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Research Articles

Research Article

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High Triglyceride Glucose Index Does Not Show the Presence and Severity of Coronary Artery Disease: A Single-Center Study

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Abstract

Objectives: The triglyceride glucose index (TyG index) calculated by fasting plasma glucose and triglycerides is associated with hypertension, diabetes and metabolic syndrome (MetS). However, the studies investigating the role of the TyG index in coronary artery disease (CAD) are limited and conflicting. In this study, we aimed to determine the role of the TyG index in the presence and severity of CAD in patients with acute coronary syndrome (ACS).

Materials and Methods: Eighty-three ACS patients (mean age: 64.64±12.79 years; male gender, 65%) and 50 control subjects with normal coronary arteries (58.50±12.28 years, male, 56%) were analyzed, retrospectively. The severity of CAD was evaluated by Gensini and SYNTAX I scores and $p < 0.05$ was considered statistically significant.

Results: The TyG index did not differ significantly between ACS patients and controls (8.97±0.72 vs. 9.06±0.72, $p=0.533$). There was no correlation between the TyG index with SYNTAX and Gensini scores. In addition, TyG index was similar in subgroup analysis of ACS patients ($p>0.05$). When the subjects were divided according to the TyG index, those with high TyG index had a higher incidence of hypertension, diabetes, and lipid parameters deterioration ($p<0.05$).

Conclusion: TyG index does not indicate the presence and severity of CAD but may be closely related to dysmetabolic conditions that predispose to CAD.

Keywords: Cardiometabolic disorders, coronary artery disease, insulin resistance, triglyceride glucose index

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Introduction

Cardiovascular disease (CVD) is still among the leading causes of morbidity and mortality[1]. One of the factors that play an important role in CVD is insulin resistance (IR) related to cardiovascular risk factors such as hyperglycemia, dyslipidemia, and hypertension. The studies investigating the effects of IR on CVD have claimed that IR may accelerate atherogenesis by vascular occlusion, inflammation and thrombosis due to the disruption of insulin signal at the cellular level even in the absence of hyperglycemia[2].

Today, a simple and inexpensive approach, the triglyceride glucose index (TyG index) derived from fasting plasma glucose and triglycerides is preferred for indirect evaluation of IR[3]. Recent studies have shown that the TyG index is associated with metabolic syndrome (MetS), arterial stiffness, carotid atherosclerosis, and coronary artery calcification (CAC)[4]. However, limited studies have reported the association of the TyG index with the presence and severity of CAD. Therefore, we aimed to evaluate the role of the TyG index in the diagnosis and progression of CAD in this study.

Materials and Methods

Study Population

In this retrospective study, we reviewed the medical records of 227 consecutive patients who underwent coronary angiography in Pamukkale University Cardiology Department between March 2020 and August 2020. The subjects diagnosed with acute coronary syndrome (ACS) consisting of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UA) were included in the patient group. The subjects with a history of angina or equivalent symptoms or a history of positive/suspicious stress test but showing normal coronary arteries during coronary angiography were determined as the control group.

Cardiomyopathies, cerebrovascular diseases, acute or chronic infections, malignancies, autoimmune diseases, severe kidney disfunction and severe liver disease were defined as exclusion criteria and finally, the study was performed with 133 subjects.

This study was approved by our institutional ethics committee in accordance with the Declaration of Helsinki (Pamukkale University Ethics Committee, date: 27/10/2020, protocol no: 020/70506). The requirement for informed consent was waived due to the retrospective design of the study.

The basic characteristics of the subjects such as age, gender, smoking, medication and laboratory parameters were analyzed retrospectively. The records obtained from fasting venous blood samples including glucose, total cholesterol, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), creatinine, C-reactive protein (CRP) and hemogram parameters were examined. The TyG index was calculated by the formula Ln [fasting triglycerides (mg/dL) x fasting blood glucose (mg/dL)/2][5]. Angiographic data obtained from cardiac catheterization laboratory records were randomly analyzed by at least two experienced clinicians who were blind to the study protocol. The left ventricular ejection fraction (LVEF) calculated by the modified Simpson method was rescanned using the hospital database. The diagnosis of acute myocardial infarction (AMI) including STEMI and NSTEMI was determined based on ESC criteria[6]. AMI was defined as elevated myocardial necrosis markers greater than the upper limit of the normal range, with either ischemic symptoms or changes in electrocardiographic or non-invasive stress images indicating ischemia. UA was defined as myocardial ischemia at rest or with minimal exertion, in the absence of myocardial necrosis. Hypertension was defined as a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg, or use of antihypertensive drugs[7]. Diabetes was defined as a fasting serum glucose level ≥126 mg/dL, HbA1c ≥6.5% or being under treatment[8].

CAD Severity Scores

Coronary lesion severity was determined using the SYNTAX I and Gensini scores. SYNTAX I score was

calculated for stenosis diameter of 50% or greater in vessels of 1.5 mm or more in diameter and the final online updated version (2.11) was used (www.syntaxscore.com[9]. The Gensini score was calculated by assigning a severity score to each coronary lesion according to the degree of narrowing and geographical importance (stenosis of 25%, 50%, 75%, 90%, and 99%, and total occlusion were given as Gensini scores of 1, 2, 4, 8, 16, and 32 points, respectively; the importance of its localization, left anterior descending coronary artery (LAD)×2.5; the proximal segment of the circumflex artery (LCX)×2.5; the mid-segment of the LAD×1.5; the right coronary artery (RCA), the distal segment of the LAD, the posterolateral artery and the obtuse marginal artery×1; and others×0.5). The total score was equal to the sum of the stenosis score and location score[10].

Statistical Analysis

All data were analyzed using SPSS v.17.0 for Windows (SPSS, Inc., Chicago, Ill., USA). Categorical variables were presented as frequencies and percentages, continuous variables were expressed as means ± standard deviation. Normal distribution was tested using the Kolmogorov-Smirnov test. A Student's t-test or Mann-Whitney U test was performed to compare the continuous variables based on the normality distribution. Correlation analysis was performed with the Spearman's coefficient of correlation. Categorical values were compared by using χ^2 test and $p<0.05$ was considered statistically significant.

Results

The clinical data of the study subjects are summarized in Table 1. Age, LVEF, HbA1c and white blood cells (WBC) differed significantly between the groups. However, there was no significant difference in hypertension and diabetes incidence, smoking, fasting glucose, creatinine, hemogram, CRP and lipid parameters. Additionally, the TyG index and TG/HDL-C did not differ significantly between the groups (TyG index, 8.97±0.72 vs 9.06±0.72, p=0.533; TG/HDL-C, 3.64±2.36 vs 3.99±2.23, p=0.395).

In the comparison based on the median TyG index, the TyG index was calculated as 8.46±0.39 and 9.56±0.51 in those with low and high TyG index, respectively ($p<0.001$). The subjects with high TyG index had an increased incidence of hypertension and diabetes, a high fasting glucose, HbA1c, total cholesterol, TG and TG/HDL-C ratio. However, HDL-C levels were significantly lower in this group ($p<0.05$) (Table 1).

In the ACS subgroup, there was no significant difference in TyG index and the ratio of patients with a high TyG index. Patients with UA had lower Gensini and SYNTAX I scores, and the patients with NSTEMI showed a higher SYNTAX I score. There was no significant difference in CAD severity scores in patients with and without STEMI (Table 2). In the correlation analysis, TyG index had a significant relationship with HbA1c, total cholesterol, HDL-C and TG/HDL-C, but there was no correlation between the TyG index and CAD severity scores (Table 3).

Discussion

In this study, we investigated the relationship between the TyG index and the presence and severity of CAD. We found that increased TyG index was more closely related to MetS components and that TyG index did not play an important role in CAD diagnosis and progression.

The researchers agree that IR contributes to plaque progression in atherogenesis by inducing apoptosis of macrophage, endolytic cells, and smooth muscle cells. However, the results of human studies on atherogenesis are inconsistent[11]. In a study evaluating IR with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), high IR was associated with increased CAC in Japanese men, but in another study, no association between HOMA-IR and CAC was observed in patients without clinical signs of CAD[12,13]. Recently, the role of the TyG index in CVD has been investigated. In one study, TyG index was an independent predictor of cardiovascular event risk in a healthy population[14]. In another study, Kim et al.[15] showed a high TyG index in a healthy population

Table 1. Baseline characteristics of subjects

Based on ACS presence	ACS group (n=83)	Control group (n=50)	p
Age (years)	64.64±12.79	58.50±12.28	0.007
Males, n (%)	54 (65)	28 (56)	0.298
Hypertension, n (%)	42 (51)	26 (52)	0.876
Diabetes mellitus, n (%)	28 (34)	15 (30)	0.656
Current smoking, n (%)	28 (34)	14(28)	0.475
LVEF (%)	47.81±9.87	53.66±9.52	0.001
Fasting glucose (mg/dL)	147.13±71.18	131.76±70.77	0.229
HbA1c (%)	7.46±1.35	9.71±2.30	0.004
Creatinine (mg/dL)	0.99±0.31	1.00±0.162	0.193
TChol (mg/dL)	169.66±33.60	181.74±40.58	0.066
LDL-C (mg/dL)	101.54±31.34	105.04±34.07	0.547
HDL-C (mg/dL)	41.06±10.11	43.76±11.34	0.157
TG (mg/dL)	160.08±72.47	135.24±74.35	0.062
Hemoglobin (g/dL)	12.97±1.96	15.21±11.14	0.083
WBC (cells/μL)	10.29±3.76	9.02±0.91	0.043
CRP (mg/dL)	5.09±16.02	3.25±5.41	0.434
TyG index	8.97±0.72	9.06±0.72	0.533
TG/HDL-C	3.64±2.36	3.99±2.23	0.395
Based on median TyG index	**Low, (n=67) (<9.01)**	**High, (n=66) (>9.01)**	**p-value**
Age (years)	62.46±14.32	62.20±11.40	0.906
Males, n (%)	45 (67)	37 (56)	0.188
Hypertension, n (%)	27 (40)	41 (62)	0.012
Diabetes mellitus, n (%)	9 (13)	34 (52)	<0.001
Current smoking, n (%)	26 (39)	16 (24)	0.071
LVEF (%)	51.25±9.85	48.74±10.29	0.153
Fasting glucose (mg/dL)	109.42±22.76	173.77±87.38	<0.001
HbA1c (%)	6.24±0.74	8.60±1.89	0.012
Creatinine (mg/dL)	1.12±1.04	1.10±1.04	0.406
TChol (mg/dL)	167.70±35.66	180.80±36.83	0.039
LDL-C (mg/dL)	103.49±31.40	102.21±33.44	0.820
HDL-C (mg/dL)	44.58±11.16	39.53±9.49	0.006
TG (mg/dL)	95.37±32.06	194.53±71.81	<0.001
Hemoglobin (g/dL)	14.17±10.11	13.45±1.36	0.568
WBC (cells/μL)	9.55±3.85	10.08±3.13	0.389
CRP (mg/dL)	5.74±17.85	3.03±4.49	0.233
TyG index	8.46±0.39	9.56±0.51	<0.001
TG/HDL-C	2.33±1.08	5.23±2.32	<0.001

LVEF: Left ventricular ejection fraction, TChol: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglycerides, WBC: White blood cells, CRP: C-reactive protein, TyG index: Triglyceride glucose index, ACS: Acute coronary syndrome, n: Number

Table 2. The clinic and angiographic data according to the presentation of acute coronary syndrome

Variables	**STEMI (n=26)**	**NSTEMI + UA (n=57)**	**p**
TyG index	8.75±0.61	9.08±0.74	0.055
TG/HDL-C	2.75±1.61	4.04±2.55	0.020
GENSINI	61.29±47.64	52.96±46.54	0.455
SYNTAX	20.98±10.40	22.83±13.41	0.535
High TyG index, n (%)	10 (39)	29 (51)	0.493
Variables	**NSTEMI (n= 38)**	**STEMI+ UA (n=45)**	**p**
TyG index	9.14±0.71	8.84±0.70	0.554
TG/HDL-C	4.05±2.26	3.29±2.41	0.147
GENSINI	65.09±47.56	47.53±45.03	0.088
SYNTAX	25.72±12.56	19.32±11.83	0.019
High TyG index, n (%)	20 (52)	19 (42)	0.344
Variables	**UA (n=19)**	**STEMI + NSTEMI (n=64)**	**p**
TyG index	8.95±0.80	8.98±0.70	0.873
TG /HDL-C	4.03±3.11	3.52±2.11	0.416
GENSINI	28.71±34.03	63.55±47.25	0.004
SYNTAX	17.05±13.51	23.80±11.88	0.038
High TyG index, n (%)	9 (46)	30 (47)	0.97

TyG index: Triglyceride glucose index, STEMI: ST-elevation myocardial infarction, NSTEMI: Non-ST-elevation myocardial infarction, UA: Unstable angina pectoris, n: Number

Table 3. Correlation analysis

TyG index	**R**	**p-value**
Age	0.044	0.616
LVEF	-0.060	0.490
HbA1c	0.742	<0.001
Creatinine	-0.015	0.865
TChol	0.282	0.001
LDL-C	0.034	0.627
HDL-C	-0.227	0.009
Hemoglobin	-0.016	0.856
WBC	0.167	0,055
CRP	-0.041	0.636
TG/HDL-C	0.706	<0.001
Gensini	0.902	0.406
SYNTAX I	0.201	0.068

TyG index: Triglyceride glucose index, LVEF: Left ventricular ejection fraction, TChol: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglycerides, WBC: White blood cells, CRP: C-reactive protein

with increased CAC scores. Unlike these studies, there was no significant difference in TyG index between patients with and without ACS in our study. However, our study population consisted of patients with ACS and symptomatic subjects with at least one cardiometabolic risk factor and a high probability of CAD due to positive or suspected ischemia in non-invasive stress test. Also, in a study involving diabetic and non-diabetic patients, a high TyG index was associated with an increased risk of CAD only in healthy subjects, not in diabetic patients. Based on this study result, the importance of glucose control in diabetic patients was highlighted. It has also been claimed that atherogenic dyslipidemia in healthy subjects may affect subclinical atherosclerosis but chronic hyperglycemia exposure may be more effective in the development of atherosclerosis in diabetic patients[16]. In another study, Vega et al.[17] also suggested that the TyG index may be a predictor of diabetes, which is a component of MetS rather than CVD. Also, the drug use may cause

different study results. Da Silva et al.[18] showed that the TyG index increased in symptomatic patients with at least one risk factor compared to CAD patients under treatment and claimed that this unexpected result may be due to uncontrollable cardiovascular risk factors in symptomatic patients. The higher HbA1c levels in control subjects due to inadequate therapy or lack of diabetes diagnosis in our study confirm the da Silva et al.'s[18] study and this may eliminate the significant difference in the TyG index in our groups. In addition, visceral fat distribution, body mass index, gender, ethnicity, age and the prolonged exposure to cardiometabolic risk factors may alter the study results.

When we divided the subjects based on the median TyG index, we found that TyG index was significantly associated with hypertension, diabetes, total cholesterol, HbA1c and HDL-C predisposing to MetS. The TyG index was also correlated with TG/HDL-C, another parameter indicating IR. The correlation between the TyG index and MetS components was clearly demonstrated in a study similar to ours[18].

Few studies have investigated the role of TyG index in determining the CAD severity. In a study, the TyG index increased in patients with a high SYNTAX I score on coronary angiography[19]. On the contrary, we could not find any relationship of TyG index with SYNTAX I and GENSINI scores. These different results of studies may be due to heterogeneity of age and gender distribution, the differences in clinical characteristics, study design, median TyG index, ethnic diversity and cardiovascular risk profiles of study populations. Also, dynamic changes in the TyG index or duration of exposure to dysmetabolic conditions may better determine the CAD severity than the presence of dysmetabolic conditions or a high TyG index. In addition, we could not find any difference in the TyG index of ACS subgroups. Similar to our study, a study did not show the relationship between the TyG index and SYNTAX I in ACS subgroups[20]. However, NSTEMI patients in our study had a higher SYNTAX I score than the other subgroups. The higher SYNTAX I score in NSTEMI patients may be explained by the advanced age of NSTEMI patients, the presence of more comorbidities and longer exposure to cardiometabolic disorders, as shown in previous studies[21].

Study Limitations

Our study had some limitations. This study was retrospective and single-center study. The study results may not be generalized to whole population due to the relatively small sample size. Other limitations of the study were that TG and glucose levels were measured once, and body mass index or waist circumference and dietary habits were not recorded. In addition, the basal insulin levels were not measured olarak so the association between the TyG index and HOMA-IR was not evaluated. Finally, we could not ignore the effects of medication on study results.

Conclusion

TyG index may be more closely related to cardiometabolic disorders predisposing to CAD. Therefore, the TyG index should be used as a predictor in determining the cardiovascular risk profile rather than the diagnosis and progression of CAD. In addition, the TyG index may be used to determine appropriate therapy strategies in the control of cardiovascular risk factors. However, large multi-center studies are needed to evaluate the role of the TyG index in CAD.

Ethics

Ethics Committee Approval: This study was approved by Pamukkale University Faculty of Medicine Hospital Ethics Review Board in accordance with the Declaration of Helsinki (27.10.2020, Protocol No: 020/70506)

Informed Consent: The requirement for informed consent was waived due to the retrospective design of the study.

