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ORIGINAL ARTICLE

Diagnostic Value of Platelets Derived Microparticles in COVID-19

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ABSTRACT

Keyword: Platelets; Microparticles; COVID-19; Polymerase Chain Reaction

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Background: Platelet microparticles (PMP) are 0.1-1-micron fragments shed from the plasma membrane of platelets that undergo stress or activation apoptosis. This work aimed to study the PMP's prognostic significance. and their relationship to thrombotic events in COVID-19 individuals. **Methods:** This prospective case-control work was conducted on 75 COVID-19 patients aged 18 years or more, both sexes, and 25 healthy individuals matched in age and sex. Patients were subdivided into two groups: Group A (n=75): individuals hospitalized with covid 19, and Group B (n=25): The healthy control group. All patients have undergone laboratory investigations [Complete blood count, serum ferritin level, C- reactive protein, D dimer, lactate dehydrogenase, Polymerase Chain Reaction for COVID-19 detection, and ELISA for PMP detection], and radiological assessment [CT chest]. **Results:** The ROC curve analysis demonstrated that PMP effectively differentiates Group A from Group B at a cutoff level of > 0.65, achieving 76% specificity, 81.3% sensitivity, 77.2% PPV and 80.3% NPV (AUC = 0.89 & p-value < 0.001). Significant positive association between PMP and age, hospital stay, and D. dimer in group A, and a significant negative correlation between PMP and Hb (P< 0.05). **Conclusions:** Circulating PMP may serve as a diagnostic biomarker for COVID-19 infections and might be included in the diagnostic method. PMP might work as promising new prognostic indicators for identifying COVID-19 individuals at risk of poor outcomes that require early treatment.

INTRODUCTION

The SARS-CoV-2 virus, responsible for the COVID-19 pandemic, is associated with increased rate of mortality due to intense pneumonia and the onset of systemic complications, such as thromboembolic events and target-organ damage [1]. As the illness advances to more lung involvement, respiratory failure (RF) and acute respiratory distress syndrome (ARDS) occur in a minority of individuals [2].

Numerous data suggest that thromboembolic events are often identified in individuals infected with SARS-CoV-2. Histological analysis and angiographic computed tomography (CT) imaging indicated microvascular thrombosis or more widespread lung thrombosis, often unaccompanied by peripheral vein thrombosis [3].

Pulmonary thrombosis may exacerbate the mismatch between ventilation and perfusion, leading to severe hypoxemia and potentially resulting in RF [4]. CT data indicates that 25% of patients with COVID-19 in medical facilities have pulmonary thrombosis, often affecting segmental and several subsegmental pulmonary arteries [5].

Membrane microparticles (MP) are submicron membrane fragments released from cells into the extracellular space after stress or damage. They can be differentiated from other categories of extracellular vesicles (e.g., exosomes) based on their composition and creation method. MP is present in plasma and other biological fluids of healthy persons, its concentrations are different in certain disorders, which include diabetes, chronic renal disease, preeclampsia, and hypertension, amongst others. Microparticles function as both indicators and facilitators of disease. [6]

Platelet microparticles (PMP) are 0.1-1-micron fragments released from the plasma membrane of platelets experiencing stress or activation-induced death. They possess a phospholipid-based component and have functioning receptors derived from platelet membranes. They are the predominant MP in the bloodstream and exhibit pro-coagulant phosphatidylserine. MP was extensively researched in many illnesses due to its role in mediating intercellular communication and its potential as a novel biomarker for disease activity [7].

MPs may function as a pro-coagulant risk factor, potentially contributing to microthrombi in the susceptible microcirculation of the brain, resulting in signs of cerebral small vessel disease (CSVD) **[8]**. Few researchers found a relationship between microparticles and covid 19.

Circulating MPs and activated platelets could serve as valuable new prognostic indicators for detecting potentially severe COVID-19 patients in need of rapid treatment, particularly among cancer patients [9].

This work aimed to study the Prognostic significance of PMP and its relationship to thrombotic complications in COVID-19 patients.

PATIENTS AND METHODS

This Prospective case-control work was carried out on 75 COVID-19 participants aged 18 or older, both sexes, and 25 healthy individuals matched in age and sex.

