TITLE PAGE

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From Hematologist's desk: The effect of COVID-19 on blood system

Dear Editor,

Fan et al critically studied the difference in hematological parameters between the ICU vs non-ICU COVID-19 cases (1). While the study underscores the pertinent hematological parameters which might help the treating physicians to anticipate ahead of time regarding the potential need of the intensive level of care in any case, it would certainly benefit from further discussion and refinement.

Concern over coagulation abnormality in COVID-19 patients: Fan et al did not discuss the coagulation parameters of their patient series (1). Currently, the exact significance of coagulopathy in COVID-19 patients is yet to be determined. But preliminary results from recent studies have shown that a high D-dimer value correlates with ICU requirement and higher mortality when compared to individuals with normal/mild elevation of the D-dimer levels (2). Tang et al recently reviewed 183 cases of COVID-19 patients and studied their coagulation pattern (3). They found

that the 21 non-survivors had significantly higher D-dimer values (p <.001), fibrin degradation product (FDP) values (p <.001), longer prothrombin time [(PT in seconds) p <.001] values when compared to survivors at admission. Fibrinogen levels [(g/L), p=0.149], antithrombin activity [AT (%), p = 0.096], and activated partial thromboplastin time [(APTT in seconds), p=0.096] were not significantly different between the two groups. Also, at follow up during the hospital stay, Tang et al found 71.4 % of non-survivors having disseminated intravascular coagulation (DIC) as compared to only 0.6% of survivors.

Lack of data of thrombosis in COVID-19 patients: Thrombosis is another hematological challenge while managing sick patients. Did any patient from Fan et al's study develop cerebrovascular thrombosis, deep venous thrombosis (DVT) or pulmonary embolism (PE)? Mao et al studied neurological manifestations of 214 COVID-19 patients and reported a 4.5% incidence of cerebral infarction (3). The incidence of DVT, PE or thrombosis anywhere else in the body has not been studied well till now in COVID-19 patients. Previous studies on SARS patients have shown the incidence of DVT and PE in 20.5% and 11.5% cases respectively. Hence, considering the fact that both SARS and SAR-CoV-2 infection has a similar pathophysiology and receptor recognition on human cells (ACE-2 receptor protein), it is likely to have similar numbers with regards to incidents of thromboembolism. Most of the studies till now on sick patients have focused on ARDS, acute kidney injury, multi-organ failure but lack data on DIC. We discuss this because diffuse

microvascular damage of lungs secondary to DIC could ultimately lead to ARDS and death of a COVID-19 patient.

Accessing the risk of bleeding in COVID-19 patients: Fan et al mentioned that the medium nadir platelet counts remained in the normal range in both the ICU and non-ICU patients (1). Did any of the patients had increased bleeding episodes? Apart from the disruption in the coagulation system, dysfunctional platelets can also contribute to increased bleeding despite being in the normal range. Till now, data on thrombocytopenia in COVID-19 patients are variable but the incidence of thrombocytopenia could go to as high as 57% amongst non-survivors (2).

Knowledge about the other endemic disorders affecting hematological parameters: Fan et al mentioned that none of their patients were moderately or severely thrombocytopenic. They also mentioned the association of severity of thrombocytopenia with endemic viral illnesses in Singapore, for instance, dengue fever. We second this thought about various other endemic viral illnesses that could coexist or covert the true diagnosis of COVID-19 disease. Yan et al from National University Health System, Singapore recently published a case series of two patients who presented to the hospital for fever and myalgia (4). On evaluation, they were found to be mildly thrombocytopenic and tested positive for dengue fever. After symptomatic treatment, they were discharged with advice for close follow. However, both the patients deteriorated, and they came back to the hospital. This time, their platelet counts worsened further with an additional note of new-onset lymphopenia. This prompted do run a test, RT-PCR for COVID-19 which came back

positive for both the patients. A repeat check for the dengue test was negative. This report by Yan et al suggests that thrombocytopenia severity could be extremely variable and other clues like clinical deterioration and lymphopenia should be looking for (4).

Possible mechanism of impact of coronavirus on hematopoiesis: Scientists have studied for the possible mechanisms of thrombocytopenia and lymphopenia in previous coronavirus outbreaks (5). Few of the proposed mechanisms in the past are [1] virus directly infecting the blood/bone marrow stromal cells via interaction with CD13 or CD66 or [2] inducing immune complexes and antibodies leading to damage to the hematological cells. Both the adhesion molecules, CD 66a, and CD13 are expressed in human bone marrow CD34+ cells and platelets. CD66a but not CD 13 is found in activated lymphocytes as well. In addition to this, medications used for the treatment of COVID-19 like steroids can also cause lymphopenia. It would be beneficial to know how many patients in Fan et al's study received corticosteroids?

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Recognizing special population upfront: It would be beneficial to know how many patients in Fan et al's study had hemato-oncological disorders at baseline if any? Knowing the background history of any benign hematological disorders like immune thrombocytopenia, or any cancer receiving chemotherapy affecting the bone marrow hematopoiesis is essential. This will help us to understand if the thrombocytopenia or lymphopenia is new for the patient or related to his/her underlying disorder. Ogimi et al studied the clinical course of human Coronavirus related lower

respiratory tract infection in hematopoietic transplant patients and found the mortality rate to be 54% in a case series of 35 patients (6).

Hence, in the current scenario of COVID-19 outbreak, it is of extreme importance to understand that cancer patients, especially the ones with bone marrow disorders, febrile neutropenia, patients on chemotherapy, transplant recipients etc. should be considered as a special population due to their higher risk of acquiring secondary infections and faster decline rate.

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