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The Relationship Between Dual Antiplatelet Treatment Score and Thrombus Burden in Patients with Acute Myocardial Infarction

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Abstract

Objectives: High thrombus burden (HTB) was an independent predictor of death, repeat myocardial infarction, and infarct-related artery intervention and stent thrombus in patients with acute myocardial infarction (AMI). This study aimed to evaluate the predictive role of the dual antiplatelet therapy (DAPT) score in the estimation of intracoronary thrombus burden in patients with AMI.

Materials and Methods: Between March 2020 and May 2020, 360 consecutive patients admitted with AMI who underwent coronary angiography at the cardiology department of our institution were retrospectively evaluated. The DAPT score has been defined as previously in the DAPT study. The thrombolysis in myocardial infarction (TIMI) thrombus grade was calculated for each patient from the diagnostic angiographic images taken before percutaneous coronary interventions. HTB was defined as TIMI thrombus grades 4 and 5 calculated according to the TIMI thrombus grading scale. The study population was divided into two groups according to their TIMI thrombus grade: low thrombus burden (LTB) (TIMI 0-3) and HTB (TIMI 4 and 5).

Results: There were 133 patients (36.9%) in the LT group and 227 patients (63.1%) in the HTB group. Patients with HTB had significantly a higher DAPT score (p=0.010) compared with LTB patients. The ability of the DAPT score to predict the

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Abstract

HTB was evaluated by receiver operating characteristic curve analysis. The cut-off value of the DAPT score for predicting the HTB was 2 (with a sensitivity of 67.8%, specificity=69.4%) according to the Youden index. Univariate regression analysis demonstrated that the DAPT score was significantly associated with the HTB. On multivariate analysis, the DAPT score (Odds ratio: 1,245, 95% confidence interval: 1,009-1,537; p=0.041) was found as an independent predictor of the HTB when the DAPT score was analyzed as a continuous variable.

Conclusion: The DAPT score is a practical score system to guide DAPT duration, accounting for both ischemic risk and bleeding risk factors. Considering the increasing number of patients with acute coronary syndromes, prediction of thrombus burden through a simple and practical scoring system may be of benefit.

Keywords: Acute myocardial infarction, DAPT score, percutaneous coronary intervention, thrombus burden

Introduction

In spite of the incidence of acute myocardial infarction (AMI) declining recently, patients with AMI still have a higher mortality than that of the general population[1,2]. The preferred treatment approach of patients with AMI is percutaneous coronary intervention (PCI). Patients with AMI are at a high risk of recurrent ischemia after PCI, and current guidelines recommend that their treatment includes individual risk factor modification and long-term dual antiplatelet therapy (DAPT)[3]. In previous reports, the association of the presence of intracoronary thrombi with procedural complications such as stent thrombosis, no-reflow, or distal embolization was shown in patients with acute AMI undergoing PCI[4].

The DAPT score is a new decision tool recently developed to identify patients most likely to provide benefit from long-term dual antiplatelet therapy[5]. The DAPT score includes the following parameters: age, diabetes mellitus (DM), myocardial infarction (MI) at presentation, prior PCI or MI, cigarette smoking, congestive heart failure (CHF) or left ventricular ejection fraction (LVEF) <30%, paclitaxel-eluting stents, stent diameter <3 mm and vein graft stent[5].

The present study evaluated the predictive role of the DAPT score in the estimation of intracoronary thrombus burden in patients with AMI.

Materials and Methods

Between March 2020 and May 2020, 426 consecutive patients admitted with AMI at the cardiology department of our institution were retrospectively evaluated. Hospital records and patient files were reviewed. AMI was determined by the appropriate guidelines[6]. AMI was defined as the presence of cardiomyocyte necrosis detected by abnormal cardiac biomarkers in a clinical setting consistent with acute myocardial ischemia and persistent ST-segment elevation or without persistent ST-segment elevation.

Patients with MI and non-obstructive coronary artery disease (n=19), a known hematological disease (n=2), a history of chronic inflammatory disease (n=1), a history of autoimmune diseases (n=1), malignancy (n=3), those using oral anticoagulants (n=5), or patients with missing clinical data (n=3) were excluded from the study. Additionally, we excluded patients (n=32) who did not undergo coronary angiography (CAG). The final study population consisted of 360 AMI patients who underwent CAG.