Each subject signed an informed consent form. This work was conducted from January 2021 to December 2022 following permission from the Ethics Committee Aswan University Hospital (approval code:).

The criteria for exclusion were individuals with other causes of pneumonia (PCR negative), under the age of 18, and with hypoxia not related to COVID-19.

Participants were subdivided into two groups: Group A (n=75): participants hospitalized with covid 19, and Group B (n=25): The healthy control group.

Each participant underwent: Full taking of history, complete physical examinations, laboratory tests [full blood picture (CBC), serum ferritin level, D dimer, lactate dehydrogenase (LDH), C- reactive protein (CRP), Polymerase Chain Reaction (PCR) for COVID 19 detection, and ELISA for PMP detection], and radiological assessment [CT chest].

Statistical analysis

Statistical analysis was accomplished employing SPSS v28 (IBM©, Armonk, NY, USA). Shapiro-Wilks test and histograms were employed to assess the data distribution normality. Parametric quantitative data were displayed as mean and standard deviation (SD) and were analyzed by unpaired student t-test. Non-parametric quantitative data was displayed as the median and interquartile range (IQR) and was analyzed utilizing the Mann Whitney-test. Qualitative parameters were displayed as frequencies and percentages (%) and analysed using the Chi-square test or Fisher's exact test, depending on suitability. The diagnostic accuracy of each test was assessed using Receiver Operating Characteristic (ROC) curve analysis. A perfect test is represented by a curve that starts at the bottom left, moves to the top left, and then proceeds to the top right. The test's overall effectiveness is measured by the area under the curve (AUC), with an AUC above 50% indicating satisfactory performance and an AUC approaching 100% reflecting optimal performance. Data correlation was analyzed using Pearson's correlation coefficient (r). Statistical significance was determined by a two-tailed P value of less than 0.05.

RESULTS

Statistically significant increase in group A when compared with group B regarding PMP (P= 0.045, 0.028, <0.001, respectively).

Table 1: comparison of PMP between studied groups.

		Group A (N = 75)	Group B (N = 25)	Stat. test	P-value
PMP	**Median**	0.95	0.5	**MW = 189**	**< 0.001 HS**
	IQR	0.66 – 1.2	0.37 – 0.64		

MW: Mann Whitney U test. HS: p-value < 0.001 is considered highly significant.

As inferred from roc curve, PMP can effectively differentiate between groups A and B at a cutoff level of > 0.65, with specificity, 81.3% sensitivity, 76% 77.2% PPV and 80.3% NPV (AUC = 0.89 & p-value < 0.001). **Figure 1**

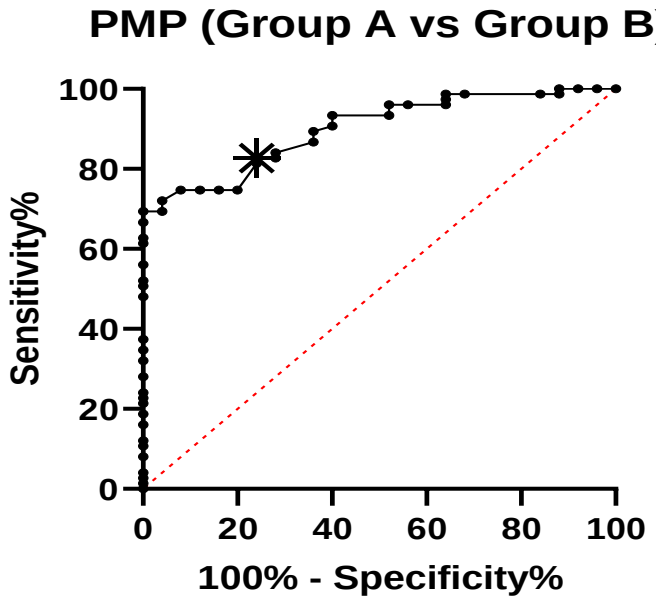

Figure 1: ROC curve between group A & group B as regard PMP

Statistically significant increased PMP in patients of CORAD 5 CT when compare d with patients of CORAD 4 CT in group A patients (p-value = 0.034). Highly statistically significant increased PMP in severe patients when contrasted with not-severe patients, and in died patients when compared with recovered patients in group A patients (p-value < 0.001). **Table 2**

