Discoveries Journals
publishing the future

DISCOVERIES 2020, Oct-Dec, 8(4): e117
DOI: 10.15190/d.2020.14

REVIEW Article

Hematologic parameters in coronavirus infection (COVID-19) and their clinical implications

Rao Muhammad Waleed[1,*], *Inbisat Sehar*[1], *Waleed Iftikhar*[1,2], *Huma Saeed Khan*[1]

[1]CMH Lahore Medical College and Institute of Dentistry, Lahore, Pakistan
[2]California Institute of Behavioral Neurosciences & Psychology, Fairfield, CA 94534, USA

**Corresponding author*: *Rao Muhammad Waleed*, CMH Lahore Medical College and Institute of Dentistry, Abdur Rehman Road, Lahore Cantonment, Pakistan; Email: raowaleed4@gmail.com

Submitted: August 11, 2020; *Revised:* Sept 11, 2020; *Accepted:* Sept. 17, 2020; *Published:* October 1, 2020;
Citation: Waleed RM, Sehar I, Iftikhar W, Khan HS. Hematologic parameters in coronavirus infection (COVID-19) and their clinical implications. *Discoveries* 2020, 8(4): e117. DOI: 10.15190/d.2020.14

ABSTRACT

Coronaviruses are a class of enveloped RNA viruses that cause infections of the respiratory tract, characterized by fever, tiredness, dry cough, diarrhea, loss of smell or taste, chest pain and shortness of breath. Many patients with mysterious pneumonia were distinguished in December 2019 in Wuhan. The pneumonia of obscure origin was found to be ascribed to a novel coronavirus and described as novel coronavirus pneumonia (NCP). The Chinese authorities initially reported the wave of mysterious pneumonia on December 31st, 2019 and it was declared as an outbreak of international concern on January 30th, 2020. A systematic search of relevant research was conducted, and a total of 58 primary research articles were identified, analyzed, and debated to better understand the hematologic profile in COVID-19 (Coronavirus disease) infection and its clinical implications. All the findings in this article manifest a true impression of the current interpretation of hematological findings of the SARS-COV-2 disease. Pathophysiology of COVID-19 disease can be better interpreted by taking into consideration the hematologic parameters. Clinical implications of the hematologic profile of COVID-19 patients including cytokine storm, coagulation profile, and thrombophilic complications are under-recognized. Therefore, this review focuses on the coagulation profile, cytokine storm, and its treatment options. The role of pre-existing thrombophilia in COVID-19 patients and how it could result in the poor prognosis of the disease is also debated. The recent data suggests that hypercoagulability could be the potential cause of fatalities due to COVID-19. Potential effects of tocilizumab, metronidazole, and ulinastatin in suppressing cytokine storm may help to treat SARS-COV-2 infection. This review also highlights the significance of thrombophilia testing in SARS-CoV-2 patients depending on the clinical features and especially in pregnant women.

Keywords

Coronavirus, COVID-19, pneumonia of unknown origin, cytokine storm, coagulopathy, D-dimer, thrombophilia.

Summary

Abbreviations

Novel Coronavirus pneumonia (NCP); World Health Organization (WHO); Coronavirus disease-2019 (COVID-19); Middle East respiratory syndrome coronavirus (MERS-CoV); angiotensin converting enzyme-2 (ACE-2); ribonucleic acid (RNA); severe acute respiratory syndrome coronavirus (SARS-CoV); intensive care unit (ICU); acute respiratory distress syndrome (ARDS); tumor necrosis factor-α(TNF-α); absolute lymphocyte count (ALC); C-reactive protein (CRP); fibrinogen degradation product (FDP); reactive oxygen species (ROS); interleukin (IL); interferon gamma (IFNγ); soluble interleukin-6 receptor (sIL-6R); membrane-bound Interleukin-6 receptor (mIL-6R); food and drug administration (FDA); prothrombin time (PT); Lupus anticoagulant (LAC);cytokine release syndrome (CRS); TH17 (T-helper 17); disseminated intravascular coagulation (DIC); venous thromboembolism (VTE); pulmonary embolism (PE); antiphospholipid syndrome (APS); activated partial thromboplastin time (aPTT); mammalian target of rapamycin (mTOR); deep vein thrombosis (DVT); low molecular weight heparin (LMWH); anticardiolipin antibody (ACA).

1. Introduction

Coronaviruses are a set of enveloped ribonucleic acid viruses, with some of them having the largest genome if compared with other RNA viruses[1]. They are distributed among humans, birds, and other mammals and are known to cause hepatic, neurologic, enteric, and respiratory diseases, ranging in symptoms from mild to severe[2]. They have a high affinity to the respiratory mucosa, thus affecting the respiratory system to a greater extent in comparison to other systems in the body[2]. Four out of the six known coronaviruses cause typical common cold symptoms in immunocompromised individuals and are not considered highly virulent[1]. The other two, i.e. Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) are highly virulent and contagious, with high mortality rates[2]. The SARS outbreaks in 2002 and 2003 were attributed to SARS-CoV[3], while the MERS outbreak in 2012 was caused by MERS-CoV[4].

