

**Dear Editor and reviewers, thanks for considering and reviewing our manuscript, and thanks for your valuable comments. This is a point to point response to your comments; we are hoping that it will satisfy your valuable queries and comments, thanks.**

**Here is point to point respond to comments:**

**Reviewer #1:**

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

**Q1:** Specific Comments to Authors: The review entitled “Hemostatic system and COVID-19 cross talks: a review of the available evidence” by Mohamed-Naguib Wifi is a comprehensive review of the hematological changes that occur in SARS CoV-2. This review is a comprehensive manuscript detailing a number of hematological parameters in other viral infections and also in the context of SARs CoV-2. However certain modifications are needed before the manuscript can be accepted. The entire manuscript requires thorough checking and editing for English and grammatical errors. There are many sentences which do not completely make sense.

**Answer: English editing is done.**

**Q2:** A list of abbreviations would be helpful.

**Answer: We added it.**

**Q3:** A figure or a box explaining the various hematological parameters that are assessed along with their implications with respect to severity of the pathology would be helpful in true appreciation of the manuscript.

**Answer: We added it.**

**Q4:** Example- an explanation of D dimer, how its levels could be affecting the pathology along with the various indicators of severity.

**Answer:** It is well known that the high level of D-dimer in COVID-19 is triggered by excessive clots and hypoxemia which is likely reflecting pulmonary vascular bed thrombosis and fibrinolysis and correlates significantly with mortality; in many

retrospective studies that conducted in COVID-19 pneumonia patients, the elevated baseline D-dimer levels are observed with inflammation but cannot be accurately correlated with venous thromboembolism (VTE) score, this could be helpful in determining whether anticoagulation is needed or not based on levels of D-dimer.

References: - Zhan H, Chen H, Liu C, et al. Diagnostic Value of D-Dimer in COVID-19: A Meta-Analysis and Meta-Regression. *Clin Appl Thromb Hemost*. 2021;27:10760296211010976. doi:10.1177/10760296211010976

- Yu B, Li X, Chen J, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. *J Thromb Thrombolysis*. 2020;50(3):548-557. doi:10.1007/s11239-020-02171-y

**Q5:** A speculative model or table detailing the various parameters that are altered in SARS Cov-2 and their implications in COVID survivability and/ or prognosis would be helpful.

**Answer: We added it in the main manuscript.**

**Q6:** References need to be updated. There are no citations from publications in 2021.

**Answer: We added a lot of citations from publications in 2021.**

**Reviewer #2:**

Scientific Quality: Grade D (Fair)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: The authors summarized coagulation disorders, management strategies, Outcome, prognosis associated with COVID-19 coagulopathy, and anticoagulation therapy for COVID-19, a narrative review of COVID-19. However, similar papers have been published. However, this is an interesting and detailed review that collects some of the points explored in an attempt to understand the mechanisms and consequences of COVID 19 infection.

Nonetheless, there are similar reviews in the literature already elsewhere (*Thorax*. 2021 Apr;76(4):412-420; *Chest*. 2021 Oct;160(4):1471-1480; *Front Med (Lausanne)*).

2021 Aug 4;8:698935; Eur Heart J Cardiovasc Pharmacother. 2021 Sep 14:pwab070), and the Authors should make an extra effort to make it novel. Hence, the current review has not enough novelty to make it interesting. I have added a few recommendations to improve the manuscript:

1. The manuscript's language needs a lot effort and careful proofreading. Since few paragraphs were written without clear thoughts about the language, moreover, The format of the manuscript is broken; please modify it.

**Answer: English editing is done.**

**Q7:** 2. The manuscript's introduction is very lengthy, so the author should concentrate on current evidence and explain why the authors work on this manuscript and its aims.

**Answer: Thanks for comments. We modified the introduction.**

**Q8:** 3. The pathogenesis of the COVID-19 related thrombosis section was written poorly without adding enough evidence. a. Pulmonary intravascular coagulation suggests that it arises due to macrophage activation syndrome-like intrapulmonary inflammation that causes vessel wall damage. So, the authors need to explain the pathophysiology/pathogenesis of pulmonary intravascular coagulopathy (PIC) and thrombosis.

**Answer:** COVID-19 pathogenesis is associated with pulmonary intravascular coagulopathy (PIC) and thrombosis but it still it differs from sepsis associated disseminated intravascular coagulation (DIC). The first explanation of the pathogenesis of PIC and thrombosis in COVID-19 directed to binding of SARS-CoV2 to ACE2 receptors that located on type II pneumocytes and possibly on vascular endothelial cells that results in lysis of the cells immediately causing activation of the endothelium and procoagulant activity with the activation of fibrin deposits and accumulation in pulmonary microcapillary venous vessels, finally ending in PIC and thrombosis.

