ISSN: 2754-4931

Journal of Gastroenterology & Hepatology Reports

SCIENTIFIC Research and Community

Review Article

Open Access

A Review on Hematological Abnormalities Related with COVID-19

Manir Hasan[1], Runa Akter[2], Mobinul Haque Adon[3] and Ishrat Jahan[1]*

[1]Department of Pharmacy, University of Asia Pacific, Dhaka-1205, Bangladesh

[2]Department of Pharmacy, Independent University Bangladesh, Dhaka-1229, Bangladesh

[3]Department of Pharmacy, State University of Bangladesh, Dhaka-1461, Bangladesh

ABSTRACT

The COVID-19 outbreak caused by the SARS-CoV-2 virus began in Hubei province, Wuhan, China. SARS-CoV-2 is a highly transmissible virus that spreads rapidly around the world. At the end of 2019, and has since spread worldwide, this virus has infected over 14 million people and killed over 600,000 people, making it a major public health problem. Coronavirus disease It is now understood to be a multisystem disease with a wide range of symptoms are caused by Covid-19. In severe COVID-19 cases, symptoms may lead to acute respiratory distress syndrome (ARDS), metabolic acidosis, multi-organ failure, and shock. Patients' conditions may deteriorate to the point of death because of these factors. Although pulmonary signs are the most common symptom, various hematological abnormalities have also been discovered. This study highlights the observed hematological abnormalities (platelet, white blood cell, and hemoglobin changes, as well as coagulation/fibrinolytic modifications), investigates their pathomechanisms, and addresses treatment options. Lymphocytopenia, thrombocytopenia, and increased D-dimer levels are all common hematological anomalies in COVID-19. These changes are more widespread and evident in patients with severe COVID-19 disease, suggesting that they could be used as a biomarker for those who require hospitalization and intensive care unit care. Coagulation anomalies should be closely monitored, and actions should be taken to prevent or lessen their negative consequences. COVID-19 effect in patients with hematological abnormalities, as well as known hematological drug toxicities of COVID-19 therapy, are also discussed.

***Corresponding author**

Ishrat Jahan, Department of Pharmacy, University of Asia Pacific, Dhaka-1205, Bangladesh.

Received: March 02, 2024; **Accepted:** March 13, 2024; **Published:** March 20, 2024

Keywords: COVID-19, Hematological Abnormalities, Coagulation, Biomarkers

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) is a highly contagious virus that spreads quickly around the world. The consequence is the outbreak in Hubei province, Wuhan, China, for the first time [1]. World Health Organization (WHO) declared a pandemic on Mar 11, 2020, due to its emergence as a global threat. According to the report submitted to WHO, over 7,200,000 infected cases and 400,000 deaths have been filed [2]. Six coronaviruses responsible for human infections such as HCoV-229E, HCoV OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, and MERS-CoV. SARS-CoV is a severe acute respiratory syndrome (SARS), and MERS-CoV is the Middle East respiratory syndrome (MERS). However, the common cold happens for the first four viruses [3]. The newly discovered β-coronavirus is a spherical or oval-shaped virus particle enveloped. Although SARS-CoV and MERS-CoV belong to the same genus, they show significant differences in genetic characteristics. The virus was recommended the name "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) by the Coronavirus Study Group of the International Committee on Virus Taxonomy after assessment [4]. It belongs to the Coronaviridae family and Coronavirinae subfamily. The alpha-, beta-, gamma-, and delta coronaviruses are four genera depending on their genetic characteristics. These are enveloped, positive-sense, single-stranded RNA viruses and are available broadly among humans, other mammals, and birds and cause respiratory, enteric, hepatic, and neurologic diseases [5].

COVID-19 can be presented by fever, dry cough, shortness of breath in most cases, lung infection, and even acute respiratory distress syndrome (ARDS) and also by some non-respiratory symptoms, e.g., headache, muscle ache, dyspnea, rhinorrhea, sneezing, sore throat, diarrhea, and vomiting are reported. Critical illness can be characterized by nausea, respiratory failure, septic shock, and organ failure [6]. Refractory metabolic acidosis, coagulation malfunction, multiple organ failure, and death in some situations indicate severe cases [7]. Most of the ill people are asymptomatic or have just subtle symptoms. Observational studies prove that older people with respiratory or cardiovascular disease may acquire a severe form.

In New York State, the incidence of multisystem inflammatory syndrome in children coincided with CoV-2 transmission and showed an association of cardiac dysfunction with dermatologic, mucocutaneous, and gastrointestinal manifestations [8].

Though 2019-nCoV can be easily transmitted in humans, there is no correlation between disease severity and transmission efficiency. Person-to-person transmission can occur efficiently through an infected person's respiratory droplets generated through coughing and sneezing as an indirect factor disease severity plays a vital role in identifying an infected one. If an infection is asymptomatic

or not showing any serious condition, the ultimate consequence is hospitalization. Otherwise, they can potentially spread the virus to their contacts while going to work and traveling [9].

One can easily spread the infection by touching the nose, eyes, or mouth with virus-infected hands. In order to fight against COVID-19 transmission, hand cleanliness, personal protective equipment, and maintaining social distancing are all required methods. The movement of uninfected persons and sick people should be restricted, and quarantine measures should be created in locations with an epidemic outbreak. To reduce transmission, urgent management strategies such as isolation, respiratory and eye protection, and hand hygiene can be adopted [7].

Although respiratory distress is the prime concern about covid-19, other cardiac, hematological, neurological, and renal complications have also been reported. Hematological abnormalities such as anomalies in platelet, white blood cell, hemoglobin levels, and coagulation/fibrinolytic alterations, along with their pathomechanisms and management, are reviewed here.

Methodology

The PubMed, Google Scholar, and Science Direct databases conveyed an online literature search. We used the search keywords for MERS-CoV, SARS-CoV-2, COVID-19, clinical results, laboratory findings, hematological abnormalities, and coagulopathy. We have shortlisted the article based on the title, abstract, and study outcome.

