ORIGINAL ARTICLE

The serum triglyceride to high-density lipoprotein (HDL) ratio in patients with acute coronary syndrome with and without renal dysfunction

Alen Džubur[1], Malik Ejubović[2], Almir Fajkić[3], Amela Dervišević[4], Azra Durak Nalbantić[1,] Ajla Avdić Agić[5], Amela Džubur[6], Mevludin Mekić[1]

[1]Clinic for Heart Disease, Blood Vessels and Rheumatism, University Clinical Centre Sarajevo, Sarajevo, [2]Department of Internal Diseases, Cantonal Hospital Zenica, Zenica, [3]Department of Pathophysiology, [4]Department of Human Physiology; School of Medicine, University of Sarajevo, Sarajevo; Bosnia and Herzegovina, [5]Marien Hospital Witten, Witten , Germany, [6]Department of Public Health, School of Medicine, University of Sarajevo, Sarajevo, Bosnia and Herzegovina

Corresponding author:

Malik Ejubović

Department of Internal Diseases,

Cantonal Hospital Zenica

Crkvice 67, 72000 Zenica,

Bosnia and Herzegovina

Phone: +387 32 447 000;

Fax: +387 32 447 000;

E-mail: ejubovic.malik@gmail.com

Alen Džubur ORCID ID: https://orcid.org/0000-0003-1198-540X

ABSTRACT

Aim To assess triglyceride – to high-density lipoprotein cholesterol (TG/HDL)-C ratio in patients with acute coronary syndrome (ACS) and to verify its association with renal dysfunction.

Methods A cross sectional study included 85 ACS patients divided in two groups with (ACS – RD) and without (ACS-nRD) presence of renal dysfunction, and 35 healthy subjects. Blood pressure, blood glucose, C-reactive protein, urea, creatinine, eGFR and serum lipids levels (total cholesterol, triglycerides, LDL-C, HDL-C) was measured in all participants. Based on the values of the measured lipid fractions TG/HDLc ratio was calculated.

Results Patients in ACS group had significantly lower HDL-C level (p<0.0005) but significantly higher TG level (p=0.046) and TG/HDL-C ratio (p<0.0005) than controls. There was a significant increase (p<0.0005) in TG/HDL-C ratio in ACS-RD group compared to ACS-nRD group. The ACS-RD group had significantly higher level of TG (p=0.001), serum urea (p=0.02) and creatinine (p<0.0005) compared to the ACS-nRD group. With a cut-off level of 1.135 TG/HDL-C ratio had a sensitivity of 77.6% and a specificity of 62.9% in distinguishing between ACS patients and healthy subjects. With cut-off value of 1.905 TG/HDL-C ratio had a sensitivity of 75.9% and a specificity of 78.6% in distinguishing between ACS patients with and without renal dysfunction.

Conclusion This study confirms the reliability of the TG/HDL-C ratio as a simple, low cost and useful marker in distinguishing between patients with ACS and healthy subjects and ACS patients with and without renal dysfunction.

Key words: eGFR, NSTEMI, STEMI, TG/HDL-C ratio

INTRODUCTION

Acute coronary syndrome (ACS) is the acute phase of myocardial ischemia, which includes clinical manifestations of unstable angina (UA), ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) (1). Many factors are involved in the pathogenesis of acute myocardial infarction (AMI), and several studies have indicated a lipid metabolism disorder as one of the key factors in the development of this disease (2). Today, there has been growing interest in the role of the triglyceride (TG) – to – high-density lipoprotein cholesterol (HDL) cholesterol (C) (TG/HDL-C) ratio as a more practical and easy to use atherogenic marker (3). According to Da luz PL et al. (4) this ratio shows promise as an attractive surrogate index of the atherogenicity of the plasma lipid profile. In the general population, an elevated serum TG/HDL-C ratio has been identified as a risk factor for cardiovascular (CV) disease and mortality (5). Previous studies have shown that there is a correlation between TG/HDL-C ratio and insulin resistance, and that TG/HDL-C ratio may be a better predictor of CV events than other lipid parameters, such as TG, low density lipoprotein-cholesterol (LDL-C) or total cholesterol/HDL-C ratio (6).

