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Research Article

The Correlation of C-Reactive Protein/Albumin, Mii-1 and Mii-2 Indexes With Hospitalization and Mortality in Stanford Type A Aortic Dissection

Stanford Tip A Aort Diseksiyonunda C-Reaktif Protein/Albumin Oranı İle Mii-1 ve Mii-2 İndekslerinin Hastaneye Yatış Süresi ve Mortalite İlişkisi

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Abstract

Aim: In this study we aimed to investigate the relationship between C-Reactive Protein (CRP)/albumin ratio, MII-1 and MII-2 indexes in hospitalization and mortality due to aortic dissection.

Material and Method: Patients who presented to our emergency department with a sudden-onset, sharp and stabbing chest pain and diagnosed with Stanford type A aortic dissection were included in the study. Patients' demographics such as age and gender, hemogram parameters, ratios, indexes, hospitalization and mortality status were recorded. Demographic features, hemogram parameters, ratios and indexes were compared between the survivor and exitus patients.

Results: A total of 71 patients who presented to the emergency department with sudden-onset stabbing chest pain and subsequently diagnosed with aortic dissection were included in this retrospective study. The median age of the patients was negatively correlated with albumin (r=-0.27, p=0.021), hemoglobin (r=-0.28, p=0.019). Hemoglobin values were significantly higher in male than in female patients. The median length of stay in the hospital was found as 10 (7-14) days. In the correlation analysis of the hemogram parameters, indexes and length of stay in the hospital; CRP and CRP/Albumin ratio were significantly correlated with length of stay in the hospital in positive direction.

Conclusion: The results of this study point out a significant correlation between CRP, CRP/albumin ratio and length of stay in hospital. This information might be helpful in rapid decision making process for early diagnosis and treatment of the disease.

Keywords: Aortic dissection, C-reactive protein/albumin, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, multi inflammatory index

Öz

Amaç: Bu çalışmamızda hastanede yatış ve aort diseksiyonuna bağlı mortalitede C-Reaktif Protein (CRP)/albümin oranı, MII-1 ve MII-2 indeksleri arasındaki ilişkiyi araştırmayı amaçladık.

Material and Methot: Acil servisimize akut başlangıçlı, keskin ve saplayıcı göğüs ağrısı ile başvurup Stanford Tip A aort diseksiyonu tanısı alan hastalar çalışmaya dahil edildi. Hastaların yaş ve cinsiyet gibi demografik bilgileri, hemogram parametreleri, oranları, indeksleri, yatış ve mortalite durumları çalışmaya alındı. Taburcu olanlar ve hayatını kaybeden hastalar arasında demografik özellikler, hemogram parametreleri, oranlar ve indeksler karşılaştırıldı.

Bulgular: Bu retrospektif çalışmaya, acil servisimize başvuran ve ardından aort disseksiyonu tanısı konan toplam 71 hasta dahil edildi. Hastaların medyan yaşı albümin (r=-0.27, p=0.021), hemoglobin (r=-0.28, p=0.019) ve prognostik nutrisyonel indeks (PNI) (r=-0.31, p=0.008) ile negatif korelasyon gösterdi. Hemoglobin değerleri erkek hastalarda kadınlara göre anlamlı derecede yüksekti. Hastanede kalış süresi median 10 (7-14) gün olarak bulundu. Hemogram parametrelerinin, indekslerin ve hastanede kalış sürelerinin korelasyon analizinde; CRP ve CRP/Albumin oranı hastanede kalış süresi ile pozitif yönde anlamlı olarak korele idi.

Sonuç: Bu çalışmanın sonuçları, CRP, CRP/albümin oranı ve hastanede kalış süresi arasında anlamlı bir ilişkiye işaret etmektedir. Bu bilgiler hastalığın erken teşhisi ve tedavisi için hızlı karar verme sürecinde yardımcı olabilir.

