

Original Article

Inflammatory prognostic index is a new predictive marker for perioperative mortality in patients undergoing type A aortic dissection surgery

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Abstract

Aim: This study aimed to investigate the potential predictive value of the inflammatory prognostic index (IPI) on perioperative mortality in patients undergoing type A aortic dissection (TAAD) surgery.

Material and Methods: A total of 111 patients who underwent TAAD surgery between July 2019 and October 2023 were evaluated. The patients were divided into two groups; mortality group (n=33) and survivor group (n=78). The independent predictors of perioperative mortality were identified using multivariate logistic regression analysis, and the cut-off values of mortality predictors were identified using a ROC curve.

Results: The mean ages were 66.4 ± 12.1 and 58.8 ± 11.0 years in the mortality and survivor groups, respectively, and the difference between the groups was statistically significant. Median cardiopulmonary bypass duration, postoperative cerebrovascular event rates, and bleeding requiring revision were significantly higher in the mortality group, while the median lengths of intensive care unit and hospital stay were significantly lower. Mean values of neutrophils, neutrophils/lymphocytes, red blood cell distribution width, mean platelet volume, C-reactive protein, creatinine, and IPI were significantly higher in the mortality group, while lymphocytes, platelet distribution width, glomerular filtration rate, and albumin were lower. Age, neutrophils, and IPI were found to be independent predictors of mortality using logistic regression analysis. An ideal cut-off value of 1.98 for IPI with 84.8% sensitivity and 85.9% specificity was determined using ROC curve analysis (AUC=0.943, 95% CI=0.899-0.986).

Conclusion: This study demonstrated that high IPI levels significantly and independently predicted perioperative mortality in TAAD patients.

Keywords: Inflammatory prognostic index, mortality, type A aortic dissection

INTRODUCTION

A multidisciplinary approach is necessary for the prompt identification and treatment of type A aortic dissection (TAAD), a life-threatening vascular disease. TAAD is associated with high mortality rates if not surgically treated, and the absolute approach should be surgery in the treatment of TAAD [1]. Once the diagnosis of TAAD is made and optimal conditions are met, surgical intervention should be performed immediately. However, even in patients undergoing emergency surgery for TAAD, once optimal conditions are achieved, perioperative mortality rate remains high and it has been reported to be between

15 and 35% in the literature [2,3]. We have created a hypothesis to understand the effect of systemic inflammation on mortality and morbidity with easily accessible, low-cost tests consisting of routine preoperative hematological and biochemical tests. Our research goal in our study is to determine the causes of mortality and morbidity in patients undergoing TAAD surgery and to take preventive measures. Therefore, in order to reduce mortality, there is a need for investigating new prognostic biomarkers, determining potential measures in patients with higher risk and subsequent therapeutic targets.

Inflammatory prognostic index (IPI) is a new prognostic biomarker

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created by combining neutrophil and lymphocyte counts as hematological markers as well as C-reactive protein (CRP) and albumin as biochemical markers ($IPI = \text{Neutrophil/Lymphocyte ratio (NLR)} \times \text{CRP/albumin}$). This biomarker has been recently developed to evaluate the immunological and inflammatory status of patients [4-9]. High levels of this new biomarker have been associated with adverse outcomes and have been shown to provide significant insight into the prognosis of cardiovascular and oncological disorders [4-9]. To the best of our knowledge, there is no study in the literature investigating the role of IPI in predicting perioperative mortality in patients with TAAD undergoing surgery. Therefore, we investigated the possible role of IPI in predicting perioperative mortality in patients undergoing surgical repair for TAAD. In addition, we also investigated other possible risk factors related to perioperative mortality of TAAD.

MATERIAL AND METHODS

Ethical Considerations

Our hospital's local ethics committee approved our study (No: 2023;15/8, Date: 13.09.2023). The Declaration of Helsinki's ethical guidelines were adhered to throughout the study's execution. Each patient enrolled in the trial received comprehensive information regarding the study and the operation, and their written and verbal agreement was obtained.

