Can D-dimer predict length of hospital stay in COVID-19 survivors? A cross-sectional study

Matthew Aldo Wijayanto[1*], Risalina Myrtha[2], Dwi Rahayu[3], Graciella Angelica Lukas[1]

[1]Department of Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
[2]Department of Cardiology and Vascular, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
[3]Department of Nutrition, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia

Abstract

Background: COVID-19 has been shown to increase the risk of thrombosis, where this mechanism occurs due to cell damage that triggers the release of various proinflammatory cytokines and chemokines, thereby activating the coagulation cascade. Thus, an increase D-dimer levels in COVID-19 patients occurs. Patients' length of hospital stay (LOS) is pivotal in order to improve patient care, lower overall expenses, and distribute resources effectively.
Purpose: This study aims to identify the association between D-dimer and other parameters as a predictor of LOS in COVID-19 survivors.
Methods: This observational analytic study included COVID-19 patients who were admitted to Universitas Sebelas Maret Hospital in Sukoharjo, Indonesia, from November 2020 to January 2021. The data were taken from the medical records of patients diagnosed with COVID-19. Age, gender, comorbidities, admission oxygen saturation, D-dimer, neutrophil-lymphocyte ratio (NLR), haemoglobin, platelet count, white blood cells (WBC), estimated glomerular filtration rate (eGFR), and LOS were analysed in this study. Binary logistic regression was applied to determine the correlation between potential predictors on LOS.
Results: A total 104 patients was included in the final analysis. The median LOS was 13 days (IQR 9-17 days). There was an increase of D-dimer in 79 patients with the median 759.39 ng/ml. Patients with prolonged LOS tend to have higher D-dimer levels (Median 924.95 vs 591.54 ng/ml, p = 0.018). However, D-dimer and other parameters were not associated with prolonged LOS in COVID-19 survivors (D-dimer p = 0.188; Age p = 0.138; Diabetes mellitus p = 0.172; NLR p = 0.859; Platelet count p = 0.097).
Conclusion: D-dimer levels do not accurately predict prolonged LOS in COVID-19 survivors. Therefore, we suggest D-dimer solely should not be used as a tool to predict a patient's LOS.

Keywords: COVID-19; D-dimer; length of hospital stay

Introduction

COVID-19, a pandemic affecting healthcare systems worldwide (di Gennaro et al., 2020), originated in late 2019 when a novel coronavirus, later identified as SARS-CoV-2, was linked to acute respiratory illnesses in Wuhan, China. Subsequently, in March 2020, this virus was officially declared a pandemic (Güner et al., 2020). It was found that COVID-19 is a systemic disease that can affect vascularisation in the pulmonary alveolar tissue, glomerular capillary loops, small intestines capillary, and myocardiocytes, and, therefore, has a high risk of thrombosis. This situation can certainly be a life-threatening situation in COVID-19 patients. Thus, anticoagulation is the

Jurnal Keperawatan Padjadjaran (JKP)

Volume 11(2), 112-117
© The Author(s) 2023
http://dx.doi.org/10.24198/jkp.v11i2.2245

Article Info

Received : March 05, 2023
Revised : July 18, 2023
Accepted : July 24, 2023
Published : August 01, 2023

Corresponding author

Matthew Aldo Wijayanto*
Department of Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia.
Address: 36 Ir. Sutami, Surakarta, 57126, Central Java, Indonesia.
Phone: +62-812-10979781,
E-mail: matthewaldo1810@gmail.com

Citation

Wijayanto, M.A., Myrtha, R., Rahayu, D., & Lukas, G.A. (2023). Can D-dimer predict length of hospital stay in COVID-19 survivors? A cross-sectional study. *Jurnal Keperawatan Padjadjaran, 11*(2), 112-117. http://dx.doi.org/10.24198/jkp.v11i2.2245

Website

http://jkp.fkep.unpad.ac.id/index.php/jkp

E-ISSN: 2442-7276
P-ISSN: 2338-5324

cornerstone treatment in thromboembolic (Ortega-Paz et al., 2021).