Renal dysfunction is a strong predictor of end-stage renal disease and CV disease. Recent studies suggest that renal function, measured by the estimated glomerular filtration rate (eGFR), is an independent prognostic factor for CV disease. Renal injury in ACS is a multifactorial phenomenon that could be promoted by underlying renal dysfunction, but it is more often influenced by a number of contributing factors (7). Thus, early identification of renal dysfunction using simple and inexpensive diagnostic tools, is essential for improving diagnosis and risk stratification and for the detection of the fundamental pathophysiological mechanisms that link renal function and ACS.

Today, there are still little data showing the correlation between TG/HDL-C and eGFR values as indicators of renal damage in patients with ACS.

The aim of this study was to assess TG/HDL-C ratio values of the patients with acute coronary syndrome (ACS) and to verify its association with types of ACS and eGFR.

PATIENTS AND METHODS

Patients and study design

The cross-sectional, clinical, comparative study was conducted among 85 patients with ACS who were admitted to the Clinic for Heart Disease, Blood Vessels and Rheumatism, University Clinical Centre Sarajevo (UCCS) between January 2015 and January 2017. The diagnosis of ACS was defined by the current guidelines (8), based on cardiac symptoms, electrocardiographic appearance, and biomarkers reflecting myocardial damage. Information about the age, gender and the history of hypertension of the patients were collected from their medical records. Individuals were not eligible for the study if they were younger than 20 years, were unable to provide consent, had a known and active urinary infection, malignancy, febrile disorder, acute or chronic inflammatory diseases, or were taking lipid-lowering therapies during the study period.

The control group consisted of 35 healthy subjects without a family history of coronary heart diseases, dyslipidaemia, hypertension, autoimmune or rheumatic diseases and with normal thyroid, renal and hepatic functions. None of the control subjects had received any medication and none were current smokers or consumers of alcohol. Written informed consent for inclusion in the study was obtained from all patients and healthy controls. The study was carried out in accordance with the Declaration of Helsinki as revised in 2000. The Ethical Committee of the Clinical Centre University of Sarajevo approved this study.

Methods

Renal function was evaluated by the estimated glomerular filtration rate (eGFR) calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula (9):

eGFR (mL/min/1.73m^2) = 175 x [Serum Creatinine (μmol/L) x 0.0113]$^{-1.154}$ x Age (years)$^{-0.203}$ (x 0.742 if female)

Renal dysfunction was defined as an eGFR < 60 ml/minute/1.73m^2.

According to eGFR, patients with ACS were divided into two groups: ACS patients with renal dysfunction (ACS-RD group; n = 29) and ACS patients without renal dysfunction (ACS-nRD group; n = 56).

The systolic and diastolic blood pressures (BP) in the arm were measured by well-trained doctors using a calibrated standard mercury sphygmomanometer while the participants were in a sitting position after a 5-min rest.

Blood was collected under aseptic precautions in the morning after overnight fast, after a 30-min rest in a semi-recumbent position from all patients and controls. Blood was taken without stasis from antecubital vein, using the vacutainer technique (10 mL vacutainer tubes; BD Vacutainer Systems, PL6 7BP, Plymouth, UK). Biochemical analyses were performed the same day at the Institute of Clinical Chemistry and Biochemistry, the UCCS. Lipid parameters were determined on automated apparatus (Dimension RxL Max, Dade Behring, Germany) using standard enzymatic methods.

Serum total cholesterol (TC) was measured by the cholesterol oxidase method, while high-density lipoprotein cholesterol (HDL-C) levels were determined by the direct homogeneous enzymatic method. Serum triglyceride (TG) levels were assayed after enzymatic hydrolysis, by the simultaneous enzymatic determination of glycerol. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula (LDL-C = TC − HDL-C − TG/5). The reference values for TG, TC, LDL-C, HDL-C (according to manufacturer's instructions) were: TC: 3.1 - 5.2 mmol/L, HDL-C: 1.06 - 1.94 mmol/L, TG: 0.11 - 1.7 mmol/L, LDL-C: 2 - 4.3 mmol/L. In addition, the TG/HDL-C ratio was calculated.

The fasting serum C-reactive protein (CRP) level was determined using the immunoturbidimetric assay (Beckman Synchron LX System). Serum concentration of creatinine (Cr) and urea were determined by kinetic colorimetric tests (Beckman Coulter, Ireland on Olympus AU 400).

