The Difference Coagulopathy Factor and Interleukin-6 between Survival and Non-survival Patients COVID-19

Yoshua Arif Putra*, Mutiara Mutiara

Department of Emergency, Murni Teguh Memorial Hospital, Medan, Indonesia

Abstract

BACKGROUND: Coronavirus disease 2019 (COVID-19) was caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus. SARS-CoV-2 infection can result in coagulopathy and an increase in inflammatory responses. Numerous studies have shown a significant difference in interleukin (IL) levels and coagulopathy parameters such as platelet, activated partial thromboplastin time (aPTT), prothrombin time (PT), and D- dimer between survivor and non-survivor patient COVID-19.

AIM: The purpose of this study is to compare the age, coagulopathy characteristics, and IL-6 levels of non-survival versus survival patients COVID-19.

METHODS: A cross-sectional and retrospective study was conducted on COVID-19 patients. The diagnostic criteria are based on the Indonesian Ministry of Health's recommendations. The patient's blood was analyzed in the hospital's central laboratory. Patients are classified into two groups based on their likelihood of surviving: Non-survival and survival. SPSS version 22 was used to analyze the data.

RESULTS: A total of 557 patients with COVID-19 were included in this study. Patients were categorized into 146 non-survival and 411 survival subgroups. There was a significant difference in the mean age, coagulopathy parameters, and IL-6 expect platelets between non-survival and survival outcomes in COVID-19 patients.

CONCLUSION: This study demonstrated a statistically significant difference in PT, aPTT, D-dimer, and IL-6 levels between the non-survival and survival groups of COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. COVID-19 was first discovered in December 2019, when a cluster of patients with pneumonia of unknown cause was discovered in Wuhan, China [2]. Indonesia reported its first case of COVID-19 on March 2, 2020. COVID-19 was declared a pandemic by the WHO on March 11, 2020 [1]. While respiratory symptoms predominate during the initial stages of infection, several studies have demonstrated that patients with severe COVID-19 develop a coagulation disorder (coagulopathy) similar to other systemic coagulopathies associated with severe infection, such as disseminated intravascular coagulation (DIC) and microangiopathic thrombosis. Sepsis-associated DIC is characterized by bleeding, whereas COVID-19 coagulopathy is characterized by thrombosis [3]. This is associated with a significant increase in mortality and morbidity [4]. Increased D-dimer levels indicate extensive thrombin formation and fibrinolysis and are associated with a poor prognosis on COVID-19 [5].

SARS-CoV-2 infection can directly or indirectly affect the coagulation cascade and immune response [6].

Direct infection of SARS-CoV-2 in vascular endothelial cells can induce platelet aggregation and coagulation factor release, further increasing coagulability [7], [8]. The infection begins in the pulmonary alveoli and affects the epithelial and endothelial cells and the infiltration of inflammatory cells, resulting in pro-inflammatory cytokines. The excessive systemic inflammatory response can eventually result in systemic endothelial damage and hypercoagulability [7], [8].

SARS-CoV-2 provokes immune response with the production of inflammatory cytokines accompanied by an interferon response and can provoke cytokine storm, characterized by increased production of many cytokines that produce long-term damage and lung tissue fibrosis [9], [10]. Pro-inflammatory cytokines appear to play a critical role in the pathophysiology of COVID-19 patients. COVID-19-infected patients can develop a severe and harmful immune response sustained by cytokines and results in alveolar infiltration by macrophages and monocytes. Interleukin-6 (IL-6) is a crucial mediator of inflammation during an infection-induced immune response. Numerous people with COVID-19 have elevated IL-6 levels [9], [10].

Identification of laboratory parameters related to coagulopathy and cytokine storm in patients with confirmed COVID-19 is crucial for determining the

prognosis of the disease to reduce mortality. Changes in D-dimer, fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet counts are the most common description of coagulopathy-related laboratory parameters in COVID-19 patients [11]. Cytokine storm and elevated coagulopathy parameters are associated with the severity of COVID-19 [9]. This study focused on the difference between coagulopathy profile and IL-6 level in survival and non-survival groups.

