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Research article

Evaluation of elevated serum liver enzymes and metabolic syndrome in the PERSIAN Guilan cohort study population

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ABSTRACT

Objective: The purpose of this study is to evaluate the association between elevated serum liver enzymes and Metabolic Syndrome (MetS) in Prospective Epidemiological Research Studies of the Iranian Adults (PERSIAN) Guilan Cohort Study (PGCS) population.

Methods: This cross-sectional study involved 10,519 individuals between the ages of 35 and 70 enrolled in the PGCS. The gathered data encompassed demographic information, anthropometric measurements, blood pressure, and biochemical indicators. MetS was defined by the National Cholesterol Education Program–Adult Treatment Panel III criteria (NCEP-ATP III). The associations between elevated liver enzymes and MetS were examined using logistic regression analysis. Odds ratio (OR) and 95 % confidence interval (CI) were calculated.

Results: The prevalence of MetS was 41.8 %, and the prevalence of elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) were 19.4, 4.6, 11.6, and 5.1 %, respectively. In the unadjusted model, elevated ALT, AST, and GGT were associated with increased odds of MetS (OR = 1.55, 95 % CI: 1.41–1.71; OR = 1.29, 95 % CI: 1.07–1.55, and OR = 1.90, 95 % CI: 1.69–2.14, respectively). These associations remained significant for ALT and GGT after adjustment for some demographic and clinical characteristics (aOR = 1.31, 95 % CI: 1.17–1.46 and aOR = 1.30, 95 % CI: 1.14–1.49, respectively). In addition, the odds of MetS increased with the number of elevated liver enzymes, up to almost 1.32-fold among subjects with three/four elevated liver enzymes.

Conclusion: The higher incidence of elevated liver enzymes was associated with an increased likelihood of MetS. Including liver markers in diagnosing and predicting MetS holds promise and is considered a possible approach.

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1. Introduction

Metabolic syndrome (MetS) or X syndrome is a complex disorder characterized by the co-occurrence of several metabolic diseases, including abdominal obesity, hypertension, insulin resistance, hyperglycemia, hypertriglyceridemia and reduced lower high-density lipoprotein cholesterol (HDL-C) [1]. MetS is undeniably linked to an elevated risk of developing cardiovascular diseases (CVD) and diabetes mellitus (DM) [2]. MetS has become one of the prominent public health challenges of the current era, with a rising trend observed in both developed and developing countries [3]. The global prevalence of MetS has been reported to range between 14 % and 32 % across different regions of the world [4]. The prevalence of MetS exhibits considerable variation worldwide, particularly in Asian countries, primarily due to significant differences in lifestyle factors and diverse ethnic groups [5,6].

A systematic review study on the Iranian population older than 19 years reported the prevalence of MetS as 10–60 %, depending on age, gender, and habitat [7]. Also, evidence has been showing an association between MetS and hepatic injuries [8]. Various markers, including alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT), have been recognized as reliable indicators for assessing liver function. These markers are also associated with DM, hypertension, and MetS [9]. Some studies have even identified an increased risk of developing MetS with elevated hepatic enzyme levels, even within the normal range [10,11]. Epidemiological investigations have demonstrated a link between non-alcoholic fatty liver disease (NAFLD), the most prevalent cause of elevated liver enzymes, and MetS [12,13].

However, the findings from previous studies exploring the association between elevated liver enzymes and MetS have exhibited some inconsistency [14,15]. Earlier research has indicated a significant association between elevated ALT and GGT levels, but not AST levels, with MetS. Additionally, certain studies have demonstrated that only a substantial increase in GGT levels is associated with all components of MetS. Due to variations in lifestyle and regional-specific characteristics and the full understanding of the relationship between elevated liver enzymes and MetS, it is necessary to conduct studies in different geographical areas worldwide [16]. Therefore, this study aimed to investigate the associations between liver enzymes and MetS in a large-scale Iranian population from the Prospective Epidemiological Research Studies of the Iranian Adults (PERSIAN) Guilan Cohort Study (PGCS).

2. Materials and methods

2.1. Study populations

This cross-sectional study was conducted on 10,519 individuals between the ages of 35 and 70 who were enrolled in the PGCS population, which is part of PERSIAN in 2022. A comprehensive PGCS profile has been published, providing detailed information [17]. The study was confirmed by the ethical committee of the Guilan University of Medical Sciences, Rasht, Iran (IR.GUMS.REC. 1401.325), and all individuals gave their consent to participate in the study.

2.2. Data collection

Data collection at the cohort center involved the registration of participants, demographic information, anthropometric measurements, blood pressure, and biochemical indicators. The demographic characteristics involved age, gender, location of residence, marital status, smoking, occupation, and education obtained with face-to-face interviews. The PERSIAN cohort protocol assessed Blood pressure using a cuff pressure gauge (MTM Munich, Germany). Weight (kg), height (cm), and waist circumference (WC) (cm), as anthropometric markers, were measured based on the cohort study protocol. History of hepatotoxic drug consumption and fatty liver disease was assessed based on the questions “Has a physician diagnosed NAFLD? (yes/no)" and “Have you used hepatotoxic drugs before? (yes/no)."

