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Immature platelets in patients with Covid-19: association with disease severity

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Abstract

Coronavirus disease 2019 (Covid-19) is associated with a high incidence of venous and arterial thromboembolic events. Currently, there are no clinical or laboratory markers that predict thrombotic risk. Circulating immature platelets are hyperreactive platelets, which are associated with arterial thrombotic events. The aim of this study was to assess whether the proportion of circulating immature platelets is associated with disease severity in Covid-19 patients. Patients admitted with Covid-19 disease were prospectively assessed. Immature platelet count (IPC) and immature platelet fraction (IPF) were measured at admission and at additional time points during the hospital course using the Sysmex XN-3000 auto-analyzer. A total of 136 consecutive patients with Covid-19 were recruited [mean age 60 ± 19 years, 49% woman, 56 (41%) had mild-moderate disease and 80 (59%) had severe disease at presentation]. The median IPF% was higher in patients with severe compared to mild-moderate disease [5.8 (3.9–8.7) vs. 4.2 (2.73–6.45), respectively, p = 0.01]. The maximal IPC value was also higher in patients with severe disease [15 (10.03–21.56), vs 10.9 (IQR 6.79–15.62), respectively, p = 0.001]. Increased IPC was associated with increased length of hospital stay. Patients with severe Covid-19 have higher levels of IPF than patients with mild-moderate disease. IPF may serve as a prognostic marker for disease severity in Covid-19 patients.

Keywords Coronavirus disease 2019 · Immature platelets · Platelet aggregation inhibitors · Reticulated platelets · SARS-CoV-2 infection · thrombosis

Highlights

- COVID-19 infection is associated with increased incidence thromboembolic events.
- We assessed the association between immature platelets and COVID-19 disease severity.
- Patients with severe disease had higher immature platelet fraction than those with mild-moderate disease.
- Increased immature platelet count predicted longer hospital stay.
- Immature platelet fraction may serve as a prognostic marker for COVID-19 disease severity.
- Anti-platelet drugs may be beneficial in patients with severe disease.

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Introduction

From the outbreak of the Coronavirus disease pandemic in 2019 (Covid-19) the disease had a global effect on morbidity and mortality. Several case series have reported a range of clinical characteristics from mild respiratory infection to multi organ failure and death [1–3]. Patients with Covid-19, especially with severe presentation, have a high incidence of venous thromboembolic events (VTE) and pulmonary embolus (PE) as well as arterial thrombotic events. [4–7]. Disease

severity and short-term mortality are associated with several hematologic abnormalities such as thrombocytopenia, lymphopenia, elevated D-dimer and fibrinogen degradation products [8–12].

Immature platelets released into the circulation from bone marrow by megakaryocytes, termed reticulated platelets (RPs), have been shown to be more pro-thrombotic and hyper-reactive than mature platelets and have high amount of dense granules which contain adenosine triphosphate (ATP), ionized calcium, and serotonin [13, 14]. RPs are known to be associated with high platelet turnover states, and have a greater predilection for thrombus formation [13–16].

Measuring the level of RPs is technically difficult and requires flow cytometry. Recently, an automated assay-immature platelet fraction (IPF) was introduced. It is performed in a simple and reproducible way by a hematology autoanalyzer (eg Sysmex XN-3000), which measures platelet count by optical fluorescence. There is a strong correlation between the levels of IPF and RPs in the blood [17].

We have recently shown that immature platelet indices such as IPF appear to be higher in patients with Covid-19 compared with patients with stable coronary artery disease, and even compared to patients with an acute coronary syndrome, known to have high levels of immature platelets [18]. Whether this increased level of immature platelets contributes to the high-rate of thromboembolic events in patients with Covid-19 and to disease severity is still unknown.

The aim of the current study was to evaluate whether the proportion of immature platelets in the circulation is associated with disease severity in patients with Covid-19.

Methods

Patients with Covid-19 disease, admitted to Assuta Ashdod Medical Center, Israel from March 2020 to October 2020 were prospectively recruited for study participation. SARS-CoV2 infection was diagnosed by reverse transcription polymerase chain reaction (RT-PCR) test. Disease severity was defined according to the Covid-19 treatment guidelines [19].

Mild illness

Individuals who have any of the various signs and symptoms of Covid-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.

Moderate illness

Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥ 94% on room air at sea level.

Severe illness

Individuals who have SpO_2 < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg, respiratory frequency > 30 breaths/min, or lung infiltrates > 50%.

Critical illness

Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Venous blood samples were drawn from each patient at 3 time points: (a) on admission to the hospital; (b) 3 days afterwards; (c) after one week of hospitalization; (d) on subsequent time point during index hospitalization. These time points were chosen in order to capture baseline IPF levels and follow its change during the hospitalization.

