bjh research paper

Immature platelets as a biomarker for disease severity and mortality in COVID-19 patients

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Received 26 February 2021; accepted for publication 30 May 2021

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Summary

COVID-19, caused by SARS-CoV-2, is a contagious life-threatening viral disease that has killed more than three million people worldwide to date. Attempts have been made to identify biomarker(s) to stratify disease severity and improve treatment and resource allocation. Patients with SARS-COV-2 infection manifest with a higher inflammatory response and platelet hyperreactivity; this raises the question of the role of thrombopoiesis in COVID-19 infection. Immature platelet fraction (IPF, %) and immature platelet counts (IPC, $\times 10^9$/l) can be used to assess thrombopoiesis. This study investigates whether the level of thrombopoiesis correlates with COVID-19 severity. A large cohort of 678 well-characterized COVID-19 patients was analyzed, including 658 (97%) hospitalized and 139 (21%) admitted to the intensive care unit (ICU). Elevated percentage IPF at presentation was predictive of length of hospitalization ($P < 0{\cdot}01$) and ICU admission ($P < 0{\cdot}05$). Additionally, percentage IPF at the peak was significantly higher among ICU patients than non-ICU patients ($6{\cdot}9 \pm 5{\cdot}1$ vs $5{\cdot}3 \pm 8{\cdot}4$, $P < 0{\cdot}01$) and among deceased patients than recovered patients ($7{\cdot}9 \pm 6{\cdot}3$ vs $5{\cdot}4 \pm 7{\cdot}8$, $P < 0{\cdot}01$). Furthermore, IPC at the peak was significantly higher among ICU patients than non-ICU patients ($18{\cdot}5 \pm 16{\cdot}2$ vs. $13{\cdot}2 \pm 8{\cdot}3$, $P < 0{\cdot}05$) and among patients on a ventilator than those not ($22{\cdot}1 \pm 20{\cdot}1$ vs.$13{\cdot}4 \pm 8{\cdot}4$, $P < 0{\cdot}05$). Our study demonstrated that elevated initial and peak values of percentage IPF and IPC might serve as prognostic biomarkers for COVID-19 progression to severe conditions.

Keywords: immature platelet, IPF, reticulated platelets, COVID-19, biomarker.

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) manifests as COVID-19, a systemic illness with multiorgan effects. Although the most common presentation is mild respiratory illness, the disease can progress to sepsis, acute respiratory failure, acute kidney injury and variable haematologic manifestations including cytopenias, disseminated intravascular coagulation and thrombosis (predominantly venous thromboembolism).[1,2] The overall mortality rate for in-hospital admissions for COVID-19 was 20·3% according to recently published data.[3] Identifying an accessible prognostic biomarker is critical in improving the determination of severe disease risk and potentially aiding in resource allocation.

Several biomarkers have been proposed to predict severity and outcomes.[4] However, the predictive role of each marker's measurement at presentation, including D-dimer, has not been consistent.[5] Recent studies showed SARS-CoV-2 alters platelet gene expression and activity resulting in platelet hyperreactivity, raising the question of the role of thrombopoiesis in COVID-19.[6,7] Therefore, evaluating a biomarker of thrombopoiesis, such as immature platelet fraction (IPF%, expressed as a percentage of the total platelet count) and IPC may have significant prognostic value. Circulating immature platelets, also known as reticulated platelets, are newly released from megakaryocytes and contain high amounts of cytoplasmic RNA.[8,9] Measuring IPF% reflects reticulated platelet numbers and may help to distinguish increased peripheral platelet destruction from bone marrow failure.[10] IPF% has been shown to be a predictive marker for severity in sepsis as well as cardiovascular death and major adverse cardiovascular events in patients with coronary artery disease

First published online 11 July 2021
doi: 10.1111/bjh.17656

and acute coronary syndrome.[10–13] Several studies have also shown that immature platelets may be a novel predictor of impaired response to anti-platelet therapy.[13–16]. IPC might better represent a real-time response of bone marrow activity and response to physiologic stressors demonstrating thrombopoiesis.[8] IPF% and IPC have been shown to reflect ongoing platelet production by the marrow in thrombocytopenia. Indeed, some reports indicate the usefulness of IPC in the prediction of imminent platelet recovery in chemotherapy-induced thrombocytopenia and in differentiating acute immune thrombocytopenia and thrombocytopenia due to acute leukaemia, a bone marrow-infiltrative process.[17–19] Notably, IPC appears not to be altered by platelet transfusions.[20]

This study aims to evaluate the relationship between clinical outcomes in COVID-19 patients and immature platelets.