2.3. Biochemical measurements

Blood samples were collected from the antecubital vein following a fasting period of 12 h. Liver enzymes, such as AST, ALT, ALP, and GGT, as well as the lipid profile, which included triglyceride (TG), total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), and fasting blood sugar (FBS), were assessed using a Biotecnica auto-analyzer (BT 1500, Italy) in medical laboratory of the cohort center. Elevated liver enzymes were defined as follows: ALT $\geq$32 U/L in males/$\geq$ 22 U/L in females, AST $\geq$37 U/L in males/$\geq$ 31 U/L in females, GGT $\geq$49 U/L in men/$\geq$ 32 U/L in females, and ALP $\geq$307 U/L in both male and female [18].

2.4. Definition of metabolic syndrome

The MetS prevalence was defined according to the National Cholesterol Education Program Adult- Treatment Panel III (NCEP-ATP III) criteria [19]. Individuals were categorized as having MetS if they had central obesity (WC $\geq$ 95 cm for males and WC $\geq$ 80 cm for females) in addition to two other four components. The components comprising the MetS involved TG $\geq$ 150 mg/dl or previous diagnosis of hypertriglyceridemia; HDL $\leq$40 mg/dl in males and $\leq$50 mg/dl in females or Specific medications for these fat disorders; systolic blood pressure (SBP) $\geq$130 mmHg or diastolic blood pressure (DBP) $\geq$85 mmHg or previously diagnosed hypertension; and FBS $\geq$100 mg/dl or previous diagnosis of DM.

2.5. Statistical analysis

This study expressed continuous variables as mean ± standard deviation (SD) and categorical variables as number (percentage). Differences in continuous and categorical variables between participants with and without MetS were tested by independent T-test and Chi-Square test (or Cochran–Armitage test for trend), respectively. We determined the association of MetS with elevated liver enzymes using logistic regression analysis. Odds ratio (OR) and 95 % confidence interval (CI) were calculated. ORs were adjusted for demographic and clinical characteristics. Model 1 was unadjusted; Model 2 was adjusted for age and sex; Model 3 was adjusted for variables in Model 2 and marital status, years of education, occupation, place of residency, wealth score index (WSI), body mass index (BMI), physical activity, smoking, hookah smoking, opium consumption, and alcohol consumption; Model 4 was adjusted for variable in Model 3 and fatty liver, hepatitis B, hepatitis C, use of lipid-lowering drugs and hepatotoxic drugs. All data analyses were done SPSS

Table 1
Demographic and clinical characteristics of the participants in the PERSIAN Guilan Cohort Study.

	Total (n = 10519)	MetS (n = 4393)	Non-MetS (n = 6126)	P
	mean ± SD or n (%)	mean ± SD or n (%)	mean ± SD or n (%)	
Age (years)				<0.001
35–44	3138 (29.8)	1071 (24.4)	2067 (33.7)	
45–54	3854 (36.6)	1565 (35.6)	2289 (37.4)	
55–64	2730 (26.0)	1373 (31.3)	1357 (22.2)	
≥ 65	797 (7.6)	384 (8.7)	413 (6.7)	
Mean ± SD	51.52 ± 8.90	52.91 ± 8.84	50.52 ± 8.81	<0.001
Sex				<0.001
Male	4886 (46.4)	1222 (27.8)	3664 (59.8)	
Female	5633 (53.6)	3171 (72.2)	2462 (40.2)	
Marital status				<0.001
Single	305 (2.9)	109 (2.5)	196 (3.2)	
Married	9526 (90.6)	3868 (88.0)	5658 (92.4)	
Widow	566 (5.4)	359 (8.2)	207 (3.4)	
Divorced	122 (1.2)	57 (1.3)	65 (1.1)	
Education level				<0.001
Illiterate	1738 (16.5)	949 (21.6)	789 (12.9)	
1–5	3312 (31.5)	1443 (32.8)	1869 (30.5)	
6–12	4831 (45.9)	1798 (40.9)	3033 (49.5)	
University	638 (6.1)	203 (4.6)	35 (7.1)	
Mean ± SD	6.63 ± 4.52	5.95 ± 4.53	7.11 ± 4.45	<0.001
Employment				<0.001
Unemployed	4781 (45.5)	2615 (59.5)	2166 (35.4)	
Employed	5738 (54.5)	1778 (40.5)	3960 (64.6)	
Habitat				0.318
Urban	4612 (43.8)	1901 (43.3)	2711 (44.3)	
Rural	5907 (56.2)	2492 (56.7)	3415 (55.7)	
Wealth Score Index				0.002
Quartile 1	2630 (25.0)	1138 (25.9)	1492 (24.4)	
Quartile 2	2630 (25.0)	1147 (26.1)	1483 (24.2)	
Quartile 3	2630 (25.0)	1060 (24.1)	1570 (25.6)	
Quartile 4	2629 (25.0)	1048 (23.9)	1581 (25.8)	
Mean ± SD	0 ± 1	−0.03 ± 0.98	0.02 ± 1.01	0.007
BMI (kg/m^2)				<0.001
Underweight	141 (1.3)	14 (0.3)	127 (2.1)	
Normal	2746 (26.1)	546 (12.4)	2199 (35.9)	
Overweight	4198 (39.9)	1721 (39.2)	2477 (40.4)	
Obese	3435 (32.7)	2112 (48.1)	1323 (21.6)	
Mean ± SD	28.14 ± 5.09	30.15 ± 4.93	26.70 ± 4.69	
Physical activity (MET)				<0.001
Quartile 1	2630 (25.0)	1338 (30.5)	1292 (21.1)	
Quartile 2	2630 (25.0)	1281 (29.2)	1349 (22.0)	
Quartile 3	2630 (25.0)	1072 (24.4)	1558 (25.4)	
Quartile 4	2629 (25.0)	702 (16.0)	1927 (31.5)	
Mean ± SD	41.26 ± 8.88	39.22 ± 7.48	42.72 ± 9.50	<0.001
Smoking	2584 (24.6)	663 (15.1)	1921 (31.4)	<0.001
Hookah smoking	1515 (14.4)	365 (8.3)	1150 (18.8)	<0.001
Opium consumption	726 (6.9)	226 (5.1)	500 (8.2)	<0.001
Alcohol consumption	1395 (13.3)	437 (9.9)	958 (15.6)	<0.001
Fatty liver disease	696 (6.6)	423 (9.6)	273 (4.5)	<0.001
Hepatitis B	22 (0.2)	15 (0240)	7 (0.16)	0.344
Hepatitis C	12 (0.1)	10 (0.16)	2 (0.05)	0.078
Use of lipid-lowering drugs	1584 (15.1)	1098 (25.0)	486 (7.9)	<0.001
Use of hepatotoxic drugs	1732 (16.5)	1094 (24.9)	638 (10.4)	<0.001

