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ORIGINAL ARTICLE / ÖZGÜN MAKALE

Prognostic value of troponin/creatinine ratio in patients with chest pain

Göğüs ağrısı olan hastalarda troponin/kreatinin oranının prognostik değeri

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ABSTRACT

Background: The aim of this study was to investigate the prognostic value of the troponin/creatinine ratio in patients presenting with chest pain and to identify laboratory values affecting mortality.

Methods: Between October 1st, 2016 and April 30th, 2019, a total of 5,079 patients (2,844 males, 2,235 females; median age: 65 years; range, 49 to 83 years) who presented to the emergency department with chest pain and whose troponin and creatinine measurements were done were retrospectively analyzed. Laboratory data and 28-day mortality rates were evaluated. The patients were divided into two groups according to 28-day mortality rates after the initial emergency department admission as survivors (n=4,793) and non-survivors (n=286).

Results: There were statistically significant differences in the white blood cell count, C-reactive protein, creatinine, high-sensitivity troponin I, and troponin/creatinine ratio between the groups ($p<0.05$). The high-sensitivity troponin I ≥31.96 pg/dL, creatinine ≥1.11 mg/dL, C-reactive protein ≥43.94 mg/L, and troponin/creatinine ratio ≥25.12 were independent predictors of 28-day mortality ($p<0.05$). A C-reactive protein value of ≥43.94 mg/L was found to be more specific (81.14%) than the other markers for mortality.

Conclusion: Troponin/creatinine ratio is a predictor of mortality in patients presenting to the emergency department with chest pain and high-sensitivity troponin I, creatinine, and C-reactive protein seem to be independent risk factors for 28-day mortality.

Keywords: Cardiac, chest pain, creatinine, renal failure, survival, troponin.

ÖZ

Amaç: Bu çalışmada göğüs ağrısı ile başvuran hastalarda troponin/kreatinin oranının prognostik değeri incelendi ve mortaliteyi etkileyen laboratuvar değerleri belirlendi.

Çalışma planı: 01 Ekim 2016 - 30 Nisan 2019 tarihleri arasında acil servise göğüs ağrısı ile başvuran ve troponin ve kreatinin ölçümleri yapılan toplam 5079 hasta (2844 erkek, 2235 kadın; medyan yaş: 65 yıl; dağılım, 49-83 yıl) retrospektif olarak incelendi. Laboratuvar verileri ve 28 günlük mortalite oranları değerlendirildi. Hastalar ilk acil servise başvuru sonrasında 28 günlük mortalite oranlarına göre sağ kalanlar (n=4793) ve sağ kalmayanlar (n=286) olmak üzere iki gruba ayrıldı.

Bulgular: Gruplar arasında beyaz kan hücre sayısı, C-reaktif protein, kreatinin, yüksek duyarlıklı troponin I ve troponin/kreatinin oranı açısından istatistiksel olarak anlamlı farklılıklar izlendi ($p<0.05$). Yüksek duyarlıklı troponin I ≥31.96 pg/dL, kreatinin ≥1.11 mg/dL, C-reaktif protein ≥43.94 mg/L ve troponin/kreatinin oranının ≥25.12 olması 28 günlük mortalitenin bağımsız öngördürücüleri idi ($p<0.05$). C-reaktif protein değerinin ≥43.94 mg/L olması, mortalite açısından diğer belirteçlere göre daha spesifik bulundu (%81.14).

Sonuç: Acil servise göğüs ağrısı ile başvuran hastalarda troponin/kreatinin oranı mortalite açısından öngördürücü olup, yüksek duyarlıklı troponin I, kreatinin ve C-reaktif protein 28 günlük mortalite için bağımsız risk faktörleridir.

Anahtar sözcükler: Kardiyak, göğüs ağrısı, kreatinin, böbrek yetmezliği, sağkalım, troponin.

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The diagnostic process of chest pain in patients with renal failure (RF) is challenging in the emergency department (ED). Since troponin frequently increases in patients with RF, it is difficult to differentiate acute coronary syndrome (ACS), and it is important for the clinician to determine whether the troponin elevation is due to a cardiac cause or not.[1] The increase in serum troponin from baseline levels in patients with RF may be an indicator of mortality.[2,3] Therefore, the identification and classification of patients with high risk of mortality is crucial.