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Authorship Contributions

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Telemedicine in Cardiology Outpatient Clinic: First Experience from a Tertiary Medical Center During the COVID-19 Pandemic

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Abstract

Objectives: A pronounced spread of coronavirus disease-2019 (COVID-19) all over the world has led to unpredictable overfilling of medical facilities, thus opening the way for the implication of digital health. We aimed at assessing first-time experience of telemedicine (TM) in the cardiology outpatient clinic of a tertiary medical center during the pandemic.

Materials and Methods: TM was used in the cardiology outpatient clinic from April 7th to May 29th, 2020. All the patients that had applied to TM were included in the study. TM was performed by phone calls. The data written by the cardiologist telecommunicating with the patients were recorded by accessing each patient's electronic file. Assessment of TM in terms of efficacy and patient satisfaction was made in August 2020 by recalling all the patients by phone.

Results: A total of 140 patients had TM visit on the appointment day. The population was older (69±13.75) with a male predominance (53.5%). Main complaints were chest pain and high blood pressure. Twenty patients had their medical drugs rearranged. Forty-two patients were invited for face-to-face cardiac evaluation. One of them was hospitalized due to heart failure. Almost all (93.6%) were very satisfied and preferred TM instead of face-to-face outpatient clinic service in terms of easy complaint expression and easy understanding of medication rearrangement (53.6%). They stated that TM was efficient in the prevention of unnecessary hospital visits and it should continue after the pandemic as well.

Conclusion: TM is a potential alternative for continuing healthcare delivery to most of the cardiac patients during the COVID-19 pandemic. Future research comparing other digital health tools is needed to accurately assess its use in cardiological care.

Keywords: Telemedicine, COVID-19 pandemic, digital health, healthcare

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Introduction

With abrupt onset of the pandemic, steeply increasing number of patients with coronavirus disease-2019 (COVID-19) caused a great pressure on hospitals and healthcare systems. In order to respond to the rapidly increasing number of COVID-19 patients, all elective medical procedures were cancelled in hospitals and outpatient clinics were suspended to reduce the risk of contraction of the virus[1,2].

However, all cardiovascular patients pose high risk to COVID-19 infection and certainly its course could be more disastrous with higher mortality and morbidity risk[3]. Therefore, health care facilities adapted themselves by introducing digital health care in order to limit the unnecessary exposure of both the patients and health care providers to corona virus[4]. Digital health defined as "collection, sharing and manipulation of digital information to improve patient health and health care delivery" has been recently provided by telecommunication technology (telemedicine) in order to deliver health care to patients not able to be admitted to hospitals[5]. Telemedicine (TM) has proved efficient towards cardiovascular patient management with considerable good outcomes in terms of mortality and morbidity[6,7]. In the light of the aforementioned prevention modalities, TM was introduced into our cardiology outpatient clinic by the beginning of April 2020. TM, used for the first time in our cardiology department, brought up multiple questions in terms of applicability and efficiency towards patients' management of cardiovascular diseases. In addition, there is a blank in the evaluation of the new digital health modalities during the pandemic period. Therefore, we aimed to accurately assess the efficiency of TM communication technology and describe the patient complaints, satisfaction, and management modalities arranged by the cardiologists towards the relevant disease in a tertiary cardiology center.

Materials and Methods

This cross-sectional study included all consecutive patients who applied to the TM outpatient service in the cardiology department of a tertiary medical center between April 7th and May 29th, 2020. Written informed consent was obtained from all patients being invited to the hospital after reopening of face-to-face cardiology outpatient clinic. The study was designed in accordance with the principles of the Declaration of Helsinki. It received approval from both the institutional ethics committee (no: 20-6T/40; date: 10.06.2020) and the Ministry of Health COVID-19 Scientific Research Oversight Committee.

Application of Telemedicine in Outpatient Cardiology Clinic

TM evaluation was conducted at the outpatient clinic until May 29th, 2020. Telephone was decided as the most appropriate tool for telecommunication. Patients applied for TM through the hospital's electronic appointment system and entered their phone numbers to the system. Demographic features, complaints, medical history, laboratory tests, hospitalization, and treatment arrangements made by the attending cardiologist during telecommunication were retrospectively assessed by examining each patient's electronic file.

Telemedicine Efficacy from a Patient's Point of View

After reopening of face-to-face cardiology outpatient clinic, the same patients were recalled by a dedicated nurse to assess their satisfaction towards TM and to provide information about nutrition, physical activity status, and medication adherence change during the pandemic (Figure). All patients were kindly requested to reply by "Yes" or "No" for a couple of questions regarding the efficacy, satisfaction, advantages and disadvantages of TM implicated for the first time in our cardiology clinic (Supplementary Table 1). A 7-item questionnaire was formed by an investigator (E.S.) and one nurse (N.M.A.) primarily experiencing TM. Phone calls were conducted in a simple and feasible way that would not bother the patient, not extend the telephone communication time and easily give sincere answers.

Figure. Dedicated nurse recalling the patients from the cardiology outpatient clinic for the assessment of telemedicine efficacy (01.08.2020)

Statistical Analysis

All the data were analyzed by the SPSS 25 software. The suitability of normal distribution of numerical variables was analyzed by the Shapiro-Wilk ($n<50$) Kolmogorv-Smirnov ($n\geq50$) test. Numerical variables were given as mean ± standard deviation with minimal and maximal ranges. Categorical variables were presented as numbers and percentage. The relation of patient reported satisfaction was analyzed with descriptive features such as age, gender and complaints. Independent two sample t-test was used for numerical variables comparison. Categorical variables were evaluated with the chi-square test. Correlation analysis between numerical variables was done with the Spearman rank test. A p-value of <0.05 (two-sided) was accepted statistically significant.

Results

Demographic Characteristics of Study Population

Demographic characteristics of the study population are shown in Table 1. In nearly two-month period, a total of 140 patients had TM evaluation on the appointment day. The population was relatively old with a mean age of 69±13.75 years and a male predominance (53.5%). During this time, 19 patients were called more than once and reassessed by TM. Interestingly 38 patients had had a COVID-19 nasal swab test. Although all tests were negative, this feature prioritized the urgent need for a remote and efficient cardiology TM service in that period. Main complaints of application were chest pain, dyspnea and high blood pressure. About half of the population (45.7%) had no complaints; instead, they had almost applied for a routine control, for electronic receipt and medication report prescription. The most common comorbidity was hypertension (HT) (57.8%) and coronary artery disease (CAD) (32.1%), followed by smoking (34.3%) and hyperlipidemia (HLP) (26.4%) as well. Regarding medication, beta blockers (45.7%) and aspirin (33.5%) were the most common used drugs before TM appointment. In addition, the rates of the use of statins, angiotensin converting enzyme inhibitor (ACE-inh), and angiotensin receptor blocker (ARB) were found in a modest rate as 25%, 27.9%, and 14.3%, respectively.

Physician Decision According to Patient Evaluation During TM

Attending physicians' decision features in accordance with the evaluation of patients during TM communication are depicted in Table 2. After evaluation, 20 patients had their medical drugs rearranged. Six of them had an increase in their drug dosage due to HT and heart failure (HF). The other 14 patients had a change in their medications mostly due to uncontrolled HT. Another important cause of change of medication was exacerbation of HF with increase in body edema and dyspnea mostly prescribing furosemide, spironolactone, metoprolol, and ramipril.

Table 1. Demographic characteristics of patients applying to cardio-telemedicine service

Evaluation of patients by telemedicine application (telephone)		**(n=140)**
Age		69±13.75
Gender	Male n (%)	75 (53.5)
	Female n (%)	65 (46.5)
Calling of patients more than once n (%)		19 (13.5)
COVID-19 PCR TEST		38 (27.1)
Positive		0
Negative, n (%)		38 (27.1)
Causes of tele-medicine application, n (%)		
Chest pain		27 (19.3)
Dyspnea		23 (16.4)
High blood pressure		19 (13.5)
Palpitations		18 (12.8)
Leg edema		8 (5.7)
No complaints		64 (45.7)
Routine control		48 (34.2)
Electronic receipt prescription		7 (5)
Electronic medication report prescription		9 (6.4)
Comorbidities, n (%)		
HT		81 (57.8)
CAD		45 (32.1)
Smoking		48 (34.3)
HLP		37 (26.4)
DM		29 (20.7)
HF		27 (19.3)
Alcohol		22 (15.7)
COPD		7 (5)
Pacemaker		2 (1.4)
ICD		3 (2.1)
Medication of patients before telemedicine, n (%)		
Beta-blockers		64 (45.7)
Aspirin		47 (33.5)
ACE-inh		39 (27.9)
Statin		35 (25)
Clopidogrel		20 (14.3)
ARB		20 (14.3)

BMI: Body mass index, COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction, HT: Hypertension, CAD: Coronary artery disease, HLP: Hyperlipidemia, DM: Diabetes mellitus, HF: Heart failure, COPD: Chronic obstructive pulmonary disease, ICD: Intracardiac defibrillator, ACE-inh: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, n: Number

Forty-two patients were invited to outpatient clinic for face-to-face cardiac evaluation. They had multiple complaints such as angina, dyspnea, high blood pressure, and advanced HF symptoms. One of them was admitted due to HF decompensation. In contrast, 18 other patients were referred to other departments due to no relevant

Table 2. Physician decision according to cardio-telemedicine interrogation with the patients (n=140)

Arrangement of medical drugs, n (%)	20 (14.3)
Increase in medical drug dosage, n (%)	6 (4.3)
Metoprolol (HT)	1
Ramipril (HT)	2
Furosemide (HF)	2
Candesartan (HT)	1
Change of medical drug prescription, n (%)	14 (10)
Amlodipine (HT)	3
Olmesartan (HT)	1
Enoxaparin (AF)	1
Spironolactone (HF)	1
Apixaban. (AF)	1
Candesartan (HT)	2
Furosemide (HF)	1
Metoprolol (HF)	1
Coraspin (CAD)	1
Ramipril (HF)	1
Perindopril (HT)	1
Electronic receipt prescription, n (%)	32 (22.9)
Electronic medication report, n (%)	23 (16.4)
Further electronic appointment, n (%)	21 (15)
Further medical tests, n (%)	43 (30.7)
INR measurement	28
Echocardiography	10
Myocardial perfusion scintigraphy	5
Invitation to cardiology outpatient clinic, n (%)	42 (30)
Angina	10
Dyspnea	10
INR test	28
Arrhythmia	3
HF exacerbation	7
Hypertension	6
Hospitalization	1 (0.7)
HF decompensation	1
Referral to other departments	18 (12.9)

Diseases abbreviated in parentheses are the causes of medication change.
HT: Hypertension, CAD: Coronary artery disease, HF: Heart failure, AF: Atrial fibrillation, INR: International normalized ratio

cardiac complaints. Medical tests were mostly done for warfarin dose arrangement: International normalized ratio (INR). The others were echocardiography and myocardial scintigraphy for CAD differential diagnosis.

Evaluation of TM

All the patients that had applied to TM were recalled in August 2020 by telephone to make an accurate assessment of this new digital application in our department. The

Table 3. Evaluation of patients applying to cardio-telemedicine service during follow-up (n=140)

Frequency of outpatient clinic visits before COVID-19 pandemic, n (%)	
First time application	47 (33.6)
Once a month	26 (18.6)
Once in 3 months	15 (10.7)
Once in 6 months	24 (17.1)
Once a year	29 (20.7)
Blood pressure monitoring, n (%)	89 (63.6)
Systolic	130.33±22.18 (70-200)
Diastolic	78.95±13.83 (40-120)
Length (meter)	1.67±0.079
Weight (kilogram)	77.86±13.21
Body mass index	27.78±4.19
Impairment of nutrition status during the pandemic, n (%)	60 (42.9)
Alteration of nutrition habit during the pandemic, n (%)	
Consume more fruits	24 (17.1)
Consume more junk foods (crisps, pastry, beer nuts, biscuits etc.)	37 (26.4)
Frequent meals (more than 3 times)	25 (17.9)
Eating more in the late evening while watching TV	39 (27.9)
Increase in salt consumption	16 (11.4)
Physical exercise habit during the pandemic, n (%)	
Every day	11 (7.9)
Frequently	11 (7.9)
No exercise	119 (85)
Decrease in physical activity during the pandemic, n (%)	68 (48.6)
Medication adherence during the pandemic, n (%)	
More adherent	21 (15)
No change	98 (70)
Not adherent	20 (14.3)

COVID-19: Coronavirus disease-2019, n: Number

relevant features are shown in Table 3 and Table 4. They were interrogated and interestingly a high portion of them (33.6%) had applied for the first time to our outpatient clinic, so not having the chance to get a face-to-face cardiac evaluation. During follow-up, after rearrangement of medications, only 89 patients (63.6%) had their blood pressure continuously monitored. The mean systolic and diastolic blood pressures were found modestly normalized in a range of 130.33±22.18 mmHg and 78.95±13.83 mmHg, respectively. On the other hand, about half of patients (42.9%) had an impairment regarding physical and nutritional status during the pandemic period, showing modestly increased body mass index in an overweight range (27.78±4.19). They began to eat more than 3 meals a day with the consumption of more junk foods such as crisps, pastry, beer nuts etc. especially in the late evening hours. A high portion (85%) as well did not make any exercise at all during that period and about half of the interrogated patients (48.6%) expressed a decrease in physical activity. There was no evident change in medication adherence in only 20 patients having some challenges remembering the time

Table 4. Evaluation of cardio-telemedicine by patients (n=140)

Prevention of unnecessary hospital application, n (%)	135 (96.4)
Hospital appointment easier than before, n (%)	133 (95)
Waiting time shortened in case of hospital referral, n (%)	129 (92.1)
Easy hospital appointment through telemedicine application, n (%)	130 (92.8)
Time for cardio-telemedicine appointment (days)	2.53±1.39 (1-8)
Time of cardio-telemedicine call (minutes)	6.68±5.0 (3-20)
Difficulty in expressing the complains during cardio-telemedicine call, n (%)	2 (1.4)
Willingness for cardio-telemedicine continuation after the pandemic, n (%)	123 (87.8)
Preference of telemedicine instead of face-to-face outpatient in terms of easy complaint expression and understanding of medication rearrangement, n (%)	75 (53.6)
Satisfaction of patients from the cardio-telemedicine service, n (%)	131 (93.6)
Non-satisfaction of patients from the cardio-telemedicine service, n (%)	9 (6.4)
Cause of non-satisfaction Not referral to hospital No need for further tests	 5 4
Relation of patient reported satisfaction with demographic features Statistics	
Age	Rho: 0.042, p=0.221
Gender	p=0.692
Angina	p= 0.699
Dyspnea	p=0.078
High blood pressure	p=0.053
Palpitations	p=0.521
Asymptomatic	p=0.915
n: Number	

Supplementary Table 1. 7-item questionnaire assessing the efficacy of telemedicine (all patients were requested to answer as yes or no)

1. Were you satisfied with the TM for continuing of healthcare in the COVID-19 pandemic?
2. If no, please state the cause
3. Did the TM application prevent unnecessary hospital visit?
4. In case of hospital referral, was the time of waiting shortened?
5. Was it easy to get an appointment for TM evaluation
6. Did you have any difficulty expressing your complaints during TM call?
7. Do you prefer TM be continued after the pandemic?
8. Which service would you prefer the most in terms of easy expression of your complaints: Face-to-face or TM?
TM: Telemedicine, COVID-19: Coronavirus disease-2019

and dose of their medications. However, almost all (93.6 %) of the patients were very satisfied and preferred TM instead of face-to-face outpatient clinic service in terms of easy complaint expression and easy understanding of medication rearrangement (53.6%). Satisfaction was found to be an important feedback for this new emerging digital health care irrespective of demographic features such as age, gender and complaints. Instead, the causes of nonsatisfaction were mainly expressed by younger patients willing further tests and referral to hospital.

Most of the patients agreed with the idea that the new digital health tool, TM, was efficient in the prevention of unnecessary hospital application, provided easier hospital appointment than before the pandemic, shortened time of waiting in case of hospital referral and it should continue after the pandemic as well. In addition, they all took attention to the time (6.68±5.0 minutes) spent during TM communication, which was used in a sufficient and efficient way.

Discussion

Implication of Telemedicine in Cardiology Outpatient Clinic

In order to prevent such steep increase in infection transmission of COVID-19 in both the patients and healthcare providers, remote control via digital health tools should be urgently implemented in the routine of outpatient clinic services[8]. Although TM has been considered by the World Health Organization as the alternative way for remote patients uncapable of coming to the medical facilities, it has become a potential alternative in the COVID-19 era in terms of efficacy of healthcare delivery and patient satisfaction[9,10]. In the light of these lifesaving alternative ways for continuing of healthcare delivery, we experienced for the first time TM practice during the extraordinary time of COVID-19 pandemic in our cardiology outpatient clinic.

The older age of the population with multiple cardiac risk factors applying to TM showed that the new digital health system was introduced in a very appropriate time where all the patients had need for the continuation of healthcare service. Although, it was a first-time experience for us, telecommunication by telephone provided high confidence in both the patient and the physician by clearly expressing themselves. Possible causes of providing high confidence during telecommunication were empathy expressing behaviors. For instance, patients expressed that listening to them and letting them guide the conversation was one of the evident clues noticed in most of the communications. Afterwards, we had 19 patients that were called for TM evaluation more than once, a feature that provides confidence and the patient not to be felt forgotten. On the other hand, telephone contact with cardiac patients before a face-to-face examination could motivate their self-consciousness of their disease. In this way, patients can become more conscious in the self-management of their cardiac disease by monitoring of their diet, blood pressure, heart rate, body weight and glucose at home.

