Am J Blood Res 2022;12(1):43-53
www.AJBlood.us /ISSN:2160-1992/AJBR0139120

Review Article

Spectrum of hematological changes in COVID-19

Smeeta Gajendra

Department of Laboratory Oncology, Dr BRA IRCH, All India Institute of Medical Sciences, New Delhi, India

Received September 14, 2021; Accepted January 24, 2022; Epub February 15, 2022; Published February 28, 2022

Abstract: Coronavirus disease 2019 (COVID-19) is caused by pathogenic and highly transmissible Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is a single stranded RNA virus. It rapidly emerged from an epidemic to a global pandemic form spreading in alarming levels. The pathogenesis involving spike protein which is present on the viral surface, plays a key role in host attachment and penetration. SARS-CoV-2 infection significantly affects respiratory system, but may involve other systems including haematopoietic system and homeostasis. Aim of the review article is to discuss spectrum of haematological changes in the blood counts, coagulation, peripheral blood and bone marrow in COVID-19 for complete understanding the disease process, the knowledge of which is helpful in early diagnosis and management of these patients. An extensive immune profiling of B and T cell population with analysis of spectrum of immune changes during the period of infection were also discussed. In COVID-19, changes in laboratory parameters and hematologic abnormalities have been reported and its association with early diagnosis, disease prognosis and severity has been repeatedly discussed in the literature. Changes in laboratory investigations help in risk stratification and early intervention. The most common laboratory finding in COVID-19 is lymphopenia. COVID-19 patients presented with coagulopathy is at high risk of morbidity and mortality. In severe COVID-19 patients, bone marrow aspirate shows histiocytic proliferation with hemophagocytosis. To understand the correlations between immune responses and severity of COVID-19, immune profiling of B and T cell population was compared with extensive clinical data. A deep understanding of the laboratory findings and haematological abnormalities associated with SARS-CoV-2 infection would help to raise disease suspicion in absence of Real time polymerase chain reaction or antibody results. Also the blood counts along with the morphological changes in peripheral blood would be helpful in prompt screening, diagnosis, prognosis and management of COVID-19 patients.

Keywords: COVID-19, SARS-CoV-2, spike protein, DIC, flowcytometry, immune profiling

Introduction

Coronavirus disease 2019 (COVID-19) is caused by pathogenic and highly transmissible Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is a single stranded RNA virus. It rapidly emerged from an epidemic to a global pandemic form spreading in alarming levels. Clinically, COVID-19 presents with a wide range of signs and symptoms of varying severity; some patients are asymptomatic to some presented with fever, breathlessness, persistent dry cough, chills, body pain, headache, loss of taste, loss of smell, gastrointestinal symptoms, thrombosis or may some have progressed to multi-organ failure. Common fatal complications include acute respiratory distress syndrome (ARDS), pneumonia, respiratory failure, venous and arterial thrombotic complications, metabolic acidosis, septic shock, acute coronary syndrome, arrhythmia, heart failure, acute kidney injury and acute necrotising encephalopathy [1, 2]. Haematopoietic system and homeostasis are also significantly affected by SARS-CoV-2 infection. Laboratory changes and hematologic abnormalities have been reported in COVID-19 patients and its association with early diagnosis, disease prognosis and severity has been repeatedly discussed in the literature. Other factors as gender, age, comorbidities including diabetes, hypertension and obesity in patients with COVID-19 are emerging as important prognostic factors. An extensive immune profiling of B and T cell population with analysis of spectrum of immune changes during the period of infection were also studied. To understand the correlations between immune responses and severity of COVID-19,

this profiling was also compared with extensive clinical data [3]. Patients developing critical levels of laboratory parameters are associated with higher mortality, so identification of critically ill patients at an early stage is important to reduce morbidity and mortality of COVID-19 patients.

SARS-CoV-2 infection pathophysiology

Coronavirus enters host body by aerosol transmission. The viral life cycle consists of: attachment (binding to the host receptor), penetration (through endocytosis or membrane fusion), biosynthesis (For replication viral proteins are made using viral mRNA), maturation (synthesis of new viral particles) and release [4]. The SARS-CoV-2 is made up of four structural proteins: a) spike (S) protein, b) nucleocapsid (N) protein, c) membrane (M) protein and d) envelop (E) protein. The Spike protein is present on the viral surface and plays a key factor in host attachment and penetration. The N, M and E proteins are vital for assembly and release of viral particles. Spike protein is made up of two functional subunits: S_1 subunit and S_2 subunit. S_1 subunit is responsible for binding of virus to the host cell receptor and S_2 subunit is responsible for fusion of viral and host cellular membranes [5]. S_1 subunit of S protein initially binds to angiotensin-converting enzyme 2 (ACE-2) which act as a functional receptor for SARS-CoV-2. ACE-2 is expressed highly on pulmonary epithelial cells. After binding, activation and two stage protease cleavage of S protein occur. First cleavage results in stabilisation of S_2 subunit of viral spike protein at the attachment site and the second cleavage results in conformational changes in viral spike protein, which further lead to fusion of viral and host cell membranes. Virus enters the pulmonary alveolar epithelial cells and undergoes replication and there is release of viral particles resulting in apoptosis of host cells. Along with that, there is release of inflammatory mediators known as cytokine storm. The important mediators are Interleukin (IL)-1, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor alpha (TNF-α), granulocyte colony stimulating factor (G-CSF), macrophage inflammatory protein-1 alpha (MIP-1α), gamma interferon-induced protein 10 (IP-10), type 1 monocyte chemoattractant protein (MCP-1) and C-X-C motif chemokine ligand 10 (CXCL-10) [6]. Both causing diffuse alveolar damage, resulting in ARDS. Few studies suggested that SARS-CoV-2 may cause invasion of host cells via the CD147-spike protein pathway. Viral invasion is facilitated by S protein attaching to CD147. CD147 is a glycoprotein, known as Basigin (BSG) or extracellular matrix metalloproteinase inducer/EMMPRIN, stimulates production of several matrix metalloproteinases. This protein is usually expressed in hematopoietic cells, mesenchymal stem cells, red blood cells (RBCs), leukocytes, epithelial and endothelial cells [7].