A group of victims with mysterious pneumonia was recorded in Wuhan in December 2019, with an epidemiological relationship to the wholesale market for wild, wet animals and seafood in Wuhan[5]. The mysterious pneumonia was discovered to be attributed to a novel coronavirus and described as novel coronavirus pneumonia (NCP)[6]. NCP was ascribed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2]. Angiotensin-converting enzyme-2 (ACE-2) is the receptor used by SARS-CoV-1 and SARS-CoV-2 to gain entry into the cell[7]. The infection proved to be highly contagious; however, with a lower mortality rate but a higher virulence rate than SARS and MERS[8]. The highly contagious and virulent state of the virus caused a worldwide pandemic that is proving challenging to tackle.

With increased research, COVID-19 is now regarded as a significant systemic infection, with its clinical manifestations suggesting the respiratory system, gastrointestinal tract, neurologic system, cardiovascular system, hematologic system, urinary system, and immune system are affected[9,10]. **Figure 1** describes the clinical presentation of COVID-19 patients taking into consideration the different body systems.

This paper reviews the hematologic systemic effects with a focus on the hemodynamic picture and parameters that are related to COVID-19, outlining the hemodynamics, coagulation parameters, cytokine storm, thrombophilic implications, and potential clinical outcomes.

2. Methodology

An organized review of relevant literature on the hematologic parameters in SARS-CoV-2 infection and its clinical implications was conducted, taking into account case studies, recent journal publications, and current research. The key search terminologies were: COVID-19, cytokine storm, hemodynamics in COVID-19, D-dimer, clinical manifestations, and coagulation. The databases used were Google Scholar, MEDLINE, PubMed, and EBSCOhost. These databases provide an effective and quick method of conducting research, organizing data per subject heading, thus facilitating effective use of keyword search terminologies. For literature to be considered, it had to address COVID-19 and its hematological features, primary sources had to be peer-reviewed and published in credible journals. A total of 100 articles satisfied the criteria for inclusion. Duplicate articles were eliminated, thus remaining with 70 articles. Articles talking on aspects other than COVID-19 and its hematological manifestations, and those that were not peer-reviewed were excluded, further narrowing down the articles to 58.

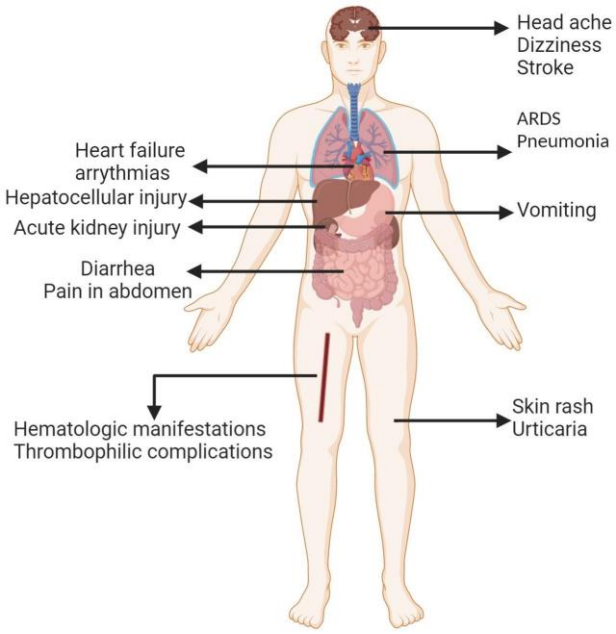

Figure 1: Clinical presentation of COVID-19 patients (adapted from Gupta et al. (2020)[11])
This figure is created using BioRender.com**.**

3. Hemodynamics

In COVID-19 patients, hematologic profiles greatly depend on the severity of the disease[12]. The summary of hematologic changes in SARS-COV-2 patients is mentioned in **Table 1**. A research paper published by Huang et al. (2020)[8] on the clinical profile of patients infected with SARS-CoV-2 showed normal hemoglobin levels and varying other blood parameters based on the disease intensity[8]. Generally, white blood cell (WBC) count of all patients was below 4×10^9/L, hence signifying leucopenia. Lymphopenia was also noted with lymphocyte counts of less than 1.0×10^9/L in 63% of patients[8]. Patients in the intensive care unit (ICU) presented with lower levels of absolute lymphocyte count (ALC). The median nadir ALC of ICU patients was found to be 0.4×10^9/L, and that of non-ICU patients was 1.2×10^9/L[8]. A study performed by Liu et al. (2020)[13] in Changsha, China, incorporating 115 confirmed COVID-19 patients, also identified lymphopenia in most patients, thus agreeing with the study findings of Huang et al. (2020)[8]. Forty-two percent of the study participants having a median age of 42 years were identified with lymphopenia[13]. These lymphopenic patients were observed having other disorders as well, such as leucopenia (48.1% vs 14.8%, P<0.001), eosinophilia (92.6% vs 54.1%, P<0.001), coronary heart disease (3.6% vs 0%, P=0.026), and hypertension (30.8% vs 10%, P=0.006)[13].

A study done by Fan et al. (2020)[14] on the hematological manifestations in 69 patients in Singapore, concur with the Chinese study findings of Liu et al. (2020)[13] and Huang et al. (2020)[8]; with lymphopenia and leucopenia noted among 23% of SARS-CoV-2 patients. Platelet counts were reported to be normal in all studies; however, mild thrombocytopenia was seen in some severe cases of the disease[14]. Neutrophilia was only seen in ICU patients, which developed during hospitalization; however, non-ICU patients tend to have normal neutrophil counts[14]. The cause of neutrophilia is still unknown, whether it is nosocomial in origin or an indication of worsening disease.

