# **ORIGINAL RESEARCH**

Bagcilar Med Bull

DOI: 10.4274/BMB.galenos.2025.39200



# Impact of Blood Product Administration in Cardiovascular Surgery Patients: Center Experience

# Kardiyovasküler Cerrahi Hastalarında Kan Ürünü Transfüzyonunun Etkisi: Merkez Deneyimi

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### **Abstract**

**Objective:** Blood transfusion is a frequent intervention in cardiovascular surgeries. However, the timing of transfusion—whether during surgery or postoperatively in the intensive care unit (ICU)—may have distinct implications for patient outcomes. This study investigates how the timing of blood product administration affects extubation time, ICU length of stay, postoperative drainage volume, cardiac and renal parameters, hemodynamic support requirements, and ICU rhythm disturbances.

**Method:** This retrospective cohort study included adult patients who underwent coronary artery bypass grafting or valve surgery. Patients were grouped based on whether they received blood products intraoperatively or during ICU follow-up. Statistical analyses included t-tests, chi-square tests, and descriptive comparisons.

**Results:** Intraoperative transfusions were associated with shorter extubation times but longer ICU stays and higher drainage volumes. In contrast, ICU transfusions correlated with delayed extubation, higher mortality, more frequent non-sinus rhythms, and increased need for hemodynamic support. These findings highlight a clear temporal distinction in risk profiles associated with transfusion timing.

**Conclusion:** The timing of blood product administration significantly affects postoperative outcomes. Intraoperative transfusions may address

### Öz

Amaç: Kardiyovasküler cerrahilerde sık uygulanan kan transfüzyonlarının, uygulama zamanına göre [(intraoperatif vs. yoğun bakım ünitesi (YBÜ)] klinik sonuçlar üzerindeki etkileri farklılık gösterebilir. Bu çalışmada, transfüzyon zamanlamasının ekstübasyon süresi, YBÜ'de kalış süresi, postoperatif drenaj hacmi, kardiyak ve renal parametreler, hemodinamik destek ihtiyacı ve YBÜ ritim değişiklikleri üzerindeki etkileri araştırılmıştır.

Yöntem: Bu retrospektif kohort çalışmaya, koroner arter bypass greftleme veya kalp kapağı cerrahisi geçiren erişkin hastalar dahil edildi. Hastalar intraoperatif veya YBÜ'de transfüzyon almalarına göre gruplandırıldı. İstatistiksel analizlerde t-testi, ki-kare testi ve betimleyici yöntemler kullanıldı.

**Bulgular:** İntraoperatif transfüzyonlar daha kısa ekstübasyon süreleriyle ilişkiliyken, YBÜ kalış süresi ve drenaj hacimleri daha yüksekti. YBÜ döneminde yapılan transfüzyonlar ise uzamış ekstübasyon süresi, daha yüksek mortalite, sık görülen ritim bozuklukları ve artmış inotrop ihtiyacı ile ilişkiliydi. Bulgular, transfüzyon zamanlamasının klinik risk profilini etkileyen önemli bir faktör olduğunu göstermektedir.

**Sonuç:** Kan ürünü transfüzyonunun zamanlaması, postoperatif sonuçlar üzerinde belirleyici bir rol oynamaktadır. İntraoperatif transfüzyonlar cerrahi kayıpların yönetiminde etkili olabilirken, YBÜ transfüzyonları daha

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Received: 30.05.2025 Accepted: 26.11.2025 Epub: 01.12.2025

Cite this article as: Turan Eİ, Balkan B, Güneysu E, İyigün T. Impact of blood product administration in cardiovascular surgery patients: center experience. Bagcilar Med Bull. [Epub Ahead of Print]



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### **Abstract**

acute surgical needs, while ICU transfusions appear to be markers of postoperative instability and poorer prognosis. Timing should be considered a key factor in transfusion decision-making.

**Keywords:** Blood transfusion (includes blood typing), cardiopulmonary bypass, heart valve surgery, intensive care

### Öz

ciddi postoperatif komplikasyonların göstergesi olabilir. Transfüzyon kararları verilirken zamanlama mutlaka göz önünde bulundurulmalıdır.