SARS-CoV-2 reported to behaves analogous to carbon monoxide in initiating cellular hypoxia and pulmonary embolism. The structural proteins of SARS-CoV-2 adhere to heme and form methemoglobin before replacing the resident oxygen and iron, and transforming heme into porphyrin. Inflammatory process might be induced by dissociative iron mediated by alveolar macrophages. SARS-CoV-2 dissociates from oxyhemoglobin, carboxyhemoglobin and glycosylated hemoglobin, thereby causing dysfunction in the exchange of oxygen and carbon dioxide in heme. The S proteins of SARS-CoV-2 use a homologous sequence to directly bind ACE2 expressed on CD34+ hematopoietic stem cells, lymphocytes, monocytes and macrophages [8]. SARS-CoV-2 may invade hematopoietic stem/progenitor cells, lymphocytes and MKs via ACE2, CD13 or CD66a receptors, resulting in cellular apoptosis, inhibited cell proliferation, lymphopenia and thrombocytopenia. SARS-CoV mediated immune response results in production of antibodies and immune complexes which mediate cellular damage and can indirectly induce apoptosis or inhibit the proliferation of hematopoietic stem/progenitor cells, thereby resulting in cytopenias. It is further postulated that, SARS-CoV-2 affects the BM microenvironment including endothelial cells, attenuating hematopoiesis. Direct virus infection and uncontrolled inflammation can cause damage to the microvascular system, destroying the vascular endothelial cell barrier, and resulting in the reduction of platelet EC adhesion molecule-1 (PECAM-1) on the cell surface and an increase in plasma soluble PECAM-1. Endothelial cell damage may lead to the overexpression of tissue factor (TF), thereby activating the exogenous coagulation system, while inhibiting anticoagulation and fibrinolysis that leading to disseminated intra-

vascular coagulation (DIC). In DIC, there is excessive inflammatory response and endothelial cell barrier destruction which promote each other, forming a feedback loop leading to systemic microvascular thrombosis, increased platelet and coagulation factors consumption, and secondary hyperfibrinolysis which is manifested as microcirculation disorders and bleeding [9].

Laboratory parameters

Change in biochemical and haematological parameters are important in identification and prognostication of COVID-19 patients.

Increased levels of lactic dehydrogenase (LDH): LDH active in the liver, lungs, heart, kidneys, brain, striated muscles and RBCs. During cytokine mediated tissue damage, LDH can be released and take part in various pathophysiological processes. As previously described in many diseases, LDH serve as a non-specific indicator of cellular death in COVID-19 [10].

Increased erythrocyte sedimentation rate (ESR): ESR is another inflammatory biomarker which is elevated in COVID-19 [11]. The exact cause is not known. However, as ESR is dependent on change in the size, shape of RBCs and concentration of plasma, it is speculated that COVID-19 may trigger the change in characteristics of RBCs or plasma, resulting in increased ESR.

Increased C-reactive protein (CRP): CRP levels increased due to overproduction of inflammatory cytokines and by tissue destruction. CRP levels are influenced and correlated with the level of inflammatory process. This can be used as a valuable early marker for diagnosis of pneumonia and predicting the possibility of progression of disease [12, 13].

Liver function abnormalities: Causes of abnormal liver function include: a) direct liver injury, b) associated inflammatory responses, c) congestive hepatopathy, d) hepatic ischemia, e) drug-induced liver injury, f) muscle breakdown [14]. Increased total bilirubin is reported in a small group of patients (1-18%) and it may indicate underlying liver injury [15]. Liver enzymes, commonly aspartate amino transferase (AST) and alanine amino transferase (ALT) elevated typically 1-2 times the upper limit of normal in COVID-19 patients. Hypoalbuminemia was reported in 55% of patients with COVID-19 who are hospitalized [12].

Renal function abnormalities: The incidence of acute kidney injury vary a lot ranging from 0.5% to more than 40% in literature. Causes may include: a) direct kidney damage which is occurred through binding of SARS-CoV-2 to ACE2 receptors (as ACE2 can express in renal tubular epithelium) [16], b) direct kidney damage may be occurred through production of pro-inflammatory cytokines and chemokines that can cause through apoptosis of the renal tubular epithelial cells, c) kidney injury by indirect pathogenesis by critical care interventions. In Covid-19, kidney damage typically manifests as impaired glomerular filtration which is manifested as increased levels of blood urea and creatinine or tubular damage which results in proteinuria in urinalysis [17].

Increased Procalcitonin (PCT): PCT is the 116-amino acid precursor of the calcium regulatory hormone calcitonin. PCT is synthesised and released mainly by thyroid parafollicular C cells along with many extra-thyroid tissues during bacterial infection, which is mediated by increased levels of IL6 and TNFα [18]. Several studies reported elevated PCT (≥0.5 ng/mL) in 6% to 30% of COVID-19 patients which may represents bacterial co-infection and that the patient is progressing into ARDS.

Increased Cardiac markers: Cause of cardiac injury includes a) direct injury of cardiomyocytes by viral infection. SARS-CoV-2 directly invade and replicates intracellularly which results in degeneration and necrosis of cardiomyocyte, which further causes loss of cardiac function and arrhythmia, b) binding to ACE2 receptor on cardiomyocytes, and c) immune mediated myocardial injury caused by inflammatory mediators [19]. Cardiac injury is manifested by increased levels of cardiac markers as cardiac troponin I (cTnI), creatine kinase (CK), creatinine kinase-muscle/brain activity (CK-MB), myoglobin (Mb), alpha-hydroxybutyrate dehydrogenase (α-HBDH), and N-terminal of the prohormone brain natriuretic peptide (NT-proBNP).

