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Review Article

Hematological abnormalities and inflammatory milieu in COVID-19

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Abstract

COVID-19 pandemic has created a lot of uncertainty with exponential surge in the number of cases. There is noteworthy and consistent alteration in the hematological profile associated with this novel virus. These hematological parameters show promise in early detection of disease, providing a clue for infection, before the conventionally used RT-PCR. These parameters also signal towards the severity of the disease and might thereby guide clinicians in a timely manner for efficient patient management. Here we discuss the variations in different parameters in the complete blood count and coagulation profile along with brief discussion about inflammatory markers associated with COVID-19.

Keywords: COVID-19, lymphopenia, coagulation profile, hematological profile, cytokines.

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1. Introduction

COVID-19 pandemic is caused by SARS-CoV-2 virus, a positive stranded RNA virus, which has striking similarities to the virus known to infect bats.[1-3] The disease, initially surfacing in China, was declared a pandemic by WHO on March 11, 2020. It has a tremendous transmission potential, thereby resulting in surge in the number of cases. The most common presentation includes fever, cough, fatigue, diarrhea, dyspnea and tachypnea.[4] Ground-glass opacities (GGO) in the lungs is the usual picture on radiological examination.[5-7] Gold standard for diagnosis of COVID-19 infection is amplification of viral RNA by RT-PCR.[3]

Various hematological parameters are being used to aid in diagnosis of COVID-19. Standard guidelines at present recommend "normal/decreased number of leukocytes" or "decreased number of lymphocytes" as one of the diagnostic criteria of SARS-CoV-2 infection. [8] There is need for swift, straightforward and sensitive surrogate markers for the disease, to aid not only in early diagnosis but in prognostication as well. It is believed that these markers can potentially help to correlate with the severity of the disease, thereby guiding management in a timely and effective manner. Various articles have been published shedding a light on how these potential markers are affected by the disease. However, corroborative evidence combined from all of these needs to exist in order to be of use in clinical practice. Here we present a meticulous review of literature of the hematological abnormalities along with brief discussion about cytokine abnormalities associated with COVID-19.

2. Materials and Methods:

A literature search was performed on PubMed, Scopus, Google Scholar and Science direct. The search strings used were "COVID-19" OR "corona virus" AND "hematological profile", "coagulopathy" AND "COVID-19", "cytokine abnormalities" AND "COVID-19" to identify relevant studies published up to 20th October,2020. A total of 16,809 results were retrieved. Observational studies and review articles related to these keywords were short-listed. In addition, the references of the short-listed articles were searched to find relevant articles. Studies such as conference abstracts, letters to editors and commentaries

were excluded. The key findings of prominent studies are presented in Table 1.

3. Results

3.1 Complete Blood Count

a. Anemia

A decrease in the haemoglobin level has been reported in individuals infected with COVID-19.[9-11]It has been suggested that a decrease in haemoglobin leads to a consequent increase in heme and iron free radicals. This results in an increase in acute phase reactants and pro-inflammatory molecules. SARS-CoV-2 is known to interact with ACE-2, CD174 and CD26 receptors which are expressed on erythrocytes. [12] This virus could thereby attack erythrocytes, leading to their lysis. This would lead to a decrease in hemoglobin and understandably the oxygen carrying capacity of blood. The pulmonary endothelium, being sensitive to these changes would be the most affected, hence the chief symptoms of this disease mainly pertain to the respiratory system. A link between anemia and disease severity has also been suggested. Cases with severe COVID-19 disease, elderly individuals, those with diabetes and other co-morbidities and those needing critical care support have been reported to have lower haemoglobin levels.[13] Anemia has also been reported to be an independent risk factor for disease severity, although further studies are required for this to be used in clinical practice. [14]

