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ORIGINAL RESEARCH

Combining Fat-to-Muscle Ratio and Alanine Aminotransferase/Aspartate Aminotransferase Ratio in the Prediction of Cardiometabolic Risk: A Cross-Sectional Study

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Purpose: Altered body composition and liver enzymes are known to be related to cardiometabolic risk. Our study aimed to evaluate the association between fat-to-muscle ratio (FMR), alanine aminotransferase/aspartate aminotransferase (ALT/AST) ratio and cardiometabolic risk.

Methods: In total, 1557 participants aged ≥40 years were included. A bioelectrical impedance analyzer (BIA) was used to measure fat mass and muscle mass. We created a cardiometabolic risk score with one point for each cardiometabolic risk factor, including elevated triglycerides (TGs), decreased high-density lipoprotein cholesterol (HDL-C), elevated blood pressure (BP), and abnormal blood glucose, yielding a score of 0–4 for each participant (≥2 for high-risk and <2 for low-risk). Logistic regression analyses were used to analyze the relationship between FMR, ALT/AST ratio and cardiometabolic risk.

Results: FMR and ALT/AST ratio were significantly higher in the high-risk group than in the low-risk group (P<0.001). FMR and ALT/AST ratio were both positively correlated with a higher cardiometabolic risk score and the presence of each cardiometabolic risk factor. In subgroup analyses categorized according to FMR and ALT/AST ratio cutoffs, the high-FMR/high-ALT/AST group had the highest cardiometabolic risk (OR=8.51; 95% CI 4.46–16.25 in women and OR=5.09; 95% CI 3.39–7.65 in men) after adjusting for confounders.

Conclusion: FMR and ALT/AST ratio were positively associated with cardiometabolic risk. Combining these two indicators improved the prediction of cardiometabolic risk.

Keywords: body composition, liver enzymes, cardiometabolic disease

Plain Language Summary

Cardiovascular disease (CVD) is the leading cause of death in adults worldwide and has become a major public health problem. Major risk factors for CVD, also known as cardiometabolic risk factors, including high TG, low HDL-C, hypertension and diabetes, etc. It is very important to screen for cardiometabolic risk factors to reduce the incidence of CVD. In this study, we investigated the relationships between FMR, ALT/AST ratio and cardiometabolic risk. We found that both FMR and ALT/AST ratio were positively associated with cardiometabolic risk and that combining the two indicators may improve their predictive ability, which may provide new strategies for earlier identification of individuals at high risk of CVD.

Introduction

Cardiovascular disease (CVD) is the leading cause of death and physical disability in adults worldwide.[1,2] Among the numerous cardiometabolic risk factors for CVD, elevated triglycerides (TGs), reduced high-density lipoprotein cholesterol (HDL-C), elevated blood pressure (BP) and abnormal blood glucose are associated with higher cardiovascular and

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all-cause mortality.[3,4] Insulin resistance (IR) is a potential mechanism of cardiometabolic risk involving target organs such as adipose tissue, skeletal muscle, and liver.[5–7] Therefore, the combined effects on fat, muscle and liver should be considered when assessing cardiometabolic risk.

In 1996, academics at the University of California, Los Angeles, (UCLA) first coined the term "sarcopenic obesity", defining it as "a coexistence of sarcopenia and obesity". There is a significant interaction between sarcopenic obesity and metabolic disease,[8] and it is also a high-risk factor for CVD. In recent years, the fat-to-muscle ratio (FMR) has also been used as a new indicator of IR and cardiometabolic disease.[9,10] Furthermore, the excessive accumulation of fat in the liver causes hepatic insulin resistance (HIR).[11] Elevated liver enzymes, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), have been interpreted as markers of hepatic steatosis and HIR.[12–14] Previous studies have shown that the ALT/AST ratio may be a reliable indicator of IR in nonobese Japanese adults and Chinese population.[15,16]

Nevertheless, studies that simultaneously consider the association between FMR, ALT/AST ratio and cardiometabolic risk are lacking, thus need to be further explored. Therefore, our study aimed to investigate the correlation of the combination of FMR and ALT/AST ratio on cardiometabolic risk.

Materials and Methods

Study Population

The present study evaluated data from 2055 individuals aged ≥40 years who underwent physical examinations and received a body composition analysis in our hospital between January 2020 and November 2021. Participants who had been diagnosed with acute illness, renal failure, active cancers, or viral hepatitis, those who used oral or injectable glucocorticoids, and those who had missing examination results or survey records were excluded from the analyses. Ultimately, 1557 participants were included in the present analyses. This study was exempted from informed consent requirements because all medical data were reviewed retrospectively and analyzed anonymously. The study was approved by the Institutional Review Board of Tongji Medical College, Huazhong University of Science and Technology.

Anthropometric and Laboratory Measurements

Anthropometric measurements were performed by trained examiners. Body composition measurements, including body weight, fat mass, and muscle mass, were measured by bioelectrical impedance analyzer (BIA) (Tsinghua Tongfang, BCA-2A, China), which is based on the theory of body impedance measurement and uses a segmented multi-frequency body impedance measurement model for body composition analysis. For the measurements to be taken, participants were asked to fast, wear light clothing, and stand barefoot on the instrument. Height was also measured without shoes on, and body mass index (BMI) was subsequently calculated. Blood pressure (BP) measurements were obtained while participants were sitting, after a period of rest for at least 10 minutes. The measurement of BP was repeated at 5-minute intervals, and the average value was taken. Laboratory measurements were tested in the hospital's central clinic lab. After ≥8 hours of fasting, venous blood samples were collected for the detection of various biochemical parameters, including the levels of total cholesterol (TC), TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), ALT, AST, uric acid (UA), and fasting blood glucose (FBG). Moreover, all participants completed a self-report questionnaire that collected information including sex, age, smoking history, drinking history, and medical history. For smoking history, individuals were defined as being either a current smoker or an ex-smoker. For drinking history, individuals were defined as being either a current alcohol drinker or an ex-drinker. The FMR was calculated as the total body fat mass divided by the total body muscle mass and was grouped into tertiles (T1-T3) from the lowest (T1) to highest (T3) values. The ALT/AST ratio was calculated by dividing ALT by AST and was also grouped into tertiles (T1-T3) from the lowest (T1) to highest (T3) values.