Pregnant females infected with SARS-CoV-2 are more susceptible to be affected by lymphopenia. Huanhuan et al. (2020)[15] study on pregnant women with NCP showed that lymphopenia was more common at a rate of 64% in confirmed pregnant females compared to the non-pregnant group (56%)[15].

Table 1: Summary of hematologic changes in COVID-19 patients

Parameters	Changes
Thrombocyte count	Decreases
Neutrophil count	Increases
Lymphocyte count	Decreases
Lactate dehydrogenase	Increases
Serum ferritin	Increases
Interleukins (IL-6, IL-2, IL-7)	Increases
C-reactive protein (CRP)	Increases
Procalcitonin	Increases
TNF-α	Increases
Prothrombin time (PT)	Prolonged
D-dimer	Increases
Fibrinogen degradation product (FDP)	Increases

Adapted from Terpos et al. (2020)[12] with permission.

The occurrence of lymphopenia varies geographically. For example, Fan et al.'s (2020)[14] study in Singapore identified only 23% of patients having lymphopenia, in comparison to Huang et al.'s (2020)[8] study in China, which reported 63% of patients. The reason for this is yet unknown, but it can be due to the immunological response to the virus that changes as it expands to other countries or due to the differences between the studied populations[16].

Lymphocyte deficiency in COVID-19 is multi-focal in origin and is a sign of severe disease and prolonged duration of hospitalization. The following mechanisms may explain the cause of lymphopenia[17]. ACE-2 receptor is expressed by lymphocytes, predisposing them to be direct virus target sites. The virus attaches to and attacks lymphocytes, destroying them in the process[17]. Secondly, the virus may cause the destruction of lymphatic organs such as thymus and spleen, predisposing to reduced lymphocyte production. Thirdly, cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 may get disordered, causing lymphocytes to undergo apoptosis. Finally, the proliferation of lymphocytes may be suppressed in critical COVID-19 patients due to increased metabolic parameters such as lactic acid, which causes hyper-lactic acidemia[17]. Treatment modalities of COVID-19 may further cause lymphopenia. Treatment with glucocorticoid causes apoptosis and migration of lymphocytes from peripheral blood[13, 18], hence contributing to a lymphopenic picture.

4. Cytokine Storm

SARS-COV-2 causes the excess formation of pro-inflammatory cytokines, leading to a phenomenon referred to as cytokine storm[19]. A cytokine storm causes vascular hyper-permeability, acute respiratory distress syndrome (ARDS), and even organ failures. It can be fatal if there is excess overproduction of cytokines[20]. The exact process of cytokine storm is illustrated in **Figure 2.**

Cytokine release syndrome (CRS) is usually related to immunity disorders that originate from the focal infected area and spreads throughout the body[21,22]**.** In COVID-19 patients, the cytokine storm can lead to death due to ARDS. It can lead to hypoxia, lung injury, fever, and arrhythmic heart in severe cases[23]. In critically ill patients, organ damage and extra-pulmonary effects of COVID-19 can be attributed to cytokine storm[23].

IL-6 levels drastically increase in COVID-19 infections due to tissue injuries, increased hematopoiesis, and immune reactions[24]. IL-6 is the basic mediator of virulence in cytokine storms[22, 25]; hence the high level of IL-6 is a sign of severe SARS-CoV-2 infection. Diabetic patients might be more vulnerable to cytokine storm due to unwarranted amounts of IL-6 production. Hence, diabetic COVID-19 patients should be dealt with care, as they could be at greater risk of organ failure and development of ARDS[26].