SD: Standard Deviation; BMI: Body Mass Index.

for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA), and the significance level was set at 0.05.

3. Results

3.1. Demographic and clinical characteristics of the participants

Table 1 outlines the demographic and clinical characteristics of the participants. The mean age of the participants was 51.52 ± 8.90 years, and 53.6 % were female. Of the participants, 90.6 % were married, 6.1 % had a university education, 54.5 % were employed, 56.2 % were rural residents, 32.7 % had obese-BMI, 24.6 % were smokers, 13.3 % consumed alcohol, 6.6 % had fatty liver disease, and 16.6 % used hepatotoxic drugs. Patients with MetS were older, more female sex, more widowed, more unemployed, reported less smoking and hookah smoking and less consumption of opium and alcohol, had low WSI, high BMI, and low psychical activity, and were more likely to have fatty liver and reported more use of lipid-lowering drugs and hepatotoxic drugs.

3.2. Prevalence of elevated live enzymes and MetS

The prevalence of elevated ALT, AST, GGT, and ALP was 19.4, 4.6, 11.6, and 5.1 %, respectively. The prevalence of elevated ALT, AST, and GGT was higher in females than in males ($P < 0.001$, $P = 0.040$, $P < 0.001$, respectively). The prevalence of elevated ALT decreased with age (P for trend<0.001), whereas the prevalence of elevated ALP increased with age (P for trend<0.001). The prevalence of MetS was 41.8 % in this study and was more prevalent in females than in males (56.3 % vs 25.0 %, $P < 0.001$). The prevalence of MetS increased with age; the lowest was 34.1 % in those aged 35–44 years (P for trend<0.001) (Table 2).

3.3. Prevalence of MetS based on elevated ALT using logistic regression

The prevalence of MetS was higher among participants with elevated ALT than those with normal ALT levels (50.5 % vs 39.7 %, P < 0.001). Similar results were also obtained for AST and GGT (P = 0.007 and P < 0.001, respectively) (Table 3 and Fig. 1). In the unadjusted model (Model 1), elevated ALT was associated with 55 % increased odds of MetS (OR = 1.55, 95 % CI: 1.41–1.71). This association remained significant after adjustment for age and sex (OR = 1.61, 95 % CI: 1.45–1.78) (Model 2). In model 3, after adjustment for other socio-demographic characteristics, the OR also remained statistically significant (OR = 1.36, 95 % CI: 1.22–1.51). In Model 4, after further adjustment for fatty liver, hepatitis B, hepatitis C, use of lipid-lowering drugs, and use of hepatotoxic drugs, participants with elevated ALT were 1.31-fold more likely to have MetS in comparison to participants with normal ALT (OR = 1.31, 95 % CI: 1.17–1.46).