Management of Cardiac Diseases by Telemedicine

Studies have shown that HT can be easily and effectively managed via TM. This could eliminate the 'white coat hypertension' phenomena, thus appropriately provide the necessary dose of antihypertensive drug[11]. Indeed, our experience with TM provided efficacy in HT management with good blood pressure monitoring during follow up. Although we did not have a high number of patients with HF, a guideline-based therapy was efficiently provided and a good feedback was obtained from the patients. This simple telecommunication model for a short time was found to be in accordance with the European Society of Cardiology consensus on the role of TM in HF patients showing a good medication management and high alertness for HF exacerbation[6].

Evaluation of Nutritional and Physical Status of Study Population During the Pandemic

The high and fast rate of infection spread made people fear from going outside so almost all the patients evaluated in this study were prisoned at home for a long time. During

this period, we queried them about any change of nutritional and physical status. Although patients were acknowledged about proper diet and healthy lifestyle modification during TM service, interestingly, about 43% of them stated an impairment in their nutritional status during the pandemic. Especially, spending a long time staying at home was the leading cause to trigger consumption of more junk food such as crisps, pastry or beer nuts. The only entertainment tool was the television making them unwittingly increase the number of meals and more frequently eat in the late hours of the evening.

It has been demonstrated that older adults (>60 years of age) are at the greatest risk of mortality due to the COVID-19 disease and consequently they represent the most affected population from the measures of social isolation[12,13]. Similar to our study population, preventive measures can expose older people to an impaired nutritional status by pushing them towards overeating mostly fast foods rich in fat, sugar and salt[14]. Undernutrition as well is another challenging issue due to socioeconomic problems commonly encountered among older people, which can lead to a worse prognosis during COVID-19 disease. One of the pioneer services was the "Great Plates Delivered" program to supply three healthy meals to older people at risk for infection, which promoted awareness of fighting infection with balanced and healthy regular meal habit[15]. Moreover, a balanced and nutritious diet has been shown to be one of the keys for a better prognosis in older adults with COVID-19 disease, so the introduction of educational programs and social facilities toward promoting healthy nutrition should be encouraged[16,17].

Medical Avoidance During the Pandemic

Medical care avoidance has been demonstrated as an unacceptable cause of decreased and late acute coronary syndrome admissions during the pandemic, thus leading to increased cardiac events[18]. This is of paramount importance as most people are frightened from contracting the COVID-19 infection and so avoid seeking medical care. However, our study showed that easy implementation of TM can provide a new way for efficacious health care continuation by applying triage for patients necessitating medical assistance and as a result overcome medical avoidance.

Telemedicine Efficacy from a Patent's Point of View

Satisfaction of patients, especially older ones, with TM has been demonstrated with video visits during the COVID-19 pandemic, a very important point underscoring the truly need of seniors for healthcare delivery[19]. Similar to this largest study, our relatively old population showed high satisfaction rates irrespective of demographic factors and complaints. This promising feature can be fundamental for future implication of TM in a routine basis for cardiac patients' follow-up.

Study Limitations

Despite having a small sample size, this study demonstrated the first experience of TM implication in the beginning of the pandemic in a tertiary medical center. It could have been more sophisticated and efficacious if other tools like video communication and email feedback would have been incorporated into the digital health service. The attending physicians were not interrogated in terms of satisfaction in order to find out the practical difficulties experienced by them. As the infrastructure of medical facilities were not ready at the beginning of the pandemic, telephone was the only simple and most reachable tool in performing TM. The TM was conducted contemporarily with the onset of the lock down of the population, so we did not make any comparison with the post lock down period. In addition, lock down measures affected mostly the older people reflecting the cause of the older age of our study population. However, we did demonstrate that the older patients could effectively use the telephone for reaching medical assistance via TM. The lack of use of a validated TM efficacy questionnaire is another limitation of the study. However, as the study was conducted in the very early period of the pandemic, there were no validated questionnaires constructed for assessing the efficacy of the TM or patient satisfaction.

However, it should be highlighted that this is the first study in Turkey describing digital health TM implication during the pandemic. Therefore, it should serve as a fundamental for constructing a more sophisticated digital health system in the future of healthcare system.

Conclusion

TM is a potential alternative for continuing healthcare delivery to most of the cardiac patients necessitating rigorous follow-up during the COVID-19 pandemic. Administrative protocols with training of healthcare providers and ethical and legislative criteria are needed for future digital health introduction in routine clinical practice. All these implications should be rearranged according to specific groups of cardiac patients, especially those with arrhythmic and advanced heart failure, integrating accurate criteria for future benefit of digitalization in modern medicine.

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Ethics

Ethics Committee Approval: The study was designed in accordance with the principles of the declaration of Helsinki. It received approval from both the Institutional Ethics Committee (20-6T/40; 10.06.2020) and the Ministry of Health COVID-19 Scientific Research Oversight Committee.

Informed Consent: Informed consent was taken from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.S., Concept: E.S., M.Z., Design: E.S., M.Z., Data Collection or Processing: E.S., Analysis or Interpretation: E.S., M.K., M.Z., Literature Search: E.S., M.K., M.Z., Writing: E.S., M.K., M.Z.

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Research Article

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The Frequency of Aspirin and Clopidogrel Resistance and Related Factors in Patients Undergoing Elective Percutaneous Coronary Intervention

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Abstract

Objectives: Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor is the mainstay of antithrombotic therapy after myocardial infarction and percutaneous coronary interventions (PCI). Despite chronic oral antiplatelet therapy, many atherothrombotic events continue to occur. Several reports in the literature have shown possible relationships between residual platelet activity and clinical outcomes, raising the possibility that "resistance" to oral antiplatelet therapy may underlie such adverse events. In this study, we aimed to determine the prevalence of aspirin and clopidogrel resistance, and related factors. We also aimed to identify the predictors of reduced antiplatelet response among patients undergoing elective PCI for stable coronary artery disease (CAD).

Materials and Methods: We retrospectively included patients who underwent an elective PCI with available aggregation inhibition test results. According to aggregation inhibition test results, patients were divided into two

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subgroups: 1-aspirin resistant/low responders and responders 2-clopidogrel resistant/low responders and responders.

Results: Totally 470 patients with aggregation inhibition test results (all 470 for clopidogrel and 464 for aspirin) were included in the study. Three hundred sixty-eight of them were male (78, 3%). The aspirin resistance group's mean age was 60.8±10.3 years, the clopidogrel resistance group's mean age was 58.89±10.1 years, and the aspirin + clopidogrel resistance group's age was 63.25±8.8 years. Overall, there were 164 patients with single (either aspirin or clopidogrel) and 16 (3%) patients with double resistance. Hypertension, statin use, and platelet count were found as independent predictors of aspirin resistance. Hyperlipidemia, gender, and leucocyte count were found as independent predictors of clopidogrel resistance.

Conclusion: 8.1% and 26.8% of stable CAD patients undergoing elective PCI showed insufficient aggregation inhibition by aspirin and clopidogrel, respectively, whereas 3% had double resistance.

Keywords: Aspirin, clopidogrel, resistance, percutaneous coronary intervention

Introduction

Cardiovascular diseases are the number one cause of mortality and morbidity globally[1]. The majority of cardiovascular diseases and their complications are of atherosclerotic origin[2]. Platelets play a major role in atherosclerotic cardiovascular disease; thus, antiplatelet therapy is the key component in treating and preventing acute and chronic coronary syndromes. Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is the mainstay of antithrombotic therapy after myocardial infarction (MI) and percutaneous coronary interventions (PCI). Antithrombotic effects of aspirin have been known for more than fifty years[3-6]. Aspirin decreases platelet aggregation by irreversibly blocking cyclooxygenase-1 mediated thromboxane A2 syntheses, a potent platelet aggregation mediator and vasoconstrictor agent[7]. P2Y12 receptor, the target of P2Y12 inhibitors, plays a key role in platelet activation and the amplification of arterial thrombus formation. The first P2Y12 inhibitor, clopidogrel, was the standard for DAPT until the newer molecules became available[8]. The newer P2Y12 inhibitors ticagrelor and prasugrel, with their fast onset action and potent antiplatelet effects and proven superiority regarding MACE (major adverse cardiac event), got a higher class of recommendation over clopidogrel in acute coronary syndrome (ACS) guidelines leaving room for the use of the latter only in patients who cannot receive or have contraindications for the others and in those receiving thrombolysis[9-11]. On the contrary, in stable coronary artery disease (CAD) patients undergoing PCI, DAPT consisting of clopidogrel and aspirin still has a class IA indication and is used in many patients[11]. As there are no randomized controlled trials investigating the use of ticagrelor or prasugrel instead of clopidogrel in stable CAD patients undergoing PCI, these agents can only be used in selected patients, e.g., in those with unsatisfactory clinical results when using clopidogrel[11]. In patients with atrial fibrillation, who undergo PCI, clopidogrel is the P2Y12 inhibitor of the triple therapy as the safety and efficacy data from randomized controlled trials (RCTs) for prasugrel and ticagrelor lack and as there are worrisome bleeding signals in registries[12,13].

Still being used in a large number of patients, as mentioned above, clopidogrel's disadvantage is its potentially variable efficacy. Despite chronic oral antiplatelet therapy, a number of atherothrombotic events continue to occur. Several reports in the literature have shown possible relationships between residual platelet activity, as measured with a variety of laboratory tests, and clinical outcomes, raising the possibility that

"resistance" to oral antiplatelet therapy may underlie such adverse events[14]. Many studies have reported antiplatelet treatment responses, but because various methods have been used in different patients, no consistent estimates of the prevalence of antiplatelet treatment resistance or its clinically significant predictors have been produced. In this study, we investigated the prevalence of aspirin and clopidogrel resistance, related factors, and the predictors of reduced antiplatelet response among patients undergoing elective PCI for stable CAD.

Materials and Methods

We retrospectively screened the patient data from January 2007 to 2009 May, as during that period, all PCI patients had a routine aggregation inhibition test 24 hours after the intervention (48 hours after the loading dose), and the treating doctor made dose/medication changes according to test results. All patients who underwent an elective PCI with an available aggregation inhibition test result were included in the study.

Resistance (hypo or non-responsiveness) is defined as "High on-treatment platelet reactivity," whereas the occurrence of a thrombotic event during therapy is defined as treatment failure[15].

Exclusion criteria: Patients on chronic DAPT, scheduled for elective PCI after an ACS, patients with hematologic and oncologic disorders, collagen disease, active infection, and chronic liver disease were not included.

Demographic data, risk factors [diabetes mellitus (DM), hypertension (HT), family history, hyperlipidemia (HL), smoking status], other comorbidities, medications [aspirin, beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACE-I/ARB), calcium channel blockers, proton pump inhibitors (PPI)] and laboratory findings, as well as indications for intervention, were recorded from patient files. Aggregation inhibition test results at post PCI 24th hour, treatment changes, and the results of control aggregation inhibition test (if any) were also recorded. According to aggregation inhibition test results, patients were analyzed in two subgroups: 1-aspirin resistant/low responders and responders 2-clopidogrel resistant/low responders and responders.

Loading dose: In our clinic, patients routinely received 300 mg clopidogrel one day prior to the elective procedure and 1x75 mg per day afterward.

Resistance: The expected on-treatment ranges were 0-300 AU for Aspirin and 0-200 AU for clopidogrel. The patients with higher levels were classified as "resistant patients" (insufficient aggregation inhibition), and other patients were classified as "normal responders," and these two groups were compared in terms of clinical and biochemical features.

Aggregation inhibition test: Aggregation inhibition by aspirin and clopidogrel was analyzed from venous blood samples obtained from antecubital vein 24 hours after the intervention (48 hours after the loading dose) by impedance aggregometry method using on the Multiplate Analyzer (Roche, Switzerland). Multiple electrode aggregometry (MEA) is a method that tests platelet function in whole blood based on whole blood impedance aggregometry. The Multiplate® has five testing areas that can be loaded with the MEA test cells, each of the test cells has two independent sensor units, which are made of two silver-coated, highly conductive copper wires. The multiplate works by measuring platelet adhesion and aggregation to these conductive wires following activation of the platelets. As aggregation increases, there is an increase in electrical impedance between the wires, which is recorded on the Multiplate® device[16]. Platelet aggregation determined by MEA is calculated from the area under the curve (AUC), which is taken from the measured electrical impedance and quantified by arbitrary aggregation units over time (AU*min). Prostaglandin E1 (PGE1) is a natural platelet inhibitor that triggers an increase in cAMP levels in the platelet. The cAMP is a so-called second messenger, i.e., an intracellular signaling

molecule. A decrease in the cAMP level in the platelet leads to platelet activation. An increase of the cAMP level counteracts platelet activation. PGE1 reagent is used in combination with adenosine diphosphate (ADP) test reagent. The addition of 20 µL PGE1 to the ADP test (9.4 nM PGE1 final concentration) induces a moderate inhibition of platelet activation in normal blood samples, but a significant increase of sensitivity of the ADP test to platelet inhibition by substances that affect platelet aggregation through ADP receptor binding is seen. Therefore, this modified test is named high-sensitive ADP test[17].

Platelet inhibition by aspirin is monitored using arachidonic acid-induced aggregometry. ADP triggers platelet activation via platelet ADP receptors. In addition, a second test is performed with the addition of PGE1, a physiological platelet inhibitor. PGE1 reduces the intracellular mobilization of calcium in platelets and thus acts synergistically to the action of clopidogrel. The use of PGE1 increased the sensitivity of the test[16].

This study was approved by the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2021-296, date:17/05/2021).

Statistical Analysis

The arithmetic mean of the data was calculated for the demographic features of the patient, and the standard deviation was calculated through the chi-square test, Mann-Whitney U test, or Fisher's exact test (mean ± standard deviation). The distribution of categorical variables was evaluated by each other. The mean of the features having any of two subtitles in terms of quantitative variables was compared with the t-test for independent groups (independent samples t-test). The correlation of two quantitative features was analyzed with the Pearson correlation coefficient. The binary logistic regression model was used as a multivariable statistical method, in which the result variable was categorized as existing/not existing. The level of significance was accepted as $p \leq 0.05$ in all analyses. SPSS for the windows 15.0 statistics package was used for the evaluation of the data.

Results

Totally 470 patients with aggregation inhibition test results (all 470 for clopidogrel and 464 for aspirin) were included in the study. Three hundred sixty-eight of them were male (n=78, 3%). The aspirin resistance group's mean age was 60.8±10.3 years, the clopidogrel resistance group's mean age was 58.89±10.1 years, and the aspirin + clopidogrel resistance group's mean age was 63.25±8.8 years. Overall, there were 164 patients with single (either aspirin or clopidogrel) and 16 (3%) patients with double resistance (both aspirin and clopidogrel).

Aspirin resistance: There were 38 patients (8,1%) with aspirin resistance. HT and HL were significantly more frequent among resistant patients, as oral antidiabetic (OAD), statin, beta-blocker, and ACE-I use. In contrast, the smoking rate was higher among normal responders (Table 1). Logistic regression analysis revealed that HT, statin use, and platelet count were independent predictors of aspirin resistance (Table 2). Aspirin resistant patients had significantly higher levels of blood urea, low density lipoprotein (LDL), CRP, and platelets. A negative correlation was detected between aspirin aggregation levels and fasting blood glucose, while C-reactive protein (CRP), leukocyte count, and platelet count had a positive correlation (Table 3).

Clopidogrel resistance: There were 126 patients (26.8%) with clopidogrel resistance. Female gender, DM, HL, and family history for ischemic heart disease were significantly more frequent among clopidogrel resistant patients, whereas the smoking rate was higher among normal responders. Body mass index (BMI), waist circumference, leucocyte count, and hemoglobulin levels were significantly higher among clopidogrel resistant groups as well as nitrate and statin use (Table 4). Independent predictors of clopidogrel resistance (CR) were HL, gender, and leucocyte count (Table 5).