Study Population and Design

This research was planned as a retrospective, single-center, risk-prediction, observational cohort study. The research fit the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guideline. We evaluated a total of 111 adult patients who underwent TAAD surgery at our hospital between July 2019 and October 2023. Patients were divided into two groups. Group 1 (mortality group) was those who experienced mortality (29.7%, n=33) and Group 2 (survivor group) was those who did not experience mortality (70.2%, n=78). Demographic characteristics (age, gender, height, weight, body mass index (BMI)), accompanying diseases (diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), hypertension (HT) and chronic renal failure (CRF), and preoperative complete blood count and biochemical parameters and echocardiographic findings of the patients were recorded. In addition, during the perioperative period, cardiopulmonary bypass (CPB) time, cross clamp time, intensive care unit (ICU) and hospital stay durations, development of cerebrovascular event (CVE), bleeding requiring reoperation and mortality were also recorded. Preoperative basic demographic and clinical characteristics, hematological and biochemical values at the admission, and perioperative data were reviewed for the analysis and then compared between the groups. IPI was the primary output variable of the study. Inclusion criteria for this study was being adult patients who underwent emergency surgical repair for TAAD. Patients who underwent redo surgery through median sternotomy, those with malignancy, active infectious disease or sepsis, autoimmune, hematological or inflammatory

diseases were excluded from the study. All patients who underwent emergency surgery due to TAAD, except for those who met the exclusion criteria, were included in the study and the sample size was determined.

Surgical Approach

Under general anesthesia, a conventional median sternotomy was performed on all patients. Before cannulation, unfractionated heparin was administered at 350 units/kg. We administer methylprednisolone at a dose of 1 mg/kg to all patients preoperatively before CPB. For arterial cannulation, our primary target artery was the right subclavian artery, and in most of the patients the right subclavian artery was used for arterial inflow. In cases where the right subclavian artery was not suitable for use, femoral artery cannulation was performed. To complete the CPB system, a two-stage venous cannulation of the right atrium was also carried out. CPB was started when the active coagulation time (ACT) exceeded 400 seconds. During CPB; a flow rate of 2-2.5 L/min/m² in the non-pulsatile phase, a mean arterial blood pressure of 50-70 mmHg, and a hematocrit level of 20-25% were achieved. The ascending aorta was cross-clamped, the heart was arrested by the administration of antegrade cardioplegia, and then an aortotomy was made. The ascending aorta, aortic arch, aortic branches, and aortic valve and root were all evaluated. If the aortic valve morphology and coaptation were normal, the aortic root was intact, and the intimal tear was localized only in the ascending aorta, a supracoronary ascending aorta replacement was performed using a Dacron graft of appropriate diameter. If the intimal tear was located in the aortic arch or its branches, the aortic replacement was extended distally. If the aortic valve morphology or coaptation was impaired, an additional aortic valve replacement or repair was performed. In all cases, distal aortic anastomosis was performed by open technique by removing aortic cross clamp. Selective antegrade cerebral perfusion was performed for brain protection with moderate hypothermia (24-28°C). When appropriate conditions were established, CPB was discontinued and patients were decannulated. Protamine sulfate was administered at a dose of 1-1.3 mg per 1 mg of heparin to neutralize the effect of heparin, and the ACT value was brought to normal limits. After achieving bleeding control, the tissues were properly closed and the operation was concluded. The same surgical team operated on each patient. All patients were moved right away to the intensive care unit following the operation.

Statistical Analysis

The Statistical Package for the Social Sciences (IBM® SPSS Statistics for Windows, Version 23.0, Armonk, NY, USA) software program was used to enter the data. To determine if continuous variables displayed a normal distribution, the Shapiro-Wilk test was employed. The normally distributed continuous variables were compared using the independent sample T test, while the abnormally distributed continuous variables were compared using the Mann-Whitney U test. The categorical variables

were compared using the Chi-Square test. Multivariate logistic regression analysis was used to examine the connection between independent predictors and the development of mortality following TAAD surgery after controlling for the pertinent variables found to be significant in univariate analyses. The optimum cut-off values for age, neutrophil, and IPI readings were found using Receiver Operating Characteristic (ROC) curve analysis. The mean±standard deviation was used to present continuous variables with a normal distribution, whereas the median (minimum-maximum) was used to present continuous variables with an abnormal distribution. Numbers (percentages) were used to represent categorical variables. Statistical significance was defined as a p value of less than 0.05.

