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Role of Platelet Indices for Cardiovascular Risk Assessment in Premenopausal Females with Metabolic Syndrome

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ABSTRACT

Objectives: The study aimed to estimate platelet indices in premenopausal females with metabolic syndrome (MetS) and the prevalence of individual risk factors of MetS and their association with platelet indices.

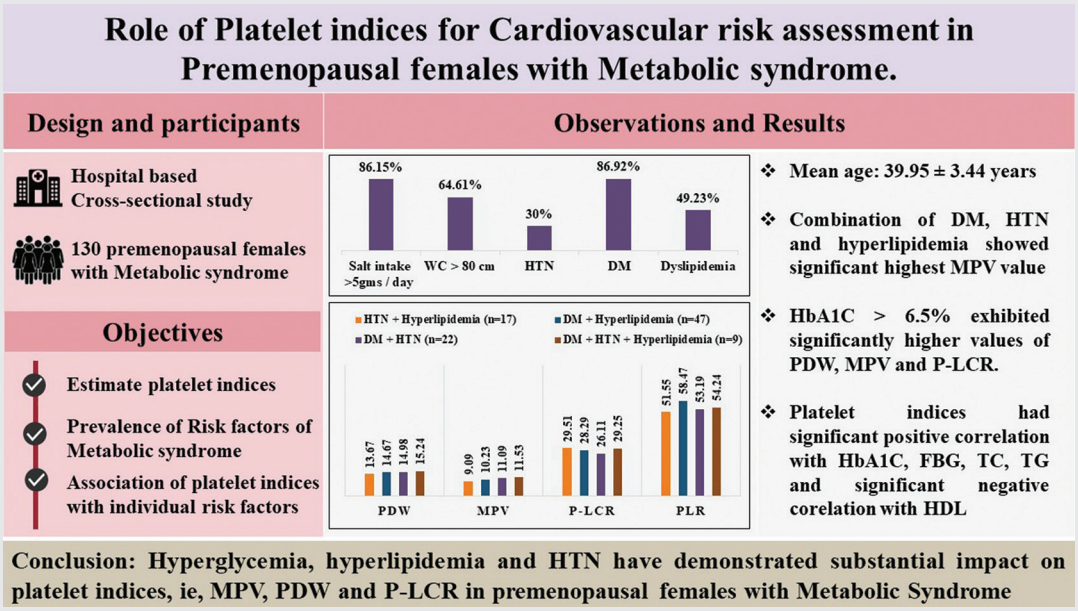
Materials and Methods: It was a hospital-based, cross-sectional, and observational study conducted for a period of 3 months with the 130 premenopausal females with MetS. The collected data comprised clinical profile, hematological parameters, fasting blood glucose (FBG), serum creatinine, and lipid profile and were subjected to statistical analysis with $P < 0.05$ as level of significance.

Results: The mean age of the participants was 39.95 ± 3.44 years. Substance abuse of tobacco and alcohol was present in 9.23% and 5.37% of participants. Salt intake more than 5 g/day was confirmed by majority (86.15%). Waist circumference >80 centimeters (cm) was noted in 64.61% of participants. Body mass index in range of 25–29.9 kilograms (kg)/m^2 and 30–40 kg/m^2 was observed in 36.92% and 60.77%, respectively. Diabetes mellitus (DM) and hypertension (HTN) had prevalence of 86.92% and 30% of participants, respectively. FBG ≥100 mg/dL was observed in 43.84% participants. The participants with DM, HTN, and hyperlipidemia showed the highest mean platelet volume (MPV) value. Patients with glycosylated hemoglobin (HbA1C) >6.5% exhibited statistically significantly higher values of platelet distribution width, MPV, and platelet–large cell ratio. Platelet indices exhibited significant positive correlation with HbA1C, FBG, total cholesterol, triglyceride, and negative correlation with high-density lipoprotein.

Conclusion: The present study highlighted the high prevalence of components associated with MetS, notably hyperglycemia, HTN, and obesity. The study also elucidated the substantial impact of DM, HTN, and hyperlipidemia on platelet indices.

Keywords: Platelet indices, Metabolic Syndrome, Premenopausal females, Cardiovascular risk

ABSTRACT IMAGE



INTRODUCTION

Metabolic syndrome (MetS) is characterized by abdominal obesity, hypertension (HTN), atherogenic dyslipidemia, and insulin resistance.[1] South Asians have genetic predisposition of increased body fat even in non-obese range. This constellation of risk factors of cardiometabolic origin is associated with two-fold risk of cardiovascular disease (CVD) and five-fold risk for incident type-2 diabetes mellitus (DM).[2] Furthermore, it has increased susceptibility for hepatic steatosis, sleep disorders, polycystic ovarian syndrome (PCOS), neurological diseases, and cancers.[3] Thus, it has drastically changed mortality and morbidity profile among the population.