D-dimer levels elevated from 3.75% up to 68% in COVID-19 patients. D-dimer is one of the products of fibrin breakdown process, namely the fibrinolysis process. Pathological and non-pathological conditions that increase both fibrin production and fibrin breakdown will increase D-dimer levels in plasma (Yao et al., 2020). This thrombosis mechanism occurs due to cell damage caused by the COVID-19 virus which triggers release of various proinflammatory cytokines and chemokines, thereby activating the coagulation cascade, and compensated by the process of fibrinolysis which makes the patient's D-dimer level increase (Kasinathan & Sathar, 2020). D-dimer levels serve as a valuable marker for assessing the severity and prognosis of COVID-19 patients, with higher levels indicating a more unfavourable outcome. Research has demonstrated that D-dimer levels surpassing 2.14 mg/L are associated with an increased risk of mortality in COVID-19 patients (Yao et al., 2020). As a result, D-dimer examinations remain an essential practice in the early evaluation of hospitalized COVID-19 patients (Zhan et al., 2021a).

The rapid spread of COVID-19 presents a significant challenge to healthcare systems, particularly hospitals, as they face an increasing caseload (Mahboub et al., 2021). Length of Hospital Stay (LOS) is a crucial metric that determines the number of days an in-patient remains hospitalized (Stone et al., 2022). It has proven to be instrumental in improving patient care, reducing overall expenses, and optimizing resource distribution based on staff and patient needs. Additionally, LOS provides valuable insights into hospital care unit efficiency and patient flow. Accurate prediction of patient LOS holds great benefits for healthcare specialists, enabling them to make informed medical decisions, allocate medical teams and resources effectively, and ensure adequate bed capacity (Abd-Elrazek et al., 2021). The use of clinical data to predict the demand for hospital and Intensive Care Unit (ICU) beds in COVID-19 patients has become indispensable in optimizing therapy effectiveness (Rees et al., 2020; Vekaria et al., 2021). Currently, there is no existing study investigating the association between D-dimer levels and LOS in COVID-19 survivors, particularly in Indonesia. Hence, the main objective of this study is to establish the correlation between D-dimer and other relevant parameters as potential predictors of LOS in COVID-19 survivors.

Materials and Methods

Design

This study follows an observational analytic design with a cross-sectional approach. The research was carried out on hospitalized patients diagnosed with COVID-19 at Universitas Sebelas Maret Hospital in Sukoharjo, Indonesia, during the period from November 2020 to January 2021. Participants were selected based on specific inclusion and exclusion criteria.

Sample and setting

The inclusion criteria in this study were patients with a positive diagnosis of COVID-19 which was confirmed through a real-time polymerase chain reaction (RT-PCR), discharged patients with the approval of medical personnel, and patients who had D-dimer examination within three days of admission. Patients who died during hospitalisation, discharged at personal request, pregnant during hospitalisation, had history of anticoagulant therapy, and who were not tested with D-dimer examination within three days of admission were excluded from this study. A total of 104 samples was obtained.

Data collection

We collected patient demographic, clinical characteristics, and laboratory data. The data was taken from the medical records of patients diagnosed with COVID-19 at the Universitas Sebelas Maret Hospital including age, gender, comorbidities, oxygen saturation at admission, D-dimer, neutrophil-lymphocyte ratio (NLR), haemoglobin, platelet count, white blood cells (WBC), estimated glomerular filtration rate (eGFR), and LOS. Admission oxygen saturation were divided into two groups (i.e., < 95% and 95%). In this study, LOS was calculated as the duration from the date the patient was admitted to the hospital until the date they were discharged. If a patient was transferred to the Intensive Care Unit (ICU) or a non-COVID-19 ward during their hospitalization, the LOS continued to be recorded until the patient was ultimately discharged from the hospital. Median was used as cut-off for prolonged LOS. All blood panels were measured using automatic haematology analyzer with flow cytometry. For calculating eGFR, we used the 2021 CKD-EPI equation. D-dimer levels were measured using a latex turbidimetric immunoassay, and the results were given in ng/ml. Elevated D-dimer defined as 500 ng/ml.

