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Association between lipoprotein-related phospholipase A2 and metabolic syndrome

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Background: Lipoprotein-associated phospholipase A2 (Lp-PLA2) has been recognized as a valuable biomarker for identifying the risk of cardiovascular diseases and inflammation. Furthermore, there is strong evidence to suggest that metabolic syndrome is closely associated with chronic inflammation. Accordingly, the present study endeavors to examine the potential correlation between metabolic syndrome and the levels of Lp-PLA2.

Methods: To explore the relationship between Lp-PLA2 levels and metabolic syndrome, and to establish the predictive cut-off value of Lp-PLA2, a retrospective analysis was conducted using medical data from a sample of 3549 Indian adults (comprising 2182 men and 1367 women) aged between 18 and 50 years, who had undergone health check-ups. In addition, the study also sought to investigate any potential differences in Lp-PLA2 levels based on sex and age.

Results: The analysis of the data indicated that participants had a mean age of 44.2 years, a mean Lp-PLA2 level of 589 IU/L, and a metabolic syndrome prevalence of 22%. Lp-PLA2 levels were significantly different between males and females, and a significant correlation was observed between Lp-PLA2 levels and clinical and metabolic characteristics, including BMI, cholesterol, and triglycerides. Interestingly, Lp-PLA2 demonstrated potential as an indicator of metabolic syndrome, particularly in females, despite other biomarkers, such as TG/HDL-C and WHR, exhibiting better area under the curve.

Conclusion: Our findings suggest that Lp-PLA2 may serve as a useful biomarker for identifying individuals at risk of developing metabolic syndrome, particularly in females. Further research is needed to explore the potential of Lp-PLA2 as a diagnostic and therapeutic target for metabolic syndrome.

Keyword: Lp-PLA2, lipoprotein, metabolic syndrome, cardiovascular risk, and lipid profile

Introduction

Lp-PLA2 was first discussed in the 1980s, and the study focused on whether the activity of Lp-PLA2 influences the peroxidation and degradation of low-density lipoprotein (LDL) ^[1]. The scientists then discovered that Lp-PLA2 played a crucial role in cardiovascular disease. According to Brilakis *et al.*, study, it indicated

that the mean Lp-PLA2 levels are related to LDL, high-density lipoprotein (HDL), total cholesterol, fibrinogen, and creatinine, and also correlated with coronary artery disease (CAD) with major adverse events. Lp-PLA2 was seen as another independent marker of CAD apart from C-reactive protein (CRP) ^[2]. Lp-PLA2 has two major functions on humans. Firstly, it has an

antioxidant function. Lp-PLA2 is secreted by macrophages, mast cells, and T cells in the inner layer of the blood vessel wall, and it exists with LDL in the blood. When the body is under oxidative stress to induce LDL partial oxidization, Lp-PLA2 can hydrolyze its oxidative part. Secondly, its inflammation-activating effect is well established. Macrophages, mast cells, and T cells will secrete more Lp-PLA2 under oxidative stress since larger spaces between endothelial cells make them migrate to the tunica intima. Besides, the macrophage in the intima will engulf oxidized LDL and turn into foam cells, which stimulates plaque growth and elevates the likelihood of a cardiovascular event^[3]. In short, Lp-PLA2 has a distinct correlation with the inflammation state.

Metabolic syndrome also has a known relationship with inflammation. With the prevalence of modern lifestyles and unhealthy eating habits, metabolic syndrome has become a major public health concern. In addition to cardiovascular disease and diabetes, metabolic syndrome is also fingered in the occurrence of chronic organ diseases, such as polycystic ovary and nonalcoholic fatty liver disease. Furthermore, individuals with metabolic syndrome typically experience metabolic overload, leading to heightened production of reactive oxygen species and inflammatory cytokines, ultimately subjecting the body to oxidative stress^[4]. This also induces adipocyte hypertrophy and macrophage accumulation to ameliorate the inflammatory state by increasing the level of insulin resistance^[5].

Therefore, in this study, we hope to explore the feasibility of Lp-PLA2 as a predictor of metabolic syndrome by analyzing the correlation between metabolic syndrome risk factors and Lp-PLA2 in the physical examination population. Also, we will estimate the cut-off value of Lp-PLA2 in high-risk metabolic syndrome populations (the presence of ≥ 3 risk factors for metabolic syndrome) to provide efficacious health management and alleviate the harm and deterioration in patients with metabolic syndrome.