Table 1: Hematological Abnormalities Associated with COVID-19

Sample Size	Findings				
	Platelet	**Coagulation Parameters**	**Red Blood Cells**	**WBCs**	**References**
99	12% Thrombocytopenia	Prothrombin time 30% decrease Increase in D-dimer 36%, LDH 76% and CRP 86%	Hb-51% decrease	9% Leucopenia 38% Neutrophilia 35% Lymphopenia	[10]
(58 Non-ICU and 9 ICU)	20% Mild thrombocytopenia Patients in the ICU are more likely to acquire neutrophilia during their stay.	LDH levels are higher in ICU patients.	HB levels in ICU patients dropped during their stay in the hospital.	29.2% Leukopenia 36.9% Lymphopenia Both were more noticeable in the ICU group.	[11]
(41)	NT	In ICU patients, prothrombin time and D-dimer levels are greater.	NT	25% Leucopenia 63% Lymphopenia	[12]
(78)	NT	CRP was significantly higher in the disease progression group; albumin was significantly lower, and D-dimer was somewhat higher in the disease progression group.	Platelets drop slightly as the disease progresses.	In the illness development and stabilization groups, there was no significant difference in WBC. In the disease progression group, lymphocytes are slightly lower.	[13]
(91) 9-severe 82-non-severe	10.9% Thrombocytopenia	24.2% D-dimer 53.8% CRP (High) 24.2% fibrinogen (Low) 47.3% albumin (Low) Severe patients have higher CRP and D-dimer levels than non-severe patients.	Hb 36.3% decreased 11% Lower Red blood cell	30.7% Lymphopenia 15.4% Lower WBC count 11% Low neutrophil 3.3% neutrophil increased Severe patients had more neutrophils and fewer lymphocytes than non-severe patients.	[14]

(452)	NT	Severe patients have higher procalcitonin, CRP, and serum ferritin levels than non-severe patients.	NT	Compared to non-severe patients, severe patients exhibited considerably larger leukocytes, neutrophils, and neutrophil-to-lymphocyte ratios and lower monocyte and eosinophil counts.	[15]
(150) 68-non survivor, 82-survivor	Platelet count is significantly lower in non-survivors than in survivors	Non-survivors had higher albumin, serum ferritin, and CRP levels than survivors.	NT	Non-survivors have a higher WBC count than survivors. The number of lymphocytes in non-survivors is much lower than in survivors.	[16]
(135) mild 95, severe 40	17% Thrombocytopenia	Prothrombin time 10.9 (10.5–11.4) Severe patients had greater D-dimer and LDH levels than mild ones.	NT	20.7% Leucopenia 50.4% Lymphopenia	[17]
(69)	Within a reasonable range	41% lactate dehydrogenase 67% CRP	Within a reasonable range	42% Lymphocytopenia	[18]
(138, 36 in ICU and 02 Non-ICU)	ICU patients had a slightly lower median platelet count than non-ICU patients.	ICU patients had considerably higher D-dimer, creatine kinase, and lactate dehydrogenase levels than non-ICU patients.	NT	ICU patients have a higher WBC and neutrophil count than non-ICU patients. The median lymphocyte count was lower than expected.	[19]
(201)	18.8% Thrombocytopenia	23.3% D-dimer Patients with ARDS had significantly higher levels. 2.1% Prolonged prothrombin time 85.6% CRP	NT	64% Lymphocytopenia Patients with ARDS have a significantly lower risk of death. 23.4% Leukocytosis 34.5% Neutrophilia 9.1% Monocyte	[20]
(90)	NT	42% CRC	NT	21% Leucopenia 3% Leukocytosis	[21]
(102)	In both survivors and non-survivors, the median platelet count was normal.	Non-survivors have a somewhat longer prothrombin time than survivors.	NT	85% Lymphocytopenia There is no difference between survivors and non-survivors.	[22]
(50)	NT	In severe individuals, procalcitonin and CRP levels are much greater.	NT	72% Lymphopenia There was no discernible difference between severe and non-severe patients.	[23]

(280)	NT	43.2% D-dimer 91.9% CRP Severe patients have much higher D-dimer and CRP levels.	NT	Decrease 19.6% Leukocytes Decrease 75.4% Lymphocyte 52.9% Eosinophil Between severe & non-severe patients, a median value for leukocytes and lymphocyte percentage was significantly lower.	[24]
(191)	7% Thrombocytopenia Thrombocytopenia was found in more non-survivors than survivors.	32% D-dimer Throughout the clinical course, non-survivors had higher levels than survivors. 6% prothrombin time	NT	40% Lymphocytopenia 17% Leukocytopenia Non-survivors had considerably fewer leukocytes and lymphocytes than survivors.	[25]

ARDS: Acute Respiratory Distress Syndrome
CRP: C-Reactive Protein
ICU: Intensive Care Unit
WBC: White Blood Cell

Hematological Abnormalities during Covid-19

The COVID-19 virus alters the humoral immune response to disease pathogenesis and clinical manifestation. An uncontrolled inflammatory response is triggered by the antiviral immune system leading to cause hematological abnormalities such as thrombocytopenia, lymphopenia, and abnormalities in granulocyte and monocyte [26]. Coagulation abnormalities, e.g., the elevation of D-dimer level and prothrombin time, have also been reported following infection. Thrombosis, including deep vein and multi-organ, has been reported. In fatal cases, disseminated intravascular coagulation (DIC) induced by MERS was also reported [27]. Figure 1 shows the proposed mechanism of hematological abnormalities (60) including thrombocytopenia, lymphopenia, neutrophilia, and other associated coagulation abnormalities.

Thrombocytopenia in Covid-19

Infecting bone marrow cells, Coronaviruses cause abnormal hematopoiesis [28]. Approximately 82% of homology in nucleotide sequence is found in SARS-CoV-2 and human SARS-CoV [29]. As a marker of granulocytes and monocytes, N CD13 (aminopeptidase) is found almost everywhere, such as epithelial cells of the respiratory tract and kidneys, the small intestine, activated endothelial cells, lymphocytes, and platelets. HCoV-229E induces growth inhibition and apoptosis in the bone marrow by taking entry through CD13 receptors leading to aberrant hematopoiesis and thrombocytopenia [30]. As a result, primary platelet formation is decreased leading to thrombocytopenia.