Data analysis

In this study, all statistical analyses were conducted using IBM SPSS Statistics Version 26. Continuous data were presented as either frequency, mean ± standard deviation, or median with interquartile ranges (IQR). The choice between the independent t-test or Mann-Whitney U test depended on whether the data followed a normal distribution. Categorical data were presented as frequency with percentages, and the differences between variables based on Length of Hospital Stay (LOS) were assessed using either Pearson's Chi-square test or Fisher's exact test. For the normality test of the data, the Kolmogorov-Smirnov test was employed. To identify the correlation between potential variables and LOS, variables with a p-value less than 0.25 in the univariate analysis were included in the binary logistic regression. A p-value less than 0.05 was

Table 1. Baseline Characteristics of Hospitalized COVID-19 Patients

Characteristics	All patients (n=104)	Length of hospital stay		p
		<13 days (n=49)	13 days (n=55)	
Age (years), median (IQR)	52 (43.25-58.75)	50 (38-57)	54 (46-61)	0.199m
Gender, n (%)				
Male	55 (52.9)	25 (59)	30 (54.5)	0.719c
Female	49 (47.1)	24 (41)	25 (45.5)	
Comorbidities, n (%)				
Without Comorbidity	53 (51)	23 (46.9)	30 (54.5)	0.439c
Hypertension	22 (21.2)	10 (20.4)	12 (21.8)	0.86c
Diabetes Mellitus	34 (32.7)	19 (38.8)	15 (27.3)	0.212c
Asthma	2 (1.9)	1 (2)	1 (1.8)	1.000f
Acute Kidney Injury	2 (1.9)	1 (2)	1 (1.8)	1.000f
Congestive Heart Failure	4 (3.8)	2 (4.1)	2 (3.6)	1.000f
Oxygen saturation at admission, n (%)				
<95%	37 (35.6)	20 (40.8)	17 (30.9)	0.292p
95	67 (64.4)	29 (59.2)	38 (69.1)	
Laboratory parameters				
D-dimer (ng/dl), median (IQR)	759.39 (485.42-1548.55)	591.54 (455.93-1187.99)	924.95 (579.03-1839)	0.018*m
NLR, median (IQR)	4.12 (2.85-6.34)	3.69 (2.36-5.83)	4.7 (3.18-6.76)	0.082m
Hemoglobin (g/dL), mean SD	13.63 1.8	13.54 1.69	13.73 1.91	0.597t
Platelet count (103/L), median (IQR)	246 (185-309)	252 (201-347)	233 (176-301)	0.201m
WBC (103/L), median (IQR)	7.59 (5.89-9.68)	6.74 (5.77-9.42)	7.77 (6.26-10.98)	0.324m
eGFR (ml/min/1,73m2), median (IQR) (n=95)	97 (58-111)	97 (64.5-116.5)	93 (54.25-108.25)	0.553m

Note: Labelled with *: significant; t: independent t test; m: mann-whitney U test; c: pearson's chi-square; f: Fisher's exact test; IQR: interquartile range; NLR: neutrophil-lymphocyte ratio; WBC: white blood cells; eGFR: estimated glomerular filtration rate based on CKD-EPI equation.

Table 2. Analysis of Potential Risk Factor for Prolonged Length of Hospital Stay

Variables	Length of hospital stay	
	OR (95% CI)	p
D-dimer (mg/dl)	1.000 (1.000-1.001)	0.188
Age (years)	1.028 (0.991-1.066)	0.138
DM (yes)	0.539 (0.222-1.308)	0.172
NLR	1.010 (0.914-1.115)	0.859

Note: DM: diabetes mellitus; NLR: neutrophil-lymphocyte count.

considered statistically significant.