Patients and methods

Study design

This study describes SARS-COV-2-infected patients evaluated at the University of Texas Southwestern Medical Center between May 2020 and January 2021. The COVID-19 patient registry has established a multiple-variable data collection to study the pathogenesis and natural history of SARS-COV-2 infection. This registry is comprised of patients from the UTSW Institutional Review Board-approved natural history protocol emphasizing cross-sectional data collection. The current study included adult patients who tested positive for SARS-COV-2 infection and had IPF% measurements, yielding a sample size of 678 patients. Variables surveyed included age, gender, race, medical comorbidities, length of stay, smoking history, dexamethasone use, remdesivir treatment history, history of anti-thrombotic agents, platelet count and IPF%.

Immature platelet fraction measurement

Immature platelet fraction was measured using a Sysmex XN-9100 automated haematology analyzer, with platelet gating using forward light scatter and identification of immature platelets by staining with polymethine and oxazine fluorescent dyes (Sysmex America, Lincolnshire, IL, USA). These fluorescent dyes bind to and fluorescently stain RNA, allowing the separation of immature (RNA-rich) and mature platelets. IPF is expressed as a percentage (reference range: 1·1–6·1%), representing the ratio of immature platelets to the total number of platelets × 100. The initial presentation (henceforth, initial) and peak (highest value) values of IPF% and initial and minimum platelet counts were presented. IPC is calculated by multiplying the IPF% by the platelet count and expressed in units 10^9/l.

Statistical methods

Descriptive statistics were presented for all variables. COVID-19 severity outcomes were defined as in-hospital death, intensive care unit (ICU) admission, length of stay in days and ventilator requirement duration in days. Two-sided Wilcoxon rank tests were conducted to examine COVID-19 severity group differences in thrombopoiesis measures including initial, peak and minimum values of IPF%, IPC, platelet counts and age at contact. Mantel–Haenszel chi-squared analysis was used to test COVID-19 severity outcome associations with categorical variables including baseline disease conditions. While P value <0·05 was used as a statistical significances criterion, results with $0{\cdot}05 < P < 0{\cdot}1$ were also reported. Logistic regression models were conducted to test independent associations of IPF% and platelet counts with severity outcomes adjusting for confounding factors. The confounding factors included are age, sex, race, pre-existing conditions of chronic kidney disease (CKD) and coronary artery disease (CAD) and dexamethasone use. The final set of covariates included in the model was determined by adding covariates systematically guided by both statistical significance of included covariates and Akaike Information Criteria (AIC). AIC calculated fit of goodness based on statistical significance and multicollinearity of covariates in the model and smaller AIC values were better. SAS version 9·4 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

Of a total of 678 patients, 52% were males. The average age was 62 ± 17 years old. Approximately a quarter of the study cohort were black (27%) and hispanic (25%) and 40% were white. Sixty-five percent of the patients had existing hypertension, while 44% had diabetes. Table I depicts baseline characteristics. The majority (83%) received dexamethasone during hospitalization.

Of the 678 patients, 97% (n = 658) were hospitalized and 56 patients died (8%). Patients who died, were admitted to ICU or on ventilator had significantly higher rates of existing conditions of CAD and CKD and were more likely to be on dexamethasone (Table I).

Peak IPF% values among deceased patients were significantly higher than those who were alive (Table II). The deceased had a tendency toward a higher value of initial IPF % than those who were alive (6·4 vs. 4·8; P = 0·09). Logistic regression adjusted for confounders showed significant associations of elevated IPF% both at initial presentation and at peak with increased risk of mortality (Fig 1). Both initial and peak IPF% were positively correlated with length of hospitalization (Table III).

Among those hospitalized (n = 658), 21% were admitted to ICU with an average length of stay of 11 ± 12 days. Initial and peak IPF% values were significantly higher among those admitted to ICU than those who were not (5·8 ± 4·6 vs 4·7 ± 2·6, $P < 0{\cdot}05$ for initial IPF% and 6·9 ± 5·1 vs 5·3 ± 8·4, $P < 0{\cdot}01$ for peak IPF%, Table II). Logistic regression adjusted for confounders showed that higher initial and

Table I. Baseline characteristics, IPF (%) and platelet counts of the study cohort (n = 678).