Table 1. Demographic and biochemical features of the groups with and without aspirin resistance

Aspirin	ASA (-) (n=426)	ASA (+) (n=38)	p-value
Age	59.5±10.2	60.8±10.3	0.42
Gender (female) (%)	90 (21.1)	12 (31.6)	0.13
Hypertension (%)	214 (50.7)	28 (73.7)	0.007*
Diabetes mellitus (%)	114 (27)	12 (31.6)	0.54
Hyperlipidemia (%)	144 (34)	22 (57.9)	0.003*
Smoking (%)	228 (54)	14 (36.8)	0.04*
BMI (weight/height^2)	28.03±3.5	29.7±13.5	0.49
Waist circumference (cm)	97.9±11.1	99.2±15.3	0.54
Family history (%)	126 (29.6)	12 (31.6)	0.79
Fasting glucose (mg/dL)	117.8±37.0	108.2±30.4	0.14
Urea (mg/dL)	17.1±5.8	19.5±6.7	0.03*
Creatine (mg/dL)	0.9±0.1	0.9±0.2	0.26
LDL (mg/dL)	120.2±32.9	135.±57.1	0.01*
HDL (mg/dL)	43.1±9.1	44.4±7.8	0.40
Platelet (10^{e3}/uL)	216912.6±58413.1	244,823.5±58,915.6	0.008*
Leucocyte (10^{e3}/uL)	8,255.7 ±6,192.3	7,467.6±1,953.7	0.46
eGFR (mL/dk)	83.1±16.2	84.4±24.2	0.77
CRP (mg/L)	4.2±2.4	21.7±20.8	<0.001*
Hemoglobin (g/dL)	13.3±1.4	13.0±2.0	0.21
Insulin (%)	59 (13.9)	4 (10.5)	0.56
OAD (%)	77 (18.1)	10 (26.3)	0.21
CCB (%)	65 (15.3)	6 (15.8)	0.93
Nitrate use (%)	133 (31.2)	14 (36.8)	0.47
Statin use (%)	138 (32.4)	18 (47.4)	0.06
Beta blocker (%)	150 (35.2)	23 (60.5)	0.002*
ACE-i (%)	129 (30.3)	18 (47.4)	0.03*
ARB (%)	67 (15.7)	6 (15.8)	0.99
PPI (%)	85 (20.0)	6 (15.8)	0.53

*ASA: Acetylsalicylic acid, BMI: Body mass index, LDL: Low density lipoprotein, HDL: High density lipoprotein, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, PDW: Platelet distribution width, OAD: Oral antidiabetic, CCB: Calcium channel blocker, ACE-i: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blockers, PPI: Proton pump inhibitor, *p<0.05 statistically significant*

A positive correlation was found between clopidogrel aggregation level and CRP, leukocyte count, and platelet count (Table 6).

Discussion

This retrospective analysis is the first study evaluating the prevalence of antithrombotic drug resistance in patients undergoing elective PCI. We found that 8.1% and 26.8% of stable CAD patients undergoing elective PCI showed insufficient aggregation inhibition by aspirin and clopidogrel, respectively, whereas 3% had double resistance.

The difference in the measurement method we used in this study is the most important feature distinguished from other studies. In current practice, many tests are available to monitor antiplatelet therapies for patients with

Table 2. Multivariable analyses of aspirin resistance with logistic regression

	p-value	OR	95% CI
Hypertension	0.02*	2.8	1.1-7.1
Smoking	0.16	0.5	0.2-1.2
Platelet	0.02*	1.4	1.3-1.8
eGFR	0.49	1.0	0.9-1.0
Statin	0.06	2.1	0.9-4.7
BMI	0.48	0.9	0.8-1
Diabetes mellitus	0.66	0.8	0.3-2

*eGFR: Estimated glomerular filtration rate, BMI: Body mass index, *p<0.05 statistically significant, OR: Odds ratio, CI: Confidence interval*

Table 3. Correlation coefficients and p-values of aspirin aggregation level and clinical and biochemical parameters

	R	p-value
Age	0.054	0.24
BMI (weight/height^2)	-0.061	0.18
FBG (mg/dL)	-0.136	0.008*
LDL (mg/dL)	0.045	0.37
HDL (mg/dL)	-0.078	0.12
Urea (mg/dL)	0.028	0.58
Waist circumference (cm)	0.011	0.82
Creatine (mg/dL)	0.019	0.71
eGFR (mL/dk)	-0.042	0.41
CRP (mg/L)	0.488	0.01*
Hemoglobin (g/dL)	-0.51	0.32
Leucocyte (10^{e3}/uL)	0.109	0.03*
Platelet (10^{e3}/uL)	0.129	0.01*

*BMI: Body mass index, FBG: Fasting blood glucose, LDL: Low density lipoprotein, HDL: High density lipoprotein, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, *p<0.05 statistically significant, Pearson Correlation test was used for analysis*

high risk. None of the currently available platelet function assays has been sufficiently validated and standardized to monitor antiplatelet therapies. In this study, the impedance aggregometry method was used to measure aspirin and clopidogrel resistance. Platelet inhibition by aspirin is monitored using arachidonic acid-induced aggregometry. Clopidogrel is detected by its inhibition of ADP-induced aggregation. Besides, a second test is performed with the addition of PGE1 and thus acts synergistically to the action of clopidogrel. Therefore, the use of PGE1 increased the sensitivity of the test[16,17].

Literature shows that the prevalence of aspirin resistance (AR) varies between 5% and 60%, while CR has been estimated to be between 16% and 50% depending on the population, dosing, time-point of assessment, and the method used for testing aggregation levels[15,18-20].

Overall, our findings are consistent with the previous reports. Our study included stable CAD patients undergoing elective PCI and assessed aggregation inhibition levels 48 hours after clopidogrel loading (24 hours after PCI). Aspirin and clopidogrel resistance was presented in 8.1% and 26.8%, respectively. In a similar

Table 4. Demographic and biochemical features of the groups with and without clopidogrel resistance

Clopidogrel	Klop (-) (n=344)	Klop (+) (n=126)	p-value
Age	59.68±10.38	58.89±10.17	0.46
Gender (female)%	56 (16.3)	46 (36.5)	0.001*
Hypertension (%)	172 (50.3)	72 (58.1)	0.13
Diabetes mellitus (%)	80 (23.4)	46 (37.1)	0.003*
Hyperlipidemia (%)	98 (28.7)	68 (54.0)	0.001*
Smoking (%)	194 (56.7)	54 (43.5)	0.012*
BMI (weight/height²)	27.7±3.6	29.1±7.	0.01*
Waist circumference (cm)	97.1±11.0	99.9±12.2	0.029*
Family history (%)	92 (26.7)	48 (38.1)	0.017*
Fasting glucose	117.3±37.1	115.6±34.7	0.67
Urea (mg/dL)	17.6±6.2	16.5±5.2	0.08
Creatine (mg/dL)	0.9±0.1	0.8±0.1	0.13
LDL (mg/dL)	120.5±37.0	123.7±33.0	0.42
HDL (mg/dL)	43.5±9.2	42.5±8.5	0.28
Platelet count (10^{e3}/uL)	217,311.1±56,949.9	221,996.6±63,025.1	0.47
Leucocyte count (10^{e3}/uL)	7,927.0±6,072.3	8,761.0±5,460.0	0.20
eGFR (mL/dk)	84.2±17.3	81.5±16.1	0.16
CRP (mg/L)	8.6±13.2	6.6±4.8	0.60
Hemoglobin (g/dL)	13.46±1.39	13.12±1.63	0.03*
Aspirin resistance (%)	24 (7.1)	14 (11.3)	0.14
Insulin (%)	55 (16.0)	10 (7.9)	0.02*
OAD (%)	70 (20.3)	19 (15.1)	0.19
CCB (%)	55 (16.0)	18 (14.3)	0.65
Nitrate use (%)	91 (26.5)	58 (46.0)	<0.001*
Statin use (%)	98 (28.5)	60 (47.6)	<0.001*
Beta blocker (%)	121 (35.2)	56 (44.4)	0.06
ACE-i (%)	101 (29.4)	48 (38.1)	0.07
ARB (%)	53 (15.4)	22 (17.5)	0.59
PPI (%)	73 (21.2)	20 (15.9)	0.19

*BMI: Body mass index, LDL: Low density lipoprotein, HDL: High density lipoprotein, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, PDW: Platelet distribution width, OAD: Oral antidiabetic, CCB: Calcium channel blocker, ACE-i: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blockers, PPI: Proton pump inhibitor, *p<0.05 statistically significant*

but smaller series, including 151 patients taking aspirin for at least one week and clopidogrel 300 mg loading 12 to 24 hours prior to elective PCI using a modified platelet aggregometry device, 19% of patients were found to be aspirin resistant[21]. In another study using the same loading dose as in our study, Gurbel et al.[22] reported that 1/3rd of the patients was clopidogrel resistant at day 5 post-stenting by measuring ADP-induced platelet aggregation. They also showed the clopidogrel response variability by serial measurements and a resistance rate of 15% on day 30.

Table 5. Multivariable analyses of clopidogrel resistance with logistic regression

	p-value	OR	95% CI
Diabetes mellitus	0.06	1.6	0.9-2.8
BMI	0.17	1.0	0.9-1.1
Smoking	0.34	0.7	0.4-1.3
Hyperlipidemia	0.001*	2.9	1.8-4.7
Leucocyte count	0.01*	1.3	1.1-1.6
Urea	0.04	0.9	0.91-0.99
Gender	0.03*	0.5	0.2-0.9

*BMI: Body mass index, *p<0.05 statistically significant, OR: Odds ratio, CI: Confidence interval*

Table 6. Correlation between clopidogrel level and clinical and biochemical parameters

	R	p-value
Age	-0.07	0.13
BMI (weight/height^2)	0.012	0.78
FBG (mg/dL)	-0.34	0.49*
LDL (mg/dL)	0.046	0.36
HDL (mg/dL)	-0.07	0.14
Urea (mg/dL)	-0.098	0.06
Waist circumference (cm)	0.056	0.26
Creatine (mg/dL)	-0.020	0.70
eGFR (mL/dk)	-0.006	0.90
CRP (mg/L)	0.386	0.04*
Hemoglobin (g/dL)	0.019	0.70
Leucocyte count (10^{e3}/uL)	0.171	0.001*
Platelet count (10^{e3}/uL)	0.115	0.024*

*BMI: Body mass index, FBG: Fasting blood glucose, LDL: Low density lipoprotein, HDL: High density lipoprotein, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, *p<0.05 statistically significant*

Factors Contributing to Antithrombotic Drug Resistance

Aspirin: Suggested causes for AR are genetic variability, non-adherence, use of enteric-coated forms, concomitant use of PPI's, body weight (under-dosing), NSAID's, and advanced atherosclerosis. There is a variety of contributing factors reported to be associated with resistance. In univariate analysis, we found a higher prevalence of HT, HL, ACE-I, beta-blocker use, and higher LDL and platelet count among aspirin resistant patients. However, only HT and platelet count were independent predictors of aspirin resistance.

The effect of gender on AR is controversial. Clinical studies reveal that AR is detected more in women (especially postmenopausal, over the age of 60), which is related to the low hemoglobin level[23,24]. In our study, no difference was detected between the genders. In a study by Helgason et al.[25], a statistically significant relationship was not found between smoking and aspirin resistance, and they attributed this result to smoking-inducing platelet activation. The data of Hung et al. [26] was also similar. However, Gum et al.[24] reported significantly higher AR among nonsmokers. In our study, the smoking rate was higher among normal responders. Likewise, Matetzky et

al.[27] also found out that the response to clopidogrel in smokers was better.

Hyperglycemia is known to cause platelet reactivation and increase thrombogenicity. Furman et al.[28] found no statistically significant difference in aspirin resistance in diabetic and non-diabetic subgroups of the patients with stable angina pectoris. We revealed similar results in this study.

Hypercholesterolemia causes aspirin resistance by increasing platelet aggregation and TXA2 level. Friend et al.[29] demonstrated that platelets' response to aspirin was decreased in hyperlipidemic patients. Likewise, our study showed that HL was more frequent among AR patients, and in multivariate analysis, statin use had a tendency to borderline significance as an independent predictor of AR. Whether this is an indirect projection of HL or attributable to the direct effects of statins needs to be further evaluated. In multivariate analysis, only HT and platelet were detected as independent predictors for AR. Data on predictors of AR are sparse. In a study including stable CAD patients, fibrinogen levels and pulse pressure were reported to be independent predictors of resistance on chronic aspirin use[30].

This study found a negative correlation between aspirin aggregation levels and fasting blood glucose, while CRP, leukocyte count, and platelet count had a positive correlation. Based on these results, we think patients with poor glycemic regulation may require strict monitoring of blood glucose to increase the effectiveness of aspirin. However, the same caution may also be required in patients with autoimmune inflammatory diseases with acute attacks.

Clopidogrel: Clopidogrel resistance or response variability is attributed mainly to the variability of genetic polymorphisms influencing absorption and isoenzyme activity, laboratory method, and drug-drug interactions[31,32].

The drug interactions that may change cytochrome p-450 isoenzymes in the liver may decrease the efficiency of clopidogrel. The most important ones among these drugs are statins[33]. In our study, while the use of statin was found out to be significantly high in the clopidogrel resistant group, it was not found as an independent predictor of CR in the logistic regression test.

The association of PPI use and insufficient response to clopidogrel was an issue of controversy. There is not enough evidence for a valid association between PPI induced low response and clinical adverse events, although some small studies show higher CR among PPI users[34]. In their study, Juurlink et al.[35] demonstrated that the dual use of clopidogrel and PPI after AMI increased the risk of re-infarction by decreasing the clopidogrel efficiency; and only pantoprazole did not inhibit the cytochrome p-450 enzyme. Arbel et al.[34] showed that omeprazole was significantly associated with more clopidogrel resistance compared to pantoprazole and famotidine. We found no association between CR and PPI use.

Likewise to PPI use, CCB and ACE-I use were also not associated with CR although Gurbel et al.[36] reported that high doses of CCB and ACE inhibitors possibly contributed to a decreased response to clopidogrel.

Demographic variables such as age, BMI, diabetes, and renal failure may also influence clopidogrel response, either directly influencing platelet function or drug metabolism[37]. We found no association with age. In a study conducted by Feher et al.[38], clopidogrel resistance was found to be significantly low in patients with a low BMI. In our study, BMI and waist circumference were significantly higher in the CR group. *In vitro* studies revealed that insulin decreased platelet aggregation by P2Y12 path inhibition. However, since the sensitivity of platelet to insulin decreases in Type 2 DM patients, P2Y12 inhibition decreases[39]. In our study, clopidogrel resistance was found to be statistically higher in a patient with DM, but in multivariate analysis, diabetes was not a predictor for the CR; however, HL [odds ratio (OR): 2.9], leukocyte count (OR: 1.3), and gender (OR: 0.5) were independent predictors of CR.

Study Limitations

As a retrospective analysis, our study has some limitations. It has been reported that the level of platelet

reactivity after a standard dose is related to the pretreatment reactivity level. As we did not routinely perform a baseline aggregation assessment, we did not have the baseline platelet reactivity levels. The lower (300 mg) loading dose of clopidogrel used during the screened period may seem like a limitation, but all the comparators were assessing the effects of CR using the same loading dose, and it is well known that clopidogrel reaches its effective plasma level 24-48 hours after a 300 mg loading dose. And lastly, resistance or non-responsiveness to antithrombotics is a laboratory phenomenon, and we did not assess the clinical consequences (e.g., stent thrombosis) of insufficient aggregation inhibition as this was beyond the scope of this study.

Conclusion

In conclusion, we found 8.1% and 26.8% of stable CAD patients undergoing elective PCI showed that insufficient aggregation inhibition by aspirin and clopidogrel, respectively, whereas 3% had double resistance. There is insufficient evidence for routine screening for aspirin and clopidogrel resistance in the clinical practice; however, platelet function testing may be considered in determining dual antiplatelet strategy in patients with a history of stent thrombosis and in patients prior to undergoing high-risk PCI.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2021-296, date:17/05/2021).

Informed Consent: Consent of patients were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.K., A.A.Ö., Concept: D.K., Design: F.N.T.Ç., Data Collection or Processing: A.K., Analysis or Interpretation: O.A., Literature Search: U.K., Writing: D.K., U.K.

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Early QTc Interval Prolongation After Primary Percutaneous Coronary Intervention May Have a Positive Impact

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Abstract

Objectives: Corrected QT (QTc) interval is prolonged in acute myocardial infarction and begins to shorten after successful reperfusion. Data on the early change of QTc after reperfusion and the prognostic significance of this change are limited. We aimed to evaluate the change of QTc interval in the first hour following successful primary percutaneous coronary intervention (pPCI) in ST-elevation myocardial infarction (STEMI) patients and its relationship with reperfusion parameters such as myocardial blush grade (MBG) and ST-segment resolution (STR%).

Materials and Methods: Patients who presented with the first STEMI episode and underwent successful pPCI were included in the study. After pPCI, MBG and STR% were calculated. QTc measurements were made from the electrocardiography (ECG) recorded at admission (Pre-pPCI QTc), 1 hour after pPCI (Post-pPCI QTc), and the 24th hour.

Results: One hundred and five patients who had successful pPCI with adequate ECG data were enrolled in the study. The mean Pre-pPCI QTc was 409±34 ms, and the mean post-pPCI QTc was 427±32 ms. A statistically significant prolongation was observed in the QTc interval after pPCI (QTc-Change) [21 ms (-3, 37 interquartile range (IQR)), p<0.001]. The median STR was 71% (60-83 IQR), and the median MBG was 2 (1-3 IQR). In the multivariable linear regression analysis, a significant relationship was observed between QTc-Change with MBG and STR% [β=9.077, 95% confidence interval (CI): 2.55-15.60, p=0.006 and β=9.315, 95% CI: 2.00-16.62, p=0.013, respectively].

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Conclusion: It was found that the QTc interval continued to prolong somewhat in the early period after successful pPCI in STEMI patients, and this QTc-Change was significantly associated with reperfusion parameters such as MBG and STR%. STR% and MBG were higher in those with higher QTc-Change.

Keywords: ST-segment elevation myocardial infarction, QTc interval, myocardial blush grade, ST-segment resolution

Introduction

The QT interval on the surface electrocardiogram (ECG) represents the time from the onset of ventricular depolarization to the completion of repolarization. Previous studies have shown that prolonged corrected QT (QTc) is associated with high arrhythmic event rates, sudden death, and all-cause mortality in the normal population and patients with acute myocardial infarction (AMI)[1-5].