The crux of MetS is adipose tissue dysfunction and secretion of proinflammatory cytokines. Interactions between blood cell components are central to immune responses, inflammation, and thrombotic events. Platelet consumption in atherosclerotic plaques and proinflammatory cytokines induce enlargement of platelets and their activation. Larger platelets have higher proportions of prothrombotic factors such as thromboxane-A_2, adenosine diphosphate, and triphosphate. Raised mean platelet volume (MPV) has been linked to inflammation and CVD risk.[4] Furthermore, activated platelets attribute to smooth muscle proliferation. Similarly, platelet distribution width (PDW) and plateletcrit have emerged as markers for proinflammatory and prothrombotic status.[4] Platelets interact with leukocytes and endothelial cells to mediate inflammation, triggering an atherosclerotic event.

There has been an escalation in prevalence and occurrence of MetS in females at younger age as compared to other population subsets globally due to sedentary lifestyle, food habits, and urbanization. Hence, prevention, identification, and disease surveillance in MetS deserve prime consideration. Diagnostic packages for screening and monitoring are challenged by its affordability and accessibility. Complete blood count (CBC) is a routinely requested investigation among patients and is inexpensive. Exploring platelet indices shall open a new dimension to its clinical application in addition to Framingham risk scoring in MetS for prediction of longitudinal cardiometabolic outcomes and designing appropriate screening and therapeutic interventions.

Aims and objectives

The primary objective was to estimate the platelet indices in premenopausal females with MetS. The secondary objectives were (a) to estimate the prevalence of individual risk factors in premenopausal females with MetS and (b) to determine the association of platelet indices with individual risk factors in premenopausal females with MetS.

MATERIALS AND METHODS

This was a hospital-based, cross-sectional, and observational study which was conducted for a period of 3 months from June 1, 2023, to August 31, 2023, in the Department of Physiology and the Outpatient Department of General

Medicine. The study was initiated after obtaining the approval from the Institutional Ethical Committee reference ID: GVPIHCMT/IEC/20230510/01 dated May 10, 2023. The study was performed according to the Declarations of Helsinki and Good Clinical Practice requirements for human subject protection.

Patient cohort

Females with MetS diagnosed as per National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP)-III criteria formed the cohort.[3]

Recruitment and screening

The eligible participants were identified by adopting a comprehensive recruitment methodology performed by a team of physicians and medical staff. Those who expressed their interest for the study participation were reviewed in detail in terms of their medical history and general health condition. They were screened for their eligibility for the study based on the following:

Inclusion criteria

The following criteria were included in the study:

1. Age ≥20 years and ≤45 years
2. Females with menstruation
3. Diagnosis of MetS in accordance with NCEP-ATP-III guidelines requiring any three of the following five.[3,5]
    a. Waist circumference (WC) ≥80 cm for females
    b. Blood pressure (BP): Systolic BP (SBP) ≥130 mm Hg or diastolic BP (DBP) ≥85 mm Hg or both or pharmacotherapy for HTN
    c. Fasting blood glucose (FBG) ≥100 mg/dL or on pharmacotherapy for DM
    d. Triglycerides (TGs) ≥150 mg/dL or on pharmacotherapy for elevated TGs
    e. High-density lipoprotein-cholesterol (HDL-C): <50 mg/dL in females or on pharmacotherapy for low HDL-C.

Exclusion criteria

The following criteria were excluded from the study:

1. Achieved menopause: naturally or surgical
2. Clinically unstable requiring hospitalization that might interfere with the participation in the study
3. History of (H/o) platelet disorders
4. H/o infectious disease, autoimmune disease, storage diseases, or malignancy
5. H/o valvular heart diseases, myocardial infarction, coronary artery disease, stroke, and arrhythmias
6. H/o anti-platelet, anticoagulant therapy or steroids preceding 4 weeks
7. H/o blood transfusion within 2 weeks
8. Severe cognitive impairment that might impede the understanding regarding the study and/or completion of the questionnaires
9. Unable to co-operate completely for the study procedure or filling of questionnaire
10. Pregnancy or lactation
11. Refusal for participation.

Patient informed consent

Before enrolment, in a non-coercive environment, all the recruited participants were given a good account of the details of the study in terms of its purpose, its design, duration, benefits, and the potential risks involved. Along with these details in the informed consent form, it was made clear to the patient that participation was strictly voluntary with guarantee of anonymity of collected data. No rewards/incentives would be awarded in return and their healthcare would not be affected regardless of study participation. Permission for the access to the medical records, interview, and blood sample collection was obtained. The consent form also specified the right to withdraw from the study at any time without any consequences.

Sample size calculation and sampling method

As per study in Indian adults by Barik *et al*., the average prevalence of MetS was 9% in females of age group 18–45 years.[6] Based on the central limit theorem, the minimum sample size was calculated as 126 using the following formula:

$$n = \frac{Z^2_{1-\alpha/2} \times p(1-p)}{d^2}$$

where,
n: Sample size
Z: Standard normal variate
d: Absolute error or precision
p: Estimated proportion
For our present study, $Z = 1.96$ (at 5% type 1 error [$P < 0.05$]), $d = 0.05$, and $p = 0.09$.

The study participants were enrolled using a non-probability sampling technique.

Data collection

The study identification number was assigned to each subject by the investigator and the data were entered into the excel sheet maintaining confidentiality and anonymity. The selected participants were subjected to face-to-face interviews and clinical examination as follows:

World Health Organization's (WHO's) STEPS approach

It involved stepwise risk factor surveillance for non-communicable diseases.[7]

Step 1

It comprised sociodemographics information and behavioral measurements through self-report using a questionnaire. It included age, gender, marital status, educational qualification, history of substance abuse for tobacco and alcohol, dietary habits and salt intake, physical activity, and medical history for HTN, DM, dyslipidemia, CVD, presence of any complications, and pharmacotherapy details.