Anahtar Kelimeler: Aort diseksiyonu, C-reaktif protein/albümin, nötrofil/lenfosit oranı, trombosit/lenfosit oranı, multi-inflamatuar indeks

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INTRODUCTION

Aortic dissection is an uncommon but potentially fatal condition that can be difficult to diagnose and treat in the emergency room. Even when appropriately diagnosed, it has an in-hospital mortality rate of 27% (1). Relatively atypical process of aortic dissection, which mimics other clinical conditions, makes the diagnosis difficult. The diagnosis of aortic dissection in the emergency department is very rare. Patients with aortic dissection mostly manifests a variaty of symptoms. Moreover, aortic dissection may also manifests present with symptoms that are more common in other diseases including heart failure, vascular insufficiency, neurologic deficits and syncope (2). Severe pain with sudden-oenset accompanying with high blood pressure suggests dissection; however lack of these findings does not exclude aortic dissection (3). Prevalence as low as 3.5/1000.000 makes the diagnosis further challenging (4). Because many patients die before arriving to the hospital, the real incidence of aortic dissection is difficult to estimate. Death may be attributed to other causes. Aortic dissection may also be missed during the initial evaluation, resulting in early mortality as a result of misdiagnosis (5).

Taking medical history and physical exam alone are unreliable in making the diagnosis of aortic dissection. Findings of multiple abnormalities on chest radiography can be used as a screening tool to screen for dissections with a sensitivity of 90% (6). In addition, echocardiography and computed tomography are also used to help diagnosis.

The most commonly used classification in aortic dissections are the DeBakey and Stanford classifications. While the DeBakey classification is an anatomical classification, the Stanford classification is more of a functional classification. According to this; Aortic dissections are divided into two types. Regardless of where the primary tear is, all dissections involving the ascending aorta are referred to as type A, and those distal to the left subclavian artery are referred to as type B. The largest part of dissections are Stanford type A and these are commonly related with more increased mortality (4).

On the other hand, researchers have focused on the development of markers and scoring systems to identify aortic dissection cases reliably. Several inflammatory markers have been successfully used to predict various diseases and medical conditions. In an interesting study, Yildiz et al. investigated the correlation of Platelet to Lymphocyte Ratio, Neutrophil to Lymphocyte Ratio and Mean Platelet Volume in Individuals Diagnosed with Gambling Disorder (7). Sevil et al. evaluated the association between the inflammatory parameters and prognosis of Bell's palsy (8). Forrer et al. investigated novel biomarkers for diagnostic work up of acute aortic dissection and reported that IL-10 shows potential as a biomarker for aortic dissection (9). Wen et al. proposed CRP as a biomarker of aortic dissection along with other numerous markers. However, the authors underlined that further studies are needed in order to introduce these biomarkers in emergency settings for rapid diagnosis of aortic dissection. Gao et al. reported that serum albumin levels are associated with in-hospital mortality in aortic dissection (10).

Multi Inflammatory Index (MII) is a new prognostic index composed of MII-1 (Neutrophil-to-lymphocyte ratio [NLR] x CRP) and and MII-2 (Platelet-to-lymphocyte ratio [PLR] x CRP). Gardini et al. used these indexes in patients receiving chemotherapy and reported that the novel MII indexes seem to help determination of prognosis. Boyuk et al. reported that MII-1 and 2 indexes that are are simple, inexpensive, and easy to obtain, these indexes are helpful in distinguishing massive and non-massive pulmonary embolism (PE) (11).

Based on this information from the literature, the objective of this study was to investigate the correlation between CRP/albumin ratio, MII-1 and MII-2 indexes in terms of hospitalization and mortality due to aortic dissection.

MATERIAL AND METHOD

After receiving the necessary ethics approval from the local ethics committee of our hospital, this study was performed retrospectively (Decision No: 2022/30, Date 22/02/2022). Patient consent was waived because of the retrospective design of the study. This study was performed in accordance with the relevant ethical items of the Declaration of Helsinki.

Patients diagnosed with Stanford Type A aortic dissection after computed tomography (CT) seen by their emergency physicians (EP) who applied to the emergency department with sudden onset, sharp and stabbing chest pain between 01 August 2015 and 01 February 2022 were included. Data of the study were obtained from the electronic record system of the hospital with the permission of the hospital management. Patients with ICD-10 code for aortic dissection were analyzed retrospectively. In the case of more than one admission, only the first admission was taken into account. The MII-1 and MII-2 were defined using the following formulas:

MII-1 = NLR (Neutrophil/Lymphocyte Ratio) x CRP

MII-2 = PLR (Platelet/Lymphocyte Ratio) x CRP

Patients' demographics such as age and gender, hemogram parameters, ratios, indexes, hospitalization and mortality status were recorded. Demographic features, hemogram parameters, ratios and indexes were compared between the survivor and exitus patients. Hemogram parameters, ratios, indexes and hospitalization were further compared between genders. Outcomes of the patients were evaluated as hospitalization, exitus our referral to another health care center.

