Role of platelet indices as diagnostic and predictive biomarkers for comorbidity of diabetes and metabolic syndrome in southern Ethiopia: A comparative cross-sectional study

Kassahun Haile, Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew

1 Department of Medical Laboratory Science, College of Medicine and Health Sciences, Wolkite University, Wolkite, Ethiopia, 2 Department of Biomedical Science, College of Medicine and Health Sciences, Wolkite University, Wolkite, Ethiopia, 3 Department of Midwifery, College of Medicine and Health Sciences, Wolkite University, Wolkite, Ethiopia, 4 School of Medical Laboratory Science, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia

* kassahaile07@gmail.com

Abstract

Background

Metabolic syndromes (MetS) and diabetes mellitus (DM) comorbidity is a growing major global public health problem with huge morbidity and mortality. It is a pro-inflammatory and prothrombotic disorder characterized by alteration of platelet indices and increased platelet activation, however, the tendency to use them in diagnosis is not yet fully evaluated in our context and there is limited evidence on the role of platelet indices in predicting and differentiating DM+MetS comorbidity in Ethiopia. Thus, this study aimed to evaluate platelet indices in HC, DM, and DM+MetS, and to determine their role in the prediction of DM+MetS comorbidity risk and the distinction between DM+MetS and DM or healthy persons in southwest Ethiopia.

Method and materials

A comparative cross-sectional study was conducted in Wolkite University specialized hospital from March to August 2021. A total of 336 study participants (112 healthy controls (HC), 112 DM, 112 DM+MetS) was included in this study. Anthropometric data were measured and the venous blood sample was collected to determine platelet indices, lipid profiles, and blood glucose levels. The SPSS version 21 statistical software was used to perform receiver operating curve (ROC), one-way ANOVA, and independent T-test analysis. The p-value for statistical significance was set at <0.05.

Result

In the present study, we found a significant difference in the mean value of PLT, MPV, and PDW between DM+MetS, DM, and HC. A statistically significant difference in the mean value of MPV and PDW was observed between HC and DM+MetS as well as DM and DM
+MetS (p-value<0.001). At the cutoff value of 9.65fl with a sensitivity of 81.3% and a specificity of 67.9%, MPV differentiates DM+MetS from HC with an AUC of 0.859. MPV can differentiate DM+MetS from DM at a cutoff value of 10.05fl with sensitivity, specificity, and an AUC of 67.9%, 65.2%, and 0.675, respectively. At the cutoff value of 9.65fl with a sensitivity of 69.6% and a specificity of 67.9%, MPV differentiates DM from HC with an AUC of 0.747. The best platelet parameter identified in this study for predicting the presence of DM+MetS comorbidity was MPV (AUC=0.859; 95%CI=0.81-0.90).

Conclusion
In this study, a significant difference in the mean value of PLT, MPV, and PDW was found between DM+MetS, DM, and HC. The mean value of platelet indices showed significant increases in DM+MetS patients in comparison to HC and DM. MPV has been identified as a good potential marker to predict DM+MetS comorbidity and to differentiate DM+MetS comorbidity from the HC or DM. Our results show that MPV could be a good hematological marker to differentiate DM+MetS comorbidity from the HC or DM, and may offer supportive information for early diagnosis, prevention, and control. Thus, the findings of this study should be taken into account for the prevention and control of DM+MetS comorbidity.

Introduction
Metabolic syndrome is an increasingly important global public health issue affecting both developed and developing nations [1–4]. The studies revealed 34.1%, 33.3%, 21.66%, 37.05%, 19.1%, 43.83%, 20.6% and 34.2% burden of MetS in Brazil [5], Finland [6], Indonesia [7], Iran [8], Uganda [9], Ghana [10], Malaysia [11], and Ethiopia [12], respectively. According to ATP III guideline [13], MetS is defined as the presence of three or more of the following conditions: waist circumference (WC) ≥102 cm in men or ≥88 cm in women; blood pressure (BP) ≥130/≥85 mm Hg; fasting blood glucose (FBS) ≥126 mg/dl; triglyceride (TG) ≥150 mg/dl and low high-density lipoprotein (HDL) < 40 mg/dl in men or < 50 mg/dl in women. Studies demonstrated a high burden of MetS in diabetic patients and DM+MetS comorbidity as an emerging public health problem that needs attention [10, 13–15]. Studies indicate a burden of MetS of 90.6%, 60.4%, 70.3% and 59.62% among diabetic patients in Ghana [16], Cameroon [17] and Ethiopia [18], respectively. Another study found that two out of three Type 2 diabetic (T2DM) patients in sub-Saharan African countries had MetS [19]. Additionally, MetS comorbidity with DM is considered a major risk factor for cardiovascular disease (CVD) and mortality in patients with DM [15, 16]. Early prediction of the risk of DM+MetS comorbidity is absolutely important for DM and MetS patient management as well as for CVD prevention, decelerating disease progression, and mortality [10, 17]. However, due to the lack of established standard screening methods, the effectiveness and reliability of MetS screening in a DM patient are not convincing, and standards for MetS diagnosis are likely to vary substantially [13, 20–22]. In addition, MetS diagnosis and determination need measurements of different parameters at a time that needs sophisticated materials and are easily affected by different factors [13, 20]. It is therefore essential to discover a biomarker that is accessible, reliable, and cost-effective from laboratory reports for early prevention and control of MetS+DM comorbidity.