Definition of Cardiometabolic Risk Factors

The International Diabetes Federation (2005) components of the metabolic syndrome (MetS) were used to define cardiometabolic risk factors: (i) high TG ≥1.7 mmol/l or drug treatment for this lipid abnormality; (ii) low HDL-C (<1.03 mmol/l in men and <1.29 mmol/l in women) or drug treatment for this lipid abnormality; (iii) elevated BP (systolic blood pressure ≥130 mmHg or/and diastolic blood pressure ≥85 mmHg) or having been diagnosed with

hypertension; and (iv) elevated FBG (≥5.6 mmol/l) or having been diagnosed with type 2 diabetes. In addition, to assess the association between FMR, ALT/AST ratio and cardiometabolic risk and to evaluate the distribution of cardiometabolic risk factors, we developed a cardiometabolic risk score. One point was conferred for each alteration of the above four factors, generating a score of 0–4 for each participant, and a high cardiometabolic risk score was identified if 2 or more points were achieved.[17] Consequently, participants were classified into a high-risk group (≥2 points) and a low-risk group (<2 points).

Statistical Analysis

Continuous variables were expressed as the mean ± standard deviation and were compared using the independent-sample *t*-test between the high-risk group and low-risk group. Categorical variables were expressed as numbers and percentages and analyzed using the chi-square test, with the alpha-split method used for further two-way comparisons. Prior studies have demonstrated sex differences in body fat distribution, so our analyses were conducted separately by sex. We recoded FMR and ALT/AST ratio into sex-specific tertiles and compared the risk of poor outcome in each tertile with that of the lowest category (reference group). Besides, receiver operating characteristic (ROC) curves of FMR and ALT/AST ratio for detecting a high cardiometabolic risk score were constructed across sex. FMR and ALT/AST ratio cutoffs were calculated based on Youden's index, and participants were divided into 4 groups according to the cutoffs: low-FMR/low-ALT/AST group, high-FMR/low-ALT /AST group, low-FMR/high-ALT/AST group, and high-FMR/high-ALT/AST group. Binary logistic regression was used to analyze the associations between FMR tertiles, ALT/AST ratio tertiles, and different subgroups with cardiometabolic risk according to sex. Model 1 was unadjusted. Model 2 was adjusted for age, smoking and drinking. Odds ratios (ORs) along with 95% confidence intervals (95% CIs) and p value were described. Statistical significance was defined as a two-tailed P value < 0.05. All analyses were performed using SPSS version 25.

Results

General Characteristics

In total, 1577 participants, of which 29.6% were women, were included in this analysis. The mean age was 56.4±9.0 years. The percentage of those with high cardiometabolic risk scores was 69% (95% CI 0.666–0.713). The prevalence was significantly higher in men (74.2%, 95% CI 0.715–0.767) than in women (56.6%, 95% CI 0.520–0.612) (p<0.001). The prevalence of independent cardiometabolic risk factors for increased TG, reduced HDL-C, elevated BP and FBG was 25.4%, 59.7%, 62.5% and 28.4% in women and 46.1%, 61.7%, 79.0% and 42.2% in men, respectively. BP abnormalities were observed most frequently among those clusters in both women and men, followed by reduced HDL-C.

Table 1 shows the baseline characteristics of individuals between the high-risk group and the low-risk group according to sex. High-risk individuals had significantly poorer performance in BMI, FMR, SBP, DBP, TG, HDL-C, LDL-C, ALT, ALT/AST ratio, UA, and FBG (p<0.001) than low-risk individuals regardless of sex. The AST was significantly higher in the high-risk group than in the low-risk group in women, with no significant difference in men. However, there was no significant difference in TC between the high-risk group and the low-risk group. The proportion of hypertensive and diabetic individuals was significantly higher in the high-risk group than in the low-risk group. Furthermore, the prevalence of a high cardiometabolic risk score was significantly higher in the highest tertile (77.1% in women, 83.6% in men) of FMR in comparison with those in tertile 2 (61.7% in women, 74.6% in men) and tertile 1 (31.2% in women, 64.4% in men) (p<0.001). A similar trend of change was also observed across tertiles of the ALT/AST ratio. The prevalence of a high cardiometabolic risk score was significantly higher in tertile 3 (76.1% in women, 84.6% in men) and tertile 2 (55.2% in women, 78.0% in men) than in tertile 1 (38.2% in women, 59.9% in men) (*P*<0.001) (Figure 1).

Distribution of Cardiometabolic Risk Factors

Figure 2 shows the gender distribution of the cardiometabolic risk scores. There was a significant difference in the distribution of cardiometabolic risk scores between men and women (p<0.001). Approximately 9.3% of participants

Table 1 Baseline Characteristics of the Study Participants According to Cardiometabolic Risk

Variables	Total (n)	Female (n=461)			Male (n=1096)		
		Low-Risk	High-Risk	*P* value	Low-Risk	High-Risk	*P* value
	1557	(n=200)	(n=261)		(n=283)	(n=813)	
Age, year	56.4±9.0	53.3±8.4	60.9±9.4	<0.001	56.0±9.0	55.9±8.6	0.953
BMI, kg/m^2	25.4±2.9	23.1±2.4	25.3±3.1	<0.001	24.7±2.5	26.3±2.7	<0.001
FMR	0.40±0.12	0.46±0.10	0.55±0.11	<0.001	0.33±0.08	0.36±0.07	<0.001
SBP, mmHg	132±30	122±15	136±15	<0.001	125±14	135±38	<0.001
DBP, mmHg	82±11	75±11	82±11	<0.001	79±11	84±11	<0.001
TC, mmol/L	4.62±0.94	4.86±0.83	4.69±0.99	0.039	4.55±0.88	4.56±0.96	0.836
TG, mmol/L	1.93±1.68	1.00±0.37	1.94±1.78	<0.001	1.16±0.46	2.43±1.89	<0.001
HDL-C, mmol/L	1.13±0.32	1.49±0.32	1.17±0.28	<0.001	1.26±0.29	0.99±0.24	<0.001
LDL-C, mmol/L	2.78±0.83	2.95±0.70	2.79±0.85	0.025	2.84±0.81	2.72±0.85	0.044
ALT, U/L	26.19±19.78	15.59±6.66	24.00±20.08	<0.001	23.93±16.83	30.28±21.54	<0.001
AST, U/L	23.18±11.29	19.63±4.79	22.78±11.71	<0.001	23.06±12.52	24.22±11.67	0.160
ALT/AST ratio	1.09±0.41	0.79±0.25	1.00±0.36	<0.001	1.02±0.39	1.21±0.42	<0.001
UA, umol/L	366.02±97.05	270.08±64.11	319.98±84.81	<0.001	370.25±76.31	402.92±91.65	<0.001
FBG, mmol/L	5.53±1.68	4.78±0.48	5.79±1.93	<0.001	4.92±1.29	5.85±1.79	<0.001
Tobacco use, n(%)	516(33.1)	4(2.0)	4(1.5)	0.703	122(43.1)	386(47.5)	0.204
Alcohol use, n(%)	503(32.3)	6(3.0)	5(1.9)	0.543	123(43.5)	369(45.4)	0.575
Hypertension, n(%)	897(57.6)	35(17.5)	169(64.8)	<0.001	98(34.6)	595(73.2)	<0.001
Diabetes, n(%)	444(28.5)	3(1.5)	94(36.0)	<0.001	7(2.5)	340(41.8)	<0.001

Abbreviations: BMI, body mass index; FMR, fat-to-muscle ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UA, uric acid; FBG, fasting blood glucose.