Methods

We retrospectively collected the medical records of Indian adults (aged between 18 and 55 years) who underwent health examinations between 2004 and 2008 at Dhanalaxmi Srinivasan Medical College and Hospital. Subjects were excluded if they were affected by any of the following exclusion criteria: (1) with pregnancy (2) who were not fasting for more than 12 hours (3) who had medication for hypertension and /or hyperlipidemia control (4) who had chronic thyroid disease, thyroidectomy or chronic liver disease; and (5) whose data were incomplete.

A total of 2182 men and 1367 women were included in the analysis. After all the subjects provided informed consent, they were subjected to anthropometric and biochemical measurements for clinical data collection, which included body height, body weight, waist circumference, blood pressure, fasting glucose, total cholesterol, triglyceride (TG), LDL, and HDL.

Laboratory Measurements

The clinical chemistry examination encompassed several measurements, including fasting blood glucose (FBG) assessed via Hexokinase enzyme assay using the Cobas Mira Chemistry System manufactured by Roche Diagnostic Systems, Montclair, NJ. Additional measurements were taken by an automatic biochemical analyzer (DxC 800, Beckman CoulterUniCel[®] DxC SYNCHRON[®], Ireland) to assess total cholesterol, LDL, HDL, and TG. Furthermore, measurements were made to determine levels of Lp-PLA2, using a quantitative test through turbidimetric immunology (ABBOTT ARCHITECT c8000/c16000). Anthropometric measures were taken to determine body weight and height using calibrated scales and meters, respectively. The body mass index (BMI) was estimated utilizing the formula: $\text{body weight (kg)} / [\text{height (m)}]^2$. The waist circumference was measured between the lowest rib and the midpoint of the iliac crest. Blood pressure was measured after a 15-minute rest, and the subject was seated using an automated sphygmomanometer on the right arm. The mean arterial pressure was calculated using the

formula: $(2/3) \times \text{diastolic pressure} + (1/3) \times \text{systolic pressure}$. Diabetes mellitus was defined as fasting glucose ≥ 7.0 mmol/L. Metabolic syndrome (MetS) was defined as subjects who exhibited three or more of the following criteria: (1) waist circumference ≥ 90 cm in men and ≥ 80 cm in women; (2) hypertriglyceridemia: TG ≥ 1.7 mmol/L (3) low HDL level < 1.03 mmol/L in men and < 1.29 mmol/L in women; (4) blood pressure $\geq 130/85$ mmHg; and (5) fasting glucose ≥ 5.6 mmol/L [6].

Statistical Analysis

At the outset of our data collection, we utilized Quantile-Quantile plots (Q-Q plots) for a visual assessment of the quantitative variable's conformity to a normal distribution. The distinctive bell-shaped curve associated with a normal distribution became apparent in our analysis. Consequently, given the confirmation of a normal distribution in the dataset, we opted for the mean and standard deviation as our preferred measures of central tendency. This choice was motivated by their sensitivity to extreme values, aligning well with the characteristics of our data. Prior research examined the connection between LDL and Lp-PLA2 levels in individuals with type 2 diabetes and found that the standardized regression coefficient of LDL was 0.11. To achieve a type I error of 1% and a power of 99%, a minimum sample size of 1966 was necessary based on the effect size observed [3].

We conducted a comparison of basic characteristics between male and female subjects, including continuous and categorical variables, using an independent sample *t*-test and chi-square test, respectively. Additionally, we analyzed the relationship between Lp-PLA2 levels and comorbidities such as hypertension, diabetes, MetS, and lipid profile, using an independent sample *t*-test and stratifying by sex. Pairwise comparisons were conducted using the Bonferroni adjustment if the overall test was significant. Subsequently, the study compared

Lp-PLA2 levels using a logistic regression model, adjusting for age and age plus BMI subgroups. Lastly, ROC curves for TG/HDL-C, Waist-to-height ratio (WHtR), and Lp-PLA2 were done for the cut-off point value and prediction power evaluation. All tests were two-tailed, and a significance level of $p < 0.05$ was set. The data analyses were conducted using SPSS 25 (IBM SPSS Inc., Chicago, IL, USA).