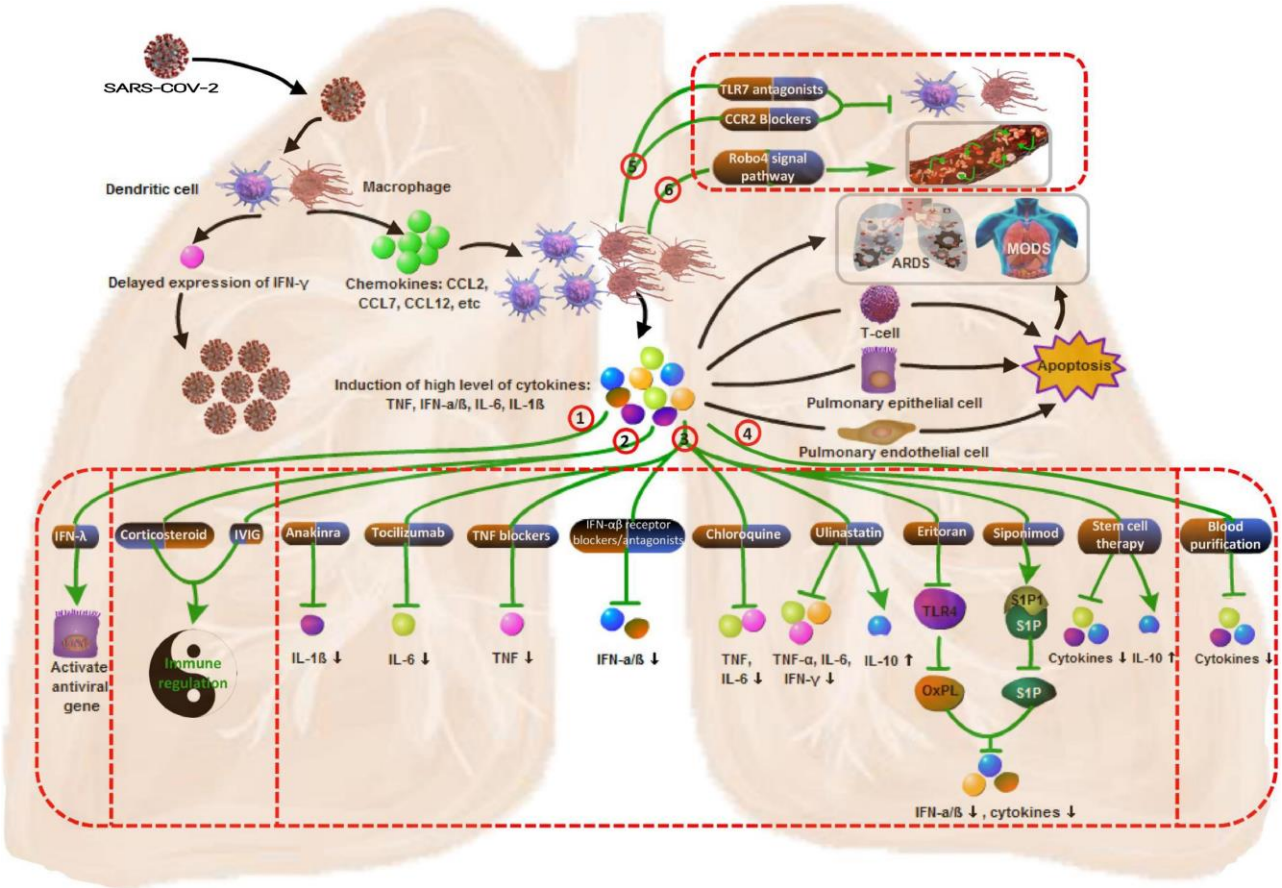

Figure 2: Cytokine storm mechanism (reproduced from Qing et al.[20] with permission)

5. Treatment of cytokine storm

Cytokine storm is now recognized as the main cause of many fatalities due to COVID-19. Medical management of cytokine storm is thus essential towards the management of COVID-19 and prevention of further deterioration. Treatment modalities primarily target IL-6, TNF, and IL-1β[27].

5.1. Metronidazole

Metronidazole is a biocidal agent characterized as a redox-active agent that decreases cytokines levels and targets IL-1 beta, IL-6, IL-8, IL-12, and TNF alpha[28]. Metronidazole also has the potential to reduce reactive oxygen species (ROS) produced by neutrophils during inflammation[29] (**Table 2).**

5.2. Tocilizumab

Tocilizumab is an antagonist of IL-6 and attaches to and blocks signaling of both soluble and membrane-bound IL-6 receptors[21, 22]. Tocilizumab serves as an effective treatment choice for patients with severe cytokine storm reactions in COVID-19[25, 30]. Le et al. (2017)[31] clinical trial with intravenous tocilizumab in patients presenting with cytokine storm showed a 69% success rate[31]**.** US Food and Drug Administration (FDA) thus validated tocilizumab for its application in severe cytokine storm treatment[25]**.**

Figure 3 illustrates how tocilizumab could effectively subdue the cytokine storm by inhibiting IL-6 signaling.

5.3. Ulinastatin

Ulinastatin is a glycoprotein that functions by producing an anti-inflammatory response. A meta-analysis by Zhang et al. (2019)[34] indicated that ulinastatin proved significantly helpful in treating ARDS[34]. Ulinastatin decreases pro-inflammatory cytokines levels (IL-6, IFN-γ, TNF-alpha) and can show promising potential as a treatment option for COVID-19[35] (**Table 3**).

Table 2: Metronidazole effects on cytokine levels in COVID-19 infection

COVID-19	Metronidazole
↑IL8	↓IL8
↑IL6	↓IL6
↑IL1B	↓IL1B
↑TNFα	↓TNFα
↑CRP	↓CRP
↑IL12	↓IL12
↑IFNγ	↓IFNγ
↑Neutrophils	↓Neutrophils
↓Lymphocytes	↑Lymphocytes lymphoproliferative properties

Reproduced from Gharebaghi et al. (2020)[28] with permission.