Statistical Analysis

Data obtained in this study were evaluated using SPSS version 23.0 (SPSS, Social Package for Social Sciences, IBM Inc., Armonk, USA). Normality of the data was

evaluated with the Kolmogorov-Smirnov test. Continuous variables are expressed as median and interquartile range and categorical variables are given as frequency (number and percentage). Hemogram and index values of the groups were examined with Mann-Whitney U test. The correlations with length of stay in hospital was examined with Spearman (rho) coefficient. Performances of the hemogram parameters and indexes in predicting mortality and diagnosis were investigated with ROC analysis. p<0.05 values were considered statistically significant.

RESULTS

A total of 71 patients who presented to the emergency department with sudden-onset stabbing chest pain and subsequently diagnosed with aortic dissection were included in this retrospective study. Median age of the patients was 58 years and 74.6% (n:53) male. In the evaluation of hemogram parameters and indexes; a negative correlation was found between age and hemoglobin (r=-0.28, p=0.019), albumin (r=-0.27, p=0.021) and prognostic nutritional index (PNI) (r=-0.31, p=0.008). Hemoglobin values were significantly higher in male than in female patients (Figure 1) (Table 1).

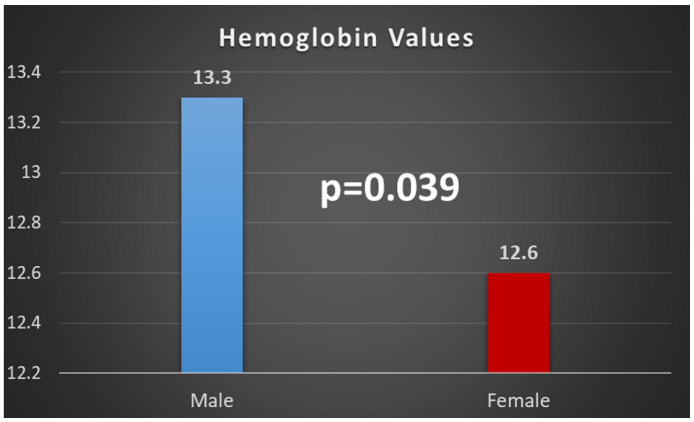

Figure 1. Hemoglobin values according to sexes

Of all patients, 25.4% (n:18) died. No significant difference was found between discharged and died patients in terms of age and gender. There was no statistically significant difference between mortality and hemogram parameters, ratios and indexes (p>0.05, Table 2).

Table 1. Hemogram parameters, ratios, indexes and hospitalization according to demographic characteristics of patients with aortic dissection

	Age		Gender		
	r	p	Female (n=18) Med (IQR)	Male (n=53)Med (IQR)	p
Hemogram					
WBC	-0.17	0.157	11.1 (9.29-14.56)	13.01 (9.5-17.3)	0.358
HGB	-0.28	0.019	12.6 (10.6-13.33)	13.3 (11.6-14.8)	0.039
PLT	-0.06	0.623	219 (180-242.5)	184 (161.5-222.5)	0.193
LYM	-0.19	0.117	1.08 (0.64-2.2)	1.3 (0.87-2.15)	0.379
NEU	-0.12	0.311	9.25 (7.08-12.8)	9.54 (6.49-14.55)	0.781
PDW	0.03	0.771	16.95 (14.65-18.05)	17.1 (12.15-18.5)	0.989
MPV	-0.08	0.488	8.56 (7.02-10.05)	8.6 (7.24-10.25)	0.561
PCT	-0.16	0.182	0.17 (0.14-0.2)	0.16 (0.13-0.2)	0.731
CRP	0.17	0.163	10.9 (1.75-77.38)	5.7 (0.9-22.55)	0.365
ALB	-0.27	0.021	38.75 (32.75-42.13)	38.1 (32.2-42.85)	0.791
Ratios					
NLR	0.09	0.473	9.68 (4.93-12.78)	7.58 (3.27-14.79)	0.534
CLR	0.19	0.113	10.09 (1.48-56.65)	3.74 (0.65-30.46)	0.278
CRP/ALB	0.19	0.119	0.29 (0.04-2)	0.15 (0.02-0.74)	0.341
Indexes					
MI index	0.19	0.119	97.06 (18.6-368.37)	35.92 (7.04-302.94)	0.348
MII index	0.18	0.129	1609.74 (359.9-12047.89)	539.11 (106.33-5282)	0.273
Length of stay*	0.112	0.425	12 (7-14)	10 (7-15.5)	0.892