3.4. Prevalence of MetS based on elevated AST using logistic regression

In the unadjusted model, participants with elevated AST were more likely to have MetS than people with normal AST (OR = 1.29, 95 % CI: 1.07–1.55). Similar results were obtained after adjusting for sex and age (OR = 1.26, 95 % CI: 1.03–1.53). In Model 3 and Model 4, there was no longer a significant association between elevated AST and MetS (OR = 1.07, 95 % CI: 0.87–1.31 and OR = 1.03, 95 % CI: 0.84–1.27, respectively). In the unadjusted model, elevated GGT was associated with 90 % increased odds of MetS (OR = 1.90, 95 % CI: 1.69–2.14). Similar results were obtained after adjusting for age and sex (OR = 1.52, 95 % CI: 1.34–1.73). The OR also remained statistically significant in Model 3 and Model 4 (OR = 1.33, 95 % CI: 1.17–1.52 and OR = 1.30, 95 % CI: 1.14–1.49, respectively).

Table 2
Prevalence of elevated live enzymes and MetS among the PERSIAN Guilan cohort study participants.

	Elevated ALT	Elevated AST	Elevated GGT	Elevated ALP	MetS
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	2043 (19.4 %)	480 (4.6 %)	1222 (11.6 %)	536 (5.1 %)	4393 (41.8 %)
Age					
35–44	673 (21.4 %)	154 (4.9 %)	346 (11.0 %)	101 (3.2 %)	1071 (34.1 %)
45–54	779 (20.2 %)	168 (4.4 %)	431 (11.2 %)	170 (4.4 %)	1565 (40.6 %)
55–64	481 (17.6 %)	126 (4.6 %)	358 (13.1 %)	202 (7.4 %)	1373 (50.3 %)
≥ 65	110 (13.8 %)	32 (4.0 %)	87 (10.9 %)	63 (7.9 %)	384 (48.2 %)
P for trend[a]	<0.001	0.617	0.111	<0.001	<0.001
Sex					
Male	873 (17.9 %)	201 (4.1 %)	350 (7.2 %)	244 (5.0 %)	1222 (25.0 %)
Female	1170 (20.8 %)	279 (5.0 %)	872 (15.5 %)	292 (5.2 %)	3171 (56.3 %)
P	<0.001	0.040	<0.001	0.659	<0.001

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase; MetS: Metabolic Syndrome.

[a] Cochran–Armitage test for trend.

Table 3
Relationship between liver enzymes and MetS among the PERSIAN Guilan cohort study participants using logistic regression analysis.

	Prevalence of MetS **n (%)**	Model 1 (Unadjusted)		Model 2		Model 3		Model 4	
		OR (95 % CI)	P	OR (95 % CI)	P	OR (95 % CI)	P	OR (95 % CI)	P
ALT									
Normal	3361 (39.7 %)	1		1		1		1	
Elevated	1032 (50.5 %)	1.55 (1.41–1.71)	<0.001	1.61 (1.45–1.78)	<0.001	1.36 (1.22–1.51)	<0.001	1.31 (1.17–1.46)	<0.001
AST									
Normal	4164 (41.5 %)	1		1		1		1	
Elevated	229 (47.7 %)	1.29 (1.07–1.55)	0.007	1.26 (1.03–1.53)	0.022	1.07 (0.87–1.31)	0.541	1.03 (0.84–1.27)	0.775
GGT									
Normal	3711 (39.9 %)	1		1		1		1	
Elevated	682 (55.8 %)	1.90 (1.69–2.14)	<0.001	1.52 (1.34–1.73)	<0.001	1.33 (1.17–1.52)	<0.001	1.30 (1.14–1.49)	<0.001
ALP									
Normal	4154 (41.6 %)	1		1		1		1	
Elevated	239 (44.6 %)	1.13 (0.95–1.35)	0.173	1.01 (0.84–1.22)	0.927	0.99 (0.82–1.21)	0.956	0.97 (0.79–1.19)	0.762
No of elevated liver enzymes									
0	2915 (38.6 %)	1		1		1		1	
1	943 (48.4 %)	1.50 (1.35–1.65)	<0.001	1.46 (1.31–1.62)	<0.001	1.30 (1.16–1.45)	<0.001	1.23 (1.10–1.38)	<0.001
2	380 (51.2 %)	1.67 (1.44–1.94)	<0.001	1.56 (1.32–1.83)	<0.001	1.31 (1.11–1.54)	<0.001	1.28 (1.08–1.52)	0.004
≥ 3	155 (57.0 %)	2.11 (1.65–2.69)	<0.001	1.74 (1.34–2.25)	<0.001	1.40 (1.07–1.84)	<0.001	1.32 (1.00–1.75)	0.047

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase; MetS: Metabolic Syndrome; OR: Odds Ratio; CI: Confidence Interval.
Model 1: Unadjusted model.
Model 2: Adjusted for age and sex.
Model 3: Adjusted for Model 2 plus marital status, years of education, occupation, place of residency, wealth score index, BMI, physical activity, smoking, hookah smoking, opium consumption, and alcohol consumption.
Model 4: Adjusted for Model 2 plus fatty liver, hepatitis B, hepatitis C, use of lipid lowering drugs, and use of hepatotoxic drugs.