References: - Belen-Apak FB, Sarialioğlu F. Pulmonary intravascular coagulation in COVID-19: possible pathogenesis and recommendations on anticoagulant/thrombolytic therapy. J Thromb Thrombolysis. 2020;50(2):278-280. doi:10.1007/s11239-020-02129-0

The second opinion is the immune mediated mechanism results in marked microvascular thrombosis and haemorrhage that are linked to extensive alveolar and interstitial inflammation sharing features with macrophage activation syndrome (MAS) in a term of lung-restricted vascular immunopathology associated with COVID-19.

References: - McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol.* 2020;2(7):e437-e445. doi:10.1016/S2665-9913(20)30121-1

**Q9:** b. The authors may consider including a subsection to explain the Immunothrombosis effect in COVID-19 and COVID-19-associated hyper inflammation, endothelial dysfunction, cytokine deregulation, and interferon responses

**Answer:** Infection with COVID-19 is supposed to induce a process of immune system hyperactivation known as immunothrombosis, in which activated neutrophils and monocytes interact with platelets and the coagulation cascade, leading to intravascular clot formation in small and larger vessels. It is supposed that the exaggerated immunothrombosis that occurred within lung microvessels is the main drive for the COVID-19 manifestations.

References: - Bonaventura A, Vecchié A, Dagna L, et al. Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. *Nat Rev Immunol.* 2021;21(5):319-329. doi:10.1038/s41577-021-00536-9

- McFadyen JD, Stevens H, Peter K. The Emerging Threat of (Micro)Thrombosis in COVID-19 and Its Therapeutic Implications. *Circ Res.* 2020;127(4):571-587. doi:10.1161/CIRCRESAHA.120.317447

Endothelial dysfunction was suggested as most striking pathophysiological event in COVID-19 that infects vascular endothelial cells leading to cellular damage and apoptosis, which in turn decrease the antithrombotic activity of the normal endothelium.

References: - Goeijenbier M, van Wissen M, van de Weg C, et al. Review: Viral infections and mechanisms of thrombosis and bleeding. *J Med Virol*. 2012;84(10):1680-1696. doi:10.1002/jmv.23354

- Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed [published correction appears in *Nat Rev Immunol*. 2020 Jun 4;:]. *Nat Rev Immunol*. 2020;20(7):389-391. doi:10.1038/s41577-020-0343-0

- Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med*. 2020;173(4):268-277. doi:10.7326/M20-2003

Like other respiratory infections, leukocyte recruitment to the lungs, a higher percentage of macrophages and neutrophils together with higher levels of pro-inflammatory cytokines (such as IL-6, IL-8 and IL-1 $\beta$ ) and chemokines (such as CCL2, CCL3, CCL4 and CCL7) that found in the bronchoalveolar fluid are the major contributor to inflammatory responses in COVID-19 infection.

References: Alon R, Sportiello M, Kozlovski S, et al. Leukocyte trafficking to the lungs and beyond: lessons from influenza for COVID-19. *Nat Rev Immunol*. 2021;21(1):49-64. doi:10.1038/s41577-020-00470-2

**Q10:** 4. Epidemiology and clinical presentation of thrombotic events in COVID-19 section, authors may include a table to explain the currently available data and clinical events because the correlation between the different data by different researchers was not clearly written for better understanding.

**Answer: We added it.**

**Q11:** 5. Laboratory abnormalities and diagnostic workup section are very important for readers and clinicians. Considering the importance of this section, authors should consider including subsections about Coagulation Abnormalities and have the subsections for derangement of coagulation and bleeding manifestations (i.e., 1. Platelet counts, 2. PT, and APTT, 3. Fibrinogen and D-Dimer, 4. Viscoelastic Tests)

**Answer:** A unique coagulopathy and procoagulant endothelial phenotype associated with proinflammatory state that occurs with COVID-19 infection has a prominent effect on elevation of fibrinogen and D-dimer/fibrin(ogen) degradation products

which in turn results in systemic hypercoagulation and frequent venous thromboembolic events.

References: Wool GD, Miller JL. The Impact of COVID-19 Disease on Platelets and Coagulation. *Pathobiology*. 2021;88(1):15-27. doi:10.1159/000512007

As reported in literatures, the incidence of thrombocytopenia ranges between 5–41.7% of COVID-19 infected patients and it varies according to the disease severity, Moreover, rebound thrombocytosis was also reported in some cases.

References: - Zhang Y, Zeng X, Jiao Y, et al. Mechanisms involved in the development of thrombocytopenia in patients with COVID-19. *Thromb Res*. 2020;193:110-115. doi:10.1016/j.thromres.2020.06.008

- Yue H, Bai X, Wang J, et al. Clinical characteristics of coronavirus disease 2019 in Gansu province, China. *Ann Palliat Med*. 2020;9(4):1404-1412. doi:10.21037/apm-20-887

In a large meta-analysis of 7,613 COVID-19 patients, it was found that in severe infection and non- survivors the platelet count was lower, this could raise the attention to have the platelet counts as a predictor of COVID-19 mortality.

