RESEARCH ARTICLE

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The Relationship Between SYNTAX II Score and Serum Pleiotrophin Level in Patients with Non-ST-Segment Elevation Myocardial Infarction

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Abstract

Background and Aim: In this study, we aimed to examine the relationship between serum pleiotrophin (PTH) levels at admission and the severity of coronary artery disease (CAD) in patients experiencing non-ST-segment elevation myocardial infarction (NSTEMI).

Materials and Methods: A total of 140 patients with NSTEMI undergoing coronary angiography were consecutively included in the study. The Synergy Between percutaneous coronary intervention with Taxus and Cardiac Surgery (SYNTAX) score was determined based on initial coronary angiography by at least two separate cardiologists.

Results: A positive correlation was found between high SSII and PTH ($r = 0.458$; $P < 0.001$). PTH could anticipate the extremity of CAD with 64.4% sensitivity and 65.3% specificity at 250 ng/mL cut-off value (area under the curve: 0.718, 95% confidence interval, 54.8 - 74.7; $P < 0.001$). Through regression analysis, PTH, hypertension, diabetes mellitus, family history, lymphocyte count, and pro-brain natriuretic peptide levels were found to be independent predictors of SSII.

Conclusion: In patients with NSTEMI, serum PTH levels were significantly associated with higher SSII, an indicator of CAD severity and cardiovascular prognosis. This study obtained positive results that will contribute to our clinical interpretation. More comprehensive studies with PTH will make a more useful contribution to our clinical judgments.

Keywords: Pleiotrophin, NSTEMI, SYNTAX score, acute coronary syndrome, coronary artery disease

INTRODUCTION

Being one of the major public health problems seen worldwide, acute myocardial infarction (MI) is a prominent agent of morbidity and mortality. Atherosclerosis holds a crucial position in the emergence of most cardiovascular (CV) disorders.[1,2] As atherosclerosis is caused by the progressive gathering of fibrous tissue and cholesterol consisting of plaques, it leads to stricture of the arterial lumen and results in non-ST-segment elevation myocardial infarction (NSTEMI). In fact, the atherosclerotic process is frequently followed by inflammation.[3,4] Various studies commonly suggest that each stage of atherosclerosis, including increased plaque instability, is mediated by inflammatory factors and consequently leads to clinical circumstances, as seen in cases of MI, unstable angina, stroke, or sudden death.[5,6]

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Pleiotrophin (PTH) is a secreted multifunctional cytokine with diverse functions in regulating angiogenesis when a tumor emerges and grows around the tissue. High levels of PTH can be experienced in various tumor cell lines as well as in the kidneys, embryonic nervous system, lungs, bones, and intestines. PTH can also play a significant role in physiological angiogenesis, along with tumorous and non-tumorous pathological angiogenesis.s[7] Several experiments conducted on models suggest that PTH provides the creation of operative neovascularization in rat CV tissues *in vivo* and *ex vivo*.[8,9] In the focal cerebral ischemia and reperfusion study on animals, it has been shown that PTH affects neuronal, glial, macrophage, and endothelial cell populations in the brain, and its level increases.[10] In a study by Palmieri et al.[11], it was shown that PTH-secreting cells can regulate proinflammatory and proregenerative changes by modulating PTH tissue levels depending on different stimuli. In the latest study, the PTH level was found to be high in the development of collateral in patients with chronic total coronary artery disease (CAD) after atherosclerosis.[12] However, no research has been conducted to assess the correlation between serum PTH levels and the prevalence of CAD in patients with NSTEMI. In this study, we assessed the severity of CAD and serum PTH rates according to the the synergy between percutaneous coronary intervention (PCI) with Taxus and Cardiac Surgery (SYNTAX) II (SYNergy between PCI with TAXus and cardiac surgery) score (SSII) in patients with NSTEMI.

MATERIALS AND METHODS

Target population

Designed in a cross-sectional and single-center plan, the study included 140 consecutive patients (18-80 years old) who applied to the emergency service with the first incident of NSTEMI from December 2021 to February 2022. SSII was calculated on the basis of angiographic findings. Considering the findings from the scoring system, the target population was separated into subgroups with SSII values of 22 in the low group, those with an SSII value between 23 and 32 in the middle group, and those with an SSII value of 33 in the high SSII group.

