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ORIGINAL ARTICLE

Association of Platelet-to-HDL Cholesterol Ratio with Metabolic Syndrome in a Japanese Health Check-up Population

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SUMMARY

Background: **The platelet-to-high-density lipoprotein cholesterol (HDL-C) ratio (PHR) has been proposed as a composite biomarker reflecting both thrombogenic and lipid-related mechanisms. However, its relationship with metabolic syndrome (MetS) has not been extensively evaluated in the general Japanese population.**
Methods: **We conducted a cross-sectional analysis of 17,581 adults (7,400 women) who underwent health check-ups between 2007 and 2024. PHR was calculated as the platelet count divided by HDL-C. MetS was defined according to the Japanese criteria. The association between PHR and MetS and its components was assessed using multivariable linear and logistic regression. Receiver operating characteristic (ROC) analysis was used to evaluate the discriminatory ability of PHR compared to other simple markers.**
Results: **PHR was significantly higher in participants with MetS ($p < 0.001$) and correlated with key components, including waist circumference, triglycerides (TG), and fasting plasma glucose. In multivariable logistic regression, PHR was independently associated with MetS in both sexes. The area under the curve (AUC) for PHR was 0.687 (95% confidence interval [CI]: 0.674 - 0.700) in men and 0.724 (95% CI: 0.700 - 0.748) in women. These values were modestly lower than those for TG and TG/HDL-C, but PHR showed utility as a non-redundant marker.**
Conclusions: **PHR is independently associated with MetS and its components in the Japanese population. Although its discriminatory performance is modest, PHR may serve as a supplementary marker in health check-up settings for identifying individuals at risk of metabolic disorders.**
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KEYWORDS

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INTRODUCTION

The platelet-to-high-density lipoprotein cholesterol (HDL-C) ratio (PHR) has recently emerged as a potential biomarker reflecting the interplay between platelet count and HDL-C levels, both of which play essential roles in inflammation, thrombosis, and lipid metabolism [1,2]. Platelets play a central role in hemostasis and act as inflammatory mediators, contributing to atherogenesis and metabolic dysfunction [3]. In contrast, HDL ex-

hibits multiple protective effects - anti-inflammatory, antioxidative, and endothelial-stabilizing actions - and modulates platelet activity and coagulation [4,5].

Elevated PHR has been associated with increased levels of pro-inflammatory cytokines, oxidative stress markers, and prothrombotic factors, all known contributors to the pathogenesis of metabolic syndrome (MetS) [6, 7]. MetS is characterized by a cluster of metabolic abnormalities, including central obesity, dyslipidemia, hypertension, and insulin resistance, and is a well-established risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [8,9]. In patients with MetS, enhanced platelet activation and systemic inflammation contribute to elevated platelet counts. Concurrently, reduced HDL-C levels - a hallmark of MetS - impair anti-inflammatory and antioxidative functions. This dual alteration exacerbates the vicious cycle of metabolic dysfunction [10,11].

PHR presents an easily accessible and cost-effective alternative to conventional inflammatory and prothrombotic markers, such as C-reactive protein (CRP) and fibrinogen. Previous studies have reported significant associations between elevated PHR and various metabolic and cardiovascular conditions, including non-alcoholic fatty liver disease (NAFLD), coronary artery disease (CAD), and T2DM [12]. However, despite increasing interest in PHR, its clinical relevance in the context of MetS - a key upstream risk factor for these diseases - remains poorly characterized.

Several knowledge gaps remain regarding the clinical and pathophysiological relevance of the PHR in the context of MetS. While PHR has been studied in relation to NAFLD and T2DM, its association with MetS remains insufficiently explored. Given the heterogeneous nature of MetS, it is crucial to determine which specific metabolic components - such as central obesity, dyslipidemia, or insulin resistance - are most strongly correlated with PHR. Elucidating these associations may help clarify the role of platelet function and lipid metabolism in MetS pathogenesis and contribute to improved risk stratification strategies [13].

Second, there is a paucity of data on PHR in Japanese populations. Ethnic differences in metabolic and lipid profiles are well documented, and cutoff values for metabolic markers often differ between Western and Asian cohorts [14,15]. Since most existing studies on PHR have been conducted in Western or Middle Eastern populations, its relevance to Japanese individuals remains uncertain. Given that MetS diagnostic criteria and lipid thresholds exhibit ethnic variability, assessing PHR's distribution and association with MetS in a Japanese-specific context is necessary [16].

Third, limited research evaluates PHR's diagnostic performance. While metabolic markers such as the homeostatic model assessment for insulin resistance (HOMA-IR) and the triglyceride (TG)/HDL-C ratio are widely used for MetS risk assessment [17], the ability of PHR to function as a diagnostic tool has not been systematically assessed using receiver operating characteristic (ROC) curve analysis. Establishing its sensitivity and specificity for MetS diagnosis is crucial for determining its clinical utility and potential integration into routine health screenings [18].

This study investigated the association between PHR and MetS in a Japanese population. By examining PHR distribution, its correlation with individual metabolic components, and its diagnostic performance using ROC analysis, this study sought to elucidate the clinical relevance of PHR and its potential utility as a biomarker for MetS risk stratification in Japanese adults.

MATERIALS AND METHODS

Study subjects

This cross-sectional study included 17,581 subjects (10,181 men and 7,400 women) who underwent health checkups at Tokai University Hachioji Hospital between April 2007 and June 2024. Only the first health check-up record of each subject, from 2007 to 2024, was included in the analysis. Medical history and information on smoking, physical activity, and alcohol intake were obtained using self-administered questionnaires and interviews conducted by nurses.