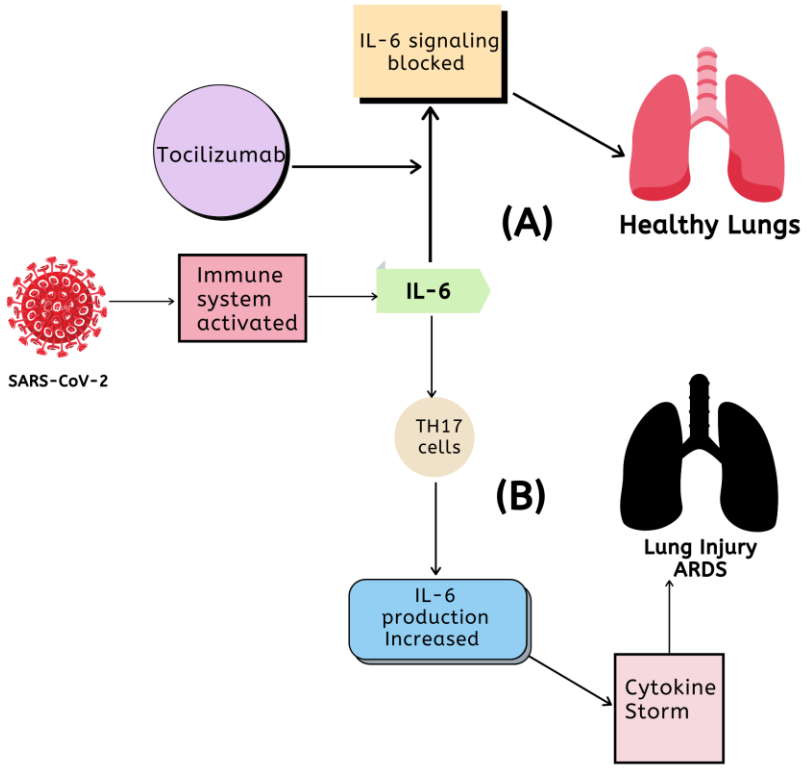

Figure 3: Effect of tocilizumab in subduing the cytokine storm (adapted from[32, 33] with permission)
A. Tocilizumab blocks IL-6 signaling thus suppressing cytokine storm;
B. IL-6 activates TH17 (T-helper 17) cells which then increases the IL-6 production. IL-6 occupies a major part in cytokine storm and hence resulting in lung injury and ARDS.

6. Coagulation Parameters

Coagulation disorders pose a serious threat to COVID-19 patients, if not appropriately managed, with excessive coagulation leading to thrombosis, as seen in hospitalized patients[37]. Thrombosis is fatal for COVID-19 patients if not promptly addressed. The sudden and rapid increase in D-dimer levels contributes to more severe COVID-19 infection[38]. The coagulation complications of COVID-19 are somewhat analogous to SARS. Deep vein thrombosis and pulmonary embolism were also found to be associated with deaths due to SARS-CoV-1[39].

A retrospective performed by Tang et al. (2020)[6] on 183 participants to elucidate the coagulation

Table 3: Effect of ulinastatin on cytokine levels

Pro-inflammatory cytokines	Ulinastatin
IFN-γ	Decreases[35, 36]
TNF-α	Decreases[35, 36]
IL-6	Decreases[35, 36]
Anti-inflammatory cytokines	**Ulinastatin**
IL-10	Increases[35, 36]

Adapted from[35, 36] with permission.

profile of COVID-19 patients, presented that fibrinogen degradation product (FDP) level was higher with increased prothrombin time (PT) in non-survivors as compared to the survivors. D-dimer levels were also found to be high in non-survivors. The standard of disseminated intravascular coagulation (DIC) was met by 71.4% of the non-survivors[6], while 0.6% of the survivors also reached the criteria of DIC[6]. Wu et al. (2020)[40] agrees with these findings in their study on 201 COVID-19 patients admitted to a hospital in Wuhan. The study found that in patients infected with SARS-CoV-2, coagulation disorders, high D-dimer levels and longer PT increased the chances of ARDS[40].

Tang et al. (2020)[6] extensively discussed the significance of high D-dimer levels. However, the authors did not allude to the role of lupus anticoagulant (LAC) on thrombosis. Harzallah et al. (2020)[37] study of 56 SARS-CoV-2 infected patients in France found that 45% of them were positive for LAC, which is a prothrombotic antibody that predisposes to increased thrombosis[37].

A study on the hematological presentations in 157 patients with SARS attributed by SARS-CoV-1, noted four disseminated intravascular coagulation (DIC) cases[41]. All those patients showed increased D-dimer levels and thrombocytopenia. Activated partial thromboplastin time (aPTT) was also prolonged. Prothrombin time was more prolonged in patients in ICU as compared to patients in the general ward[41]. These findings give weight to Tang et al. (2020)[6] study findings of DIC and allude to a higher virulence potential of SARS-COV-2 due to a higher DIC rate (71%) in SARS-CoV-2 infected patients[6].

The risk of venous thromboembolism (VTE) is substantially increased in critically ill patients of COVID-19[38]. An article by Minet et al. (2015)[42], describes general and ICU specific risk factors for VTE, as illustrated in **Figure 4**.

Moreover, pre-existing conditions in COVID-19 patients should also be taken into account while evaluating the coagulation profile. It should be noted that SARS-CoV-2 infected patients with underlying cardiac injury presented with greater coagulopathies than patients without underlying conditions[43].

7. Thrombophilic complications in pregnant women

While discussing coagulation parameters in COVID-19 infection, thrombotic complications in a pregnant woman should not be neglected. Pregnancy substantially increases the risk of hyper-coagulability and women with primary or secondary thrombophilia are more prone to pregnancy complications[44]. Therefore, the management of hyper-coagulability in a pregnant woman infected with COVID-19 needs special attention, since COVID-19 can aggravate the thrombotic complications. Moreover, pregnant women with reproductive failure are at greater risk of severe SARS-COV-2 disease, as there are chances of developing acquired thrombophilia[45]. Low molecular weight heparin (LMWH) is a good option as an anticoagulant to treat pregnant women with reproductive failures[45]. However, further research on the thrombotic complications and its treatment options in pregnant women infected with SARS-CoV-2 is the need of the hour.