Characteristics		All	In-house mortality			Admitted to ICU among hospitalized			Ventilator use among hospitalized		
			Yes (n = 56)	No (n = 622)	P*	Yes (n = 139)	No (n = 519)	P*	Yes (n = 79)	No (n = 579)	P*
Age	Years (mean±SD)	61·5 ± 16·7	70·2 ± 12·9	60·8 ± 16·7	<0·01	63·8 ± 15·7	60·7 ± 16·8	0·06	62·8 ± 13·9	61·4 ± 17·0	0·57
Gender	Males (n, %)	355 (52·4%)	38 (67·9%)	317 (51·0%)	0·02	81 (58·3%)	266 (51·3%)	0·14	50 (63·3%)	305 (50·9%)	0·04
Race/Ethnicity	White (n, %)	264 (38·9%)	24 (42·9%)	240 (38·6%)	0·36	51 (36·7%)	204 (39·3%)	0·90	33 (41·8%)	231 (38·6%)	0·75
	Black (n, %)	182 (26·8%)	6 (10·7%)	176 (28·3%)		26 (18·7%)	147 (28·3%)		15 (19·0%)	167 (27·9%)	
	Hispanics (n, %)	171 (25·2%)	18 (32·1%)	153 (24·6%)		48 (34·5%)	121 (23·3%)		22 (27·9%)	149 (24·9%)	
	Asians/American Indians/Pacific islanders (n, %)	17 (2·5%)	4 (7·1%)	13 (2·1%)		5 (3·6%)	12 (2·3%)		5 (6·3%)	12 (2·0%)	
	Other (n, %)	44 (6·5%)	4 (7·1%)	40 (6·4%)		9 (6·5%)	35 (6·7%)		4 (5·1%)	40 (6·7%)	
Active smoker	Yes (n, %)	17 (2·5%)	1 (1·8%)	16 (2·6%)	0·72	5 (3·6%)	10 (1·9%)	0·24	3 (3·8%)	14 (2·3%)	0·44
Presence of diabetes mellitus	Yes (n, %)	297 (43·8%)	26 (46·4%)	271 (43·6%)	0·68	62 (44·6%)	228 (43·9%)	0·89	34 (43·0%)	263 (43·9%)	0·88
Presence of hypertension condition	Yes (n, %)	443 (65·3%)	43 (76·8%)	400 (64·3%)	0·06	93 (66·9%)	337 (64·9%)	0·66	54 (68·3%)	389 (64·9%)	0·55
CAD	Yes (n, %)	119 (17·6%)	23 (41·1%)	96 (15·4%)	<0·01	34 (24·5%)	82 (15·8%)	0·02	24 (30·4%)	95 (15·9%)	<0·01
CHF	Yes (n, %)	102 (15·0%)	15 (26·8%)	87 (14·0%)	0·01	25 (18·0%)	74 (14·3%)	0·28	18 (22·8%)	84 (14·0%)	0·04
Presence of COPD	Yes (n, %)	57 (8·4%)	7 (12·5%)	50 (8·0%)	0·25	9 (6·5%)	47 (9·1%)	0·33	6 (7·8%)	51 (8·5%)	0·78
Asthma	Yes (n, %)	98 (14·5%)	6 (10·7%)	92 (14·8%)	0·41	15 (10·8%)	79 (15·2%)	0·19	8 (10·1%)	90 (15·0%)	0·24
CKD	Yes (n, %)	128 (18·9%)	20 (35·7%)	108 (17·4%)	<0·01	39 (28·1%)	84 (16·2%)	<0·01	23 (29·1%)	105 (17·5%)	0·01
Cancer	Yes (n, %)	108 (15·9%)	21 (37·5%)	87 (14·0%)	<0·01	28 (20·1%)	73 (14·1%)	0·08	14 (17·7%)	94 (15·7%)	0·64
On dexamethasone	Yes (n, %)	562 (82·9%)	53 (94·6%)	509 (81·8%)	0·01	126 (90·1%)	431 (83·0%)	0·03	77 (97·5%)	485 (81·0%)	<0·01

CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IPF, immature platelet fraction.
*Group differences in continuous and categorical variables were tested using a two-sided Wilcoxon rank-sum test and Mantel chi-squared statistics respectively.