Statistical analysis

The Kolmogorov-Smirnov or Shapiro-Wilk test of normality were used to test the normality and variance homogeneity of data. Data were presented as mean ± standard deviation (SD) for normally distributed variables and as median and interquartile ranges for skewed variables. Categorical variables were reported as frequency (percentage) and compared using $\chi 2$ test as appropriate. The difference in normally distributed data was tested by independent two-sample t-test. The difference in the values of parameters that showed a skewed distribution was assessed by Kruskal-Wallis, followed by Mann-Whitney U-tst. To determine the accuracy and respective best cut-off values of the TG/HDL-C ratio for differentiating patients with ACS from healthy controls, and ACS patients with renal failure from ACS patients without renal failure the Receiver Operating Characteristic (ROC) curves and their corresponding areas under the curve (AUC) were used. Accuracy rate diagnosing measures were calculated with the 95% Confidence Interval (95% CI). The optimal cut-off values were determined using the Receiver Operator Characteristic (ROC) curve analysis with the Youden index [maximum (sensitivity + specificity - 1)]. A cut-off value with the maximum Youden index of the ROC curve was defined as the optimal the TG/HDL-C ratio cut-off point to diagnose ACS and one separating ACS patients with renal insufficiency from ACS patients without renal insufficiency. A p<0.05 was considered statistically significant for all comparisons.

RESULTS

There were no significant differences between patients with ACS and control subjects with respect to gender (p=0.750) or age (p=0.156). Systolic blood pressure, diastolic blood pressure, blood glucose levels, CRP, serum urea and creatinine levels were significantly higher in ACS patients than in controls (p<0.0005). On lipid profiles, patients in the ACS group had significantly lower HDL-C level (p<0.0005), but significantly higher TG level (p=0.046) and TG/HDL-C ratio values (p<0.0005) than the control group. However, TC and LDL-C variables did not differ significantly between the groups (p=0.106, p=0.138 respectively) (Table 1).

Among patients with ACS, 43 (50.6%) had a diagnosis of STEMI and 42 (49.4%) NSTEMI. Patients in the STEMI group presented with higher values of both systolic and diastolic blood pressure, but the differences were not significant (p=0.318 and p=0.651, respectively).The median serum level of blood glucose, CRP, urea and creatinine were similar in both groups (p=0.306, p=0.453, 0.989, and p=0.840, respectively). On the lipid profiles, there were no differences

Table 1. Demographic data, clinical and biochemical parameters of the study population

Variable	ACS group	Control group	p
Males (n/%)	44 (51.8)	18 (51.4)	0.750
Females (n/%)	41 (48.2)	17 (48.6)	
Age (years)*	64.11±11.9	60.8±10.9	0.156
History of hypertension (n/%)	62/72.9	-	-
SBP (mmHg)*	158.5±17.4	119.4±9.6	<0.0005
DBP (mmHg)*	98.7±8.6	80.1±7.6	<0.0005
Blood glucose (mmol/L)	7.0 (5.5-8.9)	5.0 (496-5.4)	<0.0005
CRP (mg/L)†	7.5 (6.2-9.1)	0.8 (0.4-1.5)	<0.0005
Serum urea (mmol/L)†	7.0 (5.4-10.0)	4.3 (3.7-5.9)	<0.0005
Serum creatinine (μmol/L)†	88.0 (74.5-111.5)	64.5 (56.5-79.3)	<0.0005
TC (mmol/L)†	5.2 (4.1-6.3)	5.7 (5.1-6.2)	0.106
TG (mmol/L)†	1.6 (1.2-2.2)	1.5 (0.9-1.7)	0.046
HDL-C (mmol/L)†	1.0 (0.8-1.2)	1.4 (1.2-1.6)	<0.0005
LDL-C (mmol/L)†	3.3 (2.5-4.3)	3.6 (3.2-4.4)	0.138
TG/HDL-C ratio	1.7 (1.2-2.3)	0.9 (0.6-1.4)	<0.0005

*mean ± SD, †median (interquartile range, IQR); ACS, acute coronary syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C reactive protein; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol

in TC, HDL-C, TG, LDL-C and TG/HDL-C ratio between the STEMI and NSTEMI groups (p=0.550, p=0.323, p=0.836, p=0.171, and p=0.501, respectively) (Table 2).