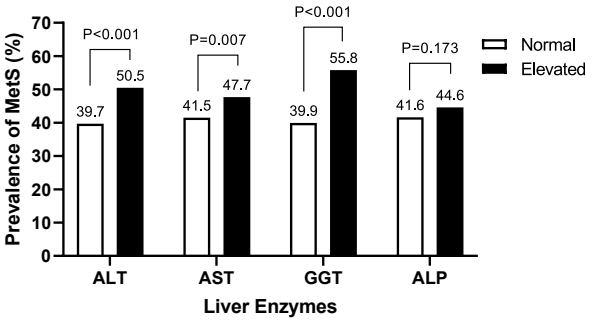

Fig. 1. Prevalence of metabolic syndrome based on elevated liver enzymes. *P*-values are based on Chi-square test.

3.5. Prevalence of MetS based on elevated ALP using logistic regression

The presence of elevated ALP was not associated with MetS in both unadjusted model (OR = 1.13, 95 % CI: 0.95–1.35) (Model 1) and all adjusted models- Model 2 (OR = 1.01, 95 % CI: 0.84–1.22), Model 3 (OR = 0.99, 95 % CI: 0.82–1.21), and Model 4 (OR = 0.97, 95 % CI: 0.79–1.19).

3.6. Prevalence of MetS based on elevated liver enzymes

The prevalence of MetS among participants with 0, 1, 2, and 3 or 4 elevated liver enzymes was 38.6, 48.4, 51.2 and 57.0 %, respectively. In other words, the prevalence of MetS increased with increasing the number of elevated liver enzymes (*P* for trend<0.001) (Table 3 and Fig. 2). In unadjusted analysis, compared with participants without any elevated liver enzymes, the OR of MetS was 1.50 (95 % CI: 1.35–1.65) for participants with one elevated liver enzyme, 1.67 (95 % CI: 1.44–1.94) for participants with two elevated liver enzymes, 2.11 (95 % CI: 1.65–2.69) for participants with three or four elevated liver enzymes, with a significant

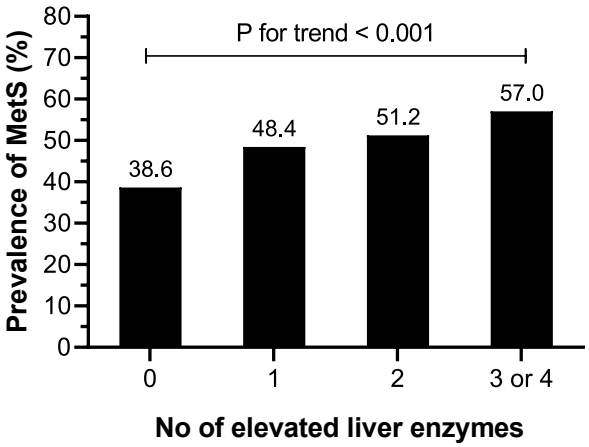

Fig. 2. Prevalence of metabolic syndrome based on the number of elevated liver enzymes. *P*-value is based on Cochran–Armitage test for trend.

trend in OR with an increasing number of elevated liver enzymes (Table 3 and Fig. 2). Similar results were obtained after adjusting for age and sex. The same pattern, but with lower ORs, was observed after adjusting for variables in Model 3 and Model 4.

4. Discussion

We found that the prevalence of MetS in the northern Iranian population was 41.8 %, which was higher than studies in the USA (22.9 %), Italy (17.0 %), Japan (5.3 %) and Philippines (14.2 %) [3,20–22]. Almost similar to our findings, the prevalence of MetS was 34.42 % and 37 % in the Rafsanjan cohort study [18] and the Kharameh cohort study [23]. In another study, Farmanfarma et al. revealed that approximately one-third of the Iranian population aged 20 and above has MetS, with geographical distribution differences among provinces [24]. This could be attributed to differences in their age, gender, culture, habits, BMI, socioeconomic status, and environmental factors [25,26]. Additionally, the prevalence of MetS can vary based on the diagnostic criteria used, study duration, and population ethnicity. Moreover, we observed that elevated ALT, AST, and GGT had a significant association with the prevalence of MetS. However, our findings revealed that odds of MetS were significantly associated with elevated ALT and GGT; no significant relationship was observed between MetS and elevated AST and ALP. In this regard, some studies reported a similar finding (55, 58). Inconsistently, Koskinen et al. found no association between elevated ALT and GGT with the risk of MetS in young adults [27]. The discussion of our study highlights the promising role of ALT and GGT determinations as potential diagnostic markers for early detection and progression prediction of Metabolic Syndrome (MetS). Several studies have demonstrated a significant association between elevated ALT and GGT levels and the presence of MetS. Findings suggest that ALT and GGT determinations offer valuable insights into early MetS detection and may serve as useful predictors of disease progression [28,29].

In another study, elevated ALP levels were associated with MetS, so participants in the highest quartile of ALP had a 3.72-fold increased risk of developing MetS (53). Consistent with the study of Khalili et al., it was revealed that the prevalence of MetS increased with the number of elevated liver enzymes [18]. In the present study, the prevalence of MetS in women was generally higher than in men. Numerous studies on varied populations have consistently reported a higher prevalence of MetS in women [30,31]. Factors such as low levels of physical activity and increased subcutaneous fat in women of all ages due to anatomical reasons may explain the higher prevalence of obesity and subsequent development of MetS compared to men (40,41). Participants with MetS were older compared to those without MetS. Other studies also found the ascending trend of aging prevalence [32,33].