Step 2

It comprised physical measurements of height, weight, WC, hip circumference (HC), pulse, and BP.

Step 3

Biochemical analysis for FBG, creatinine, and lipid profile.

Anthropometric measurements

Three readings of each were obtained and the average was calculated.[8] The patient was asked to report in early morning hours, wearing light clothes, and with overnight fasting status (12 h). For measurement of hemodynamic parameters in resting state, she was asked to avoid smoking, tea/coffee, and physical activity for minimum 2 h before obtaining the readings.

Height

It was measured using a stadiometer (IS IndoSurgicals, New Delhi, India) to the nearest 1 mm graduation. The subject was asked to stand facing directly ahead, without footwear, feet together and arms by the sides. The height was expressed in meters (m).

Weight

It was measured on a digital weighing scale (MCP Healthcare Analog Mechanical Weighing Scale, Medicare Product Inc., India) to the nearest 0.1 kilogram (kg). The weight was expressed in kg.

WC

It was measured parallel to floor, in mid-axillary line at midpoint between lower margin of last palpable rib and superior iliac crest using stretch-resistant measuring tape at the end of normal expiration, ensuring tape shall not compress the skin. WC was expressed in centimeters.

HC

It was measured around the widest portion of the buttocks using non-stretchable measuring tape. HC was expressed in centimeters.

Laboratory investigations

Assuring aseptic precautions, venous samples were drawn after 12 h of fasting. All the blood samples contained the study ID numbers only, with no personal identifiers. Samples were processed on the same day in the Institutional Central Laboratory for hematological parameters, FBG, serum creatinine, and lipid profile. Hematological parameters were analyzed as per manufacturer's protocol using a fully automated hematology analyzer AD-3200 plus (manufactured by Aspen Diagnostic Pvt. Ltd). The hematology parameters included CBC, platelet indices, namely, platelet count, MPV, plateletcrit, PDW, and platelet-large cell ratio (P-LCR).

Glycosylated hemoglobin (HbA1C) was determined using a fully automated Cobas 6000 chemistry analyzer. FBG, serum creatinine, and lipid profile were determined using Merilyzer CliniQuant Micro semi-automated biochemistry analyzer (marketed by Meril Diagnostics Pvt. Ltd., Gujarat, India).

Data analysis

Quality check for the collected data was done to ensure its completeness and accuracy. The data were organized into a Microsoft Excel spreadsheet and, then, subjected to the Statistical Package for the Social Science version – 26 for statistical analysis. The organized data were assessed for the normal distribution of the data for the consideration of the parametric statistical tests for statistical analyses.

Continuous variables were expressed as mean and standard deviations. Categorical data were computed into frequency and percentages. The distribution of platelet indices based on combination of risk factors of MetS was analyzed by analysis of variance test. The distribution of platelet indices based on glycemic control was analyzed by unpaired "*t*" test. Pearson's correlation was utilized to characterize the direction and strength of linear relationship of various platelet indices with different risk factors prevalent among patients with MetS. For all statistical analyses, $P < 0.05$ was adopted as level of significance.

RESULTS

A total of 157 female patients with MetS were recruited into the study taking into consideration the inclusion and exclusion criteria. However, 27 patients were excluded from the study due to the reasons cited in Figure 1. Hence, the data analysis was limited to 130 participants.

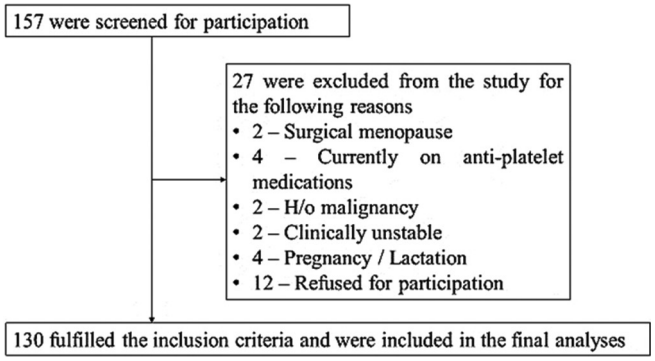


Figure 1: Flowchart of recruitment of participants. (H/o: History of.)

The mean age of the participants was 39.95 ± 3.44 years, with 33 years and 45 years being the minimum and maximum age, respectively [Table 1]. Majority of the participants belonged to the age group of 40–45 years (*n* = 56 [43.08%]). A significant proportion of participants had completed intermediate (*n* = 25 [19.23%]) and graduation (*n* = 17 [13.07%]). However, a substantial proportion of the participants were unemployed (44.61%). Few participants were involved in substance abuse, tobacco (*n* = 5 [9.23%]), and alcohol (*n* = 7 [5.37%]). Salt intake more than 5 g/day was confirmed by majority (*n* = 112 [86.15%]). Majority of the participants (*n* = 96 [73.85%]) had no involvement in regular physical activity, thus highlighting sedentary lifestyle.