Measurements

Waist circumference (WC) was measured at the umbilical level during slight expiration in the standing position. Blood pressure (BP) was measured while the participant was seated in the upper right arm using an automatic BP monitor device (TM-2655P; A&D, Tokyo, Japan). Blood samples were collected in heparin-coated tubes early in the morning after overnight fasting. Red blood cell (RBC), white blood cell (WBC), and platelet counts were measured by an automated hematology analyzer. Fasting plasma glucose (FPG) levels were measured using an L-type Glu 2 kit using the hexokinase/glucose-6-phosphate dehydrogenase method (Wako Pure Chemicals; Osaka, Japan). Fasting immunoreactive insulin (FIRI) levels were measured using a fluorescence enzyme immunoassay (ST AIA-PACK IRI; Toso, Tokyo, Japan). HOMA-IR was calculated as follows: FPG (mg/dL) × FIRI (μIU/mL)/405 [19]. Low-density lipoprotein cholesterol (LDL-C), HDL-C, and triglycerides (TG) levels were measured using visible spectrophotometry (Determiner L LDL-C, Determiner L HDL-C, and Determiner L TG II, respectively; Kyowa Medex, Tokyo, Japan). Uric acid levels were measured using an L-Type UA.M kit using the uricase-*N*-(3-sulfopropyl)-3-methoxy-5-methylaniline method (Wako Pure Chemicals; Osaka, Japan). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltranspeptidase were measured using the JSCC transferable method with L-Type AST.J2, L-Type ALT.J2 (Wako Pure Chemicals; Osaka, Japan), and Labofit g-GT (Kanto Chemical; Tokyo, Japan), respectively. Serum high-sensitivity C-reactive protein (hsCRP) levels were measured using latex agglutination turbidimetry.

Definition of metabolic syndrome

A diagnosis of MetS was defined as the presence of any three or more of the following five criteria: 1) central obesity (WC ≥ 85 cm for men or ≥ 90 cm for women), 2) elevated FPG (≥ 100 mg/dL [5.5 mmol/L]) or ongoing diabetes treatment, 3) elevated TG (≥ 150 mg/dL [1.7 mmol/L]) or drug treatment for elevated TG, 4) reduced HDL-C (< 40 mg/dL in men or < 50 mg/dL in women) or drug treatment for reduced HDL-C, and 5) elevated BP (systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg) or ongoing treatment for hypertension. These criteria were based primarily on the joint interim statement by Alberti et al. [20], with waist circumference thresholds adapted to Japanese guidelines [12].

Statistical analyses

Data were expressed as mean ± standard deviation or median (interquartile range), as appropriate. Normality was assessed using the Kolmogorov-Smirnov test. The Student's *t*-test was used to compare the means of two groups. Bonferroni's multiple comparison test was applied to compare three or more groups. Metabolic markers were evaluated after stratification by sex and the number of MetS diagnostic components. To compare clinical variables between participants with and without MetS while adjusting for age, analysis of covariance (ANCOVA) was performed separately for men and women.

In addition, subjects were stratified into quartiles based on gender-specific distributions of platelet-to-HDL cholesterol ratio (PHR) to examine trends across increasing levels. For men, the quartiles were defined as Q1 (< 121.7), Q2 (121.7 - < 154.1), Q3 (154.1 - < 194.8), and Q4 (≥ 194.8); for women, Q1 (< 103.4), Q2 (103.4 - < 128.9), Q3 (128.9 - < 164.5), and Q4 (≥ 164.5). Linear regression analysis for trend was applied across these quartiles.

Multiple linear regression analyses were conducted to identify independent variables associated with PHR. Variable selection was performed using a stepwise procedure combining forward and backward selection, with entry and stay criteria set at $p < 0.05$. The final model was selected based on the Akaike Information Criterion (AIC) to ensure model parsimony and optimal fit.

A receiver operating characteristic (ROC) curve was constructed to evaluate the model's discriminatory ability, and the area under the curve (AUC) with a 95% confidence interval (CI) was calculated. To determine the optimal cutoff value for PHR, the square root of $[(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2]$ was computed, corresponding to the point on the ROC curve closest to the upper left corner. All statistical analyses were performed using SAS Studio version 3.4 (SAS Institute, Cary, NC, USA). All p-values were two-tailed, and $p < 0.05$ was considered statistically significant.

All the study subjects gave verbal consent to use anonymized health records. The study protocol was approved by the Ethics Committee of Tokai University School of Medicine (protocol number 20R-279).

RESULTS

The baseline characteristics of the study participants, stratified by the presence or absence of MetS, are presented in Table 1. Individuals with MetS had significantly higher values for body mass index (BMI), WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), FPG, and TG, and significantly lower HDL-C levels compared to those without MetS ($p < 0.01$ for all comparisons). In addition, PHR was elevated considerably in the MetS group ($p < 0.01$). After adjusting for age using ANCOVA, the differences in BMI, WC, SBP, and FPG between the groups remained statistically significant ($p < 0.001$), indicating that these associations are independent of age. These findings are illustrated in Supplemental Table 1. Some age-adjusted means for count variables (e.g., the number of MetS components) yielded negative values due to the model-based estimation inherent in ANCOVA.

Pearson's correlation analysis was conducted to evaluate the relationship between PHR and individual components of MetS (Table 2). In both men and women, PHR showed significant positive correlations with WC, SBP, DBP, FPG, and TG ($p < 0.01$ for all). Conversely, HDL-C levels were inversely associated with PHR ($p < 0.01$). Among these factors, the strongest correlation was observed with TG in both genders ($r = 0.373$ in men, $r = 0.369$ in women; $p < 0.01$).

