggle to express themselves, and thus weaken adherence (6).

Patients who can communicate their needs are more likely to participate in care decisions and follow treatment plans (29). Strong social support systems also support better expression and adherence. Studies show that patients with limited social support and low expressive skills face more difficulties sticking with treatment, highlighting the importance of social support in maintaining participation (30,31). A patient's level of insight the ability to recognize their condition and treatment needs—may also reflect their expressive style. Patients with high self-awareness often clearly express their treatment goals and concerns, promoting adherence (32). Conversely, those with low insight may find it hard to see the value and necessity of treatment, complicating adherence (11,33). As a subcomponent of cognitive insight, expressive ability greatly influences adherence in psychiatric patients. Effective communication fosters a stronger therapeutic relationship with healthcare providers and enhances adherence. Emotional expression, coping strategies, and social support are also believed to affect TA outcomes.

The relationship between self-confidence and lack of insight in psychiatric patients is a complex interaction that significantly impacts adherence and overall mental health outcomes. Self-confidence, defined as an unwavering belief in one's own understanding, beliefs, and perspectives, is generally negatively associated with insight, which refers to recognizing and accepting one's mental illness. When measured with tools like the BCIS, self-confidence typically correlates with lower cognitive insight. BCIS assesses cognitive insight through two main components: Self-reflectiveness (the ability to evaluate oneself) and self-certainty (overconfidence in one's beliefs). Self-confidence involves excessive trust in one's beliefs and resistance to questioning them. Research shows that especially high levels of self-confidence reduce individuals' awareness of their mental state and lower their level of insight (19,34,35). Self-confidence relates to a rigid stance on one's thoughts and perceptions and often leads to resistance against external feedback and corrections. Cooke and colleagues discovered that higher self-confidence scores in patients with schizophrenia correlated with lower cognitive insight, indicating a tendency to ignore evidence that challenges their beliefs (17).

This resistance can hinder therapeutic engagement, as patients might reject treatment suggestions or not recognize the need for adherence. High self-confidence can also suppress the expressive component of cognitive insight, which enables individuals to critically evaluate their thoughts and behaviors. Studies in clinical contexts like first- episode psychosis show that individuals with high self-confidence demonstrate significantly lower expressive ability (18,36,37). This cognitive dynamic can make it harder for individuals to recognize and accept psychotic symptoms, leading to symptom worsening and clinical deterioration (24,38). Research indicates that self-confidence not only weakens cognitive insight but also reinforces maladaptive thought patterns that contribute to emotional dysregulation and are linked to worsening psychiatric symptoms (25). In summary, the relationship between self-confidence and lack of insight in psychiatric patients especially those within the psychotic disorder spectrum is a crucial interaction that complicates treatment. High levels of SC may limit expressive capacity and the ability to recognize mental states, reinforcing cognitive biases that worsen psychiatric symptoms. Addressing these cognitive processes through therapeutic interventions that improve insight and cognitive flexibility is vital for better clinical outcomes and care quality.

In this study, the finding that the "self-confidence" subdimension had no statistically significant effect on TA is noteworthy. This result suggests that individuals' excessive confidence in their thoughts and beliefs may not directly hinder TA. While the literature often links high self-confidence to poor insight and lower adherence (18,39), such a relationship was not observed here. This could be because the sample exclusively included individuals diagnosed with bipolar disorder, most of whom were receiving inpatient treatment. Additionally, the specific context of this study may further explain why the self-confidence subdimension did not significantly affect TA (12,24). These findings highlight the importance of incorporating communication- focused interventions and psychoeducation programs into psychiatric care. For example, structured psychoeducation sessions that help

patients articulate their symptoms, treatment concerns, and emotional experiences may strengthen the therapeutic relationship and improve adherence.

Communication focused therapies, like social skills training and cognitive- behavioral strategies, can further improve patients' expressive abilities by providing a safe environment for practicing emotional expression and perspective- taking (12,39). Given Turkey's cultural context, where family involvement in care is common, including family members in psychoeducation sessions could also reinforce communication skills and promote adherence by fostering a shared understanding of illness management. Overall, tailoring interventions to improve self-expression may not only boost TA but also positively influence broader psychosocial functioning. In inpatient psychiatric settings, where treatment plans are structured and closely monitored, high self-confidence might have less impact, as adherence relies more on external regulation than on individual motivation. Studies show that poor insight is linked to lower adherence and weaker therapeutic alliances in schizophrenia spectrum disorders, contexts similar to inpatient environments.

Additionally, cultural factors may influence insight dimensions; in collectivist societies like Turkey, adherence to medical authority and group- oriented values can reduce the negative effects of high self-confidence on treatment compliance. Therefore, the intensive clinical support available in inpatient care and cultural norms around authority and obedience may lessen the impact of self-confidence as a factor in TA. In these environments, patients tend to follow medication and treatment protocols more consistently due to the structured setting and ongoing professional oversight. Moreover, the influence of self-confidence may also depend on the stage of illness acceptance or the severity of psychotic symptoms. In this context, high self-confidence does not necessarily indicate treatment resistance; some patients may remain adherent to their treatment without critically questioning their choices.

In the present study, the Cronbach's alpha for the MMAS-4 was 0.61, which falls below the generally accepted threshold of 0.70 for internal consistency. This relatively low reliability may partly result from the brevity of the scale, as shorter instruments often produce lower alpha coefficients. Additionally, the MMAS-4 emphasizes a limited range of adherence behaviors, which might not fully represent the multidimensional nature of TA in psychiatric populations. While the MMAS-4 has been widely used in clinical research and its brevity provides practical advantages, the lower reliability suggests that any observed associations between TA and cognitive insight should be interpreted with caution.

An additional strength of this study is its use of SEM, which provides advantages over traditional correlational analyses. Unlike simple correlation methods that look at relationships between two variables at a time, SEM models multiple relationships simultaneously and accounts for measurement error. This approach offers a more accurate estimation of how different subdimensions of cognitive insight contribute to TA and allows for testing theoretical models in a single, comprehensive framework. Using SEM in this context introduces a new perspective to psychiatric research and reveals insights that might be missed with less advanced analytical techniques.

Strengths of the Study

This study addresses essential gaps in the literature by examining the impact of cognitive insight on TA in a sample of psychiatric patients using SEM. The integration of metacognitive constructs within a structural framework allows for a more nuanced understanding of how reflective thinking and belief certainty influence adherence behaviors. By analyzing a sample that predominantly consisted of individuals diagnosed with bipolar disorder, the study offers novel insights into the determinants of TA in this population and contributes to the development of targeted, insight-informed interventions.

Study Limitations

This study has several limitations. First, the cross-sectional design precludes any causal inferences regarding the relationship between cognitive insight and TA. Second, the sample was drawn from a single public hospital in Istanbul, which may limit the generalizability of the findings to other psychiatric populations or clinical settings. Third, the study focused on the relationship between cognitive insight subdimensions and TA within a SEM framework, and did not perform subgroup analyses based on variables such as gender, educational level, employment status, treatment duration, or presence of comorbidities. Although these factors may influence TA, they were beyond the scope of the current research questions and dataset. Future studies should incorporate these variables into their analyses to provide a more comprehensive understanding of the factors affecting adherence. Finally, self-report measures were used to assess TA and cognitive insight, which may be subject to response biases. Another limitation of this study is the relatively low internal consistency of the

MMAS-4 (Cronbach's alpha =0.61). The brevity of the scale and its narrow behavioral focus may limit the accuracy and stability of the adherence measurement. Consequently, the findings related to TA should be interpreted with caution, and future research may benefit from using longer or more comprehensive adherence instruments to improve reliability. The face-to-face administration of the questionnaires by the researcher in a psychiatric inpatient setting may have introduced response bias, as participants might have tended to provide socially desirable responses. This should be taken into account when interpreting the self-reported measures of cognitive insight and TA. Additionally, the structural equation model explained only 10.5% of the variance in TA. This indicates that a large proportion of the variability in adherence is likely explained by other psychosocial, clinical, and contextual factors not included in the model. Future research should incorporate additional variables such as illness severity, treatment history, social support, and comorbidities to improve the model's explanatory power and provide a more comprehensive understanding of the determinants of TA.

Conclusion

This study demonstrates that cognitive insight particularly the EO dimension is a critical factor influencing TA in psychiatric patients. The findings indicate that patients with a greater ability to express themselves tend to adhere more closely to treatment plans, likely due to their enhanced capacity to communicate personal experiences and engage more effectively in therapeutic interactions. In contrast, the SC dimension did not show a statistically significant impact on TA, suggesting that excessive confidence in one's beliefs may not directly hinder adherence behavior in this particular sample.

These results underscore the importance of integrating interventions that enhance communication and self-reflective abilities into psychiatric care. Improving patients' capacity to articulate their emotions and thoughts may strengthen therapeutic alliances with healthcare professionals, thereby facilitating the delivery of individualized care and promoting higher levels of adherence.

From a clinical standpoint, mental health professionals can translate these findings into practice by incorporating structured psychoeducation sessions, role-playing exercises to improve emotional articulation, and communication-focused therapies into routine care. Interventions should also be adapted to the patient's cultural and clinical context, with special consideration given to those with limited expressive abilities.

Future research should employ longitudinal and experimental designs to explore the role of cognitive insight subdimensions across diverse psychiatric populations. Testing targeted intervention programs that explicitly focus on enhancing expression and insight while assessing their impact on adherence could provide actionable evidence for improving treatment outcomes.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of İstanbul Arel University, İstanbul, Turkey (approval date: 10 February 2023; approval no: 2023/03). The research was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Informed Consent: All participants were informed about the purpose, procedures, and voluntary nature of the study, and signed informed consent was obtained.

Footnotes

Authorship Contributions

Concept: E.A., Design: E.A., Data Collection or Processing: M.A., Analysis or Interpretation: E.A., M.A., Literature Search: E.A., M.A., Writing: E.A., M.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Borba LO, Capistrano FC, Ferreira ACZ, Kalinke LP, Mantovani MF, Maftum MA. Adaptation and validation of the measuring of treatment adherence for mental health. Rev Bras Enferm. 2018;71(Suppl 5):2243-2250. English, Portuguese.
2. Mukattash TL, Alzoubi KH, Abu El-Rub E, Jarab AS, Al-Azzam SI, Khdour M, et al. Prevalence of non-adherence among psychiatric patients in Jordan, a cross sectional study. Int J Pharm Pract. 2016;24(3):217-221.
3. World Health Organization. World mental health report: transforming mental health for all [Internet]. Geneva: World Health Organization; 2022 [cited 2025 Sep 3]. Available from: https://www.who.int/publications/i/item/9789240049338?utm_source=chatgpt.com
4. Jayasree A, Shanmuganathan P, Ramamurthy P, Alwar Mc. Types of medication non-adherence & approaches to enhance medication adherence in mental health disorders: a narrative review. Indian J Psychol Med. 2024;46(6):503-510.

5. Alene M, Wiese MD, Angamo MT, Bajorek BV, Yesuf EA, Wabe NT. Adherence to medication for the treatment of psychosis: rates and risk factors in an Ethiopian population. BMC Clin Pharmacol. 2012;12:10.

6. De Las Cuevas C, de Leon J, Peñate W, Betancort M. Factors influencing adherence to psychopharmacological medications in psychiatric patients: a structural equation modeling approach. Patient Prefer Adherence. 2017;11:681-690.

7. Van Dorn RA, Desmarais SL, Petrila J, Haynes D, Singh JP. Effects of outpatient treatment on risk of arrest of adults with serious mental illness and associated costs. Psychiatr Serv. 2013;64(9):856-862.