We defined exclusion criteria as former PCI or a history of coronary artery bypass grafting, acute liver and kidney disorders, decompensated heart failure, malignancies, autoimmune diseases, hematological disorders, inflammatory or infectious diseases, and intense valvular disorders. The conclusive diagnosis of NSTEMI was defined on the basis of the latest guidelines.[13,14]

The patient's age, gender, CV risk factors, and history of CAD were documented in their records. By conducting at least two calculations or using any antihypertensive medication, we determined hypertension (HT) as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg. We also defined diabetes mellitus as fasting plasma glucose level >126 mg/dL or >200 mg/dL by taking into consideration antidiabetic drug usage or relevant measurements. After obtaining a written consent form from all patients and approval of the study protocol by the Ankara City Hospital Ethics Committee, the study protocol (approval number: 2022-2375; date: 09.02.2022) was conducted in accordance with the ethical guidelines of the 1975 Helsinki Declaration.

Laboratory assessment

Initially, we collected peripheral venous blood samples from the patients by atraumatic puncture from the antecubital vein and sent them to the laboratory for cardiac catheterization. Next, we used the Beckman Coulter AU 5800 AutoAnalyzer to measure the ratios of blood biochemical parameters and high sensitivity-C-reactive protein (hs-CRP) urea, along with uric acid, creatinine, sodium, lipid panel, potassium, and pro-brain natriuretic peptide (proBNP). We also calculated the low-density lipoprotein with the Friedewald equationusing an automated blood cell counter (Beckman Coulter LH 750; Beckman Coulter Inc., USA) to analyze variables related to complete blood count.

The blood models obtained for measuring the PTH rates were subjected to centrifugation at 3000 rpm at 4 °C for 10 min. After the process of separation, platelet-poor plasma was preserved at -80 °C for appropriate analysis. Serum PTH levels were calculated using a commercial kit named ELISA (SunRed Biotechnology Campany, Shanghai SunRed Biological Technology Co., Ltd. Hu Tai Road. Baoshan District, Sanghani, China).

All patients underwent transthoracic echocardiography. The left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method.

Angiographic assessment

Coronary angiography was performed using a Siemens Axiom Sensis XP device (Munich, Germany) and Standard Judkins technique (Expo; Boston Scientific Corporation, Natick, Massachusetts, USA). Diameter images of the coronary artery were investigated in at least two perpendicular planes, followed by digital recording of each coronary angiographic image for quantitative analysis. PCI was performed using iopromide (low osmolarity and non-ionic contrast agent) based on clinical practice regulations.

Digital angiograms were evaluated by at least two experienced and independent interventional cardiologists, followed by the calculation of SYNTAX II rates, which were detected to present no difference when compared by the interventional cardiologists. Thus, the online SSII calculator version 2.1 (www.syntaxscore.com) determined ≥1.5 mm in diameter,

each lesion causing ≥50% lumen stricture in the epicardial arteries.

Statistical analysis

We used the SPSS 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) to perform statistical analysis. Before analyzing the relation of persistent numerical variations for each group, we applied the Kolmogorov-Smirnov or Shapiro-Wilk tests to subject them to normality analysis, taking the number of samples into consideration for each group. Therefore, we determined the continuous variables with a normal distribution as mean ± standard deviation, variations with non-normal distribution as median (minimum-maximum), and categorical variables as percentage and number. In addition, we used the Kruskal-Wallis test or the analysis of variance (ANOVA) test to compare continuous variables based on the SYNTAX scores. Bonferroni analysis was used as a post-hoc test. The chi-square test was used to compare categorical variables. We also defined the independent variations indicated by the high SYNTAX score (≥33) by performing multiple logistic regression analyses. Potential confusing factors for which the unadjusted p-value was detected as <0.20 in univariate regression analysis [the presence of diabetes mellitus and HT, lymphocyte, hemoglobin, proBNP, PTH level, and high-density lipoprotein cholesterol (HDL-C)] were identified as possible risk indicators and evaluated in the multiple logistic regression model. Variables used to calculate the SYNTAX score were excluded from the final analysis. Finally, we performed receiver operating characteristic analysis to determine the cut-off rate of PTH in the calculation of a high SYNTAX score. The significance limit was accepted as $P < 0.05$.