The retrospective observational study protocol was approved by the local ethics committee of our hospital (E1-22-2362).

Baseline clinical and demographic parameters, laboratory measurements, and angiographic images of patients were gathered from the hospital's medical database.

The DAPT score was defined as previously in the DAPT study[5]. The DAPT score was calculated by assigning -2 points for age ≥75 years, -1 points for age between 65 and 75 years, 0 points for age <65 years, 1 point each for cigarette smoking, DM, MI at presentation, prior PCI or prior MI, paclitaxel-eluting stent and stent diameter <3 mm, and 2 points for vein graft stent and CHF or LVEF <30%, respectively.

The CAG was performed via the transradial or transfemoral approach using the Seldinger technique according to the operator's discretion. According to the European Society of Cardiology guidelines, an immediate invasive strategy was performed on patients with at least one very-high-risk non-ST elevation MI (NSTEMI) criterion or with ST-elevation MI (STEMI); all the remaining patients underwent CAG within 48 h after admission with a diagnosis of NSTEMI[7,8]. All the patients in the study received a loading dose of aspirin and depending on the discretion of the operator, a loading dose of clopidogrel 600 mg, or ticagrelor 180 mg, or prasugrel 60 mg on admission or after the decision to proceed with PCI were taken. Procedural decisions, including device selection and adjunctive pharmacotherapy, such as glycoprotein IIb/IIIa inhibitors, were made by the operator. All patients received 70-100 U/kg of intravenous unfractionated heparin before the PCI procedure.

Two experienced interventional cardiologists who were unaware of the DAPT score of patients reviewed the angiographic images of the study patients. In the case of inconsistency between the two cardiologists, a third interventional cardiologist's assessment was wanted. The Thrombolysis in MI (TIMI) thrombus grade was calculated for each patient from the diagnostic angiographic images taken before PCI. Thrombus burden was quantified into five grades based on the classification of Gibson et al.[9]. High thrombus burden (HTB) was defined as TIMI thrombus grades 4 and 5 calculated according to the TIMI thrombus grading scale.

The study population was divided into two groups according to their TIMI thrombus grade: low thrombus burden (LTB) (TIMI 0-3, n=113) and HTB (TIMI 4 and 5, n=227).

Statistical Analysis

All the data were analyzed using the SPSS 22.0 Statistical Package Program for Windows (SPSS; IBM, Armonk, New York, USA). A Kolmogorov-Smirnov test was used for assessing the normality of distribution. Continuous variables were presented as mean ± standard deviation and median (interquartile ranges) and categorical variables as the number of patients and percentages. A comparison between groups was made with a Student's t-test for normally distributed variables and a Mann-Whitney U test for variables without normal distribution. Categorical data from both groups were compared using the χ^2 or Fisher's exact test.

The ability of the DAPT score to predict HTB was evaluated by receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) values. The cut-off value was calculated according to the Youden index. A value of $p<0.05$ (using a two-sided test) was set as statistically significant.

Univariate and multivariate logistic regression analyses were used to evaluate the independent predictors of HTB. Variables displaying $p<0.05$ in the univariate analysis were used in a multivariate logistic regression analysis.

Results

A total of 360 patients admitted with AMI who underwent CAG constituted the final study population. There were 133 patients (36.9%) in the LTB group and 227 patients (63.1%) in the HTB group. The baseline demographic and clinical characteristics of the study groups are shown in Table 1. The mean age was 61 (29-92) years, and most study group patients (78%) were male. There were no differences between the two groups concerning age and gender. Patients with HTB had significantly a higher DAPT score (p=0.010), smoking (p=0.020) and lower LVEF (p=0.015) compared with LTB patients. There were no significant differences between the study groups in terms of the systolic blood pressure and heart rate.

There were no significant differences between the study groups with respect to the history of DM, hypertension, hyperlipidemia, CHF, peripheral arterial disease and previous cerebrovascular accident. However, compared to the patients with HTB, those with LTB had a higher prevalence of known coronary artery disease (p=0.002).

There were 141 (39.2%) patients with STEMI and 219 (60.8%) patients with NSTEMI. Patients with HTB had a significantly higher STEMI proportion (p<0.001) and lower NSTEMI proportion (p<0.001) compared with LTB patients.

