ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Can GRACE Risk Score Predict the in-hospital Symtomatic Heart Failure Development After Myocardial Infarction Without ST Segment Elevation?

GRACE Risk Skoru ST Yükselmesiz Miyokard İnfarktüsü Sonrası Semptomatik Kalp Yetersizliği Gelişimini Öngörebilir mi?

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ABSTRACT Objective: The Global Registry of Acute Coronary Events (GRACE) risk score has a prognostic significance in patients with myocardial infarction without ST segment elevation (NSTEMI). In this study, we aimed to evaluate the significance of GRACE score at day 1 in predicting the development of in-hospital symptomatic heart failure (IH-HF) in patients presenting with NSTEMI. **Material and Methods:** Consecutive patients, admitted with NSTEMI between April 2016-May 2017 were evaluated in this prospective cohort study. A total of 179 patients (112 male, the mean age: 65.4±11.2) with left ventricular ejection fraction (LV-EF) <50% and N-terminal pro B-type natriuretic peptide (NT-proBNP) level >125pg/mL along with Killip Class <II symptoms at admission were included in the study. GRACE score at day 1 was calculated according to original scoring system. During hospitalization period, patients who developed Killip Class (KC) ≥2 symptoms after day 1 to discharge were classified as IH-HF (n=55) and others were classified as NIH-HF (n=124). **Results:** The morbidity and mortality rates were higher in the IH-HF group. Not only GRACE score at day 1 but also atrial fibrillation (AF), three vessel disease, diabetes mellitus (DM) were found to be independent predictors of IH-HF. According to the ROC analysis, the patients with GRACE score at day 1 > 177.5 were found to be at higher risk for IH-HF development. **Conclusion:** The development of IH-HF in patients presenting with NSTEMI with asymptomatic left ventricular dysfunction significantly increases the morbidity and mortality rates. High GRACE score at day 1 in NSTEMI patients can be used to predict IH-HF.

Keywords: Myocardial infarction without ST segment elevation; heart failure; morbidity; mortality

ÖZET Amaç: Akut Koroner Olaylarda Küresel Kayıt (GRACE) risk skoru, ST segment yükselmesiz miyokard infarktüslü (NSTEMI) hastalarda prognostik bir öneme sahiptir. Bu çalışmada, NSTEMI ile başvuran hastalarda hastane içi semptomatik kalp yetmezliğinin (IH-HF) gelişimini öngörmede 1. gün GRACE skorunun önemini değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Nisan 2016-Mayıs 2017 tarihleri arasında NSTEMI ile başvuran ardışık hastalar bu prospektif kohort çalışmasında değerlendirildi. Sol ventrikül ejeksiyon fraksiyonu (LV-EF) <%50 ve N-terminal pro-B tip natriüretik peptid (NT-proBNP) seviyesi >125 pg/mL olan Killp sınıf < II olan 179 hasta (112 erkek, ortalama yaş: 65,4±11,2) çalışmaya dahil edildi. Birinci gün GRACE skoru orjinal skorlama sistemine göre hesaplandı. Hastanede yatış süresi sırasında, 1. günden sonra taburcu olmak üzere Killip Sınıfı (KC) ≥2 semptomları gelişen hastalar IH-HF (n=55) ve diğerleri (hastanede yatmadan) NIH-HF (n=124) olarak sınıflandırıldı. **Bulgular:** IH-HF grubunda morbidite ve mortalite oranları daha yüksekti. Birinci gün GRACE skoruna ek olarak; atriyal fibrilasyon (AF), üç damar hastalığı, diabetes mellitus (DM), IH-HF'nin bağımsız belirleyicileri olarak bulundu. ROC analizine göre, 1. gün GRACE skoru > 177,5. olan hastaların İH-HF gelişimi için daha yüksek risk altında oldukları bulundu. **Sonuç:** Asemptomatik sol ventrikül disfonksiyonu olan NSTEMI ile başvuran hastalarda IH-HF gelişimi, morbidite ve mortalite oranlarını önemli ölçüde arttırır. NSTEMI hastalarında 1. günde yüksek GRACE skoru, IH-HF'yi tahmin etmek için kullanılabilir.

