is 6.3 days.[5] This case series draws attention to the fact that GCSF can cause rapidly rising NLR ratio >3 within 24 hours of administration.

In the setting of COVID-19 illness, further rapid rise in neutrophilia with NLR ratio >5 may portend respiratory deterioration to the point of mechanical ventilation within the next 72 hours, especially in those patients who are older than age 50 and have comorbid medical conditions.

Limitations exist in our case series. This represents only a small number of patients who specifically came to our attention because they declined within 72 hours after receiving GCSF. Another limitation is missing data points regarding pre GCSF IL6 and other such markers, as these laboratory investigations were not performed on patients who initially had normal oxygenation on room air at admission.

Larger scale studies are needed to delineate the relationship between GCSF administration and progression of COVID-19 infection from mild to severe stage in high risk patients.

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SUPPORTING INFORMATION

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

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

To the Editor:

Fan *et al*. critically studied the difference in hematological parameters between the ICU vs non-ICU COVID-19 cases.[1] 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. COVID-19 is a rapidly evolving and emerging disease, and AJH readers would certainly benefit from further discussion and refinement.

Concern over coagulation abnormalities 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 a 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 non-survivors had significantly higher D-dimer values ($P < .001$), fibrin degradation product (FDP) values ($P < .001$), longer prothrombin time ([PT in seconds] $P < .001$) when compared to survivors at admission. Fibrinogen levels ([g/L], $P = .149$), antithrombin activity (AT [%], $P = .096$), and activated partial thromboplastin time ([APTT in seconds], $P = .096$) 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 end up 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] Previous studies on SARS patients have shown the incidence of DVT and PE to be in 20.5% and 11.5% cases, respectively. Hence, considering the fact that both SARS and SAR-CoV-2 infection have a similar pathophysiology and receptor recognition on human cells (ACE-2 receptor protein), it is likely to have similar numbers with regards to incidence of thromboembolism. Most of the studies until now on sick patients have focused on ARDS, acute kidney injury, and multi-organ failure, but lack data on DIC. We discuss this because diffuse microvascular damage of lungs secondary to DIC can also lead to ARDS and death of COVID-19 patients.[4]

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 have 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. Until 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.[5] 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 monitoring. 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 a RT-PCR test 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 sought to clinch the correct diagnosis.[5]

Possible mechanism of impact of coronavirus on hematopoiesis: Scientists have studied for the possible mechanisms of thrombocytopenia and lymphopenia in previous coronavirus outbreaks.[6] Few of the proposed mechanisms in the past are (a) virus directly infecting the blood/bone marrow stromal cells via interaction with CD13 or CD66 or (b) 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. Note, 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?

Recognizing special population upfront: It would be beneficial to know how many patients in the study by Fan et al 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.[7]

Hence, in the current scenario of a 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.

CONFLICT OF INTEREST

Authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors have seen the manuscript and agree to the content and data. All the authors played a significant role in the paper.

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Hematologic parameters in patients with COVID-19 infection: a reply

To the Editor:

We thank Dr Sahu and Dr Siddiqui for adding further input on the effect of COVID 19 infection on the blood system, in their correspondence to our letter to the *American Journal of Hematology*.[1]

We did not specifically look at coagulation abnormalities in our correspondence to AJH, but we have noted these have been already addressed by other publications, notably Tang et al[2] and Han et al[3] in their papers on COVID-19 associated coagulopathy.

Our initial impression at the time of our correspondence was that apart from D-dimer, the coagulation parameters such as PT, PTT and fibrinogen in non-ICU patients were less significant in identifying patients needing ICU care. While an elevated D-dimer may also reflect underlying inflammation, immobility or liver disease, patients with COVID-19 infection with markedly raised D-dimers are significantly at risk of mortality,[2] and a raised level also implies increased thrombin generation. We note that anticoagulation therapy mainly with low molecular weight heparin appears to be associated with a better prognosis in severe COVID-19 infection with markedly elevated D-dimer in a further publication by Tang et al.[4] As such, the International Society for Thrombosis and Haemostasis interim guidance on recognition and management of coagulopathy in COVID-19[5] has the recommendation that prophylactic dose low molecular weight heparin should be considered in all patients, who require hospital admission for COVID-19 infection in the absence of any contraindications.

As mentioned in our correspondence, our primary focus was on hematologic parameters and we did not cover the scope of any specific data on thrombosis and bleeding. We have however, further published in a separate letter to the *American Journal of Hematology* about the usage of blood and blood products,[6] which may answer partially the concerns of risk of bleeding in our population of patients.

None of our patients we studied with COVID-19 infection had hematologic malignancies at the point of submitting our letter, but we do recognize that these immunosuppressed patients are particularly vulnerable and may likely experience greater morbidity and mortality when having a COVID-19 infection.

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