

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Are liver function biomarkers independently associated with Framingham risk score in women?

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Introduction/Objective Given the contradictory results regarding the association of liver function biomarkers [e.g., alanine-aminotransferase (ALT), gamma-glutamyl transferase (GGT) and total bilirubin] and the risk of cardiovascular disease (CVD), we aimed to explore the relationship between these biomarkers and Framingham risk score (FRS), an established tool used in the prediction of 10-year CVD risk in the cohort of women.

Methods A total of 278 women participated in this cross-sectional study. Anthropometric, biochemical parameters, and blood pressure were obtained.

Results There was a significant increase in ALT and GGT activity, as well as a decrease in total bilirubin level in the high-risk FRS group compared to moderate-, and low-risk FRS (p for trend = 0.025, $p < 0.001$, $p < 0.001$, respectively). Multivariate logistic regression analysis showed that body mass index, triglycerides, creatinine, and high sensitivity C-reactive protein levels were the independent predictors of FRS in women [odds ratio (OR) = 1.234, $p = 0.001$; OR = 2.856, $p = 0.001$; OR = 1.090, $p = 0.002$, and OR = 1.295, $p = 0.045$, respectively]. In contrast, total bilirubin, ALT and GGT lost their independent predictions for high CVD risk.

Conclusion Liver function biomarkers (i.e. ALT, GGT, and total bilirubin) are not independently associated with FRS. It seems that some other cardiometabolic disturbances might modulate this relationship.

Keywords: cardiovascular risk; inflammation; obesity; liver function

INTRODUCTION

Cardiovascular disease (CVD) in women is still the leading cause of death in most developed and developing countries. In addition, the manifestation of heart disease differs between sexes, often leading to worse consequences in women than in men [1]. Women at menopause experience increased visceral obesity, insulin resistance, and unfavorable hormonal milieu compared with women in premenopausal period, which leads to increased CVD risk [2]. On the other hand, women of reproductive age with hypertensive disorders of pregnancy are among the populations with the highest risk for premature CVD [1].

So far, a larger number of researches dealing with this pathology has been conducted in men, but implies the need for the optimal screening of women at high CVD risk [1].

Considering a complex phenotype of CVD, a search for a variety of biomarkers that act via different biological pathways, thus preceding overt CVD, has been increased [2, 3]. Among them, liver function biomarkers have shown to be independently associated with CVD risk in many studies so far [4, 5]. In addition, the association between severity of ultrasonographic nonalcoholic fatty liver disease (NAFLD), as the commonest manifestation of hepatic disorder, and cardiometabolic risk has been reported [6].

However, research papers lack consistency, showing contradictory results on the utility of liver function biomarkers when predicting CVD risk [7–11]. There are also inconsistencies when sex influence on this relationship is concerned, as well as assumptions that association of liver function biomarkers with CVD risk was dependent on some other potential predictors' influence [12]. In line with this, although concordant results show that aspartate aminotransferase (AST) was not associated with an increased risk for CVD [13], it is still a matter of debate whether other liver function biomarkers [i.e. alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), and total bilirubin] have a causal role in the pathogenesis of CVD or they are just simple markers of coexisting CVD risk factors [7–11].

Although the relationship between NAFLD and cardiometabolic risk has been shown by some previous reports, the underlying pathophysiological mechanism of this association has not yet been clarified [6]. We speculate that obesity-related inflammation and dyslipidemia might modulate the relationship between liver enzymes and CVD risk, having in mind that the highest prevalence of NAFLD is observed in individuals with obesity or type 2 diabetes mellitus (DM2), who have a two-fold risk increase for the development and progression of CVD [14, 15].

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Given the contradictory results regarding the relationship of liver function biomarkers (i.e. ALT, GGT, and total bilirubin) and risk for CVD, we aimed to explore the relationship between these biomarkers and Framingham risk score (FRS), an established tool used in the prediction of 10-year CVD risk, in the cohort of women population [12].

METHODS

Study population

The examined cohort included 278 women who volunteered to participate in this cross-sectional study. All participants were consecutively recruited into the study when visiting the Primary Health Care Center in Podgorica, Montenegro, for their regular check-up, between October 2012 and May 2016. Women were regarded to be postmenopausal if they self-reported the absence of menstrual bleeding for more than one year. Examined women were considered to have DM2 based on previously described criteria [14, 16].