(16.7% women and 6.2% men) had no metabolic alterations, and 14.6% had all the metabolic alterations (8.7% women and 17.2% men). The majority had 2 alterations (29.3% women and 30.4% men), which was followed by 1 metabolic alteration for women (26.7%) and 3 alterations for men (26.6%).

Correlations of the FMR with Cardiometabolic Risk

Table 2 shows the association between FMR and cardiometabolic risk. There were significant differences in cardiometabolic risk according to the FMR tertile, in that a higher FMR was associated with a higher risk of a high cardiometabolic risk score and a higher prevalence of each cardiometabolic risk factor in both women and men, even after adjusting for covariates such as age, tobacco use, and alcohol use. In women, using the FMR tertile 1 as the reference, the risk of a high cardiometabolic risk score increased progressively with increasing FMR (T2 vs T1 OR=2.37 95% CI 1.43–3.92, T3 vs T1 OR=4.03 95% CI 2.31–7.04). In men, the same trend was observed (T2 vs T1 OR=1.66 95% CI 1.21–2.30, T3 vs T1 OR=3.00 95% CI 2.09–4.31).

Correlations of ALT/AST Ratio with Cardiometabolic Risk

Table 3 shows the association between ALT/AST ratio and cardiometabolic risk. In women, the ALT/AST ratio was positively associated with a higher risk of a high cardiometabolic risk score and a higher prevalence of each cardiometabolic risk factor, with participants in tertile 3 of the ALT/AST ratio having a significantly higher risk than those in tertile 1, even after adjusting for covariates such as age, tobacco use, and alcohol use. In men, although this association between ALT/AST ratio and elevated BP lost significance in the unadjusted model, it became statistically significant in the adjusted model. Otherwise, the association in men is similar to that in women. In women, using the tertile 1 ALT/AST ratio as the reference, the risk of a high cardiometabolic risk score increased progressively with increasing ALT/AST ratio (T2 vs T1 OR=1.75 95% CI 1.06–2.89, T3 vs T1 OR=5.63 95% CI 3.28–9.65). The same trend was observed in men (T2 vs T1 OR=2.46 95% CI 1.78–3.41, T3 vs T1 OR=3.96 95% CI 2.76–5.70).

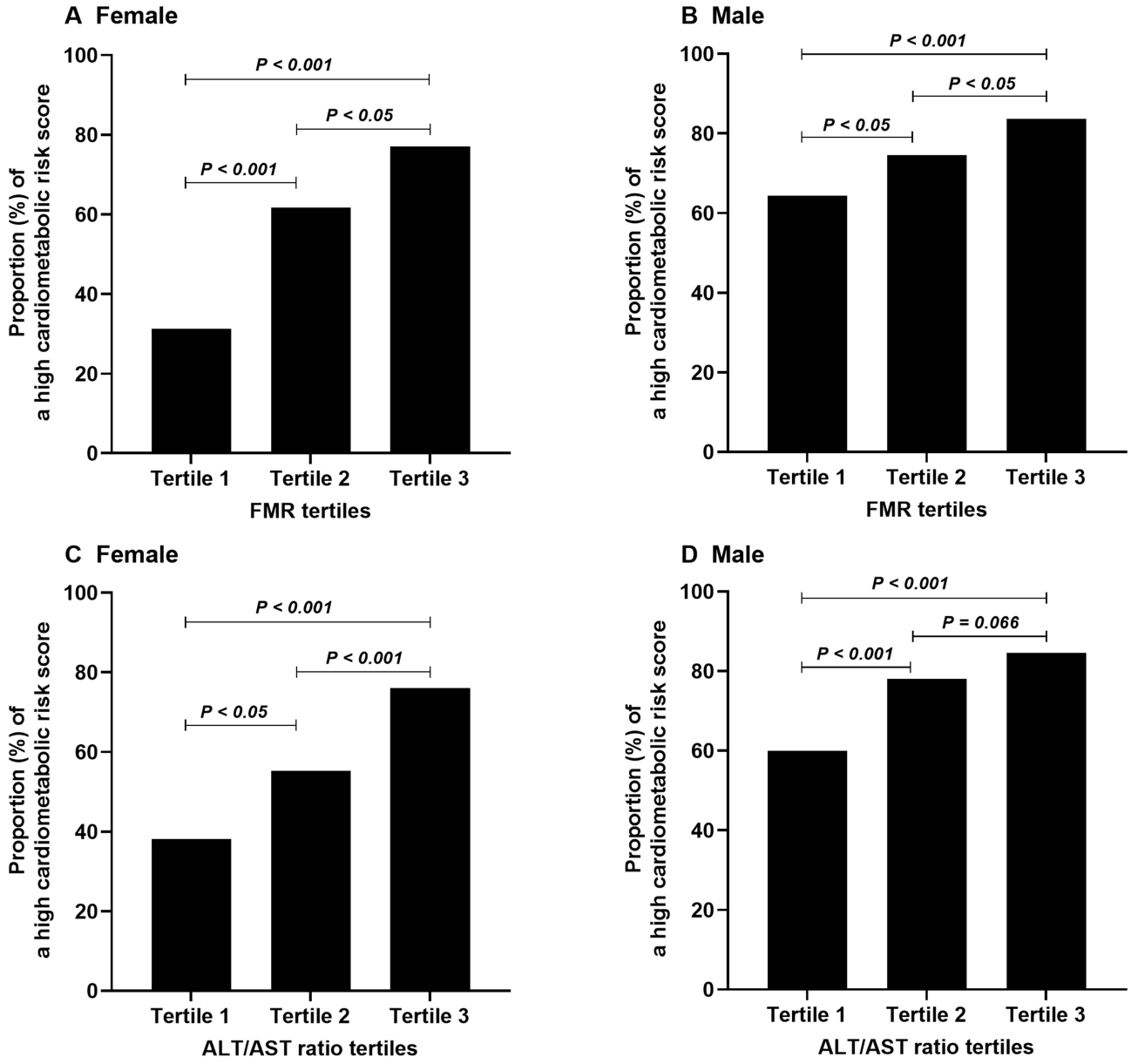

Figure 1 Proportion of a high cardiometabolic risk score according to tertile stratification of FMR in women (**A**) and men (**B**) and according to tertile stratification of ALT/AST ratio in women (**C**) and men (**D**).
Abbreviation: FMR, fat-to-muscle ratio.