Increased cytokines & chemokines: In COVID-19, the presence of an inflammatory stimulus triggers the production of a series of mediators

including cytokines and chemokines such as IL-2, IL-6, IL-7, IL-10, TNF-α, G-CSF, IP-10, MCP-1 and MIP-1α [20].

Haematological parameters

Basic haematological tests like complete blood counts (CBC) are routinely performed, easy and inexpensive, and have important role in early diagnosis of the disease. Total leucocyte count, differential count of neutrophil, lymphocyte, eosinophils and monocytes, platelet count, mean platelet volume and certain ratios of these parameters can be used as inflammatory markers in patients with COVID-19. Common haematological alterations seen in COVID-19 are: anaemia, leucocytosis or leucopenia, neutrophilia, low eosinophil count or eosinophilia, thrombocytopenia, and rarely thrombocytosis [21].

Anaemia is not a major problem, only 1.6% patients required blood transfusion [20]. Causes of reduced haemoglobin are: a) SARS-CoV-2 damages RBC membranes due to presence of angiotensin and ACE2-interacting proteins on the surface of RBCs, b) direct attack of heme by virus, c) dysregulated iron metabolism, d) blood loss that occurred during renal replacement therapy and gastrointestinal bleeding in patients with or without use of anticoagulant, e) auto-immune haemolytic anaemia within a timeframe of the cytokine storm [22].

Lymphopenia is the most common laboratory finding in SARS-CoV-2 infection, may present in 25 to more than 80% of patients on admission [12]. Causes of lymphopenia are: a) SARS-CoV-2 directly infect lymphocytes as ACE2 receptors are expressed on their surface, resulting in cell lysis [8], b) lymphocyte apoptosis caused by cytokine storm [23], c) atrophy of lymphoid organs, including spleen, associated with cytokine activation further impairing lymphocyte turnover [24], d) coexisting lactic acid acidosis, also inhibit lymphocyte proliferation by blocking lactic acid export in T cells [25].

Neutrophil count is elevated in severe COVID-19 patients. Several studies have reported that neutrophil-to-lymphocyte ratio (NLR), a clinical inflammation biomarker, is increased [26]. In addition to the NLR, neutrophil to CD4+ lymphocyte ratio (NCD4LR) and neutrophil count to albumin ratio (NAR) are also increased [27, 28]. Lymphocyte to monocyte ratio (LMR) is usually low but may me normal, increased also. Eosinopenia (defined as absolute eosinophil counts $<0.02 \times 10^9$ cells/L) was reported in more than half the patients admitted with COVID-19 by Zhang et al [29]. Similarly, eosinopenia (absolute eosinophil counts $<0.02 \times 10^9$ cells/L) was also noted in 81% of the patients at the time of admission by Du et al when they reviewed the medical records of 85 fatal cases of COVID-19 [30]. Cause of eosinophilia in COVID-19 is multifactorial, may be due to a) suppressed eosinophil mobilisation from the bone marrow (BM), b) inhibition of eosinophilopoiesis, c) reduced eosinophil-driving cytokines, and d) direct interferon-induced apoptosis. Fraissé et al described an unexpected late-onset and prolonged ICU-acquired eosinophilia in about one-third of their critically ill COVID-19 patients [31]. Exact cause of eosinophilia is not known whether it a dysregulated immune response during the cytokine storm marker or an excessive immune recovery.

Thrombocytopenia is less common than lymphopenia, reported rate varies from less than 5% to about 53.6% cases [12]. Causes of thrombocytopenia include: a) platelet production affected by direct cytopathic effect on the bone marrow CD34+ hematopoietic stem/progenitor cells through CD13 and CD66a which act as potential receptors for the internalization of SARS-CoV-2, b) impaired fragmentation of megakaryocytes and platelet production due to damage to the lung and pulmonary capillary bed caused by COVID-19, c) increased platelet consumption due to lung and pulmonary endothelial cell injury, d) liver damage may cause decrease thrombopoietin (TPO) production further hampering megakaryocyte maturation and differentiation, e) immune-mediated platelet destruction caused by anti-platelet autoantibodies which are stimulated by SARS-CoV-2 [32, 33].

Peripheral blood smear

In COVID-19, morphological changes in peripheral blood smear in all the cell lines were described in the literature. RBC morphology is predominantly normocytic normochromic (in about 70% cases) or may be dimorphic (microcytic-macrocytic), microcytic hypochromic or macrocytic. RBC series shows presence of nucleated RBCs and coarse basophilic stippling

[34]. Most common peripheral blood smear finding is presence of lymphopenic with reactive lymphocytes, of which a subset appeared monocytoid or lympho-plasmacytoid [21]. Singh et al [35] described presence of large granular lymphocyte with round to indented nuclei, condensed chromatin, few with prominent nucleoli, along with abundant pale blue cytoplasm with distinct azurophilic granules. These cells are probably natural killer cells/cytotoxic T lymphocytes. Apoptotic body and cytoplasmic pod formation were also described by Singh et al in a few lymphocytes. Large atypical, bizarre looking mononuclear cells, 2-3 times the size of RBC having irregular nuclear membrane, dense chromatin, scant to moderate cytoplasm and few with cytoplasmic granules and vacuoles (?Virocyte/?Covicyte) are also described in the literature [36]. Neutrophilia is seen in COVID-19. Neutrophils with cytoplasmic vacuolations, numerous crowded dark distinct granulations similar as toxic granulations, basophilic agranular region in the periphery of cytoplasm, and markedly condensed chromatin in the nucleus are described [21, 35]. Neutrophils with different abnormal nuclear shapes including ring shaped, pi-shaped and donut-shaped nuclei were described in the literature [34]. Singh et al described these fetus-like C-shaped nuclei with nuclear projections, as COVID nuclei [35]. Dysmorphic pictures as hypogranulations, hypolobation and pseudo-Pelger-Huet neutrophils are also seen. Apoptotic cells with liquefied nuclear chromatin and granulated or deep blue cytoplasm, reminiscent of polymorphs with nuclear fragmentation are seen. Immature granulocytes as small promyelocytes, myelocytes or metamyelocytes are frequently present in early phase. Reactive large atypical monocytes with abnormal nuclear shape and cytoplasmic vacuolations were also described [29, 37]. Rarely, leucoerythroblastic blood picture is described [38]. Morphological abnormalities in platelet were also described in COVID-19 both in patients with thrombocytosis as well as thrombocytopenia. These morphological changes includes presence of giant platelets, usually hyperchromatic, vacuolized and some showing pseudopods [39].