Ethical consideration

This study was conducted after obtaining ethical approval from the Health Research Ethics Commission of Dr. Moewardi Hospital (ethics number 393/III/HREC/2021).

Results

This study included 104 patients who were hospitalised in Universitas Sebelas Maret Hospital between November 2020 and January 2021, consisting of 55 (52.9%) males and 49 (47.1%) females. The median age of the study population was 52 years (IQR 43.25 to 58.75 years). Fifty-one percent of the patients had no comorbidity, while the most common comorbidities found in this study were diabetes mellitus (32.7%) and hypertension (21.2%). Admission oxygen saturation 95% was found on 64.4% of the population. The median of

LOS in this study was 13 days; therefore, prolonged LOS is defined as LOS 13 days. Laboratory findings collected in this study were D-dimer, haemoglobin, platelet count, WBC, and eGFR. There were 79 patients having elevated D-dimer with the median of D-dimer 759.39 mg/dl. Patients with prolonged LOS tend to have higher D-dimer levels (Median 924.95 vs 591.54 ng/ml, p = 0.018). The differences in demographic, clinical, and laboratory data between LOS of less than 13 days and LOS of 13 days or more are shown in Table I.

D-dimer, age, patients with diabetes mellitus, NLR, and platelet count were included in binary logistic regression analysis (p < 0.25). The results of the binary logistic regression are shown in Table II. There were no independent factors associated with prolonged LOS in this study. All independent factors had p 0.05 (D-dimer p = 0.188; Age p = 0.138; Diabetes mellitus p = 0.172; NLR p = 0.859; Platelet count p = 0.097).

Discussion

This cross-sectional study analysed baseline characteristics and the association between potential risk factors with prolonged LOS in COVID-19 patients at Universitas Sebelas Maret Hospital, Sukoharjo, Indonesia. We found the median of D-dimer levels in 104 COVID-19 patients was higher than the normal range (759.39 ng/ml), while the normal range is <500 ng/ml (Soni et al., 2020). Similar result was found from a retrospective study in China, where the median of D-dimer was 800 ng/ml (Yu et al., 2020). Patients with prolonged LOS tend to have higher D-dimer levels. Several studies showed COVID-19-driven pro-inflammatory state and hypoxia (Cidade et al., 2022). This condition leads to hyperactive coagulation and complement system followed by an increase in the fibrinolysis process in COVID-19 patients, resulting in an increase of plasmin activity. Increased plasmin activity will cause a significant increase in D-dimer levels (Kasinathan & Sathar, 2020; Page & Ariëns, 2021). Higher D-dimer levels are linked to greater severity (Zhan et al., 2021b). As a result, we assumed that patients with greater severity would require more time to recover.

The median LOS in this study was 13 days (IQR 9-17). Thus, LOS more than 13 days was considered as prolonged LOS. LOS was found to be heterogenic across the world. Previous retrospective cohort study at Guangzhou Eighth People's Hospital reported higher median of LOS (18 days) compared to this study (Chen et al., 2021). Nevertheless, several European countries have shorter median LOS (seven days) (Wise, 2020). This difference might be due to difference in strategies used to control COVID-19 infection (Thai et al., 2020). Hence, we assumed that LOS may vary around the world due to different criteria for patient discharge used by every country to control COVID-19 infections.

Previous study from South India showed that there was an association between D-dimer levels and LOS for COVID-19 patients (Thiruvengadam et al., 2021). However, our study clearly showed that D-dimer was not a good marker to predict prolonged LOS in COVID-19 survivors. A study from China also had a similar result where the study examined risk factors during admission that affect LOS of COVID-19 and revealed there was no relationship between D-dimer levels and the prolonged LOS in COVID-19 patients (Guo et al., 2021). D-dimer levels are influenced by many factors such as female sex, increased age, neurologic immobility, and other factors (Kabrhel et al., 2010). Therefore, the D-dimer levels during admission may vary among patients (Soni et al., 2020). We suggested to not use D-dimer as a single predictor for prolonged LOS. However, clinicians should be aware of the elevated D-dimer levels in COVID-19 since higher D-dimer levels are associated with greater severity and mortality in COVID-19 patients (Zhan et al., 2021b).

