Coagulopathy in COVID-19: A Systematic Review

Sharleen Winata[1], Andree Kurniawan[2]

[1]*Faculty of Medicine, Pelita Harapan University*
[2]*Internal Medicine, Faculty of Medicine, Pelita Harapan University*

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***Correspondance** : Andree Kurniawan Department of Internal Medicine, Faculty of Medicine, Pelita Harapan University. Boulavard Jendral Sudirman, Karawaci, Tangerang, Banten, Indonesia 15811.
E-mail : andree.kurniawan@uph.edu ORCID ID: https://orcid.org/0000-0002-5219-9029
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Abstract

Introduction: Corona Virus Disease 2019 (COVID-19) firstly appeared in Wuhan, China in December 2019 and defined as a pandemic in March 2020. COVID-19 divided into asymptomatic, mild, and severe symptoms. Coagulopathy may have happened in severe COVID-19 infection, it was also associated with high mortality in COVID-19 patients. Laboratory examination is the main protocol to identify coagulopathy, thereby it also determined the prognosis of COVID-19 patients with coagulopathy. Here, we review the current evidence describing the mechanism, diagnosis, treatment, and mortality of coagulopathy in COVID-19.

Method: We identify 8 studies and/or review articles evaluating coagulopathy in COVID-19 patients by searching PubMed and EMBASE databases.

Results: DIC is most commonly found in death with COVID-19, the risk of VTE also higher in severe COVID-19 because of immobility and long-term bed rest. Sepsis-induced DIC is associated with organ dysfunction as in the patient with viral infection as in COVID-19 infection. Sepsis-induce Coagulopathy (SIC) score, D-dimer, and prothrombin time (PT) measured at the time the patient classified as severe COVID-19. Higher D-dimer and FDP levels, longer PT and activated partial thromboplastin time (APTT) may have a poor prognosis. Treatment with Low Molecular Weight Heparin (LMWH) effective to reduced 28-day mortality in patients with SIC ≥ 4 and D-dimer > six-fold of the upper limit of normal.

Conclusion: Coagulopathy plays a big role to determine the prognosis of COVID-19 patients. Treatment with LMWH may give some benefits to COVID-19 patients.

Introduction

COVID-19 is a new type of pneumonia that began it spreads since December 2019, for the first time in Wuhan, China, caused by beta-coronavirus, Severe Acute Respiratory System Coronavirus 2 (SARS-CoV-2). Beta-coronaviruses also previously caused SARS and Middle East Respiratory Syndrome Corona Virus (MERS-CoV) that became outbreaks in 2003 and 2012, respectively.[1]

The clinical features of COVID-19 are divided into asymptomatic, mild symptoms (fever, cough, and fatigue), and severe symptoms (acute respiratory distress syndrome, metabolic acidosis, sepsis, and coagulopathy including disseminated intravascular coagulation (DIC) and venous thromboembolism (VTE)).[2] Organ dysfunction and coagulopathy were associated with high mortality in COVID-19 patients, 11.0% and 14.6%, respectively.[3,4] Patients with severe COVID-19 infection are at high risk for developing VTE because they usually became immobilized and in a state of acute inflammation that leading to hypercoagulation. On the other hand, DIC is one of the most common complications of sepsis that usually happen in severe pneumonia case.[5] In this systematic review, we will evaluate current articles related to coagulopathy and COVID-19.

Search Strategies

A comprehensive search of literature was conducted in the PubMed (NIH) and EMBASE databases (January 2019 to March 2020) using keyword combinations of the medical subject headings (MeSH) of 'coagulopathy', 'disseminated intravascular coagulation', 'consumptive coagulopathy', 'COVID-19', 'coronavirus disease 2019', and 'SARS-CoV-2'. Relevant reference lists were also manually searched.