Flowcytometry

Flowcytometric immunophenotyping can help in analysing different peripheral blood cell populations. Fan et al [21] found that the ICU patients have significantly lower CD45+, CD3+, CD4+, CD8+, CD19+ and CD16/56+ counts. The CD4 to CD8 ratio was not inverted in all groups of patients. T cells were more affected by SARS-CoV-2. A subset analysis of T cells showed that both helper T (Th) cells (CD3+ and CD4+) and suppressor T cells (CD3+ and CD8+) were lower in patients with COVID-19 [40, 41]. However, levels of CD8 T-cells are more likely to be reduced compared to CD4 T-cells. Moratto suggested that, patients with severe disease had a significantly reduced number of TCRγδ+ T cells, and an abnormal distribution of CD8+ T cell subsets, with lower proportion of naïve cells and increased percentage of effector CD45RA+ cells [41]. Rezaei et al studied peripheral lymphocyte subsets including CD4+, CD8+, CD4+CD25+FOXP3+, CD38+, CD3+HLA-DR+, CD19+, CD20+, and CD16+CD56+ cells and found an increasing trend in WBCs, total T cells, T helpers, cytotoxic T cells, activated lymphocytes, and natural killer cells among responders. They observed higher neutrophil percentage, lower lymphocyte percentage, and lower counts of total T cells, CD4+ T cells, CD8+ T cells and NK cells at day 0 of admission; lower counts of CD27+ and CD3+HLA DR+ lymphocytes at day 7 of admissions were associated with mortality in COVID-19 patients [42]. Mathew et al used high-dimensional flow cytometry to perform immune profiling of B and T lymphocyte populations. They examined six important CD8 T cell populations: naïve (CD45RA+CD27+CCR7+CD95-), central memory [CD45-RA-CD27+CCR7+ (CM)], effector memory [CD45RA-CD27+CCR7- (EM1), CD45RA-CD27-CCR7+ (EM2), CD45RA-CD27-CCR7- (EM3)], and effector memory T cells re-expressing CD45RA (EMRA) (CD45RA+CD27-CCR7-) CD8 T cells. Among the different populations of CD8 T cells in COVID-19 patients, they found increase in the EM2 and EMRA T cell populations and a decrease in EM1T cell population. There is also increase in frequency of CD39+ cells in COVID-19 patients. They also suggested that, there was a significant increase in KI67+ and also CD38+HLA-DR+ non-naïve CD8 T lymphocyte population in COVID-19 patients. They also analyzed six CD4 T lymphocyte subsets including naïve; EM1, EM2, and EM3; CM; and EMRA along with circulating T follicular helper cells [CD45RA-PD-1+CXCR5+

(cTFH)] and activated circulating TFH cells [CD38+ICOS+]. They observed a relative loss of naïve CD4 T cells with increased EM2 and EMRA T-cell populations and increased KI67+ or CD38+HLA-DR+ non-naïve CD4 T cells in COVID-19 patients [3]. B-cell population is also reduced in those with severe disease, while a significantly increased proportion of circulating CD19+CD20-CD38hiCD27hi plasmablasts is seen [42]. Methew et al suggested that there was also alteration in B cell subpopulations in patients with COVID-19. Naïve B cell subpopulations were not altered, however the class-switched (IgD-CD27+) and not-class-switched (IgD+CD27+) memory B cells were significantly reduced. CD27-IgD- B cells and CD27+CD38+ PBs were markedly increased. The expression of CXCR5 was also reduced on all major B cell subpopulations in COVID-19 patients [3]. Rendeiro et al [43] used several independent fluorochrome-conjugated antibody panels, each targeting a specific surface protein marker of T, B, NK, and myeloid-derived suppressor cells (MDSCs), for high-dimensional immune cell profiling of circulating blood by flow cytometry. They observed that there is progressive loss of circulating lymphocytes and selective expansion of NK populations and MDSCs (especially granulocytic cell-MDSCs), suggesting that the innate compartment may contribute to the immunological disarray of COVID-19 patients. He also observed that in the B-cell population, there is lower expression of CD19 and higher expression of membrane bound IgM and IgG in COVID-19 patients, which suggested that after viral exposure, B cells undergo plasmacytoid maturation and immunoglobulin switching. They also found abnormal and delayed maturation of plasma cells [43]. Zhang et al suggested that, there is presence of FSC-high monocytic population in COVID-19 which expresses higher levels of macrophage markers CD80 and CD206 [29]. Some authors suggest that there is correlation between the severity of COVID-19 and the level of HLA-DR found on monocytes; those with severe and critical COVID-19 showed reduced HLA-DR on their monocytes. The monocytes in COVID-19 contain a decreased number of classical subset (CD14++, CD16-) with an increase in intermediate (CD14+, CD16+) and non-classical subsets (CD14+, CD16++) [44]. CD64 on neutrophils and CD169 on monocytes were the two main biomarkers assessed in the study by flow cytometry for discriminating between bacterial versus COVID-19 or other viral infections [45].