RESULTS

In Group 1, 10 (30.3%) patients underwent the Bentall procedure, 10 (30.3%) patients underwent supracoronary ascending aortic replacement, 5 (15.1%) patients underwent Bentall procedure with 1/3 aortic arch replacement, 6 (12.1%) patients underwent total aortic arcus replacement with ascending aortic replacement,

and 2 (6%) patients underwent total aortic arcus replacement with ascending aortic replacement using the frozen elephant trunk (FET) technique. In Group 2, 23 (29.4%) patients underwent supracoronary ascending aorta replacement, 7 (8.9%) patients underwent ascending aorta replacement with 1/3 arcus aorta replacement, 13 (16.6%) patients underwent the Bentall procedure, 7 (8.9%) patients underwent Bentall with 1/3 arcus aorta replacement, 5 (6.4%) patients underwent the Bentall procedure with total arcus aorta replacement, 18 (23.1%) patients underwent total arcus aorta replacement with ascending aorta replacement, and 5 (6.4%) patients underwent total arcus aorta replacement with ascending aorta replacement using the FET technique.

The mean ages of patients in Group 1 and Group 2 were 66.4±12.1 and 58.8±11.0 years, respectively, with Group 1 patients being substantially older than Group 2 patients. The mean ages of patients in Group 1 and Group 2 were 66.4±12.1 and 58.8±11.0 years, respectively, with Group 1 patients being substantially older than Group 2 patients. The rates of postoperative cerebrovascular events and bleeding requiring revision were significantly higher in Group 1 than those of Group 2. (Table 1).

Table 1. Preoperative basic demographic, clinical and perioperative characteristics of the groups

Variable	Mortality group (n=33)	Survivor group (n=78)	P value
Age (years)	66.4±12.1	58.8±11.0	0.002*
Gender (male)	21 (63.6%)	53 (67.9%)	0.660
Height (cm)	168.1±9.8	167.8±9.0	0.878
Weight (kg)	79.1±15.4	81.2±12.0	0.449
BMI (kg/m ²)	28.3±3.2	28.2±3.0	0.863
LVEF (%)	55 (25-65)	55 (30-65)	0.810
DM	3 (9.1%)	10 (12.8%)	0.341
Hypertension	24 (72.7%)	59 (75.6%)	0.576
COPD	2 (6.1%)	6 (18.1%)	0.747
CRF	1 (3.0%)	4 (5.1%)	0.761
Malperfusion	7 (21.2%)	2 (2.5%)	0.001*
Rupture	7 (21.2%)	3 (3.8%)	0.001*
X-klamp time (min)	115 (55-384)	93.5 (27-244)	0.053
CPB time (min)	192 (78-523)	140.5 (55-406)	0.003*
Length of ICU stay (day)	2 (1-5)	3 (2-6)	0.006*
Length of hospital stay (day)	6 (1-10)	7 (4-12)	0.003*
Bleeding requiring revision	7 (21.2%)	6 (7.7%)	0.043*
Postoperative CVE	4 (12.1%)	2 (2.5%)	0.042*

BMI: body mass index, COPD: chronic obstructive pulmonary disease, CPB: cardiopulmonary bypass, CRF: chronic renal failure, CVE: cerebrovascular events, DM: diabetes mellitus, LVEF: left ventricular ejection fraction, IPI: inflammatory prognostic index; *Bold p values indicate statistical significance; continuous variables were presented as mean±standard deviation or median (minimum-maximum) while categorical variables were presented as number (percentage)

Group 1 exhibited significantly higher median values for neutrophil, NLR, red cell distribution width (RDW), mean platelet volume (MPV), CRP, creatinine, and IPI, whereas Group 2 exhibited significantly higher median values for lymphocyte, platelet distribution width (PDW), glomerular filtration rate (GFR), and albumin. In terms of other preoperative laboratory variables, the groups were similar and no significant differences were detected (Table 2). In the multivariate logistic regression

analysis performed to investigate the association between independent predictors and the development of mortality after TAAD surgery, age [Odds ratio (OR)=1.040 (95% confidence interval (CI)=1.010-1.070), p value=0.031], neutrophils [OR=1.035, (95% CI=1.010-1.060), p value=0.047], and IPI [OR=1.010, (95% CI=1.000-1.010), p value=0.001] reached statistical significance and were considered independent predictors of mortality (Table 3).