Figure 1 shows HR concerning MetS status and the number of MetS diagnostic components in men and women. Panels a) and c) present the mean PHR values stratified by the presence or absence of MetS in men and women, respectively. In both genders, PHR was significantly higher in individuals with MetS than those without MetS ($p < 0.01$, *t*-test). Panels b) and d) illustrate the association between PHR and the number of MetS diagnostic components in men and women. A significant trend in PHR was observed with an increasing number of MetS components (p for trend < 0.001, linear regression analysis).

A multiple linear regression analysis was performed to identify independent determinants of PHR (Table 3). In men, TG showed the strongest positive association with PHR (standardized regression coefficient [SRC] = 0.309, $p < 0.0001$), followed by WC (SRC = 0.245, $p < 0.0001$). Age (SRC = -0.175, $p < 0.0001$) and SBP (SRC = -0.037, $p = 0.0002$) were negatively associated with PHR. In women, TG was also the strongest positive determinant of PHR (SRC = 0.314, $p < 0.0001$), followed by WC (SRC = 0.296, $p < 0.0001$).

Age showed a significant negative association (SRC = -0.244, $p < 0.0001$). These results indicate that TG is the most important independent predictor of PHR for both genders.

Table 4 presents the metabolic characteristics of participants stratified by PHR quartiles (Q1 - Q4). Significant differences were observed across quartiles for several metabolic parameters, including BMI, WC, SBP, DBP, FPG, and TG ($p < 0.01$ for all comparisons, one-way

Table 1. Characteristics of study subjects stratified by sex and MetS.

MetS	Men				Women			
	no (n = 8,182)		yes (n = 1,999)		no (n = 6,937)		yes (n = 463)	
Age	50.6	± 11.8	54.6	± 10.7 **	50.4	± 11.4	57.4	± 9.9 **
BMI (kg/m^2)	23.2	± 2.9	27.2	± 3.3 **	21.6	± 3.0	29.1	± 4.1 **
Waist circumference (cm)	82.2	± 8.2	93.8	± 7.3 **	77.2	± 8.4	98.1	± 7.7 **
Systolic BP (mmHg)	121.3	± 16.9	132.9	± 16.6 **	116.4	± 18.4	136.6	± 18.4 **
Diastolic BP (mmHg)	77.6	± 12.8	85.3	± 12.2 **	71.7	± 12.5	82.7	± 12.6 **
FPG (mmol/L)	5.48	± 0.77	6.18	± 1.37 **	5.18	± 0.68	6.26	± 1.46 **
FIRI (μIU/mL)	4.80	[3.40, 6.88]	8.90	[6.30, 12.90] **	4.60	[3.30, 6.50]	10.40	[7.40, 13.80] **
HOMA-IR	1.20	[0.80, 1.70]	2.40	[1.60, 3.60] **	1.10	[0.70, 1.50]	2.80	[1.90, 4.00] **
HbA1c (mmol/mol)	36.6	± 5.5	42.1	± 9.8 **	36.6	± 4.4	43.2	± 13.1 **
TG (mmol/L)	1.01	[0.75, 1.39]	1.96	[1.45, 2.61] **	0.79	[0.59, 1.07]	1.41	[0.98, 1.99] **
HDL-C (mmol/L)	1.59	± 0.40	1.29	± 0.32 **	1.93	± 0.32	1.56	± 0.36 **
LDL-C (mmol/L)	3.20	± 0.75	3.26	± 0.81 **	3.15	± 0.81	3.47	± 0.94 **
Non-HDL-C (mmol/L)	3.60	± 0.84	3.99	± 0.95 **	3.46	± 0.89	4.04	± 0.94 **
AST (U/L)	23.1	± 9.8	28.1	± 14.6 **	20.4	± 7.0	24.8	± 10.8 **
ALT (U/L)	24.9	± 16.2	37.3	± 27.6 **	17.2	± 10.8	29.8	± 20.5 **
GGT (U/L)	27.0	[19.0, 43.0]	42.0	[29.0, 69.0] **	16.0	[13.0, 23.0]	27.0	[20.0, 44.0] **
UA (μmol/L)	356.9	±71.4	380.7	±77.3 **	267.7	± 53.5	321.2	± 71.4 **
RBC (10^6/mL)	4.84	±0.39	4.95	±0.42 **	4.41	± 0.34	4.63	± 0.36 **
Hb (g/L)	149.0	±10.1	151.0	±12.0 **	131.0	± 11.0	137.0	± 11.0 **
Ht (L/L)	0.44	± 0.03	0.45	±0.03 **	0.40	± 0.03	0.42	± 0.03 **
WBC (10^3/mL)	5.3	± 1.5	6.1	±1.5 **	5.1	± 1.4	6.1	± 1.7 **
PLT (10^4/mL)	23.2	± 5.2	23.6	± 5.6 **	24.7	± 5.9	26.5	± 6.2 **
PHR	155.3	± 53.8	194.8	± 69.7 **	136.3	± 50.5	180.5	± 63.1 **
hsCRP (mg/L)	0.40	[0.20, 0.80]	0.70	[0.40, 1.50] **	0.30	[0.20, 0.60]	1.20	[0.60, 2.40] **
No of MetS	1.0	± 1.0	3.9	± 0.7 **	0.7	± 1.0	3.7	± 0.8 **

Variables are expressed as mean ± standard deviation or median [interquartile range]. MetS metabolic syndrome, BMI body mass index, BP blood pressure, FPG fasting plasma glucose, FIRI fasting immunoreactive insulin, HOMA-IR homeostasis model assessment of insulin resistance, TG triglyceride, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, non-HDL-C non high-density lipoprotein cholesterol, AST aspartate transaminase, ALT alanine aminotransferase, GGT γ-glutamyl transpeptidase, UA uric acid, RBC red blood cell, Hb hemoglobin, Ht hematocrit, WBC white blood cell, PLT platelet, PHR platelet to high-density lipoprotein cholesterol ratio, hsCRP high-sensitivity C-reactive protein. ** $p < 0.01$ by unpaired t-test.