Secondary hemophagocytic lymphohistiocytosis (sHLH) is a phenomenon where excessive proliferation and activation of the reticuloendothelial system occurs, which results in the release of many inflammatory cytokines and the engulfment of a large number of blood cells. Cytokine storm is responsible for the destruction of the hematopoietic progenitor cells in bone marrow in pneumonic patients resulting in the decreased primary production of platelets swallowing of too many blood cells leading to the decrease of peripheral blood platelet count [31].

During pulmonary circulation, a large number of megakaryocytes can release platelets. However, continuing hypertension and oxygen toxicity worsen lung injury, resulting in fibrosis. The megakaryocyte process is ruptured, and platelet release is blocked due to the damage of pulmonary capillary beds, which affects the liberation of platelets into the pulmonary circulation. Platelet synthesis is reduced in blood circulation indirectly [32].

The immune system may also destroy the platelets in COVID-19 as the degree of autoantibodies and immune complexes increase. An association of circulating immune complexes containing platelet membrane components and the anti-platelet membrane GPIIIa49-66 IgG antibodies have been proven [33]. Reticuloendothelial cells can easily recognize the antibodies and immune complexes accumulated on the surfaces of platelets and will target the platelets for destruction, ensuing excessive platelet destruction. Immune-mediated damage occurs in those platelets with similar antigens coated by anti-platelet antibodies and immune complexes. Another important cause of excessive platelet destruction is antibodies binding to antigens on platelets using molecular mimicry [31, 34].

ITP (Immune thrombocytopenic purpura) is prevalent in elder patients with age 60 and above. Approximately (71%) of patients above 50 years had moderate-to-severe COVID-19 disease (75%). It is worthy of data collection in ITP patients' post-recovery period (21%) [35].

Pseudo-thrombocytopenia concerning COVID-19 has been described in some cases. In one case, during admission, the patient's platelet count was normal but gradually declined without any evi-dence of bleeding. The platelet count was tested using a blood sample anticoagulated with citrate and judged to be normal, as the peripheral blood smear exhibited platelet aggregation. The anomaly eventually vanished after 17 days [36].

Lymphopenia in Covid-19

A significant impact on the hematopoietic system and hemostasis is imposed by covid-19. The storm of cytokine is a vital hallmark of pathogenesis. Certainly, concentrations of interleukin-6,

interleukin1β, TNF-α, granulocyte colony stimulating factor (G-CSF), and interferon γ-inducible protein (IP10) appear in higher concentrations in plasma of Covid-19 patients and even higher in ICU patients than non-ICU patients. Unfortunately, this cytokine release syndrome is associated with lymphopenia [37]. At the entrance, lymphopenia is pinpointed in more than 80% of patients and is helpful in the prediction of disease severity [38, 39].

Cytopathic effects of the virus and T-cell apoptosis due to a dysregulated cytokine milieu are the causing factors of CD4+ and CD8+ T-cell lymphopenia [40]. The importance of CD4+ T-cells lies in the modulation of the immune response. CD4+ T depletion enhances immune-mediated pneumonitis and delayed clearance of the virus from the lungs causing reduced production of neutralizing antibodies and cytokine and reduced pulmonary recruitment of lymphocytes [41]. The adaptive antiviral response may also be impaired by lymphopenia through inadequate T-cells. Gender differences as a risk factor may be attributed to the data showing approximately 64–71% of death of male patients [42]. The involvement of B lymphocytes has also been found in Corona, as Agammaglobulinemia patients with lesser B lymphocytes had a mild clinical course in contrast to Corona patients with Common Variable Immune Deficiency [43].

The SARS-CoV-2 may enter human cells via the angiotensin-converting enzyme 2 (ACE-2) receptor in the lungs, heart, and gastrointestinal system. Lymphocytes also contain these receptors on the surfaces. The virus might trigger cell death directly by connecting to these cells [44].

T cells Consumption is a devastating outcome of covid-19. It is proven that infected CD4+ and CD8+ T cells had increased expression of programmed cell death protein 1 (PD-1) and T cell immunoglobulin and mucin domain 3 (Tim-3) on the cell surface [45]. A correlation between disease severity and intensive care requirement can be established by using these two markers are being used to. It is also noted that the expression of NKG2A on T is increased, and T cell activation markers, such as CD107a and IFN-γ, are decreased.

The expansion of T cells also interfered with the infection. T cell activating guests named MAP2K7 and SOS1 is reduced in severe infection. Expression of these genes became normal upon recovery [46].

Neutrophilia in Covid-19

Neutrophilia is induced by cytokine storm and hyperinflammatory state. In circulating granulocytes, anomalies in cytoplasmic and nuclear morphology ranging from hypo-segmented nuclei to apoptosis have been observed during hospital admission. As a result, the number of reactive lymphocytes is increased. Overlaying bacterial infection is also indicated by Neutrophilia. In ICU patients, neutrophilia (11.6 vs. 3.5 × 109/L) is common during hospitalization [47].

Although neutrophils are essential for immunity, excessive recruitment along with nuclear chroma-tin or neutrophil extracellular traps (NETs) may aggravate tissue injury, leading to death. NETs cause disruption of alveolar epithelium and endothelium, vascular damage, pulmonary edema, and hemorrhage via the dissemination of toxic molecules such as histones and proteinase 3. Production of pro-inflammatory cytokines has also been stimulated. Additionally, thrombi formation in blood vessels can be accelerated by the activities of enzymes that belong to the aggregate formed by NETS.

Fulminant neutrophilia is the most significant in ICU Patients as increased blood neutrophil counts are noted compared to other SARS-CoV2-positive patients with less severe symptoms [48]. The number of neutrophils increases parallel with the severity of the disease. The interdependence between uncontrolled neutrophil loads and acute lung pathology in fatal COVID-19 may be proved by the fact that high neutrophilia was developed before succumbing to infection.