It is underlined that hematological indices tend to be exceptionally basic, fast, and cost-effective tools, particularly in developing countries like Ethiopia with constrained assets to
distinguish early vascular complications and predict comorbidity risk. Metabolic syndrome and diabetes are pro-inflammatory and prothrombotic disorders characterized by alteration of platelet indices and increased platelet reactivity [23–25]. The evidence relates platelet activation (PLT) to MetS and DM [3, 4, 21, 25], however, the tendency to use them in diagnosis is not yet fully evaluated in our context. Platelet indices such as mean platelet volume (MPV), platelet crits (PCT), and platelet distribution width (PDW) are the indicators of increased platelet activity [23, 24] and have been identified as potential new biomarkers of disease severity and comorbidity [25]. Studies have shown that changes in platelet counts (PLT) and MPV are independently associated with the presence and severity of COVID-19 [26], tuberculosis [27], malaria [28], and hypertension [29]. In addition, MPV has demonstrated good prognostic and diagnostic value in predicting the risk of TB+DM comorbidity, and significantly distinguishes TB+DM comorbidity from TB or DM [27]. However, its role in the prediction of DM+MetS comorbidity risk and the distinction between DM+MetS and DM or healthy persons is not adequately described.

Few studies have demonstrated relations between hematological parameters and MetS [30–33], with a controversial conclusion. An increase in the PLT, PCT, and PDW were observed in older adults with MetS compared to healthy control [32]. The elevated level of MPV and the PDW significantly predict the risk of vascular complications in DM patients [33, 34]. A significantly higher level of MPV, PDW, and P-LCR was seen in T2DM patients with microvascular complications [33, 35, 36]. However, the role of platelet indexes in the prediction of DM+MetS comorbidity risk and the distinction between DM+MetS and DM or HC is not well known in Ethiopia. Thus, this study aimed to evaluate platelet indices in HC, DM, and DM+MetS, and to determine their role in the prediction of DM+MetS comorbidity risk and the distinction between DM+MetS and DM or HC in southwest Ethiopia.

Method and materials

Study area

The study was conducted in Wolkite University specialized hospital, which is located 158km far from the capital city of Ethiopia, Addis Ababa. The hospital was found in the Gubriye sub-city in the Gurage zone, Southern Nations, Nationalities and Peoples Regional State (SNNPR), Ethiopia. The hospital provides services for more than 1.2 million people living in the Gurage zone and the neighboring area. The study was conducted on DM patients attending their follow-up at the chronic illness clinic of the Wolkite University specialized hospital.

Study design and period

A facility-based comparative cross-sectional study was employed from March to August 2021.

Sample size determination and sampling technique

The sample size was determined by two populations’ mean formulae using G-power version 3.1 by considering the following assumptions: 95% confidence interval (two-sided), 80% power \((Z_{1-\alpha} + Z_{1-\beta})^2/\sigma_1^2\), and 1:1 ratio of cases to control group. Sample size \(n = (SD_1^2 + SD_2^2) (Z_{1-\alpha} + Z_{1-\beta})^2/(M_1 - M_2)^2\). Where, \(M_1\) and \(SD_1\) are the mean and standard deviation of group 1 respectively, and \(M_2\) and \(SD_2\) are the mean and standard deviation of group 2 respectively.

Taking the mean and standard deviation (SD) of MPV for DM patients and DM+MetS groups from the previous study [36], 8.81 and 1.6 for DM patients, whereas 9.34 and 1.57 for the DM+MetS group. We got a total sample size of 224 (112 DM, 112 DM+MetS). A total of 112 individuals were also recruited as healthy controls (HC) who had free of DM and MetS.
All consecutively identified study participants who had met inclusion criteria were included in the study. Inclusion criteria include; ages ≥ 18 years, diagnosed with DM based on WHO criteria [FBS ≥ 7.0 mmol/L(126 mg/dl) or 2-hour post-load plasma glucose ≥ 11.1 mmol/L(200 mg/dl) or Hba1c ≥ 48 mmol/mol(6.5%)] [2], diagnosed with MetS based on ATP III guideline [presence of 3 or more of the following conditions: WC ≥ 102 cm in men or ≥ 88 cm in women; BP ≥ 130/≥ 85 mmHg; FBS ≥ 126mg/dl; TG ≥ 150 mg/dl and low HDL-C < 40 mg/dl in men or < 50 mg/dl in women] [13], DM+MetS diagnosed DM patients along with MetS. Study participants who had bleeding manifestations, pregnancy, and previous medical history of chronic diseases that potentially affect platelet parameters, the habit of smoking cigarettes, and alcohol consumption were excluded from the study.

Data collection and laboratory procedures

Socio-demographic data collection. The data on the socio-demographic characteristics (age, gender, residence) were collected through interviews by trained nurses using a structured questionnaire developed from the related literature [30, 37].

Anthropometric data collection. Waist circumference was measured by stretch-resistant tape at the midpoint between the lower margin of the least palpable rib and the top of the hip or minimal waist. The cut-off value of WC ≥ 102cm for men and ≥ 88 cm for women were used to indicate central obesity [13]. Body weight was measured using portable weighing scales to the nearest 0.1kg and the participant was weighed without shoes and wearing very light indoor clothing. Whereas standing height without shoes was measured by an adjustable wooden measuring board and then body mass index (BMI) was calculated as weight in kilogram divided by the square of height in meter (kg/m2) [20].

Blood pressure measurement. Blood pressure (BP) was measured from the right upper arm using a mercury sphygmomanometer after the participants had rested for more than 5 minutes and then reported by millimeter mercury (mmHg). Interpreted as systolic blood pressure (SBP; ≥ 130 mmHg) or diastolic blood pressure (DBP; ≥ 85mmHg) to indicate hypertension [20].

Blood sample collection. After obtaining written informed consent from the study participants, the vein of the antecubital fossa of the forearm arm was disinfected with 70% alcohol, and a tourniquet was applied, then after the required amount of blood had been collected, the tourniquet was released.

A total of 8ml venous blood sample was collected from each study participant by a trained laboratory technologist by vacutainer tube method in two different test tubes; 4ml in a standard serum separator tube without anticoagulant for serum glucose and lipid profile analysis, and 4ml in an EDTA tube for platelet parameter determination. The blood sample collected in a serum separator tube stayed for 30 minutes at room temperature; then serum was separated by centrifugation at 4000 rpm for 5 minutes using a Rotanta-960 centrifuge. The separated serum was kept under -20˚c deep freeze until biochemical analysis was performed.