Methods

Patient

We retrospectively collected all patients, at least 18 years of age, with laboratory-confirmed COVID-19 in Murni Teguh Memorial Hospital in Medan. Confirmed cases were defined as those that have COVID clinical manifestation and real-time reverse transcription-polymerase chain reaction positive according to the Indonesian Health Ministry [1]. We retrospectively collected laboratory parameters through the medical record. There are two types of patient outcomes: Survival and non-survival. This study excluded patients with insufficient medical records and those using anticoagulant medications before admissions that may influence coagulation factors.

Data collection

Researchers obtained and analyzed medical records from 557 patients. The hospital's information system gathered information on patients' identities, laboratory results, and outcomes.

Laboratory methods

Coagulation profile and IL-6 were collected on admission. The coagulation profile consists of platelets, PT, aPTT, and D-dimer. The patient's blood was examined in the central laboratory at Murni Teguh Hospital following the hospital's standard operative procedures. The D-dimer level is tested using enzyme-linked fluorescent immunoassay with a <0.5 ug/ml reference range. Another coagulation level is tested using an automatic coagulometer. The IL-6 level is tested using electrochemiluminescence immunoassay with a reference range of <4 pg/ml.

Statistical analysis

Continuous data accorded with normal distribution and homogeneity of variance were expressed as mean ± SD and compared by independent t-test or expressed as median and compared by Wilcoxon rank-sum test. The different ages, coagulation profiles, and IL-6 with survival and non-survival patient COVID-19 were evaluated by an independent t-test. Statistical analyses were performed with SPSS (v.22.0; SPSS Inc., Chicago, IL, USA) and $p < 0.05$ was considered statistically significant.

Results

The general clinical characteristic of 557 COVID-19 cases in our study is shown in Table 1. Patients were categorized into 146 non-survival and 411 survival subgroups. The mean age of the surviving population in this study was 53.76 ± 16.2 years. The age differed significantly between the two subgroups and 66.9% of non-survivors were above 60 years. The mortality of COVID-19 was higher in men than in women (67.6% vs. 32.4%).

The blood cell test results on the initial admission are shown in Table 1. The coagulation factor levels in non-survival patients are significantly higher than the normal range. In this study, we found a significant difference between non-survival and survival groups in coagulation panel and IL-6 expect platelets.

Discussion

COVID-19, a pandemic infectious disease caused by SARS-CoV-2, is rapidly spreading worldwide. Numerous reports indicate that patients with COVID-19 embrace death due to an abnormal immune response and coagulopathy. The phenomenon of the release of many cytokines is known as cytokine syndrome [12], [13]. It has been demonstrated that abnormal coagulation function, including elevated PT, aPTT, and D-dimer, contributes to disease progression [4].

According to the WHO's report, the mortality rate in the COVID-19 patients is approximately 4%, and the epidemiological data indicate that the pandemic will continue at least for a year [14]. While several general epidemiological and clinical characteristics of COVID-19 have been reported, the distinction between survival and non-survival COVID-19 patients has not been established comprehensively and the clinical markers for predicting COVID-19 mortality are still lacking [15], [16], [17]. Due to the reasons above, this study discusses the different coagulopathy panels and IL-6 between survival and non-survival COVID-19 patients.