The mean weight, body mass index (BMI), and WC of the participants were 73.33 ± 9.12 kg, 30.74 ± 3.07 kg/m^2, and 90.04 ± 7.11 cm, respectively [Table 2]. The mean SBP and DBP were 123.5 ± 14.15 mm of Hg and 81 ± 8.01 mm of Hg, respectively, indicating a moderate elevation in both measurements.

WC >80 cm was noted in 64.61% (*n* = 84) of participants [Table 3], signifying a high prevalence of central obesity among the study population. Overweight and obesity were observed in BMI at 36.92% (*n* = 48) and 60.77% (*n* = 79), respectively. A high prevalence of DM was observed (*n* = 113 [86.92%]). FBG ≥100 mg/dL was observed in 43.84% (*n* = 57) participants. A significant portion of the participants, 36.92% (*n* = 48) and 41.54% (*n* = 54) had hypertriglyceridemia and high-density lipoprotein (HDL) levels <50 mg/dL, respectively, contributing to the overall profile of MetS. The mean values of FBG and PPBG were 102.3 ± 13.74 mg/dL and 161.2 ± 21.89 mg/dL, respectively, indicating a moderate elevation in blood sugar levels, thus reflecting impaired glycemic control [Table 4]. The mean values of total cholesterol (TC), TG, and HDL were 174.5 ± 38.73 mg/dL, 140.7 ± 25.13 mg/dL, and 46.24 ± 8.83 mg/dL indicating dyslipidemia, another key component of MetS.

Metformin was prescribed to 42.49% (*n* = 48) to participants with hyperglycemia [Table 5]. HTN was prevalent in 30% (*n* = 39) of which angiotensin-II receptor blockers (ARB) were the most commonly prescribed to 43.59% (*n* = 17). Majority of the participants (*n* = 16 [25%]) were prescribed

Table 1: Sociodemographic features of study participants with metabolic syndrome (*n*=130).

Variable	*n* (%)
Age (in years)	
18–30	0
30–35	19 (14.62)
35–40	55 (42.3)
40–45	56 (43.08)
Mean age (in years)	39.95±3.44*
Marital status	
Single	6 (4.61)
Married	124 (95.39)
Staying with	
Alone	13 (10)
Family	117 (90)
Divorced	0
Educational qualification	
Illiterate	20 (15.38)
Primary school certificate	21 (16.15)
Middle school certificate	11 (8.5)
High school certificate	25 (19.23)
Intermediate and diploma	29 (22.3)
Graduate	17 (13.07)
Profession or honors	7 (5.37)
Occupation	
Unemployed	58 (44.61)
Machine operators	17 (13.07)
Craft and related trade workers	6 (4.61)
Agricultural and fishery workers	4 (3.07)
Shop and market sales workers	11 (8.5)
Clerks and technicians	24 (18.46)
Professionals	10 (7.68)
Substance abuse	
Tobacco	5 (3.85)
Alcohol	7 (5.37)
Drugs	0
Diet	
Vegetarian	12 (9.23)
Non-vegetarian	3 (2.31)
Mixed	115 (88.46)
Salt intake	
Less than 5 g/day	18 (13.85)
More than 5 g/day	112 (86.15)
Physical activity	
Present	34 (26.15)
Absent	96 (73.85)
Duration of physical activity (in minutes)	
0–30	21 (61.76)
31–45	6 (17.65)
46–60	7 (20.59)
Mean duration of physical activity (in minutes)	19.2±11.36*

*Expressed as mean±standard deviation

Table 2: Clinical profile of the study participants with metabolic syndrome (*n*=130).

Variable	Mean±SD
Height (in meters)	1.54±0.072
Weight (in kg)	73.33±9.12
BMI (kg/m^2)	30.74±3.07
Waist circumference (cm)	90.04±7.11
Hip circumference (cm)	105.2±8.93
Waist-to-hip ratio	0.86±0.05
Pulse rate (beats/min)	86.02±11.01
SBP (mm of Hg)	123.5±14.15
DBP (mm of Hg)	81±8.01
Respiratory rate (per min)	17.6±2.37

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation

Table 3: Prevalence of risk factors of metabolic syndrome as per NCEP-ATP III criteria among the study participants.

Risk factor	*n* (%)
WC >80 cm	84 (64.61)
BMI (kg/m^2)	
23–24.9	3 (2.3)
25–29.9	48 (36.92)
30–40	79 (60.77)
H/o HTN or/and on pharmacotherapy	39 (30)
SBP >130 mm of Hg	29 (22.3)
DBP >85 mm of Hg	36 (27.7)
H/o DM or/and on pharmacotherapy	113 (86.92)
FBG ≥100 mg/dL	57 (43.84)
H/o dyslipidemia/and on pharmacotherapy	64 (49.23)
Hypertriglyceridemia (TG >150 mg/dL)	48 (36.92)
HDL <50 mg/dL	54 (41.54)

WC: Waist circumference, BMI: Body mass index, H/o: History of, HTN: Hypertension, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, DM: Diabetes mellitus, FBG: Fasting blood glucose, TG: Triglycerides, HDL: High-density lipoprotein, NCEP-ATP: National cholesterol education program- Adult treatment panel

statins. However, a notable observation was that 46.87% (*n* = 30) of the participants were not receiving any lipid-lowering therapy, highlighting the potential gaps in the management of dyslipidemia among individuals with MetS.