Exclusion criteria for all the women were the following: previously known CVD, type 1 diabetes mellitus, pregnancy, kidney diseases other than nephropathy, liver diseases other than hepatic steatosis, ethanol consumption > 20 g/day, gout, high sensitivity C-reactive protein (hsCRP) > 10 mg/L, malignant diseases, as well as unwillingness to participate in the research.

A total of 70.1% women were overweight/obese, whereas 32.4% were with DM2. Also, the majority of women (82%) were postmenopausal. A total of 14% of women used hypolipidemic drugs, whereas 26.3% were treated for hypertension. A total of 29.1% of the patients used oral hypoglycemic drugs, and 3.2% of them were on insulin therapy.

Written informed consent was obtained from all the patients. The research was carried out in compliance with the Declaration of Helsinki, while the study protocol was approved by the Ethical Committee of the Primary Health Care Center in Podgorica, Montenegro.

Anthropometric measurements

All the participants' anthropometric measurements' proceedings have been described previously [15].

Biochemical analyses

Biochemical parameters [i.e. hsCRP, creatinine, glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG), uric acid, bilirubin, AST, ALT, and GGT], were measured as described previously [14, 16].

Blood pressure was measured and glomerular filtration rate was estimated (eGFR), as was shown previously [15, 16].

The FRS calculation included information on age, sex, TC, HDL-c, smoking status, presence of diabetes, and systolic blood pressure (SBP). Thereafter, the cohort of

studied women was divided into low-risk (FRS < 10%), moderate-risk (10% ≤ FRS < 20%), and high-risk FRS status (FRS ≥ 20%) [17].

Statistical analyses

Distribution of data was tested with Kolmogorov–Smirnov test. Comparisons of continuous normal and log-normal variables were performed by ANOVA with the Tukey–Kramer *post hoc* test for subgroup differences. Skewed distributed data were compared by Kruskal–Wallis *post hoc* test. The data are shown as mean ± standard deviation (SD) for normally distributed data, geometrical mean [95% confidence interval (CI)] for log-normal distributed data [18], median (25th–75th percentile) for skewed distributed data, and as relative frequencies for categorical variables. Analysis of categorical variables was performed by using the χ^2 test for contingency tables. Categorical variables were coded as follows: smoking status (0 – non-smoker, 1 – smoker); diabetes mellitus (0 – without diabetes mellitus, 1 – patients with diagnosed diabetes mellitus), menopausal status (0 – premenopausal, 1 – postmenopausal) and therapy (0 – no therapy, 1 – therapy). To estimate the correlation between the examined cardiometabolic parameters with FRS, Spearman's correlation analysis was performed. The data were given as correlation coefficient (ρ). Independent associations between high FRS and cardiometabolic parameters were tested by univariate and multivariate binary logistic regression analyses. The low FRS category was coded as 0, while the medium and high FRS categories were coded as 1. To examine independent predictions of continuous variables, multivariate adjustment was made for all continuous variables which did not enter the FRS calculation, and which significantly correlated with FRS ($p < 0.05$), as well as categorical variables which were not included in the FRS calculation, and which showed unequal distribution between low-, moderate-, and high-risk FRS groups. Odds ratio (OR) and the 95 CI were estimated. The explained variation in FRS was given by Nagelkerke R^2 value. The Hosmer–Lemeshow test was used to examine if there was a linear relationship between the predictor variables and the log odds of the dependent variable. Receiver operating characteristic (ROC) curve analysis was used to examine diagnostic performance of each cardiometabolic parameter and the model, as well as to discriminate women with moderate and high FRS from those with low FRS. The area under the ROC curve (AUC) of 0.5–0.7 suggested that diagnostic test had low accuracy; 0.7–0.8 satisfactory accuracy, 0.8–0.9 good accuracy, while AUC higher than 0.9 suggested excellent accuracy of the diagnostic test [19]. A p -value less than 0.05 was considered statistically significant. All statistical calculations were performed in the PASW® Statistics, Version 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 summarizes general characteristics of the study groups according to their calculated FRS. Women in the