The level of IPF was determined as a part of complete blood cells count by an autoanalyzer Sysmex XN-3000 (Sysmex America Inc. Mundelein, Illinois, USA), which uses fluorescent dyes containing oxazine and ethylene glycol. This system discriminates between mature and immature platelets and reports the immature platelet fraction (IPF) as percentage and absolute number. IPC (immature platelet count) is calculated by multiplying IPF and total platelet count, representing the absolute count of immature platelets ($\times 10^3/\mu l$).

The normal reference range for IPF% and IPC used in our laboratory (as defined by Sysmex) is 1.2–8.6% and 3.6–20.0 $\times 10^3/\mu l$, respectively. The analytical error in measuring IPF is 3.6%. The association between severity of Covid-19 disease and IPF over time was evaluated.

The study was approved by the local investigational review board (ethics committee) of the Assuta Ashdod Hospital, Israel, and all subjects provided written informed consent.

Statistical analysis

Categorical variables were described as frequency rates and percentages, and continuous variables were described using median, and interquartile range (IQR) values. Continuous variables were compared using independent group t tests when the data were normally distributed; otherwise, the Mann–Whitney test was used. Statistical analyses were performed using GraphPad prism 9.1.0. Multivariant analyses

was performed using JMP software version 15.1.0—SAS Institute Inc, NC USA.

For hospitalization length Fit least square Model was used and for in-hospital mortality a logarithmic regression was used. For comparisons, a 2-sided α of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 136 consecutive patients were included in this study. Among them, 56 (41%) had mild or moderate disease and 80 (59%) had severe disease at presentation. Eight patients (5.9%) started with mild disease and deteriorated to severe disease. Mean length of hospitalization was 9.1 ± 5.5 days. Among patients who were hospitalized 6 (4.5%) required mechanical ventilation during their hospital stay; 76 (56%) were treated with dexamethasone and 51 (37.5%) received plasma during their admission. Ninety-nine patients (72.8%) were treated with low molecular weight heparin during their hospital stay [73 (91.3%) with severe disease and 26 (46.4%) with mild or moderate disease]. Overall, in-hospital mortality rate was 11.8%. Patients with mild and moderate disease were younger than those with severe disease (mean age 60 ± 19 vs 69 ± 14, respectively); 29 (52%) with mild or moderate disease and 38 (48%) with severe disease were women, and 6 (11%) with mild or moderate disease and 16 (20%) with severe disease had concurrent cardiovascular disease. The baseline characteristics of the patients are presented in Table 1.

Immature platelet indices and disease severity

The median of IPF% was higher in patients with severe Covid-19 compared to patients with mild or moderate disease [5.8 (IQR 3.9–8.7) vs. 4.2 (IQR 2.73–6.45), respectively, p = 0.01, Table 2, Fig. 1]. The median of IPF absolute number was also significantly higher in patients with severe disease compared to patients with mild or moderate disease [5.1 (IQR 3.65–7.35) vs. 4.2 (IQR 2.85–6.1), respectively, p < 0.0001, Table 2, Fig. 1]. The maximal IPC value was also significantly higher in patients with severe disease compared to patients with mild or moderate disease [15 (IQR 10.03–21.56), vs 10.9 (IQR 6.79–15.62) respectively, p = 0.001, Table 2, Fig. 1].

Platelet's indices, length of hospitalization and in hospital mortality

Multivariable models were used to examine the relationship between individual baseline characteristics including IPF levels and mortality/length of hospital stay. Advanced age was found to have the strongest impact on mortality based on logarithmic regression model (Table 3). No significant association was found between IPF or IPC and in hospital mortality. Maximal IPC was found to be associated with the length of hospitalization as was shown using least squares means model (log worth 1.338, p = 0.045, Table 4).

Discussion

To our knowledge, the current study is the first to examine the association between immature platelet indices and Covid-19 disease severity. In this prospective study, we found that immature platelet indices were higher in patients with severe disease than with mild-moderate disease. These findings imply that immature platelets may have a role in Covid-19 disease progression and severity.

Patients with Covid-19 are prone to develop thrombotic events, including venous thromboembolic events, which are related to hypercoagulability states [19, 20], and acute arterial events, which are primarily platelet mediated [21–23]. The latter may be related to states of enhanced platelet turnover, similar to the increased turnover reported in patients with acute coronary syndrome [24–26]. In patients with acute coronary syndrome elevated levels of immature platelets have been associated with increased risk for arterial thrombotic events and poor clinical outcomes [27–29].