Evidence reported that a decrease in physical activity and an increase in obesity, followed by an increase in underlying diseases such as diabetes and hypertension, are associated with a higher OR of developing MetS in old age [34]. The present study also found that individuals with MetS had higher BMI and lower physical activity levels. Patel et al. stated that the association between liver enzyme levels and the risk of MetS could have a potential relationship with excess visceral adiposity [35]. Hanley et al. have proposed that elevated liver enzymes indicate the presence of excessive fat accumulation in the liver, a characteristic feature of NAFLD [36]. The common cause of abnormal liver function found in participants with MetS and obesity was NAFLD, characterized by elevation in liver enzyme levels. The association between elevated liver enzymes and the risk of MetS is thought to be primarily explained by NAFLD, as indicated by several studies [37,38]. Likewise, we observed that the prevalence of NAFLD in patients with MetS was higher than in individuals without MetS.

Also, in this present study, users of hepatotoxic and lipid-lowering drugs had a higher prevalence of metabolic syndrome. It has been shown that GGT is a marker of oxidative stress that could be involved in increased oxidative stress, leading to reduced responsiveness to insulin and ultimately resulting in hyperglycemia [39]. Furthermore, in line with previous studies, we observed that individuals with high levels of education had a lower frequency of MetS. Maybe the reason is that individuals with higher levels of education tend to possess more health-related knowledge, exhibit improved health conditions, and adopt healthier behaviors [11,13]. Studies conducted on Japanese and Korean populations have reported a significant association between smoking and increased risk of MetS (45,46). Fan et al. found that alcohol consumption was associated with MetS [40]. On the contrary, similar to our findings,

several studies have demonstrated a significant inverse relationship between the use of cigarettes, alcohol, and opium with the frequency of MetS [41,42].

Since studies conducted in different populations have shown variations in the association between specific types of elevated liver enzymes and MetS, it may be more effective to investigate the association between the number of elevated liver enzymes and the risk of developing MetS in subsequent studies. This study has assessed the link between liver enzymes and MetS and other related factors in a large population of PGCS. Due to the cross-sectional nature of our study design, we cannot establish a direct inference regarding the association between liver enzymes and specific components of MetS, such as insulin resistance. Also, since it was impossible to identify all known causes of elevated liver enzyme, it may result in some biases in the results.

5. Conclusion

Higher elevated liver enzymes were associated with an increased likelihood of MetS. Including liver markers in diagnosing and predicting MetS holds promise and is considered a feasible approach.

Consent for publication

Not applicable.

Consent to participants

We informed all participants and all individuals provided verbal consent to participate in the study and signed the consent form in the presence of a witness. Written consent was obtained from literate individuals. In cases where the participants were unable to sign a form, because of a language barrier or cognitive decline, their legal guardian/family or an appropriate representative gave informed consent to participate on their behalf and signed a form in a written format. According to the protocol of the PERSIAN Guilan Cohort Study, all written informed consents have been documented in the PERSIAN Guilan Cohort archive. Only if the subjects are minor (below 16)/illiterate/unstable/suffering from a disorder that affects cognitive abilities informed consent obtained from legal representative.

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Ethics approval and consent to participate

