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The Assessment of Vascular Calcification, Arterial Stiffness, and Nutritional Status in Patients on Hemodialysis, A 5-Year Follow-up Study

Hemodiyaliz Hastalarında Vasküler Kalsifikasyon, Arteriyel Sertlik ve Nütrisyonel Durumun Değerlendirilmesi, 5 Yıllık Takip Çalışması

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Abstract

Objectives: This study aimed to find out the relationship between vascular calcification, arterial stiffness, and nutritional status, and investigate their effects on 5-year mortality.

Materials and Methods: This study included 79 hemodialysis patients. Fetuin-A and FGF-23 levels were measured. The average blood pressure (BP) of the previous 12 months was used. The abdominal aortic calcification (AAC) score was measured from lateral abdominal radiographs. Carotid-femoral pulse wave velocity (cf-PWV) was used for arterial stiffness assessment. The geriatric nutritional risk index (GNRI) was used for nutritional status, and calculated as the following formula; [14.89*serum albumin (g/dL)] + (41.7* body weight/ideal body weight).

Results: Twenty-five (31.6%) of 79 patients died within 5 years. When the alive and deceased groups were compared age (p=0.001), diabetes mellitus (p=0.041), GNRI (p=0.019), AAC score (p=0.009), cf-PWV (p=0.003), albumin (p=0.030), C-reactive protein (p=0.003), mean systolic BP before dialysis (p=0.018), and mean diastolic BP before dialysis (p=0.045) were significantly different between two groups, whereas Fetuin-A and FGF-23 were not. AAC score above 3 points [area under the curve (AUC): 0.682], cf-PWV above 8.1 (AUC: 0.727), and GNRI score 99.2 and lower (AUC: 0.663) had estimated 5-year mortality well. GNRI was the only independent variable (hazard ratio: 0.924, p=0.047) in multivariable cox regression analysis.

Conclusion: There was a close relationship between AAC score, GNRI, cf-PWV, and long-term mortality. The cf-PWV and its close relationship with average BP measurements must be assessed for future studies. Following GNRI must be targeted for its crucial role as an independent factor of mortality.

Key Words: Vascular Calcification, Arterial Stiffness, Nutrition, FGF-23, Fetuin-A

Öz

Amaç: Bu çalışmada vasküler kalsifikasyon, arter sertlik ve nütrisyonel durum arasındaki ilişkinin ortaya çıkarılması ve 5 yıllık mortalite üzerine etkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya 79 hemodiyaliz hastası dahil edildi. Fetuin-A ve FGF-23 kan seviyeleri ölçüldü. Önceki 12 ayın ortalama kan basıncı (KB) değerleri kullanıldı. Abdominal aortik kalsifikasyon (AAK) skoru lateral abdominal grafilerden ölçüldü. Arteriyel sertliğin değerlendirmesinde karotis-femoral nabız dalga hızı (kf-NDH) kullanıldı. Nütrsiyonel durumun değerlendirilmesi için geriatrik nütrisyonel risk indeksi (GNRI) kullanıldı. GNRI formülü; [14,89*serum albümini (g/dL)] + (41,7* vücut ağırlığı/ideal vücut ağırlığı).

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Öz

Bulgular: Yetmiş dokuz hastanın 25'i (%31,6) 5 yıl içinde öldü. Sağkalan ve ölen gruplar karşılaştırıldığında yaş (p=0,001), diabetes mellitus (p=0,041), GNRI (p=0,019), AAK skoru (p=0,009), kf-NDH (p=0,003), albümin (p=0,030), C-reaktif protein (p=0,003), diyaliz öncesi ortalama sistolik KB (p=0,018) ve diyaliz öncesi ortalama diyastolik KB (p=0,045) açısından iki grup arasında anlamlı fark bulunurken, Fetuin-A ve FGF-23 açısından fark bulunmadı. AAK skoru >3 [eğri altında kalan alan (AUC): 0,682], kf-NDH >8,1 (AUC: 0,727) ve GNRI ≤99,2 (AUC: 0,663) 5 yıllık mortaliteyi öngeren değerler olarak bulundu. Çok değişkenli Cox regresyon analizinde GNRI tek bağımsız değişkendi (tehlike oranı: 0,924, p=0,047).