SARS-CoV2 infection promotes endothelial dysfunction in the pulmonary vascular bed and possibly other vessels, resulting in microvascular thrombosis [30]. This could explain the increased D-dimer associated with severe Covid-19 [11]. When combined with enhanced platelet turnover and reactivity, the high risk for thrombotic events may be explained.

Viruses can directly cause thrombocytopenia via megakaryocytes apoptosis or destruction of platelets during viremia. Reactive thrombopoiesis may ensue thereafter. SARS-CoV2, similar to other viruses, such as H1N1 influenza infection, can cause severe systemic inflammatory response, accompanied by increased platelet consumption and eventually increased thrombosis events due to enhanced thrombopoiesis [31, 32]. Zhang et al. recently showed that SARS-CoV-2 directly activates platelets via binding of to ACE2, which may participate in thrombus formation and inflammatory responses in Covid-19 patients [33]. Thus, both a direct virus-platelet interaction, and a systemic inflammatory response to the virus with resultant enhanced thrombopoiesis may participate in the pathogenesis of thrombotic events in patients with Covid-19 disease.

Our study may have clinical implication for anti-thrombotic treatment in patients with severe Covid-19 disease. Anticoagulation is routinely used to prevent venous

Table 1 Demographic and clinical characteristics of patients with mild-moderate vs severe COVID-19 disease

	Mild- Moderate COVID-19 n = 56	Severe COVID-19 n = 80	P-Value
Demographic characteristics			
Age, median (IQR), year	60 ± 19	69 ± 14	
Women, n(%)	29 (52)	38 (48)	0.58
Weight, kg	81.3 ± 17	85 ± 16	
Smoker, n(%)	3 (5.4)	5 (6)	0.85
Past medical history			
Diabetes, n(%)	19 (34)	36 (45)	0.23
Hypertension, n(%)	28 (50)	41 (51)	0.95
Dyslipidemia, n(%)	16 (29)	32 (40)	0.2
CAD, n(%)	6 (11)	16 (20)	0.15
CHF, n(%)	3 (5.5)	8 (10)	0.35
CRF, n(%)	6 (11)	8 (10)	0.88
Atrial fibrillation, n(%)	9 (16)	8 (10)	0.28
Dialysis, n(%)	3 (5.5)	2 (2.5)	0.38
CABG, n(%)	0	2 (2.5)	–
COPD, n(%)	0	10 (12.5)	–
Asthma, n(%)	1 (1.8)	5 (6)	0.22
CVA, n(%)	4 (7)	8 (10)	0.58
Drugs			
Diabetes drugs, n(%)	9 (16)	20 (25)	0.22
Insulin	5 (9)	34 (42.5)	0.00003
ACE/ARB,n(%)	18 (32)	30 (38)	0.56
Beta blocker, n(%)	11 (20)	30 (38)	0.03
CCB, n(%)	11 (20)	10 (12.5)	0.25
Statin, n(%)	16 (29)	24 (30)	0.9
Aspirin, n(%)	12 (22)	22 (27.5)	0.45
P2Y2 Inhibitor, n(%)	6 (11)	4 (5)	0.95
NOAC, n(%)	7 (12.5)	5 (6)	0.2
Diuretics, n(%)	8 (14)	21 (26)	0.1
PPI, n(%)	24 (43)	65 (81)	< 0.00001
Treatment during hospital stay			
Plaqunil, n(%)	10 (18)	16 (20)	0.8
Remdesivir, n(%)	5 (9)	38 (47)	< 0.00001
Mebeverine, n(%)	1 (1.8)	1 (1.25)	0.8
Lopinavir/ritonavir, n(%)	0	11 (14)	–
Clexane, n(%)	25 (45)	74 (93)	< 0.00001
VIT D, n(%)	13 (23)	40 (50)	0.002
Plasma, n(%)	7 (12.5)	44 (55)	< 0.00001
Steroids, n(%)	15 (27)	61 (76)	< 0.00001
Antibiotics, n(%)	7 (12.4)	32 (40)	0.001

Dyslipidemia defined as statin use; *CRF* chronic renal failure: GFR < 60 ml/min/1.73 m2; *CAD* coronary artery disease: diagnosed by coronary angiography or cardiac computer tomography; *CHF* congestive heart failure: recent hospitalization due to CHF in the presence of reduced ejection fraction (EF) or abnormal diastolic dysfunction; *CABG* coronary artery bypass grafting; *COPD* chronic obstructive pulmonary disease; *CVA* cerebrovascular accident; *ACE/ARB* angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; *CCB* calcium channel blockers; *NOAC* novel oral anticoagulants; *PPI* proton-pump inhibitors

thromboembolism in patients with severe Covid-19. It remains unknown whether antiplatelet medications should be part of the therapeutic regimen as well, but the high levels of IPF in patients with severe disease suggest that anti-platelet drugs may have a role in this group of patients. In addition, immature platelet indices may have a role in