Table 1. General characteristics of the studied patients

Characteristics	Low risk (FRS < 10%)	Moderate risk (10% ≤ FRS < 20%)	High risk (FRS ≥ 20%)	p
n	144	65	69	
Age, years	53 (48–57)	61 (55–64) ^{a*}	66 (61–70) ^{a*, b*}	< 0.001
BMI, kg/m ²	25.5 (22.7–28.3)	28.3 (26.2–33.3) ^{a*}	31.2 (28.7–33.9) ^{a*, b*}	< 0.001
SBP, mmHg	125 (110–135)	150 (130–158) ^{a*}	140 (130–155) ^{a*}	< 0.001
DBP, mmHg	76 (68–86)	90 (80–97) ^{a*}	80 (75–90) ^{a*}	< 0.001
Smokers, %	8.33	3.08	17.40	0.015
Diabetes mellitus, %	4.86	35.38	87	< 0.001
Menopausal status, %	69.44	95.38	95.65	< 0.001
Hypolipidemics, %	0.69	13.85	42.03	< 0.001
Antihypertensives, %	2.78	26.15	75.36	< 0.001
Oral antidiabetics, %	4.17	29.23	81.16	< 0.001
Insulin therapy, %	0.69	4.62	7.25	0.032

Data are presented as median (interquartile range) and compared by Kruskal–Wallis test; categorical variables are presented as relative frequencies and compared by χ^2 test;

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FRS – Framingham risk score;

^asignificantly different from the first group; *post-hoc* Kruskal–Wallis test;

^bsignificantly different from the second group; *post-hoc* Kruskal–Wallis test;

*p < 0.05

Table 2. Clinical parameters of women in different Framingham risk score groups

Parameters	Low risk (FRS < 10%)	Moderate risk (10% ≤ FRS < 20%)	High risk (FRS ≥ 20%)	p
TC, mmol/L	5.97 ± 1.16	6.34 ± 1.11	5.93 ± 1.26	0.125
HDL-c, mmol/L	1.71 ± 0.43	1.46 ± 0.33 ^{a*}	1.25 ± 0.29 ^{a*, b*}	< 0.001
LDL-c, mmol/L	3.77 ± 1.09	4.19 ± 1.12	3.72 ± 1.21	0.052
TG, mmol/L ⁺	1.18 (1.11–1.27)	1.76 (1.59–1.95) ^{a*}	2 (1.78–2.23) ^{a*}	< 0.001
Glucose, mmol/L ⁺⁺	5.2 (4.9–5.6)	6.0 (5.2–7.2) ^{c*}	7.0 (6.2–8.1) ^{c*, d*}	< 0.001
Creatinine, μ mol/L ⁺⁺	57 (51–62)	59 (54–65) ^{c*}	64 (57–74) ^{c*}	< 0.001
Uric acid, μ mol/L ⁺	235 (226–245)	277 (254–302) ^{a*}	300 (282–320) ^{a*}	< 0.001
Total bilirubin, μ mol/L ⁺⁺	7.20 (5.80–9.32)	7.10 (5.20–9.85)	5.70 (4.17–7.12) ^{c*, d*}	< 0.001
HsCRP, mg/L ⁺	0.87 (0.74–1.02)	1.62 (1.23–2.14) ^{a*}	2.33 (1.88–2.89) ^{a*}	< 0.001
AST, U/L ⁺⁺	18 (15–21)	18 (16–22)	18 (16–22)	0.352
ALT, U/L ⁺⁺	17 (13–22)	21 (14–27) ^{c*}	19 (15–27)	0.025
GGT, U/L ⁺⁺	11 (9–16)	14 (10–16)	17 (14–25) ^{c*, d*}	< 0.001

Data are presented as arithmetic mean ± SD and compared with Student's t-test;

TC – total cholesterol; HDL-c – high density lipoprotein cholesterol; LDL-c – low density lipoprotein cholesterol; TG – triglycerides; hsCRP – high-sensitivity C-reactive protein; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; FRS – Framingham risk score;

⁺log-normal distributed data are presented as geometric mean (95% CI) and compared with Student's t-test after logarithmic transformation;

⁺⁺skewed distributed data are presented as median (interquartile range) and compared with Mann–Whitney U-test;

^asignificantly different from the low risk group; *post-hoc* Tukey–Kramer test;

^bsignificantly different from the medium risk group; *post-hoc* Tukey–Kramer test;

^csignificantly different from the low risk group; *post-hoc* Kruskal–Wallis test;