Table 2. Demographic data, clinical and biochemical parameters in the ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) group

Variable	STEMI group	NSTEMI group	p
SBP (mmH)*	160.4±17.9	156.6±17.0	0.318
DBP (mmHg)*	99.1±8.5	98.2±8.8	0.651
Blood glucose (mmol/L)†	6.7 (5.5-8.0)	7.7(5.7-9.2)	0.306
CRP (mg/L)†	7.3 (6.2-10.4)	7.5 (6.3-8.6)	0.453
Serum urea (mmol/L)†	7.0 (5.6-9.5)	7.0 (5.0-10.0)	0.989
Serum creatinine (μmol/L)†	86.0 (75.0-109.0)	88.5 (74.0-114.3)	0.840
TC (mmol/L)†	5.4 (4.4-6.3)	5.1 (4.0-6.3)	0.550
TG (mmol/L)†	1.5 (1.2-2.3)	1.6 (1.1-2.1)	0.836
HDL-C (mmol/L)†	1.0 (0.8-1.3)	1.0 (0.8-1.1)	0.323
LDL-C (mmol/L)†	3.5 (2.8-4.5)	3.1 (2.4-4.0)	0.171
TG/HDL-C ratio	1.6 (1.0-2.1)	1.7 (1.2-2.6)	0.501

*mean ± SD, †median (IQR); SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol

No significant difference in systolic blood pressure (p=0.172), diastolic blood pressure (p=0.368), serum blood glucose (p=0.08) and CRP level (p=0.265) was observed between ACS patients with and without renal dysfunction. The median serum urea and creatinine level was significantly higher in patients in the ACS-RD group than in patients in the ACS-nRD group (p=0.02 and p<0.0005, respectively). The lipid profile of these patients showed significantly higher

value of TG (p=0.001) and TG/HDL-C ratio (p<0.0005), while the differences in TC, HDL-C, LDL-C level were not significant (p=0.422, p=0.409, and p=0.676, respectively) (Table 3).

Table 3. Demographic data, clinical and biochemical parameters in the acute coronary syndrome (ACS) patients with renal dysfunction (ACS-RD group) and ACS patients without renal dysfunction (ACS-nRD group)

Variable	ACS-RD group	ACS-nRD group	p
SBP (mmHg)*	162.1±21.2	156.6±15.1	0.172
DBP (mmHg)*	99.8± 8.1	98.0±8.9	0.368
Blood glucose (mmol/L)†	8.0 (6.9-11.0)	6.4 (5.4-8.2)	0.08
CRP (mg/L)†	7.2 (6.2-8.8)	7.9 (6.3-10.0)	0.265
Serum urea (mmol/L)†	10.0 (5.8-13.3)	6.5 (5.2-8.0)	0.02
Serum creatinine (μmol/L)†	117.0 (104.0-152.5)	79.5 (70.3-93.5)	<0.0005
TC (mmol/L)†	5.6 (4.5-6.2)	5.0 (4.0-6.5)	0.422
TG (mmol/L)†	2.0 (1.5-3.1)	1.3 (1.1-1.8)	0.001
HDL-C (mmol/L)†	1.0 (0.7-1.2)	1.0 (0.9-1.2)	0.409
LDL-C (mmol/L)†	3.4 (2.9-4.1)	3.2 (2.4-4.5)	0.676
TG/HDL-C ratio	2.2 (1.7-2.9)	1.4 (1.0-1.9)	<0.0005

*mean ± SD, †median (IQR); SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol

The ROC curve for the TG/HDL-C ratio value in the total sample of ACS patients vs. healthy controls showed significant area under the curve (AUC) (Figure 1A).

The optimal cut-off values for TG/HDL-C ratio in differentiating ACS patients from healthy subjects selected by ROC curve was 1.135, with sensitivity of 77.6%, specificity of 62.9%, positive predictive value of 83.5% and negative predictive value of 53.7% (Figure 1A, Table 4).

Table 4. Optimal cut-off area under the curve with 95% confidence interval (AUC, 95% CI), sensitivity (SEN), specificity (SPE), positive (PPV) and negative predictive value (NPV), overall accuracy of the TG/HDL-C ratio in differentiating between ACS (acute coronary syndrome) patients and healthy controls and between ACS patients with and without renal dysfunction

Variable and cut-off value	Diagnostic measurements						p
	AUC (95% CI)	SEN	SPE	PPV	NPV	Overall accurate	
ACS patients vs healthy controls							
TG/HDL-C ratio (≤1.135)	0.780 (0.70-0.86)	77.6%	62.9%	83.5%	53.7%	73.3%	<0.0005
ACS patients with renal dysfunction vs ACS patients without renal dysfunction							
TG/HDL-C ratio (≤1.905)	0.800 (0.70-0.90)	75.9%	78.6%	64.7%	86.3%	77.6%	<0.0005

TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; AUC, Area under the curve; CI, Confidence interval; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value
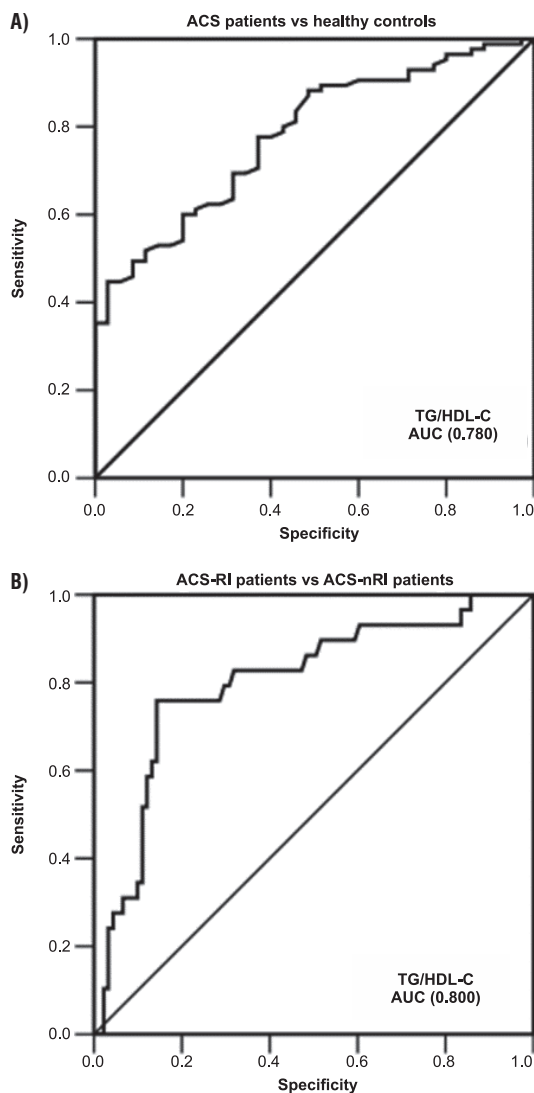
Figure 1. (A) Receiver operating characteristic (ROC) curve of the triglyceride – to high-density lipoprotein cholesterol (TG/HDL)-C ratio for differentiation between the acute coronary syndrome (ACS) patients and healthy controls; (B) ROC curve of TG/HDL-C ratio value for differentiation between ACS patients with (ACS-RI) and without (ACS-nRI) renal dysfunction

The overall accuracy of the value of the TG/HDL-C ratio in the determination of ACS patients was 73.3%. The TG/HDL-C ratio had fair diagnostic accuracy for differentiation between ACS patients and the healthy control (AUC 0.780; p<0.0005).

The optimal cut-off value for the TG/HDL-C ratio in differentiating ACS with renal dysfunction and ACS patients without renal dysfunction selected by the ROC curve (AUC 0.800; p<0.0005) was 1.905 (sensitivity 75.9%, specificity of 78.6%, positive predictive value of 64.7% and negative predictive value of 86.3%). The TG/HDL-C ratio had good diagnostic accuracy in differentiating

ACS with and without renal dysfunction with an overall accuracy of 77.6% (Figure 2B, Table 4).

DISCUSSION

The main finding of our study is that the TG/HDL-C ratio is a good diagnostic marker in differentiating ACS with and without renal dysfunction. Analysing the lipid status it was found that the values of TG and the TG/HDL-C and LDL ratio in the ACS-RD group were higher than the values in the serum of patients in the ACS-nRD group. Epidemiological studies have shown a large increase in the number of patients whose ACS development is accompanied by simultaneous renal damage. Around 20% of patients hospitalized with acute myocardial infarction in the USA will develop acute renal dysfunction, which may be partially or completely irreversible (10). The data from the American National Medical Database, which cover a period of 8 years, show that the number of patients with diagnosed terminal renal failure and myocardial infarction increased by 1.5 times, while the mortality rate of hospitalized patients increased from 22 to 25% (11). According to ACTION criteria, renal disease was identified in 31% of patients with non-ST-segment elevation myocardial infarction, and in 43% with ST-segment elevation myocardial infarction. Acute renal damage occurred in 16% and severe renal damage in 4% patients (12).