Although rare, increased troponin level are likely to result from non-cardiac causes and may mislead the clinician in the diagnosis of ACS in the ED. The main non-cardiac causes of troponin elevation are chronic kidney disease (CKD), advanced heart failure, cerebrovascular disease, acute pulmonary embolism, chronic obstructive pulmonary disease, acute non-cardiac critical illness, excessive exercise, and direct myocardial trauma.[2]

In the present study, we aimed to investigate the prognostic value of the laboratory analysis and troponin/creatinine (Trop/Cr) ratio in patients with RF presenting with chest pain.

PATIENTS AND METHODS

This single-center, retrospective cohort study was conducted at Gülhane Training and Research Hospital, Department of Emergency Medicine between October 1st, 2016 and April 30th, 2019. The lists of totally 607,488 patients were screened via the electronic health records. Patients without creatinine or troponin level measurements and those with missing clinical data were excluded (Figure 1). During the ED admission, the triage categories according to the Emergency Severity Index were examined. Finally, a total of 5,079 patients (2,844 males, 2,235 females; median age: 65 years; range, 49 to 83 years) who met inclusion criteria were enrolled.

Data collection

A form was created for each patient to be separately filled in. The form included parameters such as patient age, sex, triage category, and laboratory values obtained from blood samples taken in the ED. Additionally, Trop/Cr ratio (obtained by dividing the troponin I by the creatinine) and the prognosis of the patients were evaluated in the ED, and up to 28 days following ED admission by the hospital record systems or remote monitoring. All patients were divided into two groups according to 28-day mortality rates after the initial ED admission as survivors (n=4,793) and non-survivors (n=286).

The primary outcome measure of the study was the prognostic analysis of Trop/Cr ratio. Secondary outcomes were the laboratory analysis of risk factors for mortality.

Laboratory methods

The results of the blood tests taken at the first admission to the ED were used for the analysis. During the study period, blood samples were taken in tubes containing sodium citrate. The white blood cell (WBC)

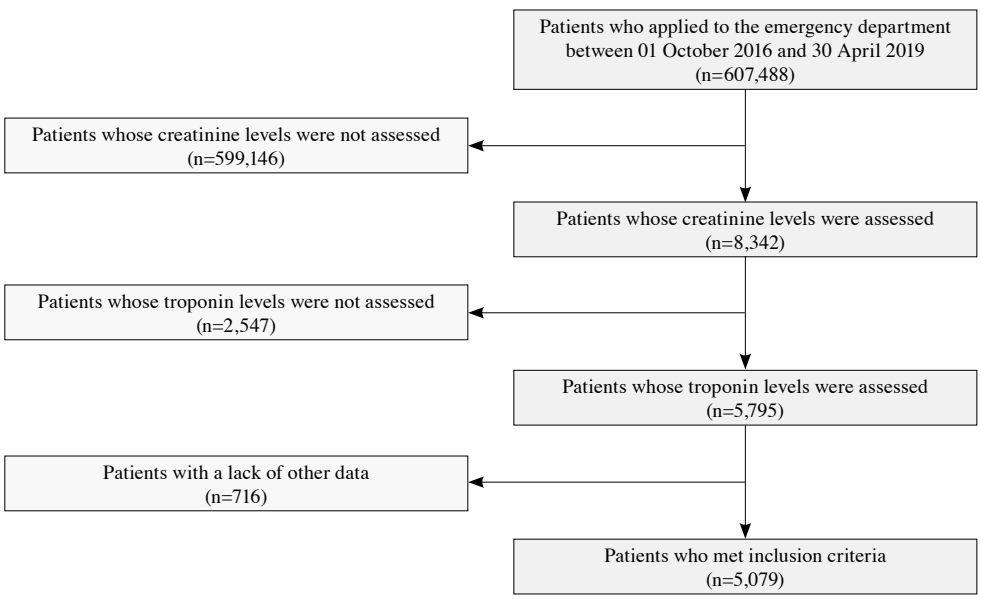

Figure 1. Study flow chart.