Acute myocardial ischemia has been shown to increase repolarization heterogeneity and prolong the QT interval[5,6]. Studies have shown that the QTc interval is prolonged in AMI and begins to shorten after successful reperfusion[7-9]. However, data on the change of the QTc interval in the early period after revascularization and the prognostic significance of this change are limited. In a study by Bonnemeier et al.[7], it was found that in patients with AMI, the OTc interval initially became prolonged in the first hour following successful primary percutaneous coronary intervention (pPCI) but it was then followed by OTc interval shortening.

ST-segment resolution (STR%) and myocardial blush grade (MBG) are among the early reperfusion parameters that have shown prognostic significance in ST-elevation myocardial infarction (STEMI) patients[10-13]. Our study aimed to evaluate the change of QTc interval during the following hour after successful pPCI in STEMI patients and its relationship to reperfusion parameters such as MBG and STR%.

Materials and Methods

A total of 150 consecutive patients admitted with STEMI were evaluated. The patients enrolled were initially selected from those with clinical history and symptoms suggestive of the first episode of acute STEMI, who had presented within 12 hours after the onset of symptoms. According to current guidelines, the diagnosis STEMI required: Chest pain lasting >20 min and ST-elevation (STE) of >1 mm in at last two contiguous ECG leads without left ventricular hypertrophy and left bundle branch block[14]. Only patients who underwent successful pPCI with thrombolysis in myocardial infarction (TIMI) flow grade 3 were included. After exclusion criteria were applied, 105 patients were enrolled in the study.

Patients excluded from the study were those with non-sinus rhythm, bundle branch block, pacemaker rhythm, prior AMI or coronary bypass grafting, coronary occlusions unsuitable for PCI, TIMI flow grade <3, and challenge to determine the end of T-waves.

Angiographic Examination and Definition

Coronary angiography, pPCI, and periprocedural care conformed to the current guidelines[14]. The culprit lesion was crossed with wire within the first 60 minutes of hospital admission in all the cases. After successful revascularization (TIMI-3 flow), MBG was calculated. TIMI flow grade has been defined as follows: TIMI 0 refers to the absence of any antegrade flow beyond a coronary occlusion; TIMI 1 flow is faint antegrade coronary flow beyond the occlusion, although filling of the distal coronary bed is incomplete; TIMI 2 flow is delayed or sluggish antegrade flow with complete filling of the distal territory; TIMI 3 flow is normal flow, which fills the distal coronary bed completely[15]. MBG is an angiographic measure of myocardial perfusion. MBG has been defined as follows: 0, no myocardial blush (MB) or

contrast density (CD); 1, minimal MB or CD; 2, moderate MB or CD but less than that obtained during angiography of a non-infarct related coronary artery; 3, standard MB or CD, comparable with that obtained during angiography of a non-infarct-related coronary artery[13].

Electrocardiographic Analysis

For each patient, standard 12-lead-ECGs (paper speed of 25 mm/s, standardization of 10 mm/1 mV) were recorded at admission, within the first hour after pPCI, and at the 24 hours after pPCI. All analyses were made by two independent observers using a magnifying glass. ECG was performed with the Nihon Kohden Electrocardiograph (model ECG 2350).

ST-Segment Resolution (STR%): STR was calculated from the ECGs taken at admission and the first hour after pPCI. The sum of STR was measured 20 milliseconds after the end of QRS complex: Leads V1-6 for anterior MI and leads II, III, and aVF for inferior infarction. ST resolution was calculated as a percentage reduction of the absolute STE in the single lead, which is associated with the infarct territory with maximum STE on the baseline ECG[10].

QTc Interval Measurement: QT intervals were measured from the recorded ECGs (baseline, 1st and 24th hours after pPCI). Measurements were made using a manual compass in either lead II for inferior MI and V2 or V5 for anterior MI, with the most prolonged QT interval being used. The maximum measured interval in successive 3-5 beats was taken. When leads II, V2, or V5 were deemed unsuitable, one of the remaining leads associated with infarct territory was chosen. QT intervals were measured from the onset of the QRS complex to the point of return of the T wave to the isoelectric line or the nadir between the T and U waves in cases the U wave was present. QT intervals were corrected for heart rate effects using a modified Bazzet's formula (QTc=QT/(R-R)1/2).

Transthoracic echocardiography was performed 24 hours after admission, and the left ventricular ejection fraction (LVEF %) was measured by the modified Simpson method.

The study approved by the local institutional ethics committee. The study protocol conforms to the Declaration of Helsinki [University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital Ethics Committee (approval date: 28/02/2020 number: 413].

Statistical Analysis

Statistical analysis was performed by using R software version 4.02 (R Project, Austria Vienna). Continuous variables were presented as mean ± standard deviations, or if a non-normal distribution was found, they were given as median, interquartile range: 25-75% (IQR). Categorical variables were expressed as percentages. The histogram and Shapiro-Wilks test were used to verify the normal distribution of data. The paired Student's t-test was used to assess QTc change after pPCI. Correlation between variables was performed using Spearman's rank or Pearson correlation test according to the distribution of data.

Outcome Variable: QTc-Change first hour after pPCI.

Statistical Modeling: Multiple linear regression analysis was used to assess the relationship of QTc-Change with the STR% and MBG after adjusting common clinical predictors (age, gender, diabetes mellitus, hypertension, peak troponin, infarct location, symptom to door time, potassium, Glycoprotein IIb/IIIa inhibitor use). Continuous variables were included in the model by restricted cubic spline transformation (3 knot) to attain the nonlinearity of data. Continuous variables were presented in regression analysis as their interquartile range (25-75 IQR). In all the statistical analyses, a p-value of <0.05 was considered statistically significant. The correction for p-value was performed where needed.

Results

One hundred and five patients who had successful pPCI with adequate ECG data were enrolled in the study. The mean age was 55±10 years in the study population. Nineteen (18%) patients were female, and 44 (42%) patients had anterior STEMI. Baseline characteristics,

clinical, laboratory, and electrocardiographic findings of patients were given in Table 1.

The mean Pre-pPCI QTc was 409±34 ms, the mean post-pPCI QTc was 427±32 ms, and the mean 24th hour QTc was 424±34 ms (Figure 1). After pPCI, the median 21 ms (-3, 37 IQR) prolongation was observed in the QTc interval and this prolongation (QTc-Change) was statistically significant (p<0.001). The median STR was 71% (60-83 IQR), the median MBG was 2 (1-3 IQR), the median symptom to door time was 3 (1.75-4 IQR) hours. The median LVEF measured at 24 hours was 55% (47-57 IQR). In-hospital mortality occurred in one patient who presented with anterior STEMI, and non-sustained ventricular tachycardia was observed within the first 24 hours after revascularization in another patient.

A weak negative correlation was observed between admission Pre-pPCI QTc and STR (%) (r=-0.237), LVEF (%) (r=-0.383) and MBG (r=-0.355). A weak positive correlation was observed between symptom to door time and pre-pPCI QTc (r=0.382). A moderate negative correlation was observed between QTc-Change and Pre-pPCI QTc (r=-0.422). A moderate positive correlation was observed between QTc change and STR% (r=0.402), MBG (r=407), and LVEF% (r=0.437). A weak negative correlation was observed between QTc-Change and symptom to door time (r=-333). In the multivariable linear regression analysis, a significant relationship was

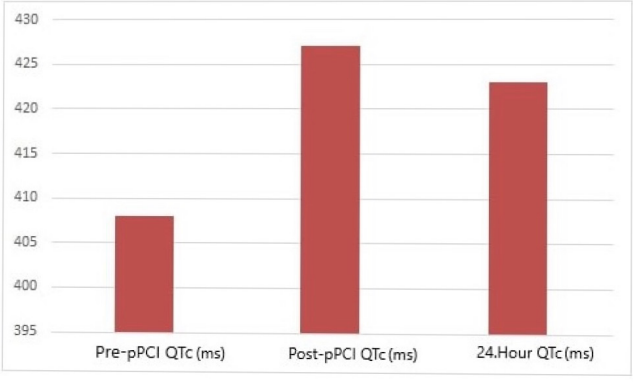

Figure 1. Temporal change of QTc interval: Pre-pPCI QTc, Post-pPCI QTc, and 24th-hour QTc
pPCI: Primary percutaneous coronary intervention, QTc: Corrected QT

Table 1. Baseline characteristics, and clinical, laboratory, and electrocardiographic findings of patients

	Total (n=105)
Age (year)	55±10
Gender (female)	19 (18%)
Diabetes mellitus	14 (13%)
Hypertension	35 (33%)
Smoking	34 (32%)
Hyperlipidemia	36 (34%)
Symptom to door time (h)	3 (1.75-4)
Troponin (ng/mL)	3.8 (0.34-21)
Peak troponin (ng/mL)	34 (13-50)
Killip class >1	21 (20%)
Infarct location (anterior)	44 (42%)
Infarct vessel	
Left anterior descending	44 (42%)
Left circumflex	23 (22%)
Right	38 (36%)
Left ventricular ejection fraction (%)	55% (47-57)
ST-segment resolution (%)	71 (60-83)
Myocardial blush grade	
0	6 (6%)
1	20 (19%)
2	44 (42%)
3	35 (33%)
Glycoprotein IIb/IIIa inhibitor use	40 (38%)
Hemoglobin (g/dL)	13.7±1.7
Creatinine (mg/dL)	0.80±0.18
Potassium (mmol/L)	4.03±0.35
Heart rate pre-pPCI (beat/min)	75±17
Heart rate post-pPCI (beat/min)	76±14
Heart rate 24th hour (beat/min)	71±11
Pre-pPCI QT interval (ms)	371±39
Post-pPCI QT interval (ms)	381±36
24th hour QT interval (ms)	392±37
Pre-pPCI QTc interval (ms)	409±34
Post-pPCI QTc interval (ms)	427±32
24th-hour QTc interval (ms)	424±34
QTc-Change (ms)	21 (-3, 37)

Values are expressed as number of patients (%), mean ± SD, or median (25th-75th percentile).
pPCI: Primary percutaneous coronary intervention, SD: Standard deviation

observed between QTc-Change with MBG and STR% (β-coefficient=9.077, 95% CI: 2.55-15.60, p=0.006 and β coefficient=9.315, 95% CI: 2.00-16.62, p=0.013, respectively). Multivariable linear regression analysis between the QTc-Change and clinical variable was given in Table 2. Partial effect plots of MBG and STR% with QTc-Change were given in Figure 2a and 2b. It is seen that as STR% and MBG increase, QTc-Change increases. In Figure 3, we summarized the relative importance of each predictor in the model. MBG was ranked as the most contributing predictor for QTc-Change, and followed by STR%.

Discussion

There are insufficient data regarding the prognostic significance of the change in the QTc interval after revascularization in STEMI patients, and our study is important in terms of showing the relationship between this QTc-change and prognostic parameters. This study showed that the QTc interval was significantly prolonged

Table 2. Multivariable Linear Regression analysis of QTc-Change with clinical variables

	β-coefficient	95% CI	p-value
Age (year) (from 48 to 61)	3.42	-4.62, 8.98	0.775
Sex (male/female)	5.18	-8.79, 19.06	0.460
Hypertension (from 0 to 1)	2.84	-9.12, 14.81	0.637
Diabetes mellitus (from 0 to 1)	-5.20	-20.98, 10.56	0.513
Troponin (ng/mL) (from 0.34 to 18.9)	-7.18	-11.33, 17.12	0.703
Symptom to door time (hour) (from 2 to 4)	-8.79	-8.79, 6.37	0.07
Infarct type (anterior/nonanterior)	1.59	-9.29, 12.48	0.772
STR% (from 60 to 83)	9.31	2.00, 16.62	0.013
MBG (from 1 to 3)	9.07	2.55, 15.60	0.006
Glycoprotein IIb/IIIa inhibitor	4.81	-4.86, 14.48	0.320
Potassium (3.8 to 4.2) (mmol/L)	-4.56	-11.21, 2.09	0.039

Regression coefficients were given according to the IQR 25-75% (interquartile-range) changes of the continuous variables. Because of nonlinearity of some data (we used restrictive cubic splines 3 knot) such-as Potassium, corresponding CI includes zero; however, p-value is significant.
STR: ST-segment resolution, MBG: Myocardial blush grade, CI: Confidence interval.

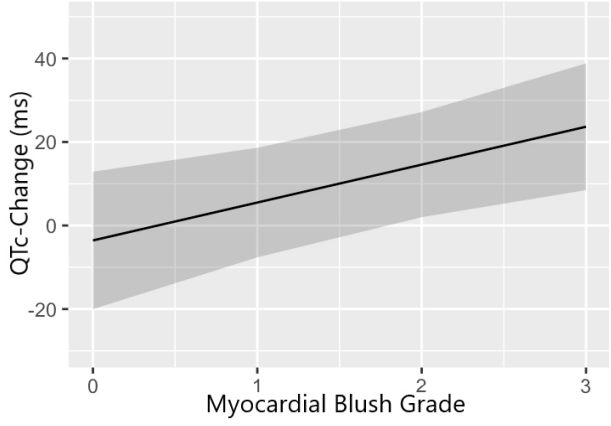

Figure 2a. Partial effect plot in the model for QTc-change and myocardial blush grade
QTc: Corrected QT

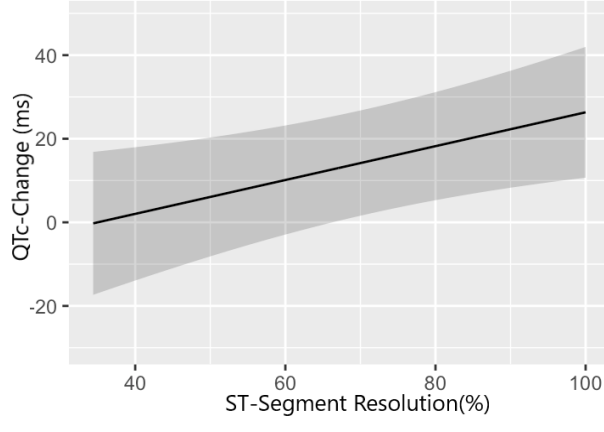

Figure 2b. Partial effect plot in the model for QTc-Change and ST-Segment resolution (%)
QTc: Corrected QT

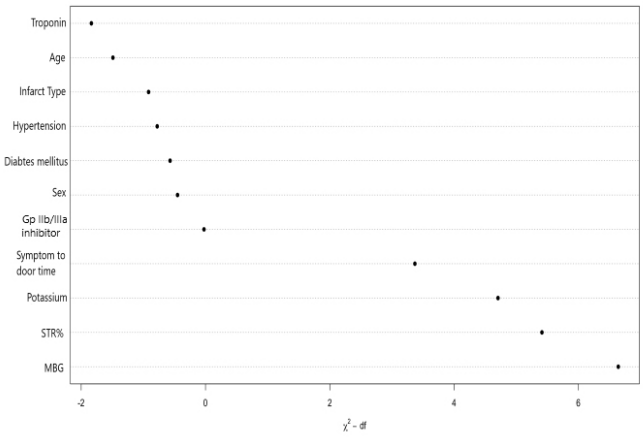

Figure 3. Relative importance of each variable in the model for QTc-change; STR%: ST-segment resolution (%), MBG: Myocardial blush grade

in the early period after successful reperfusion in STEMI patients. QTc-Change was significantly associated with STR% and MBG by multivariable linear regression analysis, and STR% and MBG were higher in patients with prolonged QTc interval. Moreover, the QTc change demonstrated a moderately negative correlation with both LVEF% and Pre-pPCI QTc.

Acute myocardial ischemia has been shown to modify the QT interval duration, increase repolarization heterogeneity, and prolong the maximum electrocardiographic QT interval[6]. Numerous mechanisms have been proposed for ischemia to prolong the QTc duration. Increased sympathetic activity, together with structural myocardial damage, electrolyte imbalance, and dysfunction of the ion channels in the acute phase of ischemia, may cause QT prolongation[9]. Many studies have shown that a long admission QTc interval is associated with a poor prognosis in AMI. In one study, a QTc interval >445 ms on admission to the emergency department was an independent predictor for all-cause mortality and heart failure in STEMI patients[16]. In our study, the Pre-pPCI QTc interval, measured on admission to the emergency department, showed a negative correlation with STR%, MBG, and LVEF%, respectively. Again, the Pre-pPCI QTc interval was prolonged in patients with increased symptom to door time in our study.

Although many studies in patients with AMI report shortening of the QTc interval after successful reperfusion, studies on the QTc interval change during the following hour after reperfusion are limited. Reperfusion may affect the QTc interval, either directly by influencing the electrophysiological milieu or indirectly by interfering with cardiac autonomic nervous control[17]. In a study by Bonnemeier et al.[7], it was found that the QTc interval continued to lengthen in the first hour after reperfusion in AMI patients who underwent pPCI and then began to shorten following hours. In our study, a significant prolongation was observed in the QTc interval (QTc-Change) at the 1st hour after successful pPCI [21 ms (-3, 37 IQR) p-value <0.001], and although a decrease was observed in the QTC interval measured at the 24th hour, it was still found to be higher than the baseline. MBG is an angiographic measure of myocardial perfusion and a strong predictor of mortality in patients with TIMI-3 flow after pPCI[12]. Furthermore, STR% is an electrocardiographic indicator of myocardial perfusion and has a strong relationship with mortality and reinfarction[10]. Even if TIMI-3 flow is provided in the infarct-related vessel, there may be a problem in myocardial perfusion at the microvascular level. Therefore, patients with low STR% and MBG are associated with heart failure and poor outcomes[10-12]. In the study of Poli et al.[13], patients with both MBG 2/3 and STR >50% immediately after pPCI showed a significant 7-day and 6-month functional recovery on echocardiography. In our study, a significant relationship was observed between QTc-Change with STR% and MBG in regression analysis. STR%, MBG, and LVEF were higher in patients with prolongation of QTc interval after pPCI. QTc-Change was lower in patients with increased symptom to door time.