The participants with DM, HTN, and hyperlipidemia showed the highest MPV value compared to the other combinations of risk factors which were statistically significant [Table 6]. The participants with HbA1C >6.5% exhibited statistically significantly higher values of PDW, MPV, and P-LCR as compared to those with HbA1C ≤6.5%, [Table 7].

Platelet count, plateletcrit, PDW, MPV, P-LCR, and platelet-to-lymphocyte ratio did not show statistically significant correlation with WC, BMI, SBP, and DBP [Table 8]. PDW and P-LCR exhibited statistically significant moderate

Table 4: Hematological and biochemical findings among study participants of metabolic syndrome (*n*=130).

Parameter	Value
Red blood cell characteristics	
Hemoglobin (g%)	11.03±1.33
Red blood cell count (millions/mm^3)	3.68±0.61
Mean corpuscular volume (fL)	86.31±8.38
Mean corpuscular hemoglobi***n*** (pg)	26.42±3.2
Mean corpuscular hemoglobin concentration (%)	30.76±3.78
Red cell distribution width (%)	14.66±1.51
White blood cell characteristics	
White blood cell count (10^3/mm^3)	7.3±1.22
Neutrophil (%)	43.63±13.25
Lymphocyte (%)	42.54±12.32
Monocyte (%)	3.34±0.93
Neutrophil-to-lymphocyte ratio	1.21±0.7
Platelet characteristics	
Platelet count (lacs/mm^3)	2.13±0.2
Mean platelet volume (fL)	10.22±1.96
Plateletcrit (%)	0.29±0.07
Platelet distribution width (%)	14.64±2.58
Platelet–large cell ratio	29.06±8.66
Platelet-to-lymphocyte ratio	54.66±17.57
Biochemical investigations	
Fasting blood glucose (mg/dL)	102.3±13.74
Post-prandial blood glucose (mg/dL)	161.2±21.89
Glycosylated hemoglobi***n*** (%)	6.21±0.88
Creatinine (mg/dL)	0.94±0.19
Total cholesterol (mg/dL)	174.5±38.73
Triglycerides (mg/dL)	140.7±25.13
High-density lipoprotei***n*** (mg/dL)	46.24±8.83

Table 5: Pharmacotherapy among the participants of metabolic syndrome (*n*=113).

Dosage combinations	*n* (%)
Pharmacotherapy for hyperglycemia (*n*=113)	
Metformin	48 (42.49)
Metformin+Sulfonylureas	32 (28.32)
Metformin+SGLT-2 inhibitors	11 (9.73)
Metformin+Thiazolidinedione	4 (3.54)
Sulfonylureas+DPP-4 inhibitors	5 (4.42)
DPP-4 inhibitors+alpha-glucosidase inhibitors	6 (5.31)
Sulfonylureas+alpha-glucosidase inhibitors	7 (6.19)
Pharmacotherapy for HTN (*n*=39)	
Beta-blockers	12 (30.77)
Angiotensin-converting enzyme inhibitors	6 (15.38)
Angiotensin-II receptor blockers	17 (43.59)
Calcium channel blockers	4 (10.26)
Pharmacotherapy for dyslipidemia (*n*=39)	
Statins	16 (25)
Fenofibrate	6 (9.38)
Niacin	12 (18.75)
No therapy	30 (46.87)

SGLT-2: Sodium glucose-linked transporters – 2, DPP-4: Dipeptidyl peptidase – 4, HTN: Hypertension

Table 6: Distribution of platelet indices in the study participants with metabolic syndrome based on combination of risk factors.

Variable	HTN+Hyperlipidemia (*n*=17)	DM+Hyperlipidemia (*n*=47)	DM+HTN (*n*=22)	DM+HTN+Hyperlipidemia (*n*=9)	*P*-value
Platelet count (lacs/mm^3)	2.08±0.75	2.18±0.29	2.21±0.24	2.18±0.22	0.772
Plateletcrit	0.3±0.07	0.29±0.07	0.26±0.06	0.28±0.05	0.239
PDW (%)	13.67±2.95	14.67±2.37	14.98±2.6	15.24±3.08	0.365
MPV	9.09±1.32	10.23±1.82	11.09±2.88	11.53±1.7	0.005*
P-LCR	29.51±11.6	28.29±8.09	26.11±8.4	29.25±7.33	0.632
PLR	51.55±14.58	58.47±18	53.19±17.5	54.24±15.07	0.431

HTN: Hypertension, DM: Diabetes mellitus, PDW: Platelet distribution width, MPV: Mean platelet volume, P-LCR: Platelet–large cell ratio, PLR: Platelet-to-lymphocyte ratio, *-*P*<0.05: Statistically significant

Table 7: Distribution of platelet indices in the study participants with metabolic syndrome based on glycemic control.