Result

A total of 3549 participants were included in the final analysis. 2182 of these participants were male. Their average age was 44.2 years. The average Lp-PLA2 level was 589 IU/L. Approximately 4.5% of the subjects were diagnosed with diabetes, and 22% already manifested MetS. Table 1 lists the basic characteristics, including cardiometabolic risk factors. The mean Lp-PLA2 level in men and women were 621.45 ± 158.56 IU/L and 537.92 ± 141.33 IU/L respectively. A significant difference of Lp-PLA2 was noted with a p -value < 0.05 among men and women respectively, similar to other factors listed in Table 1.

Table 2 presents the findings regarding the associations between the Lp-PLA2 level (a continuous variable) and clinical/ metabolic characteristics, stratified by gender. The results revealed that in both men and women, BMI, waist circumference, waist-to-height ratio, total cholesterol, triglycerides, HDL, LDL, and TG/HDL-C were significantly associated with Lp-PLA2 levels ($p < 0.05$). Furthermore, in men, SBP, DBP, and MAP demonstrated significant correlations with Lp-PLA2 ($p < 0.05$), while in women, fasting glucose presented a significant correlation with Lp-PLA2 ($p < 0.05$).

To examine whether there existed an association between particular characteristics and Lp-PLA2 levels, we stratified our sample into tertiles and conducted Pearson's correlation analysis (as shown in Table 3). The findings indicate a statistically.

Table 1: Basic Characteristics of the Study Subjects

Variables	Total (n=3549)	Male (n=2182)	Female (n=1367)	p value
Age (year)	44.21±7.01	43.78±7.03	44.90±6.92	<0.001
BMI (kg/m ²)	24.26±3.34	24.98±3.32	23.11±3.05	<0.001
Waist circumference (cm)	83.18±9.97	87.35±8.96	76.54±7.61	<0.001
Waist-to-height ratio	0.50±0.05	0.52±0.05	0.49±0.05	<0.001
SBP (mmHg)	120.24±18.00	124.42±16.46	113.56±18.34	<0.001
DBP (mmHg)	74.61±12.92	78.24±12.20	68.82±11.89	<0.001
MAP (mmHg)	89.82±14.14	93.63±13.12	83.74±13.57	<0.001
Fasting glucose (mmol/L)	5.17±1.26	5.29±1.43	4.98±0.90	<0.001
Total cholesterol (mmol/L)	5.12±0.95	5.20±0.98	4.99±0.90	<0.001
Triglycerides (mmol/L)	1.61±1.43	1.89±1.62	1.16±0.91	<0.001
LDL cholesterol (mmol/L)	3.45±0.87	3.58±0.88	3.25±0.81	<0.001
HDL cholesterol (mmol/L)	1.33±0.32	1.23±0.28	1.49±0.31	<0.001
TG/HDL-C	1.41±1.94	1.74±2.21	0.89±1.22	<0.001
Lp-PLA2 (IU/L)	589.28±157.47	621.45±158.56	537.92±141.33	<0.001
Diabetes, n (%)	1584.45%	1275.82%	312.27%	<0.001
Metabolic Syndrome, n (%)	75,221.19%	58,126.63%	17,112.51%	<0.001

Notes: Continuous data are shown as mean ± SD and compared using independent two samples *t*-test. Categorical data are shown as n (%) and compared using the Chi-square test

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; Lp-PLA2, lipoprotein-associated phospholipase A2

Table 2: Pearson's Correlation Coefficients Between Lp-PLA2 Levels and Cardiometabolic Risk Factors in Men and Women