Table 2. Laboratory data of the groups

Variable	Mortality group (n=33)	Survivor group (n=78)	P value
WBC (10³/μL)	13.13 (5.34-25.52)	11.02 (3.85-26.76)	0.098
Neutrophil (10³/μL)	9.82 (3.35-24.67)	8.5 (0.94-24.19)	0.041*
Lymphocyte (10³/μL)	1.06 (0.27-3.25)	1.46 (0.24-9.73)	0.043*
NLR	8.22 (3.96-53.6)	6.41 (0.45-26.6)	0.014*
PLR	118.9 (17.2-929.4)	122 (14.6-596.8)	0.748
Monocyte (10³/μL)	0.72 (0.21-1.69)	0.68 (0.18-6.8)	0.933
Eosinophil (10³/μL)	0.03 (0-0.41)	0.05 (0-0.7)	0.554
Hb (g/dL)	10.5 (5.1-16)	10.4 (6.2-17)	0.737
RDW (fL)	44.9 (39.4-68.7)	41.7 (34.6-54.7)	0.000*
PCT (%)	0.15 (0.02-0.60)	0.19 (0.04-0.44)	0.342
MPV(fL)	10.8 (9-13.7)	10.5 (8.5-12.5)	0.049*
PDW(fL)	12.6 (8.6-21.6)	14.7 (1-19.5)	0.034*
Platelet (10³/μL)	151 (12-589)	184.5 (17.1-514)	0.135
CRP (mg/L)	12.5 (1.2-103.9)	4.3 (0.5-32.1)	0.000*
Urea (mg/dL)	38.5 (1.5-178.5)	36.4 (16.3-171.4)	0.245
Creatinine (mg/dL)	1.27 (0.45-9.9)	0.92 (0.48-8)	0.000*
GFR (mL/min/1.73m²)	49.4 (10-108.3)	85.5 (10.5-117.6)	0.000*
Albumin (g/L)	29.8 (6.6-45.6)	32.4 (9-48.1)	0.034*
AST (IU/L)	28 (15-10075)	29 (9-1237)	0.400
ALT (U/L)	21 (7-5483)	20 (5-485)	0.349
IPI	3.56 (1.2-16.3)	0.87 (0.01-2.6)	0.000*

ALT: alanine transaminase, AST: aspartate aminotransferase, CRP: C-reactive protein, GFR: glomerular filtration rate, Hb: hemoglobin, IPI: inflammatory prognostic index, MPV: mean platelet volume, NLR: neutrophil lymphocyte ratio, PCT: plateletcrit, PDW: platelet distribution width, PLR: platelet lymphocyte ratio, RDW: red cell distribution width, WBC: white blood cell; *Bold p values indicate statistical significance; Continuous variables were presented as mean median (minimum-maximum)

Table 3. The results of multivariate logistic regression analysis to identify the independent predictors of mortality

Variable	Odds ratio	95% CI	P value
Age	1.040	1.010 - 1.070	0.031*
Malperfusion	0.347	0.155 - 0.778	0.010*
Rupture	0.588	0.226 -0.918	0.022*
CPB time	1.118	0.875 - 1.360	0.188
Neutrophil	1.035	1.010 - 1.060	0.047*
Lymphocyte	1.124	0.733 - 1.558	0.622
NLR	1.525	0.618 - 1.940	0.794
RDW	0.797	0.512 - 1.245	0.130
MPV	1.096	0.818 - 1.320	0.751
PDW	0.886	0.475 - 1.635	0.771
CRP	0.750	0.484 - 1.396	0.979
Creatinine	1.277	0.836 - 1.520	0.386
GFR	1.126	0.923 - 1.263	0.101
Albumin	1.246	0.853 - 1.602	0.358
Bleeding requiring revision	0.732	0.442 - 1.220	0.996
CVE	1.118	0.976 - 1.244	0.107
IPI	1.010	1.000 - 1.010	0.001*

CI: confidence interval, CPB: cardiopulmonary bypass, CRP: C-reactive protein, CVE: cerebrovascular event, GFR: glomerular filtration rate, IPI: inflammatory prognostic index, MPV: mean platelet volume, NLR: neutrophil lymphocyte ratio, PDW: platelet distribution width, RDW: red cell distribution width; *Bold p values indicate statistical significance

The effectiveness of age, neutrophil and IPI values in predicting mortality were evaluated by ROC analyses. Age of 62.5 constituted the optimal threshold value with 57.5% sensitivity and 62.2% specificity, neutrophil of 9.37

constituted the optimal threshold value with 57.5% sensitivity and 58.9% specificity, and IPI of 1.98 constituted the optimal threshold value with 84.8% sensitivity and 85.9% specificity (Table 4, Figure 1).