Lipid profile and glucose analysis. Fasting blood glucose and lipid profiles (total cholesterol, high-density lipoproteins, low-density lipoprotein, and triglycerides) were determined by ABX Pentra automated analyzer (Horiba ABX SAS, Montpellier, France). Lipid profiles were measured by the enzymatic colorimetric test principle, and a series of coupled enzymatic reactions were carried out to form a colored chromogenic complex. The absorbance of the colored dye was measured at a fixed wavelength and is proportional to the concentration of the lipid profile in the sample. The enzymatic method was used to determine glucose, glucose was measured by the PAP-CP, enzymatic photometric method, and then finally absorbance was measured.
Hematological parameter analysis. Four milliliters of venous blood samples were collected in an EDTA tube and hematological parameters were determined by Sysmex XP-300 automated analyzer. Complete blood counts were measured by the electrical impedance principle, cell counting is based on the detection and measurement of changes in electrical resistance (pulses) produced by cells as they traverse a small aperture. The number of pulses produced by the cell is proportional to the number of cells counted.

Data analysis and interpretation
After checking for completeness and clarity, data were entered, processed, and analyzed by SPSS version 21 statistical software (SPSS Inc., Chicago, IL). Data were presented by using descriptive statistics, tables, and figures. The Kolmogorov-Smirnov test was used to check the normal distribution of the data and all data were normally distributed. The differences between data across the groups (HC, DM, DM+MetS) were analyzed using the chi-squared test, one-way ANOVA, and independent T-test. The independent T-test was used to analyze continuous data and the chi-square test was used to analyze categorical variables. A receiver operating curve (ROC) was performed to determine the sensitivity, specificity, area under the curve (AUC), and a cutoff value for a given PLT parameter (PLT, MPV, and PDW) in discriminating the presence or absence of DM and DM+ MetS comorbidity. The p-value for statistical significance was set at <0.05.

Ethical considerations
Ethical clearance was obtained from Wolkite University Ethical Review Committee. After explaining the purpose and procedures of the study, written informed consent was obtained from each study participant, the confidentiality of their data was kept and they were assured that only aggregate data will be reported. All necessary findings of the participant were also communicated to their respective physician for proper management.

Results
Basic characteristics of study participants
A total of 336 study participants (112 HC, 112 DM, 112 DM+MetS) were enrolled in this study. The total number of males and females among the three groups was 167 (49.7%) and 169 (50.3%) respectively. The mean age of the study participants was 49.6±16.0, 50.5±15.2, and 51.1±13.2 years in HC, DM, and DM+MetS groups, respectively. In the present study, there were no statistically significant differences were observed across the three groups in age, gender, and residency (Table 1).

Comparisons of platelet indices across the groups
The mean (SD) of platelet indices was compared among the three groups (HC, DM, DM +MetS). Accordingly, statistically significant differences were observed among the three groups in the mean value of PLT, MPV, and PDW, P-value< 0.05 (Table 2).

Comparisons of platelet indices between the groups
The difference in the mean value of the platelet parameter was compared between the groups. Study participants who had DM were significantly higher MPV and PDW values compared to HC. Compared with the HC, changes in the PLT, MPV, and PDW were significantly increased in DM+MetS patients (280.7±81.0×10^9/L, 10.6±1.05FL, 11.8±1.7FL, p-value <0.05).
Compared with DM patients (10.03 ± 0.7FL, 10.7 ± 0.8FL), the changes in the MPV and PDW were significantly increased in DM+MetS patients (10.6 ± 1.05FL, 11.8 ± 1.7FL) (Table 3).

Diagnostic value of platelet parameters for DM+MetS comorbidity

ROC curve analysis was used to determine the optimal cutoff values of PLT parameters for the prediction of DM and DM+MetS comorbidity. MPV can differentiate DM patients from healthy controls at a cutoff value ≥9.65 FL with a sensitivity of 69.6%, specificity of 67.9%, and with an AUC of 0.747 (p-value < 0.001).

MPV has the largest area under the curve (AUC = 0.747; 95%CI (0.68-0.81) in a differential diagnosis of HC VS DM as well as in a differential diagnosis of HC VS DM+MetS (AUC=0.859; 95%CI (0.81-0.90) and DM VS DM+MetS (AUC=0.675; 95%CI (0.603-0.74) respectively, which showed that it is the best platelet parameter for predicting and discriminating DM+MetS comorbidity (Table 4 and Fig 1A–1C).

The sensitivity and specificity of PLT in the differentiation of DM+MetS patients from HC were 61.6% and 53.6% at a cutoff value ≥239.5×10^9/L with an AUC of 0.613. The sensitivity and specificity of MPV in a differential diagnosis of HC VS DM+MetS were 81.3% and 67.9%

Table 1. Basic characteristics of study participants in the three groups at Wolkite University specialized hospital from March to August 2021 (n=316).

| Variables          | HC        | DM        | DM+MetS   | P-value* |
|--------------------|-----------|-----------|-----------|----------|
| Age in years       | 49.6±16.0 | 50.5±15.2 | 51.1±13.2 | 0.72     |
| Gender (Male/Female)| 51/61    | 59/53     | 57/55     | 0.53     |
| Residency (Urban/Rural) | 64/48 | 66/46     | 54/58     | 0.22     |
| FBS (mg/dl)        | 79.1±8.0  | 192.3±51.4| 164.2±64.3| <0.001   |
| BMI (kg/m²)        | 22.8±1.66 | 26.9±4.31 | 26.7±3.77 | <0.001   |
| PLT (×10^9/L)      | 102.3±12.1| 124.9±10.4| 144.2±19.8| <0.001   |
| DBP (mmHg)         | 80.8±2.6  | 86.6±10.1 | 90.6±9.2  | <0.001   |
| TC (mg/dl)         | 122.9±27.8| 140.8±43.2| 155.4±44.9| <0.001   |
| TG (mg/dl)         | 112.8±15.5| 140.1±41.0| 156.2±35.9| <0.001   |
| LDL (mg/dl)        | 80.9±14.3 | 83.2±20.8 | 91.1±20.9 | <0.001   |
| HDL (mg/dl)        | 55.8±5.6  | 50.1±10.4 | 47.9±11.7 | <0.001   |