Variables	Male (n=2182)		Female (n=1367)	
	r	p value	r	p value
Age (year)	0.02	0.26	0.08	0.002
BMI (kg/m ²)	0.09	<0.001	0.07	0.01
Waist circumference (cm)	0.11	<0.001	0.09	0.001
Waist-to-height ratio	0.10	<0.001	0.09	0.001
SBP (mmHg)	0.05	0.01	0.03	0.26
DBP (mmHg)	0.06	0.01	0.03	0.23
MAP (mmHg)	0.06	0.01	0.03	0.23
Fasting glucose (mmol/L)	0.03	0.14	0.07	0.02
Total cholesterol (mmol/L)	0.38	<0.001	0.34	<0.001
Triglycerides (mmol/L)	0.05	0.01	0.09	0.001
LDL cholesterol (mmol/L)	0.44	<0.001	0.36	<0.001
HDL cholesterol (mmol/L)	-0.11	<0.001	-0.06	0.03
TG/HDL-C	0.04	0.04	0.06	0.02

Abbreviations: Lp-PLA2, lipoprotein-associated phospholipase A2; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides

Table 3: Clinical and Metabolic Characteristics According to Lp-PLA2 Status

Variables	Lp-PLA2 (IU/L)			p value	p trend
	Tertile 1	Tertile 2	Tertile 3		
Male	(n=729)	(n=726)	(n=727)		
Age (year)	43.40±7.18	43.69±7.05	44.24±6.83	0.07	0.02
BMI (kg/m ²)	24.63±3.43	24.83±3.31	25.49±3.15 ^{a,b}	<0.001	<0.001
Waist-to-height ratio	0.51±0.05	0.51±0.05	0.52±0.05 ^{a,b}	<0.001	<0.001
MAP (mmHg)	93.27±13.58	93.18±12.89	94.45±12.87	0.12	0.08
Fasting glucose (mmol/L)	5.28±1.38	5.21±1.24	5.38±1.65	0.06	0.15
Total cholesterol (mmol/L)	4.75±0.89	5.08±0.80 ^a	5.76±0.95 ^{a,b}	<0.001	<0.001
Triglycerides (mmol/L)	1.84±1.47	1.80±1.59	2.04±1.77 ^b	0.01	0.02
LDL cholesterol (mmol/L)	3.11±0.80	3.49±0.65 ^a	4.15±0.84 ^{a,b}	<0.001	<0.001
HDL cholesterol (mmol/L)	1.27±0.32	1.23±0.27 ^a	1.19±0.25 ^{a,b}	<0.001	<0.001
TG/HDL-C	1.67±1.78	1.64±2.06	1.92±2.69 ^b	0.03	0.03
Diabetes, n (%)	405.49%	354.82%	527.15%	0.15	0.18
Metabolic Syndrome, n (%)	18,525.38%	17,323.83%	22,330.67% ^b	0.01	0.02
Female	(n=460)	(n=455)	(n=452)		
Age (year)	43.70±7.06	44.99±6.70 ^a	46.03±6.79 ^a	<0.001	<0.001
BMI (kg/m ²)	22.88±2.97	22.99±3.05	23.47±3.11 ^a	0.01	0.003
Waist-to-height ratio	0.48±0.05	0.48±0.05	0.49±0.05 ^{a,b}	<0.001	<0.001
MAP (mmHg)	82.87±13.34	83.42±13.21	84.94±14.11	0.06	0.02
Fasting glucose (mmol/L)	4.90±0.66	4.96±0.95	5.09±1.04 ^a	0.003	0.001
Total cholesterol (mmol/L)	4.58±0.81	4.89±0.69 ^a	5.52±0.92 ^{a,b}	<0.001	<0.001
Triglycerides (mmol/L)	1.06±0.82	1.11±0.80	1.31±1.08 ^{a,b}	<0.001	<0.001
LDL cholesterol (mmol/L)	2.87±0.72	3.15±0.59 ^a	3.74±0.83 ^{a,b}	<0.001	<0.001
HDL cholesterol (mmol/L)	1.50±0.31	1.51±0.32	1.45±0.31 ^b	0.01	0.03
TG/HDL-C	0.80±0.97	0.83±0.94	1.04±1.61 ^{a,b}	0.005	0.003
Diabetes, n (%)	51.09%	112.42%	153.32%	0.07	0.02
Metabolic Syndrome, n (%)	459.78%	4810.55%	7817.26% ^{a,b}	0.001	0.001

Notes: ^a $p < 0.05$ when compared with group tertile 1; ^b $p < 0.05$ when compared with group tertile 2

Abbreviations: Lp-PLA2, lipoprotein-associated phospholipase A2; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides

Significant linear trend across all characteristics within the ordinal subgroups that were based on Lp-PLA2 levels ($p < 0.05$). Specifically, the prevalence of MetS among women demonstrated a rising trend as Lp-PLA2 levels increased, with rates of 9.78%, 10.55%, and 17.26% in the first, second, and third tertiles, respectively ($p < 0.05$).