Sonuç: AAK skoru, GNRI, kf-NDH ve uzun dönem mortalite arasında yakın ilişki mevcuttur. Kf-NDH ve ortalama KB ölçümleri ile yakın ilişkisi gelecekteki çalışmalar için değerlendirilmelidir. Bağımsız bir mortalite faktörü olarak kritik rolü nedeniyle GNRI skorlarının takibi hedeflenmelidir.

Anahtar Kelimeler: Vasküler Kalsifikasyon, Arteriyel Sertlik, Beslenme, FGF-23, Fetuin-A

Introduction

Cardiovascular diseases are leading the major problems in patients with chronic kidney disease, especially for end-stage kidney disease, and cause serious morbidity and mortality (1). Vascular calcification forms the basis of cardiovascular diseases. Age, diabetes mellitus, hypertension, hyperlipidemia, obesity, and tobacco are known as traditional risk factors for vascular calcification. On the other hand, poor nutrition, chronic inflammation, factors related with bone- mineral disorders, duration of dialysis, and dialysis modality constitute the non-traditional risk factors (2). Fetuin-A is a glycoprotein that acts as a protective factor for vascular calcification in end-stage kidney disease (3). FGF-23 plays a role in bone-mineral homeostasis. Higher levels of FGF-23 are correlated with abnormal mineral metabolism, but the role of FGF-23 on vascular calcification is controversial (1). Lateral abdominal radiograph is recommended by KDIGO to assess aortic vascular calcification, and it is an easy and cost-effective method to measure (4). Another vascular calcification-related definition is arterial stiffness, and pulse wave velocity is used to measure it.

Arterial stiffness and vascular calcification are emerging as markers of cardiovascular disease risk (5).

In dialysis patients, reduced protein and energy intake, hypercatabolism, metabolic acidosis, reduced physical activity, reduced anabolism, comorbidities, and dialytic treatment cause poor nutrition. It is also called protein-energy wasting (6). In the literature, the close relationship between malnutrition, inflammation, and vascular calcification is a well-known condition. Therefore, there are existing terminations like "malnutrition-inflammation-atherosclerosis syndrome" and "malnutrition-inflammation complex syndrome" (7). Geriatric nutritional risk index (GNRI), which is calculated by using body weight, height, and serum albumin level, has been recently revealed as a very simple and objective tool to assess nutritional status in chronic kidney disease. Therefore, GNRI has been used not only to assess malnutrition but also to predict mortality (8).

In this study, we aimed to measure vascular calcification by using lateral abdominal graph, vascular calcification-related parameters including FGF-23 and Fetuin-A, arterial stiffness by using carotid-femoral pulse wave velocity (cf-PWV), and nutritional risk by using GNRI in patients on hemodialysis; also to search the relationship between them. Secondly, we aimed to investigate the contribution of these parameters to 5-year mortality.

Materials and Methods

End-stage renal disease patients on hemodialysis at a university hospital were enrolled in this prospective observational cohort study. Seventy-nine patients, who were on hemodialysis for at least three months were included. Ankara University Faculty of Medicine Clinical Research Ethics Committee approved this study on February 23, 2015 (approval no: 03-111-15). Informed consent was obtained from all participants.

Data Collection

Baseline characteristics including dialysis vintage, primary renal disease, comorbidities, medications, and laboratory values were obtained from medical records. The average blood pressure of patients for the previous 12 months, just before and after dialysis session, were calculated and taken into consideration. All blood samples were taken before the mid-week dialysis. Serum Fetuin-A (BioVendor, Brno, Czech Republic) and FGF-23 (Human FGF-23 ELISA kit, Millipore Corp, ABD) levels were measured according to manufacturer instructions. The reference value of Fetuin-A was 0-100 ng/mL. The intra and inter-assay variation coefficients for Fetuin-A measurements were found to be 2.9 and 4.7%, respectively. The reference value for FGF-23 was 3,5-2433 (pg/mL). The intra and inter-assay variation coefficients for FGF-23 measurements were found to be 3.5 and 7.2%, respectively.

Lateral abdominal radiographs of patients were evaluated for abdominal aortic calcification (AAC) by using the Kouppila method (4). All AAC scores were calculated by the same physician. Lumbar vertebral segments (L1-L4) were assessed.