8. Timlin U, Hakko H, Heino R, Kyngäs H. A systematic narrative review of the literature: adherence to pharmacological and nonpharmacological treatments among adolescents with mental disorders. J Clin Nurs. 2014;23(23-24):3321-3334.

9. Klinpiboon P, Chanthapasa K. The medication use issues and challenges of mental illness exacerbation in patients with schizophrenia: a qualitative study in Thailand. Patient Prefer Adherence. 2023;17:2927-2937.

10. Lee E, Jang MH. The influence of body image, insight, and mental health confidence on medication adherence in young adult women with mental disorders. Int J Environ Res Public Health. 2021;18(8):3866.

11. Novick D, Montgomery W, Treuer T, Aguado J, Kraemer S, Haro JM. Relationship of insight with medication adherence and the impact on outcomes in patients with schizophrenia and bipolar disorder: results from a 1-year European outpatient observational study. BMC Psychiatry. 2015;15:189.

12. Özdel K, Kart A, Türkçapar MH. Cognitive behavioral therapy in treatment of bipolar disorder. Noro Psikiyatr Ars. 2021;58(Suppl 1):S66-S76.

13. Dalseth N, Reed RS, Hennessy M, Eisenberg MM, Blank MB. Does diagnosis make a difference? Estimating the impact of an HIV medication adherence intervention for persons with serious mental illness. AIDS Behav. 2018;22(1):265-275.

14. Van Camp LSC, Sabbe BGC, Oldenburg JFE. Cognitive insight: a systematic review. Clin Psychol Rev. 2017;55:12-24.

15. Hussein F, Shafik H, Eweida RS. Metacognitive abilities within personal narratives of inpatients with schizophrenia: associations with clinical insight and drug compliance. J Educ Pract. 2019;10(1):108-117.

16. Higashi K, Medic G, Littlewood KJ, Diez T, Granström O, De Hert M. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. Ther Adv Psychopharmacol. 2013;3(4):200-218.

17. López-Carrilero R, Lo Monaco M, Frígola-Capell E, Ferrer-Quintero M, Díaz-Cutraro L, Verdaguer-Rodríguez M, et al; Spanish Metacognition Group; Ochoa S. Cognitive insight in first-episode psychosis: exploring the complex relationship between executive functions and social cognition. Span J Psychiatry Ment Health. 2024;17(3):160-167.

18. Ciufolini S, Morgan C, Morgan K, Fearon P, Boydell J, Hutchinson G, et al. Self esteem and self agency in first episode psychosis: ethnic variation and relationship with clinical presentation. Psychiatry Res. 2015;227(2-3):213-218.

19. Kao YC, Liu YP. The clinical applicability of the self-appraisal of illness questionnaire (SAIQ) to chronic schizophrenic patients in Taiwan. Psychiatr Q. 2010;81(3):215-25.

20. El Abdellati K, De Picker L, Morrens M. Antipsychotic treatment failure: a systematic review on risk factors and interventions for treatment adherence in psychosis. Front Neurosci. 2020;14:531763.

21. Bora E, Özerdem A. Meta-analysis of longitudinal studies of cognition in bipolar disorder: comparison with healthy controls and schizophrenia. Psychol Med. 2017;47(16):2753-2766.

22. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale (NJ): Lawrence Erlbaum Associates; 1988.

23. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24(1):67-74.

24. Bahar G, Savaş HA, Ünal A, Savaş E, Kaya H, Bahar A. Validity and reliability study of the morisky medication adherence scale for bipolar disorder. Anatol J Psychiatry. 2014;15(2):141-149.

25. Beck AT, Baruch E, Balter JM, Steer RA, Warman DM. A new instrument for measuring insight: the beck cognitive insight scale. Schizophr Res. 2004;68(2-3):319-329.

26. Aslan S, Yavuz MF, Kaya N. Beck cognitive insight scale: a study of validity and reliability. Arch Neuropsychiatry. 2014;51(1):6-11.

27. Sharkiya SH. Quality communication can improve patient-centred health outcomes among older patients: a rapid review. BMC Health Serv Res. 2023;23(1):886.

28. Fereidooni S, Razeghian Jahromi L, Fateh N. Effectiveness of group cognitive behavioral therapy in insight and treatment adherence in schizophrenic patients: a randomized controlled trial. Jundishapur J Chronic Dis Care. 2023;12(3):e135541.

29. Hong H, Oh HJ. The effects of patient-centered communication: exploring the mediating role of trust in healthcare providers. Health Commun. 2020;35(4):502-511.

30. Koç M, Günaydın N. The relationship between treatment adherence, social support and recovery status of patients receiving psychiatric treatment. Online Turk J Health Sci. 2023;8(3):288-295.

31. Aylaz R, Kılınç G. The relationship between treatment adherence and social support in psychiatric patients in the east of Turkey. Arch Psychiatr Nurs. 2017;31(2):157-163.

32. Kokurcan A, Karadağ H, Ercan Doğu S, Erdi F, Örsel S. Clinical correlates of treatment adherence and insight in patients with schizophrenia. Arch Clin Exp Med. 2020;5(3):95-99.

33. Staring AB, Van der Gaag M, Koopmans GT, Selten JP, Van Beveren JM, Hengeveld MW, et al. Treatment adherence therapy in people with psychotic disorders: randomised controlled trial. Br J Psychiatry. 2010;197(6):448-455.

34. Sagayadevan V, Jeyagurunathan A, Lau YW, Shafie S, Chang S, Ong HL, et al. Cognitive insight and quality of life among psychiatric outpatients. BMC Psychiatry. 2019;19(1):201.

35. Cooke MA, Peters ER, Fannon D, Aasen I, Kuipers E, Kumari V. Cognitive insight in psychosis: the relationship between self-certainty and self-reflection dimensions and neuropsychological measures. Psychiatry Res. 2010;178(2):284-289.

36. Kimhy D, Vakhrusheva J, Jobson-Ahmed L, Tarrier N, Malaspina D, Gross JJ. Emotion awareness and regulation in individuals with schizophrenia: implications for social functioning. Psychiatry Res. 2012;200(2-3):193-201.

37. Lysaker PH, Vohs J, Hasson-Ohayon I, Kukla M, Wierwille J, Dimaggio G. Depression and insight in schizophrenia: comparisons of levels of deficits in social cognition and metacognition and internalized stigma across three profiles. Schizophr Res. 2013;148(1-3):18-23.

38. Liu J, Chan TCT, Chong SA, Subramaniam M, Mahendran R. Impact of emotion dysregulation and cognitive insight on psychotic and depressive symptoms during the early course of schizophrenia spectrum disorders. Early Interv Psychiatry. 2020;14(6):691-697.

39. Tiryaki A, Karahan M. The relationship between insight and symptoms in Turkish schizophrenia outpatients. Turk J Psychiatry. 2018;29(1):19-27.

ORIGINAL RESEARCH

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Retrospective Analysis of Anaesthesia Management for Lung Lobectomy via Thoracotomy

Torakotomi ile Yapılan Akciğer Lobektomi Ameliyatlarının Anestezi Yönetiminin Retrospektif Analizi

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Abstract

Objective: Lung lobectomy is a common procedure for treating pulmonary conditions, including lung cancer. Effective analgesia is crucial for minimizing postoperative pain and enhancing recovery. Traditional opioid-based analgesia (OA) is associated with significant side effects, prompting increased interest in regional anesthesia (RA) techniques. This study evaluates the impact of OA versus RA on perioperative and postoperative outcomes in lung lobectomy patients.

Method: This retrospective study included patients who underwent lung lobectomy between April 2020 to December 2022. Patients were divided into Group OA and Group RA. The collected data encompassed preoperative demographic characteristics and intraoperative hemodynamic parameters. Intraoperative timing variables included anesthesia duration, surgical duration, and one-lung ventilation (OLV) time. Postoperative outcomes consisted of intensive care unit-length of stay (ICU-LOS), hospital length of stay, durations of invasive mechanical ventilation (IMV) and non-invasive mechanical ventilation (NIMV), and mortality.

Results: Patients enrolled in the study were divided into Group OA (n=32) the Group RA (n=44). Demographic data and comorbidities were comparable between groups (p>0.05). OLV duration was slightly longer in Group OA (181.7±63.7 min) than in Group RA (161.8±59.8 min), without statistical significance (p=0.168). ICU-LOS stay was shorter in Group RA

Öz

Amaç: Akciğer lobektomisi, akciğer kanseri dahil olmak üzere çeşitli pulmoner hastalıkların tedavisinde yaygın olarak uygulanan bir cerrahi işlemdir. Etkili analjezi, postoperatif ağrının en aza indirilmesi ve iyileşmenin hızlandırılması açısından büyük önem taşır. Geleneksel opioid bazlı analjezi (OA), önemli yan etkilere neden olabilmekte ve bu durum rejyonal anestezi (RA) tekniklerine olan ilgiyi artırmıştır. Bu çalışma, OA ile RA'nın akciğer lobektomisi uygulanan hastalardaki perioperatif ve postoperatif sonuçlar üzerindeki etkisini değerlendirmektedir.

Yöntem: Bu retrospektif çalışmaya, Nisan 2020 ile Aralık 2022 tarihleri arasında akciğer lobektomisi uygulanan hastalar dahil edilmiştir. Hastalar Grup OA ve Grup RA grubu olmak üzere ikiye ayrılmıştır. Toplanan veriler, preoperatif döneme ait demografik özellikler ve intraoperatif hemodinamik parametreleri içermektedir. İntraoperatif zamanlama verileri arasında anestezi süresi, cerrahi süresi ve tek akciğer ventilasyonu (OLV) süresi yer almaktadır. Postoperatif sonuçlar ise yoğun bakımda kalış süresi (ICU-LOS), hastanede yatış süresi, invaziv mekanik ventilasyon (IMV) ve non-invaziv mekanik ventilasyon (NIMV) süreleri ile mortalite verilerini kapsamaktadır.

Bulgular: Çalışmaya katılan hastalar Grup OA (n=32) ve Grup RA (n=44) olarak ikiye ayrılmıştır. Demografik veriler ve eşlik eden hastalıklar açısından gruplar arasında anlamlı bir fark bulunmamıştır (p>0,05). OLV süresi Grup OA'da (181,7±63,7 dk) Grup RA'ya (161,8±59,8 dk) göre biraz

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Abstract

(1.32±0.77 days) compared to Group OA (2.53±2.77 days; p=0.007). In Group OA, the need for IMV was higher (18.75%) compared to Group RA (6.81%), and the mean IMV duration was also longer (25.67±19.28 hours vs. 10.67±11.54 hours); however, these differences were not statistically significant. No significant differences were observed in hemodynamic stability or non-invasive ventilation times.

Conclusion: The use of RA in patients undergoing thoracotomy for lobectomy offers significant advantages over OA, including shorter ICU length of stay and reduced need for and duration of IMV. Routine integration of RA techniques into multimodal analgesia protocols for thoracic surgery may improve patient outcomes.

Keywords: Lung lobectomy, opioid-based analgesia, perioperative care, regional anesthesia

Öz

daha uzundu, ancak istatistiksel olarak anlamlı değildi (p=0,168). Grup RA yoğun bakımda kalış süresi Grup OA grubuna kıyasla daha kısa bulunmuştur (1,32±0,77 gün vs. 2,53±2,77 gün; p=0,007). Grup OA'da IMV gereksinimi (%18,75), Grup RA'ya (%6,81) kıyasla daha yüksek olup; ortalama IMV süresi de daha uzundu (25,67±19,28 saat vs. 10,67±11,54 saat), ancak bu farklar istatistiksel olarak anlamlı değildi. Hemodinamik stabilite ve NIMV açısından ise gruplar arasında anlamlı bir fark saptanmamıştır.