Table 2. Correlation between PHR and MetS components.

	Men			Women		
	Pearson's correlation coefficients	95% CI	p	Pearson's correlation coefficients	95% CI	p
WC	0.311	0.294 - 0.329	< 0.0001	0.357	0.337 - 0.377	< 0.0001
SBP	0.042	0.023 - 0.061	< 0.0001	0.102	0.107 - 0.124	< 0.0001
DBP	0.064	0.047 - 0.086	< 0.0001	0.088	0.066 - 0.111	< 0.0001
FPG	0.067	0.047 - 0.086	< 0.0001	0.118	0.096 - 0.141	< 0.0001
TG	0.373	0.356 - 0.390	< 0.0001	0.369	0.349 - 0.389	< 0.0001

PHR platelet to high-density lipoprotein cholesterol ratio, MetS metabolic syndrome, CI confident interval, WC waist circumference, SBP systolic blood pressure, DBP diastolic blood pressure, FPG fasting plasma glucose, TG triglyceride.

Table 3. Multiple regression analysis results identify independent predictors of PHR.

Men				
	PHR			
	RC	SRC	*t*	p
Age	-0.885	-0.175	-18.7	< 0.0001
WC	1.588	0.245	26.0	< 0.0001
SBP	-0.125	-0.037	-3.7	0.0002
TG	0.206	0.309	33.70	< 0.0001
Women				
	PHR			
	RC	SRC	*t*	p
Age	-1.116	-0.244	-23.5	< 0.0001
WC	1.590	0.296	27.3	< 0.0001
TG	0.319	0.314	29.0	< 0.0001

Variable selection was made using a stepwise procedure. PHR platelet to high-density lipoprotein cholesterol ratio, RC regression coefficient, SRC standardized regression coefficient, WC waist circumference, SBP systolic blood pressure, TG triglyceride.

Table 4. Characteristics of study subjects stratified according to gender and PHR.

Men								
PHR	Q1 (n = 2,538)		Q2 (n = 2,540)		Q3 (n = 2,550)		Q4 (n = 2,547)	
Age	54.7	± 12.7	51.6	± 11.7 **	50.8	± 11.1 **	48.9	± 10.4 $^{**, \#\#, \$\$}$
BMI (kg/m^2)	22.5	± 2.8	23.5	± 3.0 **	24.5	± 3.3 $^{**, \#\#}$	25.5	± 3.7 $^{**, \#\#, \$\$}$
Waist circumference (cm)	80.5	± 8.5	83.2	± 8.4 **	85.8	± 9.0 $^{**, \#\#}$	88.4	± 9.3 $^{**, \#\#, \$\$}$
Systolic BP (mmHg)	122.5	± 17.9	122.8	± 17.1	123.9	± 17.2 $^{*, \#\#}$	124.4	± 17.3 $^{**, \#\#}$
Diastolic BP (mmHg)	78.1	± 12.7	78.8	± 12.9	79.7	± 17.2 $^{**, \#}$	80.4	± 13.2 $^{**, \#\#}$
FPG (mmol/L)	5.57	± 0.97	5.53	± 0.76	5.64	± 0.93 $^{\#\#}$	5.73	± 1.12 $^{**, \#\#, \$\$}$
FIRI (μIU/mL)	4.00	[2.84, 5.80]	4.98	[3.50, 6.96]	5.94	[4.10, 8.60] $^{**, \#\#}$	7.10	[4.80, 10.30] $^{**, \#\#}$
HOMA-IR	1.00	[0.70, 1.50]	1.20	[0.80, 1.70]	1.50	[1.00, 2.20] $^{**, \#\#}$	1.80	[1.20, 2.70] $^{**, \#\#, \$\$}$
HbA1c (mmol/mol)	37.2	± 6.4	37.0	± 5.1	37.9	± 6.7 $^{**, \#\#}$	39.1	± 8.0 $^{**, \#\#, \$\$}$
TG (mmol/L)	0.84	[0.63, 1.15]	1.03	[0.76, 1.42] **	1.24	[0.90, 1.75] $^{**, \#\#}$	1.54	[1.12, 2.22] $^{**, \#\#, \$\$}$
HDL-C (mmol/L)	1.95	± 0.40	1.60	± 0.27 **	1.40	± 0.23 $^{**, \#\#}$	1.17	± 0.20 $^{**, \#\#, \$\$}$
LDL-C (mmol/L)	2.99	± 0.72	3.19	± 0.73 **	3.32	± 0.77 $^{**, \#\#}$	3.34	± 0.77 $^{**, \#\#}$
Non-HDL-C (mmol/L)	3.30	± 0.78	3.59	± 0.81 **	3.82	± 0.86 $^{**, \#\#}$	4.01	± 0.89 $^{**, \#\#, \$\$}$
AST (U/L)	24.0	± 11.0	23.4	± 10.4	23.8	± 10.3	25.0	± 12.5 $^{**, \#\#, \$\$}$
ALT (U/L)	22.8	± 14.3	24.9	± 16.0 **	28.2	± 20.0 $^{**, \#\#}$	33.4	± 24.7 $^{**, \#\#, \$\$}$
GGT (U/L)	26.0	[19.0, 41.5]	28.0	[19.0, 46.0]	30.0	[21.0, 50.0] **	35.0	[24.0,55.0] $^{**, \#\#, \$}$
UA (μmol/L)	350.9	± 65.4	356.9	± 71.4 **	362.8	± 71.4 $^{**, \#}$	374.7	± 77.3 $^{**, \#\#, \$\$}$
RBC (10^6/mL)	4.73	± 0.41	4.85	± 0.38 **	4.90	± 0.37 $^{**, \#\#}$	4.97	± 0.40 $^{**, \#\#, \$\$}$
Hb (g/L)	147.0	±10.8	149.0	±9.9 **	149.9	±9.9 $^{**, \#}$	150.2	±10.8 $^{**, \#\#}$

Table 4. Characteristics of study subjects stratified according to gender and PHR (continued).