The abdominal aorta was divided into 4 segments corresponding to the L1-L4 vertebra. The anterior and posterior segments of each vertebra were measured separately. The score for each segment ranged from 0-3 as follows for calcific deposits: 0, no deposit; 1, less than one-third of the corresponding length of segment; 2, one-third to two-thirds of the segment; 3, more than two-thirds of the segment. The total AAC scores ranged between 0 and 24.

cf-PWV was measured with sequential tonometry according to published guidance (SphygmoCor device, AtCor Medical, New South Wales, Australia). It was used for measuring arterial stiffness (9). Cf- PWV was measured by the same healthcare professional before the mid-week dialysis after resting and in a supine position. The cf-PWV was calculated using the distance and time difference between the artery sites.

The GNRI was calculated as previously reported: GNRI= [14.89*serum albumin (g/dL)] + (41.7* body weight/ideal body weight). Body weight/ideal body weight was set to 1 when the body weight exceeded the ideal body weight (10). The ideal body weight was calculated from the height and a BMI of 22 kg/m^2.

Statistical Analysis

Normality tests were examined by using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test). Data were presented as means and SDs for normally distributed variables, and medians and interquartile range (25th-75th percentile) for non-normally distributed variables. Categorical variables were written in terms of counts and percentages. The Mann-Whitney U test, independent samples t-test were used to compare alive and deceased groups. The chi-square test or Fisher's exact test was used to compare proportions between groups, where appropriate. The estimating capacities of AAC score, GNRI, cf-PWV, Fetuin-A, and FGF-23 on mortality were analyzed by using receiver operating characteristic (ROC) curve analysis. Multivariable cox regression model for 5-year mortality was performed. Univariable analysis included age, sex, GNRI, cf-PWV, and AAC score. Variables, found to be significant in univariable analysis were put in multivariable analysis. All analyses were considered statistically significant when the p-value was <0.05. Statistical Package of Social Science 23.0 (SPSS) was used for analysis.

Results

Seventy-nine patients, who were on regular hemodialysis, were included. Mean age was 55.25±15.14, with a 46.8% female rate. Median (25th-75th) duration of hemodialysis was 40 (24-72). Median C-reactive protein (CRP) level was 6.3 (1.9-16.0) and median albumin level was 4.2 (3.9-4.2). The baseline characteristics of patients were given at Table 1 in detail. Twenty-five (31.6%) of 79 patients died within 5 years. When the alive and deceased groups were compared age (p=0.001), diabetes mellitus (DM) (p=0.041), GNRI (p=0.019), AAC score (p=0.009), cf-PWV (p=0.003), albumin (p=0.030), CRP (p=0.003), mean systolic blood pressure before dialysis (p=0.018), and mean diastolic blood pressure before dialysis (p=0.045) were significantly different between two groups (Table 2).

The estimating capacities of AAC score, GNRI, cf-PWV, Fetuin-A, and FGF-23 to predict 5-year mortality were given in Table 3, separately. AAC score of 3 points estimated 5-year mortality with 77.2% sensitivity and 63.4% specificity (p=0.005). A threshold for GNRI to predict 5-year mortality was found to be 99.2 with a 56.0% sensitivity and 70.4% specificity. Cf-PWV estimated 5-year mortality with 90.5% sensitivity and 54.0% specificity. The threshold was found as 8.1. The ROC curves were presented in Figure 1. The AUC values for Fetuin-A (p=0.886) and FGF-23 (p=0.142) were not significant.