Abbreviations
*; P-value for categorical variables (age, residence) was derived from the chi-square test and for remaining variables, it was derived from the independent t-test, BMI; body mass index, DBP; diastolic blood pressure, FBS; fasting blood glucose, HDL; high-density lipoprotein, LDL; low-density lipoproteins, SBP; systolic blood pressure, TC; total cholesterol, TG; triglyceride, kg/m²; kilogram per meter square, mg/dl; milligram per deciliters, mmHg; millimeter mercury.

https://doi.org/10.1371/journal.pone.0277542.t001

Compared with DM patients (10.03±0.7FL, 10.7±0.8FL), the changes in the MPV and PDW were significantly increased in DM+MetS patients (10.6±1.05FL, 11.8±1.7FL) (Table 3).

Table 2. Comparison of platelet indices across the groups.

| Parameter      | HC         | DM         | DM+MetS    | P-value* |
|----------------|------------|------------|------------|----------|
| PLT×10^9/L     | 249.8±62.9 | 266.7±75.7 | 280.7±81.0 | 0.008    |
| MPV (FL)       | 9.44±0.5   | 10.03±0.7  | 10.6±1.05  | <0.001   |
| PDW (FL)       | 10.4±1.3   | 10.7±0.8   | 11.8±1.7   | <0.001   |

Abbreviations
*; P-value was derived from one-way ANOVA, DM; diabetes mellitus, HC; health control, MetS; metabolic syndrome, MPV; mean cell platelet volume in femtoliter, PDW; platelet distribution width, PLT; platelet per litter.

https://doi.org/10.1371/journal.pone.0277542.t002
Table 3. Comparisons of platelet indices among the three groups.

| Parameter | HC | DM | DM+MetS | HC VS DM P-value | HC VS DM+MetS P-value | DM VS DM+MetS P-value |
|-----------|----|----|---------|----------------|-----------------------|----------------------|
| PLT×10^9/L | 249.8±62.9 | 266.7±75.7 | 280.7±81.0 | 0.07 | 0.002 | 0.18 |
| MPV(FL)   | 9.4±0.5 | 10.0±0.7 | 10.6±1.05 | <0.001 | <0.001 | <0.001 |
| PDW (FL)  | 10.4±1.3 | 10.7±0.8 | 11.8±1.7 | 0.034 | <0.001 | <0.001 |

Abbreviations:
P-value was derived from the independent t-test, DM: diabetes mellitus, HC: health control, MetS: metabolic syndrome, MPV: mean cell platelet volume in femtoliter, PDW: platelet distribution width, PLT: platelet per litter.

https://doi.org/10.1371/journal.pone.0277542.t003

Table 4. Diagnostic value of platelet indices for DM and DM+MetS comorbidity, 2021.

| Parameter | Sensitivity (%) | Specificity (%) | Cutoff value | AUC | 95%CI | P-value |
|-----------|----------------|----------------|-------------|-----|------|---------|
| HC VS DM  |                |                |             |     |      |         |
| PLT×10^9/L | 53.6% | 53.6% | ≥235 | 0.559 | 0.48-0.63 | 0.12 |
| MPV(FL)   | 69.6% | 67.9% | ≥9.65 | 0.747 | 0.68-0.81 | <0.001 |
| PDW (FL)  | 57.1% | 50.9% | ≥10.95 | 0.561 | 0.48-0.63 | 0.11 |
| HC VS DM+MetS |           |                |             |     |      |         |
| PLT×10^9/L | 61.6% | 53.6% | ≥239.5 | 0.613 | 0.54-0.68 | 0.003 |
| MPV(FL)   | 81.3% | 67.9% | ≥9.65 | 0.859 | 0.81-0.90 | <0.001 |
| PDW (FL)  | 72.3% | 50.9% | ≥10.95 | 0.698 | 0.63-0.76 | <0.001 |
| DM VS DM+MetS |         |                |             |     |      |         |
| PLT×10^9/L | 53.6% | 52.7% | ≥257 | 0.552 | 0.47-0.62 | 0.17 |
| MPV (FL)  | 67.9% | 65.2% | ≥10.05 | 0.675 | 0.603-0.74 | <0.001 |
| PDW (FL)  | 49.1% | 68.7% | ≥11.1 | 0.651 | 0.58-0.72 | <0.001 |

Abbreviations: AUC; area under the curve, DM; diabetes mellitus, HC; health control, MetS; metabolic syndrome, MPV; mean cell platelet volume in femtoliter, PDW; platelet distribution width, PLT; platelet per litter.

https://doi.org/10.1371/journal.pone.0277542.t004

Discussion

Different hematological biomarkers have been used in routine clinical practice as changes in these markers have served as prognostic markers of disease severity and comorbidity [23, 27, 28, 38], however, there is limited evidence on the role of platelet indices as a diagnostic and predictive biomarker of DM+MetS comorbidity in Ethiopia. Thus, this study aimed to evaluate platelet indices in HC, DM, and DM+MetS, and to determine their role in the prediction of DM+MetS comorbidity and the distinction between DM+MetS and DM or HC in southwest Ethiopia. We observed a significant difference in the average value of PLT, MPV and PDW between DM+MetS, DM and, HC. A statistically significant difference in the average value of MPV and PDW was found between HC VS DM and HC VS DM+MetS as well as DM and DM+MetS. At the cutoff value of 9.65fl with a sensitivity of 81.3% and a specificity of 67.9%, the MPV differentiates DM+MetS from HC with an AUC of 0.859. MPV can differentiate DM+MetS from DM at a cutoff value of 10.05fl with sensitivity, specificity, and an AUC of 67.9%, 65.2%, and 0.675, respectively. At the threshold value of 9.65fl with a sensitivity of 69.6% and a specificity of 67.9%, MPV distinguishes DM from HC with an AUC of 0.747. The best platelet indices as predictive biomarkers for comorbidity of diabetes and metabolic syndrome