Bone marrow smear

In COVID-19, BM shows trilineage hematopoiesis, sometimes with myeloid hyperplasia and/or a left shift. Severe COVID-19 patients show histiocytic proliferation with hemophagocytosis in the BM aspirates and may indicate worse clinical outcomes [21, 46]. COVID-19 may predispose to hemophagocytic lymphohistocytosis (HLH) through activation of the IL-1/IL-6 pathway, including overproduction of IL-1β by macrophages. There is an increase in pleomorphic megakaryocytes, plasma cells and macrophages in COVID-19 [47].

Coagulation profile

Coagulopathy is a high risk factor for morbidity and mortality in patients with COVID-19 [48]. In more than 70% of patients who succumb to the infection has been reported to develop DIC [49]. Apart from thrombotic complications, bleeding also causing significant morbidity in COVID-19. The thrombotic complication rate was reported as 9.5% and bleeding rate as 4.8% and major bleeding rate as 2.3% [50]. Patients with COVID-19 have prolonged prothrombin time (PT), prolonged activated partial thromboplastin time (APTT), increased D-Dimer, increased fibrin degradation products (FDP) and increased fibrinogen. Endothelial activation markers as von Willebrand factor, Factor VIII and P-selectin are increased in COVID-19. Plasminogen activator inhibitor 1 (PAI-1) which is a fibrinolytic inhibitor is also increased in COVID-19. Cause of thromboembolism in COVID 19 are: a) activation and damage of endothelial cell due to SARS-CoV-2 spike protein binding to endothelial cells through ACE2 receptors; b) hypoxia can cause endothelial dysfunction and hypercoagulability; c) increased blood viscosity due to uncontrolled release of a large amount of inflammatory mediators- cytokines and chemokines and, also due to application of hormones and immunoglobulins in severe or critically ill patients; d) reduced fibrinolysis in severe COVID-19 cases, e) complement activation may augment thrombotic complication; f) prolonged immobilization during illness, dehydration, presence of other cardiovascular risk factors; g) vascular endothelial damage may be

caused by mechanical ventilation, central venous catheterization, and surgery. Studies suggested that at initial presentation in hospitalized COVID-19 patients, elevated levels of D-dimer, platelet count, CRP, and ESR were predictive of thrombotic complications; and thrombocytopenia (platelet count <150 × 10^9/L) and elevations in D-dimer >2500 ng/mL were predictive of bleeding complications [50].

Prognostication

Haematological and biochemical changes in laboratory investigations assist in recognition of disease progression. RDW which is routinely measured with CBC appear to a nonspecific biomarker for risk stratification in COVID-19 patients. Foy et al described that elevated RDW (>14.5%) at the time of hospital admission were associated with significant increased mortality risk (11% *Vs* 31%) for patients with COVID-19 and they were 6 times more likely to die within 48 hours than the patients with normal RDW at the time of admission. Along with that they suggested that during hospitalisation, an increasing RDW was associated with increased risk of mortality (>0.5% increase in RDW increase mortality rate from 6% to 24%) [51]. Other studies also indicate RDW as marker of complication in COVID-19. In COVID-19, anaemia is an independent predictor of poor outcome as in several other respiratory diseases. The median haemoglobin level was lower in severe cases than in non-severe cases [40]. Lymphopenia in COVID-19, seems to be the most relevant severity biomarker of the infection [52]. The definition of lymphopenia is different in different studies, however lymphocyte count ≤ 1100 μL in few studies showed consistent results. Huang et al [53] and Wang et al [54] found that there was an association between lymphopenia and need of ICU care. Wu et al [55] showed an association between lymphopenia and acute ARDS development. Increased total leucocyte count and absolute neutrophil count were high risk factors for severe COVID-19 and were associated with increased risk of death [55]. NLR and platelet/lymphocyte ratio (PLR) at peak platelets have prognostic value in determining severe cases [56]. Fan et al [21] found that patient requiring ICU care had lymphopenia, neutrophila, high LDH and were of older age. A decreased lymphocyte/leukocyte count ratio has been reported indicating severe disease and/or fatal outcomes [57]. Study also suggested that increased neutrophil/lymphocyte and neutrophil/platelets ratio may be indicative of myocardial injury and increased mortality [20, 58]. Pakos et also stated that a higher rate of death mortality is associated with lower absolute monocyte count and higher NLR [40]. In addition to the NLR, NCD4LR is associated with a longer virus negative conversion time and with a prolonged virus clearance and worse immune function [28]. The LMR value may also be considered a clinical marker to show the severity of the disease. Another biomarker, the neutrophil count to albumin ratio, has also been described as a predictor of mortality in COVID-19 patients [29]. Studies suggested that thrombocytopenia is significantly associated with increased risk of severe disease, need for ICU care and mortality in COVID-19 [59]. Inflammatory indices, including increased ESR, CRP, LDH (>250 U/L) and IL-6 can also use as predictor for dismal prognosis. Increased LDH may reflect multiple organ injury and is also associated with higher risk of acute respiratory distress syndrome, need of ICU care and mortality [10, 11, 13]. Henry et al described that elevated LDH was associated with more than 6 fold increase in odds of severe disease and more than 16 fold increase in odds of mortality [10]. In COVID-19 a high CRP level (>10 mg/Liter) is associated with unfavourable aspects, such as development of ARDS, higher Troponin-T levels, myocardial injury and death [5, 55, 56, 59]. COVID-19 patients with elevated bilirubin are associated with worse prognoses and severe disease [15]. High serum ferritin levels is associated with increased death as suggested by Zhou et al. [18]. Increased levels of IL-6 and LDH have been associated with increased risk of death [55]. In COVID-19, high procalcitonin level can also be used as predictor of patients at high risk for clinical deterioration or bacterial co-infection [22, 60]. Studies also suggested that increased PCT value is associated with an approximately 5-fold higher risk of severe infection [5]. Increased levels of IL-2, IL-6, IL-7, IL-10, TNF-α, G-CSF, MCP-1, IP-10 and MIP-1α are common in patient requiring ICU care [20]. Liu et al suggested that increased LDH and CRP, lymphopenia, neutrophilia, hypoalbuminemia are predictors for the severity of COVID-19 patients [12, 13]. Plasma angiotensin II lev-