Table II. IPF (%,) IPC and platelet count by severity outcomes.

Characteristics		All	In house mortality			Admitted to ICU among hospitalized			Ventilator use among hospitalized		
			Yes (n = 56)	No (n = 622)	P*	Yes (n = 139)	No (n = 519)	P*	Yes (n = 79)	No (n = 579)	P*
IPF (%) Initial presentation	Mean±SD	4·9 ± 3·2	6·4 ± 5·7	4·8 ± 2·8	0·09	5·8 ± 4·6	4·7 ± 2·6	0·03	5·8 ± 4·3	4·8 ± 3·0	0·06
IPF (%) Peak	Mean±SD	5·3 ± 3·5	7·9 ± 6·3	5·4 ± 7·8	<0·01	6·9 ± 5·1	5·3 ± 8·4	<0·01	7·5 ± 5·0	5·4 ± 8·1	<0·01
High IPF at Initial presentation (>6·1%)	High (n, %)	164 (24·2%)	17 (30·4%)	147 (23·6%)	0·2608	44 (31·7%)	113 (21·8%)	0·02	57 (34·2%)	137 (22·9%)	0·04
High IPF at peak (>6·1%)	High (n, %)	191 (28·2%)	27 (48·2%)	164 (26·4%)	<0·01	59 (42·4%)	125 (24·1%)	<0·01	40 (50·6%)	151 (25·2%)	<0·01
IPC (x10^9/l) at initial presentation	Mean±SD	10·0 ± 6·1	11·0 ± 10·6	10·6 ± 6·2	0·31	12·1 ± 9·1	10·2 ± 5·6	0·41	12·5 ± 9·7	10·4 ± 6·0	0·50
IPC (×10^9/l) at peak	Mean±SD	13·4 ± 9·7	15·9 ± 16·8	14·0 ± 10·0	0·56	18·5 ± 16·2	13·2 ± 8·3	0·045	22·1 ± 20·1	13·4 ± 8·4	0·03
Platelet count (×10^9/l) at initial presentation	Mean±SD	222·2 ± 98·9	180·9 ± 97·4	226·0 ± 98·3	<0·01	219·7 ± 104·5	224·0 ± 98·5	0·60	221·5 ± 111·9	223·3 ± 98·0	0·07
Platelet count (×10^9/l) at peak	Mean±SD	269·1 ± 127·3	223·1 ± 119·2	273·3 ± 127·3	0·01	278·9 ± 136·1	268·8 ± 126·0	0·30	292·4 ± 137·6	268·0 ± 126·7	0·80
Platelet count (×10^9/l), minimum	Mean±SD	213·8 ± 98·7	158·4 ± 107·1	218·8 ± 96·7	<0·01	193·4 ± 101·8	220·0 ± 98·2	<0·01	185·6 ± 110·4	218·3 ± 97·4	<0·01

ICU, intensive care unit; IPC, immature platelet counts; IPF, immature platelet fraction.
*Two-sided Wilcoxon rank-sum test.

peak IPF% values were positively associated with increased risk of ICU admission (Fig 1).

Twelve percent of patients who were hospitalized (n = 79) required mechanical ventilation. Peak IPF% values among patients on mechanical ventilation were significantly higher than in those who were not on mechanical ventilation (Table II). Initial IPF% among those on mechanical ventilation had a tendency towards a higher value than among those not on mechanical ventilation (5·8 vs. 4·8; P = 0·06). Logistic regression results adjusted for confounding factors showed significant associations of initial and peak IPF% with increased risk of requiring mechanical ventilation (Fig 1).

Increased peak IPF% was significantly associated with both longer stay in ICU and longer duration on mechanical ventilation (Table II), while there was no significant correlation of initial IPF% with either ICU length of stay and duration of ventilator use among those who required ventilator support. Logistic regression results adjusted for confounding factors showed a significant association of initial IPF% with increased risk of being on mechanical ventilation [odds ratio (OR) 1·08, 95% confidence interval (CI) 1·02–1·15].

IPC (×10^9/l) at initial presentation was similar across all three severity outcome groups and not significantly correlated with length of hospital stay.