This study was approved by the ethics committees of the Guilan University of Medical Sciences [IR.GUMS.REC. 1401.325]. Informed consent was obtained from all individual participants.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Saideh Ghotbi: Validation, Methodology, Investigation, Data curation, Conceptualization. **Farahnaz Joukar:** Validation, Methodology, Data curation, Conceptualization. **Mahdi Orang Goorabzarmakhi:** Writing – review & editing, Writing – original draft. **Milad Shahdkar:** Writing – review & editing, Writing – original draft. **Saman Maroufizadeh:** Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation. **Kourosh Mojtahedi:** Writing – review & editing, Data curation. **Mehrnaz Asgharanezhad:** Writing – review & editing. **Mohammadreza Naghipour:** Writing – review & editing. **Fariborz Mansour-Ghanaei:** Validation, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] G. Fahed, L. Aoun, M. Bou Zerdan, S. Allam, M. Bou Zerdan, Y. Bouferraa, et al., Metabolic syndrome: updates on pathophysiology and management in 2021, Int. J. Mol. Sci. 23 (2022) 786.
[2] W. Li, D. Wang, X. Wang, Y. Gong, S. Cao, X. Yin, et al., The association of metabolic syndrome components and diabetes mellitus: evidence from China National Stroke Screening and Prevention Project, BMC Publ. Health 19 (2019) 1–10.
[3] H. Beltrán-Sánchez, M.O. Harhay, M.M. Harhay, S. McElligott, Prevalence and trends of metabolic syndrome in the adult US population, 1999–2010, J. Am. Coll. Cardiol. 62 (2013) 697–703.
[4] A.A. Obeidat, M.N. Ahmad, F.H. Haddad, F.S. Azzeh, Alarming high prevalence of metabolic syndrome among Jordanian adults, Pakistan J. Med. Sci. 31 (2015) 1377.
[5] M.G. Saklayen, The global epidemic of the metabolic syndrome, Curr. Hypertens. Rep. 20 (2018) 1–8.
[6] M. Gierach, J. Gierach, M. Ewertowska, A. Arndt, R. Junik, Correlation between body mass index and waist circumference in patients with metabolic syndrome, Int. Sch. Res. Notices 2014 (2014).
[7] K. Hajian-Tilaki, Metabolic syndrome and its associated risk factors in Iranian adults: a systematic review, Casp J Intern Med 6 (2015) 51.
[8] M. Asrih, F.R. Jornayvaz, Metabolic syndrome and nonalcoholic fatty liver disease: is insulin resistance the link? Mol. Cell. Endocrinol. 418 (2015) 55–65.
[9] M. GhariPour, A. Baghei, M. Boshtam, K. Rabiei, Prevalence of metabolic syndrome among the adults of central of areas of Iran (as part of" Isfahan Healthy Heart Study"), J Birjand Univ Med Sci 13 (2006) 9–15.
[10] Z. Gaeini, Z. Bahadoran, P. Mirmiran, F. Azizi, The association between liver function tests and some metabolic outcomes: Tehran Lipid and Glucose Study, Hepat. Mon. 20 (2020).
[11] H.R. Kim, M.A. Han, Association between serum liver enzymes and metabolic syndrome in Korean adults, Int. J. Environ. Res. Publ. Health 15 (2018) 1658.
[12] A.L. Han, Association of Cardiovascular Risk Factors and Metabolic Syndrome with non-alcoholic and alcoholic fatty liver disease: a retrospective analysis, BMC Endocr. Disord. 21 (2021) 1–8.
[13] G. Pagano, G. Pacini, G. Musso, R. Gambino, F. Mecca, N. Depetris, et al., Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association, Hepatology 35 (2002) 367–372.
[14] L. Zhang, X. Ma, Z. Jiang, K. Zhang, M. Zhang, Y. Li, et al., Liver enzymes and metabolic syndrome: a large-scale case-control study, Oncotarget 6 (2015) 26782.
[15] K. Lee, J.H. Yang, Which liver enzymes are better indicators of metabolic syndrome in adolescents: the Fifth Korea National Health and Nutrition Examination Survey, 2010, Metab. Syndr. Relat. Disord. 11 (2013) 229–235.
[16] S.M. Grundy, Metabolic syndrome update, Trends Cardiovasc. Med. 26 (2016) 364–373.
[17] F. Mansour-Ghanaei, F. Joukar, M.R. Naghipour, S.G. Sepanlou, H. Poustchi, K. Mojtahedi, et al., The Persian Guilan cohort study (PGCS), Arch. Iran. Med. 22 (2019) 39–45.
[18] P. Khalili, F. Ayoobi, F. Kahkesh pour, A. Esmaeili-Nadimi, M. Abassifard, C. La Vecchia, et al., Serum liver enzymes and metabolic syndrome from the Rafsanjan Cohort Study, J. Invest. Med. 71 (2023) 140–148.
[19] N. Ali, M. Samadder, J.H. Shourove, A. Taher, F. Islam, Prevalence and factors associated with metabolic syndrome in university students and academic staff in Bangladesh, Sci. Rep. 13 (2023) 19912.
[20] R. Miccoli, C. Bianchi, L. Odoguardi, G. Penno, F. Caricato, M.G. Giovannitti, et al., Prevalence of the metabolic syndrome among Italian adults according to ATP III definition, Nutr. Metabol. Cardiovasc. Dis. 15 (2005) 250–254.
[21] M. Urashima, T. Wada, T. Fukumoto, M. Joki, T. Maeda, H. Hashimoto, et al., Prevalence of metabolic syndrome in a 22,892 Japanese population and its associations with life style, Japan Med Assoc J 48 (2005) 441.