To further confirm this observation, we conducted regression analyses (as presented in Table 4), with age and BMI as covariates. The results indicated that only in the female group did Lp-PLA2 exhibit a significant p-value ($p < 0.05$)

after adjusting for age and BMI, reinforcing its potential as an indicator of MetS in this subgroup. Table 5 and Figure 1 present the ROC curves for three biomarkers: TG/HDL-C, waist-to-height ratio (WHtR), and Lp-PLA2, stratified by gender. In males, the results demonstrated that TG/HDL-C had a C-value of 0.86 (95% CI: 0.84- 0.88), WHtR had a C value of 0.84 (95% CI: 0.82-0.86), and Lp-PLA2 had a C value of 0.53 (95% CI: 0.50-0.56). In females, the results indicated that TG/HDL-C had a C value of 0.93 (95% CI: 0.91-0.95), WHtR had a C value of 0.87 (95% CI:

0.84-0.89), and Lp-PLA2 had a *C* value of 0.59 (95% CI: 0.54-0.64). These findings suggest that although TG/ HDL-C and WHR demonstrated better area under the curve, Lp-PLA2 may still have the potential to serve as an indicator of MetS, particularly among females.

Discussion

In this cross-sectional study, we aimed to investigate the association between Lp-PLA2 and MetS in a Chinese population. The study included a sample of 2182 men and 1367 women. Our

findings indicate a significant correlation between Lp-PLA2 levels and risk factors for MetS, including BMI, WHtR, total cholesterol, LDL, and HDL, particularly in the female cohort. Additionally, after adjusting for age and BMI, we observed a significant association between Lp-PLA2 levels and MetS in females, with a cut-off value of 626.5.

These results suggest that Lp-PLA2 could potentially serve as a biomarker for identifying and preventing MetS in females. The findings of this study are of great significance

Table 4: Logistic Regression Analysis of Lp-PLA2 Level and Metabolic Syndrome

Variables	Crude OR (95% CI)	p value	Adjusted OR (95% CI) in Model 1	p value	Adjusted OR (95% CI) in Model 2	p value
Male (n=2182)						
Lp-PLA2 (IU/L)	1.00 (1.000-1.001)	0.02	1.00 (1.000-1.001)	0.02	1.00 (1.000-1.001)	0.35
Lp-PLA2 (IU/L), per 100	1.08 (1.014-1.143)	0.02	1.07 (1.011-1.140)	0.02	1.03 (0.964-1.108)	0.36
Female (n=1367)						
Lp-PLA2 (IU/L)	1.00 (1.000-1.003)	0.001	1.00 (1.000-1.003)	0.01	1.00 (1.000-1.003)	0.03
Lp-PLA2 (IU/L), per 100	1.20 (1.075-1.338)	0.001	1.17 (1.045-1.314)	0.007	1.16 (1.018-1.310)	0.026

Notes: Model 1: Unadjusted, Model 2: Adjusted for age, Model 3: Adjusted for the variables in model 2 and BMI

Table 5 Cut-off Value and Prediction Power for TG/HDL-C, Waist-to-Height Ratio (WHtR), and Lipoprotein-Associated Phospholipase A2 (Lp-PLA2)

Variables	AUC	(95% CI)	Cut-off Point According to Youden's Index	Sensitivity(%)	Specificity (%)
Male					
TG/HDL-C	0.86	(0.84-0.88)	1.39	0.88	0.70
WHR	0.84	(0.82-0.86)	0.52	0.83	0.70
Lp-PLA2 (IU/L)	0.53	(0.50-0.56)	685.50	0.38	0.69
Female					
TG/HDL-C	0.93	(0.91-0.95)	1.04	0.86	0.87
WHR	0.87	(0.84-0.89)	0.49	0.92	0.67
Lp-PLA2 (IU/L)	0.59	(0.54-0.64)	626.50	0.35	0.82