Renal dysfunction is still characterized by an unclear pathophysiology and insensitive diagnostic tools that make its diagnosis difficult, particularly in the diagnosis of CV disease, especially ACS (13). Today, many researchers are trying to establish the possible role of dyslipidaemia, as one of the main pathways in ACS-RD pathogenesis.

Lipid abnormalities have long been suspected to contribute to atherosclerosis; several studies have established a strong correlation between TC, LDL-C or low HDL-C and the incidence of atherosclerosis-related diseases such as ischemic heart disease and renal failure (14).

The TG/HDL-C ratio, a novel biomarker, has been identified as an indicator of insulin resistance and atherogenic dyslipidaemia (14). Some authors have linked a high TG/HDL-C ratio as an easily obtainable atherogenic marker to coronary atherosclerosis, impaired heart rate recovery after exercise, CV and all-cause death (15,16). Bittner et al (17) reported that the TG/HDL-C ratio is a powerful predictor of total mortality independent

of important prognostic variables in patients with suspected myocardial infarction. They also found a strong relationship between the TG/HDL-C ratio and the severity of coronary artery disease, as well as subsequent CV events.

The results of his study have found that the TG/HDL-C ratio was statistically significantly higher in patients with ACS than in the control group, and the results of the ROC analysis indicated that this ratio is a good biomarker in differentiating ACS patients with and without renal dysfunction. Our results are in accordance with the results of previous studies. Maki et al. (18) found that the ratio of TG to HDL-C independently predicted carotid intima-media thickness (cIMT) progression in subjects at moderate risk of heart disease. TG/HDL-C ratio and HDL-C have been demonstrated by ROC analysis to be useful markers for the detection of the extent of coronary disorders. Recent studies also have shown that the TG/HDL-C ratio is associated with the severity of coronary disease (19).

The association between the TG/HDL-C ratio and renal disease has been established in many studies, but in the presence of the chronic renal dysfunction. Tangvarasittichai et al. (20) reported that an elevated TG/HDL-C ratio was associated with chronic renal disease, and may increase the rate of disease progression and predict decline in renal function and structural damage.

Sonmez et al (21) demonstrated that an elevated TG/HDL-C ratio predicts poor CVD outcome in subjects with CKD, and proposed this ratio as a simple, inexpensive, and reproducible marker of CVD risk in chronic renal diseases.

It is unquestionable that some lipid fractions play a role in the complex pathogenesis of CV and renal disease, but more detailed data about this are still unclear. Some authors have proposed the possible role of free fatty acids (FFA) in the common pathogenesis of these disorders (22).

It is known that FFA promotes lipid accumulation in several non-adipose tissues, primarily including cardiac and renal tissue, a phenomenon called lipotoxicity, which could explain their influence on the development of these two organs (23).

No available data were found in the literature about lipid status of patients with renal function disorders in addition to ACS. It is important to emphasize that lipid status disorders lead to atherosclerotic changes, which can accelerate the development of heart and renal disease. Olechnowicz-Tietz et al. (24) included 446 patients with both ACS and chronic renal failure, and found that moderate and severe renal function impairment was associated with the rapid development of atherosclerotic changes. The authors consider this to be a major step towards the development of CVD, especially in the case of coronary syndrome. Although a growing body of evidence supports the predictive power of the TG/HDL-C ratio overall and in certain subgroups, very few studies have analysed it in patients with renal function disorders (21, 25). Kim et al. (26) showed that in patients with normal and mild renal dysfunction a higher TG/HDL-C ratio was significantly associated with an increased risk of major adverse CV events. However, in patients with moderate renal dysfunction the TG/HDL-C ratio lost its predictive value.

Since by searching the literature we could not find any similar studies, we could not compare our results with results of other authors. Further longitudinal and comparative studies are needed to investigate the mechanisms underlying this phenomenon.

In conclusion, a connection between heart and renal function exists both in physiological and pathophysiological conditions, and it is two-way and very complex. In patients with ACS, a comorbid decline in renal function aggravates the prognosis and complicates the diagnosis and treatment of these patients. Reduced renal function is a major risk factor with both an increased risk for recurrent CV morbidity and mortality. The TG/HDL-C ratio is a good, useful, low cost and simple biomarker that can be used for recognition of possible future complications in ACS patients, especially disorders of renal function.

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TRANSPARENCY DECLARATION

Competing of interest: None to declare.

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