There were no significant differences between the study groups in medications at discharge, except for aspirin + tikagrelor and aspirin + clopidogrel. The ratio of aspirin + clopidogrel therapy prescribed at discharge was higher in the patients with LTB (p<0.001) (Table 1). In the patients with HTB, aspirin + ticagrelor was prescribed more frequently compared to the patients with LTB (p=0.001).

The fasting blood glucose (FBG) (p=0.002), aspartate transaminase (p<0.001), alanine aminotransferase

Table 1. Comparison of low thrombus burden and high thrombus burden groups according to the baseline demographics, clinical characteristics, and medications

	All groups (n=360)	LTB (n=133)	HTB (n=227)	p-value
Age (years)	61 (29-92)	62 (33-92)	60 (29-91)	0.162
Male, n (%)	284 (78.9)	99 (74.4)	185 (81.5)	0.113
DAPT score	2 (-1-6)	2 (-1-5)	2 (-1-6)	**0.010**
Smoking, n (%)	93 (25.8)	25 (18.8)	68 (30)	**0.020**
LVEF, %	45 (15-65)	46 (20-65)	45 (15-65)	**0.015**
SBP, mmHg	130 (65-180)	130 (70-170)	130 (65-180)	0.072
Heart rate, BPM	76 (38-140)	76 (43-140)	76 (38-132)	0.871
Diabetes mellitus, n (%)	179 (49.7)	61 (45.9)	118 (52)	0.262
Hypertension, n (%)	201 (55.8)	72 (54.1)	129 (56.8)	0.619
Hyperlipidemia, n (%)	146 (40.6)	53 (39.8)	93 (41)	0.835
Previous CVA, n (%)	20 (5.6)	10 (7.5)	10 (4.4)	0.813
Known CAD, n (%)	148 (41.1)	69 (51.9)	79 (34.8)	**0.002**
History of CHF, n (%)	102 (28.3)	31 (23.3)	71 (31.3)	0.105
History of PAD, n (%)	21 (16.9)	7 (15.2)	14 (17.9)	0.695
Admission diagnosis, n (%)				
STEMI	141 (39.2)	25 (18.8)	116 (51.1)	**<0.001**
NSTEMI	219 (60.8)	108 (81.2)	111 (48.9)	**<0.001**
Medications at discharge, n (%)				
Aspirin + Clopidogrel	137 (38.1)	67 (50.4)	70 (30.8)	**<0.001**
Aspirin + Ticagrelor	200 (55.6)	59 (44.4)	141 (52.1)	**0.001**
Aspirin + Prasugrel	14 (3.9)	4 (3.0)	10 (4.4)	0.585
Beta-blocker	330 (91.7)	124 (93.2)	206 (90.7)	0.410
ACEIs or ARBs	319 (88.6)	123 (92.5)	196 (86.3)	0.077
Spironolactone	87 (24,2)	31 (23,3)	56 (24,7)	0.771
Statins	335 (93,1)	124 (93,2)	211 (93)	0.919
Diuretics	83 (23,1)	28 (21,1)	55 (24,2)	0.490

LTB: Low thrombus burden, HTB: High thrombus burden, DAPT: Dual antiplatelet treatment, LVEF: Left ventricular ejection fraction, SBP: Systolic blood pressure, CVA: Cerebral vascular accident, CAD: Coronary artery disease, CHF: Chronic heart failure, PAD: Peripheral arterial disease, STEMI: ST elevation myocardial infarction, NSTEMI: Non-ST elevation myocardial infarction, ACEI: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers (p=0.029), low-density lipoprotein-cholesterol (LDL-C) (p=0.013), white blood cell (WBC) counts (p<0.001), neutrophil counts (p<0.001) and hemoglobin levels (p=0.012) were significantly higher in patients with HTB as shown in Table 2.

There were no significant differences between the study groups regarding the proportions of stent diameter <3 mm, proportions of 1 vessel disease and 3 vessel disease and proportions of by-pass graft disease. However, the patients with HTB had significantly higher proportions of 2 vessel disease (p=0.021) compared with LTB patients (Table 3).