Anahtar Kelimeler: ST segment yükselmesiz miyokard infarktüsü; kalp yetersizliği; morbidite; mortalite

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Myocardial infaction without ST segment elevation (Non-STEMI) is one of the major cardiovascular emergencies with a high risk of morbidity and mortality.[1] One of the major complications of NSTEMI is symptomatic heart failure (HF), characterized by abnormalities of cardiac structures or functions.[2] Symptomatic HF can complicate the course of NSTEMI either at admission or after admission with a severity ranging from cardiogenic shock to asymptomatic left ventricular dysfunction before discharge or months after discharge.[3,4] On the other hand, developing in-hospital symptomatic heart failure (IH-HF) was also considered to designate increased mortality.[5] The Global Registry of Acute Coronary Events (GRACE) risk score, originally was developed for prognostic assessment of patients hospitalized with acute coronary syndromes (ACS). For GRACE score (GS), ACS patients should be more than 18 years old and alive at discharge with primary end point of all-cause mortality within 6 months after discharge from the hospital.[6] This score has previously been tested to predict development of HF after discharge from the hospital in patients with ACS.[7,8] Furthermore, it was shown to predict HF admission after discharge in a large cohort of patients with ACS. However, in-hospital outcome predictive utility of GS has been rarely tested in high risk ACS patients, and to the best of our knowledge, not tested to predict in-hospital heart failure development after admission.[9] Hence, we calculated the GS via the data obtained within the first contact period of the patients who were admitted with NSTEMI and with asymptomatic left ventricular dysfunction. This modified GS to predict development of in-hospital symptomatic HF in this high risk patients with NSTEM was tested.

MATERIAL AND METHODS

STUDY POPULATION AND DESIGN

This prospective cohort selected NSTEMI patients with asymptomatic left ventricular dysfunction at admission between August 2016 and May 2017 in a tertiary health care center, as perguidelines recommendations.[10] Ethics committee approval and consent of the patients were taken for the study with the decision dated 27/09/2017 and numbered 2017-61/628. This study is designed on principles of Helsinki Declaration properly and all the subjects provided their written informed consents.

Inclusion criteria were as follows: patients diagnosed with NSTEMI, elevated cardiac enzymes and with successful percutaneous intervention of the culprit lesion, elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) levels (>125 pg/mL), the echocardiogram yielding left ventricular ejection fraction <50% together with the absence of Killip Class II-IV symptoms at admission.

Exclusion criteria were as follows: Patients without angiographically proven NSTEMI and patients presenting with NSTEMI and symptomatic HF (Killip Class II and above) at admission. Patients with history of valve surgery, simultaneous active infection, moderate to severe lung disease, moderate to severe liver disease, cerebro-vascular disease, inflammatory disease, history of heart failure before ACS, renal failure, and cardiomyopathic disease were also excluded from the study.

According to index echocardiographic analysis (of note, all patients underwent echocardiographic analysis in day 1), patients who were found to have moderate-to-severe heart valve disease, mechanical complication of AMI and index LV-EF> 50% were not included in the study.

According to index cath-lab referral, patients who did not undergo percutaneous coronary intervention (PCI) within the first 24 hours, those with critical left main lesion, those with thrombolysis in myocardial infarction (TIMI) flow grade ≤2 after PCI were also not included in the study.

Biochemical parameters were evaluated in blood samples, collected during hospitalization. and follow-up. Assessment of symptomatic status was carried out according to the Killip classification (KC). Patients who remained in KC I were all through the hospitalization included in the (no in-hospital heart failure) NIH-HF group and those who developed symptomatic HF during the hospital course (between day 1 to discharge) with KC ≥2 were included in the (in-hospital symptomatic heart failure) IH-HF group.

Killip Classification

Killip class (KC) has been shown to predict mortality in patients with ACS. According to Killip classification, patients were classified into four classes during physical examination. KC-I means no evidence of heart failure. KC-II means mild to moderate heart failure with jugular venous distention or rales involving 1/2 o rless of th eposterior lung fields or an S3. KC-III patients have overt pulmonary edema. KC-IV have cardiogenic shock or hypotension [systolic blood pressure (SBP) ≤ 90 mmHg] and evidence of low cardiac output.[11,12]

All patients received dual antiplatelet therapy. Peri-procedural anticoagulation consisted of unfractioned heparin. Clopidogrel or ticagrelor bid on top of acetyl-salicylic-acid were prescribed after PCI. Blood samples were collected from each patient immediately after presenting at the emergency department. Therapy with beta-blocker and angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) were initiated immediately in all patients. All patients received high dose (80 mg atorvastatin) statin at admission.