Cut-off FMR and ALT/AST Ratio for Detecting Cardiometabolic Risk

Figure 3 shows the ROC curves, and area under curve (AUC) values according to sex. The FMR cut-off value was higher in women than in men (0.4566 vs 0.358), while the ALT/AST ratio cut-off value was higher in men than in women (1.0513 vs 0.7947). Both FMR and ALT/AST ratio had higher sensitivity (0.828 vs.0.469 and 0.736 vs.0.633, respectively), lower specificity (0.530 vs 0.714 and 0.595 vs.0.622) and higher AUC (0.742, 95% CI 0.696–0.787 vs 0.619, 95% CI 0.581–0.658 and 0.696, 95% CI 0.648–0.744 vs 0.651, 95% CI 0.613–0.689) in women than in men. In women, the AUC of FMR was higher than that of ALT/AST ratio, whereas in men, the AUC of ALT/AST ratio was higher than that of FMR. In both women and men, the AUCs of the combination of FMR and ALT/AST ratio (0.782, 95% CI 0.739–0.824 and 0.667, 95% CI 0.631–0.704, respectively) were greater than the individual indices.

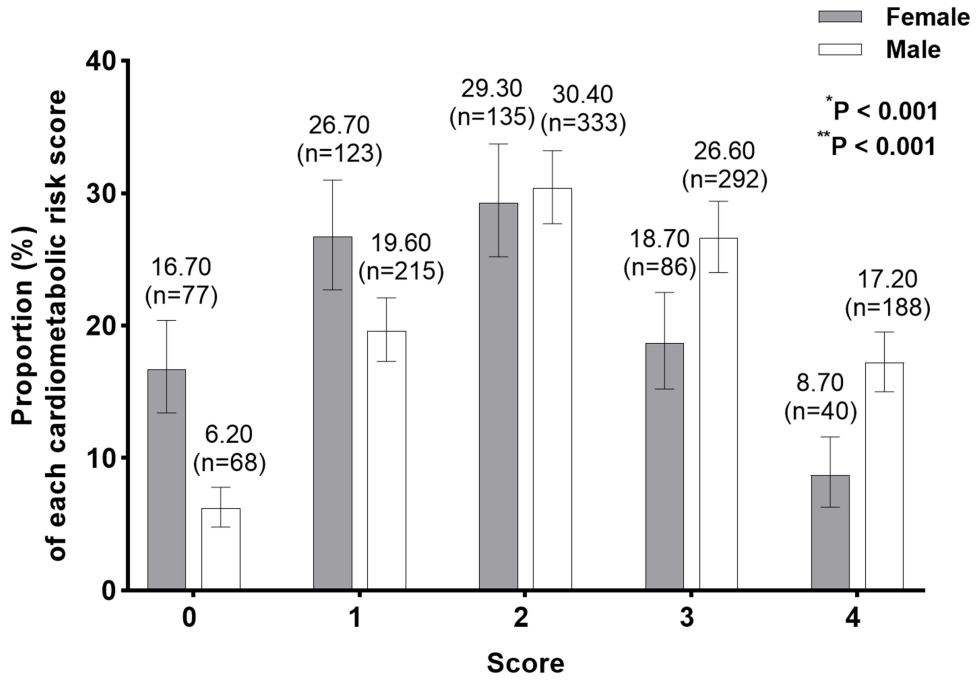

Figure 2 Proportion (95% confidence interval) of each cardiometabolic risk score category in women and men. *P value=Chi-squared test within sex. **P value=Chi-squared test between sexes.

Correlations of Combination of FMR and ALT/AST Ratio with Cardiometabolic Risk

Table 4 shows the correlations between subgroups with different combinations of FMR and ALT/AST ratio and cardiometabolic risk. The high FMR group had a higher risk of a high cardiometabolic risk score than the low FMR group in both women and men, regardless of ALT/AST ratio. Similarly, the high ALT/AST ratio group had a higher risk of a high cardiometabolic risk score than the low ALT/AST ratio group in both women and men, regardless of FMR. Among four subgroups, using the low-FMR/low-ALT/AST group as a reference, the high-FMR/high-ALT/AST group had the highest cardiometabolic risk (OR=8.51; 95% CI 4.46–16.25 in women and OR=5.09; 95% CI 3.39–7.65 in men), even after adjusting for covariates such as age, tobacco use, and alcohol use. Furthermore, in the adjusted model, the risk was higher in the low-FMR/high-ALT/AST group (OR=3.02; 95% CI 1.42–6.40 in women and OR=2.49; 95% CI 1.75–3.54 in men) than in the high-FMR/low-ALT/AST group (OR=2.10; 95% CI 1.03–4.28 in women and OR=1.74; 95% CI 1.14–2.66 in men).

Discussion

In this study, we found that both FMR and ALT/AST ratio were positively associated with higher cardiometabolic risk and the presence of each cardiometabolic risk factor, regardless of sex. The combination of FMR and ALT/AST ratio had a synergistic effect in predicting cardiometabolic risk.

Obesity, especially abdominal obesity, and IR play an important role in the development of MetS,[18] which is a cluster of cardiometabolic risk factors. However, conventional anthropometric indicators, such as BMI and waist circumference, do not accurately reflect the composition of the body. Although the excessive accumulation of body fat is a main risk factor for the development of MetS, an increase in skeletal muscle mass has a potential preventive effect on developing MetS.[19] Individuals who have a normal BMI but excess body fat associated with reduced muscle mass, have a similar risk to that of overweight or obese individuals for the development of MetS.[20] Chung et al[21] reported that the sarcopenic obese group was more closely associated with IR and MetS than the group with individuals who only had sarcopenia or obesity, and those who were nonsarcopenic and nonobese. Therefore, it is reasonable to consider that increased fat mass accompanied by decreased muscle mass presents a dual metabolic burden that can lead to a higher risk of MetS.