Table 1: Correlation between PMP level and disease severity in group A patients

		N	PMP level	P-value
Chest CT results	**CORAD 4**	7 (9.3%)	0.56 (0.49 – 0.96)	**0.034***
	CORAD 5	68 (90.7%)	0.95 (0.77 – 1.24)	
Disease stage	**Not severe**	28 (37.3%)	0.66 (0.52 – 0.84)	**< 0.001****
	Severe	47 (62.7%)	0.99 (0.95 – 1.32)	
Outcome	**Recovery**	35 (46.7%)	0.66 (0.55 – 0.88)	**< 0.001****
	Death	40 (53.3%)	1.03 (0.95 – 1.32)	

Data are presented as median (IQR) or frequency (%). CT: computed tomography, *: significant as P value < 0.05, **: highly significant as P value < 0.001

A significant positive association existed between PMP and age, hospital stay, and D. dimer in group A (P= 0.034, 0.005, 0.002, respectively), and significant negative correlation between PMP and Hb (P= 0.003), while no significant correlation between PMP and WBCs, PLTs, lymphocytes, neutrophil, monocytes, ferritin, CRP, and LDH. **Table 3**

Table 2: Correlation study between PMP and other studied data in group A patients

PMP	**Group A**	
	R	**p-value**
Age	0.245	**0.034 ***
Hospital Stay	0.323	**0.005 ***
Hb (g/dL)	-0.334	**0.003 ***
WBCs (10^9/L)	0.106	0.365
PLTs (10^9/L)	-0.165	0.157
Lymphocytes (10^9/L)	-0.142	0.223
Neutrophil (10^9/L)	0.169	0.148
Monocytes (10^9/L)	-0.044	0.706
Ferritin (ng/mL)	0.183	0.116
CRP (mg/dL)	0.16	0.171
D. Dimer (ng/m)	0.359	**0.002 ***
LDH (U/L)	0.161	0.168

r: correlation coefficient, PMP: Platelet microparticles, Hb: hemoglobin, WBCs: white blood cells, PLTs: platelet, CRP: C-reactive protein, LDH: lactate dehydrogenase, *: significant as P value < 0.05.

There were 56 patient with comorbidities (29 patients (38.7%) with DM, 43 patients (57.3%) with HTN, 3 patients (4%) with IDH, 1 patient (1.3%) with HCV and 4 smoker patients (5.3%))in group A patients while there were 19 patients (25.3%) with no comorbidities. Regarding laboratory data the mean Hb in group A patients was 11.8 ± 1.8 g/dL, the mean PLT in group A patients was 247 ± 90 10^9/L, the mean lymphocytes in group A patients was 9.3 ± 4.0 10^9/L, the mean neutrophil in group A patients was 80.7 ± 6.8 10^9/L, the mean monocytes in group A patients was 4.1 ± 3.6 10^9/L, the mean ferritin in group A patients was 599.1 ± 264.2 ng/mL, the mean CRP in group A patients was 78.4 ± 23.8 mg/dL, the mean D. Dimer in group A patients was 2610.6 ± 2215.2 ng/mL, the mean LDH in group A patients was 688.6 ± 297.4 U/L. Regarding chest CT results, there were 7 patients (9.3%) with CORAD 4 and 68 patients (90.7%) with CORAD 5 in group A patients. As

regard hospital stay, the mean hospital stay in group A patients was 7.7 ± 4.5 days. As regard disease stage, there were 28 not severe patients (37.3%) and 47 severe patients (62.7%) in group A patients. As regard outcome, there were 35 recovered patients (46.7%) and 40 died patients (53.3%) in group A patients.