Sonuç: Lobektomi amacıyla torakotomi uygulanan hastalarda RA kullanımı, OA'ya kıyasla yoğun bakımda kalış süresinin kısalması ve IMV gereksinimi ile süresinin azalması gibi anlamlı avantajlar sunmaktadır. RA tekniklerinin toraks cerrahisinde multimodal analjezi protokollerine rutin olarak entegre edilmesi, hasta sonuçlarını iyileştirebilir.

Anahtar kelimeler: Akciğer lobektomisi, opioid bazlı analjezi, perioperatif bakım, rejyonal anestezi

Introduction

Lung lobectomy, a common surgical procedure for treating various pulmonary conditions including lung cancer, often necessitates comprehensive perioperative management to optimize patient outcomes. Effective analgesia is essantial for reducing postoperative pain, facilitating early mobilization, enhancing respiratory exercises and improving overall recovery. Traditionally, opioid-based analgesia (OA) has been the main method for managing postoperative pain in thoracic surgeries. However, the use of opioids is associated with significant problems such as respiratory depression, nausea, vomiting, and prolonged hospital stays (1,2).

In recent years, regional anesthesia (RA) techniques have emerged as effective alternatives to OA, particularly in surgical approach. The choice of RA technique is generally guided by the type of thoracotomy approach used (3).

Paravertebral block (PVB) results in lower postoperative morphine consumption than erector spinae plane block (ESPB) after thoracotomy, despite similar pain scores, highlighting ESPB as a safer alternative due to its simpler anatomical approach (4). Additionally, ESPB has demonstrated non-inferior analgesic efficacy compared to PVB in abdominal surgery, supporting its potential utility in thoracic procedures as well (5). By offering superior pain relief, reducing opioid requirements, and minimizing opioid-related adverse effects, RA has the potential to significantly enhance postoperative recovery (6).

The impact of different analgesic strategies on critical perioperative outcomes such as intensive care unit length of stay (ICU-LOS), overall hospital length of stay (hLOS), and the need for postoperative mechanical ventilation remains an area of active investigation. Studies have suggested that RA may lead to improved hemodynamic stability and better postoperative pulmonary function compared to OA (7). However, evidence comparing these two approaches specifically in the context of lung lobectomy is limited.

This retrospective study aims to evaluate the effects of OA versus RA on various perioperative outcomes in patients undergoing lung lobectomy. By analyzing data from a cohort of patients, this study seeks to provide insights into the efficacy and safety of regional techniques in enhancing postoperative recovery and reducing morbidity and mortality in this patient population.

Materials and Methods

Study Design and Setting

This retrospective observational cohort study was conducted to evaluate the effects of different perioperative analgesic strategies—OA versus RA—on postoperative outcomes in patients undergoing lung lobectomy. The study was performed at University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, a tertiary care center, and included patients operated between April 2020 and December 2022. The study protocol was approved by the Local Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: 2022.12.421, date: 24/12/2022) and was conducted in accordance with the Declaration of Helsinki.

Participants

The study population consisted of adult patients aged 18 years and older who underwent elective lung lobectomy

within the specified period. Inclusion criteria required the availability of complete perioperative and postoperative data. Patients were excluded if they underwent emergency surgery, had incomplete medical records, or underwent concurrent additional surgical procedures. All eligible patients were included consecutively to reduce selection bias.

Exposure and Group Allocation

Patients were divided into two groups according to the analgesic strategy used: Group OA and Group RA, who received regional techniques or not. The choice of analgesic approach was made by the attending anesthesiologist according to clinical protocols and patient suitability, independent of the study investigators.

Anesthesia and Analgesia Protocols

As part of our standard anaesthesia protocol, we administered general anaesthesia to all patients and intubated them using a double-lumen tube. Anesthesia induction was standardized, and maintenance was achieved with sevoflurane (0.8-1 MAC) and remifentanil infusion. Mechanical ventilation was adjusted according to individual intraoperative needs.

In the Group RA, regional techniques (either PVB or ESPB) was administered preoperatively under ultrasound guidance by an experienced anesthesiologist prior to induction. At the end of surgery, patients received intravenous paracetamol (1000 mg) and tramadol (100 mg). Postoperatively, they were given intravenous paracetamol 1000 mg three times daily and tramadol 100 mg twice daily.

In the Group OA, patients received intravenous paracetamol (1000 mg) and morphine hydrochloride (0.1 mg/kg) intraoperatively. Postoperative analgesia included paracetamol 1000 mg three times daily and a continuous intravenous infusion of morphine hydrochloride (0.005-0.01 mg/kg/h). In both groups, pethidine chloride was administered as rescue analgesia if required.

Data Collection

Data were extracted retrospectively from the hospital's electronic medical record system. Demographic variables included age, sex, height, weight, body mass index, ASA classification and comorbidities. Intraoperative parameters included the duration of OLV, and hemodynamic variables [systolic arterial blood pressure (SABP), diastolic arterial blood pressure (DABP), heart rate (HR) and peripheral oxygen saturation (SpO_2)], which were recorded at three standardized time points: before induction, after OLV, and before extubation. The duration of anesthesia did not include the time required for block placement in the Group RA, as it was performed before induction.

Postoperative variables included the ICU-LOS, total hLOS, the number of patients who required invasive (IMV) or non-invasive mechanical ventilation (NIMV), the duration of ventilation among these patients, and in-hospital mortality.

Outcomes

The primary outcomes of the study were ICU-LOS and hLOS. Secondary outcomes included the need of postoperative IMV and NIMV, perioperative hemodynamic stability, and mortality.

Minimization of Bias

To minimize potential selection and information bias, only patients with complete data were included. Data abstraction was performed by trained personnel blinded to the study hypothesis.

Statistical Analysis

Since this study was designed retrospectively, no a priori power analysis was conducted. However, to assess whether the sample size was sufficient to detect clinically meaningful differences in the primary outcomes, a post-hoc power analysis was performed, indicating that the sample size was statistically adequate. The data were analysed via SPSS (Mac OS, version 27.0). The normality of the data was assessed with the Kolmogorov-Smirnov test. Normally distributed data were analyzed using independent t-tests, while non-normally distributed data were analyzed with the Mann-Whitney U test. Categorical variables were compared using chi-square or Fisher's exact tests. Continuous variables were expressed as mean ± standard deviation and categorical variables were presented as counts and percentages. Statistical significance was determined by p-values <0.05.

Results

Between April 2020 and December 2022, 76 patients undergoing lobectomy via thoracotomy were enrolled in the study (Figure 1). Patients enrolled in the study were divided into the Group OA (n=32) and the Group RA (n=44). When demographic data and comorbidities of the patients were compared, there wasn't significant difference between the groups ($p>0.05$) (Table 1).

Hemodynamic Parameters Before and After Induction

The comparison of perioperative hemodynamic parameters between Group OA and Group RA is presented in Table 2. Before induction, no statistically significant differences were observed between the groups in terms of SABP, DABP, HR and SpO_2. Specifically, SABP was 132.91±13.75 mmHg in Group OA and 131.70±14.14 mmHg in Group RA (p=0.712), while DABP was 81.69±11.06 mmHg in Group OA and 83.33±10.76 mmHg in Group RA (p=0.522). Similarly, HR and SpO_2 values were comparable between the groups (HR: 85.09±12.56 bpm vs. 89.53±14.14 bpm, p=0.163; SpO_2: 98.94±1.58% vs. 98.95±1.64%, p=0.966).

Following OLV, SABP and DABP values remained statistically similar between Group OA and Group RA (SABP: 105.38±11.67 mmHg vs. 105.91±8.52 mmHg, p=0.820; DABP: 64.56±8.93 mmHg vs. 65.81±6.69 mmHg, p=0.490). HR and SpO_2 measurements also did not differ significantly (HR: 81.66±9.64 bpm vs. 82.33±11.27 bpm, p=0.788; SpO_2: 97.28±2.88% vs. 97.07±2.72%, p=0.747).

Before extubation, no significant differences were found in SABP, HR, or SpO_2 between the two groups (SABP: 107.72±18.17 mmHg vs. 105.41±11.53 mmHg, p=0.501; HR: 83.63±11.35 bpm vs. 82.75±11.16 bpm, p=0.739; SpO_2: 99.47±1.27% vs. 99.09±1.57%, p=0.271). Although the DABP value was slightly higher in Group RA compared to Group OA (66.86±10.49 mmHg vs. 62.38±9.80 mmHg), this difference did not reach statistical significance (p=0.062).

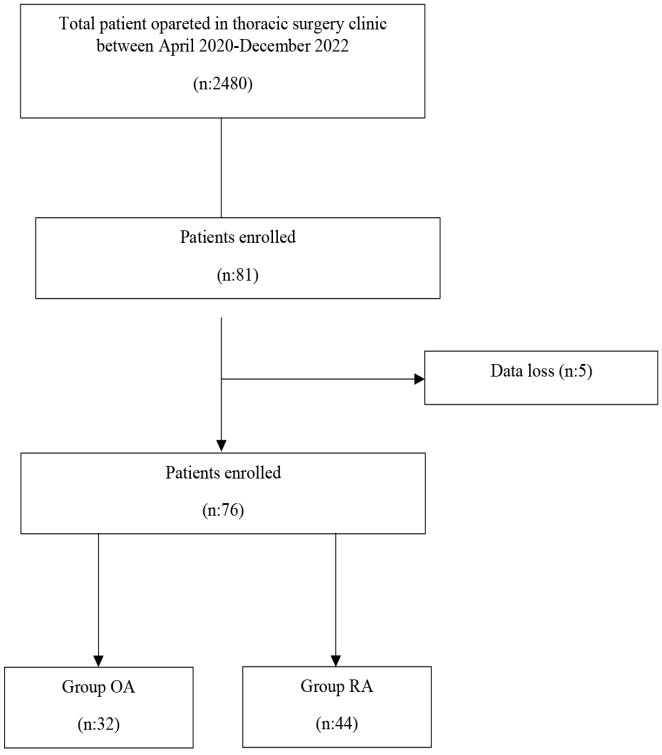

Figure 1. Flow diagram
OA: Opioid-based analgesia, RA: Regional anesthesia

Surgical, Anesthesia and OLV Durations

A comparison of surgical, anesthesia, and OLV times between Group OA and Group RA is shown in Table 3. The mean duration of surgery was 201.72±63.68 minutes in Group OA and 186.59±60.24 minutes in Group RA, with no statistically significant difference observed between the groups (p=0.295). Similarly, anesthesia time did not differ significantly between the groups, with a mean of 245.00±68.49 minutes in Group OA and 222.84±64.17 minutes in Group RA (p=0.153).

The mean duration of OLV was also found to be slightly longer in Group OA (181.72±63.68 minutes) compared to Group RA (161.82±59.79 minutes); however, this difference did not reach statistical significance (p=0.168).

Table 1. Demographical data of the patient

	Group OA [a,b] (n=32)	Group RA [a,b] (n=44)	p-value [c,d]
Age (years)	62.56±7.71	59.64±10.16	0.176
Height (cm)	169.91±7.34	171.66±7.92	0.330
Weight (kg)	76.69±12.73	76.27±13.55	0.893
BMI (kg/m²)	26.58±4.26	25.84±3.89	0.437
ASA scores			
II	9 (28.12%)	13 (29.5%)	
III	21 (65.62%)	29 (65.9%)	0.869
IV	2 (6.25%)	2 (4.5%)	
Comorbidities (n)	1.70±2.17	1.47±1.90	0.687

[a]: Mean ± standard deviation, [b]: n (%), [c]: Independent sample t-test, [d]: Chi-square test, *: p<0.05 is accepted as statistically significant difference, BMI: Body mass index, OA: Opioid-based analgesia, RA: Regional anesthesia

Hospital Stay and Mechanical Ventilation Durations

As presented in Table 4, the mean duration of stay in the ICU-LOS was significantly longer in Group OA compared to Group RA (2.53±2.77 days vs. 1.32±0.77 days, p=0.007). In contrast, hLOS did not differ significantly between the groups, with Group OA having a mean duration of 7.06±4.45 days and Group RA 7.82±3.06 days (p=0.383).