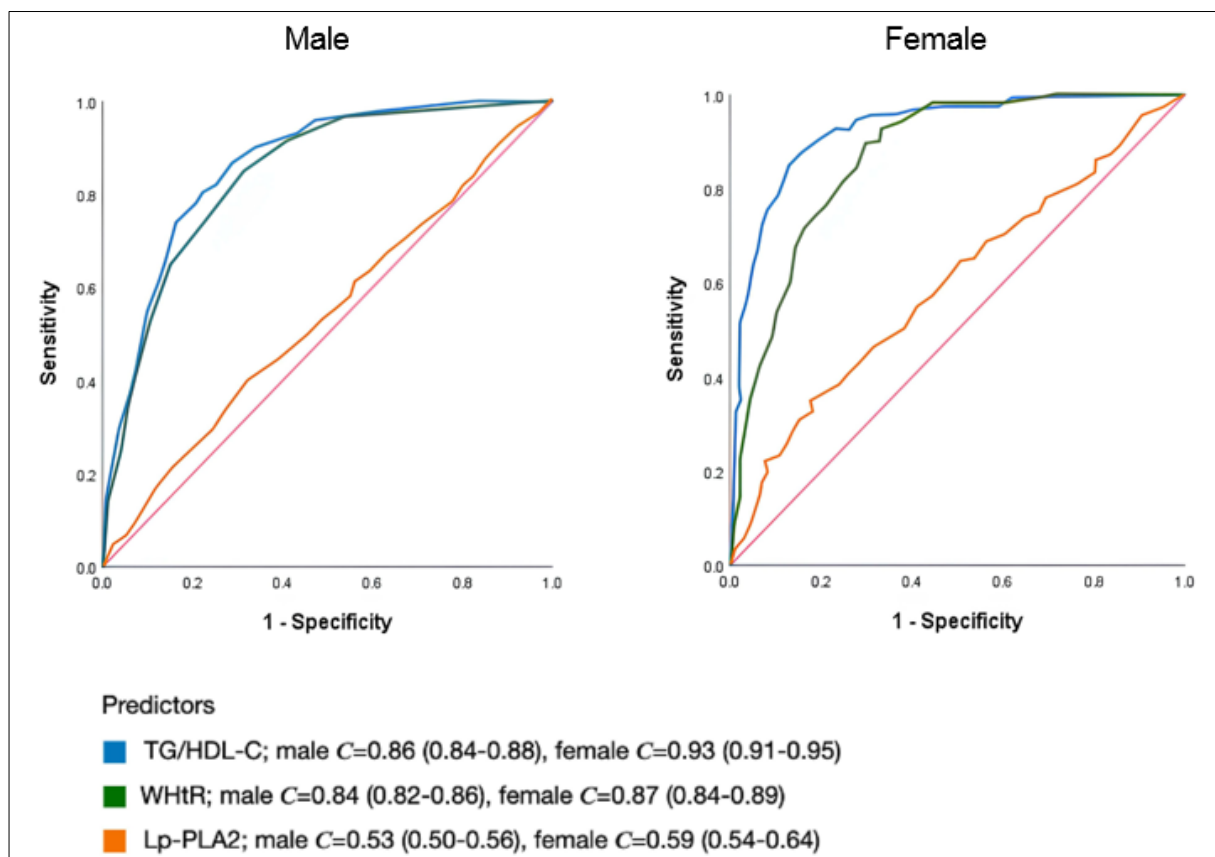


Fig 1: ROC curves assessing diagnostic performance of TG/HDL-C, WHtR, and Lp-PLA2 Stratified by Gender. ROC curves illustrate the discriminatory ability of TG/ HDL-C, WHtR, and Lp-PLA2 for predicting Mets, with gender-specific analysis. In males, TG/HDL-C ($C = 0.86$, 95% CI: 0.84-0.88) and WHtR ($C = 0.84$, 95% CI: 0.82-0.86) showed strong performance, while Lp-PLA2 had lower discrimination ($C = 0.53$, 95% CI: 0.50-0.56). Among females, TG/HDL-C excelled ($C = 0.93$, 95% CI: 0.91-0.95), surpassing WHtR ($C = 0.87$, 95% CI: 0.84-0.89). Lp-PLA2 exhibited weaker discrimination ($C = 0.59$, 95% CI: 0.54-0.64). These findings highlight gender-specific variations in biomarker efficacy for Mets diagnosis, emphasizing the need for gender-specific analyses

to healthcare professionals and policymakers, as they provide valuable insights for developing targeted prevention and treatment strategies for MetS.