The ability of the DAPT score to predict the HTB was evaluated by ROC curve analysis. The AUC value of this analysis is presented in Figure 1 [AUC=0.579, 95% confidence interval (CI)=0.520-0.638, p=0.012]. The cut-off value of the DAPT score for predicting the HTB was 2 (with a sensitivity of 67.8%, specificity =69.4%) according to the Youden index.

Univariate regression analysis demonstrated that the DAPT score, smoking, STEMI, increased FBG levels, reduced LVEF, increased LDL-C levels, increased WBC levels and increased neutrophil levels were significantly associated with the HTB, as shown in Table 4.

Table 2. Comparison of low thrombus burden and high thrombus burden groups according to the laboratory characteristics

	All groups (n=360)	LTB (n=133)	HTB (n=227)	p-value
FBG (mg/dL)	119 (48-576)	109.5 (66-576)	129 (48-371)	**0.002**
Creatinine (mg/dL)	0.8 (0-6.91)	0.8 (0.4-2.9)	0.86 (0-6.91)	0.139
eGFR (mL/min/1.73 m^2)	91 (7-137)	89 (27-137)	92 (7-127)	0.973
Albumin (g/dL)	41 (3.7-55)	41 (3.9-55)	42 (3.7-54)	0.213
AST	32 (2-627)	27 (8-627)	36 (2-553)	**<0.001**
ALT	26 (6-326)	23.5 (6-326)	27 (8-128)	**0.029**
Total cholesterol (mg/dL)	176 (75-412)	168 (75-374)	180 (84-412)	0.108
Triglycerides (mg/dL)	118 (34-2179)	120.5 (34-968)	116 (37-2179)	0.601
HDL-C (mg/dL)	35 (10-72)	36 (21-72)	34 (10-67)	0.142
LDL-C (mg/dL)	112 (15-277)	104 (15-188)	116 (16-277)	**0.013**
WBC (×10^3/μL)	9.96 (1-31)	9,305 (1-31)	10.6 (4.69-24.18)	**<0.001**
Neutrophil (×10^3/μL)	7 (0.51-76.4)	6,265 (0.51-29)	7.58 (1.24-76.4)	**<0.001**
Lymphocyte (×10^3/μL)	1,88 (1.85-2.04)	1.85 (1.75-2.04)	1.89 (1.85-2.09)	0.745
Hemoglobin (mg/dL)	14.2 (7.9-21)	13.8 (8.5-17.8)	14.4 (7.9-21)	**0.012**
Platelet (×10^3/μL)	255 (71-660)	251.5 (71-611)	256 (109-660)	0.503
CRP	15.33 (10.2)	17.14 (10.9)	14.20 (10.5)	0.995

LTB: Low thrombus burden, HTB: High thrombus burden, FBG: Fasting blood glucose, eGFR: Estimated glomerular filtration rate, AST: Aspartate transaminase, ALT: Alanine transaminase, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, WBC: White blood cell, CRP: C-reactive protein

Table 3. Comparison of angiographic data characteristics of low thrombus burden and high thrombus burden groups

	All groups (n=360)	LTB (n=133)	HTB (n=227)	p-value
Stent diameter <3 cm	114 (31.7)	41 (30.8)	73 (32.2)	0.793
Extension of CAD				
1 Vessel disease	249 (69.7)	96 (73.3)	153 (67.7)	0.268
2 Vessel disease	69 (19.3)	17 (13)	52 (23)	0.021
3 Vessel disease	24 (6.7)	10 (7.6)	14 (6.2)	0.663
By-pass graft disease	18 (11.2)	5 (8.8)	13 (12.5)	0.473

LTB: Low thrombus burden, HTB: High thrombus burden, CAD: Coronary artery disease

On multivariate analysis, the DAPT score [Odds ratio (OR): 1,245, 95% CI: 1,009-1,537; p=0.041], STEMI (OR: 4,412, 95% CI: 2,497-7,795; p<0.001), increased FBG (OR: 1,005, 95% CI: 1,001-1,008; p=0.015) and increased LDL-C levels (OR: 1,007, 95% CI: 1,000-1,014; p=0.039) were found as independent predictors of the HTB when DAPT score was analyzed as a continuous variable (Table 5).