Our study divided COVID-19 patients into survival and non-survival subgroups according to the endpoint. COVID-19 mortality was found to be higher

Table 1: Clinical characteristics of the patients with coronavirus disease 2019 on the initial admission

Characteristics	Outcome										p^a
	Non-survival					Survival					
	n	Min	Max	Median	Mean ± SD	n	Min	Max	Median	Mean ± SD	
Age (years)	146	21	84	64	63.5 ± 11.5	411	18	93	55	53.76 ± 16.2	0.001
Platelets (/µL × 10³)	146	140	557	205.5	216.5 ± 90.4	411	16	767	219	234.5 ± 98.5	0.104
PT (s)	146	11	52.6	14.7	16.33 ± 5.41	411	10	39.4	13.8	14.3 ± 2.58	0.001
aPTT (s)	146	1.3	86.4	37.35	38.42 ± 10.9	411	8.4	106.9	35.2	36.3 ± 7.06	0.001
D-Dimer (ug/dl)	146	0.16	20	1.69	2.52 ± 2.71	411	0.1	20	0.71	1.28 ± 2.09	0.001
IL-6 (pg/ml)	146	0.6	4665	88.40	254.87 ± 595	411	0.1	1121	25.5	60.05 ± 95.7	0.001

[a]Independent _t_-test. Min: Minimal, Max: Maximal, SD: Standard deviation, n: Count, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, D-dimer: Dimerized plasmin fragment, IL-6: Interleukin-6

in older adults and males according to our study. We observed a significant difference in PT, aPTT, and D-dimer levels between the non-survival and survival groups on initial admission for the coagulopathy panel. In addition, we discovered a significant difference in IL-6 levels between the non-survival and survival groups on initial admission. This means that increased inflammation and thrombus formation can affect patient survival.

It is noticed in the other studies also shown that there is a difference between D-dimer and IL-6 [12], [18], [19]. The present COVID-19 pandemic is centered on IL-6. As early as the beginning stages of the COVID-19 outbreak, IL-6 levels were deemed a valid predictor of disease severity and the need for ventilator support. According to the Pedersen's study, elevated IL-6 levels are associated with intensive care unit (ICU) hospitalization and illness recovery. Prompetchara discovered that ICU patients had 52% greater IL-6 levels than non-ICU patients [13]. There is an exaggerated inflammatory response in some cases with COVID-19 infection resulting in a cytokine storm [20]. Elevated levels of inflammation-related cytokines, including IL-6, can lead to a hypercoagulable state. Inflammation can activate endothelial cells, impairing their ability to produce plasminogen activator inhibitor-1 (PAI-1) and thus interfering with the anticoagulant mechanism [21]. In one study conducted in China, there is a significant difference in D-dimer level in the non-survival group compared to the survival group [4], [12]. Another study conducted in Madrid discovered a significant difference in IL-6 levels between the non-survival and survival groups [22]. This study has some limitations. To begin, the present study was conducted in a single location. Second, this study was retrospective, and there were some cases with no enough data. Third, we did not analyze the utility of serial coagulopathy panel and IL-6 monitoring in COVID-19 patients.

Conclusion

In summary, our study demonstrated a statistically significant difference in PT, aPTT, D-dimer, and IL-6 levels between the non-survival and survival groups of COVID-19.

References

1. Kementerian Kesehatan RI. Pedomana Pencegahan dan Pengendalian Coronavirus Disesae (CoVID-19). Kementerian Kesehatan RI; 2020. https://doi.org/10.29239/j.agrikan.9.2.i-iii

2. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. JAMA. 2020;324(8):782-793. https://doi.org/10.1001/jama.2020.12839
   PMid:32648899

3. Berkman SA, Tapson VF. COVID-19 and its implications for thrombosis and anticoagulation. Semin Respir Crit Care Med. 2021;42(2):316-26. https://doi.org/10.1055/s-0041-1722992
   PMid:33548929

4. Hadid T, Kafri Z and Al-Katib A. Coagulation and anticoagulation in COVID-19. Blood Rev. 2021;47:100761. https://doi.org/10.1016/j.blre.2020.100761
   PMid:33067035

5. Marin BG, Aghagoli G, Lavine K, Yang L, Siff EJ, Chiang SS, _et al_. Predictors of COVID-19 severity: A literature review. Rev Med Virol. 2021;31(1):1-10. https://doi.org/10.1002/rmv.2146
   PMid:32845042