The need for IMV was higher in Group OA (18.75%) compared to Group RA (6.81%), although this difference was not statistically significant (p=0.112). Similarly, the mean duration of IMV was longer in Group OA (25.67±19.28 hours) than in Group RA (10.67±11.54 hours), but this difference also did not reach statistical significance (p=0.179). The need for NIMV was comparable between the two groups (12.50% in Group OA vs. 11.36% in Group

Table 2. Comparison of hemodynamic parameters (mean ± SD)

	Group OA[a] (n=32)	Group RA[a] (n=44)	p-value[b]
Before induction			
SABP (mm/Hg)	132.91±13.75	131.70±14.14	0.712
DABP (mm/Hg)	81.69±11.06	83.33±10.76	0.522
HR (bpm)	85.09±12.56	89.53±14.14	0.163
SpO_2 (%)	98.94±1.58	98.95±1.64	0.966
After one lung ventilation			
SABP (mm/Hg)	105.38±11.67	105.91±8.52	0.820
DABP (mm/Hg)	64.56±8.93	65.81±6.69	0.490
HR (bpm)	81.66±9.64	82.33±11.27	0.788
SpO_2 (%)	97.28±2.88	97.07±2.72	0.747
Before extubation			
SABP (mm/Hg)	107.72±18.17	105.41±11.53	0.501
DABP (mm/Hg)	62.38±9.80	66.86±10.49	0.062
HR (bpm)	83.63±11.35	82.75±11.16	0.739
SpO_2 (%)	99.47±1.27	99.09±1.57	0.271

[a]: Mean ± SD: Mean ± standard deviation, [b]: Independent sample t-test, *: p<0.05 is accepted as statistically significant difference, SABP: Systolic arterial blood pressure, DABP: Diastolic arterial blood pressure, HR: Heart rate, SpO_2: Peripheral oxygen saturation, OA: Opioid-based analgesia, RA: Regional anesthesia

Table 3. Comparison of surgical, anesthesia and one lung ventilation times (mean ± SD)

	Group OA[a] (n=32)	Group RA[a] (n=44)	p-value[b]
Surgery time (min)	201.72±63.68	186.59±60.24	0.295
Anesthesia time (min)	245.00±68.49	222.84±64.17	0.153
One-lung ventilation time (min)	181.72±63.68	161.82±59.79	0.168

[a]: Mean ± SD: Mean ± standard deviation, [b]: Independent sample t-test, *: p<0.05 is accepted as statistically significant difference, pressure, HR: Heart rate, SpO_2: Peripheral oxygen saturation, OA: Opioid-based analgesia, RA: Regional anesthesia

Table 4. Comparison of hospital stay and mechanical ventilation times (mean ± SD)

	Group OA [a,b] (n=32)	Group RA [a,b] (n=44)	p-value[c,d,e]
ICU-LOS (days)	2.53±2.77	1.32±0.77	**0.007***
hLOS (days)	7.06±4.45	7.82±3.06	0.383
IMV need (n)	6 (18.75%)	3 (6.81%)	0.112
IMV duration (hours)[#]	25.67±19.28	10.67±11.54	0.179
NIMV need (n)	4 (12.50%)	5 (11.36%)	0.880
NIMV duration (hours)[#]	60.00±39.79	60.00±30.98	0.264

[a]: Mean ± SD: Mean ± standard deviation, [b]: n (%), [c]: Independent sample t-test, [d]: Chi-square test, [e]: Mann-Whitney U test, *: p<0.05 is accepted as statistically significant difference, [#]: Patients who did not develop a need were excluded
ICU-LOS: Intensive care unit length of stay, hLOS: Hospital length of stay , IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation

RA, p=0.880). Likewise, NIMV duration was similar, with both groups having a mean duration of 60.00 hours (OA: 60.00±39.79, RA: 60.00±30.98, p=0.264). No mortality was observed in either group.

Discussion

This study compared the perioperative and postoperative outcomes of patients undergoing thoracotomy for lobectomy under two different analgesic strategies. The findings highlight that RA was associated with significantly improved postoperative outcomes in terms of ICU-LOS, while IMV requirement and duration were also lower in the RA group, although these differences did not reach statistical significance. Importantly, these outcomes were achieved without compromising intraoperative hemodynamic stability.

First, our results revealed no statistically significant differences in demographic characteristics, comorbidities, or intraoperative hemodynamic parameters (SABP, DABP, HR, SpO_2) between the groups. These findings suggest that the observed postoperative differences cannot be attributed to preoperative risk factors or intraoperative instability, underscoring the specific influence of the analgesic modality used. This suggests that RA and OA maintain similar hemodynamic stability during the perioperative period, corroborating the results of a study by Ke et al. (8), which indicated that both methods provide comparable hemodynamic stability. Hamilton et al (9). reported that paravertebral and fascial plane blocks in thoracic surgery reduce opioid consumption, improve pain control, and preserve hemodynamic stability. However, in our study, the use of a standardized anesthesia protocol for all patients and close intraoperative monitoring may have allowed for rapid correction of any hemodynamic fluctuations. This could explain the lack of significant differences between the groups.

Recent studies have shown that the decrease in oxygen saturation during OLV is a physiological response, and that lung-protective ventilation strategies are effective in maintaining adequate oxygenation during this period (10-12). Although the mean SpO_2 value during OLV was approximately 97% in both groups, this still represents a relative decrease from pre-OLV baseline levels, reflecting the expected physiological effect of lung isolation. In addition, the standard deviation values suggest variability across cases and indicate that lung-protective ventilation strategies—such as the use of higher FiO_2, optimal patient positioning, and PEEP adjustments—were likely applied to maintain oxygenation above 90%, in line with current practice guidelines.

Ventilation-related lung injury and postoperative analgesia are emphasised in ERATS protocols (13,14). Importantly, a significant reduction was observed in ICU-LOS and duration of IMV in the Group RA. Patients in the Group RA had a notably shorter ICU stay and required less IMV time compared to those in the Group OA, suggesting that improved pain control may have contributed to faster respiratory recovery and stabilization. These results are consistent with findings by Hutton et al. (15), who reported the benefits of RA in reducing pulmonary complications and improving respiratory function in thoracic surgeries (16). This is also supported by the study of Kukreja et al. (17), which found that RA significantly reduces ICU-LOS and enhances recovery (16-18). The significantly shorter ICU stay observed in the RA group, along with the trend toward reduced IMV requirement and duration, may be explained by more effective postoperative pain control. This likely contributed to faster recovery of respiratory function. Adequate analgesia reduces diaphragmatic splinting, increases tidal volume, and lowers the incidence of atelectasis and hypoventilation. These physiological benefits may facilitate the earlier return of spontaneous breathing and enable quicker weaning from IMV.

In terms of mechanical ventilation times, both the duration and the need for IMV were lower in the RA group; however, these differences did not reach statistical significance. NIMV duration and requirement were found to be similar between the groups. This may be attributed to the use of similar postoperative monitoring and ventilatory protocols in both groups, and the fact that the need for NIMV was determined primarily by the patient's clinical condition rather than the analgesic technique. This aligns with findings of the studies, who reported that while RA reduces IMV duration, it does not significantly affect NIMV duration (18-20).

Only a limited number of studies have evaluated parameters such as hLOS as secondary outcomes, including different types of regional blocks (21), and these parameters remain underreported in the literature (22). Although the duration of NIMV and were numerically shorter in the Group RA, these differences did not reach statistical significance. This may reflect either the sample size limitations or multifactorial influences on these parameters beyond analgesia type. No mortality was observed in either group,

consistent with the low perioperative risk in elective thoracic surgery patients and further supporting the safety of both analgesic approaches.

Study Limitations

This study has several limitations that should be acknowledged. First, its retrospective design inherently introduces the possibility of selection bias and limits control over confounding variables. The accuracy and completeness of the data may have been affected by potential inconsistencies or omissions in medical records. Additionally, due to the retrospective nature of the study, a priori sample size estimation was not performed. However, a post-hoc power analysis was conducted to evaluate the adequacy of the available data, and it demonstrated that the statistical power was sufficient for the primary outcomes of the study.

Furthermore, the inclusion of patients from different ASA classification groups under a single category may have obscured potential differences related to comorbidity severity; this is acknowledged as an additional limitation. Although RA was performed following institutional protocols, variability in block technique, local anesthetic volume, and provider expertise were not fully standardized, which may have influenced the clinical outcomes.

Another important limitation is the absence of standardized documentation of postoperative pain scores (e.g., visual analogue scale or nutritional risk screening) and uniform quantification of opioid consumption, which precluded a direct comparison of analgesic efficacy between groups. Lastly, the relatively small sample size limits the generalizability of our findings to the broader population.

Future prospective, multicenter studies with larger cohorts and standardized outcome measures—particularly patient-centered parameters such as postoperative pain scores, opioid requirements, and recovery quality—are warranted to validate and expand upon these findings.

Conclusion

In patients undergoing thoracotomy for lobectomy, the use of RA was associated with a significant reduction in ICU-LOS. Although the need for and duration of IMV were lower in the RA group, these differences remained at the threshold of statistical significance. These outcomes were achieved without compromising intraoperative hemodynamic stability or surgical efficiency. Our findings support the potential role of RA as a valuable component of multimodal analgesic strategies in thoracic surgery. However, larger-scale prospective studies are needed to confirm these observations and to more clearly define the clinical benefits of RA in this context.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: 2022.12.421, date: 24/12/2022) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

AI programme has been used for grammar improvement in this article.

Authorship Contributions

Surgical and Medical Practices: E.M., Ö.A., O.S., C.K.B., Concept: E.M., Ö.A., O.S., C.K.B., F.G.Ö., Design: E.M., Ö.A., O.S., C.K.B., F.G.Ö., Data Collection or Processing: E.M., Ö.A., O.S., C.K.B., Analysis or Interpretation: E.M., Ö.A., O.S., F.G.Ö., Literature Search: E.M., Ö.A., O.S., C.K.B., Writing: E.M., Ö.A., O.S.

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References

1. Khanna AK, Saager L, Bergese SD, Jungquist CR, Morimatsu H, Uezono S, et al. Opioid-induced respiratory depression increases hospital costs and length of stay in patients recovering on the general care floor. BMC Anesthesiol. 2021;21(1):88.
2. Razi SS, Stephens-McDonnough JA, Haq S, Fabbro M, Sanchez AN, Epstein RH, et al. Significant reduction of postoperative pain and opioid analgesics requirement with an enhanced recovery after thoracic surgery protocol. J Thorac Cardiovasc Surg. 2021;161(5):1689-1701.
3. Mehta S, Jen TTH, Hamilton DL. Regional analgesia for acute pain relief after open thoracotomy and video-assisted thoracoscopic surgery. BJA Educ. 2023;23(8):295-303.
4. Duran M, Kus A, Aksu C, Cesur S, Yorukoglu HU, Hosten T. Comparison of postoperative opioid consumption of paravertebral block and erector spinae plane block after thoracotomy: a randomized controlled trial. Cureus. 2024;16(5):e59459.
5. Fan Q, Liu H, Li Y, Dai H, Wang Y. Comparison of ultrasound-guided erector spinae plane block and thoracic paravertebral block for postoperative analgesia after laparoscopic nephrectomy: a randomized controlled non-inferiority clinical trial. Minerva Anestesiol. 2023;89(6):520-528.