Table 1: Baseline characteristics of patients

Variables	n=79
Age, mean ± SD	55.25±15.14
Sex, female, n (%)	37 (46.8)
Duration of hemodialysis, months	40 (24-72)
Dialysis vintage, n (%)	
Three times a week	68 (86.1)
Two times a week	11 (13.9)
Primary renal disease, n (%)	
Diabetes mellitus	14 (17.7)
Hypertension	27 (34.2)
Chronic glomerulonephritis	7 (8.9)
Amyloidosis	2 (2.5)
Chronic pyelonephritis	6 (7.6)
Polycystic renal disease	2 (2.5)
Nephrolithiasis	1 (1.3)
ANCA-associated vasculitis	1 (1.3)
Other	3 (3.8)
Unknown	16 (20.3)
Comorbidities, n (%)	
Diabetes mellitus	20 (25.3)
Hypertension	69 (87.3)
Hyperlipidemia	15 (19)
Coronary artery disease	26 (32.9)
Cerebrovascular event	6 (7.6)
Peripheral artery disease	6 (7.6)
Heart failure	8 (10.1)
Body mass index, kg/m^2	25.4 (21.5-28.4)
Kt/v	1.8 (1.5-2.0)
Calcium, mg/dL	8.9 (8.5-9.3)
Phosphorus, mg/dL	5.2 (4.3-6.3)
Albumin, g/dL	4.2 (3.9-4.2)
CRP, mg/L	6.3 (1.9-16.0)
LDL, mg/dL	85 (62-98)

The date was presented as median (25th-75th) when otherwise stated
CRP: C-reactive protein, LDL: Low-density lipoprotein, K: Dialyzer clearance of urea, T: Dialysis time, V: Volume of distribution of urea, SD: Standard deviation

Table 2: The comparison of vascular calcification and related parameters between the alive and deceased group after a 5-year follow-up

	Alive (n=54)	Deceased (n=25)	p-value
Age, median (min.-max.)	53.5 (20-77)	64 (23-81)	**0.001**
Sex, female	29 (53.7)	8 (32.0)	0.072
Duration of hemodialysis, month	37.5 (18.5-75.0)	44.0 (30.5-84.0)	0.476
DM	10 (18.5)	10 (40.0)	**0.041**
HT	47 (87.0)	22 (88.0)	0.905
GNRI,	102.7 (98.7-104.3)	99.0 (95.9-102.9)	**0.019**
AAC score	0 (0-13.7)	12.5 (3.0-19.2)	**0.009**
cf-PWV, m/s	7.9 (6.9-9.9)	9.5 (8.6-12.5)	0.003
FGF-23, pg/mL	118.4 (37.3-311.7)	263.5 (71.5-943.7)	0.159
Fetuin-A,ng/mL	38.1 (29.2-42.9)	34.9 (28.8-46.7)	0.883
Albumin, g/dL	4.0 (3.9-4.2)	4.0 (3.7-4.1)	**0.030**
CRP, mg/L	7.1 (2.2-11.8)	14.4 (7.3-28.0)	0.003
LDL, mg/dL	83.5 (62.0-105.5)	85.0 (69.5-95.5)	0.828
Systolic blood pressure before dialysis, mean ± SD	117±16	127±18.4	**0.018**
Systolic blood pressure after dialysis, mean ± SD	107±18.8	118±21	0.325
Diastolic blood pressure before dialysis, mean ± SD	70±9.8	72±10	**0.045**
Diastolic blood pressure after dialysis, mean ± SD	65±11.2	68±8.6	0.395

Statistically significant data were highlighted as bold
AAC: Abdominal aortic calcification, cf-PWV: Carotid-femoral pulse wave velocity, CRP: C-reactive protein, DM: Diabetes mellitus, FGF-23: Fibroblast growth factor-23, GNRI: Geriatric nutritional risk index, HT: Hypertension, LDL: Low-density lipoprotein, SD: Standard deviation

Table 3: The estimating capacities of AAC score, GNRI and cf-PWV to predict mortality

	AUC (95% CI)	Cut-off	Sensitivity	Specificity	p-value
AAC score	0.682 (0.564-0.786)	>3	77.2	63.4	**0.005**
GNRI	0.663 (0.548-0.766)	≤99.2	56.0	70.4	**0.012**
cf-PWV	0.727 (0.608-0.826)	>8.1	90.5	54.0	**<0.001**
Fetuin-A	0.510 (0.395-0.625)	≤35	56.0	61.1	0.886
FGF-23	0.599 (0.482-0.708)	>263	52.0	70.4	0.142

Statistically significant data were highlighted as bold
AAC: Abdominal aortic calcification, AUC: Area under the curve, GNRI: Geriatric nutritional risk index, cf-PWV: Carotid-femoral pulse wave velocity, FGF-23: Fibroblast growth factor-23