6. Joly BS, Siguret V, Veyradier A. Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. Intensive Care Med. 2020;46(8):1603-6. https://doi.org/10.1007/s00134-020-06088-1
   PMid:32415314

7. Vrints CJ, Krychtiuk KA, Van Craenenbroeck EM, Segers VF, Price S, Heidbuchel H. Endothelialitis plays a central role in the pathophysiology of severe COVID-19 and its cardiovascular complications. Acta Cardiol. 2021;76(2):109-24. https://doi.org/10.1080/00015385.2020.1846921
   PMid:33208052

8. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020;7(6):e438-40. https://doi.org/10.1016/S2352-3026(20)30145-9
   PMid:32407672

9. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol. 2021;93(1):250-256. https://doi.org/10.1002/jmv.26232
   PMid:32592501

10. Guirao JJ, Cabrera CM, Jiménez N, Rincón L, Urra JM. High serum IL-6 values increase the risk of mortality and the severity of pneumonia in patients diagnosed with COVID-19. Mol Immunol. 2020;128(1):64-68. https://doi.org/10.1016/j.molimm.2020.10.006
   PMid:33075636

11. Kander T. Coagulation disorder in COVID-19. Lancet Haematol. 2020;7(9):e630-2. https://doi.org/10.1016/S2352-3026(20)30218-0
   PMid:32659213

12. Huang Y, Lyu X, Li D, Wang L, Wang Y, Zou W, _et al_. A cohort study of 676 patients indicates Ddimer is a critical risk factor for

the mortality of COVID-19. PLoS One. 2020;15(11):1-11. https://doi.org/10.1371/journal.pone.0242045

PMid:33166991

13. Liu X, Wang H, Shi S, Xiao J. Association between IL-6 and severe disease and mortality in COVID-19 disease: A systematic review and meta-analysis. Postgrad Med J. 2021;1-9. https://doi.org/10.1136/postgradmedj-2021-139939

PMid:34083362

14. World Health Organization. Novel Coronavirus (COVID-19) Situation. Geneva: World Health Organization. Available from: https://covid19.who.int [Last accessed on 2022 Feb 18].

15. Guan W, Ni Z, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. https://doi.org/10.1056/nejmoa2002032

16. Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States. Diagnosis. 2020;7(2):91-6. https://doi.org/10.1515/dx-2020-0046

PMid:32352401

17. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, 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

18. Yu HH, Qin C, Chen M, Wang W, Tian DS. D-dimer level is associated with the severity of COVID-19. Thromb Res. 2020;195(1):219-25. https://doi.org/10.1016/j.thromres.2020.07.047

PMid:32777639

19. Naymagon L, Zubizarreta N, Feld J, van Gerwen M, Alsen M, Thibaud S, et al. Admission D-dimer levels, D-dimer trends, and outcomes in COVID-19. Thromb Res. 2020;196(1):99-105. https://doi.org/10.1016/j.thromres.2020.08.032

PMid:32853982

20. Wang J, Saguner AM, An J, Ning Y, Yan Y, Li G. Dysfunctional coagulation in COVID-19: From cell to bedside. Adv Ther. 2020;37(7):3033-9. https://doi.org/10.1007/s12325-020-01399-7

PMid:32504450

21. Colling ME, Kanthi Y. COVID-19-associated coagulopathy: An exploration of mechanisms. Vasc Med (United Kingdom). 2020;25(5):471-478. https://doi.org/10.1177/1358863X20932640

PMid:32558620

22. Donoso-Navarro E, Arribas Gómez I, Bernabeu-Andreu FA. IL-6 and other biomarkers associated with poor prognosis in a cohort of hospitalized patients with COVID-19 in Madrid. Biomark Insights. 2021;16:6-8. https://doi.org/10.1177/11772719211013363

PMid:34103886