6. Kianian S, Bansal J, Lee C, Zhang K, Bergese SD. Perioperative multimodal analgesia: a review of efficacy and safety of the treatment options. Anesthesiol Perioper Sci. 2024;2(1):9.

7. Sertcakacilar G, Tire Y, Kelava M, Nair HK, Lawin-O'Brien ROC, Turan A, et al. Regional anesthesia for thoracic surgery: a narrative review of indications and clinical considerations. J Thorac Dis. 2022;14(12):5012-5028.

8. Ke HH, Liou JY, Teng WN, Hsu PK, Tsou MY, Chang WK, et al. Opioid-sparing anesthesia with dexmedetomidine provides stable hemodynamic and short hospital stay in non-intubated video-assisted thoracoscopic surgery: a propensity score matching cohort study. BMC Anesthesiol. 2023;23(1):110.

9. Hamilton C, Alfille P, Mountjoy J, Bao X. Regional anesthesia and acute perioperative pain management in thoracic surgery: a narrative review. J Thorac Dis. 2022;14(6):2276-2296.

10. Wang QY, Zhou Y, Wang MR, Jiao YY. Effects of starting one lung ventilation and applying individualized PEEP right after patients are placed in lateral decubitus position on intraoperative oxygenation for patients undergoing thoracoscopic pulmonary lobectomy: study protocol for a randomized controlled trial. Trials. 2024;25(1):500.

11. Rawley M, Harris E, Pospishil L, Thompson JA, Falyar C. Assessing provider adherence to a lung protective ventilation protocol in patients undergoing thoracic surgery using one-lung ventilation. AANA J. 2022;90(6):439-445.

12. Min S, Yoon S, Choe HW, Jung H, Seo JH, Bahk JH. An optimal protective ventilation strategy in lung resection surgery: a prospective, single-center, three-arm randomized controlled trial. Updates Surg. 2025;77(3):925-935.

13. Hyde DJ. Editorial: current opinion in anesthesiology: new editor announcement. Curr Opin Anaesthesiol. 2019;32(6):697.

14. Semenkovich TR, Hudson JL, Subramanian M, Kozower BD. Enhanced recovery after surgery (ERAS) in thoracic surgery. Semin Thorac Cardiovasc Surg. 2018;30(3):342-349.

15. Hutton M, Brull R, Macfarlane AJR. Regional anaesthesia and outcomes. BJA Educ. 2018;18(2):52-56.

16. Piennette PD, Morris SE, Northern T. Current review of analgesia and regional anesthesia practices for rib fracture and chest wall trauma. Curr Anesthesiol Rep. 2022;12(3):407-416.

17. Kukreja P, Herberg TJ, Johnson BM, Kofskey AM, Short RT, MacBeth L, et al. retrospective case series comparing the efficacy of thoracic epidural with continuous paravertebral and erector spinae plane blocks for postoperative analgesia after thoracic surgery. Cureus. 2021;13(10):e18533.

18. Bartels K, Frendl G, Sprung J, Weingarten TN, Subramaniam B, Martinez Ruiz R, et al. Postoperative pulmonary complications with adjuvant regional anesthesia versus general anesthesia alone: a sub-analysis of the Perioperative Research Network study. BMC Anesthesiol. 2022;22(1):136.

19. Bachoumas K, Levrat A, Le Thuaut A, Rouleau S, Groyer S, Dupont H, et al. Epidural analgesia in ICU chest trauma patients with fractured ribs: retrospective study of pain control and intubation requirements. Ann Intensive Care. 2020;10(1):116.

20. Blaine KP. Recommendations for mechanical ventilation during general anesthesia for trauma surgery. Curr Anesthesiol Rep. 2022;12(2):183-191.

21. Sandeep B, Huang X, Li Y, Xiong D, Zhu B, Xiao Z. A comparison of regional anesthesia techniques in patients undergoing video-assisted thoracic surgery: a network meta-analysis. Int J Surg. 2022;105:106840.

22. Feray S, Lubach J, Joshi GP, Bonnet F, Van de Velde M; PROSPECT Working Group *of the European Society of Regional Anaesthesia and Pain Therapy. PROSPECT guidelines for video-assisted thoracoscopic surgery: a systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia. 2022;77(3):311-325.

ORIGINAL RESEARCH

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Mothers' Knowledge, Attitudes, and Practices Regarding Probiotics, Their Components, and Uses in Preschool Children

Okul Öncesi Çocuklarda Annelerin Probiyotikler, İçerikleri ve Kullanım Alanları Hakkındaki Bilgi, Tutum ve Davranışları

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Abstract

Objective: This study aimed to evaluate the knowledge, attitudes, and practices of mothers with at least one preschool-aged child regarding probiotics, their components, and their uses.

Method: Between January 2020 and April 2020, a 22-item questionnaire was administered to mothers of preschool-aged children. The survey assessed socio-demographic characteristics, awareness of probiotics, use of probiotics for their children, factors influencing their use, and mothers' knowledge, attitudes, and perceptions regarding probiotics.

Results: A total of 136 mothers participated in the study [age range: 23-52 years, mean ± standard deviaton (SD): 33.38±5.5 years]. The participants' children were aged between 3 months and 5 years (mean ± SD: 2.73±1.52 years). Among the mothers, 116 (85.3%) reported awareness of the term probiotic, and 69 (50.7%) reported using probiotics for their children. The most commonly used strain was ***Bacillus clausii.*** Of those who had heard of probiotics, 66 (56.8%) had learned about them through TV, newspapers, magazines, or the internet, while 36 (31.0%) had heard about them from healthcare professionals. A total of 87 mothers (75%) stated that they would not use probiotics without consulting a doctor. Additionally, 72 mothers (62.1%) considered probiotics as dietary supplements. Among the participants, 58.1% believed probiotics help prevent diseases, and 52.9% knew they contain a high concentration of live microorganisms. Higher education and income levels, employment, and having a professional occupation were significantly associated with greater awareness and use of probiotics for their children.

Öz

Amaç: Okul öncesi dönemde en az bir çocuğu olan annelerin probiyotikler, içerikleri ve kullanım alanları hakkında bilgi düzeyi, tutum ve davranışlarının incelenmesi amaçlanmıştır.

Yöntem: Ocak 2020-Nisan 2020 tarihleri arasında okul öncesi dönemde çocuğu olan annelerin sosyo-demografik özellikleri, probiyotik farkındalığı, çocukları için probiyotik kullanım durumları, kullanımı etkileyen faktörler, probiyotikler hakkında bilgi düzeyleri, davranış ve düşüncelerini belirlemeye yönelik 22 sorudan oluşan anket formu uygulandı.

Bulgular: Çalışmaya 136 anne katıldı [min: 23, maks: 52, ortalama ± standart sapma (SS): 33,38±5,5]. Katılımcıların çocukları minimum 3 ay, maksimum 5 yaşında idi (ortalama ± SS: 2,73±1,52). Katılımcıların 116'sı (%85,3) probiyotikler hakkında farkındalığa sahipti. Altmış dokuz kişinin (%50,7) daha önce çocuğu için probiyotik kullandığı saptandı. En çok kullanılan suş *Bacillus clausii* idi. Daha önce probiyotik terimini duyanların 66'sı (%56,8) TV-gazete-dergi-internetten, 36'sı (%31,0) sağlık çalışanından duymuştu. Doktora danışmadan probiyotik kullanmayacak 87 kişi (%75) idi. Yetmiş iki kişi (%62,1) probiyotiklerin besin takviyesi olduğunu düşünüyordu. Katılımcıların %58,1'i probiyotiklerin hastalıkları önlemeye yardımcı olduğunu, %52,9'u yüksek oranda canlı mikroorganizma içerdiğini biliyordu. Annelerin eğitim ve gelir düzeylerinin yüksek olması, çalışıyor ve meslek sahibi olmaları, probiyotik farkındalığının artması ve çocukları için probiyotik kullanımının daha yaygın olmasıyla ilişkili bulundu.

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Abstract

Conclusion: Awareness of probiotics among mothers is high. Higher levels of education, income, employment, and professional status are associated with greater awareness and usage of probiotics. While TV, newspapers, magazines, and the internet are the most common sources of information about probiotics, physician recommendations strongly influence decisions to use them.

Keywords: Dietary supplements, preschool children, probiotics

Öz

Sonuç: Annelerin probiyotik farkındalığı yüksektir. Yüksek eğitim ve gelir düzeyi, çalışma durumu ve meslek sahibi olmak probiyotik farkındalığını ve kullanma oranlarını artırmaktadır. Annelerin probiyotikleri en çok duydukları kaynaklar TV-gazete-dergi-internet iken probiyotik kullanma kararında doktor tavsiyesi güçlü bir etkendir.

Anahtar kelimeler: Gıda takviyesi, okul öncesi çocuk, probiyotikler

Introduction

Probiotics (PBs) are non-pathogenic live microorganisms, many of which are part of the normal human gut flora, and they provide health benefits to the host when consumed in adequate amounts (1). First defined in 1960 as "bacterial species believed to be beneficial to the digestive system", PBs were later characterized by the World Health Organization in 2001 as "live microorganisms that, when administered in adequate amounts as part of food, confer a health benefit on the host". For a microorganism to be considered a probiotic, it must originate from human sources, be resistant to secretions from organs such as the stomach and bile, maintain viability in the gastrointestinal system (GIS), stimulate an immune response, produce antimicrobial substances, and be non-pathogenic (2).

PBs are commonly used for various GIS-related conditions, including acute gastroenteritis, antibiotic-associated diarrhea, constipation, and necrotizing enterocolitis. However, studies have also suggested potential benefits in non-GIS areas, such as allergic diseases, cardiovascular health, immune system support, and urogenital health (3).

Over the past decade, publications on probiotic indications in the pediatric population have highlighted the global significance of this topic. Nevertheless, more comprehensive studies are needed to establish definitive evidence (4,5). An additional factor influencing probiotic use in children is parental attitudes, with mothers playing a particularly critical role due to their primary responsibilities in childcare.

This study aims to assess the knowledge, attitudes, and behaviors of mothers with at least one preschool-aged child regarding PBs.

Materials and Methods

Data Gathering Tool and Process

The study was conducted between January 1, 2020, and April 1, 2020, among patients who visited the Family Medicine outpatient clinics of University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital and agreed to participate. A 22-item questionnaire, prepared based on a literature review, was administered to mothers of preschool-aged children. The questionnaire aimed to assess participants' socio-demographic characteristics, awareness of PBs, probiotic use for their children, factors influencing their use, and knowledge, attitudes, and perceptions regarding PBs.

Participants who reported previous probiotic use for their child were asked to specify the name of the most recent commercial product or probiotic food they had used. Foods such as kefir and yogurt were categorized as natural probiotics, while the probiotic strains contained in commercial forms were recorded for those who used such products.

The study included mothers who had at least one child older than three months and five years of age or younger, completed the questionnaire in full, and agreed to participate. Mothers who did not meet these criteria, provided incomplete or erroneous responses, or declined to participate were excluded. A total of 208 questionnaires were collected; after eliminating incomplete or incorrect forms, 136 questionnaires were included in the final analysis.

A post-hoc power analysis was conducted for the chi-square test, assuming a medium effect size (Cohen's w=0.3). With a sample size of 136 and a significance level of 0.05, the achieved power was 93.8%, indicating that the study had a strong ability to detect significant associations.