Men								
PHR	**Q1 (n = 2,538)**		**Q2 (n = 2,540)**		**Q3 (n = 2,550)**		**Q4 (n = 2,547)**	
Ht (L/L)	**0.439**	**± 0.03**	**0.443**	**±0.03** **	**0.446**	**±0.03** **	**0.447**	**±0.03** **, ##
WBC (10^3/mL)	**4.77**	**± 1.26**	**5.21**	**±1.23** **	**5.66**	**±1.39** **, ##	**6.29**	**±1.65** **, ##, $$
PLT (10^4/mL)	**18.0**	**± 3.6**	**22.0**	**± 3.6** **	**24.1**	**± 3.8** **, ##	**27.9**	**± 5.3** **, ##, $$
PHR	**99.2**	**± 16.5**	**137.9**	**± 9.4** **	**173.2**	**± 11.6** **, ##	**241.6**	**± 51.2** **, ##, $$
hsCRP (mg/L)	**0.29**	**[0.17, 0.61]**	**0.36**	**[0.20, 0.71]**	**0.45**	**[0.24, 0.95]**	**0.68**	**[0.36, 1.45]** **, ##, $$
No of MetS	**1.1**	**± 1.3**	**1.4**	**± 1.4** **	**1.7**	**± 1.4** **, ##	**2.2**	**± 1.5** **, ##, $$
Women								
PHR	**Q1 (n = 1,848)**		**Q2 (n = 1,835)**		**Q3 (n = 1,854)**		**Q4 (n = 1,855)**	
Age	**53.2**	**± 11.5**	**51.0**	**± 11.7** **	**50.2**	**± 11.6** **	**49.2**	**± 10.8** **, ##
BMI (kg/m^2)	**20.5**	**± 2.6**	**21.3**	**± 3.0** **	**22.4**	**± 3.3** **, ##	**24.1**	**± 4.2** **, ##, $$
Waist circumference (cm)	**74.5**	**± 8.0**	**76.6**	**± 8.7** **	**79.5**	**± 9.4** **, ##	**83.6**	**± 10.4** **, ##, $$
Systolic BP (mmHg)	**115.5**	**± 18.9**	**116.4**	**± 18.8**	**118.0**	**± 19.0** **	**120.6**	**± 19.2** **, ##, $$
Diastolic BP (mmHg)	**71.1**	**± 12.6**	**71.8**	**± 12.6**	**72.6**	**± 12.8** **	**74.1**	**± 13.1** **, ##, $$
FPG (mmol/L)	**5.16**	**± 0.65**	**5.20**	**± 0.77**	**5.25**	**± 0.79** **	**5.40**	**± 0.92** **, ##, $$
FIRI (µIU/mL)	**4.00**	**[2.90, 5.40]**	**4.40**	**[3.20, 6.00]** **	**5.01**	**[3.60, 7.10]** **, ##	**6.40**	**[4.40, 9.60]** **, ##, $$
HOMA-IR	**0.90**	**[0.70, 1.30]**	**1.00**	**[0.70, 1.40]** *	**1.20**	**[0.80, 1.70]** **, ##	**1.50**	**[1.00, 2.30]** **, ##, $$
HbA1c (mmol/mol)	**36.5**	**± 4.0**	**36.9**	**± 4.8**	**37.2**	**± 5.4** **	**38.7**	**± 7.4** **, ##, $$
TG (mmol/L)	**0.69**	**[0.53, 0.89]**	**0.75**	**[0.58, 0.98]** **	**0.84**	**[0.63, 1.14]** **, ##	**1.06**	**[0.77, 1.54]** **, ##, $$
HDL-C (mmol/L)	**2.32**	**± 0.42**	**2.00**	**± 0.31** **	**1.79**	**± 0.27** **, ##	**1.49**	**± 0.27** **, ##, $$
LDL-C (mmol/L)	**3.07**	**± 0.77**	**3.11**	**± 0.79**	**3.19**	**± 0.81** **, ##	**3.30**	**± 0.86** **, ##, $$
Non-HDL-C (mmol/L)	**3.30**	**± 0.81**	**3.39**	**± 0.85** *	**3.54**	**± 0.89** **, ##	**3.77**	**± 0.98** **, ##, $$
AST (U/L)	**21.7**	**± 7.6**	**20.5**	**± 6.5** **	**20.1**	**± 7.5** **	**20.3**	**± 7.8** **
ALT (U/L)	**17.5**	**± 10.9**	**17.0**	**± 9.8**	**17.4**	**± 11.7**	**20.1**	**± 14.9** **, ##, $$
GGT (U/L)	**16.0**	**[13.0, 24.0]**	**16.0**	**[13.0, 23.0]**	**16.0**	**[12.0, 24.0]**	**18.0**	**[13.0, 27.0]** **, ##, $$
UA (µmol/L)	**261.7**	**±53.5**	**261.7**	**± 53.5**	**267.7**	**± 59.5** *, #	**285.5**	**± 65.4** **, ##, $$
RBC (106/mL)	**4.36**	**±0.34**	**4.40**	**± 0.33** **	**4.44**	**± 0.33** **, ##	**4.52**	**± 0.36** **, ##, $$
Hb (g/L)	**131.7**	**± 9.4**	**131.1**	**± 10.5**	**131.2**	**± 11.1**	**129.8**	**± 14.2** **, ##, $$
Ht (L/L)	**0.40**	**±0.03**	**0.40**	**± 0.03**	**0.40**	**± 0.03**	**0.40**	**± 0.04** **
WBC (10^3/mL)	**4.43**	**±1.2**	**4.83**	**± 1.20** **	**5.25**	**± 1.33** **, ##	**5.92**	**± 1.54** **, ##, $$
PLT (10^4/mL)	**19.5**	**± 3.6**	**23.2**	**± 3.5** **	**25.9**	**± 4.0** **, ##	**30.7**	**± 6.0** **, ##, $$
PHR	**85.2**	**± 13.2**	**115.9**	**± 7.3** **	**145.2**	**± 10.2** **, ##	**209.4**	**± 47.6** **, ##, $$
hsCRP (mg/L)	**0.22**	**[0.10, 0.40]**	**0.28**	**[0.20, 0.60]**	**0.34**	**[0.20, 0.70]** *	**0.55**	**[0.30, 1.40]** **, ##, $$
No of MetS	**0.7**	**± 1.0**	**0.8**	**± 1.1** *	**0.9**	**± 1.2** **, ##	**1.3**	**± 1.4** **, ##, $$