(P-value <0.001), while, 67.9% and 65.2% in the differential diagnosis of DM VS DM+MetS (P-value <0.001). Whereas, the sensitivity and specificity of PDW in a differential diagnosis of HC VS DM+MetS patients were 72.3% and 50.9% (p-value <0.001), while 49.1% and 68.7% in the differential diagnosis of DM VS DM+MetS (p-value <0.001).
parameter identified in this study to predict the presence of DM+MetS comorbidity was MPV (AUC=0.859; 95%CI=0.81-0.90).

In this study, the mean value for PLT, MPV and PDW demonstrated a statistically significant difference between the HC, DM and DM+MetS groups. Our conclusion was consistent with studies across the globe [30]. The possible reason that justifies the observed difference might be the effect of the disorder on the PLT parameters, as MetS and DM are considered as one of the proinflammatory and prothrombotic disorders [36], which may result in alteration of the platelet indices and contribute to the observed difference.

In our study, we found that mean levels of PLT, MPV and PDW were significantly higher in patients with DM+MetS than in healthy controls. Our finding was in agreement with the studies reported from different parts of the world [30, 36]. Ding et al indicated that a higher level of MPV was significantly associated with MetS complications [30]. Jesri et al revealed that platelet counts were significantly increased with the severity of MetS after adjusting for other covariates [39] as well as Fang et al showed that higher platelet counts were significantly associated with MetS complications [40]. Increased platelet activation and vascular reactivity secondary to insulin resistance, oxidative stress, inflammation, hyperglycemia and non-enzymatic glycosylation in patients with DM+MetS [41, 42] may contribute to an increase in...
platelet parameters. Contrary to our findings, a study conducted in Taiwan showed that there is no significant difference in the mean PLT between MetS and the healthy control group [41]. This could be due to the difference in sample size and haematological analyzer.

According to our findings, MPV was significantly distinguished DM+MetS comorbidity from HC at a cutoff value of 9.65fl with a sensitivity of 81.3%, specificity of 67.9%, and with an AUC of 0.859. Consequently, MPV was implicated as a good biomarker for predicting the presence of DM+MetS comorbidity in this study. This finding was consistent with the study reported in China [30], and another similar study showed that MPV and PCT significantly distinguish TB+DM comorbidity from TB or DM individuals [27]. In addition, a study conducted in Turkey suggested that elevated MPV could significantly predict advanced fibrosis in chronic hepatitis C patients at a cutoff value greater than 7.3 FL with 76% sensitivity and 59% specificity [43]. The probable reason that justifies this relationship might be due to increased platelet activation in DM+MetS patients in response to inflammatory stimuli which may lead to enlargements of platelet size and alteration of its indices. Several studies suggested that MetS is a proinflammatory and prothrombotic state and characterized by alteration of platelet indices [36]. MPV is a surrogate marker of platelet activation which refers to the mean size of platelets and is associated with a wide variety of diseases stage [24, 27, 44]. A study conducted in India revealed that MPV was significantly increased with the severity of the preeclampsia in pregnant women, and had good discriminatory value with the severity of the disease; it discriminated healthy controls and severe preeclampsia with 74.6% diagnostic accuracy at a cutoff value greater than 9.05 FL, as well as it discriminated healthy controls and non-severe preeclampsia with 69.4%, 9.05 FL, 50.0%, and 82.4% diagnostic accuracy, cutoff value, sensitivity, and specificity, respectively [45]. Another study suggested that elevated MPV should alert physicians for hypothyroidism and MPV significantly predict hypothyroidism at a cutoff value greater than 9.47 FL with 80% sensitivity and 72% specificity [46].

The mean level of PDW showed a statistically significant difference between DM+MetS patients and HC in this study. The PDW cutoff value was 10.95fl to distinguish DM+MetS patients from HC with sensitivity, specificity, and an AUC of 72.3%, 50.9%, and 0.698, respectively. Different previous studies suggested that MPV and PDW were elevated in some clinical conditions [34, 36, 41, 44]. Buch et al revealed that MPV and PDW were significantly increased in diabetic patients with complications as compared to diabetics without complications and healthy groups; also they suggested MPV and PDW as good predictive biomarkers for diabetic vascular complications [34]. Patients with DM+MetS comorbidity have a high risk of microcirculation complications, which may probably lead to platelet hyperactivity and increased platelet volume that may result in an elevated PDW. Aktas et al suggested that elevated PDW could serve as a diagnostic tool for irritable bowel syndrome and a significantly higher mean value of PDW was found in the irritable bowel syndrome groups as compared to the control group [47]. Another study revealed that the mean level of PDW showed a statistically significant difference between liver steatosis patients and control groups, and PDW values higher than 16.25% have 83% sensitivity and 57% specificity in predicting liver steatosis [48].

The mean level of PLT showed a statistically significant difference between DM+MetS patients and HC. Our finding was in agreement with a study reported from South Carolina [39] and China [49]. The pathophysiology of MetS favored by inflammation, insulin resistance, oxidative stress, and endothelial dysfunction [4], which may trigger platelet hyperactivity and may result in observed differences in the PLT count.