The reliability and validity of the 10 items assessing mothers' knowledge and attitudes toward PBs were also evaluated. Internal consistency was examined using Cronbach's alpha, which was calculated as 0.96, indicating excellent reliability. Exploratory factor analysis was performed, and according to the Kaiser criterion, a single factor with an eigenvalue of 9.48 was identified, while all other factors had eigenvalues

below 1. This result supports the unidimensional structure of the scale. The questionnaire was developed based on a review of the literature and expert input; however, no formal pilot study was conducted prior to data collection, which we acknowledge as a methodological limitation.

Statistical Analysis

Statistical analysis was performed using SPSS 25.0 for Windows. Descriptive statistics were presented as frequencies and percentages for categorical variables, and as means, standard deviations (SDs), minimums, and maximums for numerical variables. Comparisons of proportions in independent groups were conducted using the chi-square test. Fisher's exact test was used when the chi-square test was not applicable. A statistical significance level of $p<0.05$ was considered significant.

Ethics

This descriptive study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital with the approval number 2503, dated September 3, 2019. All participants provided informed consent.

Results

A total of 136 mothers participated in the study. Among the participants, 84 (61.8%) were under 35 years of age, while 52 (38.2%) were 35 years or older (mean ± SD: 33.38±5.5 years; range: 23-52 years). A total of 31 participants (22.8%) had an education level below high school, and 41 (30.1%) reported having no income or an income below the minimum wage. Seventy-five participants (55.1%) were actively employed, while 50 (36.8%) were homemakers, and 24 (17.6%) were self-employed or working in the private sector. Regarding the age of their children, 61 participants (44.9%) had a child aged 2 years or younger, whereas 75 (55.1%) had a child older than 3 years (range: 3 months-5 years).

When asked about their awareness of the term "probiotic", 116 mothers (85.3%) stated that they were aware of it at least once. Among these 116 participants, 66 (56.8%) had learned about PBs through TV, newspapers, magazines, or the internet, while 36 (31.0%) had learned about them from healthcare professionals. Sixty-nine participants (50.7%) had previously used PBs for their child. Regarding their perception of probiotics, 72 participants (62.1%) believed that PBs were dietary supplements, whereas 17 (12.5%) considered them beneficial microorganisms for gut health. Eleven participants (9.5%) stated that they did not know what PBs were, while 8 participants (6.9%) believed they were medications. Furthermore, 87 mothers (75.0%) stated that they would consult a doctor before using probiotics.

The perceptions of participants with Pb awareness regarding specific foods classified as PBs are shown in Figure 1. Yogurt (n=112, 96.5%) and kefir (n=100, 86.2%) were most commonly recognized as probiotic foods.

The most frequently consumed probiotic foods at home were homemade yogurt (n=76, 55.9%) and while the least consumed were boza (a fermented beverage, n=98, 72.1%) and turnip juice (n=74, 54.4%).

Participants' responses to knowledge statements about PBs are presented in Table 1. Among these, 58.1% believed

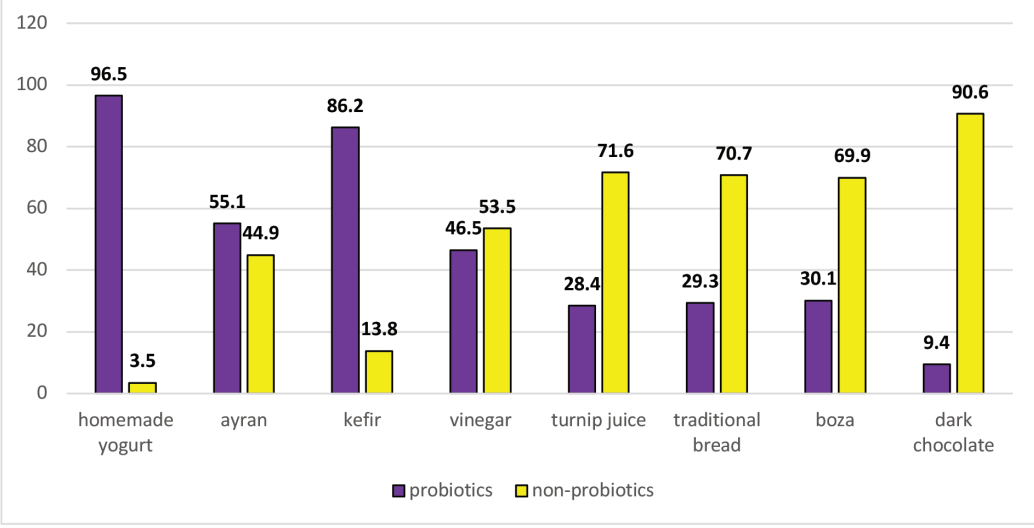

Figure 1. Participants' opinions on whether certain foods are probiotics, among those with probiotic awareness (%)

PBs help prevent diseases, 52.9% knew PBs contain a high concentration of live microorganisms, 50% thought PBs have therapeutic effects for certain diseases, 47.1% believed PBs do not increase cancer risk, and 43.4% stated that PBs prevent diarrhea.

Of the 69 participants who had used PBs at least once, 28 (40.6%) reported using them occasionally when their child was sick, and 34 (49.3%) had used PBs for a duration between 10 days and 6 months. A total of 41 participants (59.4%) used PBs upon a doctor's recommendation, while 14 (20.3%) were influenced by their social circle or family, and 9 (13.0%) followed the advice of a pharmacist. Among those who had used probiotics, 58 participants (84.1%) reported benefiting from probiotic foods and supplements, and 62 (89.9%) stated that they would recommend PBs to others.

Among the 69 participants who provided information about the PBs they used, *Bacillus clausii* (n=20, 14.7%) was the most commonly reported strain, followed by natural probiotic sources such as kefir and yogurt (n=12, 8.8%) (Table 2).

The relationships between participants' age groups, their children's age groups, educational levels, income levels, employment status, and awareness or use of PBs for their children are presented in Table 3. Participants with high school education or above, those earning at least the minimum wage, and those with professional occupations were significantly more likely to report probiotic awareness (p=0.000 for all). Similarly, these groups had higher rates of using PBs for their children (p=0.000, p=0.004, and p=0.000, respectively).

Discussion

Although various studies in the Turkish literature have examined knowledge, attitudes, and practices regarding PBs in different population groups, research specifically addressing mothers' knowledge, usage patterns, and influencing factors remains limited. This study, therefore, holds importance in addressing this gap (6,7).

In studies conducted in Turkey, the percentage of participants who responded "yes" to knowing what PBs are has ranged from 20.2% to 73.3% (6,8-12). In a study by Zemzemoğlu et al. (8), 55.6% of participants reported knowing what PBs are. When asked about their level of knowledge, 68.6% described it as moderate, while 25.4% described it as low (8). In this study, 85.3% of participants reported probiotic awareness. Variability in reported knowledge levels in the literature may stem from differences in the socio-demographic characteristics of the study populations.

A study by Yücel Şengün et al. (9) found that postgraduate degree holders were the group with the highest knowledge of PBs (66.7%). Similarly, Pehlivan and NURT (13) observed a general increase in probiotic knowledge with higher educational levels. Another study found that mothers with higher education and income levels, as well as those who were employed, were more likely to know what PBs are compared to mothers with lower education and income levels or those who were unemployed (6). In the study by Gültekin Ulusan et al. (7), participants with higher education levels and incomes exceeding their expenses had significantly greater knowledge of PBs. Consistent with the literature, higher education levels, income levels, and employment status were significantly associated with greater awareness of PBs in the present study.

Table 1. Participants' responses to statements about probiotics n (%)

Statement	No knowledge/ never heard	Disagree	Neutral	Agree	Total
Probiotics have therapeutic effects for some diseases	31 (22.8)	13 (9.6)	24 (17.6)	68 (50.0)	136 (100)
Probiotics contain a high number of live microorganisms	30 (22.1)	15 (11.0)	19 (14.0)	72 (52.9)	136 (100)
Microorganisms in probiotics are always alive	31 (22.8)	27 (19.9)	52 (38.2)	26 (19.1)	136 (100)
Probiotics help prevent diseases	29 (21.3)	11 (8.1)	17 (12.5)	79 (58.1)	136 (100)
Probiotics increase the risk of cancer	35 (25.7)	64 (47.1)	28 (20.6)	9 (6.6)	136 (100)
Probiotics stimulate appetite	32 (23.5)	31 (22.8)	50 (36.8)	23 (16.9)	136 (100)
Probiotics prevent diarrhea	31 (22.8)	17 (12.5)	29 (21.3)	59 (43.4)	136 (100)
Probiotics contribute to eye health	34 (25.0)	19 (14.0)	62 (45.6)	21 (15.4)	136 (100)
Probiotics contribute to skin health	35 (25.7)	17 (12.5)	36 (26.5)	48 (35.3)	136 (100)
Probiotics help with weight loss	33 (24.3)	24 (17.6)	37 (27.2)	42 (30.9)	136 (100)

A study among healthcare professionals identified the most common reasons for not consuming PBs as the lack of perceived need (60.8%), not knowing what probi PBs otics are (41.7%), and not considering them natural (41.7%) (14). Another study found that among those not consuming probiotics, 54.7% were unaware of what PBs are, 24.7% did not feel the need, and 10.4% did not consider them natural (15). In another study, reasons for not using PBs included high cost (36.4%), lack of need (30.3%), not considering them natural (27.3%), and lack of knowledge about PBs (6.1%) (11). In this study, the most frequently reported reasons for not using PBs included a lack of perceived need (32.8%), lack of probiotic awareness (29.8%), and not considering them natural (7.4%).

In a study where students were asked about the benefits of probiotics, 84.3% reported experiencing benefits, and 82.4% stated they would recommend PBs to others (8). Another study reported that approximately 90% of women who used PBs during pregnancy and postpartum for their babies perceived benefits from their use (6). Similarly, 84.6% of postmenopausal women expressed satisfaction with probiotic-containing foods (11). In alignment with these findings, 84.1% of participants in the present study who had used PBs reported experiencing benefits, and 89.9% stated they would recommend them to others.

A study by Köse et al. (14) found that participants most commonly learned about PBs from the internet, followed by advertisements, newspapers, and magazines. Another study reported that 41.6% of participants had learned about PBs through advertisements, 35.6% through the internet, 32.7% from their social circle or family, and 31.7% from experts (16). In yet another study, the sources influencing probiotic consumption were TV, newspapers, and magazines (13.7%), the internet (12.8%), and social circles (6.2%) (17). In this study, the most frequently reported sources of awareness included TV, newspapers, magazines, and the internet (56.9%). However, only 2.9% of participants reported using PBs based on recommendations from these sources. The strongest influence on probiotic use was found to be doctor recommendations (59.4%). Consistent with this, 75.0% of participants stated that they would consult a doctor before using probiotics.

In this study, 44.8% of participants indicated that PBs could help address digestive system problems, while 13.8% believed they could be beneficial for immune system support. Similarly, a study found that 81.8% of women believed PBs benefit digestive problems, and the remainder thought they were helpful for immune system issues (11).