els in COVID-19 patients were significantly higher and strongly correlated with viral load and lung injury [20]. D-dimer levels above 1 μg/mL at admission were associated with a greater chance of death. Increased ALT, highly sensitive cardiac troponin I, serum ferritin (>300 ng/mL), CK, D-dimer, prothrombin time and creatinine were associated with decreased survival and increased requirement for ICU [20]. Increased level of D-dimer reflect the progression to DVT and pulmonary embolism, and can predict severity and mortality of COVID-19 disease [33]. Marwah et al suggested NLR above 7.4, urea to albumin ratio above 0.28 and (ALP × ALT) to albumin index above 238 (specific to the Caucasian group) can be used as severity indicators by clinicians and appropriate intervention should be taken to reduce the rate of mortality in COVID-19 patients [61]. Few studies established relationship between flowcytometric immune proofing of COVID-19 patients with disease severity. Rendeiro et al found that in patients with COVID-19, an increased CD25+ T cells was indicative of a higher state of activation and increase in CD95+ with disease progression [43].

COVID-19 disease has prominent manifestations related to hematopoietic system and often associated with a major blood hypercoagulability. Routine hematology parameters are important predictors of COVID-19 severity. The monitoring of hematological parameters is essential and can assist in the identification of patients who will need care in the Intensive care unit. It causes a spectrum of haematological changes, ranging from mild cytopenia to some patients develop a severe proinflammatory state which can be associated with a unique coagulopathy. The lymphopenia, thrombocytopenia, and elevated D-dimer and CRP levels are the common hematological abnormalities in COVID-19. Studies has reported leucopenia with moderate to severe lymphopenia and mild thrombocytopenia at the time of hospital admission. Lymphopenia is the most common laboratory finding in COVID-19. There is presence of reactive lymphocytes, of which a subset appeared monocytoid or lympho-plasmacytoid. Large atypical, bizarre looking mononuclear cells are also commonly seen. Neutrophilia with dyspoiesis may be noted. COVID-19 may predispose to hemophagocytic lymphohistocytosis in bone marrow. More studies regarding changes of lymphocyte subsets, such as CD4+ T cells, CD8+ T cells, B cells, and NK cells in patients with COVID-19 and their correlation with the severity and outcome of the patients are required to get a clarity about dynamics of lymphocyte subsets. The severity of COVID-19 depends on several factors including age, gender, and the presence of existing comorbidities such as diabetes, hypertension, or respiratory disease. Several time consuming risk scores are designed by combining patient characteristics, physiological parameters, biochemical parameters, and radiological features. Abnormalities in routine laboratory and hematological tests have the potential to indicate severity in COVID-19, in a quick, practical and economical way. Haematological and biochemical changes in laboratory investigations assist in prognostication and recognition of disease progression. So, serial monitoring of these markers as D-dimer levels may be considered in view of practical clinical decisions making. Patient outcome can be improved by taking preventive measures for thromboprophylaxis and by early identification of potentially lethal complications including DIC that will reduced overall morbidity and mortality in COVID-19 patients. A deep understanding of the laboratory findings and haematological abnormalities associated with SARS-CoV-2 infection would help to raise disease suspicion in absence of Real time polymerase chain reaction or antibody results. Also the blood counts along with the morphological changes in peripheral blood would be helpful in prompt screening, diagnosis, prognosis and management of COVID-19 patients. Flow cytometry immunophenotyping of peripheral blood may help to predict the risk of clinical progression and dynamic changes in patients with COVID-19. Patients developing critical levels of haematological and biochemical parameters are associated with severe disease and higher mortality, so identification of critically ill patients at an early stage is important to reduce morbidity and mortality of COVID-19 patients. Careful evaluation of laboratory indices at baseline and during the disease course can assist clinicians in modulating treatment approach and promptly provide intensive care when needed.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Smeeta Gajendra, Department of Laboratory Oncology, Dr BRA IRCH, All India Institute of Medical Sciences, New Delhi 110029, India. Tel: 9013590875; E-mail: drsmeeta@gmail.com

References

[1] Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, Li P, Zhou Y, Lin YF, Duan Q, Luo G, Fan S, Lu Y, Feng A, Zhan Y, Liang B, Cai W, Zhang L, Du X, Li L, Shu Y and Zou H. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. J Infect 2020; 80: 656-665.

[2] Baj J, Karakuła-Juchnowicz H, Teresiński G, Buszewicz G, Ciesielka M, Sitarz E, Forma A, Karakuła K, Flieger W, Portincasa P and Maciejewski R. COVID-19: specific and non-specific clinical manifestations and symptoms: the current state of knowledge. J Clin Med 2020; 9: 1753.

[3] Mathew D, Giles JR, Baxter AE, Oldridge DA, Greenplate AR, Wu JE, Alanio C, Kuri-Cervantes L, Pampena MB, D'Andrea K, Manne S, Chen Z, Huang YJ, Reilly JP, Weisman AR, Ittner CAG, Kuthuru O, Dougherty J, Nzingha K, Han N, Kim J, Pattekar A, Goodwin EC, Anderson EM, Weirick ME, Gouma S, Arevalo CP, Bolton MJ, Chen F, Lacey SF, Ramage H, Cherry S, Hensley SE, Apostolidis SA, Huang AC, Vella LA; UPenn COVID Processing Unit, Betts MR, Meyer NJ and Wherry EJ. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. Science 2020; 369: eabc8511.

[4] Yuki K, Fujiogi M and Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol 2020; 215: 108427.

[5] Cascella M, Rajnik M, Cuomo A, Dulebohn SC and Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). 2021 Mar 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.