RESULTS

The demographic, basic clinical, and laboratory findings of the study population are shown in Table 1, which statistically presents a remarkable difference among these three groups with respect to age, gender, diabetes mellitus, smoking, CAD, family history, PTH, lymphocyte, proBNP level, and LVEF ($P < 0.05$). However, univariate logistic regression analysis indicated that diabetes mellitus, HT, lymphocyte count, HDL-C, proBNP, and PTH levels were independent predictors of the high SSII group. In multivariate logistic regression analysis, PTH and proBNP were determined as independent predictive values for the high SSII group [odds ratio (OR), 1.003; 95% confidence interval (CI), 1.001-1.005; p<0.001; OR, 1; 95% CI, 1.0-1.001, p=0.031, respectively, Table 2]. Moreover, a positive relationship was detected between PTH and a high SSII score and neutrophil-to-lymphocyte ratio (respectively $r = 0.458$; $P < 0.001$, Figure 1, $r = 0.176$; $P < 0.038$). In addition, we found that PTH could predict the extremity of coronary artery failure with 64.4% sensitivity and 65.3% specificity at 250 ng/mL cut-off value (Area under the curve: 0.718, 95% CI, 54.8-74.7; $P < 0.001$, Figure 2).

DISCUSSION

In this study, we determined a considerable connection between serum PTH levels and the severity of CAD in patients

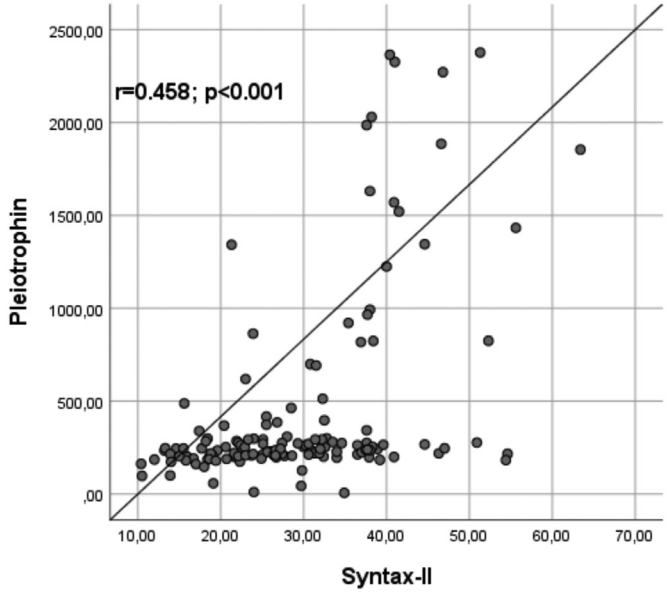

Figure 1: Correlation between pleiotrophin and the SYNTAX II score

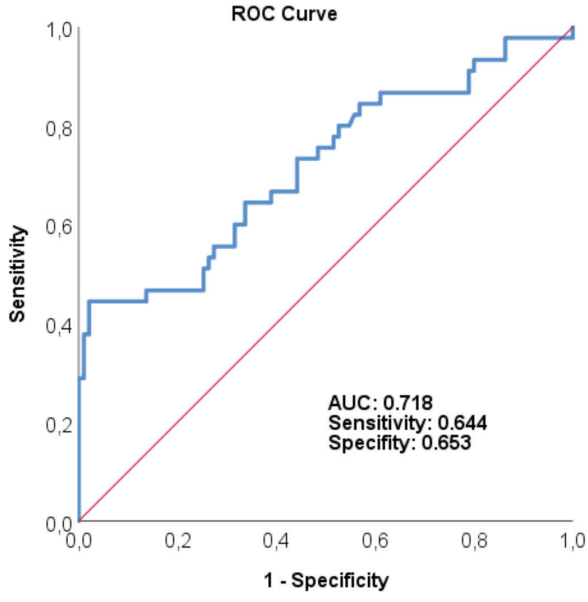

Figure 2: Analysis curve for pleiotrophin to predict coronary artery disease severity