Table 4: Comparison of demographic data, PMP between studied groups (n=100), and description of comorbidities, laboratory data, and Chest CT in group A patients (n = 75)

		Group A (N = 75)	**Group B (N = 25)**	**P-value**
Age (years)		68 (61 – 75)	62 (52 – 70)	**0.045***
Sex	**Male**	32 (42.7%)	17 (68%)	**0.028***
	Female	43 (57.3%)	8 (32%)	
Comorbidities	**No comorbidities**	19 (25.3%)	---	---
	DM	29 (38.7%)	---	---
	HTN	43 (57.3%)	---	---
	IHD	3 (4%)	---	---
	HVC	1 (1.3%)	---	---
	Smoking	4 (5.3%)	---	---
Laboratory data	**Hb (g/dL)**	11.8 ± 1.8	---	---
	WBCs (10^9/L)	13.8 ± 5.7	---	---
	PLTs (10^9/L)	247.0 ± 90.1	---	---
	Lymphocytes (10^9/L)	9.3 ± 4.0	---	---
	Neutrophil (10^9/L)	80.7 ± 6.8	---	---
	Monocytes (10^9/L)	4.1 ± 3.6	---	---
	Ferritin (ng/mL)	599.1 ± 264.2	---	---
	CRP (mg/dL)	78.4 ± 23.8	---	---
	D. Dimer (ng/m)	2610.6 ± 2215.2	---	---
	LDH (U/L)	688.6 ± 297.4	---	---
Chest CT results	**CORAD 4**	7 (9.3%)	---	---
	CORAD 5	68 (90.7%)	---	---
PMP		0.95 (0.66 – 1.2)	0.5 (0.37 – 0.64)	**< 0.001****
Hospital stays		7.7 ± 4.5	---	---
Disease stage	**Not severe**	28 (37.3%)	---	---
	Severe	47 (62.7%)	---	---
Outcome	**Recovery**	35 (46.7%)	---	---
	Death	40 (53.3%)	---	---

Data are presented as mean ± SD, median (IQR) or frequency (%). DM: diabetes mellitus, HTN: hypertension, IHD: ischemic heart disease, HVC: hepatitis C virus, Hb: hemoglobin, WBCs: white blood cells, PLTs: platelet, CRP: C-reactive protein, LDH: lactate dehydrogenase, PMP: Platelet microparticles, *: significant as P value < 0.05.

A significant relation existed among outcome and WBCs, and CRP (P= 0.046, 0.001, respectively), and highly significant relation between outcome and ferritin, D. Dimer, and LDH (P < 0.001) in

group A patients, while there was no significant relationship between outcome and other studied laboratory data (Hb, PLTs, lymphocytes, Neutrophil and monocytes) in group A patients.

Table 5: Relation between outcome and studied laboratory data in group A patients

Group A	**Outcome**		**P-value**
	Recovery (N = 35)	**Death (N = 40)**	
Hb (g/dL)	12.2 (11.2 - 12.5)	11.7 (10.2 - 12.8)	0.325
WBCs (10^9/L)	11.5 (8 - 17)	14.8 (11.5 - 17.9)	**0.046 ***
PLTs (10^9/L)	244 (190 - 319)	233.5 (154.5 - 312.5)	0.675
Lymphocytes (10^9/L)	9.1 (6.8 - 11. 3)	10.5 (6.9 - 11.3)	0.621
Neutrophil (10^9/L)	81 (78 - 87)	79.5 (77 - 84)	0.499
Monocytes (10^9/L)	3.6 (3.1 - 4.5)	3.6 (3.02 - 4.1)	0.970
Ferritin (ng/mL)	480 (400 - 526)	588 (523.5 - 748.5)	**< 0.001 ****
CRP (mg/dL)	70 (48 - 84)	92 (81.2 - 105.7)	**0.001 ***
D. Dimer (ng/m)	880 (500 - 2300)	3100 (2070 - 4474.5)	**< 0.001 ****
LDH (U/L)	480 (376 - 596)	776 (633.7 - 944.7)	**< 0.001 ****

Data are presented as median (IQR). Hb: hemoglobin, WBCs: white blood cells, PLTs: platelet, CRP: C-reactive protein, LDH: lactate dehydrogenase, *: significant as P value < 0.05, **: highly significant as P value < 0.001.