**Anahtar kelimeler:** Kalp kapağı cerrahisi, kan transfüzyonu (kan grubu tayını dahil), kardiyopulmoner bypass, yoğun bakım

# Introduction

Cardiovascular surgeries are critical interventions that often require the administration of blood products. While advancements in surgical techniques and perioperative care have significantly improved patient outcomes, these procedures are still associated with substantial morbidity and mortality, particularly in the postoperative period. One of the crucial components of perioperative management in cardiovascular surgery is the use of blood products to address intraoperative and postoperative blood loss. However, the administration of blood products carries its own set of risks and complications, which can influence patient recovery and outcomes (1,2).

The necessity of blood product administration in the perioperative period has been associated with various adverse outcomes, including prolonged mechanical ventilation, extended intensive care unit (ICU) stays, and increased rates of infection (3). Specifically, in the context of cardiovascular surgery, blood product administration has been associated with increased postoperative complications and longer recovery times (4). The physiological stress induced by major surgeries, compounded by the immunomodulatory effects of blood products, can exacerbate these complications, making postoperative management particularly challenging. The primary aim of this study is to evaluate the impact of the timing of blood product administration on mortality in patients undergoing cardiovascular surgery. The secondary aims include assessing the association of intraoperative and postoperative transfusions with morbidity-related outcomes, such as extubation time, length of hospital stay, postoperative drainage volume, revision surgery rates, and need for inotropic support.

# **Materials and Methods**

### Study Design

This retrospective cohort study was conducted to evaluate the impact of timing of blood product administration during the intraoperative period versus the postoperative period in the ICU on clinical outcomes in patients who underwent cardiovascular surgery [coronary artery bypass grafting (CABG) and valve replacement surgeries]. Ethical approval for the study was obtained from the Institutional Ethics Committee of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (approval number: 2023.09.94).

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Given the retrospective nature of the study, the need for informed consent was waived by the IRB. Patient confidentiality was maintained by anonymizing the data during the analysis.

### **Study Population**

The study included adult patients aged 18 years or older who underwent elective or emergency CABG or valve replacement surgery between 2016 and 2022 and were subsequently admitted to the ICU. Patients were included only if complete medical records were available. Those with incomplete documentation, those who underwent surgical procedures other than cardiovascular surgery, and those with an aortic cross-clamp duration exceeding 120 minutes were excluded. Patients who did not require postoperative ICU follow-up were also excluded.

### **Grouping of Patients**

Patients were classified according to the timing of transfusion. Those who received blood products during surgery were categorized as the intraoperative transfusion group, regardless of whether additional transfusions were subsequently required in the ICU. Patients who did not receive any intraoperative transfusions but required blood product administration during ICU follow-up were categorized as the postoperative (ICU) transfusion group. This classification ensured mutually exclusive groups and enabled clear evaluation of the impact of transfusion timing on clinical outcomes.

### **Data Collection**

Data were retrieved retrospectively from electronic medical records. Data collected included demographic variables [age, sex, body mass index (BMI)], comorbidities (diabetes mellitus and hypertension), intraoperative data on inotropic support and transfusion, and postoperative outcomes, including extubation time, length of ICU stay, drainage volumes on postoperative days 0 and 1, and lactate levels at baseline and 24 hours.

### **Outcome Measures**

The primary outcomes were time to extubation and length of ICU stay. Secondary outcomes included postoperative drainage volume (on days 0 and 1) and preoperative lactate levels. In addition to comparing patients who did or not receive blood products, all outcome measures were analyzed separately for two key transfusion periods: Intraoperative and ICU. This allowed the evaluation of how transfusion timing influenced recovery profiles and clinical risks.

### Transfusion Protocol

Transfusion decisions were individualized based on hemodynamic status, laboratory results, and clinical context. Transfusion was typically considered when hemoglobin fell below 7 g/dL in stable patients and below 8 g/dL in hemodynamically unstable patients. In this study, the term "blood product" encompassed erythrocyte suspension, fresh-frozen plasma (FFP), and platelet transfusion; however, all transfused patients received at least ES. These criteria were consistent with international transfusion guidelines, balancing the risks and benefits of blood product administration (5,6).

### **Extubation Criteria**

Early extubation was encouraged to optimize recovery. Patients were considered ready for extubation if they demonstrated hemodynamic stability without significant arrhythmias or hypotension, adequate spontaneous breathing and gas exchange, neurologic responsiveness, sufficient muscle strength, and strong cough reflex. Extubation was performed using a stepwise weaning protocol once these conditions were met.