b. Leukocyte abnormalities

Leucocytosis (chiefly neutrophilia) is noted only in a small number of studies. [15,16] A meta-analysis reported leucocytosis to be more prevalent in patients with severe disease (11.4%) compared to non-severe ones (4.8%).[15] It appears to foreshadow a bacterial infection or superinfection.[15] The exact mechanism of neutrophilia is yet to be ascertained, but it seems likely to be secondary to an exaggerated cytokine state. Data to support this hypothesis includes the presence of certain nuclear and cytoplasmic changes, morphological abnormalities ranging from hyposegmented nuclei to apoptosis in granulocytes within the circulation, in admitted COVID-19 patients.[17] Increased neutrophil counts have also been reported in ICU patients compared to those not requiring intensive care support.[18] Various studies have reported an increase in neutrophil to lymphocyte ratio (NLR), particularly in patients with severe disease, and this has been linked to clinical deterioration.[16,19,20] A study reported NLR value of $\geq$5 in majority (80%) of the patients with severe disease.[21] Monocyte counts have been reported to be decreased and lower absolute monocyte counts (AMC) have been associated with worse outcome. [10,21] Monocyte to lymphocyte ratio (MLR) has also been reported to be higher in COVID-19 patients.[10] Platelet to lymphocyte ratio (PLR) has also been reported to be higher and a potential prognostic tool as well.[10,22] Thus, NLR, PLR, and MLR are potential surrogate diagnostic tools and NLR and PLR can serve as promising prognostic tools as well.

c. Lymphopenia

Lymphopenia is a prominent finding and has been reported unanimously in majority of the studies, although relative lymphocytosis has also been documented and linked to a better prognosis and rapid recovery. [23]

Lymphocyte counts have been observed to vary with the course of the disease. Normal to slightly decreased counts is observed during the initial periods of infection in a background of nonspecific symptoms, whereas significant lymphopenia is seen later in the disease course, heralded by a worsening clinical picture. This could be reactionary to a surge in cytokines, called the “cytokine storm” and is thought to represent a malfunctioning immunological response to COVID-19. [15,24] It is known that lymphocytes express the ACE2 receptor on their surface and that this novel virus particularly affects cells with increased expression of this receptor.[25] These include the pulmonary, cardiac and gastrointestinal cells, hence the symptoms of the disease. Other plausible mechanisms include direct viral toxicity via its attachment to these cells, chemotaxis or increased lysis due to excess cytokines.[7,26]

Zhang *et al* [4] and Guan *et al* [27] reported lymphopenia in a high number of patients (75.4% and 83.2% respectively) in their studies. Zhang *et al*[4] reported the lymphocyte percentages to be lower but not the absolute counts, in severe cases compared to the non-severe ones. A recent meta-analysis reported that approximately 35–70% of the cases were observed to have lymphopenia, being a more frequent feature in those who succumbed to this novel infection.[15] There is evidence to suggest a possible prognostic value of depressed lymphocyte counts. A study assessing 67 laboratory confirmed patients in Singapore reported a lymphocyte count of <0.6 x 109/L to be a predictor for ICU requirement.[18] An association between lymphopenia and ICU requirement was also suggested by Wang *et al*[3] and Huang *et al*,[7] and an association between lymphopenia with disease progression to ARDS was suggested by Wu *et al*.[1,10] Lower CD4 and CD8 counts have been documented in various studies. [28-30] These counts have also been linked to severity of the disease. The CD4/CD8 ratio on the other hand has been observed to be unchanged in both severe and non-severe cases in various studies, although a decrease in the ratio has also been reported. [29,31-34]

d. Eosinopenia

Eosinopenia (defined as a reduction of circulating eosinophils <0.01 × 109/L) has also been reported frequently in COVID-19.[4,24] The inflammatory milieu in COVID-19 is thought to cause a migratory shift of these cells from the periphery into the pulmonary vasculature.[35] An association between eosinopenia and

disease severity has been reported. Zhang *et al*[4] reported a fall in eosinophil count (<0.02 × 109/L), and this drop was found to be more prevalent in severe cases (60.7%) compared to non-severe ones (47.6%). Du *et al*[36] reported eosinopenia to be present in a majority (81%) of the cases who succumbed to this infection. Another study has reported eosinophil count to be "zero" in 60% of COVID-19 patients, and the absence of eosinophils as a potential clue towards early detection of infection. [37] Persistent eosinopenia in their study also co-related with disease severity. Liu *et al* [38] have also described eosinopenia in their study. Interestingly, they reported low eosinophil counts in patients on admission, and gradually improving counts in those who improved. Lopinavir use in their study has been linked with improvement in the eosinophil counts and in the clinical picture. They have suggested a possible role of rising eosinophil counts to be a marker for recovery of COVID-19 patients.[38] Eosinopenia can be a promising tool for prognostication of SARS-CoV-2 patients.