Table 2 Immature platelets indices in according to Covid-19 disease severity

	Mild-Moderate Covid-19 n = 56	SEVERE Covid-19 n = 80	P Value
IPF (%)	4.2 (2.73–6.45)	5.8 (3.9–8.7)	P = 0.01
IPF ($\times 10^3$/μl)	4.2 (2.85–6.1)	5.1 (3.65–7.35)	P < 0.0001
Max. IPC ($\times 10^3$/μl)	10.9 (IQR 6.79–15.62)	15 (IQR 10.03–21.56)	P = 0.001

p values were calculated using Mann–Whitney test

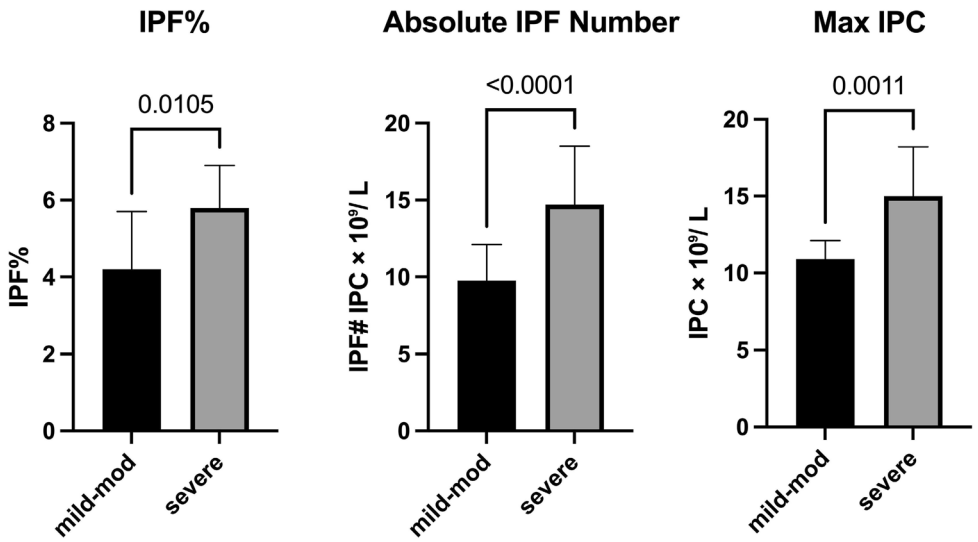

Fig. 1 Association between platelets indices and Covid-19 severity

Table 3 Factors associated with mortality in logarithmic analysis

Variable	LogWorth	p-value
Age	1.489	0.034
Body weight	1.123	0.075
Hemodialysis	1.053	0.089
IHD	0.928	0.118
Max IPC	0.479	0.321
Diabetes mellitus	0.289	0.515

IHD ischemic heart disease, *IPC* immature platelet count

risk stratification of patients with Covid-19, as maximal IPC was associated with the length of hospital stay—a marker of disease severity in this group of patients.

There are several limitations in our study. First it is a single center, non-randomized observational trial with a relatively small sample size. Second, there were differences in treatment protocols between the two groups. Third, about 6% of the patients changed their disease severity status during hospitalization.

Table 4 Factors associated with length of hospitalization

Source	LogWorth	p-value
Max IPC	1.338	0.045
Body weight	0.947	0.112
Hyperlipidemia	0.875	0.133
Hemodialysis	0.852	0.140
IHD	0.680	0.208
Age	0.677	0.210
Hypothyroidism	0.674	0.211
Smoker	0.625	0.236
CHF	0.546	0.284
Max IPF%	0.527	0.296
Hypertension	0.386	0.411
Diabetes mellitus	0.285	0.519

IHD ischemic heart disease, *CHF* congestive heart failure, *IPF* immature platelet fraction, *IPC* immature platelet count

Conclusions

Patients with severe Covid-19 disease appear to have enhanced platelet turnover, reflected by high level of immature platelets compared to patients with mild or moderate Covid-19 disease. This finding may have clinical

implications for risk stratification and anti-thrombotic treatment in patients with Covid-19.

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Author contributions AC and EY prepared the manuscript, including tables and figures, in consultation with EIL and AM and assisted by MC, GB, NKL, TM, EH performed the statistical analysis and created the draft figures. All the authors critically revised the manuscript and approved the final version to be published.

Declarations

Conflict of interest There are no relevant financial or non-financial competing interests to report.

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