Variables are expressed as mean ± standard deviation or median [interquartile range]. PHR platelet to high-density lipoprotein cholesterol ratio, BMI body mass index, BP blood pressure, FPG fasting plasma glucose, FIRI fasting immunoreactive insulin, HOMA-IR homeostasis model assessment of insulin resistance, TG triglyceride, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, non-HDL-C non high-density lipoprotein cholesterol, AST aspartate transaminase, ALT alanine aminotransferase, GGT γ-glutamyl transpeptidase, UA uric acid, RBC red blood cell, Hb hemoglobin, Ht hematocrit, WBC white blood cell, PLT platelet, hsCRP high-sensitivity C-reactive protein, MetS metabolic syndrome.
*** p < 0.05, ** p < 0.01 (Q1 vs. Q2, Q3, Q4), # p <0.05, ## p < 0.01, (Q2 vs. Q3, Q4), $ p < 0.05, $$ p < 0.01 (Q3 vs. Q4) by Bonferroni's multiple comparison test.**

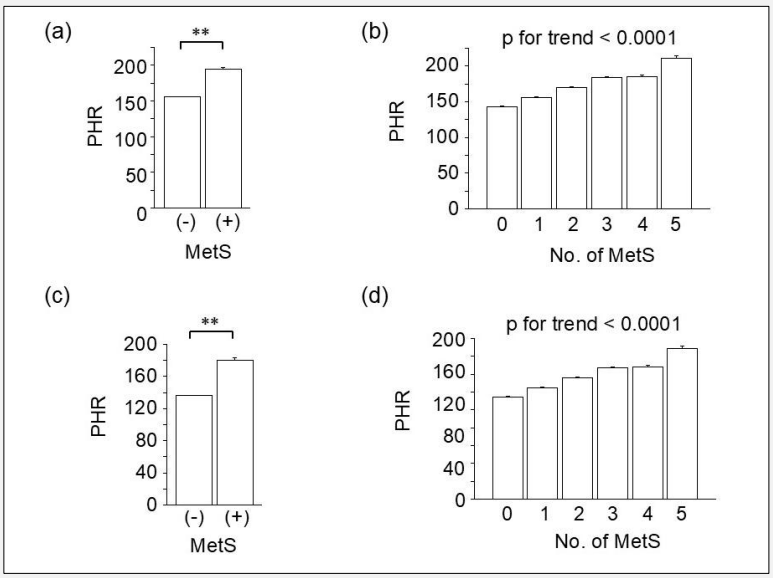

Figure 1. Distribution of PHR values by MetS status.

Bar graphs illustrating the mean PHR values stratified by MetS status and the number of MetS components in men and women.
a) Mean PHR values in men with and without MetS, b) Mean PHR values in men stratified by the number of MetS components, c) Mean PHR values in women with and without MetS, d) Mean PHR values in women stratified by the number of MetS components.
PHR platelet-to-high-density lipoprotein cholesterol (HDL-C) ratio, MetS metabolic syndrome.
**** p < 0.01 by *t*-test. p for trend by linear regression analysis.**

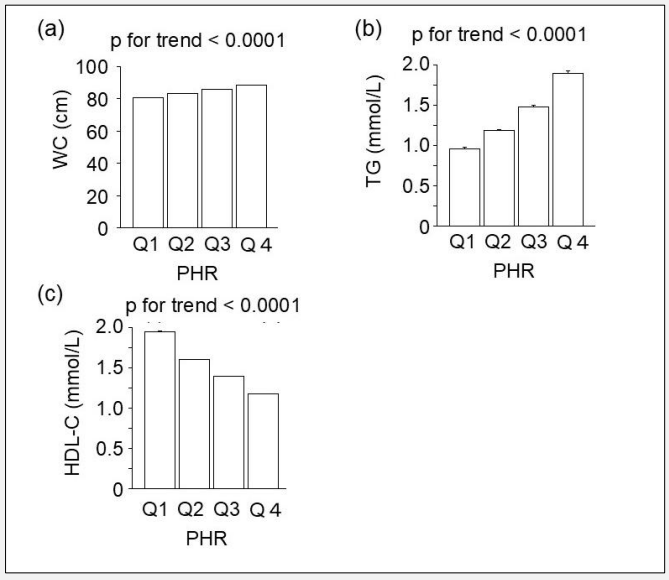

Figure 2. Association between PHR and MetS components in men.