# **Inotropic Drug Initiation Protocol**

Inotropic support was initiated in cases of hemodynamic instability following surgery. Indications included clinical and biochemical evidence of low cardiac output syndrome, including hypotension, oliguria, cool extremities, altered mental status, and elevated lactate levels. During

surgery, inotropes such as dobutamine, norepinephrine, or epinephrine were administered when significant hemodynamic compromise persisted despite adequate fluid resuscitation. Initiation was guided by visual assessment of contractility after cross-clamp removal and supported by blood pressure monitoring and arterial blood gas analysis. A mean arterial pressure below 65 mmHg that was refractory to fluids also constituted an indication. Doses were titrated according to each patient's response to achieve adequate perfusion and prevent complications.

### **Agitation**

In this study, agitation was defined as a Richmond agitation-sedation scale (RASS) score of +2 or higher. For intubated patients, agitation was identified by observable behaviors, including restlessness, frequent non-purposeful movements, attempts to remove the endotracheal tube or other invasive lines, and resistance to care. These behaviors, documented by ICU nurses or physicians, were used as criteria to classify patients as agitated. In cases where RASS scoring was not explicitly recorded, the clinical documentation of agitation-related interventions (e.g., physical restraints, additional sedation) was also considered indicative of agitation.

## **Results Interpretation**

The results were interpreted to assess the association between administration of blood products postoperative clinical outcomes. The analysis focused on identifying significant differences in extubation times, ICU length of stay, and postoperative drainage volumes between patients who received blood products and those who did not. Additionally, preoperative ejection fraction (EF), creatinine (Cr), blood urea nitrogen (BUN), the need for inotropic and vasopressor support after cross-clamping and while in the ICU, and electrocardiogram (ECG) rhythms in the ICU were analyzed to assess cardiac and renal function, hemodynamic stability, and cardiac complications. Lactate and hemoglobin levels were also analyzed to assess metabolic response and recovery. The comprehensive evaluation of these variables provided insights into the multifaceted impact of blood product administration on patient outcomes following cardiovascular surgery.

# **Statistical Analysis**

Data were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Parametric tests (independent samples t-test) were applied to normally distributed data, whereas non-

parametric tests (Mann-Whitney U test) were used for data not conforming to a normal distribution. Continuous variables were expressed as mean ± standard deviation or median (Q1, Q3) and compared using the independent-samples t-test or the Mann-Whitney U test, as appropriate. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant.

# **Results**

A total of 500 patients were included in the study. During the intraoperative period, 163 patients required administration of blood products, of whom 98 received FFP and 17 received platelet suspension. The remaining 337 patients did not receive any blood products. In the intensive care unit, 385 patients required a transfusion: 242 received FFP, 65 received platelet suspension, and 115 did not receive any transfusion.

Table 1 presents the comparison of demographic characteristics between patients who did or did not receive transfusions during the intraoperative period and the ICU follow-up. A significantly higher proportion of female patients received intraoperative transfusions (p=0.005). Hypertension was more common in the intraoperative transfusion group (p=0.004); no significant difference was found between ICU groups. There were no significant differences in the prevalence of diabetes mellitus or COPD between the transfusion and non-transfusion groups. Patients who received transfusions were significantly older in both periods (p=0.000 for both), whereas BMI values were similar across all groups.

Table 2 presents a comparison of preoperative determinants and postoperative outcomes between patients who

received intraoperative transfusions and those who did not. Patients in the transfusion group had significantly shorter extubation times (p<0.001) but experienced longer hospital stays (p<0.001). Postoperative drainage volumes were higher in the transfusion group on both day 0 and day 1 (p=0.028 and p=0.023, respectively). Although preoperative EF, glomerular filtration rate (GFR), BUN, creatinine, and lactate levels were similar between the groups, preoperative hemoglobin levels were significantly lower in the transfusion group (p<0.001).