Problems of COVID-19 Patients with Coagulopathy

Zhou et al. found risk factors of mortality in COVID-19 patients are older age, high Sequential Organ Failure Assessment (SOFA) score, and D-dimer greater than 1 μg/mL on admission (81% of non-survivor had D-dimer levels of > 1 μg/mL on admission). They also found that D-dimer levels and prothrombin time (PT) were associated with death.[6] Patients with a high level of D-dimer and sepsis associated with 28-day mortality in the emergency department.[7] Tang et al. also revealed that non-survivors had higher D-dimer and fibrinogen degradation product (FDP) levels, longer PT and activated partial thromboplastin time (APTT) than survivors on admission, so conventional coagulation tests in COVID-19 was associated with prognosis.[8]

Mechanism of Coagulopathy in COVID-19

DIC is most commonly found in death with COVID-19.[8] Sepsis-induced DIC is associated with organ dysfunction as in the patient with viral infection as in COVID-19 infection. In sepsis, the system of blood coagulation is shifted toward the hypercoagulable state which is acute inflammatory mediator induced tissue factor expression in CD14+ monocyte and endothelial cells.[9] Antithrombin also decreased in sepsis because of consumption by the formation of thrombin-antithrombin complexes and degradation by proteases that released from activated neutrophil, so free thrombin circulated and activate platelet and fibrinolysis pathway,[10] but the level of fibrinolytic activity is too low to counteract the systemic deposition of fibrin clots in SIRS.[11] High level of plasminogen activator inhibitor-1 (PAI-1) that originates from endothelial cells also has a big role in predicting multiple organ dysfunction in sepsis-induced DIC.[12]D-dimer and FDP is elevated in all patients who were died in the late stages of COVID-19. Risk of VTE also higher in severe COVID-19 because of immobility and long-term bed rest.[13] On the other hand, severe COVID-19 cause hypoxia that increased risk of thrombosis because of increased blood viscosity and hypoxia-inducible transcription factor-dependent signaling pathways.[14]

Diagnosis of Coagulopathy in COVID -19

The earlier phase of sepsis-induced DIC can be detected using International Society on Thrombosis and Hemostasis new scoring system, named "sepsis-induced coagulopathy" (SIC) (Figure 1).[15] Tang et al started to use this scoring when the patients classified as severe COVID-19 that define by meeting any one of these: respiratory rate ≥ 30 breaths/minute, arterial oxygen

saturation ≤ 93% at rest, and PaO2/FiO2 ≤ 300 mmHg.[13]Beside SIC, D-dimer and PT also measure at the time the patient classified as severe COVID-19. In the previous study, they used ISTH diagnostic criteria for DIC (Figure 2) and found that 71.4 % non-survivor and 0,6% survivor matched in ≥ 5 points or the grade of overt-DIC.[16] DIC was detected in median time of 4 days after admission to hospital.[8] Platelet count may not be sensitive to detect coagulopathy in COVID-19, due to the reactively increased thrombopoietin following pulmonary inflammation.[17] ISTH recommended to measure fibrinogen level besides of D-dimer, PT, and platelet count in the guidance of DIC, this

recommendation can be used in COVID-19 infection.[18] Tang et al. found that D-dimer and PT level increased, and fibrinogen level decreased at days 10 and 14 in non-survivors.[8] Other researcher noted that for early identification of severe COVID-19 cases, monitoring the level of D-dimer and FDP can be helpful as their levels higher in severe COVID-19 infections than in milder forms.[10]

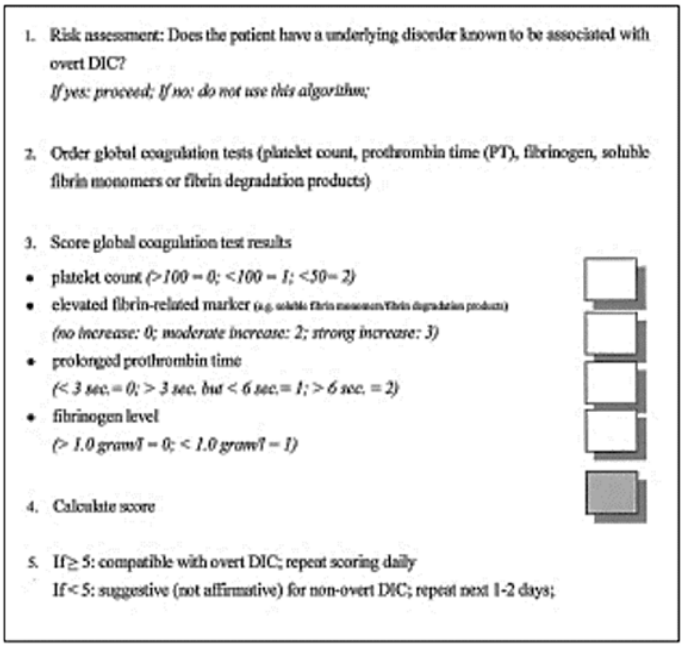

Figure 1. International Society on Thrombosis and Hemostasis (ISTH) diagnostic algorithm for the diagnosis of overt DIC[16] cited from Taylor J, et al. Thromb Haemost. 2001;86(5):1327–30.