[6] Parasher A. COVID-19: current understanding of its pathophysiology, clinical presentation and treatment. Postgrad Med J 2021; 97: 312-320.

[7] Karimi Shahri M, Niazkar HR and Rad F. COVID-19 and hematology findings based on the current evidences: a puzzle with many missing pieces. Int J Lab Hematol 2021; 43: 160-168.

[8] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T and Chen Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020; 12: 8.

[9] Mei H and Hu Y. Characteristics, causes, diagnosis and treatment of coagulation dysfunction in patients with COVID-19. Zhonghua Xue Ye Xue Za Zhi 2020; 41: 185-191.

[10] Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M and Lippi G. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: a pooled analysis. Am J Emerg Med 2020; 38: 1722-1726.

[11] Ponti G, Maccaferri M, Ruini C, Tomasi A and Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci 2020; 57: 389-399.

[12] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY and Zhong NS; China Medical Treatment Expert Group for COVID-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708-1720.

[13] Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Feng C, Zhang Z, Wang L, Peng L, Chen L, Qin Y, Zhao D, Tan S, Yin L, Xu J, Zhou C, Jiang C and Liu L. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020; 63: 364-374.

[14] Moon AM and Barritt AS 4th. Elevated liver enzymes in patients with COVID-19: look, but not too hard. Dig Dis Sci 2020: 66: 1767-1769.

[15] Liu Z, Li J, Long W, Zeng W, Gao R, Zeng G, Chen D, Wang S, Li Q, Hu D, Guo L, Li Z and Wu X. Bilirubin levels as potential indicators of disease severity in coronavirus disease patients: a retrospective cohort study. Front Med (Lausanne) 2020; 7: 598870.

[16] Xiang HX, Fei J, Xiang Y, Xu Z, Zheng L, Li XY, Fu L and Zhao H. Renal dysfunction and prognosis of COVID-19 patients: a hospital-based retrospective cohort study. BMC Infect Dis 2021; 21: 158.

[17] Han X and Ye Q. Kidney involvement in COVID-19 and its treatments. J Med Virol 2021; 93: 1387-1395.

[18] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H and Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-1062.

[19] Li L, Zhou Q and Xu J. Changes of laboratory cardiac markers and mechanisms of cardiac injury in coronavirus disease 2019. Biomed Res Int 2020; 2020: 7413673.

[20] Letícia de Oliveira Toledo S, Sousa Nogueira L, das Graças Carvalho M, Romana Alves Rios D

and de Barros Pinheiro M. COVID-19: review and hematologic impact. Clin Chim Acta 2020; 510: 170-176.
[21] Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, Mucheli SS, Kuperan P and Ong KH. Hematologic parameters in patients with COVID-19 infection. Am J Hematol 2020; 95: E131-E134.
[22] Lazarian G, Quinquenel A, Bellal M, Siavellis J, Jacquy C, Re D, Merabet F, Mekinian A, Braun T, Damaj G, Delmer A and Cymbalista F. Autoimmune haemolytic anaemia associated with COVID-19 infection. Br J Haematol 2020; 190: 29-31.
[23] Liao YC, Liang WG, Chen FW, Hsu JH, Yang JJ and Chang MS. IL-19 induces production of IL-6 and TNF-alpha and results in cell apoptosis through TNF-alpha. J Immunol 2002; 169: 4288-97.
[24] Chan JF, Zhang AJ, Yuan S, Poon VK, Chan CC, Lee AC, Chan WM, Fan Z, Tsoi HW, Wen L, Liang R, Cao J, Chen Y, Tang K, Luo C, Cai JP, Kok KH, Chu H, Chan KH, Sridhar S, Chen Z, Chen H, To KK and Yuen KY. Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility. Clin Infect Dis 2020; 71: 2428-2446.
[25] Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, Gottfried E, Schwarz S, Rothe G, Hoves S, Renner K, Timischl B, Mackensen A, Kunz-Schughart L, Andreesen R, Krause SW and Kreutz M. Inhibitory effect of tumor cell-derived lactic acid on human T cells. Blood 2007; 109: 3812-9.
[26] Cavalcante-Silva LHA, Carvalho DCM, Lima ÉA, Galvão JGFM, da Silva JSF, Sales-Neto JM and Rodrigues-Mascarenhas S. Neutrophils and COVID-19: the road so far. Int Immunopharmacol 2021; 90: 107233.
[27] Wang H, Zhang Y, Mo P, Liu J, Wang H, Wang F and Zhao Q. Neutrophil to CD4+ lymphocyte ratio as a potential biomarker in predicting virus negative conversion time in COVID-19. Int Immunopharmacol 2020; 85: 106683.
[28] Varim C, Yaylaci S, Demirci T, Kaya T, Nalbant A, Dheir H, Senocak D, Kurt R, Cengiz H and Karacaer C. Neutrophil count to albumin ratio as a new predictor of mortality in patients with COVID-19 ınfection. Rev Assoc Med Bras (1992) 2020; 662 Suppl 2: 77-81.
[29] Zhang D, Guo R, Lei L, Liu H, Wang Y, Wang Y, Qian H, Dai T, Zhang T, Lai Y, Wang J, Liu Z, Chen T, He A, O'Dwyer M and Hu J. Frontline science: COVID-19 infection induces readily detectable morphologic and inflammation-related phenotypic changes in peripheral blood monocytes. J Leukoc Biol 2021; 109: 13-22.
[30] Du Y, Tu L, Zhu P, Mu M, Wang R and Yang P. Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study. Am J Respir Crit Care Med 2020; 201: 1372-1379.
[31] Fraissé M, Logre E, Mentec H, Cally R, Plantefève G and Contou D. Eosinophilia in critically ill COVID-19 patients: a French monocenter retrospective study. Crit Care 2020; 24: 635.
[32] Pavord S, Thachil J, Hunt BJ, Murphy M, Lowe G, Laffan M, Makris M, Newland AC, Provan D, Grainger JD and Hill QA. Practical guidance for the management of adults with immune thrombocytopenia during the COVID-19 pandemic. Br J Haematol 2020; 189: 1038-1043.
[33] Aggarwal M, Dass J and Mahapatra M. Hemostatic abnormalities in COVID-19: an update. Indian J Hematol Blood Transfus 2020; 36: 1-11.
[34] Kaur G, Sandeep F, Olayinka O and Gupta G. Morphologic changes in circulating blood cells of COVID-19 patients. Cureus 2021; 13: e13416.
[35] Singh A, Sood N, Narang V and Goyal A. Morphology of COVID-19-affected cells in peripheral blood film. BMJ Case Rep 2020; 13: e236117.
[36] Nath D, Madan U, Singh S, Tiwari N, Madan J and Agrawal R. CBC parameters and morphological alterations in peripheral blood cells in COVID-19 patients: their significance and correlation with clinical course. International Journal of Health and Clinical Research 2020; 3: 95-108.
[37] Ahnach M, Ousti F, Nejjari S, Houssaini MS and Dini N. Peripheral blood smear findings in COVID-19. Turk J Haematol 2020; 37: 310-302.
[38] Mitra A, Dwyre DM, Schivo M, Thompson GR 3rd, Cohen SH, Ku N and Graff JP. Leukoerythroblastic reaction in a patient with COVID-19 infection. Am J Hematol 2020; 95: 999-1000.
[39] Zini G, Bellesi S, Ramundo F and d'Onofrio G. Morphological anomalies of circulating blood cells in COVID-19. Am J Hematol 2020; 95: 870-872.
[40] Erdinc B, Sahni S and Gotlieb V. Hematological manifestations and complications of COVID-19. Adv Clin Exp Med 2021; 30: 101-107.
[41] Moratto D, Chiarini M, Giustini V, Serana F, Magro P, Roccaro AM, Imberti L, Castelli F, Notarangelo LD and Quiros-Roldan E. Flow cytometry identifies risk factors and dynamic changes in patients with COVID-19. J Clin Immunol 2020; 40: 970-973.
[42] Rezaei M, Marjani M, Mahmoudi S, Mortaz E and Mansouri D. Dynamic changes of lymphocyte subsets in the course of COVID-19. Int Arch Allergy Immunol 2021; 182: 254-262.