Table 4. The results of ROC curve analysis of the identified predictors

	AUC (95% CI)	Cut-off value	P value	Sensitivity (%)	Specificity (%)
Age	0.656 (0.547-0.765)	62.5	0.009	57.5	62.2
Neutrophil	0.623 (0.514-0.732)	9.37	0.041	57.5	58.9
IPI	0.943 (0.899-0.986)	1.98	0.000	84.8	85.9

AUC: area under the curve, CI: confidence interval, IPI: inflammatory prognostic index, ROC: receiver operating characteristic

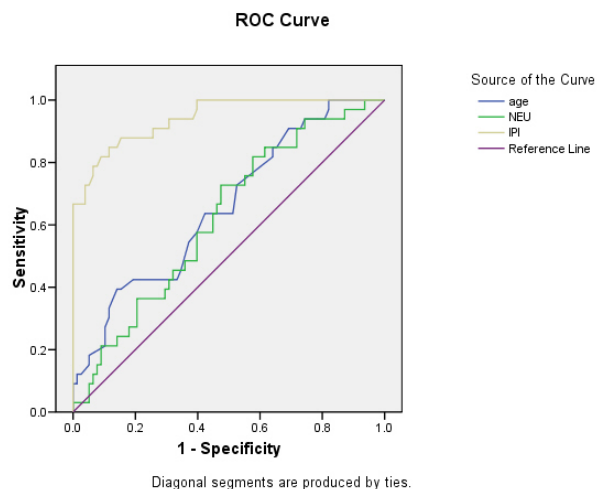


Figure 1. ROC curves of the identified predictors of mortality

DISCUSSION

Patients in the mortality group of our study were substantially older than those in the survivor group. Analysis of hematologic and biochemical markers revealed that the mortality group's median values for albumin, PDW, GFR, and lymphocytes were significantly lower than those of the survivor group. Furthermore, the mortality group's median values for neutrophil, NLR, RDW, MPV, CRP, creatinine, and IPI were considerably greater than those of the survivor group. Age, neutrophils, and IPI were found to be statistically significant in the multivariate analysis. These parameters were found to be independent predictors of mortality in patients undergoing TAAD surgery. The most important result of our study is that IPI significantly and independently predicts mortality after TAAD surgery. In addition, IPI was found to be the parameter with the highest sensitivity and specificity rates according to ROC analyses.

The exact mechanisms affecting mortality after TAAD surgery are still unclear. Medial disruption of the aorta artery, arterial wall remodeling, and aorta wall weakening are all significantly influenced by systemic inflammation [10]. Biomarkers of inflammation and acute phase reactions are associated with in-hospital mortality and morbidity in TAAD [11]. According to certain research in the literature, mortality and morbidity following TAAD surgery are predicted by the inflammatory and immune-based impacts of hematological parameters as CRP, albumin, and NLR [11-13]. To assess the association between hematological indices and in-hospital mortality in TAAD patients, a systematic review and meta-analysis study comprising 18 papers and 2875 patients was carried out. According to this meta-analysis, TAAD patients who had elevated CRP levels before surgery had a considerably higher probability of mortality in the hospital [14]. A high neutrophil count was demonstrated to be an independent risk factor for in-hospital mortality in a study involving 467 patients that

examined the prognostic value of neutrophil count on in-hospital mortality in patients with TAAD [15]. Xu et al. [13] examined the importance of NLR in a meta-analysis study investigating its prognostic value in aortic diseases. A total of 4066 patients and 14 studies were included in this meta-analysis. According to the study's findings, people with aortic disease who had high NLR values had a far higher chance of mortality following surgical repair. Another study that examined the prognostic value of serum albumin for patients with acute aortic dissection involved 777 patients. It was found that hypoalbuminemia raised in-hospital mortality and highlighted the significance of serum albumin level monitoring in the treatment of acute aortic dissection patients [16].

In the univariate analysis of our study, we determined that the median values of lymphocyte count, PDW, albumin and GFR were significantly lower while neutrophil count, NLR, RDW, MPV, creatinine, CRP and IPI were significantly higher in mortality group than in survivor group. All laboratory parameters identified as significant in the univariate analysis were incorporated into the multivariate logistic regression analysis. However, other laboratory parameters except for neutrophil and IPI lost their significance, and hence only neutrophil and IPI reached the significance levels and were identified as the independent predictors of mortality.