Coagulation Abnormalities in Covid-19

Thromboembolic diseases in corona disease in association with high mortality have increasingly attracted attention [49]. Coagulopathy is a common abnormality. The emerging venous thromboembolism (VTE) in anticoagulated COVID-19 patients is unknown. According to the reports, 6–69% of critically ill patients developed venous thromboembolism (VTE) [50].

Another study reported that of 75 ICU corona patients, about 33.3% of patients experienced a thromboembolic event [51]. Few of them experienced serious thromboembolic complications staying in ICU, such as pulmonary embolism in (sub) segmental arteries (21.3%), pulmonary embolism in central artery (5.3%) ischemic-CVA (2.7%) deep vein thrombosis (4.0%).

Autopsy findings with a prevalence of 58% thrombosis (in 7 of 12) with 33% complicating pulmonary embolism (4 patients) indicated a high occurrence of venous thromboembolism (VTE) and justified giving anticoagulant thromboprophylaxis [52]. Cytokine storm and hyperinflammation were attributed to the risks of resulting in coagulopathy, Propagating intravascular coagulation, platelets dysfunction, endothelialitis, in-situ thrombosis and micro-thrombosis [53-55]. An alliance between COVID-19 and VTE has also been confirmed by many studies [56].

In an autopsy assessment of 12 cases, 58 percent of the patients exhibited deep venous thrombosis, according to a recent study (DVT). Microthrombi were commonly identified within tiny pulmonary arteries, even though four people (33%) had PE [52]. Similarly, autopsies in China have identified disseminated microvascular thrombi in a variety of organs. Another autopsy examination of 21 COVID-19 patients claimed significant PE in four as well as microthrombi in alveolar capillaries in five (45%). In their glomerular capillaries, three had thrombotic microangiopathy symptoms [57].

An increasing number of incidences of thrombosis in an artery, such as stroke and acute coronary syndromes, has also been delineated in COVID-19. Unsurprisingly, ultrasonography reports of asymptomatic ICU patients indicated an incidence of thrombosis of 25% (20/81) [58]. Another report demonstrated a 20% to 30% prevalence of thrombosis and major thromboembolic sequelae in COVID-19 ICU patients [59].

Sepsis-induced coagulopathy" (SIC) is an ascending hallmark of severe corona characterized by high D-dimer levels and boosting fibrinogen [53]. SIC is a progenitor state to DIC and is correlated to promoting prothrombin time (PT) and D-dimer but without hypofibrinogenemia [60].

On top of that, excess levels of fibrin-related biomarkers and prolonged PT and PTT are often perceived. However, the degree is less notable compared to the bacterial sepsis-induced coagulopathy/DIC. Implications of cytokines and chemokines such as tumor necrosis factor (TNF)-α, IL-1β, and monocyte chemoattractant protein-1 are also reported [12].