Variable	HbA1C		*P*-value
	≤6.5 (*n*=90)	>6.5 (*n*=40)	
Platelet count (lacs/mm^3)	2.11±0.15	2.17±0.28	0.1147
Plateletcrit	0.29±0.07	0.3±0.07	0.4536
PDW (%)	14.15±2.5	15.89±2.39	0.0003*
MPV	9.98±1.64	10.8±2.5	0.0281*
P-LCR	27.66±8.66	32.87±6.46	0.0009*
PLR	53.01±16.7	58.11±19.01	0.1262

PDW: Platelet distribution width, MPV: Mean platelet volume, P-LCR: Platelet–large cell ratio, PLR: Platelet-to-lymphocyte ratio, HbA1C: Glycosylated hemoglobin. * *P*<0.05: Statistically significant

positive correlation with HbA1C [Table 9]. PDW, MPV, and P-LCR exhibited statistically significant positive correlation with FBG. PDW and MPV exhibited statistically significant positive correlation with TC. PDW, MPV, and P-LCR exhibited statistically significant positive correlation with TG. Platelet count, PDW, MPV, and P-LCR exhibited a significant weak negative correlation with HDL.

DISCUSSION

The present study aimed to study platelet indices among the premenopausal females with MetS and deduce the clinical repercussions in context to the various risk factors associated with MetS.

In the present study, approximately 85% study participants with MetS belonged to age group of 35–45 years. A study by Krishnamoorthy *et al.,* highlighted steady escalation of disease burden among females from 13% in 18–29 years to 50% in 50–59 years attributed to increase in prevalence of PCOS, hormonal contraceptive usage among women.[9] A study by Pandey *et al.,* done in Mumbai in 2010 in 498 women in the age group of 35–66 years revealed the prevalence of 45% and 55% in premenopausal and postmenopausal women, respectively.[10] Menopause, either natural or surgical, is characterized by decline in estrogen levels and is associated with fourfold risk of premature cardiovascular morbidity and mortality mediated by alteration in lipid metabolism, adiposity, and prothrombotic status.

Table 8: Association of platelet indices with anthropometric risk factors and blood pressure in female participants with metabolic syndrome.

Variable	r-score	*P*-value
Waist circumference		
Platelet count	−0.087	0.325
Plateletcrit	−0.0184	0.8354
PDW (%)	−0.118	0.811
MPV	0.02363	0.7896
P-LCR	0.04664	0.5982
PLR	−0.1308	0.1379
Body mass index		
Platelet count	0.008	0.927
Plateletcrit	−0.08999	0.3086
PDW (%)	−0.05962	0.5005
MPV	−0.05822	0.5106
P-LCR	−0.06297	0.4766
PLR	−0.03	0.73
Systolic blood pressure		
Platelet count	0.1293	0.142
Plateletcrit	−0.1203	0.1726
PDW (%)	0.00079	0.9929
MPV	0.05627	0.5249
P-LCR	−0.09251	0.2952
PLR	0.0327	0.7119
Diastolic blood pressure		
Platelet count	−0.0917	0.2991
Plateletcrit	0.1177	0.1822
PDW (%)	−0.01004	0.9097
MPV	0.05654	0.5229
P-LCR	0.1259	0.1536
PLR	0.0592	0.5031

PDW: Platelet distribution width, MPV: Mean platelet volume, P-LCR: Platelet–large cell ratio, PLR: Platelet-to-lymphocyte ratio, r: Pearson "r" score. *P*<0.05: Statistically significant

Table 9: Association of platelet indices with glycemic profile among female participants with metabolic syndrome.

Variable	r-score	*P*-value
Glycosylated hemoglobin		
Platelet count	0.1153	0.1915
Plateletcrit	0.04047	0.6475
PDW (%)	0.328	0.00014*
MPV	0.1332	0.1309
P-LCR	0.3088	0.00035*
PLR	0.1224	0.1654
Fasting blood glucose		
Platelet count	0.1228	0.164
Plateletcrit	0.1321	0.1341
PDW (%)	0.2617	0.002636*
MPV	0.1982	0.0238*
P-LCR	0.2958	0.0006345*
PLR	0.0891	0.313
Total cholesterol		
Platelet count	−0.0004	0.9959
Plateletcrit	0.01605	0.8561
PDW (%)	0.5774	<0.00001*
MPV	0.2971	0.00059*
P-LCR	0.1257	0.1542
PLR	0.1076	0.2229
Triglycerides		
Platelet count	0.1336	0.13
Plateletcrit	0.1283	0.1459
PDW (%)	0.4722	<0.0001*
MPV	0.2747	0.00156*
P-LCR	0.3351	0.000097*
PLR	0.1065	0.2277
High-density lipoproteins		
Platelet count	−0.1923	0.02836*
Plateletcrit	−0.1413	0.1087
PDW (%)	−0.1917	0.02893*
MPV	−0.1897	0.03063*
P-LCR	−0.252	0.003818*
PLR	−0.0969	0.2727

PDW: Platelet distribution width, MPV: Mean platelet volume, P-LCR: Platelet large cell ratio, PLR: Platelet to lymphocyte ratio, r: Pearson 'r' score, *: *P* -value <0.05 – statistically significant