Table 1. Baseline demographic, clinical, and laboratory characteristics of patients

Characteristics at the time of admission	Survivors (n=4,793)				Non-survivors (n=286)				Total (n=5,079)				*p*
	n	%	Median	Range	n	%	Median	Range	n	%	Median	Range	
Age (year)			65	49-81			65	49-83			65	49-83	>0.05
Sex													>0.05
Female	2,698				162				2,860				
Male	2,095				124				2,219				
WBC ($\times 10^3/\mu L$)			10.41	5.00-15.82			12.35	6.48-18.22			10.51	5.00-18.22	≤0.05
Hb (g/dL)			12.04	9.79-14.29			11.47	9.46-13.48			12.00	9.46-14.29	≤0.05
CRP (mg/L) (min-max)			22	0-531			78	3-506			43	3-531	≤0.05
Urea (mg/dL)			45	9-342			84	17-513			46	9-513	≤0.05
Cr (mg/dL)			1.23	0.5-10.93			2.22	0.56-10.94			1.28	0.5-10.94	≤0.05
eGFR			57.96	27.23-88.69			49.08	17.94-80.22			57.45	17.94-88.69	≤0.05
Lactate (mmol/L)			2	0.1-14.7			2.2	0.6-21			2	0.1-21	≤0.05
Trop (pg/dL)			30.2	3-25183			96.6	3-25826			31.9	3-25826	≤0.05
Trop/Cr			24	0.1-25313			51	0.1-7970			25	0.1-25313	≤0.05
Triage													≤0.05
Red	1,997	41.6			174	60.8			2,171	42.7			
Yellow	2,796	58.4			58	20.4			2,854	56.2			
Black	0	0			54	18.8			54	1.1			

WBC: White blood cell count; Hb: Hemoglobin; CRP: C-reactive protein; Cr: Creatinine; eGFR: Estimated glomerular filtration rate; Trop: Troponin; Trop/Cr: Troponin/creatinine ratio.

count, hemoglobin (Hb), neutrophil count, lymphocyte count, platelet count, creatinine, and C-reactive protein (CRP) concentration values were analyzed in the biochemistry laboratory using the Pentra DF Nexus Horiba medical device (HORIBA ABX SAS, Kyoto, Japan), and high-sensitivity troponin- I (hs-Trop-I) value was analyzed at a room temperature using the Unicel DxI 600 medical device (Beckman Coulter Inc., CA, US). Reference ranges of the parameters in which these blood samples are as follows: WBC count ($4.5\text{-}11.0\times10^3/\mu L$), Hb (13.5-16 g/dL), neutrophil count ($2\text{-}12\times10^3/mL$), lymphocyte count ($1\text{-}4.9\times10^3/mL$), platelet count ($156\text{-}373\times10^3/\mu L$), creatinine value (0.70-1.20 mg/dL), CRP value (0-5 mg/L), and hs-Trop-I (0.01-17.5 pg/mL).

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 20.0 software (IBM Corp., Armonk, NY, USA). For quantitative data, the normality of the distribution was assessed using the Kolmogorov-Smirnov test. Parametric tests (independent samples t-test and the Tukey's post-hoc test) were applied to the data with normal distribution, and non-parametric tests (Mann-Whitney U test and Kruskal-Wallis test) were also applied. Continuous data were expressed in median (min-max), while categorical data were expressed in number and frequency. The area under the receiver operating characteristic (ROC) curve was used to evaluate the diagnostic accuracy and to determine a cut-off value to classify patient groups as patients with higher and lower creatinine levels according to this threshold. The cumulative survival rate was calculated using the Kaplan-Meier method, and the survival differences between the groups were compared using the log-rank test. Data were initially included in a univariate analysis to identify variables associated with 28-day mortality. Significant variables were, then, used for a stepwise forward logistic regression analysis. In addition, sensitivity and specificity were calculated for mortality. A p value of <0.05 was considered statistically significant.

RESULTS

Baseline demographic, clinical, and laboratory characteristics of the patients are given in Table 1. Of all patients, 1,891 patients had RF, and 68 of them were in the acute setting.