Maximum IPC (×10^9/l) was significantly higher among those admitted to ICU and who required ventilator than among those who were not (Table II) and positively correlated with length of hospitalization (Spearman correlation; Table III). After adjusting for confounders, maximum IPC was significantly associated with increased risk of ICU admission (OR 1·05, 95% CI 1·03–1·07) and requiring ventilator during hospitalization (OR 1·06, 95% CI 1·04–1·08). However, maximum IPC was not associated with in-hospital death.

A third of patients were on anti-platelet agents and nearly all were on an anti-coagulant (99%). Thirty-nine percent of patients were placed on prophylactic dose anti-coagulation and 61% were placed on therapeutic dose anti-coagulation. Initial, peak and minimum platelet counts were significantly lower among COVID-19 patients who died compared to those who survived (Table II). Initial or peak platelet counts were not associated with either hospitalization or ICU admission, while lower minimum platelet counts were significantly associated with ICU and mechanical ventilation use (Table II). After adjusting for confounders, initial (OR 0·994, 95% CI 0·99–0·998) and peak platelet counts were significantly associated with decreased risk of mortality (OR 0·996, 95% CI 0·993–0·999), although not associated with ICU admission or ventilator use. Lower minimum platelet counts increased odds of mortality (OR 0·99, 95% CI 0·989–0·997), ICU admission (OR 0·998, 95% CI 0·996–1·00) and ventilator use (0·997, 95% CI 0·994–1·00).

Minimum platelet counts were significantly lower among the patients admitted to ICU than those not (Table II) and negatively correlated with length of hospital stay (Spearman correlation −0·21, P < 0·01; Table III).

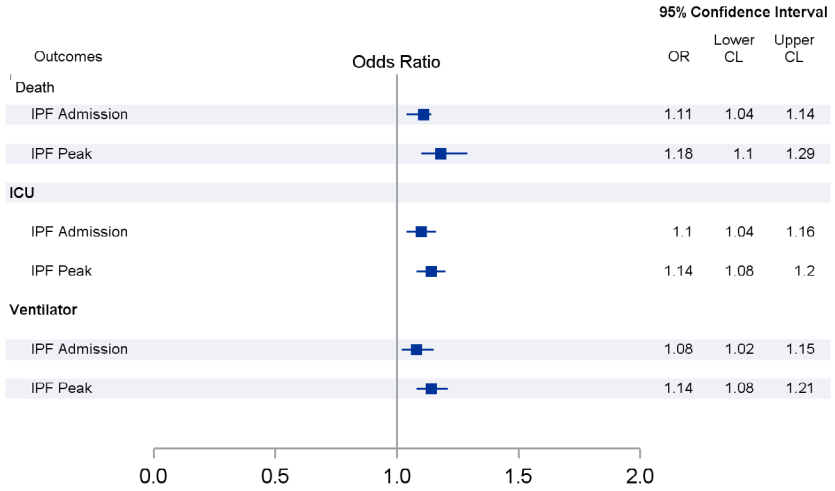

Fig 1. Logistic regression results of immature platelet fraction (IPF, %) on death, intensive care unit (ICU) and mechanical ventilation requirement. The 95% confidence interval [lower confidence limit (CL)–upper CL] of odds ratios (OR) does not include '1' and is statistically significant under $\alpha = 0{\cdot}05$. [Colour figure can be viewed at wileyonlinelibrary.com]

Discussion

Biomarkers predicting severity and outcomes in COVID-19 patients have demonstrated inconsistent results. Higher IPF %, reflecting increased thrombopoiesis, correlated with active and severe inflammatory conditions in our prior study.[8] This relationship has been speculated to be related to IL-6-mediated inflammation, which is a strong stimulator of platelet production.

In our current study of a large, hospitalized cohort of COVID-19 patients, we found that higher initial and peak IPF% values were significantly associated with severe outcomes in several significant aspects: ICU admission, mechanical ventilation requirement, length of hospital stay and in-house mortality. Likewise, maximum IPCs were significantly associated with severe outcomes in ICU admission and mechanical ventilation requirement during hospitalization. Although patients with COVID-19-associated thrombocytopenia typically have only mild thrombocytopenia, we also found that lower platelet counts at initial presentation and during hospitalization were strongly associated with in-house mortality. In contrast to IPF%, initial and peak platelet counts were not associated with either hospitalization or ICU outcomes.