In the present study, consumption of tobacco and alcohol was reported by 10% and 5% participants, respectively. National Family Health Survey (NFHS-5) (2019–21), India, reported tobacco abuse in 7% and alcohol consumption in 1.3% in women aged 15–49 years.[11] The present study revealed consumption of salt more than 5 g/day by almost 85% of participants, which is a definite concern to be addressed. A systematic review by Johnson *et al.,* highlighted that the average salt intake in India was 11 g/day which exceeded the 5 g/day recommendation by the WHO.[12] The Systematic Review and Dose-Response Meta-Analysis of 36 reports emphasized on 6% increase in risk of CVD for every 1-g increase in dietary sodium intake.[13]

In the present study, almost 75% of participants were not indulged in regular physical activity, thus projecting prevalence of sedentary lifestyle among women. A meta-analysis on association of sedentary behavior with MetS revealed that more time spent being sedentary increased the risk of MetS by 73% (odds ratio: 1.73), irrespective the gender of the individual.[14] The SLIM trail illustrated the long-term effects of combination of diet and exercise intervention to not only improve glucose tolerance but also de-escalate the cardiovascular risk.[15] Thus, exercise and dietary modifications can reduce prevalence of MetS or/and arrest the progression of the disease. Furthermore, physical activity should be emphasized in women during and after pregnancy as well as during the perimenopausal phase to control weight.

In the present study, DM was the most prevalent component of MetS in almost 85% of participants. FBG above 100 mg/dL was reported in 43.84% participants, which is in alignment with the NFHS-4 findings of overall prevalence of 49.6% in Indian females aged 15–49 years.[16] In the present study, SBP and DBP were elevated in 22.3% and 27.7%, respectively, and HTN was observed in 30% which again goes in accordance of 30% prevalence rate in Indian females aged 15–49 years as per NFHS-4. The prevalence of abdominal obesity was 64.61% in the present study which is quite higher than findings of 3.8% in NFHS-4.[16]

In the present study, the mean weight of the female participants was 73.33 ± 9.12 kg and the mean BMI was 30.74 ± 3.07 kg/m^2. The mean WC was 90.04 ± 7.11 cm. These findings are suggestive that a significant portion of the participants are likely to be overweight or obese. Although BMI defines obesity, central adiposity is clinically assessed by WC measurement. Large WC, which mirrors increased intra-abdominal fat accumulation, can secrete adiponection, leptin, resistin, tumor necrosis factor-alpha, and interleukins which play a key role in insulin resistance and cardiometabolic risk.[17]

The present study also showed moderate elevation in both SBP and DBP, highlighting the link between HTN and MetS, in which obesity and insulin resistance are key features. Other contributing factors are sympathetic overactivity, excess activation of renin-angiotensin-aldosterone system (RAAS), baroreceptor dysfunction, elevated levels of inflammatory mediators, oxidative stress and endothelial dysfunction. In the present study, platelet indices did not show statistically significant correlation with SBP and DBP. However, a population-based longitudinal study of 6515 cases conducted in Beijing by Yang K *et al*., highlighted positive association of MPV with SBP and negative association of PDW with SBP in females.[18] Also Mendelian randomization studies by Xu Y *et al*., and Chiu P-C *et al.*, concluded that higher platelet count had casual association with elevated blood pressure.[19,20] Thus, elevated BMI, waist circumference, blood

pressure and dysglycemia collectively portray the clinical repercussions of MS.

The pharmacological management of MetS embraces a multifaceted approach addressing the individual components and involves anti-diabetic drugs, anti-hypertensive drugs, and lipid-lowering agents. In the present study, metformin was the most prescribed drug for pharmacotherapy for glycemic control. Pharmacotherapy with metformin in addition to lifestyle modification is recommended by the American Diabetic Association as the first line of management for hyperglycemia/insulin resistance due to its efficacy, affordability, weight neutrality, and safer profile.[21] In the present study, ARB was the drug highest prescribed anti-hypertensive drug. This finding goes in accordance with the study by Farský *et al.*[22] MetS patients with HTN need aggressive treatment for nephroprotective, angioprotective, and metabolic effects.[21] ACE inhibitors and ARB both target RAAS mechanism mediating their effects on albuminuria reduction, reduction of BP, and improvement of insulin resistance.

In the present study, statins were the highest prescribed drug for management of dyslipidemia and this finding stands in alignment with the recommendations of AHA.[23] Statins form the cornerstone in management of dyslipidemia with MS to reduce risk of atherosclerotic events. The target for fenofibrate and niacin are to lower triglycerides and raise HDL, whose prescription was confirmed by few participants in our present study. However almost half of the participants were not receiving any lipid-lowering therapy which represents a substantial disparity between those at risk and those successfully treated. These findings are similar to GENOA Study and DETECT-Study Group which highlighted the suboptimal statin therapy among the population.[24,25] The 'From The Heart' study had reflected not only poor knowledge of CVD risk amongst patients but also potential gaps in physician implementation of recommendations in the ACC/AHA cholesterol guidelines.[23] This demands a comprehensive approach streamlining therapy, challenging patient profile and barriers to drug adherence to bridge the gap between diagnosis and treatment.

In the present study, MetS participants with DM, HTN, and hyperlipidemia showed a highest MPV value compared to the other combinations of risk factors which were statistically significant. This observation underscored the potential impact of these specific risk factors on MPV, which had association with platelet activity and heightened risk of atherogenic events. Similar findings were noted in studies by Abdel-Moneim *et al.*[26] and Nardin *et al.*[27] in patients with MetS and emphasized the role of platelet indices as diagnostic and predictive biomarkers for comorbidity of MetS.