Echocardiographic Evaluation

Transthoracic echocardiography was performed using the Philips HD11 system (Philips Healthcare, Best, the Netherland) with a 3.2 MHz transducer. Measurements were made according to the American Society of Echocardiography criteria. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson biplane method

GS

The GS was calculated by means of a computer program (www.outcomes-umassmed.org/grace/acs_risk) during the admission to the hospital.

Coronary Angiography

Coranary angiographies were performed using the Siemens artis zeego system (Siemens Helthcare, Erlangen, Germany). Patients with successful percutaneous coronary intervention (PCI) procedure (TIMI flow >2 after stenting) within the first 24 hours were considered in the cohort. Intervention was based on the discretion of the primary operator. Elective PCI was recommended for the other lesions according to the judgement of the primary operator. All implanted stents were drug eluting stents (DES) in the cohort. Patients were followed in the hospital period after NSTEMI: 1) vessel disease (VD) indicated that there was one vessel with >70% stenosis; 2) VD showed that there were two vessels with >70% stenosis and 3) VD indicated that there were three vessels with >70% stenosis.[13]

STATISTICAL ANALYSIS

Statistical Package for Social Sciences 22.0 (SPSS Inc., Chicago, IL, USA) and Med Calc, release 12.3.0.0 (MedCalc Software, Belgium) were used for statistical analysis. The Kolmogorov-Smirnov test was used to test normality of distribution of continuous variables. Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range as appropriate. Categorical variables were expressed as percentages. Group means for continuous variables were compared with the Student's *t*-test or the Mann-Whitney U test, as appropriate. The Chi-square test or Fisher exact test examined the correlation between categorical variables. To find independent associates of IH-HF, variables with a p value of ≤ 0.25 at the univariate analysis were selected for backward stepwise multiple regression analyses. To make a Receiver Operating Characteristic (ROC) analysis, the patients were divided into two groups; as the ones with IH-HF or NIH-HF. The area under the ROC curve analysis, cut-off value for GS, 95% confidence intervals, sensitivity and specificity values were determined. The calculated p-values less than 0.05 were considered statistically significant.

RESULTS

There were 179 Non-STEMI patients with asymptomatic left ventricular dysfunction at admission and mean age of patients with IH-HF were older than those with NIH-HF (Table 1). There were no difference between groups with regard to gender distribution and hypertension prevalence. Atrial fibrillation (AF), diabetes mellitus (DM) were more prevalent, GS at day 1, heart rate, cTn-I, creatinine, and NT-proBNP levels were higher in the IH-HF group.

TABLE 1: Patients with in-hospital symptomatic heart failure (IH-HF) and with no-in-hospital heart failure (NIH-HF) with regard to general characteristics, laboratory, echocardiography and angiographic findings.