Statistically significant p values are shown in bold font. IQR: Interquartile range (25^{th}-75^{th} percentiles). Mann-Whitney u test, r: Spearman (rho) correlation coefficient. *: The analysis was made over discharged patients (16 female, 37 male; total 53 patients).

Table 2. Evaluation of demographic features, hemogram parameters, ratios and indexes according to mortality status

	AD		p
	Discharged (n=53)	Exitus (n=18)	
Age, Year, Med (IQR)	57 (49-68)	60 (50.25-72.25)	0.574
Gender - Male, n (%)	37 (69.81)	16 (88.88)	0.130a
Hemogram, Med (IQR)			
WBC	11.7 (8.52-16.7)	13.45 (10.27-16.63)	0.428
HGB	13.1 (11.45-14.2)	13.1 (10.43-14.73)	0.984
PLT	187 (164-231.5)	184.5 (157.5-225)	0.942
LYM	1.22 (0.83-2.18)	1.31 (0.79-2.17)	0.921
NEU	9.16 (6.47-14.85)	10.17 (7.88-13.98)	0.588
PDW	16.9 (12-18.3)	17.4 (16.48-18.7)	0.125
MPV	8.67 (7.26-10.25)	8.03 (6.87-9.9)	0.428
PCT	0.17 (0.13-0.2)	0.17 (0.13-0.2)	0.776
CRP	4.9 (1.1-18.75)	18.5 (0.83-69.95)	0.190
ALB	38.1 (32-42.6)	38.9 (32.78-41.9)	0.802
Ratios, Med (IQR)			
NLR	9.2 (2.8-15.2)	7.4 (5.7-14.2)	0.947
CLR	3.3 (1-21.6)	24.9 (0.3-86.5)	0.229
CRP/ALB	0.1 (0-0.6)	0.5 (0-1.8)	0.224
Indexes, Med (IQR)			
MI index	30.3 (8.6-253)	285.9 (7.3-679.2)	0.191
MII index	539.1 (114.6-4768)	4173.7 (97.4-20223.7)	0.209

Statistically significant p values are shown in bold font. IQR: Interquartile range (25th-75th percentiles). Mann-Whitney U test, a: Fisher's Exact test

Table 3. Correlation analysis of hemogram parameters, indexes and length of stay in the hospital

Indexes	AD (nd=53)	
	r	p
Hemogram		
WBC	-0.09	0.520
HGB	-0.05	0.698
PLT	0.00	0.978
LYM	0.13	0.346
NEU	-0.13	0.341
PDW	-0.16	0.246
MPV	0.16	0.263
PCT	0.11	0.448
CRP	0.29	0.037
Albm	0.05	0.740
Ratios		
NLR	-0.18	0.202
CLR	0.18	0.190
CRP/Alb	0.27	0.046
Indexes		
MII-1 index	0.17	0.231
MII-2 index	0.18	0.201

The median length of stay in the hospital was found as 10 (7-14) days. Age and gender distribution of the discharged patients was similar (p=0.425, p=0.892) (Table 1). In the correlation analysis of the hemogram parameters, indexes and length of stay in the hospital; CRP and CRP/ALB ratio were significantly correlated with length of stay in the hospital in positive direction (Table 3).

DISCUSSION

In our study, in the correlation analysis of hemogram parameters, indices and hospital stay; We found that CRP and CRP/Albumin ratio were positively and significantly correlated with the length of hospital stay. However, MII-1 and MII-2 indices, which have recently been used in the literature, were not significant.

Aortic dissection is a serious medical condition with high rates of morbidity and mortality. Aortic dissection manifests with develops quickly in an intimal flap due to blood streaming into the media and pressing the intima and adventitia apart. The destruction of the ingredients of the aorta is influenced by several risk factors that induce infiltration of inflammatory cells in the aortic wall, apoptosis of vascular smooth muscle cells and inflammatory reaction.