In the present study, platelet indices did not show statistically significant correlation with WC and BMI, which are in accordance with the findings by Alzahrani *et al.*[28] Mahadeo *et al.,* had observed significant association with plateletcrit and WC.[29] Bailasan and Remal had observed positive correlation between platelet indices and BMI.[30]

In the present study, MetS patients with poor glycemic control (HbA1C >6.5%) exhibited statistically significantly higher values of PDW, MPV, and P-LCR as compared to those with HbA1C ≤6.5%. These findings are in alignment with the studies by Dwivedi and Davangeri.[31] Studies conducted by Agrawal *et al.* gave the observations that platelet indices were significantly higher among patients with hyperglycemia as compared to healthy controls.[32] In the present study, PDW and P-LCR exhibited statistically significant positive correlation with HbA1C, similar to findings by Bailasan and Remal.[30] MPV, PDW, and P-LCR exhibited statistically significant positive correlation with FBS, similar to findings by Dwivedi and Davangeri.[31] Hyperglycemia can prompt upregulation of platelet membrane glycoproteins production and their non-enzymatic glycation as well as interfere with intracellular signaling systems resulting in platelet activation.[33] Hyperglycemia-induced oxidative stress, larger platelets, and platelet-derived prothrombotic factors collectively catalyze endothelial dysfunction and platelet aggregation triggering an atherosclerotic plaque formation.

In the present study, participants with MetS exhibited statistically significant positive correlation of PDW and MPV with TC similar to observations by Singh *et al.*[34] PDW and MPV also exhibited statistically significant positive correlation with TG similar to studies by Bailasan and Remal[30] and Mahadeo *et al.*[29] The potential link between elevated TG and TC with platelet size variability can predispose to a prothrombotic state. In the present study, platelet count, PDW, MPV, and P-LCR exhibited statistically significant negative correlation with HDL similar to studies by Dwivedi and Davangeri.[31] Due to anti-inflammatory properties, elevated HDL levels can be associated with reduced platelet activation and better platelet functions, hence better cardiovascular profile.

Thus, the present study provided valuable insights into complex interplay between MetS and various risk factors and their implications for the health of premenopausal females. With increasing prevalence of obesity and insulin resistance in females at younger age, CVD events are in surge, escalating socioeconomic strain and affecting productivity. MetS itself represents as a single risk factor for many adverse clinical outcomes. Progression to an adverse clinical event is influenced by the presence of risk factors and prevention-seeking behavior. Hence, early diagnosis and management shall help to prevent or delay micro as well as macrovascular complications.

Managing MetS shall improve overall reproductive health and fertility in premenopausal women. Special focus is needed toward females as they often ignore their health or procrastinate visit to the physicians. The constellation of risk factors associated with MetS has a substantial

impact on platelet structure and function. In conjunction to other risk assessment tools like glycemic profile, lipid profile, BP measurements, analysis of platelet indices can provide valuable insights into micro-vascular health and the likelihood of developing complications. However, they should not be used as stand-alone predictors for clinical events. Platelet indices shall add prognostic information to Framingham risk scoring in MetS, thus extending substantial clinical and epidemiological support and shared-decision making in primary care settings. Platelet indices are cost-effective and a part of CBC panel. Its integration into clinical practice shall broaden the assessment of cardiovascular risk and enhance risk stratification among patients. Implementation of holistic disease-preventive measures such as lifestyle modifications and regular monitoring of health profile can delay the accumulation of risk factors and postpone an adverse clinical event in premenopausal females with MetS.

Limitation of study

The conclusion of the study should be considered with respect to the following limitations. The recruitment of the patients was based on non-probable sampling which was easily accessible and has a chance of selection bias. The nature of the study was cross-sectional, in which correlations were identified. However, the direction of causation cannot be determined. Furthermore, single-centered study has the challenge of external validity and its applicability to the general population. The present study represents a snap-shot of the effect of MetS on platelet indices. Further, research with longer follow-up shall aid comprehensive insights to delve into the nature of these relationships and to determine the clinical utility of platelet indices as independent predictors of cardiovascular events.

CONCLUSION

The present study conducted on premenopausal females with MetS threw light on the intricate relationship between various risk factors and their clinical implications. It highlighted the high prevalence of components associated with MetS, notably hyperglycemia, HTN, and obesity, aligning with the national trends. Despite the pharmacological management involving drugs such as metformin, ARBs, and statins, a significant proportion of participants did not receive adequate treatment for their respective conditions, revealing a treatment gap. The study also elucidated the substantial impact of DM, HTN, and hyperlipidemia on platelet indices, notably MPV and PDW, highlighting their potential as biomarkers for associated comorbidities. However, while these indices provide valuable insights, their use as sole predictors for clinical events is cautioned. Implementing community-based screening and integrating platelet indices into risk assessment may enhance early detection and holistic preventive strategies, ultimately improving health outcomes and reducing long-term healthcare burdens in premenopausal females with MetS.

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Ethical approval

The research/study approved by the Institutional Review Board at GVPIHCMT, number GVPIHCMT/IEC/20230510/01, dated May 10, 2023.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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