The mean level of MPV and PDW were significantly increased in the DM+MetS patients compared with DM patients in the present study. This finding was in line with the studies conducted in China [30, 49], and India [34, 36, 50]. MPV differentiated DM+MetS patients from DM patients at a cut-off value of 10.05fl with sensitivity, specificity, and an AUC of 67.9%,
65.2%, and 0.675, respectively. These findings have been supported by the findings of previous literature. For instance, Rajagopal et al concluded that MPV levels were increased with increasing severity of hypertension and suggested it as a cost-effective diagnostic and predictive marker for hypertensive vascular complications [29]. In addition, another study revealed that MPV clearly distinguishes TB+DM comorbidity from DM or TB patients [27].

MPV is a widely used hematological marker of platelet size and activity and is associated with accelerated thrombopoiesis and an increased risk of cardiovascular diseases [24, 51]. In the present study, the mean value of MPV and PDW were significantly increased in the DM patients as compared to HC. MPV can differentiate DM patients from HC at a cutoff value of 9.65fl with a sensitivity of 69.6%, specificity of 67.9%, and with an AUC of 0.747, which was significant. Our finding was in line with studies reported from Turkey [35, 52, 53], India [34, 35, 54], and China [55]. Several studies suggest that platelet sensitivity in DM patients increases due to the action of the various platelet aggregation inductors including ADP, thrombin, and collagen as well as metabolic abnormalities associated with insulin resistance that affect the functional activity of platelet [30, 42, 56], which could likely result in an alteration of platelet indices in patients with DM.

Conclusion

In this study, a significant difference in the mean value of PLT, MPV, and PDW was found between DM+MetS, DM, and HC. The mean value of platelet indices showed significant increases in DM+MetS patients in comparison to HC and DM individuals. MPV has been identified as a good potential marker to predict DM+MetS comorbidity and to differentiate DM+MetS comorbidity from the HC or DM. MPV can significantly differentiate patients with DM from HC. Our results show that MPV could be a good hematological marker to differentiate DM+MetS comorbidity from the HC or DM, and may offer support for early diagnosis, prevention, and control. Thus, the findings of this study should be taken into account for the prevention and control of DM+MetS comorbidity.

Supporting information

S1 File. English version questioner.
(DOCX)

S2 File. DM+MetS SPSS data set.
(SAV)

Acknowledgments

We would like to acknowledge data collectors and hospital staff for their support during the data collection. We are also grateful to all study participants for giving all relevant information for the study.

Author Contributions

Conceptualization: Kassahun Haile.

Data curation: Kassahun Haile, Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew.

Formal analysis: Kassahun Haile, Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew.

Funding acquisition: Kassahun Haile, Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew.
Investigation: Kassahun Haile, Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew.

Methodology: Kassahun Haile, Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew.

Project administration: Kassahun Haile, Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew.

Resources: Kassahun Haile, Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew.

Software: Kassahun Haile, Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew.

Supervision: Kassahun Haile, Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew.

Validation: Kassahun Haile, Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew.

Visualization: Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew.

Writing – original draft: Kassahun Haile.

Writing – review & editing: Kassahun Haile, Rebie Kedir, Abebe Timerga, Ayenew Mose, Mesay Arkew.

References

1. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep.2020: 1–11.

2. World Health Organization. Classification of Diabetes Mellitus. Geneva: World Health Organization; 2019.

3. Huh JH, Kang DR, Kim JY. Metabolic Syndrome Fact Sheet 2021: Executive Report. Cardiometab Syndr J. 2021; 2(1):125–34.

4. McCracken E, Monaghan M. Pathophysiology of the metabolic syndrome. Clin Dermatol 2017; 36(1): 14–20. https://doi.org/10.1016/j.clindermatol.2017.09.004 PMID: 29241747

5. Sergio Lobato F, Sandra Souza L, Ricardo Dos S. Metabolic Syndrome and Associated Factors in Adults of the Amazon Region. PLoS One. 2016; 11(12):1–14.

6. Haverinen E, Paalanen L, Palmieri L, Padron-Monedero A, Noguer-Zambrano I. Comparison of metabolic syndrome prevalence using four different definitions-a population-based study in Finland. Arch Public Heal. 2021;1–9. https://doi.org/10.1186/s13690-021-00749-3 PMID: 34949223

7. Elizabeth H, Herningtyas T. Prevalence and distribution of metabolic syndrome and its components among provinces and ethnic groups in Indonesia. BMC Public Health. 2019;1–12.

8. Jahangiry L, Khosravi-far L, Sarbakhsh P, Kousha A. Prevalence of metabolic syndrome and its determinants among Iranian adults: evidence of IraPEN survey on a bi-ethnic population. Sci Rep. 2019;1–7.

9. Yacov LB, Ainembabazi P, Stark AH, Kizito S. Prevalence and sex-specific patterns of metabolic syndrome in rural Uganda. BMJ. 2020;1–7.

10. Osei-Yeboah J, Owiredu WKBA, Norgbe GK, Lokpo SY, G Yamfi J, Allotey EA, et al. The Prevalence of Metabolic Syndrome and Its Components among People with Type 2 Diabetes in the Ho Municipality, Ghana: A Cross-Sectional Study. Int J Chronic Dis. 2017;1–8.

11. Rizal M, Manaf A, Nawi AM, Tauhid NM, Otthman H, Rizam M, et al. Prevalence of metabolic syndrome and its associated risk factors among staffs in a Malaysian public university. Sci Rep. 2021;1–11.

12. Fenta K, Aregay A, Berhe AA, Woldegebriel G, et al. Magnitude, components and predictors of metabolic syndrome in Northern Ethiopia: Evidence from regional NCDs STEPS survey. PLoS One. 2021; 16(6):1–11.

13. Michael B. The National Cholesterol Education Program Adult Treatment Panel III guidelines. JAOA. 2003; 103(1):1–5.

14. Chilliaron JJ, Flores-le-roux JA, Goday A, Benaiges D, Carrera MJ. Metabolic Syndrome and Type-1 Diabetes Mellitus: Prevalence and Associated Factors. Rev Esp Cardiol. 2010; 63(4):423–9.