Aortic dissection is a difficult diagnosis for clinicians due to its rarity and the fact that its symptoms are likely to match those of more prevalent illnesses. Especially in the

emergency department the diagnosis of aortic dissection is further challenging, because 20% of aortic dissections presents without chest pain and 6% without any pain (3).

Although chest X-ray and CTA are reliable in the diagnosis, biomarkers might provide valuable information about the course of the disease. Several biomarkers can be found in peripheral blood to help diagnostic and prognostic work up in aortic dissection (12). Studies have proposed cardiac troponins, C-reactive protein (CRP), IL-6, matrix metalloproteinases, smooth muscle myosin heavy chain, creatine kinases, calponin, soluble elastin fragments, D-dimer and pro-brain natriuretic peptide as diagnostic and prognostic biomarkers (13). The concentration of these markers in the blood may be related to symptomatology. The CRP-albumin ratio, rather than either marker alone, may provide a better evaluation of the inflammatory process. The CRP-albumin ratio is a novel inflammatory prognostic indicator in the development of cardiovascular disease, according to several studies (9,10,14).

In the present study, we investigated the relationship between CRP/albumin ratio, MII-1 and MII-2 indexes, length of stay and mortality due to aortic dissection.

CRP is an easy to obtain, inexpensive and simple biomarker used in daily clinical practice. Its role in the immunological pathways in aortic dissection is evidenced by a significant increase in CRP and pro-inflammatory cytokines in patients with aortic dissection (15). Elevated CRP values point out high rates of morbidity and mortality in cardiovascular diseases (16). CRP value has been reported to be significantly increased in patients with complications of acute aortic dissection, including pleural effusion and impaired oxygenation (17). Plasma CRP concentrations > 15 mg/dL have been reported to be an important marker of poor prognosis. Because, CRP levels are rarely raised within several hours after onset, CRP has low diagnostic value in emergency settings (18). Sakakura et al. stated that peak CRP value was a strong predictor od long-term events in aortic dissection (19). In a systematic review, Vrsalović and Presečki showed that there was a significant correlation between elevated serum levels at admission and in-hospital and mid-term mortality (20). In our study, CRP was statistically significantly correlated with length of stay in positive direction (r=0.29, p=0.037). However, no statistically significant correlation was found between CRP and mortality.

Recently, CRP/albumin ratio has been proposed instead of each parameter separately to better predict outcomes in a wide range of conditions including malignancy, sepsis and acute mental illness (21-22). Yazar et al. reported that serum CRP/albumin ratio may be associated with the etiopathogenetic process of idiopathic Parkinson disease (23). Demir et al. proposed that CRP/albumin ratio can be used to indicate lung involvement in COVID-19 patients in whom chest CT is contraindicated (24). Kahraman et al. associated CRP/albumin ratio with increased mortality rate in patients with isolated severe aortic stenosis following aortic valve repair (25). In our study, similar to CRP, CRP/albumin ratio was statistically significantly correlated with length of stay in positive direction (r=0.27, p=0.046). However, no statistically significant correlation was found between CRP and mortality.

It has been suggested that indexes that involve platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and CRP levels have a prognostic value in many clinical situations (11). A novel correlation has been recently reported between multi-inflammatory indexes (MI-1 and MII-2), including NLR, PLR and CRP values and prognosis and severity of inflammatory related cancers (26). In our study, MII indexes were not correlated with length of stay and mortality from aortic dissection. In addition, we could not compare with other studies as this is the first study on this issue in the literature.

Study Limitations

Major limitations of this study are the relatively small number of patients and retrospective design. In addition, it was conducted in a single center. Furthermore, more novel markers could be investigated in regards to aortic stenosis. However, being the first in the literature on this topic increases the strength of our study. We believe that our findings will be encouraging for further more comprehensive prospective studies.

CONCLUSION

The results of this study point out a significant correlation between CRP, CRP/albumin ratio and length of stay in hospital. None of the above parameters were correlated with mortality. This information might be helpful in the rapid decision making process for early diagnosis and treatment of the disease. On the other hand, there is a need for a cut-off value in predicting prolonged length of stay due to aortic stenosis.

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Conflict of interest: *The authors declare that they have no competing interest.*

Ethical approval: *After receiving the necessary ethics approval from the local ethics committee of our hospital, this study was performed retrospectively (Decision No: 2022/30, Date 22/02/2022).*

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