Variable	IH-HF(n=55) mean±std.dev median (25^{th}-75^{th})	NIH-HF (n=124) mean±std.dev median (25^{th}-75^{th})	p value
Age (years)	73.9 (±10.3)	62.0 (±7.1)	<0.001
Hypertension, n (%)	20 (%36.3)	44(%35.4)	0.918
Diabetes mellitus, n (%)	26 (%47.7)	36 (%29.1)	0.019
Systolic Blood Pressure (mmHg)	132.2 (±26.8)	139.6 (±28.2)	0.176
Diastolic blood pressure (mmHg)	75.3 (±15.1)	86.7 (±18.5)	<0.001
Heart rate (per minute)	86.6 (±28.5)	75.3 (±15.1)	<0.001
Peak troponin-I (ng/ml)	32.9 (12.8-61.4)	12.8 (2.4 -23,7)	<0.001
Creatinine on admission (mg/dl)	1.38 (±0.41)	0.91 (±0.36)	<0.001
Hemoglobin on admission (g/dl)	12.2 (±2.3)	13.2 (±1.8)	0.005
Platelets (x1000)	242 (150-335)	231 (166-312)	0.418
GRACE score at day 1	204.2(±31.8)	136.3 (±30.3)	<0.001
Peak NT-proBNP (pg/ml)	1783 (420-3754)	238(148-445)	<0.001
LV-ejection fraction at day 1, (%)	38.7 (±9.8)	44.1 (±5.1)	<0.001
Estimated systolic pulmonary artery pressure (mmHg)	34.2±9.2	26.1±7.4	p<0.001
Intensive care unit stay (days)	5.6 (2.6-6,6)	3.1 (1.5-4,7)	<0.001
Total hospital stay (days)	8 (4-10)	6 (2-8)	<0.001
Atrial fibrillation on admission, n (%)	19 (%38.0)	11 (%8.9)	<0.001
Arrest, in hospital period, n (%)	8 (%14.5)	0	<0.001
Mortality, n (%)	4 (%7.2)	0	<0.001
Clopidogrel/ticagrelor	39%/61%	37%/63%	0.813
Angiographic findings			
One vessel disease	24 (%43.6)	65 (%52.4)	0.278
Two vessel disease	18 (%32.7)	49 (%39.5)	0.386
Three vessel disease	13 (%23.6)	10 (%8.1)	0.006

Data are expressed in numbers (%), mean ± SD, or median and interquartile range.

Chi-square, Fisher-exact, Independent sample t-test and Mann-Witney U tests. Cx: Circumflex; LAD: Left Anterior Descending; LV: left ventricle; BNP: b-type natriuretic peptide; STD: ST segment deviation; AKI: acute kidney injury; RAAS: renin-angiotensin-aldosterone system; RCA: Right Coronary Artery.

Hemoglobin level and diastolic blood pressure were significantly lower in IH-HF group, whereas, SBP was similar in both groups.

Appropriate therapy was initiated immediately in all patients as per hospital protocol. However, ACEI/ARB therapy was hold in 38% of patients with IH-HF (n=21), beta blocker therapy was hold in 61% of patients with IH-HF (n=34) due to hemodynamic instability and/or acute kidney injury. Hence, patients who received ACEI&ARB (p=0.029) and beta blocker (p<0.001) in the intensive care period were significantly lower in the IH-HF group.

The average length of stay in intensive care unit and in the ward was significantly longer in patients with IH-HF compared to those with NIH-HF (p<0.001 for both, Table 1).

Echocardiography and Coronary Angiography Findings

Echocardiographic LV-EF was lower in IH-HF group (38.7±9.8 vs. 44.1±5.1%, p<0.001). Estimated systolic pulmonary artery pressure (sPAP) was higher in IH-HF group compated to NIH-HF group (34.2±9.2 vs. 26.1±7.4, p<0.001). Three vessel coronary artery disease (CAD) was more frequent in IH-HF group compared to NIH-HF group (p=0.006).

Heart Failure by KC

In our study, 55 of the patients (27.5%) developed KC≥ 2 in the hospital between day 1 to discharge in

TABLE 2: Univariate and multivariate analysis of risk factors determining symptomatic in-hospital ischemic heart failure.

	Univariate analysis		Multivariate analysis	
Variables	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Ejection Fraction	6,1 (1.9-14.6)	<0.001	4.4 (1.5-8.3)	<0.001
GRACE score at day 1	5.8 (1.4-12.2)	<0.001	3.6 (1.3-7.1)	<0.001
Atrial Fibrillation	4,7(2.2-11.6)	<0.001	2.3 (1.5-4.0)	<0.001
Three vessel coronary disease	3.4(1.6-8.3)	<0.001	1.7(1.1-2.5)	0.023
Diabetes Mellitus	2.1(1.5-4.4)	0.019	1.5(1.0-2.3)	0.036
Hemoglobine	1.3 (0.9-1.6)	0.032	1.2(0.5-2.6)	0,066
Diastolic Blood Pressure	1.2 (0.7-1.9)	0.096	1.0 (0.5-1.4)	0.114

this cohort. Eight patients (4.4%) experienced cardiac arrest during hospital period and four patients died during their hospital stay (%2.2), and all belonged to IH-HF group. Independent predictors of IH-HF were shown in Table 2. In multivariate regression analysis; GS, presence of AF, presence of three-vessel disease and presence of DM were found to be the independent predictors of IH-HF. The GS at day 1 cut-off value which predicts the development of IH-HF was calculated as 177.5 (AUC: 0.754; p <0.001; 95% CI: 0.675-0.833; sensitivity, 71%; specificity, 73%) (Figure 1).