15. Agyemang-Yeboah F, Ackon B, Eghan J, Annani-akollor ME, Togbe E, Donkor S, et al. Evaluation of Metabolic Syndrome and Its Associated Risk Factors in Type 2 Diabetes: A Descriptive Cross-Sectional Study at the Komfo Anokye Teaching Hospital, Kumasi, Ghana. Biomed Res Int. 2019;1–8. https://doi.org/10.1155/2019/4562904 PMID: 31187045
16. Kengne AP, Limen SN, Sobngwi E, Djouogo CFT, Nouedou C. Metabolic syndrome in type 2 diabetes: comparative prevalence according to two sets of diagnostic criteria in sub-Saharan Africans. Diabetol Metab Syndr. 2012; 22(4):1–8. https://doi.org/10.1186/1758-5996-4-22 PMID: 22650602
17. Kassa BM AG. Metabolic syndrome among type 2 diabetic patients in Ethiopia: a cross-sectional study. BMC Cardiovasc Disord. 2018; 1–12.
18. Shibabaw W, Yirga T, Gedew M, Asmare Y, Anthony D. Metabolic syndrome among type 2 diabetic patients in Sub-Saharan African countries: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2020; 1–26.
19. Ekoru K, Doutmage A, Bentley AR, Chen G, Zhou J, Shriner D, et al. Type 2 diabetes complications and comorbidity in Sub-Saharan Africans. EClinicalMedicine. 2019; 16:30–41. https://doi.org/10.1016/j.eclinm.2019.09.001 PMID: 31832618
20. International Diabetes Federation. The IDF consensus worldwide definition of metabolic syndrome. 2006.
21. Gesteiro E, Megiá A, Guadalupe-Grau A, Fernandez-Veledo S, Joan Vendrell. Early identification of metabolic syndrome risk: A review of reviews and proposal for defining pre-metabolic syndrome status. Nutrition, Metabolism, and Cardiovascular Diseases. 2021; 2557–74.
22. Zhang X, Cui X, Li F, Wang S, Liu X. Association between diabetes mellitus with metabolic syndrome and diabetic microangiopathy. Exp Ther Med. 2014; 8:1867–73. https://doi.org/10.3892/etm.2014.1992 PMID: 25371746
23. Alberca RW, Solis-Castro RL, Solis-Castro ME, Cardoso F, Jose A, Oliveira LDM, et al. Platelet-Based Biomarkers for Diagnosis and Prognosis in COVID-19 Patients. MDPI. 2021; 2019:1–8. https://doi.org/10.3390/ijms22104701 PMID: 34685377
24. Korniluk A, Koper-Lenkiewicz OM, Kami J, Kemono H, Dymicka-Piekarska V. Mean Platelet Volume (MPV): New Perspectives for an Old Marker in the Course and Prognosis of Inflammatory Conditions. Mediat Inflamm. 2019; 1–8. https://doi.org/10.1155/2019/9213074 PMID: 31148950
25. Rajagopal L, Paramasivam YG. Role of Mean Platelet Volume (MPV) as a Predictive Marker for Hypertensive Vascular Complications - A Cross-Sectional Study in a Tertiary Care Hospital. J Evid Based Med Sci. 2020; 65:310–5.
26. Khalid A, Jaffar MA, Khan T, Lail RA, Ali S, Aktas G, et al. Hematological and biochemical parameters as diagnostic and prognostic markers in SARS-COV-2 infected patients of Pakistan: a retrospective comparative analysis. Hematology. 2021; 26(1):529–42. https://doi.org/10.1080/16078454.2021.1950898 PMID: 34334100
27. Xu F, Qu S, Wang L, Qin Y. Mean platelet volume (MPV): new diagnostic indices for co-morbidity of tuberculosis and diabetes mellitus. BMC Infect Dis. 2021; 1–9.
28. Bayleyegen B, Asrie F, Yalew A, Woldu B. Role of Platelet Indeces as a Potential Marker for Malaria Severity. J Parasitol Res. 2021; 1–9.
29. Rajagopal L, Paramasivam YG. Role of Mean Platelet Volume (MPV) as a Predictive Marker for Hypertensive Vascular Complications - A Cross-Sectional Study in a Tertiary Care Hospital. J Evid Based Med Heal. 2020; 7(35):1839–43.
30. Ding Q, Wang F, Guo X, Liang M. The relationship between mean platelet volume and metabolic syndrome in patients with type 2 diabetes mellitus. Medicine. 2021; 1–7.
31. Olana C, Seifu D, Menon MKC, Natesan G. Abnormal hematological indices and anthropometric parameters associated with type 2 Diabetes. Int J Biomed Adv Res. 2019; 10(1).
32. Yang X, Zhang L, Yang X, Zhang L, Ma Q, Sun H, et al. Platelet parameters in Chinese older adults with metabolic syndrome. Endocr Connect. 2020; 9(7):696–704. https://doi.org/10.1530/EC-20-0209 PMID: 32567552
33. Rajagopal L, Arunachalam S, Abdullah SM. Can Mean Platelet Volume and Platelet Distribution Width be used as Predictive Markers for Impeding Diabetic Vascular Complications? J Clin Diagnostic Res. 2018; 12(2):10–4.
34. Buch A, Kaur S, Nair R, Jain A. Platelet volume indices as predictive biomarkers for diabetic complications in Type 2 diabetic patients. J Lab Physicians. 2020; 9:84–8.
35. Aktas G, Kocak MZ, Duman TT, Erkus E, Atak BM, Sit M, et al. Mean Platelet Volume (MPV) as an inflammatory marker in type 2 diabetes mellitus and obesity. Bali Med J. 2018; 7(3):650–3.
36. Maheswara U, Aditya R, Sourya K, Sartham A, Neema S. Study of Platelet Indices in Patients with Metabolic Syndrome. Int J Recent Surg Med Sci. 2019; 5:10–4.