ROC: Receiver operator characteristic, AUC: Area under the curve

Table 1: Demographics, clinical, and laboratory data according to the SYNTAX II score groups

Parameters	SYNTAX score			*P*-value
	Low group (≤22; *n*=39)	Intermediate group (23-32; *n*=56)	High group (≥33; *n*=45)	
Age, years	55.2±9.1[a]	61.1±9.8[a, b]	67.3±8.9[b]	<0.001
Male sex, *n* (%)	32 (22.9)	44 (31.4)	22 (15.7)	0.001
Hypertension, *n* (%)	26 (18.6)	35 (25.0)	15 (10.7)	0.31
Diabetes mellitus, *n* (%)	23 (16.4)	39 (27.9)	21 (15.0)	0.028
Active smoker, *n* (%)	15 (10.7)	15 (10.7)	27 (19.3)	<0.001
Family history of CAD, *n* (%)	30 (21.4)	45 (32.9)	39 (27.9)	<0.001
Creatinine (mg/dL)	0.77 (0.68-0.92)	0.77 (0.62-0.95)	0.88 (0.66-1.0)	0.284
Uric acid (mg/dL)	5.5±1.4	5.8±1.9	5.7±1.6	0.583
Triglyceride (mg/dL)	165 (75-236)	114 (67-162)	95 (67-146)	0.086
LDL-C (mg/dL)	120 (110-143)	124 (105-152)	126 (105-157)	0.943
HDL-C (mg/dL)	42.0 (37.1-46.0)	43.5 (35.0-46.9)	43.5 (39.0-47.8)	0.520
Hemoglobin (mg/dL)	13.9±1.3	14.0±1.5	13.4±1.5	0.05
WBC ($\times10^3$/μL)	10.0 (8.9-11.9)	10.3 (7.8-12.3)	9.8 (8.2-12.2)	0.786
Neutrophil ($\times10^3$/μL)	6.2 (5.0-8.7)	6.8 (5.0-9.4)	7.6 (5.9-9.8)	0.411
Lymphocyte ($\times10^3$/μL)	1.7 (1.3-3.2)	1.8 (1.2-2.4)	1.3 (0.9-2.0)	0.020
Platelet ($\times10^3$/μL)	240 (204-278)	226 (202-318)	240 (206-308)	0.814
proBNP (pg/mL)	165 (97-343)	287 (118-866)	672 (163-2080)	<0.001
hs-C-reactive protein (mg/dL)	0.5 (0.3-0.9)	0.4 (0.3-0.9)	0.4 (0.3-1.0)	0.984
LVEF (%)	50.0 (46.0-55.0)	45.0 (40.0-50.0)	40 (30.0-45.0)	<0.001
Pleiotrophin (ng/mL)	207.7 (185.4-245.6)	248.1 (208.8-293.8)	277.1 (231.9-1476.8)	<0.001

LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, WBC: White blood cell, BNP: Brain natriuretic peptide, LVEF: Left ventricular ejection fraction, [a]In the post hoc analysis of the Bonferroni test, it was found to be statistically significant in the high group, [b]In the post hoc analysis of the Bonferroni test, it was found to be statistically significant in the low-risk group

with NSTEMI. Thus, it can be considered to be the first study conveyed on humans in the sense of showing a remarkable relationship between high serum PTH levels and the severity of CAD.

In our study, the relationship between hospital admission serum PTH levels and the severity of CAD calculated by SSII was analyzed. Thus, high serum PTH levels are associated with severe coronary atherosclerosis in NSTEMI. In addition to the positive correlation between PTH and SSII, increased PTH levels were found to have an independent predictive value for the severity of CAD.