Table 1. ISTH SIC Scoring System[15]

Item	Score	Range
Platelet count (x10^9/L)	1	100-150
	2	<100
PT-INR	1	1.2-1.4
	2	>1.4
SOFA score	1	1
	2	≥ 2
Total score for SIC	≥ 4	

Treatment of Coagulopathy in COVID-19

In Tang and colleagues' study that included 449 patients with severe COVID-19 infection, 99 of them were treated with heparin, mainly low molecular weight heparin (LMWH) for 7 days at prophylactic doses. The result was no difference in 28-day mortality between patients who received LMWH and those who did not. So, if there isn't any contraindication (active bleeding and platelet count less than $25x10^9$/L), prophylactic doses LMWH should be given in all patient including non-critical patients who required hospital admission for COVID-19 infection. In those with SIC score ≥ 4 and D-dimer > six-fold of the upper limit of normal, anticoagulant therapy (LMWH) associated with decreased mortality.[13] Besides that, LMWH also has other benefits such as against VTE in critically ill patients and its anti-inflammatory properties in COVID-19 infection where pro-inflammatory cytokines raised.[19–21] All immobilized and severely ill patients with COVID-19 should receive thromboprophylaxis unless there is any contraindication (for CrCl >30: LMWH or Fondaparinux subcutaneous (s.c) according to the license, for CrCl < 30 or acute kidney injury (AKI): unfractionated heparin 5000 unit s.c twice daily or three times daily or dose-reduced LMWH). ISTH has an algorithm to manage coagulopathy in COVID-19 based on simple laboratory markers (D-dimer, PT, platelet count, and fibrinogen). (Figure 2)[18]

Liu et al. suggest the use of anticoagulant in the early sign of elevated D-dimer in COVID-19 patients, they found that Dipyridamole (DIP), an antiplatelet, has the effectiveness to prevent hypercoagulability if given early in severe COVID-19 infection. It also has other benefits in COVID-19 infection such as broad spectrum of antiviral,[22] anti-inflammatory effect,[23] and anti-fibrotic effect.[24] DIP prevent the increased of D-dimer levels and increased platelet and leukocyte count.[22] Recent data showed data immune-thrombosis played a big role other than DIC.[25] In order to that modulation of inflammation could make a difference. Steroid and anti Il-6 could give several benefits in particular conditions.[26-28] By giving tocilizumab, anti Il-6 blocker for instance could improve inflammation parameters.[29] Several parameters D-Dimer and CRP had been proved as several severity markers in COVID-19.[30] These showed interaction between inflammation and thrombosis. Responses of inflammation to COVID-19 also influence by gut microbiota.[31] By modulating angiotensin-converting enzyme 2 may give benefit.[32] Others part also should concomitantly be controlled for instances the cardiovascular risk factors which also played extensive roles in COVID-19.[33,34] People have these cardiovascular risk factors should continue their medications[35-37], because in some particular conditions could give benefits to survival of COVID-19 when got infected.