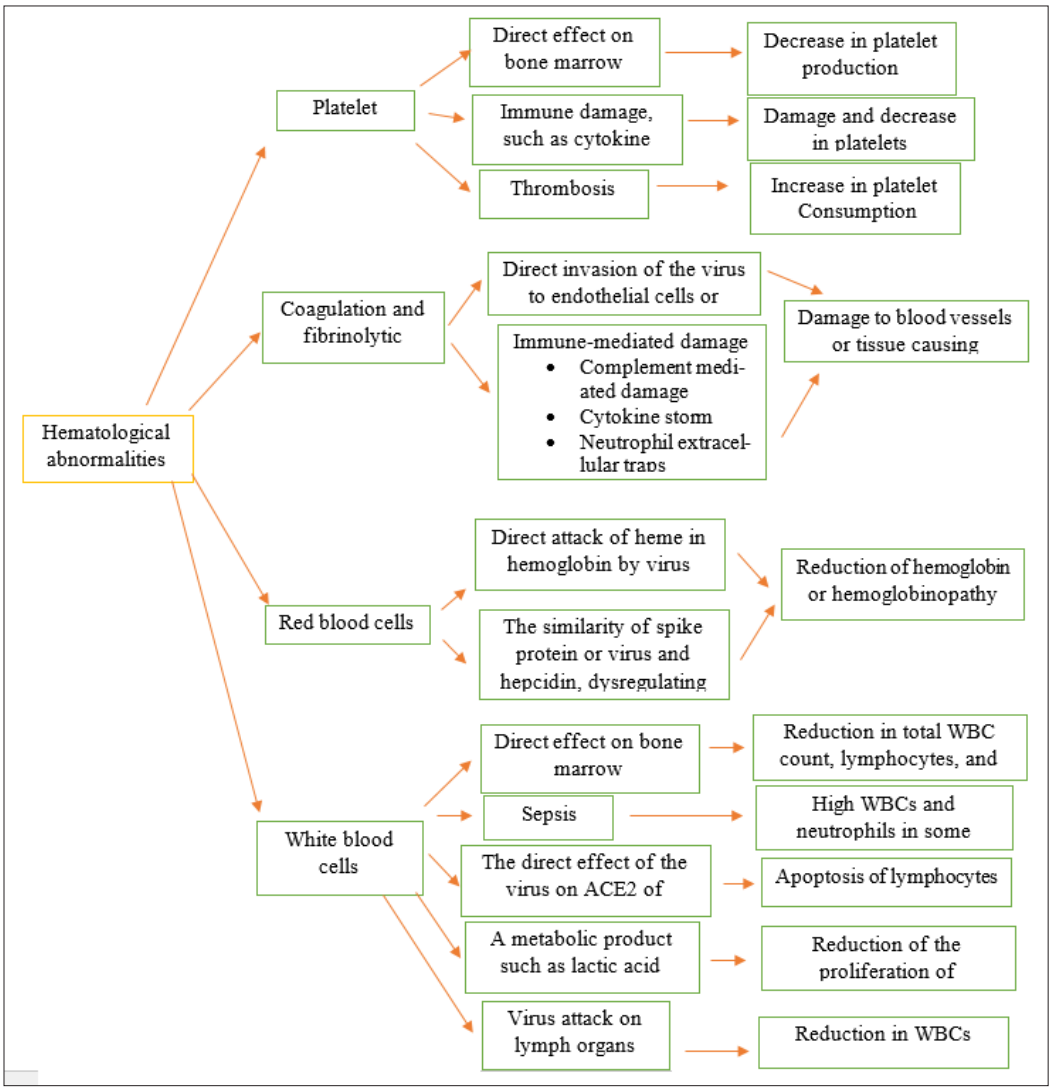

Figure 1: Profile of the Probable Mechanisms of Hematological Abnormalities

Coagulation and Fibrinolytic System

Injury induced by Neutrophil extracellular traps (NETs) may be an element for thrombosis. Three autopsy cases concluded that the alveolar space was infiltrated by excess neutrophils [61]. In order to prevent and control thromboembolic events, NETs may be easily targeted as a potential therapeutic option. The coagulation system can be activated by the activation of different complement pathways [62]. The responsible factors are increased platelet activity/aggregation, prothrombinase and tissue factor activity, and even the release of VWF by endothelial cells. Over-activation of the complement system in COVID-19 is responsible for a hypercoagulable state that, is proved by several studies.

Hematological Cancers

Patients with malignancy are at significantly higher risk of severe infections that can directly affect the immune system. Their risk of infections is increased due to myelosuppressive chemotherapy. It was found by a multicenter study that patients with hematologic, lung or metastatic (stage IV) cancer had more severe diseases than those without malignancy [63]. Another study found that patients with hematologic malignancies are vulnerable to SARS-CoV-2, considering age and low hemoglobin levels to be risk factors for poor outcomes [64].

Transfusion and Covid-19

Usually, transfusions are not required in COVID-19 patients, not even in difficult situations. In a retrospective analysis published in 2020, 13.4% of attended coronavirus sufferers got exchanges, with eleven percent receiving red blood cells and fewer than two% receiving platelets or plasma. COVID-19 patients who were hospitalized had a lesser need for exchanges than other attended sufferers, according to this study. Because of isolation in specific places with welfare discussions, the pandemic has had an impact on blood donations. It was tested as severe acute respiratory syndrome coronavirus-two virus in the blood of eighteen indicative and subclinical individuals to estimate the risk of transfusion-related transmission. Although no RNA was found, further investigations incorporating a larger number of patients are necessary.

Biomarkers

The ongoing COVID-19 outbreak has demanded the quick development of serum disease severity markers. Specific biomarkers such as CRP, nourish reductase, D-dimer, and hemoglobin have appeared as a valuable symbol of diagnosis, while temporality (Table 3).

Table 2: Biomarker Irregularities Held by Serious Disorder

Hematological biomarkers		Biochemical biomarkers		Coagulation biomarkers	Inflammatory biomarkers	Potential new biomarkers	
↑	↓	↑	↓	↑	↑	↑	↓
WBC count	Lymphocyte count	ALT	Albumin	PT	ESR	Hcy	Ang-(1-7)
Neutrophil count	Platelet count	AST		D-dimer	CRP	Ang II	Ang-(1-9)
	Eosinophil count	Total bilirubin			Serum ferritin	NLR	Alamandine
	T cell count	Blood urea nitrogen			PCT	MLR	
	B cell count	CK			IL-2		
	NK cell count	LDH			IL-6		
		Myoglobin			IL-8		
		CK-MB			Il-10		
		Cardiac					
		Troponin I					
		Creatinine					

WBC: White Blood Cell
NK: Natural Killer
ALT: Alanine Aminotransferase
AST: Aspartate Aminotransferase
CK: Creatine Kinase
LDH: Lactate Dehydrogenase
PT: Prothrombin Time
ESR: Erythrocyte Sedimentation Rate
CRP: C-Reactive Protein
PCT: Procalcitonin
IL: Interleukin
Hcy: Homocysteine
Ang: Angiotensin
NLR: Neutrophil-Lymphocyte Ration
MLR: Monocyte-Lymphocyte Ratio

We can easily differentiate by counting hematologic biomarkers such as WBC, lymphocyte, neutrophil, neutrophil-lymphocyte ratio (NLR), platelet, eosinophil, and hemoglobin Covid-19. A cohort study including 450 COVID-19-positive patients showed that overactivity of immune response is strongly associated with the markers [14]. In the case of severe cases, lower lymphocytes, higher leukocyte counts, and higher NLR, as well as lower percentages of monocytes, eosinophils, and basophils compared to mild cases, are found [15].

In non-survivors increased cardiac troponin levels (weighted mean difference (WMD): 32.7 ng/L) were found, which is the consequence of both viral myocarditis and cardiac injury from disease progression to multiple organ failure (MOF) [44].

We can use CRP as an early predictor for severe COVID-19 as it has been associated with disease development. It is also reported by correlation analysis that CRP (R ¼ 0.62, $p < .01$), erythrocyte sedimentation rate (ESR) (R ¼ 0.55, $p < .01$) and granulocyte/lymphocyte ratio (R ¼ 0.49, $p < .01$) were associated with CT severity scores positively. The immunological biomarkers of IL-6 and serum ferritin are reported to be significantly increased in non-survivors vs. survivors (WMD: 4.6 pg/mL and 760.2 ng/mL, respectively) and as compared to severe vs. non-severe disease (WMD: 1.7 pg/mL and 408.3 ng/ mL, respectively) [42].

Abnormal coagulation parameters may characterize poor prognosis. In the case of non-survivor, noticeable increments of D-dimer and FDP levels are common. The increment of D-dimer is frequent in patients with COVID-19 (36–43%) and is allied to severe complications and death [65].

Increased plasma levels of Hcy are significantly responsible for vascular damage in both small and large vessels. The risk of degenerative and atherosclerotic processes in coronary, cerebral, and peripheral circulatory systems may be elevated with concentrations above the 90th percentile [66].

Increased level of Ang II in avian influenza A-infected patients indicates that Ang II is a biomarker for lethality in flu infections. A strong correspondence has been found between increased IL-6 and vascular macrophage accumulation and the degree of endothelial dysfunction produced by Ang II [67].