The most important cause of CAD is coronary atherosclerosis. The triggering mechanism of acute coronary syndrome (ACS) is the emergence of an intracoronary thrombus caused by the erosion or rupture of the atherosclerotic coronary plaque and the inclusion of matrix materials and thrombogenic core from the plaque into the circulation.[15] Within this context, inflammation has a great influence together with numerous other risk agents, especially cardiac inflammation, which results in a life-threatening complication of NSTEMI by causing issues of morbidity and mortality for the general public.[16]

In many studies, patient populations with ACS have been broadly examined for various clinical findings.[17] In the majority of these studies, the SYNTAX score I was assessed, and its relationship with the severity of CAD was revealed. However, the SYNTAX score I is not satisfactory for clinical assessment in the presence of complex CAD. Therefore, the recently developed SSII can enable both clinical and anatomical assessment. In addition to anatomical data, SSII includes clinically remarkable prognostic variations, such as gender, age, and creatinine clearance. Chronic obstructive pulmonary disorder, peripheral artery disease, and LVEF are common independent markers of mortality in patients with stable CAD enrolled in the SYNTAX test.[18,19] Studies conducted with SYNTAX have reported that SSII predicts mortality better.[20,21] Therefore, the SSII scores can effectively demonstrate the individualized chance of mortality associated with each revascularization procedure. In addition, it has been recently demonstrated by research that SSII can

Table 2: Univariate and multivariate logistic regression analysis for the assessment of independent predictors of high SYNTAX scores

	Univariate		Multivariate	
	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**
Diabetes mellitus	0.038	2,147 (1,043-4.42)	0.897	1,068 (0.392-2,908)
Hypertension	0.001	3,588 (1,698-7,584)	0.166	2,025 (0.745-5,503)
Family history of CAD	0.339	0.615 (0.227-1,666)		
Uric acid	0.879	0.984 (0.795-1,217)		
Sodium	0.271	0.944 (0.852-1,046)		
WBC	0.503	0.959 (0.85-1,083)		
Neutrophil	0.364	1,059 (0.936-1,197)		
Lymphocyte	0.010	0.574 (0.376-0.877)	0.823	0.946 (0.581-1,54)
Hemoglobin	0.017	0.733 (0.568-0.947)	0.391	0.867 (0.626-1,201)
MCV	0.108	1,055 (0.988-1,127)		
Platelet	0.536	1,002 (0.996-1,007)		
Triglyceride	0.163	0.998 (0.995-1,001)		
Total cholesterol	0.486	0.998 (0.991-1,004)		
LDL-C	0.825	1,001 (0.992-1,011)		
HDL-C	0.071	1,035 (0.997-1,074)	0.222	1,029 (0.983-1,078)
proBNP	0.006	1 (1-1,001)	0.031	1 (1-1,001)
hs-CRP	0.965	0.997 (0,866-1,147)		
Pleiotrophin	<0.001	1,003 (1,001-1,004)	<0.001	1,003 (1,001-1,005)

CAD: Coronary artery disease, WBC: White blood cell, MCV: Mean corpuscular volume, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, pro-BNP: Brain natriuretic peptide, hs-CRP: High-sensitivity C-reactive protein, OR: Odds ratio, CI: Confidence interval

independently predict the incidence of all-cause deaths in patients suffering from 1-or 2-vessel failures.[22]

PTH, an 18-kDa secretory protein, is involved in various biological functions, such as migration, survival, and growth of cells, angiogenesis, neurite outgrowth, and tumor growth.[23,24] As a multifunctional cytokine, it is also known as a heparin-binding growth-associated molecule, osteoblast-specific factor-1, heparin-binding growth factor-8, or neurite outgrowth promoting factor, and is remarkably conserved across several species.[25]