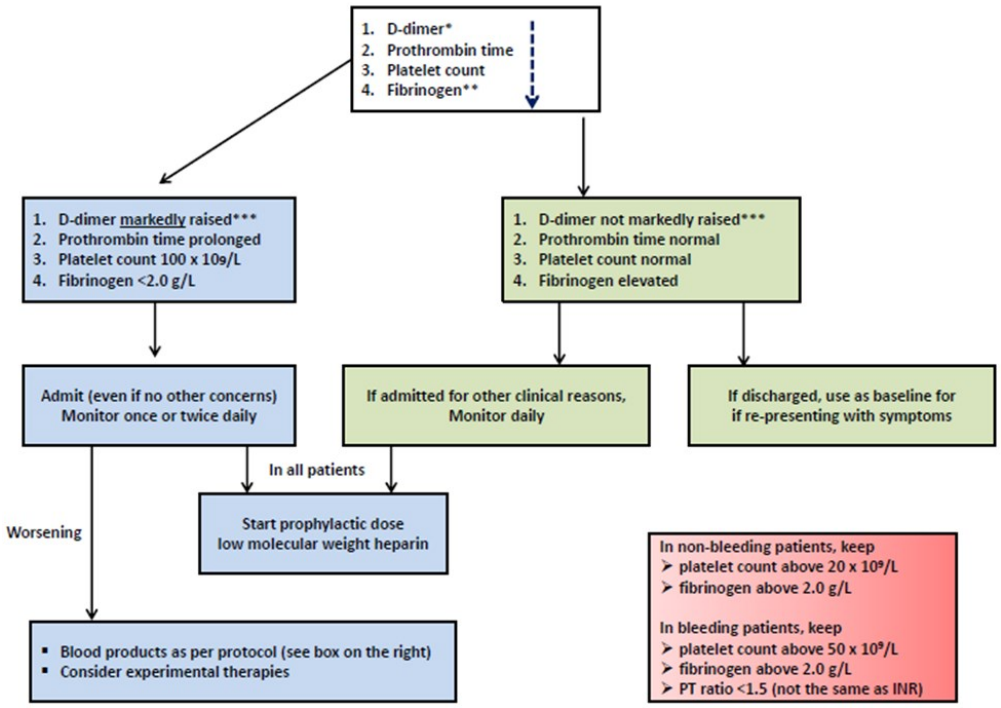

Figure 2. Algorithm for Management of Coagulopathy in COVID-19 Based on Simple Laboratory Markers. Cited from Thachil J, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost [Internet]. 2020;n/a(n/a):0–2.

* The list of markers is given in the decreasing order of importance
** Performing fibrinogen assays may not be feasible in many laboratories but monitoring the levels can be helpful after patient admission
*** Although a specific cut-off cannot be defined, a 3 to 4 folds increase in D-dimer values may be considered significant

Conclusion

Coagulopathy plays a big role in determinate the prognosis of COVID-19 patients, DIC mostly appeared in died patients. D-dimer levels and FDP can be used to evaluate prognosis. In the guidance for DIC, D-dimer level, PT, platelet count, and fibrinogen measurement are recommended by ISTH and can be used in COVID-19 patients. LMWH in prophylactic doses should be given in all patient including non-critical patients who required hospital admission for COVID-19 infection if they didn't have any contraindications. Treatment with LMWH gave some benefits in COVID-19 patients, especially reduced mortality in patients with SIC score ≥ 4 and D-dimer levels >six-fold of the upper limit of normal.

Authorhsip contributions

Concept: A.K; Design: S.W.; Data Collection or Processing: S.W, A.K.; Analysis or Interpretation: S.W. , A.K.; Literature search: S.W., A.K., Writing: S.W, A.K.

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References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33. https://doi.org/10.1056/NEJMoa2001017

2. Beverley Hunt; Andrew Retter; Claire McClintock. Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19. 2020;

3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet [Internet]. 2020;395(10223):507-13. Tersedia pada: http://dx.doi.org/10.1016/S0140-6736(20)30211-7 https://doi.org/10.1016/S0140-6736(20)30211-7

4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - J Am Med Assoc. 2020;1-9. https://doi.org/10.1001/jama.2020.1585

5. Voves C, Wuillemin WA, Zeerleder S. International Society on Thrombosis and Haemostasis score for overt disseminated intravascular coagulation predicts organ dysfunction and fatality in sepsis patients. Blood Coagul Fibrinolysis. 2006;17(6):445-51. https://doi.org/10.1097/01.mbc.0000240916.63521.2e

6. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet [Internet]. 2020;395(10229):1054-62. Tersedia pada: http://dx.doi.org/10.1016/S0140-6736(20)30566-3 https://doi.org/10.1016/S0140-6736(20)30566-3