The mortality was observed in 286 (5.6%) patients during the study period. Ninety patients were

Table 2. Sensitivity and specificity in terms of 28-day mortality using Trop ≥31.96 pg/dL. Cr ≥1.11 mg/dL. CRP ≥43.94 mg/L and Trop/Cr ≥25.12

Trop ≥31.96 pg/dL	Mortality Yes	Mortality No	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Positive	209	2330	73.08	51.29	52.52	8.23	96.96
Negative	77	2463					
Cr ≥1.11 mg/dL	**Mortality Yes**	**Mortality No**	**Sensitivity (%)**	**Specificity (%)**	**Accuracy (%)**	**PPV (%)**	**NPV (%)**
Positive	234	2275	81.82	52.53	54.18	9.33	97.98
Negative	52	2518					
CRP ≥43.94 mg/L	**Mortality Yes**	**Mortality No**	**Sensitivity (%)**	**Specificity (%)**	**Accuracy (%)**	**PPV (%)**	**NPV (%)**
Positive	178	904	62.2	81.14	80.07	16.45	97.30
Negative	108	3889					
Trop/Cr ≥25.12	**Mortality Yes**	**Mortality No**	**Sensitivity (%)**	**Specificity (%)**	**Accuracy (%)**	**PPV (%)**	**NPV (%)**
Positive	195	2345	68.18	51.07	52.04	7.68	96.42
Negative	91	2448					

Cr: Creatinine; CRP: C-reactive protein; Trop: Troponin; Trop/Cr: Troponin/creatinine ratio; PPV: Positive predictive value; NPV: Negative predictive value.

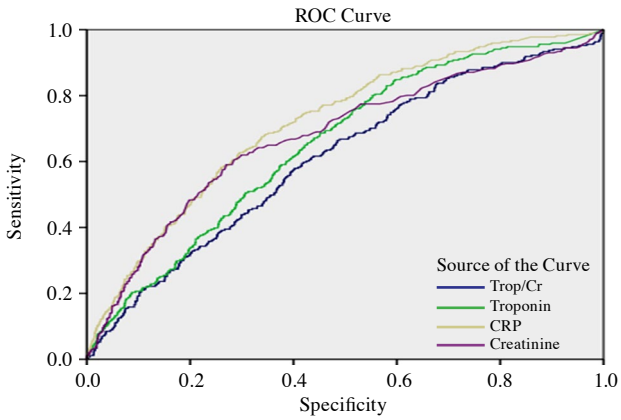

Figure 2. ROC curve analysis of hs-Trop-I, CRP, creatinine, and Trop/Cr ratios at 28-day mortality evaluation. The predictive performance increases when the area under the curve value gets close to one.

ROC: Receiver operating characteristic; hs-Trop-I: High-sensitivity troponin I; CRP: C-reactive protein; Trop/Cr: Troponin/creatinine ratio.

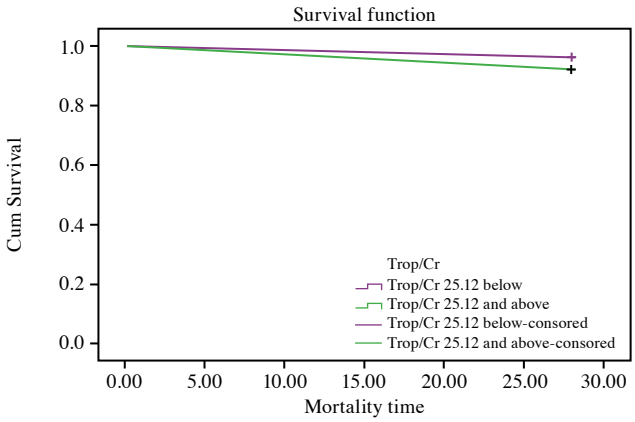

Figure 3. Kaplan-Meier survival curve for Trop/Cr ratio. The relationship between Trop/Cr ratio and mortality is depicted.

Trop/Cr: Troponin/creatinine ratio.

Table 3. Cox regression analysis for the prediction of 28-day mortality

Variables for 28-day	Odds ratio	95% CI	*p*
C-reactive protein	1.742	1.374-2.209	<0.001
Cr	2.988	2.288-3.903	<0.001
Lactate	1.171	1.142-1.200	<0.001
Trop	2.734	2.107-3.546	<0.001
Trop/Cr	2.149	1.677-2.700	<0.001

Cr: Creatinine; Trop: Troponin; Trop/Cr: Troponin/creatinine ratio.

hospitalized in the chest diseases clinic, 114 in the cardiology clinic, and 82 in the intensive care unit before death. The most common causes of mortality were pulmonary embolism (n=131), acute myocardial infarction (AMI) (n=114), and arrhythmia (n=41).