References: -Li Q, Cao Y, Chen L, et al. Hematological features of persons with COVID-19. *Leukemia*. 2020;34(8):2163-2172. doi:10.1038/s41375-020-0910-1

-Jiang SQ, Huang QF, Xie WM, Lv C, Quan XQ. The association between severe COVID-19 and low platelet count: evidence from 31 observational studies involving 7613 participants. *Br J Haematol*. 2020;190(1):e29-e33. doi:10.1111/bjh.16817

Several mechanisms of COVID-19-associated thrombocytopenia have been reported such as direct viral-platelet interaction activation, platelet autoantibody formation, with subsequent platelet clearance, splenic/hepatic sequestration and/or marrow/megakaryocyte suppression owing to inflammatory response, direct viral infection or reduced thrombopoietin level.

References: Amgalan A, Othman M. Exploring possible mechanisms for COVID-19 induced thrombocytopenia: Unanswered questions. *J Thromb Haemost*. 2020;18(6):1514-1516. doi:10.1111/jth.14832

COVID-19 infection has a significantly elevated vWF levels together with increased FVIII clotting activity, this likely reflects the combined effect of the greater release of Weibel-Palade bodies from endothelial cells and the acute-phase reaction meanwhile ADAMTS13 activity was found mild-to-moderately reduced in COVID-19 patients.

References: -Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost.* 2020;18(7):1738-1742. doi:10.1111/jth.14850

-Escher R, Breakey N, Lämmle B. ADAMTS13 activity, von Willebrand factor, factor VIII and D-dimers in COVID-19 inpatients. *Thromb Res.* 2020;192:174-175. doi:10.1016/j.thromres.2020.05.032

-Blasi A, von Meijenfildt FA, Adelmeijer J, et al. In vitro hypercoagulability and ongoing in vivo activation of coagulation and fibrinolysis in COVID-19 patients on anticoagulation. *J Thromb Haemost.* 2020;18(10):2646-2653. doi:10.1111/jth.15043

Fibrinogen level is increased to 5.0–7.0 g/dL in average for COVID-19 infected patients, CRP is also increased as an acute-phase reactant associated with elevated IL-6.

References: -Henry BM, Lippi G, Plebani M. Laboratory abnormalities in children with novel coronavirus disease 2019. *Clin Chem Lab Med.* 2020;58(7):1135-1138. doi:10.1515/cclm-2020-0272

-Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med.* 2020;58(7):1021-1028. doi:10.1515/cclm-2020-0369

-Pavoni V, Gianesello L, Pazzi M, Stera C, Meconi T, Frigieri FC. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. *J Thromb Thrombolysis.* 2020;50(2):281-286. doi:10.1007/s11239-020-02130-7

Antithrombin is known to be consumed during coagulation, and the mild antithrombin deficiency was described in COVID-19 infection while protein C was not decreased in any of the patients assessed.

References: Takahashi H, Takakuwa E, Yoshino N, Hanano M, Shibata A. Protein C levels in disseminated intravascular coagulation and thrombotic thrombocytopenic purpura: its correlation with other coagulation parameters. *Thromb Haemost.* 1985;54(2):445-449

Mildly prolonged aPTT clotting times was reported in some COVID-19 patients implying a prothrombotic state.

References: Tan CW, Low JGH, Wong WH, Chua YY, Goh SL, Ng HJ. Critically ill COVID-19 infected patients exhibit increased clot waveform analysis parameters consistent with hypercoagulability. *Am J Hematol.* 2020;95(7):E156-E158. doi:10.1002/ajh.25822

COVID-19-associated thrombocytopenia is mostly affecting clot formation kinetics and clot strength on Quantra viscoelastic analysis, however the details of in vivo fibrinolysis in COVID-19 have not yet been fully investigated.

References: Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost.* 2020;18(7):1747-1751. doi:10.1111/jth.14854

Bleeding is rare in the setting of COVID-19, transfusion therapy should be restricted for those with active bleeding, requiring an invasive procedure, or who are at an otherwise high risk for bleeding complications and accordingly to be managed similar to those in ISTH guidelines for DIC.

References: Wada H, Thachil J, Di Nisio M, et al. Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines [published online ahead of print, 2013 Feb 4]. *J Thromb Haemost.* 2013;10.1111/jth.12155. doi:10.1111/jth.12155

As regarding COVID-19 induced coagulopathy, we can conclude that it meets criteria of sepsis-induced coagulopathy (SIC) which defined as a reduced platelet count, increased INR, and higher organ dysfunction score.

