EDITORIAL

Is Immature Granulocyte Count a Potential Prognostic Marker for Upper Gastrointestinal Tract Bleeding? A New Road to Explore

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Intensive care physicians all over the world are trying to find out parameters that can be used to prognosticate and thus appropriately triage patients presenting in a medical emergency with various pathologies. Upper gastrointestinal bleeding (UGIB) is one such common medical emergency encountered in the emergency room (ER) and intensive care unit (ICU). The UGIB is associated with significant morbidity and mortality. It is known that UGIB related to malignancy and variceal bleeding have a poor prognosis compared to other causes.[1] Certain clinical factors that mark poor prognosis in UGIB are advanced age, low hemoglobin, uremia, and presence of comorbidities. Also, the degree of bleeding is an important contributor to the patient's prognosis of any cause. It is a real challenge to identify patients who rebleed and carry poor prognosis on the day of admission. Identifying such patients is important to triage high-risk patients so that the treatment is tailored and resources are well utilized. But, identifying such patients at risk of poor outcomes can be difficult to predict in emergencies.[2,3] Certain scores are used in clinical practice to identify patients with a poor outcome like the Rockall score, Glasgow Blatchford Scoring (GBS), modified GBS, AIMS65, etc.[4,5] These scores utilize clinical data, diagnosis, and endoscopic findings to predict the risk of rebleeding, length of stay, and mortality. But these are not real time and not simple to do at the bedside. There is a need for a bedside tool that can predict the prognosis of patients with UGIB, which should be easy to do/simple, reliable, repeatable, and cost-effective.

In this issue of the journal, Cihan Bedel and colleagues[6] have tried to show the utility of immature granulocyte count (IGC) and immature granulocyte (IG) percentage as a potential marker to predict mortality in patients with UGIB presenting to ER.

Immature granulocytes (includes promyelocytes, myelocytes, metamyelocytes) are premature granulocytes that are released from bone morrow during infection and inflammatory conditions. The presence of immature granulocytes in peripheral blood indicates leukopoiesis and may represent the earliest indicator of bone marrow stimulation by infection, inflammation, or any other stimuli. It is known that when there is peripheral utilization of leukocytes, in response the bone marrow produces more leukocytes, and there occurs a left shift in leukocyte lineage. The cells that constitute the premature lineage are band forms that are more matured compared to other cells, metamyelocytes, promyelocytes, and myelocytes. For decades, the band form of neutrophils was used to identify infections.[7] But, the measurements are more subjective; wide interrater variability, lack of standard definition for identification, and poor repeatability[7] made band forms less attractive. Now new advanced hematologic analyzers provide immature granulocyte counts quickly, without additional blood, and are repeatable. Moreover, the cells are more defined morphologically leading to more accurate measurements. It is more studied in patients with infection and sepsis.[8–14] It is shown that the IGC > 0.3 and IG > 3% are more specific to identify bacterial infections.[15] Though these studies are promising, there is a lot of concerns to use IGC as an indicator or a marker of sepsis. First, it has a varied cut-off ranging from 0.2 to 3%, as shown in different studies; second, it's not clear which one to use, IGC or IG%; third, a single static value may not be of help as shown in a recent study where repeated time-series values along with leukocyte count are needed to predict the course of infection and sepsis.[16,17] Also, the left shift wasn't found in patients with certain severe infections,[18] and the left shift is not noticed in the extremely early phase of infections,[19] which further questions its utility to accurately identify the infection.

Apart from infection, the utility of IGC is studied in patients with inflammation and pancreatitis.[20–22] So, hypothetically IGC and IG% levels can be potentially used in any condition that is driven by systemic inflammation. Moreover, it is known that massive hemorrhage and shock induces systemic inflammation,[23] which in turn leads to multiorgan damage.

Cihan Bedel et al.,[6] retrospectively studied 213 patients who presented to ER during 7 months' period with UGIB and showed the utility of IGC and IG% as a potential marker to predict mortality. But the results have to be taken with a pinch of salt. Upper gastrointestinal bleeding was defined by authors as the hemorrhage into the lumen between the proximal duodenum up to the Treitz ligament and the upper esophageal sphincter, which was identified by noticing the presence of at least one of the symptoms

of melena, hematochezia, hematemesis, vomiting in the form of coffee grounds, and blood in the nasogastric aspirate. The definition used may be a more practical one for clinical settings but melena, hematochezia, etc., always don't represent bleeding from the upper gastrointestinal tract. Also, we can't rule out the interplay between infection triggers of UGIB (common in variceal bleeding) and the inflammation stimulated by disease process, massive hemorrhage. All these may influence the outcome of patients rather than IGC count, which may be a bystander. Moreover, the authors didn't mention the severity of the illness, which is known to affect the outcome. Interestingly, they found the IGC with a cut-off of 0.17 and IG% with a cut-off of 0.95 predicted mortality in patients with UGIB presented to ER with sensitivity and specificity of 60% and 84.4, 66.7, and 75.7%, respectively. Both parameters showed moderate discrimination (area under the curve was around 0.7 for both) to predict 30 day mortality in patients with UGIB. So, low sensitivity and specificity of IGC and IG% with only moderate discrimination questions its utility and applicability in real practice. Though IGC is increased in patients with UGIB, we can't rule out the influence of other factors like coexisting sepsis or underlying infection as it is not mentioned by the authors.

Measuring and monitoring IGC is more useful in predicting sepsis or differentiating sepsis from other nonsepsis-related deteriorations,[13,14] and it is shown to be a marker of severity of infection rather than a predictor of mortality.[24] Immature granulocyte count alone shouldn't be used to predict or diagnose sepsis; rather, it can be used with other parameters to support the diagnosis. It can be used as a potential monitoring parameter to monitor the progress of a patient with sepsis with treatment. Though IGC is easy to measure, repeatable, quick, and cost-effective, it can't replace existing markers and severity scores to predict prognosis in patients with UGIB. Immature granulocyte count can be an add on to available predictors and further studies are required to strengthen the evidence.

Do IGC levels vary with the cause of UGIB is not studied by the author, which may be of interest. Authors have mentioned variation of treatment among patients, selection bias due to the nonavailability of serial IGC values, and a single-center study involving only small participants as limitations of the study.[6] Also, the cause of UGIB (variceal vs. nonvariceal bleeding), the severity of illness, the need for further intensive care, organ dysfunction which can influence patient outcomes, have not been studied. It may be interesting to know the utility of IGC in such conditions in predicting outcomes.

Apart from the limitations that it is a retrospective study, this study had only 7% as nonsurvivors. Prediction of mortality with fewer events and a small sample population is a real concern. Further studies in the field may throw more light on the utility of IGC and other derived hematological parameters as a marker of illness severity. Currently, IGC can be a potential marker for early identification or exclusion of infections; further studies are required for more validity and routine clinical use.

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