Our study aimed to investigate the potential of Lp-PLA2 level as a biomarker of MetS across different age groups. For the concern of clinical practice and hormone alternation, we categorized the participants by age for screening the possible MetS disease. In our findings, total cholesterol and LDL were significantly related to Lp-PLA2 and exhibited a trend as Lp-PLA2 increased regardless of age. This result revealed the theory that Lp-PLA2 coexists with LDL in the blood and the LDL level is strongly correlated with total cholesterol [5]. Moreover, in Jabor *et al.* research,

there was also a strong correlation between Lp-PLA2 and LDL within acute coronary syndrome patients or the LDL level after 12 weeks of recovery. The result implied that LDL may be the major determinant of Lp-PLA2 in serum [6] and it had similar findings to this study.

Aside from total cholesterol and LDL level, other lipid profiles had a significant relationship to Lp-PLA2, including TG and HDL-C. The mechanism may be TG, HDL-C, and Lp-PLA2 production in the human body originating from adipose tissue [7]. This pathway also contributed to atorvastatin intervention within coronary heart disease patients with a reduction of the Lp-PLA2 mass by 26% [8]. In our study, TG to HDL ratio was an item of variables in the analyses, and the

results all had a significant correlation to Lp-PLA2. According to other related research, a high TG/HDL ratio was related to coronary disease [9], insulin resistance [10] and atherosclerosis [11]. Besides, Krawczyk *et al.* had a similar finding as our study that a high TG/HDL ratio had the potential to be the prediction of MetS [12].

Furthermore, a significant linear trend was observed between waist circumference, one of the diagnostic criteria, and the Lp-PLA2 level in our study, which aligns with the findings of da Silva *et al.* that revealed a positive correlation between waist circumference and Lp-PLA2 level among adolescents, reflecting the activity of Lp-PLA2 [13]. Similarly, a study conducted among adults showed a significant association between central obesity, represented by higher waist circumference, and Lp-PLA2 levels [14]. Hence, the correlation between waist circumference and Lp-PLA2 level may be applicable to all age groups. Additionally, our study found that WHtR had a significant association with Lp-PLA2 by gender. WHtR has been identified as a predictor of coronary heart disease by Hsieh and Yoshinaga [15] and as an obesity-related indicator for hypertension and MetS in Rodrigues *et al.*'s study [16], indirectly supporting the association between Lp-PLA2 and MetS.

Additionally, we analyzed the potential of Lp-PLA2 level as a biomarker of MetS across different genders, considering the scarcity of studies that have examined the association between MetS and Lp-PLA2 levels. A recent investigation sought to address this knowledge gap by recruiting 60 participants with diabetes mellitus and assessing the impact of obesity, lipid profiles, and blood pressure on Lp-PLA2 levels. The findings demonstrated a significant correlation between these factors and Lp-PLA2 levels. Moreover, subgroup analyses revealed a sex-specific difference in the relationship between these variables and Lp-PLA2 levels. Specifically, body fat and mean arterial pressure were found to be more strongly associated with Lp-PLA2 levels in males, while low-density lipoprotein cholesterol and triglycerides were more strongly associated with Lp-PLA2 levels in females [3]. This observation is consistent with the

findings presented in Table 2 of our study, and suggests that Lp-PLA2 could serve as a potential predictor of MetS in the Asian population.

Besides, regarding the link between Lp-PLA2 and diabetes, Nelson *et al.* presented compelling pathways, indicating that Lp-PLA2 could potentially contribute significantly to the onset of insulin resistance, consequently elevating the risk of type 2 diabetes. One proposed mechanism revolves around the inflammatory activity associated with Lp-PLA2's hydrolysis of oxidized phospholipids. This process is hypothesized to induce insulin resistance, a key precursor to diabetes. Elevated Lp-PLA2 levels are considered not only as potential markers of heightened adipose tissue inflammation but also as contributors to metabolic processes that underlie insulin resistance and pancreatic β -cell failure [17].