Bar graph illustrating the mean values of metabolic parameters across PHR quartiles (Q1 - Q4) in men.
PHR platelet-to-high-density lipoprotein cholesterol (HDL-C) ratio, MetS metabolic syndrome, WC waist circumference, TG triglycerides.
p for trend by linear regression analysis.

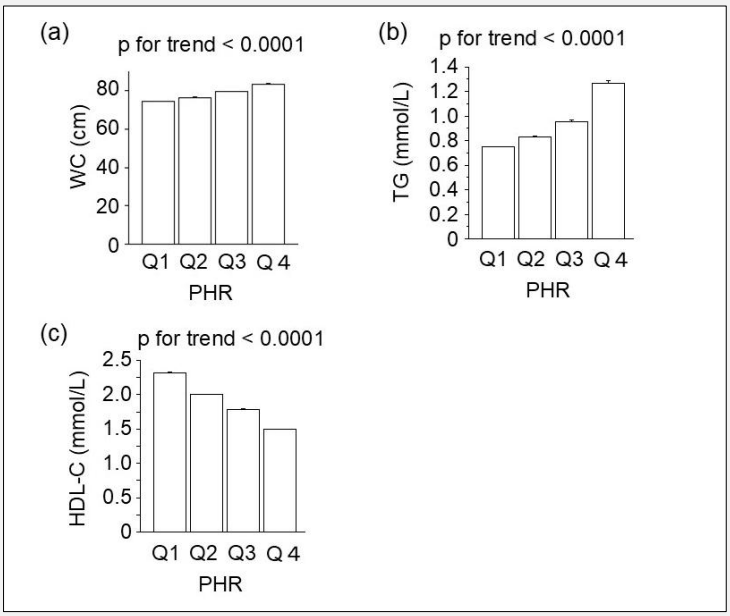

Figure 3. Mean values of MetS components across PHR quartiles in women.

Bar graph showing the mean values of metabolic parameters across PHR quartiles (Q1 - Q4) in women.
PHR platelet-to-high-density lipoprotein cholesterol (HDL-C) ratio, WC waist circumference, TG triglycerides.
p for trend by linear regression analysis.

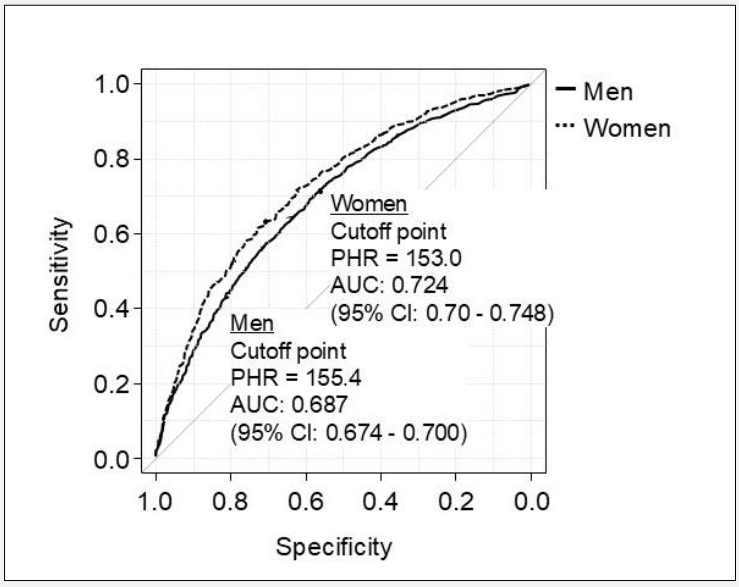

Figure 4. ROC curve analysis of PHR for MetS.

ROC curves evaluating the diagnostic performance of PHR for MetS in men and women.
ROC curve receiver operating characteristic curve, PHR platelet-to-high-density lipoprotein cholesterol (HDL-C) ratio, MetS metabolic syndrome, AUC area under the curve.

ANOVA). Participants in the highest PHR quartile (Q4) had significantly higher values for these parameters than those in the lower quartiles.

Figure 2 and Figure 3 depict the relationships between PHR quartiles and key MetS components in men and women, respectively. In both genders, higher PHR quartiles were associated with significantly increased WC and TG levels, and decreased HDL-C levels (p for trend < 0.001, linear regression analysis). These results indicate that increasing PHR is linked to more adverse lipid and anthropometric profiles in both men and women.

A ROC curve analysis was conducted to evaluate the ability of PHR to discriminate MetS (Figure 4). AUC was 0.687 (95% confidence interval [CI]: 0.674 - 0.700) in men and 0.724 (95% CI: 0.700 - 0.748) in women. The optimal cutoff values for PHR in predicting MetS were 154.0 for men (sensitivity: 71.7%, specificity: 56.1%) and 153.0 for women (sensitivity: 60.3%, specificity: 70.3%).

Supplemental Table 2 presents the ROC analysis comparing PHR with other MetS-related markers, including WC, TG, and the TG/HDL-C ratio. While PHR showed slightly lower AUC values than individual diagnostic components such as TG, it retained moderate discriminatory ability.

DISCUSSION

This study demonstrated a significant association between PHR and MetS in a Japanese population. Elevated PHR levels were observed in individuals with MetS and were positively correlated with waist circumference, triglycerides, and fasting plasma glucose, while inversely correlated with HDL-C. These findings suggest that PHR reflects multiple metabolic disturbances commonly seen in MetS, including abdominal obesity, dyslipidemia, and impaired glucose regulation. The results are consistent with previous studies indicating that PHR may be modulated by systemic inflammation, insulin resistance, and lipid metabolism abnormalities, all of which contribute to the pathogenesis of MetS [21]. The biological mechanisms underlying the association between PHR and MetS may be mediated by metabolic inflammation. Elevated triglyceride levels, which showed the strongest correlation with PHR in this study, have been reported to promote platelet activation and systemic inflammation [22]. Hypertriglyceridemia and low HDL-C are established hallmarks of MetS, contributing to endothelial dysfunction and atherogenesis [23, 24].