According to the 28-day mortality rate, there were significant differences in terms of triage classification, hospitalization, WBC, CRP, urea, creatinine, and hs-Trop-I ($p<0.05$). However, no significant difference was observed in terms of age and sex between the groups ($p>0.05$) (Table 1). The median Trop/Cr ratio was 51 (range, 0.1 to 7,970) in survivors and 24 (range, 0.1 to 25,313) in non-survivors, indicating a statistically significant difference ($p<0.05$).

The ROC curve analysis of hs-Trop-I, CRP, creatinine, and Trop/Cr ratios was performed to identify the possible predictors of 28-day mortality. In terms of 28-day mortality, the creatinine under the curve (AUC) was 0.676 (95% confidence interval [CI]: 0.640-0.712; $p<0.05$), the troponin AUC was 0.652 (95% CI: 0.621-0.684; $p<0.05$), the Trop/Cr ratio AUC was 0.609 (95% CI: 0.574-0.643; $p<0.05$), and the CRP AUC was 0.717 (95% CI: 0.687-0.748; $p<0.05$) (Table 2, Figure 2). The sensitivity, specificity, and accuracy rates were 73%, 51%, and 52%, respectively using a cut-off value of 31.96 pg/dL for troponin I level for 28-day mortality. In the ROC analysis, the cut-off value of creatinine was 1.11 mg/dL, and the sensitivity, specificity, and accuracy rates were 81%, 52%, and 54%, respectively. For CRP value, using a cut-off value of 43.94 mg/L, which is the study average, the sensitivity, specificity and accuracy rates were 62%, 81%, and 80%, respectively. The Trop/Cr ratios were found to have a sensitivity of 68%, a specificity of 51%, and an accuracy of 52% (Table 2).

Subgroup analysis of non-survivors during 28-day follow-up showed that 209 of 286 patients (73.0%) had hs-Trop-I ≥31.96 pg/dL; 234 (81.8%) had creatinine ≥1.11 mg/dL; 178 (62.2%) had CRP ≥43.94 mg/L, and 195 (68.2%) had Trop/Cr ratio ≥25.12 ($p<0.001$). Figure 3 depicts the Kaplan-Meier survival curve for the Trop/Cr ratio relative to the cut-off values. Patients with a Trop/Cr ratio above the threshold had a significantly higher mortality rate than those with a Trop/Cr ratio below the threshold ($p<0.001$), indicating that patients with a high Trop/Cr ratio had a higher mortality rate. Independent predictors of 28-day mortality were found to be hs-Trop-I ≥31.96 pg/dL, creatinine ≥1.11 mg/dL, CRP value ≥43.94 mg/L, and Trop/Cr ratio ≥25.12 ($p<0.05$; Table 3). According to odds ratio (OR) calculation, the creatinine, troponin, and Trop/Cr ratios were found to be the highest

predictors of 28-day mortality. The AUC value of CRP was higher than the other parameters (Figure 3).

DISCUSSION

To the best of our knowledge, our study is the first to investigate the Trop/Cr ratio in determining the prognosis in patients presenting with chest pain. Comparing the survivors and the non-survivors, the established cut-off values of hs-Trop-I, creatinine, CRP, and Trop/Cr ratios of the non-survivors were found to be risk factors for mortality.

Troponin tests are routinely used for the diagnosis of ACS in patients with CKD presenting with chest pain. Although current studies have shown that cardiac troponin I is a better predictor of acute myocardial injury than other cardiac markers in dialysis patients presenting with chest pain, it is known that baseline levels of serum troponins increase in patients with RF.[2-4] On the other hand, according to the study of Van Lente et al.,[5] the predictiveness of serum troponins in a group of kidney patients who presented with chest pain decreased. In the results of the study conducted in Brazil, troponin positivity was observed in 31.3% of the patients, which was not associated with coronary angiographic findings.[6] The troponin cut-off point with the best selectivity value is 0.605 ng/dL. The cut-off point was even higher in the subgroup with RF, and it prevented correct interpretation.[6] Again, in a meta-analysis conducted with 17 studies and 8,644 chest pain patients, the use of hs-Trop-I was compared with traditional troponin in patients with RF.[7] Despite the increase in the sensitivity of high-sensitivity troponin, the number of patients diagnosed with myocardial infarction (MI) and the number of patients requiring additional testing did not significantly differ between the groups. The use of hs-Trop-I did not show any additional clinical advantage.[7-9] For this reason, it is thought that it would be beneficial to use Trop/Cr ratios instead of additional troponin in the evaluation of ACS in patients with RF.