8. Pre-existing Thrombophilic Disorders And COVID-19

Thrombophilia is described as a state of hyper-coagulability and comprises two types, i.e., primary (hereditary) and secondary (acquired)[46].

8.1. Factor V Leiden mutation

Factor V Leiden mutation is the most common hereditary thrombophilia[47]. In Leiden variants, pulmonary embolism (PE) is less common than deep vein thrombosis (DVT), mainly manifesting in the

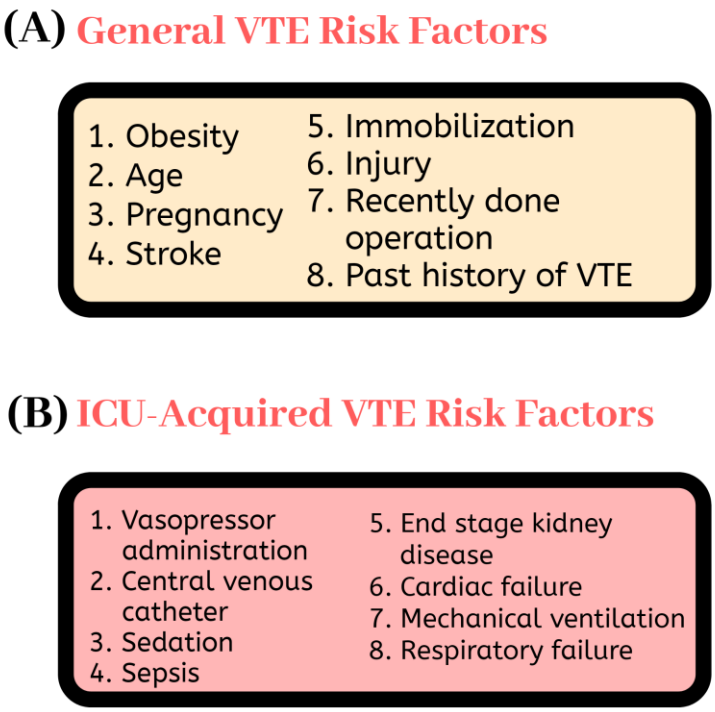

Figure 4: General and ICU acquired venous thromboembolism risk factors
(adapted from Minet et al. (2015)[42] with permission)

legs. VTE risk is also increased in Factor V Leiden patients[48]. A study shows an elevated risk of PE and DVT in COVID-19 patients and alludes to a direct correlation with the severity of the disease[49]. Therefore, patients with mutated factor V Leiden are more susceptible to COVID-19, since this factor potentially increases the risk for VTE.

8.2. Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a vasculopathy, as well as a cause of thrombophilia. Renal complications of the antiphospholipid syndrome include nephropathy, renal artery stenosis, and end-stage kidney disease[50]. In primary APS, the triggering of the mTOR (mammalian target of rapamycin) pathway in vascular endothelium results in vascular lesions[51]. The lesions are also present in carotid, coronary, and mesenteric arteries that may lead to ischemia, myocardial infarction, and stroke[52]. Based on the fact that underlying cardiovascular disorders in patients with SARS-CoV-2 infection, multiplies the severity of disease[53], APS patients with vascular lesions may experience a more severe form of COVID-19, with a higher mortality rate. Anticardiolipin antibody (ACA) and lupus anticoagulant (LPA) are present in APS and thus, increases the chances of thrombosis and thrombocytopenia[54]. According to a study, 45% of COVID-19 patients out of 56 were LAC (lupus anticoagulant) positive[37]. From this, it can be inferred that patients of the antiphospholipid syndrome could be more susceptible to COVID-19, due to increased thrombotic complications.

8.3. Nephrotic syndrome

The nephrotic syndrome, which is a glomerular disease characterized by edema, proteinuria, hyperlipidemia, and hypoalbuminemia[55], causes thrombophilia. According to a recent study, out of 10461 patients with nephrotic syndrome, 15 had acute cerebral damage, and D-dimer levels were increased in 13 out of those 15 patients.

Coagulopathy was observed in 9 out of the 15 patients[56]. In a study of 100 nephrotic syndrome patients, it was observed that 53 out of 100 had elevated D-dimer levels[57]. A cohort study involving 201 patients showed that coagulation disorders, elevated D-dimer levels, and longer PT amplifies the chances of ARDS in SARS-CoV-2 infected patients[40]. Hence, patients suffering from nephrotic syndrome and COVID-19 have poor outcomes and are at increased possibility of having critical COVID-19 infection. Thus, it can be inferred that pre-existing nephrotic syndrome may increase the risk of hyper-coagulability in COVID-19 patients.

Regular testing for pre-existing thrombophilic conditions in COVID-19 patients is not usually suggested. However, depending on the clinical feature of patients, testing for thrombophilia should not be delayed, since unmanaged thrombophilia can lead to fatal complications[58].