Furthermore, our multiple linear regression analysis identified waist circumference and triglycerides as PHR's most significant independent predictors, underscoring the complex interplay between visceral adiposity, dyslipidemia, and platelet dynamics [25].

Notably, participants in the highest PHR quartile (Q4) were significantly younger and exhibited higher RBC and WBC counts than those in the lowest quartile (Q1). This inverse age trend across PHR quartiles may be partly attributable to higher hematopoietic activity in younger individuals, who typically have elevated counts of platelets, RBCs, and WBCs. Additionally, increased WBC counts - a marker of chronic low-grade inflammation - have been independently associated with insulin resistance and the development of MetS [26,27]. These findings suggest that age-related differences in hematologic and metabolic profiles may influence PHR values, particularly in younger individuals.

Several studies have previously linked PHR to metabolic disorders such as NAFLD, insulin resistance, and CVD [28,29]. However, the relationship between PHR and MetS has not been extensively investigated, particularly in Asian populations. Our findings support this association and demonstrate a clear dose-response relationship between increasing PHR quartiles and worsening metabolic parameters.

The present study expands upon previous research using quartile-based analysis, allowing for a more detailed stratification of PHR levels compared to studies using tertiles or median splits. This approach provides more substantial evidence for a potential dose-dependent relationship between PHR and MetS [2].

Moreover, our findings are consistent with previous reports indicating that platelet-related parameters, including platelet count and the platelet-to-lymphocyte ratio (PLR), are significantly associated with the presence and severity of metabolic syndrome [30]. Unlike platelet activation markers such as mean platelet volume (MPV) or soluble P-selectin, PHR primarily reflects platelet count rather than platelet function or activation. Therefore, while PHR may be an indirect marker of systemic inflammation and metabolic dysfunction, it does not directly capture platelet activation.

Given its simplicity and accessibility, PHR may serve as a practical biomarker for risk stratification of MetS in clinical settings. Unlike inflammatory markers such as CRP or fibrinogen, which require additional biochemical assays, PHR can be readily calculated from standard hematological parameters, offering a cost-effective approach to metabolic risk assessment.

Nevertheless, while PHR demonstrated a significant association with MetS in this study, it should not be considered a standalone diagnostic tool. Its predictive performance relative to conventional metabolic indices, such as HOMA-IR or the triglyceride-glucose (TyG) index, remains to be established. Combining PHR with these established markers may enhance diagnostic accuracy in evaluating MetS and related metabolic conditions.

Although the present study focused on individuals who met the diagnostic criteria for MetS, PHR may also be elevated in earlier stages of metabolic dysfunction. Jialal et al. [2] demonstrated that PHR is a valid biomarker of nascent MetS, supporting its potential to identify individuals who do not yet fulfill the full diagnostic criteria but exhibit early metabolic abnormalities.

Given that PHR is derived from routine laboratory parameters and reflects both inflammatory and lipid-related processes, it may be a practical tool for preliminary risk stratification. Additionally, it may help encourage lifestyle modifications in individuals undergoing general health check-ups.

Notably, although SBP showed a significant upward trend across PHR quartiles in the unadjusted analysis (Table 4), it exhibited an inverse association with PHR in the multivariate regression model (Table 3). This apparent inconsistency may be attributed to the influence of confounding variables such as age and WC, which are positively correlated with both SBP and PHR. In multivariate analyses, the unique contribution of each variable is estimated after controlling for others; thus, the shared variance between SBP and other predictors may suppress or even reverse the observed association. This phenomenon, referred to as a suppressor effect, highlights the need to carefully interpret multivariate results, particularly in collinearity among predictors [31]. Ethnic and regional differences in lipid metabolism and inflammatory profiles may limit the generalizability of our findings. For instance, Western populations exhibit lower HDL-C and triglyceride levels than Japanese individuals, possibly leading to a higher baseline PHR. Jialal et al. [2] demonstrated that PHR is a valid biomarker of nascent metabolic syndrome in a U.S. cohort. At the same time, a recent analysis by Chen et al. [32] using data from the National Health and Nutrition Examination Survey (NHANES) reported significant associations between PHR and diabetes and prediabetes. These findings reinforce the clinical relevance of PHR in non-Asian populations but also highlight the potential need for ethnicity-specific reference values and interpretative thresholds.

This study has several limitations. First, its cross-sectional design limits the ability to establish causal relationships between PHR and MetS. Longitudinal studies are needed to determine whether elevated PHR predicts the future development of MetS and its associated complications. Second, although PHR was related to various metabolic disturbances, it was not directly compared with established indices of insulin resistance, such as HOMA-IR or TyG index. Future research should evaluate whether PHR offers incremental diagnostic value when combined with these conventional markers. Third, the study population was limited to Japanese individuals. Given known ethnic differences in lipid metabolism and MetS prevalence, further studies are warranted to explore the applicability of PHR across diverse populations.

CONCLUSION

This study demonstrates that elevated PHR is significantly associated with MetS and its key components, particularly WC, TG, and HDL-C levels. These findings support the potential use of PHR as a cost-effective and straightforward marker for metabolic risk assessment in clinical and public health settings. Further longitudinal studies are warranted to validate PHR's predictive value for MetS development and clarify its pathophysiological role in metabolic disorders.

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Declaration of Interest:
There are no conflicts of interest to declare.

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