e. Thrombocytopenia

Thrombocytopenia is frequently considered a poor prognostic factor in sepsis, and an indicator of mortality.[39] In a study carried out on 41 patients carried out in Wuhan, platelet counts less than 100 x 10^9/L were found only in 5% of the patients, with one case amongst those requiring critical care and one amongst those who did not. In the same study, platelet counts <150 x 10^9/L were seen in 95% patients, with no difference amongst patients requiring or not requiring critical care. However, this study was limited by sample size. [7] Guan *et al* [27] also reported thrombocytopenia in 36.2% patients on admission. Ameta-analysis comprising 1779 patients (400 critically ill) reported significantly lower platelet counts in critical patients compared to mild to moderate cases. When cases were compared based on survival, a more dramatic drop in platelet counts was noted. Lower counts were associated with a five times increased risk of serious infection. [40]

Various mechanisms have been hypothesized for the development of thrombocytopenia. Xu *et al*[41] have described a three pronged hypothesis wherein thrombocytopenia may arise as a result of diminished platelet synthesis, along with heightened platelet destruction and increased utilization. SARS-CoV-2 may directly attack cells in the bone marrow disrupting hematopoiesis leading to failure of platelet production. Alternatively, thrombocytopenia may occur secondary to generation of autoantibodies against platelets mediating their destruction. In SARS it was observed that mechanical ventilation, in the setting of a preliminary infection in the background, initiated a deleterious cycle of endothelial damage thus triggering the coagulation cascade and thrombosis in the pulmonary vasculature resulting in consumption of platelets.[42] A similar mechanism might be responsible for COVID-19 as well. A persistent low grade disseminated intravascular coagulation (DIC) in the background was also proposed as a reason for thrombocytopenia in SARS.[42] However, due to notable differences between SARS and SARS-CoV-2, these mechanisms can't be attributed to COVID-19 with certainty.[43]

3.2 Coagulopathy

Coagulopathy complicates a number of infections. The breech in the continuity of the endothelial cells, complicated by infectious pathogens, results in increased reactionary thrombin generation and affects fibrinolysis which is an important contradictory response. This creates a pro-coagulable milieu, the process being enhanced by release of pro-inflammatory mediators (chiefly IL-6 and TNF-alpha) from the breeched endothelium.[44] Similarly, coagulopathy has been frequently reported in this novel infection and often complicates the clinical picture.[44,45] Also, the increased activation of tissue factor, along with the "TF-activated factor VIIa complex", contributes to uncontrolled thrombosis. [46] Exaggerated degradation of fibrin on the other hand contributes to elevated D-dimer levels.[47] Guan *et al*[27] have reported coagulopathy to be one of the most noteworthy adverse prognostic factors in those with severe disease who tend to progress to multi-organ failure. Tang *et al*[45] also highlighted the development of coagulopathy to be a consistent feature associated with a poor outcome and a possible predictor of mortality. In their report, the most common finding observed in patients requiring hospital admission was elevated D-dimer levels. Tang *et al*[45] also documented a rather small PT prolongation (15.5 s) at admission in those who succumbed to the disease compared to 13.6s in those who recovered. Similar PT prolongation on admission was also observed in another study, again in those requiring ICU support.[7] APTT prolongation on the other hand was found to be minimal when compared to that in cases of overt DIC and sepsis, being attributed to the elevated levels of factor VIII. [45] Also, the elevated APTT has been linked to the presence of lupus anticoagulant, and the two have been documented to increase simultaneously. [48] It has been well documented that the elderly and those with co-morbidities are at an increased risk of mortality associated with the infection and interestingly, D-dimer levels were reported to be increased in both these cohorts.[27] Guan *et al*[27] in their report on 1099 patients reported a D-dimer ≥0.5 mg/litre in approximately 47% patients (43% of patients in case of mild to moderate disease and about 60% in those who had severe disease). Zhang *et al*[4] also described the D-dimer levels to be significantly increased in critical cases compared to the mild to moderate ones and reported elevated antiphospholipid antibodies and thromboembolic events amongst many severe cases. In yet another study, D-dimer