Table 2. Characteristics of participants who used probiotics at least once (n=69)

Characteristic	n (%)
Recommendation source	
TV, newspapers, magazines, internet	2 (2.9)
Social circle and family	14 (20.3)
Doctor	41 (59.4)
Pharmacist	9 (13.0)
Does not remember	3 (4.3)
Duration of probiotic use	
Occasionally when ill	12 (17.4)
10 days or less	16 (23.2)
10 days-6 months	23 (33.3)
6 months or more	11 (15.9)
Does not remember	7 (10.1)
Perceived benefit from probiotics	
Benefited	58 (84.1)
Did not benefit	8 (11.6)
Neutral	3 (4.3)
Recommendation to others	
Would recommend	62 (89.9)
Would not recommend	4 (5.8)
Neutral	3 (4.3)
Classification of probiotics used	
Bifidobacterium animalis	8 (11.6)
Mixed microorganisms	4 (5.8)
Saccharomyces boulardii	3 (4.3)
Yogurt/kefir	12 (17.4)
Bacillus clausii	20 (29.0)
Does not remember	11 (15.9)
Lactobacillus reuteri	9 (13.0)
Lactobacillus rhamnosus	2 (2.9)

Another study reported that approximately 80% of men and women believed PBs benefited the digestive system, while about 20% thought they supported the immune system (13). A study among students found that 67.9% consumed PBs for digestive issues, 17.9% for immune system support, and 17.9% for circulatory system problems (18). PBs are predominantly associated with gastrointestinal health benefits, particularly due to their frequent recommendation in the management of diarrhea-related conditions. Literature suggests that approximately 80% of the immune cells in humans are located in gut-associated lymphoid tissue. When gut health is compromised, immune system function can also deteriorate. PBs may support the immune system by enhancing the production and activation of immune cells, influencing the gut-brain axis, and competing with harmful microorganisms in the gut.

Table 3. Relationship between socio-demographic characteristics and participants' awareness of the term "probiotic" and probiotic use for their children n (%)

Characteristic	Awareness of probiotic term			Probiotic use for their children		
	Heard	Not heard	p	Used	Not used	p
Mother's age						
Under 35 years	73 (86.9)	11 (13.1)	0.500	44 (52.4)	40 (47.6)	0.626
35 years and older	43 (82.7)	9 (17.3)		25 (48.1)	27 (51.9)	
Child's age						
Under 3 years	53 (86.9)	8 (13.1)	0.637	29 (47.5)	32 (52.5)	0.502
3 years and older	63 (84.0)	12 (16.0)		40 (53.3)	35 (46.7)	
Education level						
Below high school	14 (45.2)	17 (54.8)	**0.000***	6 (19.4)	25 (80.6)	**0.000**
High school and above	102 (97.1)	3 (2.9)		63 (60.0)	42 (40.0)	
Income level						
Below minimum wage	27 (65.9)	14 (34.1)	**0.000**	13 (31.7)	28 (68.3)	**0.004**
Minimum wage and above	89 (93.7)	6 (6.3)		56 (58.9)	39 (41.1)	
Employment status						
Unemployed	44 (72.1)	17 (27.9)	**0.000**	23 (37.7)	38 (62.3)	**0.006**
Employed	72 (96.0)	3 (4.0)		46 (61.3)	29 (38.7)	
Occupation						
Homemaker	33 (66.0)	17 (34.0)	**0.000**	13 (26.0)	37 (74.0)	**0.000**
Civil servant/private sector/self-employed	83 (96.5)	3 (3.5)		56 (65.1)	30 (34.9)	

*: Fisher's exact test

Regular consumption of probiotic-rich foods can positively impact gut microbiota and contribute to immune system activation (19).

To achieve the expected benefits of probiotic products, they must be consumed regularly and consistently, and the number of live microorganism cells ingested must exceed a certain threshold (9).

Naturally occurring PBs can be found in foods such as yogurt, kefir, pickles, certain types of cheese, traditional bread, and boza. They are also available as dietary supplements in tablet, capsule, or powder forms. A study found that although mothers lacked sufficient knowledge about PBs and which products contained them, they consumed natural probiotic foods daily (6). In the present study, when participants were asked about the PBs they used for their children, only 17.2% mentioned yogurt or kefir, while the remainder cited commercial products. This may indicate a lack of awareness regarding probiotic-containing foods, as some participants incorrectly classified certain foods as probiotics.

In the study, the probiotic foods most frequently consumed daily or more than once a week were yogurt (55.9%; 33.8%), and ayran (35.3%; 51.5%). In a study conducted with postmenopausal women, 50% of participants consumed yogurt every other day, 16.7% consumed it daily, 25% consumed kefir every other day, and 65% consumed kefir daily (11). Another study found that 51.4% of participants consumed yogurt daily, while 7.5% consumed kefir once a week, with yogurt being the most recognized probiotic food (12). While the frequency of probiotic food consumption in the present study was relatively high, knowledge regarding probiotic foods remained limited.

The most commonly recognized benefits of PBs were their ability to help prevent certain diseases (58.1%), treat certain diseases (50.0%), and contain high amounts of microorganisms (52.9%). Fifty-nine participants (43.4%) believed that PBs prevent diarrhea. In one study, 84% of participants thought PBs help fight infections, 80% believed they treat diarrhea, and 80% recognized their high microorganism content (20). Another study found that 56.3% of men and 43.9% of women believed PBs contain high amounts of microorganisms, while approximately 56% of all participants believed PBs strengthen the immune system (13).

In this study, *B. clausii* was identified as the most frequently used strain. According to the World Gastroenterology Organization's global guidelines on prebiotics and probiotics, there is no specific recommendation for the use of *B. clausii* in pediatric populations (1). However, recent evidence suggests that *B. clausii* may have potential benefits in the prevention and treatment of diarrhea in both pediatric and adult populations (21,22). This may explain why *B. clausii* was the most commonly used strain in this study.

Study Limitations

In this study, as the data were collected through self-reported questionnaires, there is a risk of bias, including social desirability and recall bias. Additionally, the study was conducted in a single region and included mothers who voluntarily participated, which may limit the generalizability of the findings to other populations.

Another limitation is that the questionnaire was not subjected to a formal pilot test to ensure comprehensibility before data collection. Furthermore, although internal consistency and factor analysis demonstrated excellent reliability (Cronbach's alpha =0.96) and a coherent unidimensional construct (eigenvalue of the first factor =9.48), no formal content validity index was calculated. These methodological shortcomings should be considered when interpreting the results.

Conclusion

The study demonstrates that while most mothers reported awareness of probiotics, only a portion were aware of their potential benefits. Higher education and income levels, employment status, and having a professional occupation were associated with greater awareness and use of PBs for their children. The most common sources of information about PBs were TV, newspapers, magazines, and the internet, while doctor recommendations were identified as having a strong influence on mothers' decisions to use probiotics.

To enhance the positive public health impact of probiotics, we recommend increasing educational broadcasts and articles in visual and written media. Additionally, healthcare providers should offer informative guidance to mothers about probiotics, their benefits, and their applications, as this could positively influence mothers' knowledge, attitudes, and behaviors regarding probiotics.

Ethics

Ethics Committee Approval: This descriptive study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital with the approval number 2503, dated September 3, 2019.

Informed Consent: All participants provided informed consent.

Footnotes

Authorship Contributions

Concept: G.Z.Ö., Design: G.Z.Ö., O.P.Ö., Data Collection or Processing: Y.G.A., G.Z.Ö., O.P.Ö., Analysis or Interpretation: Y.G.A., G.Z.Ö., Literature Search: Y.G.A., O.P.Ö., Writing: Y.G.A., G.Z.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. World Gastroenterology Organisation Global Guidelines Probiotics and Prebiotics. [cited 2024 Jan 2]. Available from: https://www.worldgastroenterology.org/UserFiles/file/guidelines/probiotics-and-prebiotics-english-2023.pdf.
2. Gökırmaklı Ç, Seydim Z. Effects of probiotics on colon microbiota: recent studies. J Biotechnol and Strategic Health Res. 2020;4(3):212-224.
3. Bridgman SL, Azad MB, Field CJ, Letourneau N, Johnston DW, Kaplan BJ, et al. Maternal perspectives on the use of probiotics in infants: a cross-sectional survey. BMC Complement Altern Med. 2014;14:366.
4. Martinelli M, Banderali G, Bobbio M, Civardi E, Chiara A, D'Elios S, et al. Probiotics' efficacy in paediatric diseases: which is the evidence? A critical review on behalf of the Italian Society of Pediatrics. Ital J Pediatr. 2020;46(1):104. Erratum in: Ital J Pediatr. 2020;46(1):116.
5. Schneider R, Sant'Anna A. Using probiotics in paediatric populations. Paediatr Child Health. 2022;27(8):482-502. English, French, French.
6. Cevik Guner U, Kissal A. Mothers' knowledge, attitudes and practices regarding probiotic use during pregnancy and for their infants in Turkey. Public Health Nutr. 2021;24(13):4297-4304.
7. Gültekin Ulusan A, Başpınar MM, Basat O, Ulusan C, Geylani Güleç S. Probiotic product use and awareness in mothers of 0-5 age group children. Journal of Izmir Faculty of Medicine. 2023;2(2):98-104.
8. Zemzemoğlu TEA, Uludağ E, Uzun S. Determination of university students' knowledge and consumption of probiotics. GIDA. 2019;44(1):118-130.
9. Yücel Şengün İ, Kırmızıgül A, Özaydın İ, Yarım H. Determining consumers' knowledge and consumption of probiotic and prebiotic foods: the example of Izmir/Bornova. GIDSA. 2020;45(1):103-114.

10. Yurttaş M, YIlmaz A. Knowledge and consumption of probiotic products among health college students. GUSBD 2017;6(2):64-69.

11. Küçük SC, Yıbar A. Knowledge and consumption of probiotics among postmenopausal women. J Res Vet Med. 2021;40(2):125-130.

12. Zeren R. Determination of knowledge and consumption level of probiotic nutrient on adult individuals. Thesis, Haliç University / Institute of Health Sciences / Department of Nutrition and Dietetics, Istanbul: 2015.

13. Pehlivan B, NUTRT. Evaluation of frequency of adults' probiotic food consumption and levels of knowledge. BARNAT. 2021;15(1):1-4.

14. Köse B, Aydın A, Özdemir M, Yeşil E. Determination of the knowlege level and consumption of probiotic, prebiotic and sinbioticals on healthcare prosfesional. Academic Gastroenterology Journal. 2019;18(2):67-72.

15. Aydın M, Açıkgöz İ, Şimşek B. Knowledge and consumption of probiotics among students at Isparta Suleyman Demirel University. Food Technology Electronic Journal. 2010;5(2):343-354.

16. Nagata S, Chiba Y, Wang C, Yamashiro Y. The effects of the Lactobacillus casei strain on obesity in children: a pilot study. Benef Microbes. 2017;8(4):535-543.

17. Derin DÖ, Keskin S. Determination of probiotic product consumption among food engineering students: the case of Ege University. GIDA. 2013;38(4):215-222.

18. Güleç M. Knowledge and consumption of probiotic products among secondary school teachers: the case of Ceyhan District. [cited 2023 Dec 23]. Available from:https://avesis.gazi.edu.tr

19. Yapıcıoğlu Yıldızdaş H. Probiotics and the immune system in children. Klinik Tıp Pediatri. 2016;8(3):5-10.

20. Özgül AA, Bozat C, Seziş M, Badur Y, Özcan ÖÖ, Sarıyer ET, et al. Knowledge and consumption of probiotic foods among individuals in the workforce. IGUSABDER. 2020;(12):365-378.

21. Sudha MR, Jayanthi N, Pandey DC, Verma AK. Bacillus clausii UBBC-07 reduces severity of diarrhoea in children under 5 years of age: a double blind placebo controlled study. Benef Microbes. 2019;10(2):149-154.

22. Acosta-Rodríguez-Bueno CP, Abreu Y Abreu AT, Guarner F, Guno MJV, Pehlivanoğlu E, Perez M. Bacillus clausii for gastrointestinal disorders: a narrative literature review. Adv Ther. 2022;39(11):4854-4874.