In addition, Gonçalves *et al.*'s study delves into the molecular intricacies of Lp-PLA2, elucidating its heightened presence in symptomatic plaques and its associations with proinflammatory cytokines [18]. Simultaneously, English *et al.*'s cross-sectional investigation further elucidates the correlations existing between Lp-PLA2, platelet-activating factor (PAF), and conventional cardiovascular risk factors [19]. Crucially, the correlation between Lp-PLA2 and PAF, TNF- γ , and IL-6 signifies a potential role in activating pro-inflammatory cascades. This interplay underscores the complex nexus between Lp-PLA2, insulin resistance, and inflammation, urging further exploration for its implications in metabolic syndrome and cardiovascular health.

Moreover, the function and activity of Lp-PLA2 are influenced by estrogen. Estrogen functions as 17 β -estradiol (E2) in the human body, which can promote the healing of endothelial cells, and also lower the inflammation state by reducing the cytokines produced by monocytes and macrophages [20]. The role of estrogen in influencing the hepatic lipid profile and preventing the development of nonalcoholic fatty liver disease/steatohepatitis (NAFLD/NASH) is of significant interest. Estrogen has been shown to induce hepatic production of very low-density lipoprotein (VLDL), which plays a crucial role in

lipid assembly and secretion. Consequently, men and postmenopausal women, who have lower levels of estrogen, may have an increased risk of developing NAFLD/NASH due to their impaired hepatic lipid assembly and secretion [21]. This suggests that sex differences play a significant role in the lipid profile and MetS, with estrogen levels being a key determinant of the lipid profile and the development of NAFLD/NASH.

In summary, it can be inferred that reduced levels of estrogen in males make them more susceptible to central obesity. Additionally, numerous studies have established a significant association between body mass index (BMI), waist circumference, and MetS as above mentioned. After accounting for these two variables, the predictive ability of Lp-PLA2 is eliminated. In contrast, premenopausal women have a lower accumulation of central adiposity due to estrogenic support when compared to males. Therefore, we collected participants between 18 to 55 years and discussed the Lp-PLA2 by gender in our study, and the result showed a relatively strong relationship between MetS among female participants. The ROC curve analysis revealed that Lp-PLA2 had higher prediction power in females than in males, and the cut-off point of Lp-PLA2 was 626.5 in the female group in our study. These results demonstrated that gender is an important factor to consider when using Lp-PLA2 as a biomarker for MetS.

The present study boasts a significant advantage with respect to its large sample size ($n = 3549$), which enabled the analysis and estimation of MetS. However, it is important to acknowledge the limitations of our investigation. Firstly, the study design adopted a cross-sectional approach, thus precluding the establishment of causality. Secondly, the sample population was drawn from individuals participating in routine health examinations, which may have resulted in selection biases, as these individuals are more likely to prioritize their health. As such, there is a possibility of underestimating the prevalence of certain characteristics such as blood pressure and lipid profile if this group is taken to be representative of the entire population. Thirdly, we employed a questionnaire to collect personal

data, which may have unintentionally overlooked some medical history due to individual cognitive biases. Additionally, we did not factor in socio-economic-related variables such as education, income, and lifestyle, which are important determinants of MetS. Finally, the present study only measured Lp-PLA2 mass, rather than Lp-PLA2 activity, due to the limited availability of laboratory determinations. Nonetheless, previous research has demonstrated a correlation between Lp-PLA2 activity and MetS [22]. Additional investigations are warranted to elucidate the association among carotid sonography, Lp-PLA2 levels, and MetS.

Conclusion

Our research establishes a significant association between Lp-PLA2 and various metabolic risk factors, underscoring its potential as an independent risk factor for metabolic syndrome, especially in females. The implications of our findings point towards Lp-PLA2 as a promising biomarker for identifying individuals at risk of developing metabolic syndrome, with a particular emphasis on its relevance in the female population. Moving forward, further investigation is imperative to unveil the full diagnostic and therapeutic potential of Lp-PLA2 in addressing metabolic syndrome.

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