In one study evaluating patients who underwent elective PCI, it was observed that QTc was prolonged in 100% of patients during balloon inflation and began to decrease immediately after deflation, and QTc prolongation

could be the earliest sign of transmural ischemia[18]. In a study of AMI patients comparing successful with unsuccessful reperfusion, it was found that the QTc interval peaked towards the 12th hour in the revascularization group and started to shorten afterward, and it was observed that it continued to increase without peaking in the patient group without reperfusion. LVEF% was better in the patient groups with transient prolongation[19]. In our study, LVEF% measured at the 24th hour was higher in patients with a prolonged QTc interval after reperfusion. Considering that cellular mechanisms are disrupted for a longer period in myocardial infarction than in elective balloon angioplasty (just as echocardiographic stunning does not improve immediately after reperfusion), the QT interval may continue to prolong for a while until the electrophysiological factors that cause QT prolongation recover and then begin to shorten. Reflecting on the relationship of QTc-Change with prognostic parameters such as STR, MBG, LVEF%, and symptom to door time, the moderate prolongation in the early period in the QTc interval may be an indicator of viable myocardial tissue, just like in myocardial stunning. The reversible impairment of ventricular repolarization after reperfusion for patients without adverse event may be interpreted as "electrical stunning" of the ventricular myocardium[7].

The moderate prolongation of the QTc interval in the early hours after pPCI may be prognostically valuable due to its association with better myocardial perfusion and better left ventricular function in some patient groups.

Study Limitations

An important limitation of this study was the small cohort of patients. Another limitation of the study was that the QTc interval change was not monitored after the first hour. Perhaps, examining the relationship of QT prolongation with parameters such as the infarct area may be valuable in terms of showing the presence of living tissue.

Conclusion

It was found that the QTc interval continued to prolong somewhat in the early period after successful pPCI in STEMI patients, and this QTc-Change was significantly associated with reperfusion parameters such as MBG and STR%. STR% and MBG were higher in those with higher QTc-Change.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital Ethics Committee (approval date: 28/02/2020, number: 413).

Informed Consent: Informed consent form was obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Ç., Concept: M.Ç., T.A., Ç.G., Design: M.Ç., Ö.B., F.I., A.K., Data Collection or Processing: M.Ç., Ö.B., F.I., T.G., Analysis or Interpretation: A.K., T.A., Ç.G., Literature Search: E.E., Ö.B., Writing: M.Ç., E.E., C.K., N.Ö.

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E Journal of Cardiovascular Medicine

Research Article

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Assessment of Left Atrial Volumes and Functions in Patients with Coronary Slow Flow

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Abstract

Objectives: Coronary slow flow phenomenon (CSFP) is the slow or late progression of the opaque material to the distal vascular structures during angiography in patients with normal or near-normal coronary arteries. This study aims to evaluate left atrial volumes and functions using conventional transthoracic and tissue Doppler echocardiographic parameters in patients with CSFP.

Materials and Methods: According to criteria determined by Gibson, 50 patients with slow flow in at least one coronary artery were included as cases, and 40 subjects with normal coronary flow were included as controls.

Results: In the transmitral and tissue Doppler analysis, mitral early velocity (E), mitral late velocity/mitral early velocity (E/A), and Em were significantly lower in the coronary slow flow (CSF) group. LA, Am, mitral early velocity/early

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diastolic velocity (E/Em), LAV_{max}, LAV_{min}, LAV_{preA}, index volumes, LAAEV, LATEV, and LAAEF were found to be higher in the CSF group. A significant positive correlation was observed between Frame LAD and LAAEF (r=0.66, p<0.001) and between Frame LAD and E/Em (r=0.34, p<0.001). A significant negative correlation was found between LAAEF and E/A ratio (r=-0.4, p=0.003). There was also a significant positive correlation between LAPEF and E/A (r=0.44, p<0.001) and between the mean frame and LAAEF (r=0.4, p=0.002).

Conclusion: Impaired LV diastolic functions and significant changes in LA volumes were found in patients with CSFP.

Keywords: Coronary slow flow, left atrial functions, echocardiography, left atrial volume

Introduction

Coronary slow flow (CSF) is the slow or late progression of the opaque material to the distal vascular area without coronary artery stenosis (>50%) during angiography[1]. CSF may present with chronic coronary syndrome or acute coronary syndrome[2,3]. The underlying pathophysiological causes of this phenomenon are microvascular dysfunction, vasomotor dysfunction[1,4-6], diffuse atheroma plaques that do not cause stenosis in the coronary lumen, diffuse calcification, and diffuse intimal thickening[7,8].

Previous studies have shown that CSF is an atherosclerotic process, which increases microvascular resistance and affects both small and large vessels. Left ventricular (LV) diastolic dysfunction (LVDD) is among the earliest findings of ischemic heart disease and affects left atrial (LA) functions. LA functions may also be affected by valvular diseases, coronary artery disease (CAD), heart failure, and diastolic dysfunction. LA functions are important for cardiac output, and decreased LA functions are associated with atrial arrhythmias and ischemic stroke. LV systolic and diastolic dysfunction in CSF has been shown in previous studies[9]. However, the effects of CSF on LA functions have not been well established, and only limited data are available about this condition. Therefore, this research will assess LA volumes and functions in patients with CSF using conventional transthoracic and tissue Doppler echocardiographic parameters.

Materials and Methods

Coronary angiographies were performed in patients, who had been diagnosed with stable or unstable angina with myocardial ischemia detected by noninvasive tests. According to criteria determined by Gibson et al.[10], 50 patients with CSF in at least one coronary artery were included as cases, and 40 patients without ≥50% coronary stenosis were enrolled as controls. The study design was approved by the Ethics Committee of Dicle University. The participants' demographic data, medical histories, and laboratory parameters were collected from our hospital's electronic database. The participants' physical characteristics, such as body surface area (BSA), waist circumference, weight, height, and body mass index (BMI), were measured. Individuals were excluded from the study if they had ≥50% stenosis of the coronary arteries, myocardial infarctions, significant valvular heart disease, diabetes mellitus (DM), hypertension (HT), left ventricular systolic function of <50%, left and right bundle branch block, atrial fibrillation, chronic kidney disease, or congenital heart disease.

Coronary angiographies were performed according to the Judkin's[11] standard technique. The thrombolysis in myocardial infarction (TIMI) frame count (TFC) method was employed to measure coronary flow[10]. The starting point was set to be the moment when the contrast material touched the side of the artery and began to progress. The ending point was set as the moment when the contrast agent reached the distal part of the mustard for the left

anterior descending artery (LAD), when the first side of the posterolateral artery was given for the right coronary artery (RCA), and when the longest distal branch was observed for circumflex artery (Cx). The LAD frame was standardized by dividing it by 1.7 because of its length. The number of frames obtained by shooting at 12 fps was multiplied by a constant number of 2.4, following Gibson et al.[10]. Patients with a frame number of 20.2±3.0 for RCA, 36±2.6 for LAD, and 22±4.1 for Cx were diagnosed as having CSF.

For all participants, standard M-mode, 2D images, and Doppler recordings were completed using a 3.5Mhz probe and a simultaneous echocardiogram with a GE Vingmed Vivid S-5 echocardiography device. Echocardiographic examination was performed by a single researcher.

LV M-mode parameters, LV wall thickness, LV end-systolic diameter (LVESD), and LV end-diastolic diameter (LVEDD) measurements were obtained from the parasternal long axis plane[12]. The LV ejection fraction (LVEF) was measured according to Teicholtz's formula. Pulse wave Doppler velocity findings were examined via apical four-chamber images taken from three consecutive cycles. Mitral late velocity (A), mitral early velocity (E), deceleration time (DT), and isovolumetric relaxation time (IVRT) were also evaluated. Tissue Doppler examination was performed from the apical four-chamber window by placing the sample volume on the junction of the lateral anulus and the wall. Early diastolic velocity (Em), systolic myocardial velocity (Sm), and late diastolic velocity (Am) were calculated from the mitral lateral wall with tissue Doppler evaluation. E/A and E/Em ratios were also calculated. The average of three consecutive measurements for each parameter was recorded. After standard echocardiographic evaluation, LA sizes and volumes were examined. LA sizes were measured via the parasternal long axis and the apical four-chamber images. LA volume was evaluated using the modified Simpson method from the apical four-chamber images[13,14]. Atrial volume was adjusted according to BSA in all patients. The maximum volume LA (Vol_{max}) was measured just before the mitral valve opening. The preatrial contraction volume (Vol_{pre-A}) was measured at the time of the onset of the P wave in the echocardiogram. The LA minimum volume (Vol_{min}) was measured at the time of the mitral valve's closing. The emptying volume of the LA was calculated using the available volumes[15].

LA passive emptying volume (LAPEV) = Vol_{max} - Vol_{pre-A}

LA passive emptying fraction (LAPEF) = LA_{PEV}/Vol_{max}

LA conduit volume (LACV) = LV stroke volume - (Vol_{max}-Vol_{min})

LA active emptying volume (LAAEV) = Vol_{pre-A} - Vol_{min},

LA active emptying fraction (LAAEF) = LA_{AEV}/Vol_{pre-A},

LA total emptying volume (LATEV) = Vol_{max} - Vol_{min},

LA total emptying fraction (LATEF) = LA_{TEV}/Vol_{max}

Statistical Analysis

SPSS 18 program was used for statistical evaluation. For comparing variables, the Student's t-test or Mann-Whitney U test were used. The chi-square and Fischer's Exact test were used for categorical variables. Pearson correlation analysis method was used for correlation analysis between variables. Parametric variables were expressed as mean ± standard deviation and categorical variables were expressed as percentage. Statistical significance was accepted when p-value was <0.05.

Results

The study consisted of 90 patients, 50 for the CSF group and 40 for the control group. Male gender was higher in the CSF group (p=0.02). We did not find a difference between the two groups for age, HT, DM, smoking, blood pressure, heart rate, BMI, and BSA. Hyperlipidemia was higher and statistically significant in the CSF group (p=0.01) (Table 1).

Platelet, mean platelet volume, neutrophil/lymphocyte ratio (NLR), low-density lipoprotein (LDL), and C-reactive protein were significantly higher in the CSF group (Table 2).

Table 1. Demographic characteristics of the study groups

	CSF (n=50)	Control group (n=40)	p-value
Gender, male (n, %)	40 (80)	23 (57.5)	0.020
Age (years)	48.6±12.5	47.8±6.0	NS
Body surface area (BSA)(m^2)	1.98±0.2	1.91±0.1	NS
Systolic blood pressure (mmHg)	120±11	119±13	NS
Diastolic blood pressure (mmHg)	73±8	74±9	NS
Heart rate (bpm)	72±10	78±9	NS
Body mass index (BMI) (kg/m^2)	28±3.6	27.4±3.2	NS
Hyperlipidemia (n, %)	19/38	6/15	0.010
Smoking (n, %)	22/44	14/35	NS
Hypertension (n, %)	10/20	14/35	NS
Diabetes mellitus (n, %)	3/6	3/7.5	NS

CSF: Coronary slow flow, NS: Non-significant, n: Number

Table 2. Baseline hematological and biochemical parameters in the study

	CSF (n=50)	Control group (n=40)	p-value
White blood cell count ($10^3/\mu L$)	8.7±2.2	8.2±2.0	NS
Hemoglobin (g/dL)	14±1.9	13.8±1.5	NS
Hematocrit (%)	42.4±5.3	42.2±4.5	NS
Platelet count ($10^3/mm^3$)	245±56	221±27	0.010
MPV (μm^3)	8.4±0.9	7.9±0.7	0.010
Neutrophil ($10^3/mm^3$)	5.6±2.1	4.7±1.4	0.020
Lymphocyte ($10^3/mm^3$)	2.4±0.8	2.6±0.2	NS
Neutrophil/lymphocyte ratio	2.5±1.6	1.8±0.5	0.010
RDW (%)	13.9±1.0	13.4±0.6	0.006
Creatinine (mg/dL)	0.83±0.2	0.77±0.1	NS
CRP (mg/dL)	1.6±0.4	0.9±0.2	<0.001
Glucose (mg/dL)	102±18	103±22	NS
Total cholesterol (mg/dL)	189±48	179±32	NS
LDL (mg/dL)	108±31	91±24	0.006
HDL (mg/dL)	41±10	51±14	<0.001
Triglyceride (mg/dL)	190 (110-279)	157 (96-237)	NS

Significant p-values are shown in bold.
CSF: Coronary slow flow, MPV: Mean platelet volume, RDW: Red blood cell distribution width, CRP: C-reactive protein, LDL: Low density lipoprotein, HDL: High density lipoprotein, NS: Non-significant, n: Number

We did not find statistical variation between the two groups for LVEDD, LVESD, EF, LVEDV, LVESV, A, and Sm. In Doppler analysis, E, E/A, and Em were significantly lower in the CSF group. LA, Am, E/Em, LAV_{max}, LAV_{min}, LAV_{preA}, index volumes, LAAEV, LATEV, and LAAEF were higher in the CSF group. LAPEV, LAPEF, and LAV conduit were found to be lower in the CSF group (Tables 3 and 4).

Coronary angiographic findings were statistically different between the two groups. As expected, the number of frames for CSF patients was higher than the control group (Table 5).

Table 3. Echocardiographic parameters of the patients

	CSF (n=50)	Control group (n=40)	p-value
EF (%)	60±3	60±2	NS
LVEDD (cm)	4.7±0.2	4.4±0.2	NS
LVESD (cm)	3.0±0.2	2.9±0.4	NS
IVS (cm)	1.1±0.1	1.0±0.09	NS
LVDV (mL)	73.1±21.5	71.2±13.6	NS
LVSV (mL)	34.8±9.1	30.1±6.9	NS
LA diameter (cm)	3.6±0.2	3.3±0.1	**<0.001**
Mitral-E (m/s)	0.65±0.1	0.73±0.1	**<0.001**
Mitral-A (m/s)	0.68±0.1	0.66±0.1	NS
E/A	0.99±0.2	1.16±0.3	**0.003**
Em (m/s)	0.099±0.02	0.12±0.02	**<0.001**
Am (m/s)	0.12±0.02	0.10±0.02	**0.010**
Em/Am	0.83±0.2	1.2±0.3	**<0.001**
Sm (m/s)	0.095±0.02	0.092±0.02	NS
E/E'	7.1±2.1	5.9±1.3	**0.003**

Significant p-values are shown in bold.
LV: Left ventricular, CSF: Coronary slow flow, A: Mitral late velocity, E: Mitral early velocity, Em: Early diastolic velocity, Sm: Systolic myocardial velocity, EF: Ejection fraction, LVEDD: LV end-diastolic diameter, LVESD: LV end-systolic diameter, IVS: intact ventricular septum, NS: Non-significant, n: Number

Table 4. Left atrial volumes, index volumes and fractions

	CSF (n=50)	Control group (n=40)	p-value
LAV_{max} (mL)	33±10	21.6±4.6	**<0.001**
$LAVI_{max}$ (mL/m^2)	16.6±4.6	11.3±2.1	**<0.001**
LAV_{min} (mL)	12.7±5.2	9.5±2.5	**<0.001**
$LAVI_{min}$ (mL/m^2)	6.4±3.3	5.0±1.3	**<0.001**
LAV_{preA} (mL)	25.4±7.6	13±3.5	**<0.001**
$LAVI_{preA}$ (mL/m^2)	12.8±2.8	6.8±2.6	**<0.001**
LATEV (mL)	20.3±7.5	12.1±2.8	**<0.001**
LATEVI (mL/m^2)	10.1±3.6	6.3±1.5	**<0.001**
LAPEV (mL)	7.6±3.8	8.6±2.6	**0.010**
LAPEVI (mL/m^2)	3.8±1.9	4.5±1.4	**0.010**
LAAEV (mL)	12.3±3.8	3.5±2.1	**<0.001**
LAAEVI (mL/m^2)	6.2±1.9	1.85±0.8	**<0.0001**
LACV (mL)	22.5±11.1	29±6.2	**<0.001**
LAVCVI (mL/m^2)	11.3±5.1	15.1±2.9	**<0.001**
LATEF (%)	61.4±9.4	57.3±6.4	NS
LAPEF (%)	23±9.1	39±9.6	**0.003**
LAAEF (%)	48±12.8	27±9.1	**0.008**

Significant p-values are shown in bold.
NS: Non-significant, CSF: Coronary slow flow, n: Number

A significant positive relationship was observed between Frame LAD and E/Em (p<0.001) and between Frame LAD and LAAEF (p<0.001). The graphs showing the relationship between Frame LAD and LAPEF, LAAEF, LATEF are shown in Figure 1. A significant positive relationship was observed between the Mean Frame and LAAEF (p=0.002) and between LAPEF and E/A (p<0.001). The relationship between the Mean Frame and LAAEF and the relationship between LAAEF and E/A is shown in Figure 2. Correlation analyses are shown in Table 6.

