Immature Platelet Fraction and COVID-19: *Maturing* prognostic links!

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Abstract

Prompted by the combination of an ever-evolving comprehension of the platelet activation as a pivotal perpetuator of an ongoing systemic inflammatory process and an encouraging literature on the prognostic role of immature platelet fraction (IPF) in septic and prothrombotic settings, we present an elaborated account of the possible prognostic links between IPF and Coronavirus disease 2019 (COVID-19).

Keywords
- COVID-19
- Immature platelet fraction
- Platelets
- Prognostication
- SARS-CoV-2 infection
- Sepsis
- Thromboembolic events

Introduction

Platelets (miniature anucleate cells) are peculiarly intriguing with regard to the diversity of their pathobiophysiological roles, extending much beyond hemostasis-thrombosis to the evolving reputation as immune mediators, staging the complex interactions between the immune system, leukocytes, endothelial cells, and the clotting cascade.[1,2]

As an extension of the same, the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) and platelet communion continues to captivate an increasing attention of the fraternity. This becomes all the more pertinent amid an enhanced acknowledgment of the vascular and coagulation links of the ongoing Coronavirus disease 2019 (COVID-19)-related endotheliitis, which is the cornerstone of lethal thromboembolic consequences.[3-5]

Background

While the platelet-related parameters such as mean platelet volume (MPV) and MPV/platelet count ratio have been investigated for their ability to augment the differentiation of COVID-19 from the influenza pneumonia and for the severity prediction in COVID-19 with promising results, the immature platelet fraction (IPF) has received much lesser scrutiny as the platelet activation readouts of prognostic importance in COVID-19.[6,7]

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Herein, IPF denotes the proportion of the total platelet pool constituted by the young immature reticulated cells and constitutes an important, inexpensive, an automated hematological marker of an accentuated platelet turnover.[1,7] Quite remarkably, the combined account of the initial encouraging literature on the prognostic role of IPF, in septic and prothrombotic clinical settings, endorses a strong case for exploring the predictive abilities in COVID-19.[7-12]

IPF in a Septic Setting

Wu and colleagues demonstrated the prognostic role of reticulated platelets percentage (RP%), wherein a higher RP% emerged as a major predictor of mortality with an area under the curve of 0.867 in their prospective evaluation of a septic cohort.[8] The depiction of the predictive value was robust to a subsequent multilogistic regression analysis. Considering the pivotal role of microcirculatory alterations and coagulation disturbances in sepsis, Muronoi et al delineated an extended role of the admission-IPF in predicting subsequent disseminated intravascular coagulation (DIC) and poor outcomes.[9]

Interestingly, Park and the group outlined the highest sensitivity and specificity of IPF compared with biomarkers such as lactate, C-reactive protein (CRP), and procalcitonin, in distinguishing the septic and nonseptic population while studying 312 general ward patients.[10] However, the predictive value of IPF declined in delineating the sepsis severity in their study.**<sup>**[10]

IPF in a Prothrombotic Setting

In context of prothrombotic setting, platelet activation has been extensively studied in acute coronary syndromes (ACS) and strokes. The immature RPs, newly released into the circulation from the marrow by the megakaryocytes, possess highly dense granular and residual messenger ribonucleic acid (mRNA) content. These immature forms are proposed to demonstrate an elevated hyperactivity and an enhanced thrombotic propensity, as delineated in their association with thrombotic events in cardiovascular and cerebrovascular settings.[1,7] IPF has emerged as an independent predictor of major adverse cardiovascular event and cardiovascular mortality in the ACS subset.[11,12]

At the same time, the recent literature on the role of RP% as a predictor of perioperative myocardial injury (PMI) is noteworthy, particularly when PMI is described to be associated with poor outcomes.[13] Meershoek and colleagues conducted an observational cohort study comprising 2289 patients undergoing major noncardiac surgery wherein the incidence of PMI (troponin I > 0.06 mg/L) and the 30-day mortality was significantly higher for subjects with a preoperative RP ≥ 2.82% (36.1%; 8.6%, respectively) in contrast to those demonstrating a normal preoperative RP percentage (28.3%; 3.6%, respectively).[14]

Extrapolating the Links to COVID-19

While a COVID-19 infection also incurs a considerable prothrombotic risk, the seminal work of Cohen and colleagues on the prospective comparison of IPF among 47 COVID-19 patients, 100 acute myocardial infarction (AMI) patients, and 64 stable cardiovascular disease predisposed patients, is impressive.[4,5,7,15-18] They described that IPF on admission was significantly higher in the COVID-19 cohort (4.8%; interquartile range [IQR]: 3.4–6.9) compared with the stable cohort (3.5%; IQR: 2.7–5.1) and comparable to the AMI cohort (4.55%; IQR: 3.0–6.75). Similarly, the maximal in-hospital IPF was also substantially higher for the COVID-19 and the AMI group of patients in contrast to the stable cardiovascular patients.[7]

Although their study does not suggest an association of IPF with COVID-19 disease severity, a small sample size of COVID-19 patients with severe disease could have very well precluded the power of the study to assess the same. Nevertheless, given the fact that the three groups were well-matched for their cardiovascular predisposition, a quantitative estimation of enhanced platelet turnover can assist in the management of COVID-19 patients, particularly backed by a motivated exploration of thromboembolic events in COVID-19 patients with an elevated IPF.[7]

Talking primarily of acute respiratory distress syndrome (ARDS, also a severe complication of sepsis), autopsies of patients succumbing to ARDS have revealed accentuated platelet accumulation in the pulmonary vasculature.[19] Alongside the demonstration of platelet activation in the bronchoalveolar lavage of ARDS patients, there is understandably an enhanced likelihood of encouraging results emerging from further exploration of the prognostic links between IPF and COVID-19.[20]

Discussion

Several additional factors surface on a closer evaluation of this research area:

(i). IPF or RP% is a readily available parameter subject to flow cytometric or hematological analysis, given the large size, high granularity, and ribonucleic acid content (augmenting fluorescence signal) of these immature forms and often considered superior to the MPV as a platelet immaturity index.[1]

(ii). Moreover, the intriguing combination of thrombocytopenia and prothrombotic events in COVID-19 raises a very likelihood of platelet hyperactivity being at the heart of the matter.[7]

(iii). Ahead of the prognostic relevance, IPF and related indices have also been outlined to be predictors of antiplatelet therapy response.[21]

(iv). Recognition of IPF-based high risk of prothrombotic events can potentially assist in individualizing the antithrombotic regimen in COVID-19.

Conclusion

The aforementioned discussion suggests a possible role of cost-effective platelet activation parameters like IPF in parsimonious prognostication of COVID-19, with the subsequent risk-based implementation of optimally individualized management scheme.

Authors' Contributions

JJ: conceptualization and analysis.
RM: conceptualizing and writing the original draft.
NM: supervising, and reviewing and editing the manuscript.

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Consent for Publication

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Competing Interests

The authors declare that they have no competing interests.

Conflict of Interest

We do not have any conflict of interest, or any commercial or financial interest in this material, and agree to abide by the rules of your journal regarding publication of this article.

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