^dsignificantly different from the medium risk group; *post-hoc* Kruskal–Wallis test;

*p < 0.05

high-risk FRS group were older and had higher body mass index (BMI) than those in low- and moderate-risk FRS groups. Also, women in the moderate-risk FRS group were older and had higher BMI than women in the low-risk group. SBP and DBP were significantly lower in the low-risk FRS group than in the moderate- and high-risk group. As expected, the high-risk FRS group had significantly higher percentage of smokers, women with DM2, women on hypolipidemic, antihypertensive, oral hypoglycemic and insulin therapies, compared to low- and moderate-risk FRS groups. Higher percentage of postmenopausal women were in the moderate- and high- FRS group than in the low-risk one.

Although TC was entered into the FRS calculation algorithm, its concentration was not significantly different between low-, moderate-, and high-risk FRS group of women (Table 2). The HDL-c concentration was higher

in the first than in the second and third risk group. Also, its concentration was higher in the moderate- than in the high-risk FRS group. The opposite was found for glucose concentration in women. Moreover, TG, creatinine, uric acid, and hsCRP concentrations were higher in the moderate- and high-risk FRS groups than in the first one. The lowest bilirubin concentrations were determined in the high-risk FRS group. ALT activities were higher in the moderate- than in the low-risk FRS group, whereas GGT activities were the highest in the high-risk FRS group.

Beside parameters used in its algorithm, FRS significantly positively correlated with BMI, DBP, TG, glucose, creatinine, uric acid, hsCRP, ALT, and GGT. Significant negative correlations were established between FRS and HDL-c, which was used for its calculation, and between FRS and total bilirubin (Table 3).

Table 3. Bivariate Spearman's correlation analysis between Framingham risk score and other general and clinical parameters

Parameters	FRS	
	P	p
Age, years	0.703	< 0.001
BMI, kg/m ²	0.578	< 0.001
SBP, mmHg	0.606	< 0.001
DBP, mmHg	0.447	< 0.001
TC, mmol/L	0.172	0.004
HDL-c, mmol/L	-0.510	< 0.001
LDL-c, mmol/L	0.201	0.001
TG, mmol/L [†]	0.559	< 0.001
Glucose, mmol/L ^{††}	0.639	< 0.001
Creatinine, μmol/L ^{††}	0.279	< 0.001
Uric acid, μmol/L [†]	0.459	< 0.001
Total bilirubin, μmol/L ^{††}	-0.241	< 0.001
HsCRP, mg/L [†]	0.435	< 0.001
AST, U/L ^{††}	0.035	0.564
ALT, U/L ^{††}	0.120	< 0.001
GGT, U/L ^{††}	0.407	< 0.001

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; TC – total cholesterol; HDL-c – high density lipoprotein cholesterol; LDL-c – low density lipoprotein cholesterol; TG – triglycerides; hsCRP – high-sensitivity C-reactive protein; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; FRS – Framingham risk score

[†]log-normal distributed data are presented as geometric mean (95% CI) and compared with Student's t-test after logarithmic transformation;

^{††}skewed distributed data are presented as median (interquartile range) and compared with Mann-Whitney U-test

Table 4. Odds ratios (OR) after univariate and multivariate logistic regression analysis for parameters predicting Framingham risk score risk

Predictors	Unadjusted OR (95% CI)	p	Nagelkerke R ²
BMI, kg/m ²	1.300 (1.210–1.396)	0.015	0.328
TG, mmol/L	4.358 (2.817–6.743)	< 0.001	0.273
Creatinine, μmol/L	1.060 (1.033–1.088)	< 0.001	0.120
Total bilirubin, μmol/L	0.915 (0.854–0.980)	0.011	0.036
HsCRP, mg/L	1.375 (1.204–1.571)	< 0.001	0.132
ALT, U/L	1.028 (1.003–1.054)	0.021	0.025
GGT, U/L	1.026 (1.004–1.049)	0.021	0.032
Model	Adjusted OR (95% CI)	p	Nagelkerke R ²
BMI, kg/m ²	1.234 (1.088–1.399)	0.001	0.725 (for the model)
TG, mmol/L	2.856 (1.545–5.277)	0.001	
Creatinine, μmol/L	1.090 (1.033–1.150)	0.002	
Total bilirubin, μmol/L	0.930 (0.823–1.052)	0.249	
HsCRP, mg/L	1.295 (1.085–1.490)	0.045	
ALT, U/L	1.008 (0.955–1.063)	0.782	
GGT, U/L	1.003 (0.963–1.004)	0.893	