DISCUSSION

A global epidemic of viral pneumonia, known as coronavirus disease (COVID-19), has affected millions and poses an ongoing danger to many more [10]. As the illness advances to more affection to the lungs, RF and ARDS occur in a minority of individuals [2].

Coagulopathy has garnered attention in COVID-19 patients because of aberrant coagulation markers, particularly elevated D-dimer and fibrin degradation products, which correlate with the severity of the disease [11, 12].

Numerous adhesion molecules and ligands may enhance interactions between platelets and the endothelium. P-selectin (CD62 marker) produced by platelets plays a vital function in connecting homeostasis and inflammation [13].

Circulating microparticles (MPs) are extracellular vehicles (EVs) measuring 0.1–1 μm, released from cells due to activation or stress. Based on their biological origins, MPs possess distinct collections of lipids, proteins, and RNAs that may facilitate intercellular communication [14]. MPs have been documented in almost all thromboembolic disorders due to their procoagulant phospholipid content [15].

The MPs are proposed to be involved in inflammation, thrombosis, and angiogenesis. Platelet-derived MPs (PDMPs) are said to possess several coagulant functions. Some research indicate that they are highly procoagulant due to the presence of the anionic phospholipid (PS), which is the primary source of PS + MPs in bloodstream, accounting for 70-90% of all circulating MPs; nevertheless, other studies have revealed anticoagulant properties for PMPs **[16]**. Due to COVID-19 being a recently emerged infectious illness, little research has focused on extracellular vehicles (EVs), especially MPs, and their role in the disease's development **[17]**. Therefore, additional studies are necessitated to evaluate the diagnostic and prognostic impact of PMPs.

cross-sectional case-control work was performed on 100 persons who were allocated into two groups; group A, which included 75 participants admitted with COVID-19 (ICU patients and not ICU patients), and Group B (control group), which included (25) healthy subjects. Patients were hospitalized at Aswan University Hospital during January 2021 to December 2022.

In the comparison of PMP between studied groups, our study revealed that PMP is significantly higher in group A (0.95 ± 0.32) in comparison with group B (0.49 ± 0.17).

The ROC curve analysis revealed that PMP was more effective in distinguishing between group A and group B at a cutoff level of > 0.65.

many studies have reported increase level of PMP with COVID-19 ,In **Zaid et al., [18]** study Blood specimens were collected from 115 consecutive individuals with COVID-19, categorized as non-severe (n=71; 32 females and 39 males) and severe (n=44; 18 females and 26 males). The severity of COVID-19 (severe vs non-severe) was determined at patient admission following the American Thoracic Society standards for community-acquired pneumonia.

Zaid et al., [18] indicated that the total number of PMPs was significantly raised in the two groups of those with COVID-19 (severe and non-sever patients) in comparison to healthy individuals.

Likely, Abdel Maksoud et al., [16] an observational work involved 57 participants in two groups; Group A comprised 25 individuals in the active COVID-19 phase, confirmed by PCR positive, whereas Group B consisted of 32 patients in the post-COVID-19 convalescent phase, having been PCR negative for the virus for up to 4 weeks. In group A, there were 12/25 females (48%) and 13/25 males (52%), while in group B, there were 25/32 (78.1%) females and 7/32 (21.9%) males [16] , Abdel Maksoud et al., [16] found that a high substantial variation was elicited between the two groups (the active COVID-19 stage & post-COVID-19 convalescent stage) as regards the PMPs levels (mean ± SD: 38.7 ± 10.6 IU/mL and 18.9 ± 15.3 IU/mL) correspondingly there was an increase in PMP in active COVID -19 stage in comparing with post-COVID-19 convalescent stage). In the same way, significantly greater levels of PMPs had been stated in COVID-19-affected individuals contrasted to healthy controls [9].

In same line **Zahran et al.,** [9] study twenty-three malignant individuals who tested positive for COVID-19 via RT-PCR were identified at the Clinical Oncology Department, alongside nineteen non-cancer individuals quarantined at Al Rajhi Hospital of Assiut University for the same issue over a two-month period (June and July 2020). Additionally, twenty healthy individuals were included for comparative analysis. The findings revealed significantly elevated PMPs levels in COVID-19-affected patients in comparison with healthy controls .