IPI, a newly developed biomarker, consists of the combination of CRP, albumin, and NLR. It is a non-invasive, cost-effective, accessible, and readily formulated parameter that concurrently indicates the patients' immunological and inflammatory condition. Numerous research on cardiovascular and cancer patients have utilized it as a novel and significant measure to assess survival [4-9]. IPI was first reported in the literature by Dirican et al. [4] The authors analyzed the predictive value of IPI for survival in their study on 685 patients with non-small cell lung cancer. They demonstrated that IPI was an independent predictor of overall survival. IPI was found to be the best predictor indicator of long-term survival in a different trial that involved 65 patients with metastatic colorectal cancer receiving regorafenib [5]. Additionally, following on-pump coronary artery bypass grafting (CABG), we investigated the predicted association between IPI and new-onset atrial fibrillation. In a study of 343 patients, we showed that IPI predicted the development of new-onset atrial fibrillation after on-pump CABG surgery [6].

To the best of our knowledge, there is no published study yet investigating the relationship between IPI and mortality after TAAD surgery. We found in our study that IPI predicted survival for patients who underwent TAAD surgery. We showed that the IPI of 1.98 constituted the optimal threshold value in patients who developed mortality after TAAD surgery. It predicted early in-hospital mortality with a sensitivity of 84.8% and a specificity of 85.9%.

Numerous studies in the literature have demonstrated that hemodynamic instability following TAAD surgery is linked to longer hospital stays, a higher risk of stroke, and a higher mortality rate [15-19]. Our research found that, in line with the literature, revision due to bleeding, increased risk of stroke, and duration of stay in intensive care and hospital were statistically significantly increased. As a result, it is thought that identifying high-risk patients for TAAD surgery is important for taking the necessary precautions before surgery.

The mortality rate of 29.7% in our series might seem high to contemporary practice. However, there were some explainable reasons that caused this situation. One of these reasons was that our center was relatively newly established (5 years ago) and thus our team was not very experienced. Another one was that although our center was relatively new, it was established as a tertiary referral center and thus patients from long distances outside the city were also accepted for surgery which resulted in delays in the start of the operation after diagnosis.

It is known that malperfusion and aortic rupture in emergency TAAD surgery are associated with high morbidity and mortality rates. In many studies in the literature, acute kidney injury, intestinal ischemia, sepsis and focal neurological deficits were found to be associated with in-hospital mortality in the postoperative ICU follow-up of patients after organ malperfusion [20-24]. In our study, the postoperative outcomes of malperfusion and aortic rupture were found to be similar to the literature. Therefore, early detection and interdisciplinary management of patients at risk continue to be of vital importance in the postoperative period.

We revealed that higher preoperative IPI values were associated with higher mortality rates in TAAD patients undergoing surgery, as the main finding of our study. However, although the risk of mortality was revealed to be higher in TAAD patients with higher IPI levels, this situation did not change our indication for surgery, and these patients also underwent urgent surgical intervention. On the other hand, it might be necessary to develop additional preventive and protective strategies to reduce mortality in patients with higher preoperative IPI values. These strategies include performing the surgical procedure not only more carefully and meticulously but also faster, keeping aortic cross clamp, CPB and operation times as short as possible, monitoring more closely in the postoperative period, being more alert to potential complications and making early interventions if necessary.

Study Limitations

There were various limitations in our investigation. Our study's primary drawback was its retrospective and single-centered design. Other limiting factors are the relatively small patient population of the study, the limited number of parameters, and the lack of correlation analysis with different predictive markers of the inflammatory response.

CONCLUSION

To the best of our knowledge, there are currently no published studies looking into the relationship between IPI and mortality following TAAD surgery. According to our research, age, neutrophil, and IPI were independently predicted risk factors for mortality after TAAD surgery. Our study's most notable finding was that IPI significantly and independently predicted mortality following TAAD surgery. However, more meticulously designed studies with greater patient participation rates are also needed to produce more definitive scientific evidence.

Ethics Committee Approval: Bursa City Hospital Clinical Research Ethics Committee 2023;15/8, Date: 13.09.2023.

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