Model: BMI, DBP, LDL-c, TG, creatinine, uric acid, total bilirubin, hsCRP, ALT, and GGT (all continuous variables); menopausal status and hypolipidemic therapy (categorical variable);

BMI – body mass index; TG – triglycerides; HsCRP – high-sensitivity C-reactive protein; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase

Logistic regression analysis was used to test if any of cardiometabolic parameters which were not used in FRS algorithm and showed significant correlations ($p < 0.05$) with FRS, had potential to predict high CVD risk (Table 4). Those predictors were continuous variables such as BMI, DBP, LDL-c, TG, creatinine, uric acid, total bilirubin, hsCRP, ALT, and GGT, as well as categorical variables

such as menopausal status and hypolipidemic therapy. Predictors were unadjusted and adjusted for other parameters and tested by univariate and multivariate analysis, respectively (Table 4). Significant OR for tested predictors from univariate analysis were shown in Table 4. It was shown that BMI, TG, creatinine, total bilirubin, hsCRP, ALT, and GGT were significant predictors for higher FRS. As BMI rose for 1 kg/m², TG for 1 mmol/L, creatinine for 1 μmol/L, hsCRP for 1 mg/L, ALT for 1 U/L, and GGT for 1 U/L, probability for higher CVD risk rose by 30%, 4.358 times, 6%, 37.5%, 2.8%, and 2.6%, respectively. As total bilirubin concentration rose by 1 μmol/L, probability for higher CVD risk decreased by 8.5%. Nagelkerke R² showed that each predictor in univariate analysis, BMI, TG, creatinine, total bilirubin, hsCRP, ALT, and GGT could explain the variation in higher risk for CVD occurrence by 32.8%, 27.3%, 12%, 3.6%, 13.2%, 2.5%, and 3.2%, respectively. All predictors tested in univariate analysis (BMI, DBP, LDL-c, TG, creatinine, uric acid, total bilirubin, hsCRP, ALT, GGT, menopausal status, and hypolipidemic therapy) were further tested in multivariate logistic regression analysis in order to determine their independent association with high FRS. Namely, four parameters having significant odds in univariate analysis (BMI, TG, creatinine, and hsCRP) kept independent predictive power for high CVD risk in the model. In contrast, total bilirubin, ALT, and GGT lost their independent predictions for high CVD risk. In multivariate analysis, as BMI rose by 1 kg/m², TG by 1 mmol/L, creatinine by 1 μmol/L, and hsCRP by 1 mg/L, probability for higher CVD risk rose by 23.4%, 2.856 times, 9%, and 29.5%, respectively. Nagelkerke R² of 0.725 showed that the model could explain 72.5% of variation in the FRS.

Thereafter, a ROC analysis was used to discriminate women with low risk from those with moderate and high risk of developing CVD (Table 5). The calculated AUC for BMI, TG, and hsCRP indicated satisfactory accuracy, whereas ROC analysis showed low accuracy for creatinine, total bilirubin, ALT, and GGT as diagnostic tools. The calculated AUC for the model (which included BMI, DBP, LDL-c, TG, creatinine, uric acid, total bilirubin, hsCRP, ALT, GGT, menopausal status, and hypolipidemic therapy) was 0.944, which suggested excellent clinical accuracy. Also, the model had higher sensitivity than single predictors (Table 5, Figure 1).