The elevated levels of PMPs in active COVID-19 primarily result from the inflammatory conditions induced directly by viral activity **[16].**

We also noticed that there was a Correlation between PMP level and outcome in group A, with highly statistically substantial ($p < 0.001$) increased PMP in dead patients (1.12 ± 0.26) when compared with recovered patients (0.76 ± 0.28) in group A patients.

In the same line C Wang Al., 2022 found that coagulation abnormalities caused by PMPs exacerbate the mortality and complications of pandemic illnesses, including COVID-19 and other acute inflammatory conditions.

The study also shows a positive correlation between PMP, and hospital stay ($p = 0.005$).

In group A patients, the analysis revealed a significant positive correlation between PMP levels and both age ($p = 0.034$) and D-Dimer ($p = 0.002$). Conversely, a notable negative correlation was observed between PMP and Hb ($p= 0.003$).

Relation between outcome and studied laboratory data in group A patients, there were statistically significant ($p= 0.046$) increased WBCs in dead patients (14.8 ± 5.7) when compared with recovered patients (12.6 ± 5.5) in group A patients and significant ($p = 0.001$) increased CRP in died patients (86.5 ± 24.3) when compared with recovered patients (69.1 ± 19.6). As well as Highly statistically significant ($p< 0.001$) increased ferritin in dead patients (662.9 ± 222.9) when compared with recovered patients (526.1 ± 291). Highly statistically significant ($p< 0.001$) increased D. Dimer in dead patients (3528.7 ± 2233) when compared with recovered patients (1561.4 ± 1684). Highly statistically significant ($p < 0.001$) increased LDH in dead patients (824.2 ± 293.2) when compared with recovered patients (533.6 ± 218.2). Nevertheless, no significant ($p > 0.05$) correlation was

noticed between outcome and other studied laboratory data (Hb, PLTs, lymphocytes, Neutrophils, and monocytes).

In the same line **Zaid et al.** [18] identified that D-dimers, CRP, and LDH levels assessed at admission significantly linked to mortality(CRP: r=0.35, P=0.0002; LDH: r=0.40, P≤0.0001) . Moreover, age exhibited a significant association with mortality however, it didn't correlate with the length of hospital stays (r=0.10, P=0.2856).

In our work, we found a positive association between PMP level and disease severity in group A patients, the present study detected statistically significant ($p < 0.001$) increased PMP in severe patients (who are admitted to ICU) (1.12 ± 0.27) when compared with not-severe patients (who are admitted in the ward) (0.67 ± 0.2) in group A patient. Also, a highly significant ($p = 0.034$) increased PMP in patients of CORAD 5 CT (0.98 ± 0.32) when compared with patients of CORAD 4 CT (0.68 ± 0.27) in group A patients.

We recommend conducting additional studies to evaluate the temporal variation of PMPs throughout the disease progression, their efficacy in predicting therapeutic response, and their pathogenic impact on facilitating venous thrombosis within a larger patient cohort. To achieve a more precise understanding of the prognostic value and biological role of PMPs in COVID-19, it is crucial to conduct thorough studies that encompass both mild and moderate cases of the active virus. Additionally, assessing PMPs at an early stage could serve as a valuable tool for detecting individuals at risk of developing severe COVID-19, enabling timely medical intervention.

Limitations: A primary drawback was that our research was conducted at a single center. Extensive prospective multicenter investigations are required to corroborate our findings. Second, the findings cannot be inferential at the population level as only a specific group of people was included.

CONCLUSIONS

As a result of the continuous inflammatory process brought on by virus activity, PMP levels rise among individuals with active COVID-19 infection. PMP can be used to discriminate between COVID-19 infections at a cutoff level of > 0.65, with 81.3% sensitivity, 76% specificity, 77.2% PPV and 80.3% NPV. Circulating PMP could be utilized as a diagnostic biomarker of COVID-19 infections and could enter the diagnostic algorithm. PMP might serve as promising new prognostic indicators for identifying COVID-19 individuals at risk of poor outcomes that require urgent treatment.

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