Regarding clinical outcomes, the transfusion group had significantly higher rates of revision surgery (p<0.001), postoperative agitation (p=0.029), and requirement for both cross and ICU inotropic support (p<0.001 for both). No statistically significant differences were observed between the groups with respect to ICU rhythm (defined as any rhythm other than sinus rhythm) or in-hospital mortality (p=0.388 and p=0.427, respectively). These findings suggest that intraoperative transfusion is associated with a more complex postoperative course, including higher complication rates and prolonged recovery (Table 2).

Table 3 compares preoperative determinants and postoperative outcomes between patients who did or did not receive transfusions during ICU follow-up. Patients in the transfusion group had significantly longer extubation times (p<0.001), longer hospital stays (p<0.001), and notably higher drainage volumes on postoperative days 0 and 1 (p<0.001 for both). Preoperative hemoglobin levels were significantly lower, and preoperative EF was slightly reduced, in the transfusion group (p<0.001 and p=0.048, respectively). Additionally, preoperative BUN levels were higher in transfused patients (p=0.001), whereas no significant differences were observed in lactate, GFR, or Cr levels.

Table 1. Demographic variables of the patients								
	No transfusion in intraoperative period (n=337)	Transfusion in intraoperative period (n=163)	p-value	No transfusion in ICU follow-up (n=115)	Transfusion in ICU follow-up (n=243)	p-value		
Gender (female/male)	123/214	81/82	0.005*	36/79	95/148	0.153**		
HT	22	131	0.004*	79	167	0.996**		
DM	156	81	0.475**	52	113	0.820**		
COPD	54	33	0.243**	22	65	0.600**		
Age (years)	71.53±12.80	67.04±11.36	0.000***	66.95±13.25	73.41±11.81	0.000***		
BMI	27.06±4.14	27.90±4.22	0.168***	27.36±4.52	26.99±3.95	0.618***		

HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, BMI: Body mass index, \*: Fisher's exact test was applied, ICU: Intensive care unit, \*\*: Chi-square test was applied, \*\*\*: Independent Sample t-test was applied

Postoperatively, the need for revision surgery was markedly higher among patients who received ICU transfusions (p=0.001). These patients also exhibited a higher incidence of non-sinus rhythms (p=0.024). ICU, cross inotropic support, and agitation rates did not differ significantly

between the groups. Notably, in-hospital mortality was significantly higher in the ICU transfusion group (p=0.035), indicating an association between ICU transfusion and adverse clinical outcomes (Table 3).

	No transfusion (n=337)	Transfusion (n=163)	p-value
Extubation (hours)	12 (8,17)	17 (10.5,22)	0.000*
Discharge day	2 (1,3)	2 (2,4)	0.000*
Orainage day 0 (mL)	400 (200,600)	450 (300,700)	0.028*
Orainage day 1 (mL)	150 (50,300)	200 (100,400)	0.023*
Preoperative EF (%)	53.25±10.01	52.07±10.15	0.224*
_actate preanesthesia (mmol/L)	1.02±0.37	0.95±0.41	0.153*
Preoperative HB (g/dL)	12.77±1.99	11.88±2.07	0.000*
Preoperative GFR (mL/min/1.73 m²)	79.13±22.11	76.85±25.88	0.382*
Preoperative BUN (mg/dL)	21.74±9.81	21.70±16.26	0.971*
Preoperative Cr (mg/dL)	1.02±0.50	1.00±0.52	0.703*
Revision	26	35	0.000**
Agitation	9	11	0.029**
Cross inotropic support	169	125	0.000**
CU inotropic support	145	103	0.000**
CU rhythm****	69	64	0.388***
Non-survivors	26	16	0.427***

EF: Ejection fraction, HB: Hemoglobin, GFR: Glomerular filtration rate, BUN: Blood urea nitrogen, Cr: Creatinin, ICU: Intensive care unit, \*: Independent Sample t-test was applied, \*\*\*: Fisher's exact test was applied, \*\*\*: Chi-square test was applied, \*\*\*: Rhythm other than sinus rhythm

Table 3. Comparison of preoperative determinants and postoperative outcomes between transfusion status in intensive care unit follow-up