Our study confirmed the findings of a recent much smaller study regarding mortality.[21] Another recent study has demonstrated an increased IPF% at admission and during hospitalization in COVID-19 patients compared to other patients with acute myocardial infarction (also known to have increased platelet turnover), but did not find that IPF% was predictive of disease severity.[22] However, our larger study was able to demonstrate that IPF% may be predictive of disease severity measured by need for ICU admission or ventilator use.

We did not find any significant association between immature platelet indices and COVID-19 disease severity measured by the quick COVID-19 Severity Index (qCS; Table SI). This may be secondary to the limitations of the qCSI score as this score is most useful for predicting the respiratory decompensation 24 h after admission. Therefore, it may not be reflective of the patient's entire hospitalization course.[23] Furthermore, existing conditions of CAD and CKD also appear to have more severe COVID-19 disease manifestations.

Our results support the hypothesis that ongoing inflammation in COVID-19 stimulates thrombopoiesis in the most severe patients. This is likely mediated by pro-inflammatory cytokines such as IL-6, IFN and IL-17 which directly and indirectly stimulate thrombopoiesis. In this scenario, higher platelet production may be an acute-phase reactant and a biomarker of COVID-19-associated inflammation. Another possibility is that immature platelets play an actual pathophysiologic role in the process of immune response to SARS-CoV-2 by increased platelet–neutrophil and platelet–T cell aggregate formations, which supports the growing evidence of platelet-mediated immunity.[6,7]

The principal advantage of adopting IPF% and IPC as a prognostic marker is accessibility. The IPF% and IPC can be attained along with the routine complete blood count (CBC) from haematology analyzers with minimal additional cost or technician's involvement. This is especially important given the COVID-19-related testing burden on laboratories and in institutions without the resources for the rapid development of new assays or measurement of cytokine profiles. Additionally, IPF% and IPC can be measured in blood samples up to 24 h after collection.[24]

In conclusion, our study shows that IPF%, IPC and platelet counts may serve as easily accessible prognostic

Table III. Correlations (Spearman ρ) between IPF(%), IPC and Platelet counts with the length of stay in the hospital, ICU and on a ventilator.

		IPF (%)		IPC ($\times 10^9$/l)		Platelets ($\times 10^9$/l)		
	Mean±SD	Initial presentation	Peak	Initial presentation	Peak	Initial presentation	Peak	Minimum
Days*								
Length of hospital stay* (n = 576)	8·3 ± 7·9	0·15 ($P < 0·01$)	0·22 ($P < 0·01$)	0·01 ($P = 0·94$)	0·23 ($P < 0·01$)	−0·13 ($P < 0·01$)	0·11 ($P < 0·01$)	−0·21 ($P < 0·01$)
ICU stay* (n = 123)	11·3 ± 11·6	0·01 ($P = 0·87$)	0·22 ($P = 0·02$)	0·05 ($P = 0·72$)	0·20 ($P = 0·16$)	−0·03 ($P = 0·74$)	0·12 ($P = 0·20$)	0·09 ($P = 0·29$)
On ventilator (n = 79)	15·1 ± 14·2	−0·04 ($P = 0·74$)	0·19 ($P = 0·09$)	0·05 ($P = 0·78$)	0·18 ($P = 0·31$)	−0·07 ($P = 0·56$)	0·10 ($P = 0·39$)	0·06 ($P = 0·60$)

ICU, intensive care unit; IPC, immature platelet counts; IPF, immature platelet fraction; ρ = Spearman rank correlation.
*There are missing observations.

biomarkers that predict severe outcomes among COVID-19 patients. These findings support the novel use of IPF% and IPC to assist in the clinical assessment of COVID-19 patients and resource allocation. Further studies are needed to characterize the role of immature platelets in COVID-19 pathophysiology and possible treatment intervention and its feasibility as a biomarker for hospital admission and thrombosis prediction.

Acknowledgements

We would like to thank Clements University Hospital/UT Southwestern Medical Center ICU team, Mereeja Varghese from the UTSW IT department and Monika Ruscheinsky from the UTSW Department of Pathology for their expert assistance in this study.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Correlations (Spearman ρ) between immature platelet fraction (IPF, %), immature platelet counts (IPC) and platelet counts with quick COVID-19 Severity Index (qCSI).

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