CASE REPORT

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Management of Bacille Calmette-Guérin Vaccine Adverse Event: Case Report

Bacille Calmette-Guérin Aşısı İstenmeyen Etki Yönetimi: Olgu Sunumu

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Abstract

Bacillus Calmette-Guérin (BCG) vaccine is used worldwide as an important preventive vaccine against tuberculosis. It is a safe vaccine with a low incidence of serious side effects. However, some adverse events may be observed. An 8-month and 6-day-old male infant was presented to the well-child clinic. The patient was vaccinated with BCG when he was two months old. Two months after the vaccination, an induration occurred on the left shoulder and persisted for approximately 5 mm in size. Over the past week, induration and redness had gradually increased, and one day before the presentation, it had grown outward with a small amount of pus. There was no accompanying lymphadenopathy. There were eczematous lesions on the trunk, arms and face. Immunodeficiency was excluded by medical history, physical examination and laboratory tests. Conservative treatment was preferred and it was observed to heal with scar formation in a short period.

Keywords: BCG, vaccine adverse event, vaccination

Öz

Bacillus Calmette-Guérin (BCG) aşısı tüm dünyada tüberkülozu önlemek için kullanılan önemli bir aşıdır. Ciddi yan etki insidansı düşük, güvenli bir aşıdır. Ancak bazı istenmeyen etkiler görülebilir. Sekiz ay 6 günlük erkek bebek, çocuk sağlığı izlem polikliniğine başvurdu. Olguya, iki aylıkken BCG aşısı yapılmıştı. Aşıdan iki ay sonra, sol omuzda yaklaşık 5 mm boyutunda bir endürasyon oluşmuştu. Son bir haftadır endürasyon ve kızarıklık giderek artmış ve başvurudan bir gün önce az miktarda irinle birlikte dışarı doğru büyümüştü. Eşlik eden lenfadenopati yoktu. Gövde, kollar ve yüzde ekzematöz lezyonları vardı. Anamnez, fizik muayene ve laboratuvar testleri ile immün yetmezlik dışlandı. Konservatif tedavi tercih edildi ve kısa sürede skar oluşturarak iyileştiği görüldü.

Anahtar kelimeler: Aşı istenmeyen etki, aşılama, BCG

Introduction

Despite being a preventable and curable disease, 1.5 million people die from tuberculosis (TB) every year (1). It is particularly risky in children under five years of age because it can develop into a disseminated miliary form and meningitis (2). Bacillus Calmette-Guérin (BCG) vaccine is used worldwide as an important preventive vaccine against TB (1,3). The BCG coverage is also important for overall infant health. The studies have demonstrated that BCG protects against a range of non-TB infections, reducing all-cause mortality risk (4).

The national vaccination program in our country includes the BCG vaccine (5). It is a safe vaccine with a low incidence of serious side effects (5,6). However, some adverse events may be observed (3,5,6). The present case aims to explain the management of the vaccine adverse events after BCG vaccination.

Case Report

An 8-month and 6-day-old male infant was admitted to the well-child clinic due to increasing swelling on the left shoulder where the BCG vaccination was administered. It was

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performed in the second postnatal month. In the postnatal fourth month, redness began at the vaccination site and was followed by induration that persisted, approximately 5 mm in size. Over the past week, induration and redness had gradually increased, and one day before the presentation, they had grown outward with a small amount of pus (Figure 1). Medical history: 39 gestational week, 2810 g, born by caesarean section. No problems after birth. In the fourth postnatal month, eczematous rash appeared on the cheeks after wearing woollen clothing. Over time, itchy rashes spread throughout the body and were diagnosed as eczema. He was exclusively breastfed for five and a half months, and then he started complementary feeding. He had no food allergies. He had no other illnesses and had never been hospitalized. Physical examination: Weight 8200 g [23rd percentile; -0.27 standard deviation score (SDS)], height 72 cm (56th percentile; 0.17 SDS), head circumference 44.8 cm (36th percentile; -0.35 SDS). There was an induration measuring approximately 12x15 mm in size on the left arm, with a crust measuring 5x6 mm (Figure 2). There was no pain, fever, lymphadenopathy, or hepatosplenomegaly. He had eczematous lesions on his trunk, arms and face. Laboratory tests: leukocytes 9.03×10^9/L, lymphocytes 5.62×10^9/L, neutrophils 2.2×10^9/L, monocytes 0.74 × 10^9/L, eosinophils 4.9×10^9/L, and basophils 0.03×10^9/L. T cell subsets were normal: CD3 54%, CD4 40%, CD8 11%, CD19 35%, CD16+CD56+ 10%. Total immunoglobulin (Ig) E was 26.6 U/mL (0-29), IgA was 0.35 g/L, IgG was 4.16 g/L, IgM was 0.37 g/L, and (anti-HBs) was 749.24 IU/L (positive). Immune deficiency was ruled out. Conservative treatment was preferred. Within approximately ten days, the scab, redness, and induration subsided. It healed, leaving scar tissue. The child is now 20 months old, and the eczematous lesions have disappeared over time, with no additional pathology developing during follow-up.

Discussion

The BCG vaccine is a live attenuated bacterial vaccine derived from Mycobacterium bovis. In our country, the vaccine is administered intradermally into the left deltoid region when children are 2 months old (5). In individuals who have not previously been exposed to TB bacilli, approximately 3-4 weeks after vaccination, an induration approximately 5 mm in diameter forms at the vaccination site. The induration is bluish-red in colour and drains by the 6th week. This ulcerative lesion forms a crust by the 8th week and heals within a few weeks, leaving scar tissue (3,5,7). Scarring generally occurs 12 weeks after vaccination, although it has been reported that this period may be 6 months or longer (7,8). Sometimes, within a week after vaccination, induration and oozing pus can be observed at the vaccination site. This early reaction is called the "Koch phenomenon" and demonstrates that the child may have been previously infected with TB (5).

Adverse events following BCG vaccination are mostly local reactions: Abscess, injection site reaction (ulceration), suppurative/non-suppurative lymphadenopathy, and keloid. These are dependent on the skill and method of vaccine administration, the vaccine strain and dose used, gender, age, and the individual's immune status (1,3,5)

Figure 1. Clinical image showing a protruding swelling at the vaccination site

Figure 2. Clinical appearance of the lesion as observed at the time of presentation

BCGitis is a general term for local inflammatory reactions caused by the BCG vaccine. There is also ipsilateral regional lymph node enlargement (3,9). BCG lymphadenitis occurs in 1-2% of cases. It typically develops as a result of an exaggerated immune response to the attenuated mycobacterial strain in the vaccine. As a result of the excessive local immune response, the lesion is characterised by axillary, cervical, or supraclavicular lymphadenopathy, redness, and tenderness near the arm where the vaccine was administered. Physical examination may reveal local swelling and lymphadenopathy. The diagnosis is typically based on clinical findings. Ultrasound or needle aspiration biopsy may be used. Lymphadenitis can present in two forms: non-suppurative or suppurative (3,5,9,10).

Serious adverse events following BCG vaccination are rare; BCG osteitis affecting the epiphysis of long bones (0.01-300 per million doses), may occur 4-24 months after vaccination. Disseminated BCG disease (0.19-1.56/1,000,000) is seen particularly in children with uncontrolled HIV infection or immunodeficiency on average 8 months after vaccination. (1,3,6).

The previous studies demonstrated that local complications (injection site reactions, suppurative/non-suppurative lymphadenitis) following BCG vaccination can be managed using various strategies (9-13). The efficacy of anti-tuberculous therapy in treating local complications of BCG is unclear (13). In a study investigating adverse events after BCG vaccination, one-third of children were referred with injection site reactions, which were mostly managed conservatively, and almost all resolved completely, supporting the generally adopted “watch and wait” approach for this type of adverse event. Two-thirds of children were referred with lymphadenitis following BCG vaccination; in half of these cases, there was evidence of suppuration. There is no clear consensus regarding the management of suppurative BCG lymphadenitis (13). Needle aspiration, surgical drainage, and anti-TB therapy could be administered in the management of these events (9-13). The high risk of complications, especially in children with suppressed immune systems, should be taken into consideration (3,10,13).

In conclusion, following BCG vaccination, some adverse events may be observed. The presented case was considered a local vaccine adverse event. We performed conservative treatment (watch and wait) due to the absence of lymphadenopathy discharge or abscess, and immunodeficiency, and the formation of a crust. Spontaneous healing was seen within a short period (approximately 10 days) by forming a scar.

Ethics

Informed Consent: Written and verbal informed consent was obtained from the patient’s parent(s).

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

References

1. World Health Organization. WHO position papers on BCG vaccines. [Internet] Available from: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers/bcg
2. Tapaç NN, Alabaz D. Tüberküloz epidemiyolojisi; dünya (Dünya Sağlık Örgütü verileri) ve Türkiye verileri. Alabaz D (editör). Çocukluk çağında tüberküloz enfeksiyonlarına güncel yaklaşım. 1. baskı. Ankara: Türkiye Klinikleri, 2025:4-10.
3. Alabaz D. Bacillus Calmette-Guérin aşısının komplikasyonları. Alabaz D (editör). Çocukluk çağında tüberküloz enfeksiyonlarına güncel yaklaşım. 1. baskı. Ankara: Türkiye Klinikleri, 2025:31-35.
4. Stougaard SW, Benn CS, Aaby P, Nielsen S, Schaltz-Buchholzer F. Using real-life data to model the impact of increasing BCG vaccination coverage and scar prevalence on all-cause infant mortality. Ann Epidemiol. 2023;86:90-97.e7.
5. Çuhacı Çakır B, Duyan Çamurdan A. BCG aşıları. Gökçay G (editör). Aşılar. 1. baskı. Ankara: Türkiye Klinikleri, 2021:52-59.
6. Okuno H, Satoh H, Morino S, Arai S, Ochiai M, Fujita K, et al. Characteristics and incidence of vaccine adverse events after Bacille Calmette-Guérin vaccination: a national surveillance study in Japan from 2013 to 2017. Vaccine. 2022;40(33):4922-4928.
7. Huang CY, Chi H, Chang L, Chiu NC. Typical time courses and appearance of skin reactions at the site of BacillusCalmette-Guérin vaccination for infants inoculated at 5-8 months of age. Vaccine. 2023;41(8):1529-1535.
8. Faridi MM, Krishnamurthy S. Abortive reaction and time of scar formation after BCG vaccination. Vaccine. 2008;26(3):289-290.
9. Ladeira I, Carvalho I, Correia A, Carvalho A, Duarte R. BCGitis in children. Rev Port Pneumol. 2014;20(3):172-173.
10. Elsidig N, Alshahrani D, Alshehri M, Alzahrani M, Alhajjar S, Aljummah S, et al. Bacillus Calmette-Guérin vaccine related lymphadenitis in children: management guidelines endorsed by the Saudi Pediatric Infectious Diseases Society (SPIDS). Int J Pediatr Adolesc Med. 2015;2(2):89-95.
11. Çiftçi E, İnceli HB, Özdemir H, Haskoloğlu Ş, Doğu F. Local abscess due to BCGitis. J Pediatr Inf. 2022;16(4):295.
12. Venkataraman A, Yusuff M, Liebeschuetz S, Riddell A, Prendergast AJ. Management and outcome of Bacille Calmette-Guérin vaccine adverse reactions. Vaccine. 2015;33(41):5470-5474.
13. Al Waili B, Al Mufarajii N, Al Hashmi S, Al Ajmi A, Al Sukaiti N. Bacillus Calmette-Guérin vaccine-related complications in children in Oman. Ann Saudi Med. 2021;41(1):24-30.