37. Solomon S, Mulugueta W. Disease burden and associated risk factors for metabolic syndrome among adults in Ethiopia. BMC Cardiovasc Disord. 2019; 5:1–8. https://doi.org/10.1186/s12872-019-1201-5 PMID: 31655560
38. Mammo M, Garadew G, Tilahun M, Solomon M, Yideg G, Zegeye B. Platelet Indices and Its Association with Microvascular Complications Among Type 2 Diabetes Mellitus Patients in Northeast Ethiopia: A Cross-Sectional Study. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2021: 14 865–874.
39. Jesri A, Okonofua EC, Egan BM. Platelet and White Blood Cell Counts Are Elevated in Patients With the Metabolic Syndrome. J Clin Hypertens. 2005; 7(12). https://doi.org/10.1111/j.1524-6175.2005. 04609.x PMID: 16330892
40. Fang K, Cheng Y, Su C, Wang Y. Higher platelet counts are associated with metabolic syndrome independent of fatty liver diagnosis. J Chinese Med Assoc. 2016;1–8. https://doi.org/10.1016/j.jcma.2016. 07.003 PMID: 27686501
41. Chang Y, Pei C, Pei D, Tang S, Hsu C, Chen Y, et al. Association Between Platelet Count and Components of Metabolic Syndrome in Geriatric Taiwanese Males. Int J Gerontol. 2012; 6:215–9.
42. Suslova TE, Sitzhevskski AV, Ogurkova ON, Kravchenko ES, Kologrivova IV, Anfinogenova Y, et al. Platelet hemostasis in patients with metabolic syndrome and type 2 diabetes mellitus: cGMP- and NO-dependent mechanisms in the insulin-mediated platelet aggregation. Front Physiol. 2015; 5:1–8. https://doi.org/10.3389/fphys.2014.00501 PMID: 25601838
43. Koskel MA. Prediction of Fibrosis in Chronic Hepatitis C by Mean Platelet Volume and Platelet to Lymphocyte Ratio. National Journal of Health Sciences.2021; 6:48–52.
44. Leal-Santos FA, Silva SBR, Crepaldi NP, Nery AF, Martin TOG, Alves-junior ER, et al. Altered platelet indices as potential markers of severe and complicated malaria caused by Plasmodium vivax: a cross-sectional descriptive study. Malar J. 2013;1–6.
45. Sachan R, Patel ML, Vandana, Sachan P, Shyam R. Role of platelet count and mean platelet volume and red cell distribution width in the prediction of preeclampsia in early pregnancy. J Family Med Prim Care. 2021; 10:838–43.
46. Bilgin S, Tel B, Kahveci G, Duman T, Kurtkulagi O, Yurum S et al. Hypothyroidism is Strongly Correlated with Mean Platelet Volume and Red Cell Distribution Width. National Journal of Health Sciences. 2021; 6:7–10.
47. Aktas G, Duman TT, Atak BM, Kurtkulagi O, Bilgin S, Basaran et al. Irritable bowel syndrome is associated with novel inflammatory markers derived from hemogram parameters. Fam Med Prim Care Rev. 2020; 22(2): 107–110.
48. Aktas G, Duman TT, Atak BM, Kurtkulagi O, Bilgin S, Basaran et al. Liver steatosis is associated with both platelet distribution width, neutrophil/Lymphocyte ratio and Lymphocyte/monocyte ratio. Prim Health Care.2020; 10(4): 001–004.
49. Chang HW, Chang JB, Li PF, Chen JH, Huang CL, Liang YJ. The Association of Hematological Parameters and Metabolic Syndrome in an Older Population: A Cross-sectional and Longitudinal Study. J Med Sci. 2016; 36(5):180–7.
50. Jindal S, Gupta S, Gupta R, Kakkar A, Singh H V, Jindal S, et al. Platelet indices in diabetes mellitus: indicators of diabetic microvascular complications. Hematology. 2011; 16(2):86–9. https://doi.org/10. 1179/102453311X12902908412110 PMID: 21418738
51. Ye G, Chen Q, Chen X, Liu Y, Yin T, Meng G. The prognostic role of platelet-to- lymphocyte ratio in patients with acute heart failure: A cohort study. Sci Rep. 2019;1–8.
52. Akbay E, Turgutalp K, Onur O, Kykirim A. Mean Platelet Volume and Related Factors in Patients at Different Stages of Diabetic Nephropathy: A Preliminary Study. Clin Appl Thromb. 2014; 20(2):190–5. https://doi.org/10.1177/1076029612456734 PMID: 22914809
53. Yilmaz T, Yilmaz A. Relationship between Altered Platelet Morphologic Parameters and Retinopathy in Patients with Type 2 Diabetes Mellitus. J Ophthalmol. 2016. https://doi.org/10.1155/2016/9213623 PMID: 27190641
54. Apuroopa M, Sruhti N, Rao DNC, Gayathri D, Prasanthi M, Ranga D. Relevance of platelet indices in predicting prothrombotic activity in type 2 diabetes mellitus in correlation with HbA1C. J Dent Med Sci. 2019; 18(1):5–8.
55. Li Z, Wang J, Han X, Yuan J, Guo H, Zhang X, et al. Association of mean platelet volume with incident type 2 diabetes mellitus risk: the Dongfeng-Tongji cohort study. Diabetol Metab Syndr. Biomed Central; 2018;4–11. https://doi.org/10.1186/s13098-018-0333-6 PMID: 29651306
56. Mattered AM, Estheba NE, Elshora OA, Mohamed WS. Mean platelet volume and neutrophil to lymphocyte ratio in prediction of early diabetic nephropathy in type 2 diabetics. Clin Res Rev. 2019; 13 (2):1469–73.