Table 2 Association Between Tertiles of Fat-to-Muscle Ratio and Cardiometabolic Risk Factors

Outcome Variables	Tertile of FMR	Female						Male					
		Model 1			Model 2			Model 1			Model 2		
		OR	(95% CI)	P value	OR	(95% CI)	P value	OR	(95% CI)	P value	OR	(95% CI)	P value
Elevated TG	T1	Ref			Ref			Ref			Ref		
	T2	1.97	1.12–3.45	0.019	1.94	1.07–3.50	0.028	1.83	1.36–2.47	<0.001	1.96	1.44–2.67	<0.001
	T3	2.79	1.61–4.83	<0.001	2.75	1.49–5.08	0.001	2.12	1.58–2.86	<0.001	2.88	2.09–3.96	<0.001
Reduced HDL-C	T1	Ref			Ref			Ref			Ref		
	T2	2.16	1.37–3.41	0.001	2.00	1.23–3.26	0.005	1.29	0.96–1.74	0.092	1.39	1.03–1.88	0.031
	T3	2.71	1.70–4.32	<0.001	2.51	1.48–4.27	0.001	1.50	1.11–2.02	0.008	1.68	1.23–2.30	0.001
Elevated blood pressure	T1	Ref			Ref			Ref			Ref		
	T2	3.45	2.16–5.52	<0.001	2.04	1.22–3.42	0.007	1.34	0.96–1.86	0.088	1.25	0.89–1.76	0.192
	T3	6.89	4.10–11.57	<0.001	3.08	1.72–5.51	<0.001	3.28	2.20–4.89	<0.001	2.76	1.84–4.15	<0.001
Hyperglycemia	T1	Ref			Ref			Ref			Ref		
	T2	2.60	1.44–4.67	0.001	1.70	0.92–3.17	0.093	1.45	1.07–1.96	0.018	1.45	1.06–1.97	0.019
	T3	5.36	3.04–9.46	<0.001	2.91	1.56–5.43	0.001	2.76	2.04–3.73	<0.001	2.54	1.86–3.46	<0.001
A high cardiometabolic risk score	T1	Ref			Ref			Ref			Ref		
	T2	3.56	2.22–5.70	<0.001	2.37	1.43–3.92	0.001	1.62	1.18–2.23	0.003	1.66	1.21–2.30	0.002
	T3	7.45	4.48–12.38	<0.001	4.03	2.31–7.04	<0.001	2.81	1.98–3.99	<0.001	3.00	2.09–4.31	<0.001

Notes: Elevated TG, TG ≥ 1.7 mmol/l or drug treatment for elevated TG. Reduced HDL-C, HDL-C < 1.03 mmol/l in men or <1.29 mmol/l in women, or drug treatment for reduced HDL-C. Elevated blood pressure, SBP ≥ 130 mmHg or/and DBP ≥ 85 mmHg, or previously diagnosed hypertension. Hyperglycemia, FBG ≥ 5.6 mmol/l or previously diagnosed type 2 diabetes.

Abbreviations: TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FMR, fat-to-muscle ratio; OR, odds ratio; CI, confidence interval.

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Table 3 Association Between Tertiles of ALT/AST Ratio and Cardiometabolic Risk Factors

Outcome Variables	Tertile of ALT/AST Ratio	Female						Male					
		Model 1			Model 2			Model 1			Model 2		
		OR	(95% CI)	P value	OR	(95% CI)	P value	OR	(95% CI)	P value	OR	(95% CI)	P value
Elevated TG	T1	Ref			Ref			Ref			Ref		
	T2	1.07	0.61–1.88	0.817	1.01	0.57–1.79	0.973	2.20	1.63–2.97	<0.001	2.16	1.59–2.94	<0.001
	T3	2.47	1.47–4.15	0.001	2.43	1.44–4.11	0.001	3.00	2.21–4.06	<0.001	2.65	1.94–3.62	<0.001
Reduced HDL-C	T1	Ref			Ref			Ref			Ref		
	T2	1.99	1.26–3.13	0.003	1.85	1.16–2.93	0.009	1.61	1.20–2.17	0.001	1.63	1.21–2.19	0.001
	T3	3.53	2.18–5.70	<0.001	3.67	2.24–6.01	<0.001	2.36	1.74–3.21	<0.001	2.34	1.71–3.21	<0.001
Elevated blood pressure	T1	Ref			Ref			Ref			Ref		
	T2	1.80	1.14–2.85	0.012	1.50	0.89–2.51	0.127	1.40	0.98–1.99	0.063	1.55	1.08–2.23	0.017
	T3	2.69	1.67–4.33	<0.001	2.55	1.50–4.32	0.001	1.38	0.97–1.96	0.074	1.78	1.23–2.57	0.002
Hyperglycemia	T1	Ref			Ref			Ref			Ref		
	T2	2.29	1.29–4.06	0.005	2.05	1.12–3.76	0.021	1.75	1.29–2.36	<0.001	1.90	1.40–2.58	<0.001
	T3	4.38	2.52–7.62	<0.001	4.76	2.63–8.61	<0.001	1.82	1.35–2.46	<0.001	2.22	1.62–3.04	<0.001
A high cardiometabolic risk score	T1	Ref			Ref			Ref			Ref		
	T2	2.00	1.27–3.15	0.003	1.75	1.06–2.89	0.03	2.37	1.72–3.28	<0.001	2.46	1.78–3.41	<0.001
	T3	5.17	3.16–8.47	<0.001	5.63	3.28–9.65	<0.001	3.68	2.59–5.25	<0.001	3.96	2.76–5.70	<0.001

Notes: Elevated TG, TG ≥ 1.7 mmol/l or drug treatment for elevated TG. Reduced HDL-C, HDL-C < 1.03 mmol/l in men or <1.29 mmol/l in women, or drug treatment for reduced HDL-C. Elevated blood pressure, SBP ≥ 130 mmHg or/and DBP ≥ 85 mmHg, or previously diagnosed hypertension. Hyperglycemia, FBG ≥ 5.6 mmol/l or previously diagnosed type 2 diabetes.

Abbreviations: TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; OR, odds ratio; CI, confidence interval.