level was found to be elevated in those patients needing ICU care (2.4 mg/L) than those not requiring it (0.5 mg/L).[7]Wada *et al* [49] also noted a substantial increase in D-dimer levels and PT, along with a drop in antithrombin and fibrinogen levels in those who succumbed to the infection. Similar data has also been reported in other case reports.[4,18]The hyperinflammatory state reported in COVID-19 has been associated with abnormalities in the coagulation parameters as a result of augmented synthesis of clotting factors by the hepatocytes.[50] The possibility of coagulopathy to be useful as a risk stratification tool has also been suggested, although presently this is centered on the presence of severe pneumonia and the widely documented laboratory parameter, "lymphopenia".[51] The use of PT and D-dimer as tools for assessing prognosis and severity in COVID-19 has also been suggested.[52] Tang *et al* [49] managed severe cases with prophylactic dose of LMWH (low molecular weight heparin) and reported no difference in mortality over a 28 day period in the 2 cohorts, however, if a sepsis induced coagulopathy (SIC) score [53] was applied, then anticoagulant therapy amongst those with a score of $\geq$4, was shown to improve prognosis.[49] A benefit of anticoagulation was also observed in those with D-dimer elevation six times the upper limit of normal. The anti-inflammatory properties of LMWH, may help to counteract, albeit minimally, the SARS-CoV-2 induced cytokine storm. [7,49,54,55]

3.3 Inflammatory markers

Increased levels of serum C- reactive protein (CRP), serum amyloid A, D-dimer, creatine kinase, ferritin, ESR and LDH have been reported in a number of studies and CRP levels have been reported to be markedly elevated in critical cases.[9] Studies on SARS-CoV-2 in Wuhan have implicated a number of cytokines in the pathogenesis of this novel disease, notably 1β, IL-6, and TNF-α. These cytokines are also reported to be increased in SARS-CoV-1 and MERS-CoV. [55,56] Viral load has also been related to increased cytokine levels.[57] TNF-α induces hyaluronic acid synthesis in the alveolar epithelium.[58] HA (hyaluronan) increases fluid inflow in the pulmonary alveoli, understandably resulting in worsening of the clinical picture, and hence its correlation with the need of critical care support. The picture of multiple bilateral lobular pneumonia in SARS-CoV-2 infection is linked with elevated IL-1β, IL-7, IL-8, IL-9 levels.[7]

IL-6 plays a rather deleterious role in disease progression. It is known to activate vascular endothelium derived growth factor (VEGF) in the pulmonary endothelium, contributing to respiratory abnormalities. [59] Along with IL-6, IFN-γ has been an unswerving marker of patient deterioration and ICU admission in COVID-19. [60] It has been observed that TNF-α levels, alongside IL-6, increase early in the course of the disease and tend to remain elevated.[61] TNF-alpha, IL-6 and IL-10 levels have been an important feature of worsening clinical picture, increasing in patients on critical care support, compared to non-ICU ones, while minor elevations in levels of IL-6 were seen in non-severe cases.[61,62]

Another study reported a 52% increase in IL-6 levels in critically ill patients requiring ICU care, and highlighted an association of these increased levels with neutrophilia, lymphocytopenia and an elevated CRP level. [63] Although most patients tend to recover once the initial cytokine surge is combated by a limiting IFN-gamma response, a second cytokine wave can occur. Acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) which usually develop in severe cases have been suggested to be a consequence of this. [64]

Anti-inflammatory drugs have been brought into the picture in an attempt to limit this inflammatory response. Use of dexamethasone has been reported to be of maximum benefit in moderate to severe cases, compared to non-critical ones.[65] Considering the numerous adverse effects associated with glucocorticoids, focus was shifted to steroid sparing immunosuppressants inhibiting the aforementioned cytokines (IL-6 inhibitor tocilizumab, IL-1Receptor blocker anakinra, JAK1/2 inhibitor baricitinib). The recently reported immunosuppressant, JAK1/2 inhibitor, Ruxolitinib, has shown promise in curbing this cytokine surge.[60] Recent reports have highlighted the association of COVID-19 with acute kidney injury (AKI) and the putative role of IL-6in its causation.[66] Levels of IL-6 in individuals with AKI have been found to correlate strongly with mortality.[67] IL-6 can stimulate and worsen renal disease by increasing the sensitivity of tubular cells to various fibrosis inducing cytokines and may also stimulate the proliferation of cells in the mesangium, thereby worsening membranoproliferative glomerulonephritis (MPGN) in the predisposed individuals.[68]