Although we did not find significant association between age, NLR, patients with diabetes mellitus, platelet count and prolonged LOS, previous study reported that older age and NLR were associated with longer LOS (Chen et al., 2021; Zhao et al., 2016). Older age might be associated with decreased immune responses to control viral replication (Busse & Mathur, 2010), An elevated NLR can indicate an increase in neutrophils, which may be associated with bacterial infections and worsening infections. Simultaneously, a decrease in lymphocyte count suggests a weakened immune function. NLR is considered to be a potential marker for assessing inflammation and the severity of various diseases, including infectious diseases like COVID-19 (Ye et al., 2020). A retrospective cohort study found weak evidence of diabetes mellitus associated with longer LOS because diabetes mellitus might suppress immunological function (Wu et al., 2020). Patients with thrombocytopenia were associated with increased LOS and mortality (Zhu et al., 2021). Further evidence is needed to explain the association between platelet and LOS. Different results between this study and others might be due to different criteria for patient discharge used by every country in order to control COVID-19 infections.

This study's findings have provided an updated major review of predictor prolonged LOS especially among COVID-19 survivors in Indonesia. We strictly chose our sample using the inclusion and exclusion criteria; therefore, making the result more reliable. However, this study has some limitations. First, this is a unicentral study hence making it lack of heterogeneity, and has low sample size. Second, we only used the first D-dimer examination. Thus, D-dimer levels may vary in every patient depending on their clinical condition. It is recommended to identify the correlation between serial D-dimer and LOS in hospitalised COVID-19 survivors.

Conclusion

D-dimer serum levels do not accurately predict prolonged LOS in COVID-19 survivors. Therefore, we suggested D-dimer solely should not be used as a tool in order to predict a patient's LOS. However, the presence of elevated D-dimer levels in COVID-19 should be highly noted by clinicians, as higher D-dimer levels have been linked to greater severity and mortality.

Declaration of Interest

The authors declare no conflict of interest in this study.

Acknowledgment

The authors would like to thank the Faculty of Medicine of Universitas Sebelas Maret and Universitas Sebelas Maret Hospital for their cooperation and hospitality.

Funding

This study did not received any funding or grant

Data Availability

The corresponding author will provide the datasets used and/or analyzed during the current study upon reasonable request.

References

Abd-Elrazek, M. A., Eltahawi, A. A., Abd Elaziz, M. H., & Abd-Elwhab, M. N. (2021). Predicting length of stay in hospitals intensive care unit using general admission features. *Ain Shams Engineering Journal, 12*(4), 3691–3702. https://doi.org/10.1016/j.asej.2021.02.018

Busse, P. J., & Mathur, S. K. (2010). Age-related changes in immune function: Effect on airway inflammation. *Journal of Allergy and Clinical Immunology, 126*(4), 690–699. https://doi.org/10.1016/j.jaci.2010.08.011

Chen, F. J., Li, F. R., Zheng, J. Z., Zhou, R., Liu, H. M., Wu, K. Y., Zhang, B., Dong, H., Lu, J. Y., Lei, C. L., & Wu, X. B. (2021). Factors associated with duration of hospital stay and complications in patients with covid-19. *Journal of Public Health and Emergency, 5*(6), 1–12. https://doi.org/10.21037/jphe-20-74

Cidade, J. P., Coelho, L., Costa, V., Morais, R., Moniz, P., Morais, L., Fidalgo, P., Tralhão, A., Paulino, C., Nora, D., Valerio, B., Mendes, V., Tapadinhas, C., & Póvoa, P. (2022). Predictive value of D-dimer in the clinical outcome of severe COVID19 patients: Are we giving it too much credit? *Clinical and Applied Thrombosis/Hemostasis, 28.* https://doi.org/10.1177/10760296221079612