[43] Rendeiro AF, Casano J, Vorkas CK, Singh H, Morales A, DeSimone RA, Ellsworth GB, Soave R, Kapadia SN, Saito K, Brown CD, Hsu J, Kyriakides C, Chiu S, Cappelli LV, Cacciapuoti MT, Tam W, Galluzzi L, Simonson PD, Elemento O, Salvatore M and Inghirami G. Profiling of immune dysfunction in COVID-19 patients allows early prediction of disease progression. Life Sci Alliance 2020; 4: e202000955.

[44] Patterson BK, Francisco EB, Yogendra R, Long E, Pise A, Rodrigues H, Hall E, Herrera M, Parikh P, Guevara-Coto J, Triche TJ, Scott P, Hekmati S, Maglinte D, Chang X, Mora-Rodríguez RA and Mora J. Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection. Front Immunol 2022; 12: 746021.

[45] Bourgoin P, Soliveres T, Barbaresi A, Loundou A, Belkacem IA, Arnoux I, Bernot D, Loosveld M, Morange PE, Michelet P, Malergue F and Markarian T. CD169 and CD64 could help differentiate bacterial from COVID-19 or other viral infections in the emergency department. Cytometry A 2021; 99: 435-445.

[46] Harris CK, Hung YP, Nielsen GP, Stone JR and Ferry JA. Bone marrow and peripheral blood findings in patients infected by SARS-CoV-2. Am J Clin Pathol 2021; 155: 627-637.

[47] Rahman A, Niloofa R, Jayarajah U, De Mel S, Abeysuriya V and Seneviratne SL. Hematological Abnormalities in COVID-19: a narrative review. Am J Trop Med Hyg 2021; 104: 1188-1201.

[48] Wool GD and Miller JL. The impact of COVID-19 disease on platelets and coagulation. Pathobiology 2021; 88: 15-27.

[49] Tang N, Li D, Wang X and Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18: 844-847.

[50] Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ and Rosovsky RP. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020; 136: 489-500.

[51] Foy BH, Carlson JCT, Reinertsen E, Padros I Valls R, Pallares Lopez R, Palanques-Tost E, Mow C, Westover MB, Aguirre AD and Higgins JM. Association of red blood cell distribution width with mortality risk in hospitalized adults With SARS-CoV-2 infection. JAMA Netw Open 2020; 3: e2022058.

[52] Duarte FB, Lemes RPG, Duarte IA, Duarte BA and Duarte JVA. Hematological changes in Covid-19 infections. Rev Assoc Med Bras (1992) 2020; 66: 99.

[53] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J and Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.

[54] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X and Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061-1069.

[55] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J and Song Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020; 180: 934-943.

[56] Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, Psaltopoulou T, Gerotziafas G and Dimopoulos MA. Hematological findings and complications of COVID-19. Am J Hematol 2020; 95: 834-847.

[57] Deng Y, Liu W, Liu K, Fang YY, Shang J, Zhou L, Wang K, Leng F, Wei S, Chen L and Liu HG. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: a retrospective study. Chin Med J (Engl) 2020; 133: 1261-1267.

[58] Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X and Lu Z. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 2020; 5: 811-818.

[59] Lippi G, Plebani M and Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta 2020; 506: 145-148.

[60] Lippi G and Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chim Acta 2020; 505: 190-191.

[61] Marwah M, Marwah S, Blann A, Morrissey H, Ball P and Wandroo FA. Analysis of laboratory blood parameter results for patients diagnosed with COVID-19, from all ethnic group populations: a single centre study. Int J Lab Hematol 2021; 43: 1243-1251.