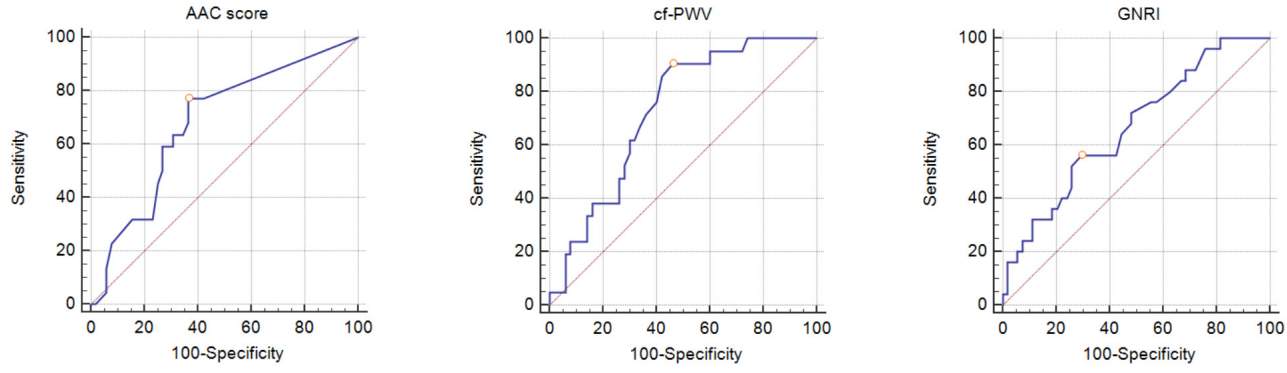

Figure 1: ROC curves of AAC score, cf-PWV, and GNRI to predict the 5-year mortality

ROC: Receiver operating characteristic, AAC: Abdominal aortic calcification, cf-PWV: Carotid-femoral pulse wave velocity, GNRI: Geriatric nutritional risk index

Univariable and multivariable cox regression analysis was shown in Table 4.

Multivariable cox regression analysis for 5-year mortality estimation included age, cf-PWV, AAC score, GNRI. Hazard ratio (95% confidence interval) for GNRI was 0.926 (0.861-0.996) (p=0.039). There was no statistically significant difference for others.

Discussion

In this study, we investigated the effect of AAC score measured via lateral lumbar radiography, cf-PWV, GNRI, FGF-23 and Fetuin-A on long-term mortality, in patients on hemodialysis. After 5-year follow-up, 31.6% of patients died. AAC score, GNRI, cf-PWV, CRP and albumin levels were worse than alive group in deceased group. Therefore, median age and the rates of DM were lower in survivals, as expected. FGF-23 and Fetuin-A levels were not different between groups. The mean systolic and diastolic blood pressure before dialysis were higher in deceased group. Therefore, we highlighted the significant estimating capacities of AAC score, cf-PWV, and GNRI. Fetuin-A and FGF-23 failed to estimate 5-year mortality. On the other hand, only GNRI was independently associated with 5-year mortality in multivariable analysis.

Vascular calcification is known to be a major risk factor especially for patients on dialysis. There are so many factors contribute to it, and it is a complex process. "KDIGO clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder" recommend to use lateral abdominal radiograph to detect vascular calcification (11). Therefore, it is a simple and easy method and not affected by volume status of patients. In convenient with this recommendation, we use lateral abdominal radiography to assess vascular calcification. AAC score had shown to be related with mortality for patients on dialysis. For example, in a recently published systematic review and meta-analysis, AAC (abdominal X-ray or computed tomography) was reported to be associated with high risk of all-cause mortality among patients on dialysis. All-cause mortality was assessed in 6 studies in this paper (12). Similar with this data, we showed the association of AAC score with mortality.