Inflammation plays a vital role in the pathogenesis of COVID-19. Both NLR and PLR reflect the patient's inflammatory state. NLR (absolute neutrophil count divided by the absolute lymphocyte count) & (platelet count divided by absolute lymphocyte count) have been validated as prognostic markers in various disorders such as cardiac conditions, solid tumors, sepsis, pneumonia, and acute respiratory distress syndrome (ARDS).

Covid-19 Hematological Abnormalities Management

Platelets

Due to the rarity of severe thrombocytopenia in coronavirus sufferers, it is hardly used. There have been hardly any occurrence

outlines of coronavirus sufferers developing ITP or TTP, all of which have had beneficial results.

System of Coagulation and Fibrinolysis

For inpatients, the International Society on Infarction and Surgical operation approves programmer antiplatelet prevention in the company of Enoxaparin. Additionally, the NSAID characteristics of heparin occur effectively in coronavirus sufferers. Further, serious coronavirus contamination can be exacerbated by liver impairment, which can increase hemolysis and the possibility of hemorrhage. Therefore, the dose and type of anticoagulant should be modified foundation on the analytic gravity of the disorder and concurrent unit dysfunction. Obese persons, according to the study, require greater doses. A larger antithrombotic prophylactic dose reduced the risk of symptomatic venous thrombosis by 50% in patients with a higher BMI (> 40 kgm2),

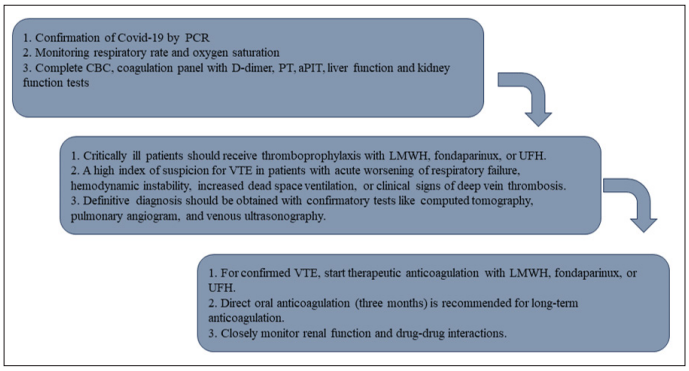

Figure 2: In Desperately Ailing Coronavirus Sufferer in ICU, a Proposed Anticoagulant Therapy Protocol was developed

Antithrombotic prophylaxis after discharge is a topic of growing controversy. 4.8/1,000 discharges were related to VTE during the 6-week post-discharge interval. On the other hand, hospitalization for other acute medical diseases did not have a significantly increased risk. As a result, the value of routine post-discharge thromboprophylaxis is debatable.

A fraught dosage of anticonvulsant may be useful to the sufferer in the company of pyemia-persuaded coagulopathy. In a retroactive inquiry, Tang, 2020 discovered that taking heparin reduced temporality in the sufferer that one connected the pyemia-persuaded coagulopathy conduct or had highly elevated D-dimer values [68]. In individuals who have experienced a thromboembolic event or are at high risk of thromboembolic illness, therapeutic anticoagulation is recommended. Patients receiving constant kidney renewal treatment, extracellular layer perfusion, or extracellular filter or catheter thrombosis should also consider therapeutic anticoagulation. In COVID patients who are critically ill, heparin resistance has been discovered. Anti-factors may help guide treatment in these patients [52]. The fact that more than half of VTE cases were detected on the first acknowledgment emphasizes the importance of preliminary observation and treatment. Program showing, on the other hand, is not recommended in the event of a pandemic since it is unfeasible. Clinical criteria determine if imaging is required. While a replacement for an enlightened high-resolution procedure, apart from echography, has been recycled to diagnose VTE by adequate consciousness (hundred percent) and particularity (ninety-five-point eight percent). Based on a study of right cerebrospinal fluid purpose in the middle of medically dubious individuals, bedside heart sonography may recommend the detection of respiratory thrombus.

Patients taking prednisolone should be transitioned to another warfarin-like polyose since seal observation of the multinational distributed rate would be hard while COVID-19 desolation. Because it requires less frequent monitoring, low molecular weight heparin (LMWH) is preferable to unfractionated heparin. Direct oral anticoagulants may be used if the patients can tolerate oral ingestion. Antivirals like ritonavir, lopinavir, or darunavir, as well as anti–IL-6 medicines like tocilizumab, are used to treat COVID-19 infections, and physicians should be conscious of potential pharmacological cooperation. Furthermore, in the context of a severe illness accompanied by heart appliance, reduced elimination of straight vocal medicament may raise the danger of hemorrhage. As a result, in critically ill patients, straight oral anticoagulants should be avoided.

Anticoagulant trials in COVID-19 patients are now being conducted in several clinical trials. Anticoagulants should be used with caution in patients with hypercalcemia illnesses like bleeder's disease and blood disorders. Although D-dimer has limited profitability in the identification of venous thromboembolism, it can be utilized to rule out the respiratory word Hippo thesaurus in individuals with a small medical intuition. Patients who need to be admitted to the hospital should receive thromboprophylaxis, according to Thachil, 2020, to lower the chance of negative consequences [69]. A more deliberate medical check on revascularization might be advantageous.

Red Blood Cells

Even though bloodlessness has been documented within certain individuals, no learning has proven that receiving blood transfusions, for this reason, improves outcomes. Transfusions and chelation therapy should be continued for patients with hemoglobinopathies and COVID-19.

White Blood Cells

COVID-19–related inflammation has been studied with corticosteroids. When it was determined that a sufferer who got six milligrams per day of dexamethasone for up to ten days had an 8–26% lower death rate, the recovery trial gained much attention [70]. Several clinical trials using glial stem cells as a coronavirus therapy are currently being conducted. By using MSCs to treat seven patients and found a rise in lymphocyte count as well as a drop in C reactive protein and cytokine secreting T and natural killer cells within 3–6 days. However, the costs of such operations and the time it takes to receive therapeutic authorization must be considered.