Discussion

The main findings of this study were as follows: the patients with HTB had a higher DAPT score compared to with patients with LTB. DAPT score ≥2 had a sensitivity of 67.8%, a specificity of 69.4% and an AUC of 0.579 for predicting HTB. The DAPT score, STEMI, increased FBG levels and increased LDL-C levels were found to be significant independent predictors of HTB.

Table 4. Univariate logistic regression analysis for prediction of high thrombus burden

	Odds ratio (95% CI)	p-value
DAPT	1,302 (1,099-1,543)	**<0.002**
Smoking	1,848 (1,099-3,106)	**0.021**
STEMI	4,515 (2,719-7,495)	**<0.001**
Glucose	1,004 (1,001-1,007)	**0.011**
LVEF	0.978 (0.951-0.994)	**0.011**
CRP	1,024 (0.986-1,063)	0.390
Albumin	0.997 (0.989-1,004)	0.485
Urea	1,002 (0.989-1,015)	0.766
Creatinine	1,087 (0.654-1,805)	0.749
TC	1,003 (0.998-1,009)	0.189
TG	1,000 (0.999-1,001)	0.989
HDL-C	0.981 (0.956-1,005)	0.123
LDL-C	1,007 (1,001-1,014)	**0.016**
WBC	1,122 (1,047-1.202)	**0.001**
Neutrophil	1,212 (1,045-1,203)	**0.001**
Lymphocyte	1,101 (0.866-1,401)	0.432

STEMI: ST-segment elevation myocardial ınfarction, LVEF: Left ventricular ejection fraction, CRP: C-reactive protein, TC: Total cholesterol, TG: Triglyceride, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, WBC: White blood cell

Coronary atherosclerotic plaque rupture or erosion provokes thrombocyte aggregation and activation of coagulation, causing the formation of thrombus that leads to AMI[10]. A HTB has been connected with increased

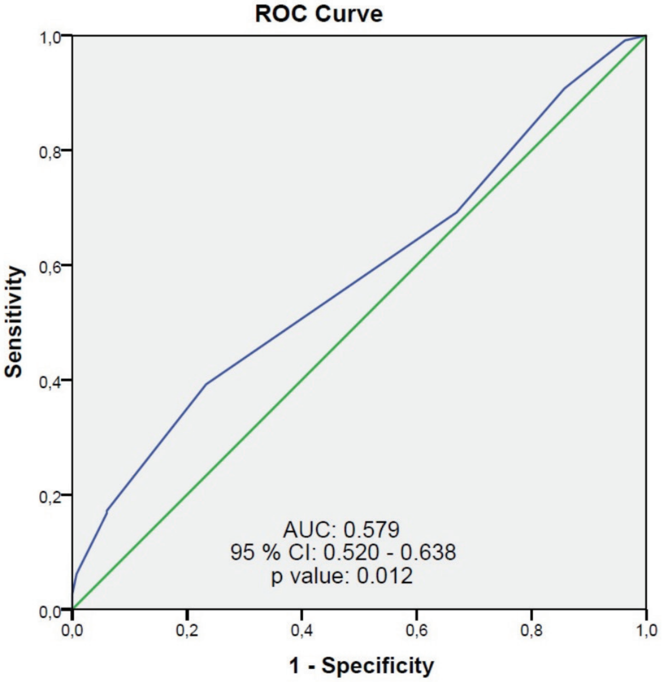

Figure 1. Receiver operating characteristics curve analysis of DAPT score in predicting high thrombus burden

DAPT: Dual antiplatelet treatment, AUC: Area under the curve, CI: Confidence interval

Table 5. Multivariate logistic regression analysis for prediction of high TIMI thrombus burden

	Odds ratio (95% CI)	p-value
DAPT	1,245 (1,009-1,537)	**0.041**
Smoking	1,759 (0.927-3.338)	0.084
STEMI	4,412 (2,497-7,795)	**<0.001**
Glucose	1,005 (1,001-1,008)	**0.015**
LVEF	0.996 (0.970-,1,023)	0.763
CRP	1,024 (0.986-1,063)	0.390
LDL-C	1,007 (1,000-1,014)	**0.039**
WBC	0.987 (0.784-1,243)	0.912
Neutrophil	1,086 (0.861-1,371)	0.486