9. Conclusion

- COVID-19 is now considered more as a systemic infection rather than the common flu.
- Hemodynamics of COVID-19 disease gives an in-depth view of the pathophysiology of the disease and possible management and treatment options.
- Hemodynamic picture of patients infected with SARS-CoV-2 is greatly dependent on the severity of the disease.
- Lymphopenia, thrombocytopenia, eosinophilia, neutrophilia, and leucopenia in general are some findings seen in most of the COVID-19 patients especially in ICU ones.
- Hematologic manifestations of COVID-19 patients resemble in many aspects to those observed in SARS and MERS patients.
- A significant number of deaths due to COVID-19 infection can be attributed to cytokine storm and cytokine release syndrome.
- IL-6 signaling plays a drastic part in the cytokine storm. Therefore, drugs inhibiting cytokine storm can help in treating the infection.
- Metronidazole, tocilizumab, and ulinastatin potentially decrease cytokine levels and thus could suppress cytokine storm.
- Non-survivors of SARS-CoV-2 disease showed higher D-dimer levels, prothrombin time, and fibrinogen degradation products, if compared to survivors.
- Pre-existing thrombophilic conditions, including both hereditary and acquired thrombophilia, worsens the COVID-19 disease and are a poor prognostic marker for the disease.
- The inverse may also be true, i.e., COVID-19 can exacerbate thrombophilia, due to a rise in D-dimer levels and longer PT.
- In itself, the disease actuates a hyper-coagulable state and is linked to a higher risk for VTE due to excessive inflammation, hypoxia, and immobilization, particularly in severely ill COVID-19 patients.
- Management of coagulation-related complications in pregnant women with SARS-CoV-2 infection is challenging and further research on this aspect should be undertaken.
- Testing for pre-existing acquired thrombophilia in a COVID-19 patient should only be performed if the clinical presentation suggests so.

Acknowledgements

All the authors are grateful to our affiliated institution, CMH Lahore Medical College and Institute of Dentistry, Lahore, Pakistan for its unwavering support.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Su S, Wong G, Shi W, Liu J, Lai A, Liu W. Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. Trends in Microbiology 2016;24(6):490-502.
2. Zhu N, Zhang D, Wang W, Yang B, Jingdong S. A Novel Coronavirus from Patients with Pneumonia in China, 2019. The New England Journal of Medicine. 2020;2:727-35.
3. WHO. 2019 [cited 2020 August 8]. Available from: https://www.who.int/ith/diseases/sars/en/.
4. WHO. 2019 [cited 2020 August 8]. Available from: https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov).
5. Li Q, Guan X, Wu P, Wang X, Tong Y, Ren R. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. The New England Journal of Medicine. 2020;382(12).

6. Tang N, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostsis. 2020;18(4):844-7.
7. Guo Y-R, Cao Q-D, Hong Z-S, Tan Y-Y, Chen S-D, Jin H-J, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. Military Medical Research. 2020;7(1):1-10.
8. Huang C, Wang Y, Li X, Ren L, Zhao J. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395(10223):497-506.
9. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurology. 2020 Jun 1;77(6):683-690.
10. Madjid M, Naeini P, Solomon S, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System. JAMA Cardiology. 2020.
11. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nature Medicine. 2020;26(7):1017-32.
12. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. American Journal of Hematology. 2020;95(7):834-47.
13. Liu J, Li H, Luo M, Jiyang L, Lingzhen W, Lin X. Lymphopenia acted as an adverse factor for severity in patients with COVID-19: a single-centered, retrospecive study. Research Square. 2020(1).
14. Fan B, Chong V, Chan S, Lim G, Lim K, Tan G. Hematologic parameters in patients with COVID-19 infection. Journal of Hematology. 2020;95(6):131-4.
15. Huanhuan L, Liu F, Li J, Zhang T. Clinical and CT imaging features of COVID-19 pneumonia: Focus on pregnant women and children. Journal of Infection. 2020;80(5):7-13.
16. Frater J, Zini G, Onofrio G, Rogers H. COVID-19 and the clinical hematology laboratory. International Journal of Lab Hematology. 2020 Jun;42 Suppl 1:11-18.
17. Tan L, Wang Q, Zhang D. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Sig Transduct Target Ther. 2020;33(5).
18. Xiong Y, Liu Y, Cao L, Wang D, Guo M, Jiang A, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerging Microbes & Infections. 2020;9(1):761-70.
19. Cascella M, Rajnik M, Cuomo A, Dulebohn S, Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). StatPearls. 2020.
20. Qing Y, Bili W, Mao J. Cytokine Storm in COVID-19 and Treatment. Journal of Infection. 2020.
21. Zhang W, Zhao Y, Zhang F. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clinical Immunology. 2020:214-5.
22. Zhang C, Zhao W, Jia-Wen L, Hong Z, Gui-Qiang W. The cytokine release syndrome (CRS) of sever COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. International Journal of Antimicrobial Agents. 2020; 55(5):105954.
23. Wang H, Ma S. The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction syndrome. The American journal of emergency medicine. 2008;26(6):711-5.
24. Russell B, Moss C, George G, Santaolalla A, Cope A. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience. 2020;14(1022).
25. Liu B, Li M, Zhou z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome CRS)? Journal of autoimmunity. 2020 Jul;111:102452.
26. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev. 2020 Mar 31;e33213321.
27. Wang L, Zhang Y, Zhang S. Cardiovascular Impairment in COVID-19: Learning from Current Options for Cardiovascular Anti-Inflammatory Therapy. Frontiers in Cardiovascular Medicine. 2020 Apr 30;7:78.
28. Gharebaghi R, Heidary F, Moradi M, Parvizi M. Metronidazole; a Potential Novel Addition to the COVID-19 Treatment Regimen. Archieves of Academic Emergency Medicine. 2020;8(1).