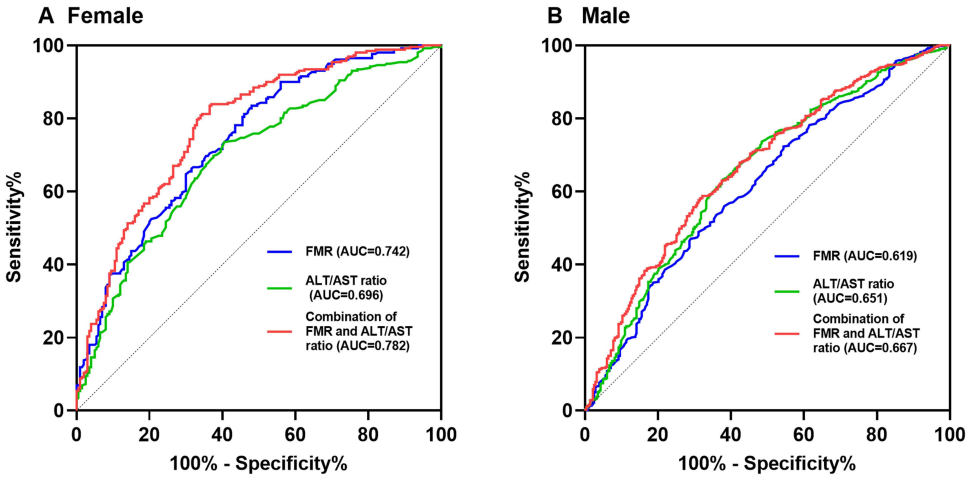

Figure 3 ROC curves of FMR and ALT/AST ratio for the detection of cardiometabolic risk in women (**A**) and men (**B**).
Abbreviations: ROC, receiver operating characteristic; FMR, fat-to-muscle ratio; AUC, area under curve.

In recent years, FMR has been identified as a reliable indicator that can reflect the alteration of body fat and muscle mass. Xu et al[22] found that FMR was highly predictive of MetS among Han and Bouyei populations. The same findings have been observed in other countries. The FMR demonstrated good discriminatory power for detecting MetS in young Colombian adults and in Korean adults.[10,23] Our results are consistent with the above studies. The present analysis revealed that FMR was significantly associated with the prevalence of a high cardiometabolic risk score. With increasing FMR tertiles, the risk of developing dyslipidemia, elevated blood pressure, and hyperglycemia increased progressively. Consistent with our results, Baek et al[24] reported that decreased muscle mass and increased fat mass were associated with an increased risk for dyslipidemia, and a Taiwanese group showed that FMR was strongly associated with hypertension in a large population-based survey including 66,829 participants.[25] In addition, Gamboa-Gomez et al[26] demonstrated that FMR was strongly associated with all categories of glucose metabolic disorder. In summary, FMR is a noninvasive and convenient indicator of cardiometabolic risk.

Nevertheless, while FMR integrates two anthropometric indices and can assess the combined effect of body fat and muscle mass, it neglects liver fat accumulation. Some studies suggest that liver fat accumulation is a sensitive and early indicator of metabolic dysfunction.[27,28] Increased whole-body adiposity without a concomitant increase in liver fat is not associated with augmented metabolic dysfunction.[29] The ALT/AST ratio is significantly correlated with the degree of fatty infiltration of the liver[30] and is also one of the best markers of IR.[15,16] For this reason, we further investigated the relationship between ALT/AST ratio and cardiometabolic risk. The current study showed that ALT/AST ratio was positively associated with the prevalence of a high cardiometabolic risk score. Moreover, the risk of dyslipidemia, elevated blood pressure and hyperglycemia increased significantly in the highest ALT/AST ratio tertile group compared to the lowest ALT/AST ratio tertile group. The results are confirmed by other studies as well. Kohsari et al[31] suggested

Table 4 Association of Different Subgroups with a High Cardiometabolic Risk Score According to the Cutoffs of Fat-to-Muscle Ratio and ALT/AST Ratio

Groups	Female						Male					
	Model 1			Model 2			Model 1			Model 2		
	OR	(95% CI)	P value	OR	(95% CI)	P value	OR	(95% CI)	P value	OR	(95% CI)	P value
Low-FMR/Low-ALT/AST	Ref			Ref			Ref			Ref		
High-FMR/Low-ALT/AST	4.19	2.19–8.03	<0.001	2.10	1.03–4.28	0.041	1.76	1.16–2.67	0.008	1.74	1.14–2.66	0.011
Low-FMR/High-ALT/AST	3.04	1.48–6.26	0.002	3.02	1.42–6.40	0.004	2.46	1.74–3.48	<0.001	2.49	1.75–3.54	<0.001
High-FMR/High-ALT/AST	14.15	7.67–26.09	<0.001	8.51	4.46–16.25	<0.001	5.03	3.35–7.54	<0.001	5.09	3.39–7.65	<0.001

Abbreviations: FMR, fat-to-muscle ratio; OR, odds ratio; CI, confidence interval.

that the ALT/AST ratio was positively associated with the incidence of MetS among the Iranian Kurdish population, and a study encompassing 808 Korean adolescents showed that a lower AST/ALT level was associated with clusters of MetS components.[32] Simultaneously, the AST/ALT ratio was negatively associated with the incidence of type 2 diabetes mellitus in the Japanese population, as concluded by a large retrospective cohort study.[33] Altogether, hepatic transaminases, which are inexpensive and routinely tested in clinical settings, may provide useful information to identify subjects with cardiometabolic risk.

Furthermore, our study investigated whether the combination of FMR and ALT/AST ratio had synergistic effects in predicting cardiometabolic risk. The results confirmed the cooperative interaction, as the AUCs of combination FMR and ALT/AST ratio to predict a high cardiometabolic risk score were greater than that of either FMR or ALT/AST ratio alone, and the cardiometabolic risk in the high-FMR/high-ALT/AST group was significantly higher than that in other subgroups. In addition, AUCs for FMR and ALT/AST ratio and ORs for each subgroup were higher in women than in men, suggesting that early screening and intervention for FMR and ALT/AST ratio in women is more relevant to reduce cardiometabolic risk. Potential mechanisms underlying the combined effects on cardiometabolic risk have been summarized based on previous studies as follows: First, with excess energy consumption, the regulatory function of energy storage in subcutaneous adipose tissue is limited, and excessive fat accumulates in the muscle and liver, leading to muscle and hepatic insulin resistance and contributing to metabolic disorders.[34,35] Second, as an active endocrine organ, adipose tissue expansion is associated with the upregulation of proinflammatory adipokines, such as leptin, interleukin-6 and resistin, and the downregulation of anti-inflammatory adipokines, such as adiponectin and omentin-1, resulting in metabolic dysfunction and CVD.[36] Third, insulin-stimulated plasma glucose uptake mainly occurs in skeletal muscle, so loss of muscle mass can induce IR. Moreover, skeletal muscle can release myokines, such as irisin and actin, which exert anti-inflammatory effects. Skeletal muscle dysfunction, due to reduced mass or to fat infiltration, can lead to impaired myokine secretion and action, thus promoting MetS and CVD.[37,38] Last, fatty liver disease can contribute to the development of atherosclerotic lesions and cardiometabolic abnormalities by releasing inflammatory mediators and hepatic factors, and by affecting lipid profiles and glycemic control.[39]