	No transfusion (n=115)	Transfusion (n=243)	p-value
Extubation (hours)	7.5 (5.2,9)	10 (6,14)	0.000*
Discharge day	1 (1,1)	1.25 (1,2)	0.000*
Drainage day 0 (mL)	200 (110,300)	262.5 (200,450)	0.000*
Drainage day 1 (mL)	50 (0,100)	100 (0,200)	0.000*
Preoperative EF (%)	54.64±9.08	52.40±10.35	0.048**
Lactate preanesthesia (mmol/L)	1.068±0.428	0.981±0.333	0.059**
Preoperative HB (g/dL)	13.39±2.01	12.18±1.92	0.000**
Preoperative GFR (mL/min/1.73 m²)	80.71±22.65	76.32±23.88	0.149**
Preoperative BUN (mg/dL)	19.27±8.78	23.19±9.73	0.001**
Preoperative Cr (mg/dL)	0.98±0.38	1.03±0.54	0.149**
Revision	1	26	0.001***
Agitation	3	6	1****
Cross inotropic support	54	126	0.387***
ICU inotropic support	50	107	0.921***
ICU rhythm****	27	86	0.024**
Non-survivors	4	24	0.035**

EF: Ejection fraction, HB: Hemoglobin, GFR: Glomerular filtration rate, BUN: Blood urea nitrogen, Cr: Creatinin, ICU: Intensive care unit, \*: Mann-Whitney U test was applied, \*Independent Sample t-test was applied, \*\*: Fisher's exact test was applied, \*\*: Chi-square test was applied, \*\*\*\*Rhythm other than sinus rhythm

# **Discussion**

This study demonstrates that the timing of administration of blood products-whether during surgery or in the ICU—significantly affects postoperative outcomes in patients undergoing cardiovascular surgery. Our findings revealed that intraoperative transfusions were associated with shorter time to extubation, suggesting a potential benefit in the immediate management of surgical blood loss. However, these transfusions also correlated with longer ICU stays, increased drainage volumes, and greater need for inotropic support, indicating a more complex postoperative course. In contrast, ICU transfusions were associated with higher mortality, delayed extubation, prolonged ICU stay, and more frequent cardiac rhythm disturbances, reflecting ongoing hemodynamic instability and possibly more severe postoperative complications. These findings underscore the importance of determining not only whether to transfuse but also when to transfuse, because the timing of transfusion may serve as a surrogate marker for surgical complexity and patient risk.

Results of our study indicate that patients who received blood products intraoperatively had significantly different outcomes compared with those who did not. Specifically, extubation time was significantly shorter in patients who received intraoperative blood products than in those who did not. Additionally, the length of ICU stay was notably longer in the transfusion group than in the no-transfusion group. These results align with previous studies indicating that administration of blood products is associated with prolonged ICU stays (7,8).

Intraoperative blood product administration is beneficial for stabilizing patients during acute surgical blood loss; however, it has also been associated with prolonged extubation times and extended ICU stays, suggesting a more complicated postoperative course (9-12). In our study, patients who received intraoperative transfusions demonstrated significantly longer ICU stays than nontransfused patients, despite having shorter initial extubation times. Horvath et al. (13) similarly reported a strong association between transfusion exposure and both delayed weaning from mechanical ventilation and increased ICU length of stay. Ghiani et al. (4) also emphasized that transfusions are common in patients requiring prolonged ventilation and are strongly linked to delayed recovery trajectories. One possible explanation for these findings lies in the immunomodulatory effects of transfusions, which may exacerbate systemic inflammation, contribute to

postoperative complications, and thereby prolong recovery (14). Taken together, these results highlight the complex balance between the immediate benefits of intraoperative transfusion for hemodynamic stabilization and the longer-term risks associated with extended ICU care, underlining the importance of judicious transfusion practices and targeted perioperative optimization strategies for cardiovascular surgery patients.

Transfusion-related immunomodulation (TRIM), which is known to exacerbate inflammatory responses and increase the risk of complications such as infections and delayed wound healing, has been well documented (14). Understanding these mechanisms is crucial for developing interventions that can mitigate these adverse effects and improve recovery trajectories for patients undergoing major surgeries.

It is well established that preoperative anemia is associated with increased morbidity and mortality in surgical patients; and optimizing preoperative hemoglobin levels can reduce the need for transfusions and improve postoperative outcomes (15,16). Consistent with these studies, our findings emphasize the importance of identifying and correcting anemia before surgery to minimize the risk of blood product administration and associated complications.