7. Rodelo JR, De La Rosa G, Valencia ML, Ospina S, Arango CM, Gómez CI, et al. D-dimer is a significant prognostic factor in patients with suspected infection and sepsis. Am J Emerg Med [Internet]. 2012;30(9):1991-9. Tersedia pada: http://dx.doi.org/10.1016/j.ajem.2012.04.033 https://doi.org/10.1016/j.ajem.2012.04.033

8. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020; https://doi.org/10.1111/jth.14768

9. Tom van der Pol; Marcel Levi; Sander J.H. van Deventer. Differential Effects of Anti-Tumor Necrosis Factor Monoclonal Antibodies on Systemic Inflammatory Responses in Experimental Endotoxemia in Chimpanzees. 1994; https://doi.org/10.1182/blood.V83.2.446.446

10. Madoiwa S. Recent advances in disseminated intravascular coagulation: Endothelial cells and fibrinolysis in sepsis-induced DIC. J Intensive Care. 2015;3(1):1-8. https://doi.org/10.1186/s40560-015-0075-6

11. Sawdey M, Podor T, Loskutoff D. Regulation of plasminogen activator inhibitor type 1 (PAI-1) gene expression in cultured bovine aortic endothelial cells (BAES). Fibrinolysis. 1988;2:20. https://doi.org/10.1016/0268-9499(88)90387-6

12. Madoiwa S, Nunomiya S, Ono T, Shintani Y, Ohmori T, Mimuro J, et al. Plasminogen activator inhibitor 1 promotes a poor prognosis in sepsis-induced disseminated intravascular coagulation. Int J Hematol. 2006;84(5):398-405. https://doi.org/10.1532/IJH97.05190

13. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost [Internet]. 2020; Tersedia pada: http://www.ncbi.nlm.nih.gov/pubmed/32220112 https://doi.org/10.1111/jth.14817

14. Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. Thromb Res [Internet]. 2019;181(January):77-83. Tersedia pada: https://doi.org/10.1016/j.thromres.2019.07.013 https://doi.org/10.1016/j.thromres.2019.07.013

15. Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost. 2019;17(11):1989-94. https://doi.org/10.1111/jth.14578

16. Taylor J, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation: On behalf of the scientific subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and . Thromb Haemost. 2001;86(5):1327-30. https://doi.org/10.1055/s-0037-1616068

17. Menter DG, Kopetz S, Hawk E, Sood AK, Loree JM, Gresele P, et al. Platelet "first responders" in wound response, cancer, and metastasis. Cancer Metastasis Rev. 2017;36(2):199-213. https://doi.org/10.1007/s10555-017-9682-0

18. Wada H, Thachil J, Di Nisio M, Mathew P, Kurosawa S, Gando S, et al. Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines. J Thromb Haemost. 2013;11(4):761-7. https://doi.org/10.1111/jth.12155

19. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

20. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med [Internet]. 2020;1-13. Tersedia pada: http://www.ncbi.nlm.nih.gov/pubmed/32109013 https://doi.org/10.1101/2020.02.06.20020974

21. Poterucha TJ, Libby P, Goldhaber SZ. More than an anticoagulant: Do heparins have direct anti-inflammatory effects? Thromb Haemost. 2017;117(3):437-44. https://doi.org/10.1160/TH16-08-0620

22. Liu X, Li Z, Liu S, Chen Z, Zhao Z, Huang Y, et al. Therapeutic effects of dipyridamole on COVID-19 patients with coagulation dysfunction. medRxiv. 2020;2020.02.27.20027557. https://doi.org/10.1101/2020.02.27.20027557

23. Huang B, Chen Z, Geng L, Wang J, Liang H, Cao Y, et al. Mucosal Profiling of Pediatric-Onset Colitis and IBD Reveals Common Pathogenics and Therapeutic Pathways. Cell [Internet]. 2019;179(5):1160-1176.e24. Tersedia pada: https://doi.org/10.1016/j.cell.2019.10.027 https://doi.org/10.1016/j.cell.2019.10.027

24. Insel PA, Murray F, Yokoyama U, Romano S, Yun H, Brown L, et al. CAMP and Epac in the regulation of tissue fibrosis. Br J Pharmacol. 2012;166(2):447-56. https://doi.org/10.1111/j.1476-5381.2012.01847.x

25. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost [Internet]. 2020;n/a(n/a):0-2. Available from: https://doi.org/10.1111/jth.14810 https://doi.org/10.1111/jth.14810

26. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med [Internet]. 2020 Jul 17 [cited 2021 Jan 27]; Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2021436

27. Hariyanto TI, Hardyson W, Kurniawan A. Efficacy and Safety of Tocilizumab for Coronavirus Disease 2019 (Covid-19) Patients: A Systematic Review and Meta-analysis. Drug Res (Stuttg). 2021 Jan 5. doi: 10.1055/a-1336-2371. Epub ahead of print. PMID: 33401328. https://doi.org/10.1055/a-1336-2371

28. Widysanto A, Kurniawan A, Lugito NPH, Yuniarti M, Gunawan C, Angela, et al. Experience of using tocilizumab for treatment in Indonesian patients with severe COVID-19. Cytokine. 2021 Feb Vol 138. doi: 10.1016/j.cyto.2020.155393. PMID: 33333393 https://doi.org/10.1016/j.cyto.2020.155393

29. Hariyanto TI, Kurniawan A. Tocilizumab administration is associated with the reduction in biomarkers of coronavirus disease 2019 infection. J Med Virol. 2020;(July):1-5.

30. Hariyanto TI, Japar KV, Kwenandar F, Damay V, Siregar JI, Lugito NPH, et al. Inflammatory and hematologic markers as predictors of severe outcomes in COVID-19 infection: A systematic review and meta-analysis. Am J Emerg Med [Internet]. 2021;41:110-9. Available from: https://doi.org/10.1016/j.ajem.2020.12.076 https://doi.org/10.1016/j.ajem.2020.12.076

31. Lugito NP, Kurniawan A, Damay V, Chyntya H, Sugianto N. The role of gut microbiota in SARS-CoV-2 infection: Focus on angiotensin-converting enzyme 2. Curr Med Issues 2020;18:261-3. DOI: 10.4103/cmi.cmi_80_20
https://doi.org/10.4103/cmi.cmi_80_20

32. Hariyanto, T., Japar, K., Damay, V., Kwenandar, F., Sieto, N., & Kurniawan, A. (2020). The Use of ACE inhibitor/ARB in SARS-CoV-2 Patients: A Comprehensive Narrative Review. Asian Journal of Medical Sciences, 11(6), 113-120. https://doi.org/10.3126/ajms.v11i6.29911
https://doi.org/10.3126/ajms.v11i6.29911

33. Kwenandar F, Japar KV, Damay V, Hariyanto TI, Tanaka M, Lugito NPH, Kurniawan A. Coronavirus disease 2019 and cardiovascular system: a narrative review. Int J Cardiol Heart Vasc. 2020 Jun 3;29:100557. doi: 10.1016/j.ijcha.2020.100557. eCollection 2020 Aug. PMID:32550259
https://doi.org/10.1016/j.ijcha.2020.100557

34. Hariyanto TI, Kurniawan A. Anemia is associated with severe coronavirus disease 2019 (COVID-19) infection. Tranfus Apher Sci. 2020 Dec;59(6):102926. doi:10.1016/j.transci.2020.102926. Epub 2020 Aug 28. PMID: 32893135.
https://doi.org/10.1016/j.transci.2020.102926

35. Hariyanto TI, Kurniawan A. Metformin use is associated with reduced mortality rate from coronavirus disease 2019 (COVID-19) infection. Obes Med. 2020 Sep 1;19:100290.
https://doi.org/10.1016/j.obmed.2020.100290

36. Hariyanto TI, Kurniawan A. Statin therapy did not improve the in-hospital outcome of coronavirus disease 2019 (COVID-19) infection. Diabetes Metab Syndr Clin Res Rev. 2020 Nov 1;14(6):1613-5.
https://doi.org/10.1016/j.dsx.2020.08.023

37 Hariyanto TI, Kurniawan A, Statin and outcomes of coronavirus disease 2019 (COVID-19): A systematic review, meta-analysis, and meta-regression, Nutrition, Metabolism and Cardiovascular Diseases, https://doi.org/10.1016/j.numecd.2021