This study had several strengths. To our knowledge, FMR and ALT/AST ratio were combined for the first time to predict cardiometabolic risk, thus considering the integrated effects of fat, muscle and liver on glucose and lipid metabolism. Besides, the synergistic effects of FMR and ALT/AST ratio was revealed, though the mechanisms involved were not yet fully elucidated. Additionally, the results of our study may provide an alternative approach to identify individuals at high cardiometabolic risk. Nonetheless, our study also has some limitations. First, due to the cross-sectional nature of the study, we were unable to validate the causal relationship. A longitudinal study may be necessary in the future. Second, in this study, body composition was measured by BIA rather than by dual-energy X-ray, CT or MRI, which are more accurate, but their high cost and harmful radiation make them difficult to popularize in clinical practice. Last, this study is a single-center retrospective study, which limits the generalization of the findings to other populations.

Conclusion

This study suggests that FMR and ALT/AST ratio are both positively associated with cardiometabolic risk in adult men and women aged 40 years and over, and that combining the two indicators may improve their predictive capability. Thus, simple, low-cost, and convenient anthropometric measurements of FMR and laboratory tests of ALT/AST ratio, which assess the comprehensive effects of fat, muscle and liver, may be a useful strategy to help screen individuals at high cardiometabolic risk. Future prospective and intervention studies should examine the association between combined indicators and cardiometabolic risk, and it may be plausible to develop strategies for early screening and prevention of cardiometabolic disease to reduce the occurrence of CVD.

Abbreviations

FMR, fat-to-muscle ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIA, bioelectrical impedance analyzer; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; CVD, cardiovascular disease; IR, insulin resistance; HIR, hepatic insulin resistance; BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP,

diastolic blood pressure; MetS, metabolic syndrome; OR, odds ratio; CI, confidence interval; ROC, receiver operating characteristic; AUC, area under curve.

Data Sharing Statement

The data are available from the corresponding author on request.

Ethics Approval and Informed Consent

This study was conducted in accordance with the tenets of the Declaration of Helsinki. The study was approved by the Institutional Review Board of Tongji Medical College, Huazhong University of Science and Technology. Patient informed consent was waived because all medical data were retrospectively reviewed and analyzed anonymously.

Author Contributions

All authors made substantial contributions to the work reported, whether in terms of conception, study design, execution, data acquisition, analysis and interpretation, or in all of these areas. All authors participated in drafting, revising or critically reviewing the article, and have agreed on the journal to which the article will be submitted. All authors reviewed and agreed to all versions of the article before submission, during revision, the final version accepted for publication, and any major changes made at the revision stage. And they all agree to take responsibility for the content of the article.

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References

1. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392(10159):1736–1788.
2. Kyu HH, Abate D, Abate KH, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392(10159):1859–1922.
3. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56(14):1113–1132. doi:10.1016/j.jacc.2010.05.034
4. Guembe MJ, Fernandez-Lazaro CI, Sayon-Orea C, Toledo E, Moreno-Iribas C, Investigators RS. Risk for cardiovascular disease associated with metabolic syndrome and its components: a 13-year prospective study in the RIVANA cohort. *Cardiovasc Diabetol*. 2020;19(1):195. doi:10.1186/s12933-020-01166-6
5. Lee JJ, Pedley A, Hoffmann U, Massaro JM, Levy D, Long MT. Visceral and intrahepatic fat are associated with cardiometabolic risk factors above other ectopic fat depots: the Framingham heart study. *Am J Med*. 2018;131(6):684–692 e612. doi:10.1016/j.amjmed.2018.02.002
6. Kim SH, Jeong JB, Kang J, et al. Association between sarcopenia level and metabolic syndrome. *PLoS One*. 2021;16(3):e0248856. doi:10.1371/journal.pone.0248856
7. Muzurović E, Mikhailidis DP, Mantzoros C. Non-alcoholic fatty liver disease, insulin resistance, metabolic syndrome and their association with vascular risk. *Metabolism*. 2021;119:154770. doi:10.1016/j.metabol.2021.154770
8. Khadra D, Itani L, Tannir H, Kreidieh D, El Masri D, El Ghoch M. Association between sarcopenic obesity and higher risk of type 2 diabetes in adults: a systematic review and meta-analysis. *World J Diabetes*. 2019;10(5):311–323. doi:10.4239/wjd.v10.i5.311
9. Liu D, Zhong J, Ruan Y, Zhang Z, Sun J, Chen H. The association between fat-to-muscle ratio and metabolic disorders in type 2 diabetes. *Diabetol Metab Syndr*. 2021;13(1):129. doi:10.1186/s13098-021-00748-y
10. Seo YG, Song HJ, Song YR. Fat-to-muscle ratio as a predictor of insulin resistance and metabolic syndrome in Korean adults. *J Cachexia Sarcopenia Muscle*. 2020;11(3):710–725. doi:10.1002/jcsm.12548
11. Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes*. 2001;50(8):1844–1850. doi:10.2337/diabetes.50.8.1844
12. Vozarova B, Stefan N, Lindsay RS, et al. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes*. 2002;51(6):1889–1895. doi:10.2337/diabetes.51.6.1889
13. Liu C, Shao M, Lu L, Zhao C, Qiu L, Liu Z. Obesity, insulin resistance and their interaction on liver enzymes. *PLoS One*. 2021;16(4):e0249299. doi:10.1371/journal.pone.0249299