CI: Confidence interval, DAPT: Dual antiplatelet therapy, STEMI: ST-segment elevation myocardial infarction, LVEF: Left ventricular ejection fraction, CRP: C-reactive protein, LDL-C: Low density lipoprotein cholesterol, WBC: White blood cell

1-month mortality and high rates of stent thrombosis in patients with STEMI who underwent PCI[11]. It was previously reported that the HTB was associated with impaired epicardial and myocardial perfusion, coronary micro and distal embolization, and no-reflow[12]. Distal embolization increases the risk of procedural complications, such as microvascular obstruction, no-reflow, and increased infarct size[13]. The HTB in patients with NSTEMI was an independent predictor of the 30-day adverse events and early-late stent thrombosis[14]. It is been known that a large thrombus burden is an independent predictor of death, repeat MI, and infarct-related artery intervention and stent thrombus[13-15]. Therefore, the early assessment of indicators of intracoronary thrombus burden is crucial and might lead to receiving appropriate therapy for reducing thrombus grade before and during the procedure. Previous studies have shown that C-reactive protein (CRP) levels, albumin levels, CRP to albumin ratio, neutrophil-lymphocyte ratio and baseline troponin I levels are independent predictors of HTB in patients with AMI[12,13,16].

Other recent studies have reported that the CHA_2DS_2-VASc score and PRECISE-DAPT score were established to be independently associated with intracoronary thrombus burden[13,17]. The DAPT score is a simple and practical scoring system that includes risk factors for ischemic cardiac events. The DAPT score was developed to determine the DAPT duration according to ischemia risk after PCI[18]. Besides its ability to predict ischemic risk, the association of the DAPT score with adverse cardiac events was previously demonstrated in the literature[19]. Previous studies have reported that the coronary disease severity and ischemic events are associated with a high DAPT score[20,21]. According to the DAPT study, patients with a high DAPT score had a highly calculated ischemic risk and were found to benefit from extended time DAPT[22]. It was observed in our study that the DAPT score was found to be a significant independent predictor of HTB. The DAPT score may be associated with thrombus burden, as it includes ischemic risk factors such as DM, prior MI or PCI, cigarette smoking, CHF and renal insufficiency. Compared with non-diabetic patients, erythrocyte aggregation is higher than in patients with diabetes.

Hyperglycemia stimulates thrombosis and raises the releasing of pro-inflammatory mediators by activating the inflammatory pathway[23]. It is known that DM disrupts normal endothelial function[24]. It has been reported that endothelial dysfunction is associated with HTB[25]. In our study, in patients with HTB, FBG was higher compared to patients with LTB. Additionally, in our study, increased glucose levels were demonstrated to be an independent predictor of HTB in patients with AMI. Previously, oxidized LDL-C has been shown to be associated with a HTB[26]. In our study, LDL-C levels were higher in patients with HTB and increased LDL-C levels were an independent predictor of thrombus burden.

Large intracoronary thrombus has been demonstrated in 16.4% of patients with AMI[27]. It is known that even though the existence of effective antiplatelet, the intracoronary thrombus is a risk factor for adverse cardiovascular events[12]. The duration of dual antiplatelet therapy requires a careful evaluation of the balancing between ischemia risks and bleeding risk for individual patients.

Study Limitations

Our study has several limitations. The study was designed retrospective, single-centre and the sample size was small. The absence of intravascular medical imaging modalities restricted our information on the thrombus burden size.

Conclusion

The DAPT score is a practical score system to guide DAPT duration, accounting for both ischemic risk and bleeding risk factors. Considering the increasing number of patients with acute coronary syndromes, prediction of thrombus burden through a simple and practical scoring system may be of benefit.

Ethics

Ethics Committee Approval: This study was approved by the Ankara City Hospital Ethics Committee (approval number: E1-22-2362).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Çakmak Karaaslan Ö, Design: Çakmak Karaaslan Ö, Data Collection or Processing: Çakmak Karaaslan Ö, Özilhan MO, Çöteli C, Analysis or Interpretation: Çakmak Karaaslan Ö, Özilhan MO, Çöteli C, Literature Search: Çakmak Karaaslan Ö, Maden O, Selçuk H, Selçuk MT, Writing: Çakmak Karaaslan Ö, Özilhan MO, Çöteli C.

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