Gennaro, F., Pizzol, D., Marotta, C., Antunes, M., Racalbuto, V., Veronese, N., & Smith, L. (2020). Coronavirus diseases (COVID-19) current status and future perspectives: A narrative review. *International Journal of Environmental Research and Public Health, 17*(2690), 1–11. https://doi.org/10.3390/ijerph17082690

Güner, R., Hasanoğlu, İ., & Aktaş, F. (2020). Covid-19: Prevention and control measures in community. *Turkish Journal of Medical Sciences, 50,* 571–577. https://doi.org/10.3906/sag-2004-146

Guo, A., Lu, J., Tan, H., Kuang, Z., Luo, Y., Yang, T., Xu, J., Yu, J., Wen, C., & Shen, A. (2021). Risk factors on admission associated with hospital length of stay in patients with COVID-19: A retrospective cohort study. *Scientific Reports, 11*(7310). https://doi.org/10.1038/s41598-021-86853-4

Kabrhel, C., Courtney, D. M., Camargo, C. A., Plewa, M. C., Nordenholz, K. E., Moore, C. L., Richman, P. B., Smithline, H. A., Beam, D. M., & Kline, J. A. (2010). Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. *Academic Emergency Medicine, 17*(6), 589–597. https://doi.org/10.1111/j.1553-2712.2010.00765.x

Kasinathan, G., & Sathar, J. (2020). Haematological manifestations, mechanisms of thrombosis and anti-coagulation in COVID-19 disease: A review. *Annals of Medicine and Surgery, 56,* 173–177. https://doi.org/10.1016/j.amsu.2020.06.035

Mahboub, B., Bataineh, M. T. A., Alshraideh, H., Hamoudi, R., Salameh, L., & Shamayleh, A. (2021). Prediction of COVID-19 Hospital length of stay and risk of death using artificial intelligence-based modeling. *Frontiers in Medicine, 8*(592336), 1–9. https://doi.org/10.3389/fmed.2021.592336

Ortega-Paz, L., Capodanno, D., Montalescot, G., & Angiolillo, D. J. (2021). Coronavirus disease 2019–associated thrombosis and coagulopathy: Review of the pathophysiological characteristics and implications for antithrombotic management. *Journal of the American Heart Association, 10*(3), 1–24. https://doi.org/10.1161/JAHA.120.019650

Page, E. M., & Ariëns, R. A. S. (2021). Mechanisms of thrombosis and cardiovascular complications in COVID-19. *Thrombosis Research, 200,* 1–8. https://doi.org/10.1016/j.thromres.2021.01.005

Rees, E. M., Nightingale, E. S., Jafari, Y., Waterlow, N. R., Clifford, S., Pearson, C. A. B., Jombart, T., Procter, S. R., & Knight, G. M. (2020). COVID-19 length of hospital stay: A systematic review and data synthesis. *BMC Medicine, 18*(270), 1–22. https://doi.org/10.1101/2020.04.30.20084780

Soni, M., Gopalakrishnan, R., Vaishya, R., & Prabu, P. (2020). D-dimer level is a useful predictor for mortality in patients with COVID-19: Analysis of 483 cases. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews, 14,* 2245–2249. https://doi.org/10.1016/j.dsx.2020.11.007

Stone, K., Zwiggelaar, R., Jones, P., & Mac Parthaláin, N. (2022). A systematic review of the prediction of hospital length of stay: Towards a unified framework. In PLOS Digital Health (Vol. 1, Issue 4). https://doi.org/10.1371/journal.pdig.0000017

Thai, P. Q., Toan, D. T. T., Dinh, T. S., Hoang, T. H. van, Luu, N. M., Xuan Hung, L., Ngo, V. T., Luu, N. H., Duong, H. L., Luong, N. K., Nguyen, T. K., & Le, T. H. (2020). Factors associated with the duration of hospitalization among COVID-19 patients in Vietnam: A survival analysis. *Epidemiology and Infection, 148*(e114), 1–7. https://doi.org/10.1017/S0950268820001259