14. Gómez-Sámano MA, Cuevas-Ramos D, Mehta R, Brau-Figueroa H, Meza-Arana CE, Gulias-Herrero A. Association of alanine aminotransferase levels (ALT) with the Hepatic insulin resistance index (HIRI): a cross-sectional study. *BMC Endocr Disord*. 2012;12:16. doi:10.1186/1472-6823-12-16
15. Kawamoto R, Kohara K, Kusunoki T, Tabara Y, Abe M, Miki T. Alanine aminotransferase/aspartate aminotransferase ratio is the best surrogate marker for insulin resistance in non-obese Japanese adults. *Cardiovasc Diabetol*. 2012;11:117. doi:10.1186/1475-2840-11-117
16. Zhao L, Cheng J, Chen Y, et al. Serum alanine aminotransferase/aspartate aminotransferase ratio is one of the best markers of insulin resistance in the Chinese population. *Nutr Metab*. 2017;14:64. doi:10.1186/s12986-017-0219-x
17. Lopez-Lopez JP, Cohen DD, Ney-Salazar D, et al. The prediction of metabolic syndrome alterations is improved by combining waist circumference and handgrip strength measurements compared to either alone. *Cardiovasc Diabetol*. 2021;20(1):68. doi:10.1186/s12933-021-01256-z
18. Kim SR, Lerman LO. Diagnostic imaging in the management of patients with metabolic syndrome. *Transl Res*. 2018;194:1–18. doi:10.1016/j.trsl.2017.10.009
19. Kim G, Lee SE, Jun JE, et al. Increase in relative skeletal muscle mass over time and its inverse association with metabolic syndrome development: a 7-year retrospective cohort study. *Cardiovasc Diabetol*. 2018;17(1):23. doi:10.1186/s12933-018-0659-2
20. Coelho C, Bragança M, de Oliveira BR, et al. Incidence of metabolic syndrome in adults with healthy weight, normal weight obesity, and overweight/obesity. *Nutrition*. 2021;85:111134. doi:10.1016/j.nut.2020.111134
21. Chung JY, Kang HT, Lee DC, Lee HR, Lee YJ. Body composition and its association with cardiometabolic risk factors in the elderly: a focus on sarcopenic obesity. *Arch Gerontol Geriatr*. 2013;56(1):270–278. doi:10.1016/j.archger.2012.09.007
22. Xu K, Zhu HJ, Chen S, et al. Fat-to-muscle ratio: a new anthropometric indicator for predicting metabolic syndrome in the Han and Bouyei Populations from Guizhou Province, China. *Biomed Environ Sci*. 2018;31(4):261–271. doi:10.3967/bes2018.034
23. Ramirez-Velez R, Carrillo HA, Correa-Bautista JE, et al. Fat-to-muscle ratio: a new anthropometric indicator as a screening tool for metabolic syndrome in young Colombian people. *Nutrients*. 2018;10(8):1027. doi:10.3390/nu10081027
24. Baek SJ, Nam GE, Han KD, et al. Sarcopenia and sarcopenic obesity and their association with dyslipidemia in Korean elderly men: the 2008–2010 Korea national health and nutrition examination survey. *J Endocrinol Invest*. 2014;37(3):247–260. doi:10.1007/s40618-013-0011-3
25. Chen YY, Fang WH, Wang CC, et al. Fat-to-muscle ratio is a useful index for cardiometabolic risks: a population-based observational study. *PLoS One*. 2019;14(4):e0214994. doi:10.1371/journal.pone.0214994
26. Gamboa-Gomez CI, Simental-Mendia LE, Rodriguez-Moran M, Guerrero-Romero F. The fat-to-lean mass ratio, a novel anthropometric index, is associated to glucose metabolic disorders. *Eur J Intern Med*. 2019;63:74–78. doi:10.1016/j.ejim.2019.03.017
27. Fabbrini E, Magkos F, Mohammed BS, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *Proce Nat Acad Sci*. 2009;106(36):15430–15435. doi:10.1073/pnas.0904944106
28. Rotman Y, Neuschwander-Tetri BA. Liver fat accumulation as a barometer of insulin responsiveness again points to adipose tissue as the culprit. *Hepatology*. 2017;65(4):1088–1090. doi:10.1002/hep.29094
29. Magkos F, Fabbrini E, Mohammed BS, Patterson BW, Klein S. Increased whole-body adiposity without a concomitant increase in liver fat is not associated with augmented metabolic dysfunction. *Obesity*. 2010;18(8):1510–1515. doi:10.1038/oby.2010.90
30. Zou Y, Zhong L, Hu C, Sheng G. Association between the alanine aminotransferase/aspartate aminotransferase ratio and new-onset non-alcoholic fatty liver disease in a nonobese Chinese population: a population-based longitudinal study. *Lipids Health Dis*. 2020;19(1):245. doi:10.1186/s12944-020-01419-z
31. Kohsari M, Moradinazar M, Rahimi Z, Pasdar Y, Shakiba E. Liver enzymes and their association with some cardiometabolic diseases: evidence from a large kurdish cohort. *Biomed Res Int*. 2021;2021:5584452. doi:10.1155/2021/5584452
32. Lee K, Yang JH. 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*. 2013;11(4):229–235. doi:10.1089/met.2012.0153
33. Chen L, Zhang K, Li X, et al. Association between aspartate aminotransferase to alanine aminotransferase ratio and incidence of type 2 diabetes mellitus in the Japanese population: a secondary analysis of a retrospective cohort study. *Diabetes Metab Syndr Obes*. 2021;14:4483–4495. doi:10.2147/DMSO.S337416
34. Sinha R, Dufour S, Petersen KF, et al. Assessment of skeletal muscle triglyceride content by (1)H nuclear magnetic resonance spectroscopy in lean and obese adolescents: relationships to insulin sensitivity, total body fat, and central adiposity. *Diabetes*. 2002;51(4):1022–1027. doi:10.2337/diabetes.51.4.1022
35. Seppälä-Lindroos A, Vehkavaara S, Häkkinen AM, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. *J Clin Endocrinol Metab*. 2002;87(7):3023–3028. doi:10.1210/jcem.87.7.8638
36. Rana MN, Neeland IJ. Adipose tissue inflammation and cardiovascular disease: an update. *Curr Diab Rep*. 2022;22(1):27–37. doi:10.1007/s11892-021-01446-9
37. Tanaka M, Okada H, Hashimoto Y, et al. Relationship between metabolic syndrome and trunk muscle quality as well as quantity evaluated by computed tomography. *Clin Nutr*. 2020;39(6):1818–1825. doi:10.1016/j.clnu.2019.07.021
38. Wu H, Liu M, Chi VTQ, et al. Handgrip strength is inversely associated with metabolic syndrome and its separate components in middle aged and older adults: a large-scale population-based study. *Metabolism*. 2019;93:61–67. doi:10.1016/j.metabol.2019.01.011
39. Francque S. The liver and the cardiovascular system: two of a kind? *J Am Heart Assoc*. 2021;10(8):e020286. doi:10.1161/JAHA.121.020286