References: -Iba T, Levy JH, Warkentin TE, et al. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. *J Thromb Haemost.* 2019;17(11):1989-1994. doi:10.1111/jth.14578

-Iba T, Levy JH, Yamakawa K, et al. Proposal of a two-step process for the diagnosis of sepsis-induced disseminated intravascular coagulation. *J Thromb Haemost.* 2019;17(8):1265-1268. doi:10.1111/jth.14482

D-Dimer is discussed in another section.

**Q12:** 6. The management strategies section needs some improvements in terms of including a section to discuss current guidelines for managing the COVID-19 associated coagulopathy by different academic societies. The authors have already added the guidelines by ISTH. However, authors should include guidelines by the British Thoracic Society, American Society of Hematology, and expert panel reports by CHEST/AIPPD/AABIP.

**Answer:** The British Thoracic Society recommends therapeutic LMWH for in-patients with Covid-19 disease who are managed on general wards and require supplemental oxygen, while the patients with no evidence of VTE or other indication for therapeutic anticoagulation who require high-flow oxygen, CPAP, NIV for severe ventilatory failure or invasive ventilation should receive less than therapeutic dosing.

References: BTS Guidance on Venous Thromboembolic Disease in patients with COVID-19-Updated August 2021 - Recently published data

The Italian Society of Thrombosis and Hemostasis (SISET) strongly recommends prophylactic anticoagulation with LMWH, UFH, or fondaparinux for the entire duration of the hospital stay, and for 7–14 days more after hospital discharge.

References: Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). *Blood Transfus.* 2020;18(3):167-169. doi:10.2450/2020.0083-20

American College of Chest Physicians and Global Covid-19 Thrombosis Collaborative Group both recommends standard dose anticoagulation for in-patients with Covid-19 disease and ICU/Critical Care patients, meanwhile SIGN and NICE NG-191 exerts intermediate dose/ standard dose anticoagulation for those patients.

References: -Moore LK, Trischler T, Brosnahan S, et al. Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. *Chest*. 2020;158(3):1143-1163. doi:10.1016/j.chest.2020.05.559

-Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020;75(23):2950-2973. doi:10.1016/j.jacc.2020.04.031

-SIGN. The prevention and management of thromboembolism in hospitalised patients with COVID-19-related disease.

2020:[https://www.sign.ac.uk/media/1691/sg\\_prevention\\_of\\_thromboembolism\\_in\\_hospitalised\\_patients.pdf](https://www.sign.ac.uk/media/1691/sg_prevention_of_thromboembolism_in_hospitalised_patients.pdf)

-NICE. COVID-19 rapid guideline: managing COVID-19.

<https://www.nice.org.uk/guidance/NG191>. 2021

Most of the international guidelines and recommendations (ISTH-IG, ACF, CDC, and ASH) adopt stopping anticoagulation in patients who developed bleeding or severely thrombocytopenic, furthermore, they also do not recommend a particular platelet count threshold. .

References: Mousa, N., Abdel-Razik, A., Mousa, E., Elbadrawy, T., Hosni, K., Mousa, A., Taha, A., Elmetwalli, A. Coagulopathy in COVID-19 from Pathogenesis until Treatment: A systemic Review. *Medical Journal of Viral Hepatitis*, 2021; 5.2(2): 3-8. doi: 10.21608/mjvh.2021.158270

Furthermore, the expert panel reports by CHEST/AIPPD/AABIP stated that empiric use of therapeutic anticoagulation regimens in ICU patients with COVID-19 is not clearly beneficial and may be harmful, while its use in hospitalized, noncritically ill patients with COVID-19 still remains uncertain.

References: COVID-19 RESEARCH FROM THE JOURNAL CHEST

<https://www.chestnet.org/topic-collections/covid-19/research-guidelines>

Many International and National guidance regarding VTE thromboprophylaxis has been published, however, further larger studies are required to investigate the potential therapeutic approach.

**Q13:** 7. The authors' manuscript lacks a conclusion.

**Answer:** We added the conclusion.

## **EDITORIAL OFFICE'S COMMENTS**

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

### **Science editor (1)**

This review presents other viral infections as well as some hematological parameters in the context of SAR CoV-2. The language of this manuscript needs to be revised. It is suggested to supplement a chart explaining the various hematological parameters assessed and their impact on the severity of the pathology, the pathogenesis of the COVID-19-related thrombosis component needs to add sufficient evidence, and in addition, the novelty of this manuscript needs to be highlighted

Language Quality: Grade C (A great deal of language polishing)

Scientific Quality: Grade C (Good)

### **Company editor-in-chief (2)**

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Methodology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. However, the quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend:

<https://www.wjgnet.com/bpg/gerinfo/240>. Please provide the original figure

documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor

Dear Editor and reviewers, thanks for considering and reviewing our manuscript, and thanks for your valuable comments. This is a point to point response to your comments; we are hoping that it will satisfy your valuable queries and comments, thanks. English editing was done and figure are attaches as powerpoint.