DISCUSSION

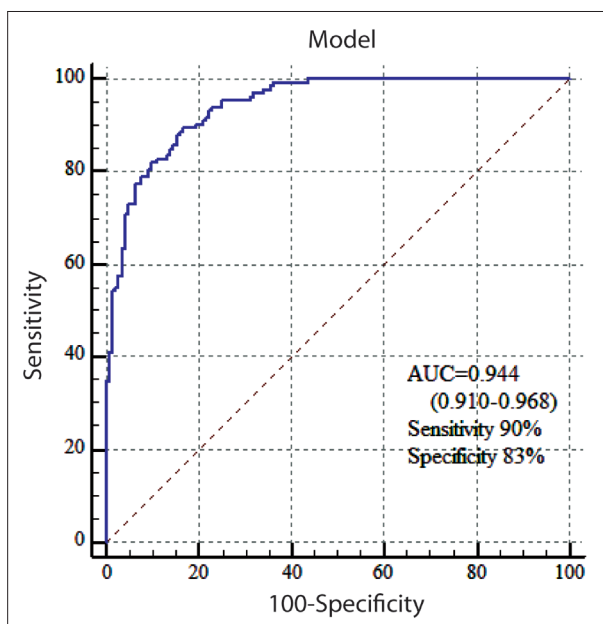
The findings of the current study reveal that liver function biomarkers (i.e. ALT, GGT, and total bilirubin) are not independently associated with FRS, even though there was a significant increase in ALT and GGT activity, as well as a decrease in total bilirubin level in the high-risk FRS group compared to the moderate- and low-risk FRS group (Table 2). In addition, although all these biomarkers correlated with FRS in Spearman's non-parametric correlation analysis (Table 3), in multivariate logistic regression analysis these biomarkers lost their independent predictions for high CVD risk (Table 4). This may give rise to the

Table 5. Receiver operating characteristic analysis for single parameters and the model discriminatory abilities regarding Framingham risk score in the studied patients

Predictors	AUC (95% CI)	SE	Sensitivity (%)	Specificity (%)	p
BMI, kg/m ²	0.800 (0.748–0.845)	0.026	81	66	< 0.001
TG, mmol/L	0.781 (0.728–0.828)	0.027	83	64	< 0.001
Creatinine, μmol/L	0.649 (0.590–0.705)	0.033	31	94	< 0.001
Total bilirubin, μmol/L	0.588 (0.521–0.654)	0.034	40	76	0.012
HsCRP, mg/L	0.739 (0.684–0.790)	0.029	79	58	< 0.001
ALT, U/L	0.594 (0.528–0.661)	0.034	79	37	0.006
GGT, U/L	0.693 (0.631–0.755)	0.031	63	70	< 0.001
Model	0.944 (0.910–0.968)	0.012	90	83	< 0.001

Model: BMI, DBP, LDL-c, TG, creatinine, uric acid, total bilirubin, hsCRP, ALT and GGT (all continuous variables); menopausal status and hypolipidemic therapy (categorical variable);

AUC – area under the ROC curve; BMI – body mass index; TG – triglycerides; hsCRP – high-sensitivity C-reactive protein; ALT – alanine aminotransferase; GGT-gamma-glutamyl transferase

**Figure 1.** Discriminatory ability of the model regarding cardiovascular disease risk

assumption that these biomarkers might only be bystanders in CVD prediction, instead of direct contributors to CVD onset and progression.

Indeed, previous findings have shown that the association of GGT with FRS is dependent on the other potential predictors [12]. Furthermore, the addition of GGT to traditional risk factors does not improve CVD risk prediction [8, 20].

Concerning the ALT activity in relation to CVD risk, several large sample studies reported that ALT is positively associated with CVD events and long-term mortality in middle-aged adults, independently of other cardiometabolic factors [21, 22, 23]. However, some others suggest

that ALT level is not a reliable marker for screening for the CVD occurrence in the general population [7], whereas some of them found an inverse relationship between ALT levels in the normal range and adverse cardiovascular and non-cardiovascular outcomes [24].

Similar discordant results were also found for bilirubin. While some studies report its independent relationship with CVD risk [5, 9], others claim the opposite [11]. Moreover, the addition of total bilirubin to traditional risk factors showed no significant improvement in prediction of CVD risk [9].

There is also sex difference concerning the relationship between liver enzymes and CVD risk, showing that GGT was positively associated only with higher levels of FRS in women, but not in men [12]. On the other hand, ALT showed a significant inverse relationship with FRS in men, while this relationship remained significant in women only for lower and intermediate FRS status [12].