Thiruvengadam, G., Lakshmi, M., & Ramanujam, R. (2021). A study of factors affecting the length of hospital stay of COVID-19 patients by cox-proportional hazard model in a South Indian Tertiary care hospital. *Journal of Primary Care and Community Health, 12,* 1–7. https://doi.org/10.1177/21501327211000231

Vekaria, B., Overton, C., Wiśniowski, A., Ahmad, S., Aparicio-Castro, A., Curran-Sebastian, J., Eddleston, J., Hanley, N. A., House, T., Kim, J., Olsen, W., Pampaka, M., Pellis, L., Ruiz, D. P., Schofield, J., Shryane, N., & Elliot, M. J. (2021). Hospital length of stay for COVID-19 patients: Data-driven methods for forward planning. *BMC Infectious Diseases, 21*(700), 1–15. https://doi.org/10.1186/s12879-021-06371-6

Wise, J. (2020). A third of covid-19 patients admitted to UK hospitals die. *BMJ (Clinical Research Ed.), 369,* 1. https://doi.org/10.1136/bmj.m1794

Wu, S., Xue, L., Legido-Quigley, H., Khan, M., Wu, H., Peng, X., Li, X., & Li, P. (2020). Understanding factors influencing the length of hospital stay among non-severe COVID-19 patients: A retrospective cohort study in a Fangcang shelter hospital. *PLoS ONE, 15*(10), 1–14. https://doi.org/10.1371/journal.pone.0240959

Yao, Y., Cao, J., Wang, Q., Shi, Q., Liu, K., Luo, Z., Chen, X., Chen, S., Yu, K., Huang, Z., & Hu, B. (2020). D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. *Journal of Intensive Care, 8*(49), 1–11. https://doi.org/10.1186/s40560-020-00466-z

Ye, W., Chen, G., Li, X., Lan, X., Ji, C., Hou, M., Zhang, D., Zeng, G., Wang, Y., Xu, C., Lu, W., Cui, R., Cai, Y., Huang, H., & Yang, L. (2020). Dynamic changes of D-dimer and neutrophil-lymphocyte count ratio as prognostic biomarkers in COVID-19. *Respiratory Research, 21*(169), 1–7. https://doi.org/10.1186/s12931-020-01428-7

Yu, B., Li, X., Chen, J., Ouyang, M., Zhang, H., Zhao, X., Tang, L., Luo, Q., Xu, M., Yang, L., Huang, G., Liu, X., & Tang, J. (2020). Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: A retrospective analysis. *Journal of Thrombosis and Thrombolysis, 50,* 548–557. https://doi.org/10.1007/s11239-020-02171-y

Zhan, H., Chen, H., Liu, C., Cheng, L., Yan, S., Li, H., & Li, Y. (2021a). Diagnostic value of D-dimer in COVID-19: A meta-analysis and meta-regression. *Clinical and Applied Thrombosis/Hemostasis, 27,* 1–10. https://doi.org/10.1177/10760296211010976

Zhan, H., Chen, H., Liu, C., Cheng, L., Yan, S., Li, H., & Li, Y. (2021b). Diagnostic value of D-dimer in COVID-19: A meta-analysis and meta-regression. *Clinical and Applied Thrombosis/Hemostasis, 27*. https://doi.org/10.1177/10760296211010976

Zhao, L., Dai, Q., Chen, X., Li, S., Shi, R., Yu, S., Yang, F., Xiong, Y., & Zhang, R. (2016). Neutrophil-to-lymphocyte ratio predicts length of stay and acute hospital cost in patients with acute ischemic stroke. *Journal of Stroke and Cerebrovascular Diseases, 25*(4), 739–744. https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.11.012

Zhu, Y., Zhang, J., Li, Y., Liu, F., Zhou, Q., & Peng, Z. (2021). Association between thrombocytopenia and 180-day prognosis of COVID-19 patients in intensive care units: A two-center observational study. *PLoS ONE, 16*(3), 1–15. https://doi.org/10.1371/journal.pone.0248671