29. Shakir L, Javeed A, Ashraf M, Riaz A. Metronidazole and the immune system. Pharmazie. 2011;393(8).

30. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19. Journal of Translational Medicine. 2020 Apr 14;18(1):164.

31. Le R, Li L, Yuan W, Shord S, Nie L, Bahru H. FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. The Oncologist 2018; 23(8): 943-7.

32. Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. Cytokine & Growth Factor Reviews. 2020;53:25-32.

33. Smetana K, Jr., Brábek J. Role of Interleukin-6 in Lung Complications in Patients With COVID-19: Therapeutic Implications. In Vivo. 2020;34(3 Suppl):1589-92.

34. Zhang X, Zhu Z, Jiao W, Liu W, Liu F, Zhu X. Ulinastatin treatment for acute respiratory distress syndrome in China: a meta-analysis of randomized controlled trials. BMC Pulmonary Medicine. 2019;19(1):196.

35. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607-13.

36. Wang H, Liu B, Tang Y, Chang P, Yao L, Huang B, et al. Improvement of Sepsis Prognosis by Ulinastatin: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front Pharmacol. 2019;10:1370.

37. Harzallah I, Debliquis A, Drenou B. Lupus anticoagulant is frequent in patients with Covid-19. Journal of Thrombosis haemostasis. 2020 Aug;18(8):2064-2065.

38. Zhai Z, Li C, Chen Y, X LZ, Z, Gerotziafas G, Liu P. Prevention and Treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A Consensus Statement before Guidelines. Thrombosis and Haemostasis. 2020 Jun;120(6):937-948.

39. Lew TW, Kwek TK, Tai D, Earnest A, Loo S, Singh K, et al. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. Jama. 2003;290(3):374-80.

40. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. 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(7): 934-943.

41. Wong RS, Wu A, To KF, Lee N, Lam CW, Wong CK et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. BMJ. 2003 Jun 21; 326(7403): 1358-62.

42. Minet C, Potton L, Bonadona A. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. Critical Care. 2015;19(1):287-9.

43. Shi S, Qin M, Shen B, Cai Y et al. Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China. JAMA Cardio. 2020(e200950).

44. Simcox LE, Ormesher L, Tower C, Greer IA. Thrombophilia and Pregnancy Complications. Int J Mol Sci. 2015;16(12):28418-28.

45. Kwak-Kim J, Ota K, Sung N, Huang C, Alsubki L, Lee S et al. COVID-19 and immunomodulation treatment for women with reproductive failures. Journal of Reproductive Immunology. 2020; 141: 103168.

46. Obradovic D. Thrombophilia and thrombosis. Medicinski pregled. 2005;58(7):368-74.

47. Dautaj A, Krasi G, Bushati V. Hereditary thrombophilia. Acta Biomed. 2019;90(10):44-6.

48. Kujovich J. Factor V Leiden Thrombophilia. Genet Med. 2011 Jan;13(1):1-16.

49. Cui S, Chen S, Li X, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. Journal of Thrombosis and Haemostsis. 2020 Jun;18(6):1421-1424.

50. Siddique S, Risse J, Canaud G. Vascular Manifestations in Antiphospholipid Syndrome (APS): Is APS a Thrombophilia or a Vasculopathy? Curr Rheumatol Rep. 2017;19(64).

51. Velasquez M, Rojas M, Cadavid A. Mechanisms of Endothelial Dysfunction in Antiphospholipid Syndrome: Association with Clinical Manifestations. Front Physiol. 2018 Dec 21;9:1840.

52. Canaud G, Bienaime F, Tabarin F. Inhibition of the mTORC pathway in the antiphospholipid syndrome. New England Journal of Medicine. 2014;371(4):303-12.

53. Zheng Y, Ma Y, Zhang J, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardio. 2020;17(5):259-60.

54. Shapiro S. The lupus anticoagulant/ antiphospholipid syndrome. Annu Rev Med. 1996:533-53.

55. Wang C, Greenbaum L. Nephrotic Syndrome. Pediatr Clin North Am. 2019;66(1):73-85.

56. Yang M, Pan X, Liang Z. Clinical Features of Nephrotic Syndrome with Cerebral Hemorrhage. Med Sci Monit. 2019;25:2179-85.

57. Sexton D, Clarkson M, Mazur M, Plant W, Eustace J. Serum D-dimer concentrations in nephrotic syndrome track with albuminuria, not estimated glomerular filtration rate. Am J Nephrol. 2012;36(6):554-60.

58. Cohoon KP, Mahé G, Spyropoulos AC. The underrecognized prothrombotic vascular disease of COVID-19. Res Pract Thromb Haemost. 2020;4(5):942-3.