Although impaired renal function causes increased the cardiovascular risk, it has been shown in previous studies that impaired cardiac function causes impaired renal function.[10] Considering that the main source of creatinine, which is a directly controlled biomarker in renal function controls, is muscle tissue, its relationship with coronary artery disease (CAD) is quite obvious. Therefore, it has been studied to increase the sensitivity and specificity of the relationship between cardiac markers and other biomarkers with cardiac events.[10,11] To illustrate, serum creatinine-to-cystatin C ratio was evaluated and found to be significant to investigate major adverse events in CAD.[11] Troponins, on the other hand, exist as a heterogeneous mixture in the blood and are an indicator of cardiomyocyte necrosis. Although hs-Trop-I is a superior marker in acute cardiac ischemia that reaches higher peak levels in AMI, it has been investigated as a sensitive biomarker for mortality and morbidity along with other markers.[12,13] It has even been suggested that the ratio of troponin subtypes to each other may be a biomarker for the identification of different types of myocardial injury.[13] Moreover, it has been reported that the ratio of creatine kinase and troponin, another indicator of muscle breakdown, can be a parameter that can be used to differentiate MI from other pathologies.[14] Similarly, Liu et al.[15] suggested that serum creatinine and serum albumin-to-creatin ratio values were predictive markers to determine the high-risk scale in patients with AMI. Our results also support that hs-Trop-I or Trop/Cr ratio associated with muscle breakdown may be a predictor of 28-day mortality. In the Kaplan-Meier analysis, patients with a low Trop/Cr ratio had a longer survival, and patients with a low Trop/Cr ratio had a lower mortality rate according to the ROC curve. These results suggest that a low Trop/Cr ratio is associated with a low risk for patients and a low Trop/Cr ratio can be used for discharge.

A prospective case-series evaluating 56 patients with kidney disease at different stages showed that cardiac troponin I levels were higher than the normal value in 32% of the patients and it was associated with myocardial damage, and high troponin I levels were associated with increased in-hospital mortality.[4] Sensitivity and specificity for cardiac troponin I were reported to be 94% and 100%, respectively. The present study suggested that the troponin I value for 28-day mortality was significantly higher, with an OR of 2.734 indicating mortality, and the sensitivity and specificity rates of 31.96 pg/dL, which we gave as cut-off to troponin I, were 73% and 51%, respectively.

In the study of Roppolo et al.,[16] there might be an increase in markers due to inflammation in patients with RF, suggesting that the continuation of renal replacement therapy might cause plaque rupture and cardiac events. The literature review consists of the studies supporting that CRP value may contribute to the ability to predict mortality.[17] In a retrospective cohort study in which a total of 574 dialysis patients were included and followed for 3.5 years, 60% of the patients were male and their median age was 66.0 (range, 55.0 to 73.5) years and 111 (19.3%) patients

had major adverse cardiovascular events.[18] High CRP values were also found to be significantly associated with chronic heart disease and prolonged duration of dialysis treatment. When the relationship between CRP and mortality was evaluated with the Kaplan-Meier test, an increased mortality risk was observed.[18,19] Consistent with the 28-day mortality estimation, CRP was significantly higher.

The main limitation is the retrospective design of study. The findings of study should be confirmed with more comprehensive prospective investigations.

In conclusion, troponin/creatinine ratio was found to be independent predictors of 28-day mortality in patients presenting to the emergency department with chest pain. Additionally, high-sensitivity troponin I, creatinine, and C-reactive protein values seem to be risk factors for mortality in these patients.

Ethics Committee Approval: The study protocol was approved by the Health Sciences University, Training and Research Hospital Ethics Committee (date: 25.06.2019, no: 2019/12). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: H.C., S.G.; Design: H.C., S.G.; Control/supervision: H.C.; Data collection and/or processing: S.G.; Analysis and/or interpretation: H.C.; Literature review: H.C.; Writing the article: H.C.; Critical review: H.C., S.G.; References and fundings: H.C., S.G.; Materials: S.G.; Other H.C., S.G.

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