Discussion

CSF prevalence is 1% in patients with ACS[16]. In the TIMI-IIIA study, coronary arteries were found to have normal or non-significant CAD in 4% of patients with the diagnosis of unstable angina pectoris[17]. Atherosclerosis is a chronic, multifactorial and progressive process starting from early childhood. In intracoronary ultrasonography studies, atherosclerotic changes were observed in the coronary arteries of patients with CSF, and these lesions progressed to the media layer rather than the lumen.

Table 5. Coronary angiography parameters

	CSF (n=50)	Control group (n=40)	p-value
Frame LAD	36±8.9	29.5±2.5	<0.001
Frame CorLAD	20.5±5.1	17.3±1.5	<0.001
Frame Cx	24.3±7.8	20.7±2.4	0.006
Frame RCA	26±8.7	19.6±1.7	<0.001
Frame mean	28.7±5.6	23.3±1.7	<0.001

Significant p-values are shown in bold.
LAD: Left anterior descending artery, Cx: Circumflex artery, RCA: Right coronary artery, CSF: Coronary slow flow, n: Number

Table 6. Correlation analysis

	LAPEF	LAAEF	LATEF	E/A	E/Em
Frame LAD	r=-0.19 p=0.100	r=0.66 p<0.001	r=0.43 p<0.001	r=0.4 p=0.004	r=0.341 p<0.001
Frame CorLAD	r=-0.28 p=0.040	r=0.1 p=0.200	r=-0.17 p=0.900	r=0.31 p=0.024	r=0.01 p=0.900
Frame Cx	r=-0.2 p=0.100	r=0.05 p=0.600	r=-0.12 p=0.400	r=-0.27 p=0.590	r=0.06 p=0.66
Frame RCA	r=0.1 p=0.500	r=0.10 p=0.400	r=0.13 p=0.360	r=-0.1 p=0.460	r=0.08 p=0.560
Mean Frame	r=-0.16 p=0.260	r=0.42 p=0.002	r=0.24 p=0.090	r=-0.24 p=0.080	r=0.3 p=0.070
LAPEF	1	r=-0.14 p=0.330	r=0.52 p<0.001	r=0.44 p<0.001	r=0.12 p=0.380
LAAEF	r=-0.13 p=0.340	1	r=0.76 p<0.001	r=-0.40 p=0.003	r=0.14 p=0.330
LATEF	r=0.52 p<0.001	r=0.76 p<0.001	1	r=-0.05 p=0.700	r=0.17 p=0.210

LAD: Left atrial, LAD: Left anterior descending artery, Cx: Circumflex artery, RCA: Right coronary artery, A: Mitral late velocity, E: Mitral early velocity, Em: Early diastolic velocity, Sm: Systolic myocardial velocity, LAPEV: LA passive emptying volume, LAPEF: LA passive emptying fraction, LATEF: LA total emptying fraction, n: Number

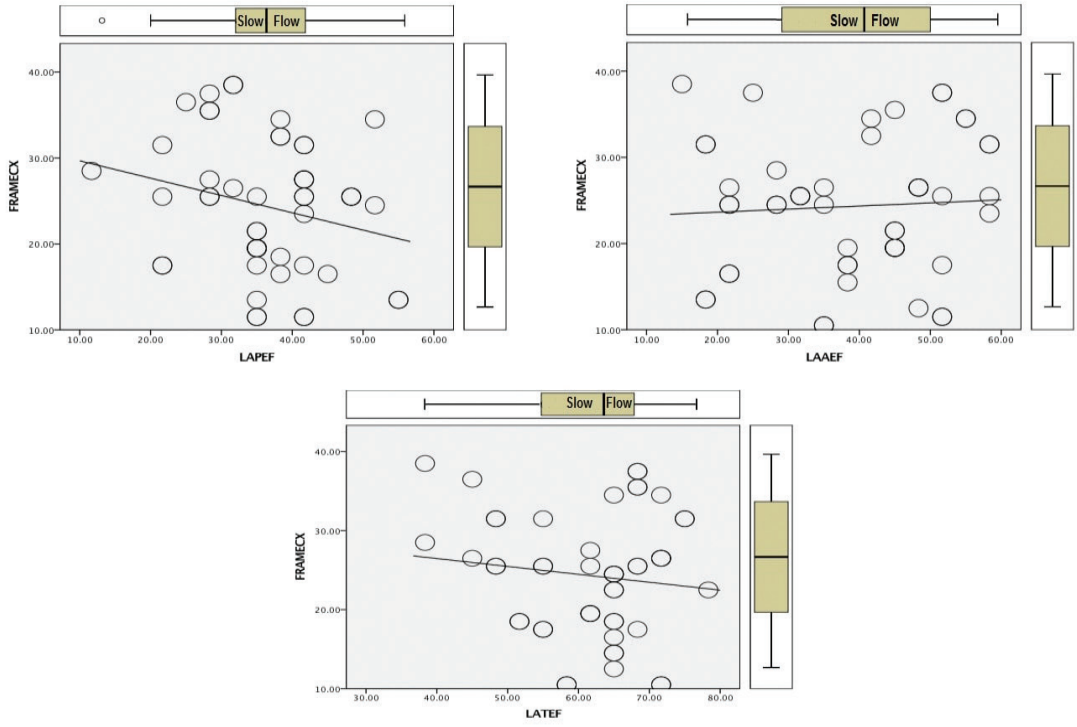

Figure 1. Charts showing correlations between Frame LAD and LAPEF, LATEF, and LAAEF

LAD: Left anterior descending artery, LAPEF: LA passive emptying fraction, LATEF: LA total emptying fraction, LAAEF: LA active emptying fraction

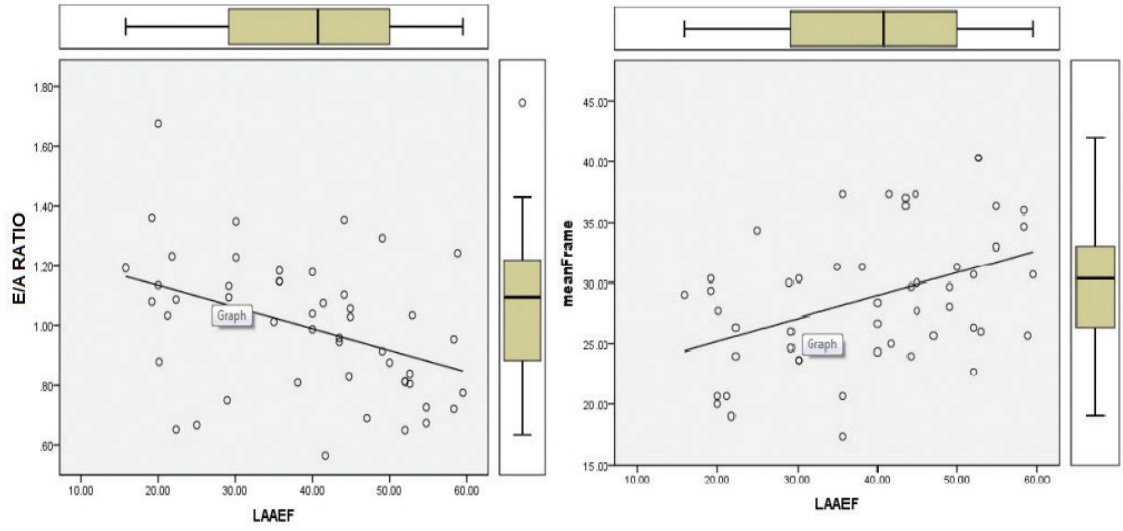

Figure 2. Correlation graphs between LAAEF and E/A, Mean Frame and LAAEF

LAAEF: LA active emptying fraction, A: Mitral late velocity, E: Mitral early velocity

Widespread calcification, intimal irregularity, atheroma plaques were observed in the vessel wall[7,8]. Therefore, CSF is believed to be an early process of atherosclerotic CAD.

Many studies have demonstrated that diastolic functions impair before LV systolic function in CAD. Although it is non-obstructive CAD, CSF affects left ventricular diastolic functions by causing ischemia at the microvascular level[18]. Li et al.[19], Wang et al.[20] and Suner et al.[9] showed that LV diastolic functions were significantly reduced in patients with CSF. Pritchett et al.[21] showed that the LA volume index indicated the severity of diastolic dysfunction. In our study, we found the E, E/A, and Em parameters to be lower in the CSF patients ($p<0.001$, $p=0.003$, $p=<0.001$, respectively). The Am was higher in the CSF group than in the control group ($p=0.01$). Em/Am was lower in the CSF group than in the control group ($p<0.001$). Our findings were consistent with studies showing LVDD in patients with CSF.

Tsang et al.[22] reported that the left atrial volume index was a sensitive morphophysiological indicator of diastolic functions and a useful parameter for future cardiovascular mortality and morbidity. LA volume and fractions may show the severity of LVDD[23]. In our study, LAV_{max}, LAV_{min}, LAV_{preA}, and index volumes were higher for the CSF group ($p<0.001$). E/Em was higher in the CSF group than in the control group ($p=0.003$). The E/Em ratio correlates with pulmonary capillary pressure and LV end-diastolic pressure. The LV filling consists of three-phase and involves the depot function of the LA during ventricular systole, active pump function in the late diastole, the passive conduit function in the early diastole. Left atrial mechanical ejaculation function is important for patients with LVDD[24]. Despite the decrease in passive filling in early diastole in cases such as ischemia, HT, and old age with which LV diastolic function impairs, active atrial pump function in late diastole has been found to maintain adequate cardiac output[25,26]. This contribution of LA to LV is explained by the Frank-Starling mechanism[27]. In our study, we found that LAPEV and fraction were low, LAAEV and fraction were increased. This can be explained as the compensation for keeping the LV stroke volume constant. While LV diastolic functions decrease, LA pump functions increase. However, this increase is not continuous, and after a certain point, LA myocyte functions may decrease due to intrinsic causes.

LA has three functions: Reservoir function, conduit function, and pump function[28]. The conduit function consists of two phases: passive discharge phase (fast filling phase) and diastasis phase. The passive phase depends on the relaxation, compliance, and viscoelastic properties of the myocardium, and the diastasis phase usually depends on LV compliance[29]. LAV conduit and index volumes were lower in CSF patients than in the control patients ($p<0.001$). This finding may support the reduction of LV compliance due to ischemia in patients with CSF.

A significant negative relationship between E/A and LAAEF was observed and it can be concluded that impaired diastolic functions will cause a rising in left atrial active functions. We found a significant positive relationship between Frame LAD and LAAEF, E/Em. There was no such relationship with RCA and Cx. These findings show that as the frame of LAD increases, left atrial contractions increase, and LA pressure increases. It can be explained by the fact that LAD feeds the larger myocardial area and causes greater microvascular ischemia.

Conclusion

Impaired LV diastolic functions and significant changes in LA volumes were found in patients with CSFP. We well know that increase in LA volumes causes high atrial fibrillation rates, stroke, and death. Therefore, maintaining the sinus rhythm in patients with CSF is becoming more important.

Ethics

Ethics Committee Approval: After the protocol for the study was prepared, approval was obtained from the Ethics Committee of Dicle University Faculty of Medicine (decision no: 190, date: 26/12/2015).

Informed Consent: All patients included in the study were informed about the study in accordance with the

ethical principles of human research, as stated in the second Helsinki declaration. All of the patients accepted to participate the present study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.A., E.T., H.Ç., Concept: B.A., H.Ç., Design: B.A., T.P., H.Ç., Data Collection and Process: B.A., T.P., M.Ö., A.A., M.K., Analysis or Interpretation: B.A., E.T., Literature Search: B.A., E.T., Writing: B.A., E.T.

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Research Article

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Total Serum Protein Predicted Mortality in Patients with St-elevation Myocardial Infarction Who Underwent Primary Percutaneous Coronary Intervention: Results of 8-Year Follow-up

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Abstract

Objectives: ST-elevation myocardial infarction (STEMI) is globally one of the leading causes of mortality. Determining modifiable mortality predictors to improve outcomes is critical. Total serum protein (TSP) is a composite indicator of immunity, nutrition, and inflammation and it plays a vital role in biological pathways contributing to cardiovascular diseases. TSP level has not been evaluated in patients with STEMI in the prediction of mortality previously.

Materials and Methods: The patients diagnosed with STEMI between March 2007 and May 2009 were included in the study. TSP was obtained at admission to the hospital. Follow-up period of the study was 8 years and primary endpoint was all-cause mortality. Participants were separated according to the presence of mortality and clinical parameters compared between these two groups.

Results: The mean age of the total 99 patients was 61±12.4 years and 82 (82.8%) of them were male. While left ventricular ejection fraction (LVEF) (p=0.001), serum albumin (p=0.014), and TSP (p<0.001) were lower, serum creatinine was

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higher (p=0.003) in the mortality group. Diabetes mellitus (p=0.007), increased age (p=0.027), LVEF (p=0.006), serum creatinine level (p=0.023), and TSP (hazard ratio: 0.159, 95% confidence interval: 0.062-0.408, p<0.001) predicted mortality independently.

Conclusion: TSP level predicted all-cause mortality independently in STEMI patients who underwent primary percutaneous coronary intervention during 8-year follow-up.

Keywords: ST-elevation myocardial infarction (STEMI), total serum protein (TSP), mortality, acute coronary syndrome, malnutrition

Introduction

ST-elevation myocardial infarction (STEMI) is still responsible for a large number of deaths globally, despite modern medical and interventional treatment options and early revascularization[1]. Therefore, determining the high-risk patient group is essential to provide earlier and intensive treatment modalities and for closer follow-up. Although many clinical factors that predict clinical outcomes in patients with STEMI have been identified, these scoring tools consisted of many clinical factors and were evaluated for less than 5 years. Besides, results were controversial[2]. Since clinical conditions such as myocardial fibrosis, ventricular remodeling, recurrent myocardial infarction (MI), ventricular dilatation, and arrhythmias, which are associated with mortality, occur in a long course, it can be asserted that longer follow-up could give more accurate results for mortality.

Serum albumin represents approximately half of the TSP and is the primary determinant of metabolic homeostasis. Albumin regulates microvascular permeability and plasma oncotic pressure, and has an antioxidant function. Hypoalbuminemia is a robust prognostic marker in patients with coronary artery disease (CAD)[3,4]. In addition, an elevated level of globulin, referred to as gamma gap (difference between TSP and albumin), was associated with a worse outcome. Gamma gap-related mortality was demonstrated to be caused by inflammation. However, it has been evaluated with a scarce number of studies[5].

On the other hand, total serum protein (TSP) is a composite indicator of immunity, nutrition, and metabolic balance by including albumin and globulin. Impaired nutritional status and immunity were shown to contribute to the prognosis of patients with CAD[6]. Therefore, TSP evaluation could be more beneficial to predict outcomes than albumin and globulin alone. Nevertheless, the prognostic value of TSP predicting mortality in STEMI has not been studied yet.

By considering the pivotal roles of TSP in cardiovascular diseases (CVDs), we postulated that a total protein could provide better mortality risk prediction above and beyond the known clinical risk factors, single protein, and established biomarkers. It was aimed to examine the role of TSP in predicting mortality in STEMI patients who underwent p-PCI during 8-year follow-up.

Materials and Methods

Study Population

This retrospective and observational study was carried with STEMI patients admitted to our clinic between March 2007 and May 2009. The sociodemographic data, past medical histories and detailed physical examinations of each patient were acquired at admission by experienced cardiologists and recorded in the database system of the hospital. Patients with ≥1 mm ST-elevation in consecutive leads related to one of the major coronary arteries' tertiaries on electrocardiography were accepted STEMI and delivered to angiography laboratory, immediately[1].

The STEMI diagnosis was confirmed by coronary angiogram. Institutional review board approved the study with 40465587-050.01.04-75 number on 09.04.2021 and the informed consent was obtained from patients or parents.

Cardiovascular Risk Factors

The diagnoses of hypertension and diabetes mellitus (DM) were established according to the current guidelines[7]. The presence of familial history of CAD was defined as the development of atherosclerotic CVD or death from CVD in a first-degree relative (ie, parent or sibling) prior to age of 55 years for males or 65 years for females. Those who smoke at least 1 cigarette a day were defined as a regular smoker. Body mass index (BMI) was obtained by the weight/[height (cm)^2] formula.

Laboratory Analysis

Suitable samples for routine biochemistry, hemogram, creatinine kinase-MB (CK-MB), troponin, and inflammation markers were received from all patients at admission. Glucose and lipid parameters were evaluated after at least 8 hours of fasting and were determined using standard methods. CK-MB and troponin-I (Tn-I) measurements were repeated at 4-hour intervals. As the laboratory indicates Tn-I above 50 ng/mL as >50 ng/mL, it was included in the analysis as 50 ng/mL. Blood samples obtained at the admission were immediately centrifuged, and the obtained serum specimen was awaited in a freezer at −20 °C. The amount of TSP was measured using colorimetric assay with the Beckman Synchron LX20.

