bjh commentary

Immature platelets in COVID-19 infection

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This is a commentary on Welder *et al.* Immature platelets as a biomarker for disease severity and mortality in COVID-19 patients. *Br J Haematol.* 2021;**194**:530–536.

Pandemics have become more frequent events beginning in the latter part of the 20th century due to the brevity of time needed to travel between distant regions of the world. The current COVID-19 or SARS-CoV-2 pandemic exemplifies the challenges facing healthcare delivery systems and health practitioners across the world, not only to treat, but also to use every available tool to diagnose and predict those patients more likely to develop complications related to the infection. Attempts to treat have included looking at old approaches of passive immunity in the form of COVID-19 convalescent plasma (CCP), to help those battling the disease despite limited knowledge of its potential efficacy.[1] Unfortunately, the use of CCP has shown in randomised clinical trials, limited-to-no survival benefit to recipients, even when the plasma contained high antibody titres.[2] It is in this climate that, along with basic science research, observational studies of COVID-19 patients can offer additional information of ways in which they could be risk-stratified.

Thromboembolic complications related to COVID-19 infection cause in-hospital challenges in a significant number of such patients and are, thus, responsible for substantial mortality.[3] In this setting, platelets in some COVID-19 patients establish not only a prothrombotic, but also a pro-inflammatory milieu in which a number of coagulation irregularities occur, as shown by prolongation of prothrombin and activated partial thromboplastin times as well as concomitant thrombocytopenia. This suggests that analysing platelets more closely could be a clinical approach to determining patients who are at greater risk.[4,5] Along these lines, reports indicating that remaining platelets of COVID-19 patients are more prone to respond to agonists in a background of a higher mean platelet volume, which is a reflection of a higher number of larger platelets in circulation and higher expression of P selectin,[6] argue that looking at immature platelets is a logical step towards understanding platelet count changes in COVID-19 patients.

Immature platelets represent the youngest platelets newly released into circulation that are larger and with a greater content of ribonucleic acids compared to mature circulating platelets.[7] It is these differences that are readily detectable by current modern hematology analysers with fluorescence capability that is reported as a percentage of the total platelet count, the immature platelet fraction (IPF). These are equivalent to the reticulated platelets reported by different analysers. Importantly, testing for immature platelets does not delay results of a complete blood count since they can be obtained at the same time. This immature platelet count (IPC) is currently of interest in the literature in several clinical settings where platelet count disorders lead to production changes in the bone marrow. Consequently, in consumptive processes the marrow can either produce a higher number of immature platelets in response to thrombocytopenia or fail to respond, as seen in marrow failure or diseases where compensation is impaired.[8,9]

It is with this in mind that the work of Welder *et al.* describing their findings looking at the interplay of lower platelet counts in COVID-19 patients and immature platelets at time of hospital admission, how they quantitatively changed when patients required subsequent intensive care unit (ICU) admission with or without ventilator support, and when disease severity resulted in death, is an interesting and promising report.[10] Parameters, including comorbidities that could also be predictive of disease outcomes, were also analysed by these investigators. Utilising a large cohort of 678 patients of whom the vast majority 658 (97%) required hospitalization due to the infection and received dexamethasone, they saw that increases in the IPF was predictive of patients who would end up requiring longer hospitalization (5·8% vs. 4·7%). This increase appeared not to be relevant to ethnicity or age. Furthermore, peak increases in IPF and IPC were also predictive of those patients who required ICU admission and longer duration of ventilator support. Finally, IPF increases also predicted those patients succumbing to disease

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complications since their IPF was higher at every point during hospitalization, thus indicating a constant increased output in immature platelets.

To understand these findings, these IPF and calculated IPC increases need to be put in the context of the thrombocytopenia at presentation. These patients' lower platelet counts ($180{\cdot}9 \times 10^9$/l vs. 226×10^9/l) may drive a higher output from the marrow of immature platelets to compensate for peripheral losses. In the case of those patients with greater coagulopathy and thrombocytopenia, IPF and IPC could be increased because of the higher level of platelet consumption,[11] and this potentially translates into a likelihood that these patients' presentation is of greater severity. It must be said that the IPF/IPC were collected at the time of patient's hospitalisation and analysed post hoc once sufficient data from a large number of patients was collected. Nevertheless, despite its retrospective nature, this study may provide an additional way of testing and giving insight into those patients who may have increased complications later in their disease course. It would be of interest next to establish if these counts are included as part of diagnostic algorithms, and if the earlier intervention in patients undergoing these IPF/IPC changes result in decreased ICU admissions and, potentially, mortality? This ought to be the focus of future investigation.

In summary, as the numbers of COVID patients in many countries appear to be on the decline due greater access to vaccination, others are seeing second and third infection waves in which the contagiousness of the emergent variants makes the effectiveness of current vaccines a matter of concern. Importantly, the data presented by this group as well as the lower platelet counts of these patients show that corresponding changes by the bone marrow in immature platelets production may be indicative of the body's response to platelet decreases during COVID-19 infection.

Conflict of interest

The author declares no conflict of interest.

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