Conclusion

In coronavirus, hematological irregularities like tumor infiltrating, a blood disorder, and assessing D-dimer and C-reactive protein levels are also frequent. Another is also common and conspicuous in individuals with acute coronavirus disease, suggesting thus they could be appropriate while a bio-marker to identify those needing rehabilitation and intensive care unit therapy. Because thorough testing to determine agglomeration problems is impossible in a pandemic, sequential D-dimer scanning can be analyzed in light of therapy decisions. Agglomeration irregularities must be consistently observed, and attempts must be made to intercept or alleviate their election reaction.

References

1. Mohan BS, Nambiar V (2020) COVID-19: an insight into SARS-CoV-2 pandemic originat-ed at Wuhan City in Hubei Province of China. J Infect Dis Epidemiol 6: 1-8.
2. Kronbichler A, Kresse D, Yoon S, Lee KH, Effenberger M, et

al. (2020) Asymptomatic pa-tients as a source of COVID-19 infections: A systematic review and meta-analysis. International journal of infectious diseases 98: 180-186.
3. Chan PK, Chan MC (2013) Tracing the SARS-coronavirus. Journal of thoracic disease 5: S118.
4. Xu P, Zhou Q, Xu J (2020) Mechanism of thrombocytopenia in COVID-19 patients. Annals of hematology 99: 1205-1208.
5. Weiss SR, Leibowitz JL (2011) Coronavirus pathogenesis. Advances in virus research 81: 85-164.
6. Shanmugaraj B, Malla A, Phoolcharoen W (2020) Emergence of novel coronavirus 2019-nCoV: need for rapid vaccine and biologics development. Pathogens 9: 148.
7. She J, Jiang J, Ye L, Hu L, Bai C, et al. (2020) 2019 novel coronavirus of pneumonia in Wuhan, China: emerging attack and management strategies. Clinical and translational medicine 9: 19.
8. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, et al. (2020) Multisystem in-flammatory syndrome in children in New York State. New England Journal of Medicine 383: 347-358.
9. Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E (2020) A novel corona-virus emerging in China-key questions for impact assessment. New England Journal of Medicine 382: 692-694.
10. Chen N, Zhou M, Dong X, Qu J, Gong F, et al. (2020) Epidemiological and clinical charac-teristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The lancet 395: 507-513.
11. Fan BE (2020) Hematologic parameters in patients with COVID-19 infection: a reply. American journal of hematology 95: E215.
12. Huang C, Wang Y, Li X, Ren L, Zhao J, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet 395: 497-506.
13. Liu W, Tao ZW, Wang L, Yuan ML, Liu K, et al. (2020) Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chinese medical journal 133: 1032-1038.
14. Qian G Q, N -B Yang, F Ding, A H Y Ma, Z -Y Wang, et al. (2020) Epidemiologic and clin-ical characteristics of 91 hospitalized patients with COVID-19 in Zhejiang, China: a retro-spective, multi-centre case series 113: 474-481.
15. Qin C, Zhou L, Hu Z, Zhang S, Yang S, et al. (2020) Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clinical infectious diseases 71: 762-768.
16. Ruan Q, Yang K, Wang W, Jiang L, Song J, et al. (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 46: 846-848.
17. Wan S, Yi Xiang, Wei Fang, Yu Zheng, Boqun Li, et al. (2020) Clinical features and treat-ment of COVID-19 patients in northeast Chongqing. J Med Virol 92: 797-806.
18. Wang Z, Yang B, Li Q, Wen L, Zhang R (2020) Clinical features of 69 cases with corona-virus disease 2019 in Wuhan, China. Clinical infectious diseases 71: 769-777.
19. Wang D, Hu B, Hu C, Zhu F, Liu X, et al. (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama 323: 1061-1069.
20. Wu C, Chen X, Cai Y, Zhou X, Xu S, et al. (2020) Risk factors associated with acute respir-atory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine 180: 934-943.
21. Xu X, Yu C, Qu J, Zhang L, Jiang S, et al. (2020) Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. Eur J Nucl Med Mol Imaging 47: 1275-1280.
22. Yang X, Yu Y, Xu J, Shu H, Liu H, et al. (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine 8: 475-481.
23. Zachariah P, Johnson CL, Halabi KC, Ahn D, Sen AI (2020) Epidemiology, clinical fea-tures, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a chil-dren's hospital in New York city, New York. JAMA Pediatr 174: 202430.
24. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, et al. (2020) Coagulopathy and antiphospholipid antibodies in patients with Covid-19. New England Journal of Medicine 382: e38.
25. Zhou F, Yu T, Du R, Fan G, Liu Y, et al. (2020) Clinical course and risk factors for mortali-ty of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet 395: 1054-1062.
26. Yang J, Zheng YA, Gou X, Pu K, Chen Z, et al. (2020) Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Inter-national journal of infectious diseases 94: 91-95.
27. Giannis D, Ziogas IA, Gianni P (2020) Coagulation disorders in coronavirus infected pa-tients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. Journal of Clinical Virology 127: 104362.
28. Yang M, Ng MH, Li CK (2005) Thrombocytopenia in patients with severe acute respiratory syndrome. Hematology 10: 101-105.
29. Chan JF, Kok KH, Zhu Z, Chu H, To KK, et al. (2020) Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerging microbes & infections 9: 221-236.
30. Yeager CL, Ashmun RA, Williams RK, Cardellichio CB, Shapiro LH, et al. (1992) Human aminopeptidase N is a receptor for human coronavirus 229E. Nature 357: 420-422.
31. Xu P, Zhou Q, Xu J (2020) Mechanism of thrombocytopenia in COVID-19 patients. Annals of hematology 99: 1205-1208.
32. Lefrançais E, Ortiz-Muñoz G, Caudrillier A, Mallavia B, Liu F, et al. (2017) The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. Nature 544: 105-109.
33. Nardi M, Tomlinson S, Greco MA, Karpatkin S (2001) Complement-independent, peroxide-induced antibody lysis of platelets in HIV-1-related immune thrombocytopenia. Cell 106: 551-561.
34. Zou Q, Zheng S, Wang X, Liu S, Bao J, et al. (2020) Influenza A-associated severe pneu-monia in hospitalized patients: risk factors and NAI treatments. International Journal of Infectious Diseases 92: 208-213.
35. Bhattacharjee S, Banerjee M (2020) Immune thrombocytopenia secondary to COVID-19: a systematic review. SN comprehensive clinical medicine 2: 2048-2058.
36. Li H, Wang B, Ning L, Luo Y, Xiang S (2020) Transient appearance of EDTA dependent pseudothrombocytopenia in a patient with 2019 novel coronavirus pneumonia. Platelets 31: 825-826.
37. Lu R, Zhao X, Li J, Niu P, Yang B, et al. (2020) Genomic characterisation and epidemiolo-gy of 2019 novel coronavirus: implications for virus origins and receptor binding. The lancet 395: 565-574.