The *PTH* gene is deactivated in the postnatal period and is in small amounts in most adult tissues. Upregulation of PTH in adults supports tumoral and non-tumor pathological angiogenesis and physiological angiogenesis. PTH has been observed in microglia and macrophages in neovascular endothelial cells and neovasculature around the infarcted rat brain secondary to ischemic injury. However, the expression of PTH was remarkably reduced in injured neurons that were unlikely to survive, highlighting the regulative role of PTH in postischemic renewal.[10] An important controversy regarding the therapeutic role of proangiogenic agents is their protumorigenic potential, which can lead to undesirable consequences. In another study, it was shown that *PTH* gene delivery has a functional effect in a severe ischemic hindlimb model in mice with low tumorigenic potential.[26] The effect of PTH on cardiac tasks has not yet been entirely elucidated. Research conducted *in vitro* suggests that PTH is upregulated when cardiomyocytes begin to grow out of pluripotent stem cells.[27] Research conducted on a rodent heart revealed that strong PTH staining can be seen in peri-infarction and infarct regions, similar to cerebral infarction. Moreover, it has been stated that there is an increase in PTH value during the removal of cellular residues, remodeling in heart failure, and scar formation.[28] PTH can be assessed for potential future benefits in vascular bioprosthesis engineering.[11] In a study, it was reported that serum PTH levels in patients with angina pectoris were associated with maintaining coronary collateral circulation. However, serum PTH levels were not detected in patients with ACS.[12] Başyiğit et al.[29] It was determined that the serum concentration of PTH in the patients was related to ACS. Despite animal models, few studies are available on human cells; therefore, this research can be considered as the first attempt to support the therapeutic impact of this effective molecule in humans. This study confirms the score of PTH as a biomarker showing the relationship between CAD severity and PTH.

In our study, in addition to PTH, proBNP, hs-CRP, lymphocyte, hemoglobin, HDL-C level, diabetes mellitus, HT, and family

history of CAD were assessed. Statistically significant levels were obtained by univariate logistic regression analysis, except for hs-CRP. In addition, proBNP was found to be an independent predictor of SSII in multivariate regression analysis. The fact that these variables were statistically significant supports our hypothesis.

Although hs-CRP was found to be insignificant in demonstrating the severity of CAD in our study, it is an independent risk agent for CAD.[30] Numerous studies have revealed that high levels of hs-CRP can be linked with a high atherosclerosis progression rate in the carotid vessels and the risk of stroke.[31] This indicates that hs-CRP may be associated with inflammation. However, a wide variety of controversial articles are available on hs-CRP and its effect on the treatment, diagnosis, and prevention of all primary and secondary CAD cases. The main reason the hs-CRP level was insignificant in our study may be that we did not reach a sufficient number of patients.

In our study, we hypothesized that PTH, an anti-inflammatory factor, may be correlated with the existence of NSTEMI and the extremity of CAD. Thus, we examined the relationship between high PTH rates, the incidence of NSTEMI, and the severity of CAD. Lab findings showed that PTH rates in NSTEMI patients were positively and remarkably correlated with high SSII. In addition, it was determined that there was an independent predictive variable for high SSII in the regression analysis. Nevertheless, further studies are required to clarify the prognostic effect of PTH rates in patients with ACS.

Study limitations

Some limitations of this study are as follows: the presence of a single center and therefore a small sample size. Because the study was designed in a cross-sectional plan, no follow-up data could be obtained. Second, we could only calculate PTH rates at admission, but not convey serial measurements owing to financial issues. In fact, measuring PTH levels after the acute phase of infarction could reveal additional information. Third, other possible inflammatory and pro-angiogenic factors have not been assessed simultaneously in the same population. If the interaction between PTH and proangiogenic factors is demonstrated with simultaneous studies, it will provide more precise results.

CONCLUSION

In patients with NSTEMI, serum PTH levels were significantly associated with higher SSII, an indicator of CAD severity and CV prognosis. It also has an independent predictive value for high SSII. This outcome could pave the way for a more aggressive pharmacoinvasive treatment strategy in patients with high SYNTAX scores. However, larger prospective examinations are required to detect the effect of PTH rates in patients with ACS.

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Ethics

Ethics Committee Approval: After obtaining a written consent form from all patients and approval of the study protocol by the Ankara City Hospital Ethics Committee, the study protocol (approval number: 2022-2375; date: 09.02.2022) was conducted in accordance with the ethical guidelines of the 1975 Helsinki Declaration.

Informed Consent: Informed consent was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G.N., O.K., F.B., B.Ş., M.C., Concept: S.G.N., O.K., F.B., B.Ş., M.C., Design: S.G.N., O.K., F.B., B.Ş., M.C., Data Collection or Processing: S.G.N., O.K., Analysis or Interpretation: S.G.N., O.K., F.B., B.Ş., M.C., Literature Search: S.G.N., O.K., F.B., B.Ş., M.C., Writing: S.G.N., O.K., B.Ş., M.C.

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