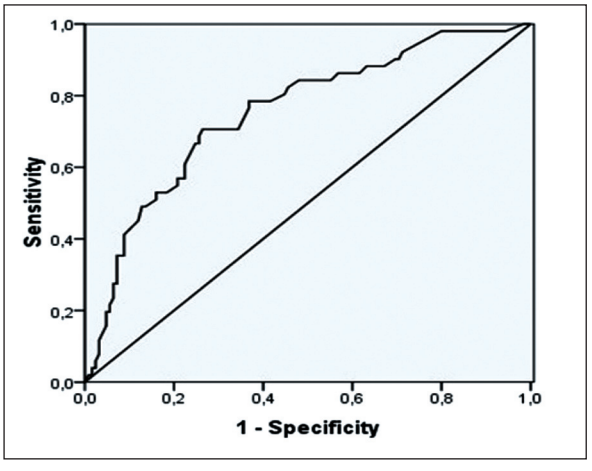

FIGURE 1: Receiver operating characteristic (ROC) curve. The GRACE risk scoreat day 1 cut-off value which predicts the IH-HF group was calculated as 173.5 (AUC: 0.714; (p <0.001; 95%CI: 0.646-0.845; sensitivity, 72%; specificity, 74%). (AUC: Area Under the Curve; CI: Confidence Interval; IH-HF: In-hospital symptomatic Heart Failure).

DISCUSSION

In our study, the significance of GRACE risk score at day 1 in predicting the development of in-hospital symptomatic heart failure in the patients with NSTEMI with asymptomatic left ventricular dysfunction at admission (KC=1, LV-EF <50% and NT-proBNP ≥125 pg/ml) was investigated. It was designated that high GS at day 1 was associated with the development of IH-HF. The development of acute heart failure after NSTEMI significantly increases the morbidity and mortality rates.[14-17] High risk patients who are asymptomatic at the time of admission may become decompensated due to various reasons. On the other hand, GS as a scoring system was started to be used for prognostic evaluation in the patients with ACS after the GRACE study in 2003.[18] Its calculation is recommended in NSTEMI patients according to American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines.[19,20] The usefullness of the GRACE risk score to establish the risk of HF after acute coronary syndrome (ACS) seems to have significant consequences.[6,21,22] After an ACS, the patient is at a risk of developing HF.[23] Therefore, the risk stratification of ACS patients to predict HF is important. However, in-hospital prognosis has rarely been evaluated in high risk patients with NSTEMI. In our study, GS at day 1 was able to predict those patients who developed symptomatic HF with in the hospital, so widening the indication of GRACE in ACS patient cohorts.

There are several parameters which are used for GS calculation. The first of these is the variable of age. The GRACE risk model does not give points for the age <30 years while it gives 100 additional points to the age ≥90 years. As is known, the morbidity and mortality after ACS increases with age. In our study,