38. Guan WJ, Liang WH, He JX, Zhong NS (2020) Cardiovascular comorbidity and its impact on patients with COVID-19. European Respiratory Journal 55: 2001227.
39. Tan L, Wang Q, Zhang D, Ding J, Huang Q, et al. (2020) Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal transduction and targeted therapy 5: 33.
40. Wang X, Xu W, Hu G, Xia S, Sun Z, et al. (2020) SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. Cellular and Molecular Immunology 20: 554.
41. Chen J, Lau YF, Lamirande EW, Paddock CD, Bartlett JH, et al. (2010) Cellular immune responses to severe acute respiratory syndrome coronavirus (SARS-CoV) infection in senescent BALB/c mice: CD4+ T cells are important in control of SARS-CoV infection. Journal of virology 84: 1289-1301.
42. Henry BM, De Oliveira MH, Benoit S, Plebani M, Lippi G (2020) Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clinical Chemistry and Laboratory Medicine (CCLM) 58: 1021-1028.
43. Quinti I, Lougaris V, Milito C, Cinetto F, Pecoraro A, et al. (2020) A possible role for B cells in COVID-19? Lesson from patients with agammaglobulinemia. Journal of Allergy and Clinical Immunology 146: 211-213.
44. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G (2020) Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clinica chimica Acta 507: 167-173.
45. Diao B, Wang C, Tan Y, Chen X, Liu Y, et al. (2020) Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Frontiers in immunology 11: 827.
46. Ouyang Y, Yin J, Wang W, Shi H, Shi Y, et al. (2020) Downregulated gene expression spectrum and immune responses changed during the disease progression in patients with COVID-19. Clinical Infectious Diseases 71: 2052-2060.
47. Fan BE (2020) Hematologic parameters in patients with COVID-19 infection: a reply. American journal of hematology 95: E215.
48. Huang I, Pranata R (2020) Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. J Intensive Care 24: 36.
49. Levi M, Thachil J, Iba T, Levy JH (2020) Coagulation abnormalities and thrombosis in patients with COVID-19. The Lancet Haematology 7: e438-e440.
50. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, et al. (2020) High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. Journal of Thrombosis and Haemostasis 18: 1743-1746.
51. Beun R, Kusadasi N, Sikma M, Westerink J, Huisman A (2020) Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. International journal of laboratory hematology 42: 19-20.
52. Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, et al. (2020) Autopsy find-ings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Annals of internal medicine 173: 268-277.
53. N Tang, D Li, X Wang, Z Sun (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb. Haemost 18: 844-847.
54. Manne BK, Denorme F, Middleton EA, Portier I, Rowley JW, et al. (2020) Platelet gene expression and function in patients with COVID-19. Blood 136: 1317-1329.
55. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, et al. (2020) Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. New England Journal of Medicine 383: 120-128.
56. Tan BK, Mainbourg S, Friggeri A, Bertoletti L, Douplat M, et al. (2021) Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis. Thorax 76: 970-979.
57. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, et al. (2020) Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology 77: 198-209.
58. Cui S, Chen S, Li X, Liu S, Wang F (2020) Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis 18: 1421-1424.
59. Klok FA, Kruip MJ, Van der Meer NJ, Arbous MS, Gommers DA, et al. (2020) Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis research 191: 145-147.
60. Rahman A, Niloofa R, Jayarajah U, De Mel S, Abeysuriya V, et al. (2021) Hematological Abnormalities in COVID-19: A Narrative Review. The American journal of tropical medicine and hygiene 104: 1188-1201.
61. Betsy J Barnes, Jose M Adrover, Amelia Baxter-Stoltzfus, Alain Borczuk, Jonathan Cools-Lartigue, et al. (2020) Targeting potential drivers of COVID-19: neutrophil extracellular traps. J Exp Med 217: e20200652.
62. Fletcher-Sandersjöö A, Bellander BM (2020) Is COVID-19 associated thrombosis caused by overactivation of the complement cascade? A literature review. Thrombosis research 194: 36-41.
63. Mengyuan Dai, Dianbo Liu, Miao Liu, Fuxiang Zhou, Guiling Li, et al. (2020) Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. Cancer Discov 10: 783-791.
64. Lattenist R, Yildiz H, De Greef J, Bailly S, Yombi JC (2020) COVID-19 in adult patients with hematological disease: analysis of clinical characteristics and outcomes. Indian J Hematol Blood Transfus 37: 181-185.
65. Lippi G, Favaloro EJ (2020) D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. Thrombosis and haemostasis 120: 876-878.
66. Graham IM, Daly LE, Refsum HM, Robinson K, Brattström LE, et al. (1997) Plasma homocysteine as a risk factor for vascular disease: the European Concerted Action Project. Jama 277: 1775-1781.
67. Gomolak JR, Didion SP (2014) Angiotensin II-induced endothelial dysfunction is temporally linked with increases in interleuk in-6 and vascular macrophage accumulation. Frontiers in physiology 29: 396.
68. Tang N, Li D, Wang X, Sun Z (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of thrombosis and haemostasis 18: 844-847.
69. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, et al. (2020) ISTH interim guidance on recognition and management of coagulopathy in COVID-19. Journal of Thrombosis and Haemostasis 18: 1023-1026.

70. Horby P, Wei Shen Lim, Jonathan Emberson, Marion Mafham, Jennifer Bell, et al. (2020) Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. MedRxiv. https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1.full.pdf.