4. Conclusion

The widely reported changes in simple laboratory parameters show promise in aiding in diagnosis and prognostication of COVID-19. A basic investigation such as a complete blood count can reveal lymphopenia, eosinopenia, thrombocytopenia, increased NLR, MLR and PLR which are promising surrogate markers for early detection of COVID-19. The degree of lymphopenia, increased NLR, PLR as well as derangement in coagulation parameters (elevated D-dimer levels, PT prolongation) are valid indicators of assessing the severity and risk stratification of the disease.

Table 1: Key findings of prominent studies

Serial No.	Authors	Type of Study	Abnormality in Complete Blood Count and Coagulation parameters(if reported and it's prevalence)	Prominent Findings
1	Li Q *et al*[24]	Retrospective; case-control, N: 105	Eosinopenia;78.8%	Eosinopenia, in combination with other laboratory abnormalities, may help in early identification of patients.
2	Zhang JJ *et al*[4]	Retrospective N: 140	Eosinopenia; 52.9% Lymphopenia; 75.4%	Decreased eosinophil count along with lymphocytopenia may be used as markers of infection.
3	Guan WJ *et al*[27]	Retrospective N: 1099	Lymphopenia; 83.2%	Lymphopenia is more prevalent in patients with severe disease as compared to non-severe ones.
4	Tang N *et al*[49]	Retrospective; N:499	D-dimer: Total: 1.94 (0.90 - 9.44) Survivors: 1.47 (0.78 - 4.16) Non-survivors: 4.70 (1.42-21.00)	Treatment with LMWH is associated with a reduced mortality in severe cases of COVID-19 with deranged coagulation profile. D-dimer, age and PT were positively and platelet count was inversely associated with 28 day mortality. 28 day mortality was lower in heparin users with SIC score $\geq$ 4, compared from non-users (40% vs 62.4%), and D-dimer elevations >6 times upper limit of normal (32.8% vs 52.4%)
5	G. Lippi *et al*[40]	Meta-analysis; N: 1779	Severe cases have lower platelet counts: (Weighted mean difference: −31 × 109/L; 95% CI, from −35 to −29 × 109/L)	Platelet count can help in risk stratification of cases and thrombocytopenia is a prominent biomarker for severe COVID-19 infection.
6	Ifeanyi OE *et al*[26]	Review Article	-	Lymphopenia, along with leucocytosis and thrombocytopenia, serve as important laboratory parameters in COVID-19.
7	Huang *et al*[7]	Observational study (41 patients)	Lymphopenia (< 1.0 x 109/L) :63%	Lymphopenia is a more frequent finding of patients requiring critical care support than those who do not. (85% vs 54%), the result being statistically significant
8	Fan *et al*[18]	Observational study (67 patients)	Lymphopenia:36.9% Thrombocytopenia:20%	Lymphopenia and elevated LDH levels may indicate the need for critical care support in COVID-19 infection.
9	Lian J *et al*[16]	Retrospective cohort study; N : 232	NLR values based on disease severity:- Mild/Severe:2.68(1.96-4.42) Critical – 9.67(6.86-21.10)	NLR can serve as an important predictor of severe illness in older adults with COVID-19 infection.
10	Pakos IS *et al*[21]	Retrospective analysis; N : 242	Lower median absolute monocyte count (AMC) (0.4 vs 0.5) and median platelet count (169 vs 213), in non-survivors vs survivors	NLR and AMC have a direct and inverse association respectively, with mortality in COVID-19 patients.
11	Peng J *et al*[10]	Multicenter cross-sectional study; N: 485	NLR(mean$\pm$SD):3.29 ± 2.76 MLR(mean$\pm$SD): 0.34 ± 0.17 PLR(mean$\pm$SD): 169.51 ± 97.51	MLR can serve as a biomarker to differentiate COVID-19 positive patients from those not infected with the virus.

(NLR: neutrophil to lymphocyte ratio, AMC: absolute monocyte count, SD: standard deviation, PLR: platelet to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, LDH: lactate dehydrogenase)

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