[22] F.E.R. Punzalan, R.G. Sy, T. Ty-Willing, Prevalence of metabolic syndrome among adult Filipinos, in: Int. Congr. Ser. vol. 1262, Elsevier, 2004, pp. 442–445.
[23] H.-A. Nikbakht, A. Rezaianzadeh, M. Seif, H. Ghaem, Prevalence of metabolic syndrome and its components among a population-based study in south of Iran, Persian Kharameh cohort study, Clin Epidemiol Glob Heal 8 (2020) 678–683.
[24] K.K. Farmanfarma, M.A. Kaykhaei, H.A. Adineh, M. Mohammadi, S. Dabiri, A. Ansari-Moghaddam, Prevalence of metabolic syndrome in Iran: a meta-analysis of 69 studies, Diabetes Metab Syndr Clin Res Rev 13 (2019) 792–799.
[25] Y. Mokhayeri, S.M. Riahi, S. Rahimzadeh, M.A. Pourhoseingholi, S.S. Hashemi-Nazari, Metabolic syndrome prevalence in the Iranian adult's general population and its trend: a systematic review and meta-analysis of observational studies, Diabetes Metab Syndr Clin Res Rev 12 (2018) 441–453.
[26] M. Naghipour, F. Joukar, H.-A. Nikbakht, S. Hassanipour, M. Asgharnezhad, M. Arab-Zozani, et al., High prevalence of metabolic syndrome and its related demographic factors in North of Iran: results from the Persian Guilan cohort study, Internet J. Endocrinol. 2021 (2021).
[27] J. Koskinen, C.G. Magnussen, M. Kähönen, B.-M. Loo, J. Marniemi, A. Jula, et al., Association of liver enzymes with metabolic syndrome and carotid atherosclerosis in young adults. The Cardiovascular Risk in Young Finns Study, Ann. Med. 44 (2012) 187–195.
[28] M. Music, A. Dervisevic, E. Pepic, O. Lepara, A. Fajkic, B. Ascic-Buturovic, et al., Metabolic syndrome and serum liver enzymes level at patients with type 2 diabetes mellitus, Med. Arch. 69 (2015) 251–255, https://doi.org/10.5455/medarh.2015.69.251-255.
[29] S. Wang, J. Zhang, L. Zhu, L. Song, Z. Meng, Q. Jia, et al., Association between liver function and metabolic syndrome in Chinese men and women, Sci. Rep. 7 (2017) 44844, https://doi.org/10.1038/srep44844.
[30] W.N.W. Mohamud, A al-S Ismail, A. Sharifuddin, I.S. Ismail, K.I. Musa, K.A. Kadir, et al., Prevalence of metabolic syndrome and its risk factors in adult Malaysians: results of a nationwide survey, Diabetes Res. Clin. Pract. 91 (2011) 239–245.
[31] K. Zeng, S. Wang, L. Zhang, Y. Zhang, J. Ma, Gender Differences in Prevalence and Associated Factors of Metabolic Syndrome in First-Treatment and Drug-Naïve Schizophrenia Patients, 2023.
[32] J. Xiao, C.-L. Wu, Y.-X. Gao, S.-L. Wang, L. Wang, Q.-Y. Lu, et al., Prevalence of metabolic syndrome and its risk factors among rural adults in Nantong, China, Sci. Rep. 6 (2016) 38089.
[33] B. Amirkalali, H. Fakhrzadeh, F. Sharifi, R. Kelishadi, F. Zamani, H. Asayesh, et al., Prevalence of metabolic syndrome and its components in the Iranian adult population: a systematic review and meta-analysis, Iran. Red Crescent Med. J. 17 (2015).
[34] H. Khosravi-Boroujeni, N. Sarrafzadegan, M. Sadeghi, H. Roohafza, M. Talaei, S.-K. Ng, et al., Secular trend of metabolic syndrome and its components in a cohort of Iranian adults from 2001 to 2013, Metab. Syndr. Relat. Disord. 15 (2017) 137–144.
[35] D.A. Patel, S.R. Srinivasan, J.-H. Xu, W. Chen, G.S. Berenson, Persistent elevation of liver function enzymes within the reference range is associated with increased cardiovascular risk in young adults: the Bogalusa Heart Study, Metabolism 56 (2007) 792–798.
[36] A.J.G. Hanley, K. Williams, A. Festa, L.E. Wagenknecht, R.B. D'Agostino Jr, S.M. Haffner, Liver markers and development of the metabolic syndrome: the insulin resistance atherosclerosis study, Diabetes 54 (2005) 3140–3147.
[37] M. Homsanit, A. Sanguankeo, S. Upala, K. Udol, Abnormal liver enzymes in Thai patients with metabolic syndromes, J. Med. Assoc. Thail. 95 (2012) 444.
[38] F. Angelico, M. Del Ben, R. Conti, S. Francioso, K. Feole, D. Maccioni, et al., Non-alcoholic fatty liver syndrome: a hepatic consequence of common metabolic diseases, J. Gastroenterol. Hepatol. 18 (2003) 588–594.
[39] G. Tarantino, A. Caputi, JNKs, insulin resistance and inflammation: a possible link between NAFLD and coronary artery disease, World J Gastroenterol WJG 17 (2011) 3785.
[40] A.Z. Fan, M. Russell, J. Dorn, J.L. Freudenheim, T. Nochajski, K. Hovey, et al., Lifetime alcohol drinking pattern is related to the prevalence of metabolic syndrome. The Western New York Health Study (WNYHS), Eur. J. Epidemiol. 21 (2006) 129–138.
[41] A. Onat, H. Özhan, A.M. Esen, S. Albayrak, A. Karabulut, G. Can, et al., Prospective epidemiologic evidence of a "protective" effect of smoking on metabolic syndrome and diabetes among Turkish women—without associated overall health benefit, Atherosclerosis 193 (2007) 380–388.
[42] M.R. Carnethon, C.M. Loria, J.O. Hill, S. Sidney, P.J. Savage, K. Liu, Risk factors for the metabolic syndrome: the coronary artery risk development in young adults (CARDIA) study, 1985–2001, Diabetes Care 27 (2004) 2707–2715.