We speculate that some other cardiometabolic disturbances (e.g. obesity-related dyslipidemia and inflammation) might modulate the relationship between liver function biomarkers and CVD risk. In line with this, unlike liver function biomarkers (i.e. ALT, GGT, and total bilirubin), BMI, TG, hsCRP, and creatinine were the independent predictors of FRS in women in our study (Table 4), showing that as BMI rose by 1 kg/m², TG by 1 mmol/L, creatinine by 1 μmol/L, and hsCRP by 1mg/L, probability for higher CVD risk rose by 23.4%, 2.856 times, 9%, and 29.5%, respectively, suggesting that the mentioned model could explain as much as 72.5% of variation in the FRS. Moreover, a ROC analysis used to discriminate women without low risk from those at moderate and high risk for developing CVD, revealed that calculated AUC for BMI, TG, and hsCRP indicated satisfactory accuracy, whereas ROC analysis showed low accuracy for creatinine, total bilirubin, ALT, and GGT as diagnostic tools (Table 5).

One of the potential explanations for such findings may lie in the obesity status and its relationship with CVD [25]. In our study, a total of 70.1% of examined women were overweight/obese. Moreover, the majority of individuals with NAFLD are obese [15], which was found to be the independent risk factor for progression of this hepatic disorder [6]. Namely, in the obese state, an increase in free radicals' production, a decrease in antioxidant defense [14, 26], as well as low-grade inflammation with consequent insulin resistance [15, 27], lead to an increased free fatty acids hepatic influx. These pathophysiological processes further aggravate increased lipogenesis and triglyceride storage, thus promoting dysfunction of hepatocytes [28]. All of these metabolic disturbances may lead to increased ALT and GGT activity, and to a decreased bilirubin level [6, 25]. Moreover, not only do high levels of free fatty acids in addition to insulin resistance lead to hepatocytes dysfunction, but they also promote endothelial dysfunction, reduce production of nitric oxide, vasoconstriction, and inflammation with consequent initiation and progression of atherosclerosis [29, 30], thus further supporting the link between obesity, high triglycerides, and inflammation level and CVD.

The limitations of this study need to be reported. Namely, the cross-sectional design of our study does not allow us to establish the causal link between liver function biomarkers and CVD risk. Also, we have included only women population in our study. Thus, longitudinal studies comprising both sexes are needed to explore the mechanism of this relationship in order to elucidate if liver function biomarkers have a causal role in the pathogenesis of CVD.

CONCLUSION

Liver function biomarkers (i.e. ALT, GGT, and total bilirubin) are not independently associated with FRS. It seems that some other cardiometabolic disturbances (e.g.

obesity-related dyslipidemia and inflammation) might modulate this relationship. New large sample-size studies with longitudinal design and with both sexes included are needed to clarify the potential mechanism of the relationship between liver function biomarkers and CVD risk.

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Conflict of interest: None declared.

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Да ли су биомаркери функције јетре независно повезани са Фрамингхамским скором за ризик у женској популацији?

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САЖЕТАК

Увод/Циљ С обзиром на контрадикторне резултате који се односе на повезаност биомаркера функције јетре [аланин-аминотрансферазе (АЛТ), гама-глутамил трансферазе (ГГТ) и укупног билирубина] и ризика за појаву кардиоваскуларних болести, циљ студије је био да се испита повезаност између ових биомаркера и Фрамингхамског скор за ризик (ФСР), алгорита за процену 10-годишњег ризика за појаву кардиоваскуларних болести у кохорти женске популације.

Метод У овој студији пресека учествовало је укупно 278 жена. Мерени су антропометријски, биохемијски параметри и крвни притисак.

Резултати Уочен је статистички значајан пораст активности АЛТ и ГГТ, као и пад вредности укупног билирубина у групи са високим статусом ФСР, у поређењу са средњим и ниским

ФСР ($p = 0,025$, $p < 0,001$, $p < 0,001$, редом). Мултиваријантна логистичка регресиона анализа показала је да су индекс телесне масе, вредности триглицерида, креатинина и високоосетљивог с-реактивног протеина независни предиктори ФСР код жена ($OR = 1,234$, $p = 0,001$; $OR = 2,856$, $p = 0,001$; $OR = 1,090$, $p = 0,002$ и $OR = 1,295$, $p = 0,045$, редом). С друге стране, укупни билирубин, АЛТ и ГГТ су изгубили независну предикцију за високи ризик за појаву кардиоваскуларних болести.

Закључак Биомаркери функције јетре (тј. АЛТ, ГГТ и укупни билирубин) нису независно повезани са ФСР. Претпоставља се да неки други кардиометаболички поремећаји могу утицати на ову повезаност.

Кључне речи: ризик за појаву кардиоваскуларних болести; инфламација; гојазност; функција јетре