PWV is an indicator of arterial stiffness, and independent predictor of mortality in this population. Its cut-off value was presented as 10m/s for cf-PWV (13). In our study, we found 8.1 as cut-off value to predict mortality. It was lower than the suggested thresholds. However, although it has a high sensitivity, specificity rate was low. It is known that vascular calcification, cf-PWV and blood pressure are related and interacted with each other. In this study, it should be emphasized that we assessed average value of blood pressures for both before and after hemodialysis among 1 year before the cf-PWV measurements. The mean systolic and diastolic blood pressure before dialysis were significantly higher in deceased group but also cf-PWV. There have been emerging and motivating researches in this area including follow up studies assessing the changes of cf-PWV (14). Yakar et al. (15) emphasized the effect of increasing age and systolic blood pressure on PWV in their study. They also indicated the importance of controlling blood pressure. The relationship between blood pressure and PWV is an important issue. In another study, it was claimed that elevated baseline PWV may decease response to treatment of hypertension (16). In this point of view, we can say that the following and controlling blood pressure and cf-PWV, long exposure to high blood pressure needs to be investigated especially for patients on hemodialysis assessing all contributing factors.

The only independent factor in multivariable analysis was GNRI. GNRI is calculated by using albumin level and body weight. Bouillanne et al. (17) reported the GNRI as a simple and accurate tool for assessing the risk of morbidity and mortality in older hospitalized patients. After that, Yamada et al. (10) modified the nutritional risk index formula and showed that this scoring is reliable in assessing nutritional status in chronic HD patients. Following researches showed GNRI as mortality predictor on dialysis patients (18,19). Therefore, in a recently published mini-review the relationship of GNRI with all-cause and cardiovascular mortality in patients on dialysis was summarized (8). Our result was similar with this data.

Table 4: Multivariable cox regression model for 5-year mortality

	Univariable		Multivariable	
	Exp (B) 95% CI	p-value	Exp (B) 95% CI	p-value
Age	1.059 (1.023-1.096)	0.001	1.036 (0.989-1.085)	0.135
Sex	2.048 (0.883-4.750)	0.095		
cf-PWV	1.190 (1.056-1.340)	0.004	1.047 (0.866-1.264)	0.637
AAC, score	1.064 (1.014-1.116)	0.011	1.040 (0.968-1.117)	0.284
GNRI	0.954 (0.910-1.000)	0.049	0.926 (0.861-0.996)	0.039
Fetuin-A	1.009 (0.982-1.038)	0.507		
FGF-23	1.000 (1.000-1.000)	0.879		

GNRI: Geriatric nutritional risk index, cf-PWV: Carotid-femoral pulse wave velocity, FGF-23: Fibroblast growth factor-23, CI: Confidence interval

Malnutrition in patients on hemodialysis was known to be associated with vascular calcification and related parameters. Albumin, as a component of GNRI and negative acute phase reactant plays an important role for the evaluation of hemodialysis patients. Therefore, Fetuin-A is known as a negative acute phase reactant. However, in our study, we could not find any significant data. In a review and meta-analysis, lower Fetuin-A was conducted to be associated with increased mortality risk independent of diabetes and inflammation in dialysis patients (20). On the other hand, we measured FGF-23 levels, and we could not show any relation with survival. In fact, there are studies assessing the effect of FGF-23 on cardiovascular risk (21). However, there are no consistent data about that.

Study Limitations

It is a single center study and 79 maintenance hemodialysis patients were enrolled. The pathogenesis and related factor are various. Because of these reasons, multivariable analysis requires many variables and needs large sample. More comprehensive and large sample studies are needed. On the other hand, we investigated the AAC score, cf-PWV, FGF-23, Fetuin-A and GNRI in one long-term mortality study. In future, mortality risk estimation models may be composed and our study set light to that kind of studies.

Conclusion

In conclusion, the triangle of vascular calcification, nutritional status and inflammation requires to be assessed regularly in patients on hemodialysis. Calculating AAC score by using lateral abdominal graph and using it in mortality prediction model is rational. The assessment of cf-PWV and its close relationship with average blood pressure measurements must be kept in mind for such models. Finally, following GNRI must be targeted for its crucial role as an independent factor of mortality.

Ethics

Ethics Committee Approval: Ankara University Faculty of Medicine Clinical Research Ethics Committee approved this study on February 23, 2015 (approval no: 03-111-15).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.Ö., N.D., Design: Y.Ö., N.D., Data Collection and/or Processing: Y.Ö., Analysis and/or Interpretation: Y.Ö., Ş.E., Z.K.Ç., M.G., M.H., Literature Search: Ş.E., Z.K.Ç., M.G., M.H., Writing: Y.Ö., Ş.E., Z.K.Ç., M.G., M.H., N.D.

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