the mean age of the patients in the IH-HF group was higher. One of the reasons for GS to be predictive of IH-HF was deteremined to be age. It is known that the increase in heart rate, other than age, is not a good indicator in the patients with ACS. There is a relationship between cardiac function and heart rate in the patients with heart failure. In the GS model, the heart rate <50 / min gives 0 point, the heart rate between 90-109/min gives 15 points and the heart rate > 200/min gives 46 points. When the results of the study were evaluated, the heart rates of the patients with IH-HF at admission period were higher. An additional assessment is not available for the patients with high grade AV-block while GS is calculated. The development of high-grade AV-block after ACS is a poor prognostic indicator. Due to this situation which can be interpreted as a deficiency in the scoring system, the patients with high-grade av-blocks were not included in the study. Another parameter which is used for GS is SBP. GS increases as SBP falls. SBP <80 mmHg provides 58 points while SBP between 160-199 mmHg provides 10 points of contribution. There was no statistically significant difference between the study groups in terms of mean blood pressure values at the time of admission. Creatinine, which is one of the components of the GS gives 1 point when it is ≤0.39 and 21 points when it is ≥2 mg/dl. In our study, the creatinine values of IH-HF group were significantly higher at the admission period. As is known, the KC is used to assess the severity of ischemic heart failure. Depending on KC, the patients get a score between 0-59 points in GS. Only the patients with KC-I were included at the admission period. The GS and other characteristics of those who became decompensated among these were evaluated. Therefore, the Killip classification was KC-I for all patients, and its contribution of score was zero. The presence of cardiac arrest at admission period is represented by 39 points. However, in our study, the patients who were brought to the hospital with cardiac arrest were not included in the study. However, the patients who were admitted to the hospital as KC-I and developed cardiac arrest during the follow-up period were included in the study. In-hospital cardiac arrest rate was found to be higher in the IH-HF group. The other two components of GS are cardiac enzyme elevation (14 points) and ST segment change (28 points). In our study, cardiac enzymes were higher in the IH-HF group and ST segment change was greater in this group. It was determined that the GS calculated by the parameters discussed above were increased in the IH-HF group. As a result of the statistical analysis, it was determined that the age and creatinine which were used in the calculation of GS were among the predictors of IH-HF. As described previously, GS is calculated using eight different variables. Considering these parameters, the presence or levels of some of these variables are important. Although the variables other than age and creatinine do not have significant impact alone on the development of IH-HF, their significance in the score of GS were discussed previously. The fact that GS has more odds ratios than the sum of age and creatinine suggests that the reason for predicting the development of IH-HF was associated with the variables other than these two parameters. It is clear that the association of high GS level with IH-HF development is not explained by age and creatinine. It will be more useful to calculate and evaluate the score as a whole.

Of note, other than GS, EF, AF, three vessel disease, DM was found to predict IH-HF. In our study, PCI was performed in all patients. There were some differences in terms of prevalence and severity of CAD. As it is already known, as CAD prevalence and severity increase, survival decreases in HF patients, hence, three vessel disease is the predictor of IH-HF.[24-27] During PCI, only the culprit lesion were intervened. However, it seems that revascularization of the lesions other than the culprit lesion may be beneficial in preventing the development of IH-HF in patients presenting with NSTEMI and with asymptomatic left ventricular dysfunction, though, it remains to be established.

During the study period, eight (4.4%) patients died. All of these patients were in the IH-HF group. The mortality rates were reported between 4-9% in previous studies.[23-26] Our results were in agreement with the previous data.

LIMITATIONS

First of all, this is a prospective analysis of the data of single tertiary care center. Several potentially missed

data remain as confounders of the study results. Besides, only in-hospital period was considered as per study protocol. Hence, findings should be replicated in other cohorts. On the other hand, by longer follow-ups, particularly in the vulnerable phase after discharge, additional information can potentially be obtained. Furthermore, determination of the amount of necrotic myocardium by examinations such as MRI or PET may have been beneficial, however, it is not a routine practice to do so in contemporary management. Hence, findings should better be replicated in prospective cohorts.

CONCLUSION

As a result, after NSTEMI presenting with asymptomatic low LV-EF, IH-HF may ensue. In our study, GS at day 1 was determined to be a strong predictor of IH-HF. It was found that the IH-HF risk was particularly increased in patients with GS>177.5. In NSTEMI patients with echocardiographic low ejection fraction, in addition to the other factors, the GRACE risk score at day 1 can be used for the assessment of IH-HF development.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *İlker Gül, Bihter Şentürk;* ***Design:*** *İlker Gül, Bihter Şentürk;* ***Control/Supervision:*** *Bihter Şentürk;* ***Data Collection and/or Processing:*** *Bihter Şentürk, İlker Gül;* ***Analysis and/or Interpretation:*** *Bihter Şentürk, İlker Gül;* ***Literature Review:*** *İlker Gül;* ***Writing the Article:*** *İlker Gül;* ***Critical Review:*** *Bihter Şentürk.*

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