Patients receiving intraoperative blood products had higher postoperative drainage volumes on both the day of surgery and the first postoperative day. This finding suggests that these patients may have undergone more invasive procedures or experienced greater surgical trauma, necessitating blood transfusions. Increased drainage volumes indicate greater postoperative fluid loss and can complicate recovery by increasing the risk of anemia and hypovolemia, which may further necessitate blood transfusions (1).

A systematic review explored the significance of blood lactate kinetics in critically ill patients. It found that lactate levels are markers of tissue perfusion and stress and that monitoring these levels can provide insights into patient recovery and the effects of interventions such as blood transfusions (17).

No significant differences were found in BMI between patients who received blood products and those who did not, indicating that BMI was not a determinant of blood product administration in our cohort. Additionally, the prevalence of comorbidities such as diabetes mellitus and hypertension did not differ significantly between the groups. These findings highlight that the need for blood products is more strongly associated with the severity of the surgical procedure and intraoperative blood loss than with patient demographics or baseline health status. This supports the notion that surgical factors, rather than patient characteristics, primarily drive the need for transfusions.

Previous studies have shown that patients with lower cardiac function are more likely to require transfusions, possibly due to their reduced ability to tolerate intraoperative and postoperative blood loss (18-20). Consistent with these findings, our study demonstrated that preoperative EF was lower in the transfusion group than in the no-transfusion group.

Preoperative Cr levels did not differ significantly between the groups, indicating similar baseline renal function. However, preoperative BUN levels were significantly higher in the transfusion group compared to the notransfusion group. This suggests that patients with higher BUN levels, potentially indicating preoperative renal stress or dysfunction, are more likely to require blood product administration. This finding is also consistent with the previous study (10).

The need for inotropic and vasopressor support post-crossclamping was significantly greater in the transfusion group compared with the no-transfusion group. This indicates a greater need for hemodynamic support in patients receiving blood products, likely due to increased cardiovascular instability or more complex surgical interventions. Mufti et al. (9) reported similar findings in their study.

Mufti et al. (9) also demonstrated an association between blood transfusion and an increased risk of cardiac arrhythmias. Our findings are consistent with their study; in the transfusion group, we observed a higher prevalence of ECG abnormalities.

# **Study Limitations**

This study is retrospective in nature, which inherently limits the ability to establish causality between blood product administration and clinical outcomes. While associations can be identified, the retrospective design precludes definitive conclusions about causal relationships. Additionally, the study was conducted at a single center, which may limit the generalizability of the findings to other institutions or patient populations with differing practices or demographics. The reliance on electronic medical records and clinical documentation may introduce reporting or data-entry biases, potentially affecting the accuracy and completeness of the dataset. Furthermore,

the study does not account for potential confounders such as surgeon experience, intraoperative management strategies, or variations in transfusion thresholds, all of which could influence patient outcomes. Lastly, the lack of detailed data on transfusion-related complications, such as TRIM or transfusion-associated circulatory overload, limits the ability to evaluate specific risks associated with blood product administration.

# **Conclusion**

This study highlights the importance of timing in blood product administration for cardiovascular surgery patients. While intraoperative transfusions may aid in managing acute surgical blood loss and allow earlier extubation, ICU transfusions appear to reflect ongoing postoperative instability and are associated with worse outcomes, including higher mortality. These findings highlight the need for a timing-conscious, individualized approach to transfusion strategies. Future multicenter prospective studies are warranted to refine transfusion protocols and improve postoperative recovery and survival.

### **Ethics**

Ethics Committee Approval: Ethical approval for the study was obtained from the Institutional Ethics Committee of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (approval number: 2023.09.94).

**Informed Consent:** Given the retrospective nature of the study, the need for informed consent was waived by the IRB.

### **Footnotes**

In this study, Artificial General Intelligence (AGI) has been utilized to enhance the readability of the paper, ensuring that the findings and discussions are accessible and comprehensible to a wider audience.

### **Authorship Contributions**

Surgical and Medical Practices: E.İ.T., B.B., Concept: E.İ.T., B.B., Design: E.İ.T., B.B., Data Collection or Processing: E.İ.T., B.B., E.G., T.İ., Analysis or Interpretation: E.İ.T., B.B., E.G., T.İ., Literature Search: E.İ.T., B.B., E.G., T.İ., Writing: E.İ.T., B.B., E.G., T.İ.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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