Coronary Angiography and Percutaneous Coronary Intervention

Coronary angiography was conducted urgently using the Judkins technique in all patients. Left anterior descending and circumflex coronary arteries were viewed from at least four different angles and the right coronary artery from at least two different angles. The coronary artery with total occlusion was revascularized with the coronary balloon and/or stent immediately after imaging. Thrombolysis in Myocardial Infarction (TIMI) flow was evaluated. In epicardial arteries with a diameter of ≥1.5 mm, any lesion that caused at least 50% lumen narrowing compared to the closest segment was considered as significant stenosis. Intervention to the total occluded coronary artery at first angiogram was determined as the revascularization strategy. In case of a severe lesion other than the culprit lesion, elective PCI was planned. Patients were treated following the current guidelines and awaited in the coronary intensive care unit until stabilization was achieved[8].

Transthoracic Echocardiography

Detailed two-dimensional echocardiography was carried out in all patients before discharge and during routine follow-up by using Philips Epiq 7 systems (Andover, MA) and a 2.5–3.5-MHz transducer. Left atrial and ventricular dimensions and septal and posterior wall thickness were gained by M-mode echocardiography. In addition, conventional Doppler and Tissue Doppler parameters were obtained. Left ventricular ejection fraction (LVEF) was measured from left ventricular dimensions.

Exclusion Criteria

Patients complicated with PCI-related coronary dissection, coronary rupture, acute or hyperacute stent thrombosis, previous cardiovascular surgery with any indication, end-stage liver or kidney disease, malignancy, history of radiotherapy or chemotherapy, collagen vascular disease, history of cerebrovascular event, endocrine disorders, active or chronic inflammatory disease, moderate to severe valvular heart disease, pulmonary embolism, myocarditis, cardiogenic shock, previous cardiomyopathy and those with a BMI of 18.5 and/or below were excluded from the study.

Clinical Follow-up and Primary Endpoint

The primary endpoint of the study was all-cause mortality. The patients were followed for approximately 8 years. Mortality data were obtained by assessing the

hospital medical records and national death database. In case mortality data could not be reached, direct phone calls to patients or their relatives were performed.

Statistical Analysis

SPSS 23.0 version software package (Chicago, IL) was employed to analyze the obtained data. A two-tailed p-value of ≤0.05 was accepted as statistical significance. The Kolmogrov-Smirnov test and visual histograms were conducted to assess the normality assumption of variables. The homogeneity of variances was tested with the Levenes's test. While continuous variables were stated as mean ± standard deviation, categorical variables were presented with percentages. The chi-square test was employed to compare the categorical groups. While the two-tailed Student's t-test was conducted for parameters that were normally distributed, continuous parameters that were non-normally distributed were analyzed with the Mann-Whitney U test. The univariate regression analysis was carried out to assess the effects of the various variables on mortality. A p-value (2-tailed) of less than 0.05 was identified as statistical significance. The variables with unadjusted p<0.1 were accepted to be confounding factors and included in the multivariable Cox logistic regression analysis. The predictive value of TSP for mortality was estimated by areas under the receiver operating characteristic (ROC) curve. Cumulative surveys of above and below the determined TSP value were compared by the Kaplan-Meier analysis.

Results

The mean age of a total 99 patients was 61±12.4 years, and 82 (82.8%) of them were male. Patients were separated into two groups according to the presence of mortality. The mortality group was older (p=0.05) and had a higher rate of DM (p=0.02). Both groups exhibited similar characteristics in terms of gender (p=0.246), hypertension (p=0.456) and other demographic features (Table 1).

The time from the onset of the STEMI-related complaints to the percutaneous intervention was determined as the pain-to-balloon time, and although it did not reach statistical significance, it was found to be longer in the mortality group [270 (150-450) vs 330 (220-480), p=0.259]. On the other hand, TIMI flow after revascularization (p=0.001) and LVEF (45.4±10.5 vs 38.6±6.9, p=0.001) were lower in the mortality group. Furthermore, serum creatinine (0.93±0.22 vs 1.1±0.46 mg/dL, p=0.003) and fasting blood glucose [105 (92-122) vs 119 (97-176), p=0.008] were higher in the mortality group. Although they were within the normal range in both groups, hemoglobin (14.2±1.5 vs 13.2±1.3 g/dL, p=0.002), albumin (4.2±0.32 vs 4.0±0.33 mg/dL, p=0.014), and TSP (7.2±0.51 vs 6.8±0.45 mg/dL, p<0.001) were lower in the mortality group (Table 1).

Backward multivariable Cox regression analysis demonstrated that DM [hazard ratio (HR)=3.073, 95% confidence interval (CI)=1.361-6.931, p=0.007], age (HR=1.045, 95% CI=1.005-1.086, p=0.027), LVEF (HR=0.934, 95% CI=0.890-0.981, p=0.006), serum creatinine level (HR=3.025, 95% CI:=1.162-7.877, p=0.023), and TSP (HR=0.159, 95% CI=0.062-0.408, p<0.001) were determined as independent predictors of mortality (Table 2).

ROC analysis showed that TSP value below 6.95 mg/dL predicted mortality with 73.8% sensitivity and 69% specificity (AUC=0.211, p<0.001) (Figure 1). Additionally, the Kaplan-Meier curve showed that TSP <6.95 mg/dL increased the risk of mortality starting from the early phase up to 8 years of follow-up (Figure 2).

Discussion

It was found that TSP, age, presence of DM, serum creatinine level, and LVEF were independent predictors of mortality after 8-year follow-up in STEMI patients who underwent p-PCI. The role of TSP in predicting mortality after long-term follow-up has not been studied previously.

TSP consists of albumin and globulin fraction, including enzymes, complements, and carrier proteins. These proteins are mainly responsible for inflammation, immunity, and nutritional balance[6,8]. C-reactive protein, pro-brain natriuretic peptide (pro-BNP), fibrinogen, and

Table 1. Baseline characteristics of the study population.

Variable	Mortality (-) (n=68)	Mortality (+) (n=31)	All patients (n=99)	p-value
	Demographic data			
Age (years)	58.4±11.5	66.9±12.8	61±12.4	0.005
Gander (male), n (%)	58 (85.3)	24 (77.4)	82 (82.8)	0.246
Diabetes mellitus, n (%)	11 (16.2)	14 (45.2)	25 (25.3)	0.002
Hypertension, n (%)	24 (35.3)	12 (38.7)	36 (36.4)	0.456
Hyperlipidemia, n (%)	41 (60.3)	15 (48.4)	56 (56.6)	0.187
Current smoking, n (%)	30 (44.1)	8 (25.8)	38 (38.4)	0.183
BMI (kg/m²)	27.5±3.9	27.3±4.8	27.5±4.1	0.849
PBT (sec)	270 (150-450)	330 (220-480)	270 (172-450)	0.259
Heart rate (beat/min)	81 (62-94)	84 (70-91)	83 (69-92)	0.854
LV EF (%)	45.4±10.5	38.6±6.9	43.6±10.1	0.001
Killip				
1, n (%)	57 (83.8)	23 (74.2)	80 (80.8)	0.264
≥2, n (%)	11 (16.2)	8 (25.8)	19 (19.2)	
Laboratory data				
Peak CK-MB (ng/uL)	235 (128-300)	300 (175-300)	108 (94-139)	0.253
Peak Troponin (ng/uL)	45.2±10.8	46.9±8.9	45.7±10	0.471
WBC (10^3/μL)	11.06±3.9	12.8±5.1	11.5±4.3	0.082
Hemoglobin (g/dL)	14.2±1.5	13.2±1.3	13.9±1.5	0.002
Creatinine (mg/dL)	0.93±0.22	1.1±0.46	0.97±0.30	0.003
Fasting glucose (mg/dL)	105 (92-122)	119 (97-176)	108 (94-139)	0.008
HsCrp (mg/dL)	0.39 (0.29-1.11)	0.76 (0.210-1.48)	0.43 (0.25-1.28)	0.093
Total Protein (mg/dL)	7.2±0.51	6.8±0.45	7.1±0.5	<0.001
Albumin (mg/dL)	4.2±0.32	4.0±0.33	4.1±0.33	0.014
Type of MI (anterior), n (%)	30 (44.1)	18 (58.1)	48 (48.5)	0.202
Angiographic data				
IRA count				
1	23 (33.8)	4 (12.9)	27 (27.3)	0.020
2	25 (36.8)	12 (38.7)	37 (37.4)	
3	20 (29.4)	15 (48.7)	35 (35.4)	
IRA				
LAD	31 (45.6)	18 (58.1)	49 (49.5)	0.389
RCA	25 (36.8)	8 (25.8)	33 (33.3)	
CX	12 (17.6)	5 (16.1)	17 (17.2)	
Final TIMI flow, n (%)				
0-1	5 (7.4)	3 (9.7)	8 (8.1)	0.001
2	8 (11.8)	14 (45.2)	22 (22.2)	
3	55 (80.9)	14 (45.2)	69 (69.7)	
Medication at discharge				
ASA, n (%)	68 (100)	27 (87.1)	95 (96)	0.734
Clopidogrel, n (%)	68 (100)	29 (98.3)	97 (98.9)	0.987
CCB, n (%)	3 (4.4)	0 (0)	3 (3)	0.405
BB, n (%)	65 (95.6)	24 (77.4)	89 (89.9)	0.121
Statin, n (%)	66 (97.1)	27 (87.1)	93 (93.9)	0.747
ACEI/ARB n (%)	65 (95.5)	29 (93.5)	94 (94.9)	0.153

BMI: Body mass index, PBT: Paint o balloon time, LVEF: Left ventricle ejection fraction, CK-MB: Creatine kinase, WBC: White blood count, HsCrp: High sensitive C-reactive protein, MI: Myocardial Infarction, IRA: Infarct related artery, LAD: Left anterior descending artery, RCA: Right coronary artery, CX: Circumflex artery, ASA: Acetyl salicylic acid, CCB: Calcium channel blocker, BB: Beta blocker, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blockers, n: Number

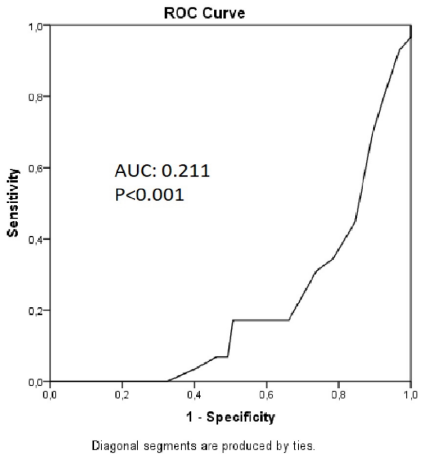

Figure 1. TSP <6.95 mg/dL predicted mortality with 73.8% sensitivity and 69% specificity

TSP: Total serum protein, ROC: Receiver operating characteristic, AUC: Area under the curve

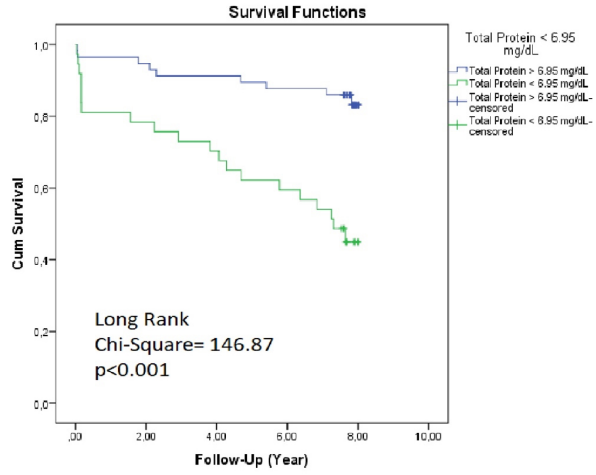

Figure 2. Kaplan-Meier curve showing TSP <6.95 mg/dL increases the risk of mortality for 8 years of follow-up

TSP: Total serum protein, Cum: Cumulative

Table 2. Regression analysis for mortality predictors

	Univariable			Multivariable		
Variable	**OR**	**95%CI**	**p-value**	**OR**	**95%CI**	**p-value**
Diabetes mellitus	3.240	1.593-6.591	0.001	3.073	1.361-6.931	0.007
Fasting glucose	1.008	1.004-1.013	<0.001			
Age	1.055	1.021-1.090	0.001	1.045	1.005-1.086	0.027
LVEF	0.933	0.895-0.972	0.001	0.934	0.890-0.981	0.006
Hemoglobin	1.103	1.082-1.124	0.018			
Serum creatinine	4.716	2.097-10.604	<0.001	3.025	1.162-7.877	0.023
Total Protein	0.246	0.113-0.535	<0.001	0.159	0.062-0.408	<0.001
Albumin	0.275	0.107-0.702	0.007			
IRA count	1.818	1.120-2.951	0.016			
Final TIMI flow	0.515	0.330-0.802	0.003			

LVEF: Left ventricle ejection fraction, IRA: Infarct related artery, TIMI: Thrombolysis in myocardial infarction, OR: Odds ratio, CI: Confidence interval

albumin are also established proteins among TSP, which was shown to play an active role in CVDs. These proteins have also been shown to be associated with mortality in MI patients[9]. Albumin constitutes the major component, and its effects on the cardiovascular system are responsible for most of the functions of TSP[4]. On the other hand, few studies were conducted with globulin or gamma gap evaluating their effects on prognosis. Low globulin is also shown to be associated with the atherosclerosis development starting from the fatty streaking phase, and gamma globulin therapy prevents the progression of atherosclerosis[5]. On the contrary, an elevated amount of globulin and its equivalent, albumin to globulin ratio, is related to higher mortality rate. We found that albumin

could not predict mortality independently. Our results have supported the fact that a decrease in globulin level increases mortality rate. Thus, it can be postulated that the globulin has more effects than known and plays an active role in the post-MI course. However, the predictive role of the alteration in the albumin level seems superior to that of the other proteins, yet further prospective studies are needed.

Albumin affects the cardiovascular system by regulating plasma oncotic pressure, microvascular permeability, maintenance of acid-base balance, and the transport of many endogenous and exogenous molecules[3,9]. Hypoalbuminemia was demonstrated to be associated with elevated adverse outcomes in various clinical settings such as heart failure, stroke, peripheral artery disease, renal failure, and CAD[10,11]. Besides, albumin has a substantial role in the atherosclerotic process in line with following mechanisms: (I) Heparin-like platelet inhibition function, (II) Prostacyclin (PGI2), which is a natural vasodilator and platelet aggregation inhibitor and functions upon albumin concentration, and (III) Homocysteine, which is known to induce atherosclerosis and acts by binding to albumin. Therefore, a reduction in the albumin level diminishes the anti-atherosclerotic effects of PGI2 and homocysteine. Furthermore, hypoalbuminemia is shown to induce the new MI in patients with CAD[12].

Albumin is a highly antioxidant component of TSP. STEMI causes cellular dysfunction by creating reactive oxygen species (ROS) followed by oxidative stress, and albumin absorbs these ROS radicals[13]. In addition, bilirubin and nitric oxide, the antioxidant molecules, function depending on albumin. The decreased albumin is associated with elevated oxidative stress and consequent myocardial damage[14]. Thus, a higher mortality rate, when the TSP level is lower, can be explained by decreased antioxidant activity. Meanwhile, albumin is also a negative acute-phase reactant inversely correlated with inflammation, and it is a marker of a potency of inflammatory response secondary to STEMI[15].

It is important to state that albumin has a substantial role in the pharmacokinetics of cardiovascular drugs, especially clopidogrel and aspirin. Previous experimental studies found that low albumin level was associated with aspirin resistance in CAD patients[16,17]. Correspondingly, it can be asserted that lower TSP level is associated with decreased cardiovascular drug efficacy. Further studies regarding the relationship of TSP with cardiovascular pharmacology are needed.

Immune response initiates to repair myocardial damage just after MI. Immunoglobulins, cytokines, and complements have a crucial role in this immune response. It is established that patients with suppressed immunity are more vulnerable to future adverse clinical events after MI[5,18]. Hence, it can be asserted that lower TSP is related to an inadequate immune response, which is associated with increased mortality. On the other hand, malnutrition was shown to be associated with poor outcomes in patients with malignancy, undergoing surgery, and with CAD in several studies[19,20]. For that purpose, albumin and albumin-based indices such as prognostic nutritional index, nutritional risk index, and mini nutritional assessment were used to predict outcomes in various clinical settings[21]. With this respect, it could be argued that TSP is a better malnutrition marker than albumin or globulin alone.

Study Limitations

This is a single-center study with a limited number of patients. The effect of albumin level on mortality through possible reduction of drug efficacy was ignored. Secondly, the changes in patient-related cardiovascular risk factors, medications and device therapies, follow-up centers, and new interventions may affect adverse event rates over decades. Non-cardiovascular mortality may be higher than expected in 8 years.

Conclusion

TSP is an independent predictor of all-cause mortality in patients with STEMI, who underwent p-PCI, during 8-year follow-up. It could be possible to improve the mortality rate by regulating the total protein level in these patients.

Ethics

Ethics Committee Approval: Recep Tayyip Erdoğan University Ethics Committee has approved the study with 40465587-050.01.04-75 number on 09.04.2021 and the informed consent were obtained from patient or parents.

Informed Consent: Informed consent were obtained from patient or parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.S.Y., F.K., Design: A.S.Y., F.K., Data Collection or Processing: A.S.Y., M.Ç., Analysis or Interpretation: A.S.Y., A.G.Ö., M.Ç., Literature Search: A.S.Y., M.Ç., Statistical Analysis: M.Ç., F.K., Writing: A.S.Y., Critical review: A.G.Ö., F.K.

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