Differences In D-Dimer Levels Of Moderate And Severe Covid-19 Patients Treated At Hajj Adam Malik Hospital, Medan

Denny Hadi[1], Jelita Siregar[2*], Noni Novisari Soeroso[3]

[1]Department of Clinical Pathology, Faculty of Medicine, University of North Sumatera / RSUP H. Adam Malik Medan, Indonesia
[2,3] Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of North Sumatera / RSUP H. Adam Malik Medan, Indonesia
*Corresponding Author:
Email: dennyhadi@gmail.com

Abstract.

An outbreak of coronavirus disease 2019 (COVID-19), initially reported in December 2019 in Wuhan, Hubei Province, China, emerged as a mysterious pneumonia caused by the novel β-coronavirus, 2019-nCoV. Among hospitalized COVID-19 patients, elevated D-dimer levels and impaired hemostasis have been commonly observed, often associated with disease severity and mortality. This study aimed to assess differences in D-dimer levels among mild, moderate, and severe COVID-19 patients in a cross-sectional design involving 36 confirmed COVID-19 patients hospitalized at H. Adam Malik General Hospital Medan. Conducted from August to October 2021 at the Departments of Clinical Pathology and Pulmonology and Respiratory Medicine, the study used consecutive sampling. The participants had an average age of 50.92 years, with hypertension and diabetes mellitus being the most common comorbidities. The average D-dimer level was 1324.28 ng/mL (SD = 2360.45 ng/mL), ranging from 100 ng/mL to 13,420 ng/mL. A significant difference in D-dimer levels was observed between patients with moderate and severe COVID-19, highlighting its potential role in evaluating disease progression and severity.

Keywords: *COVID-19, D-Dimer Levels, Disease Severity, Hemostasis Impairment and Hospitalized Patients.*

I. INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, first reported as a mysterious pneumonia outbreak in Wuhan, China, in December 2019, has since become one of the most significant global health crises of the 21st century. The disease, caused by the novel β-coronavirus known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) [1][2], was declared a pandemic by the World Health Organization (WHO) on March 11, 2020, due to its rapid global spread and significant morbidity and mortality [3], [4]. SARS-CoV-2 infection predominantly presents with respiratory symptoms; however, it has become increasingly evident that its pathophysiology extends far beyond the respiratory system, involving multisystemic complications, including hyperinflammatory and hypercoagulable states. In particular, patients over the age of 65 with comorbidities such as hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and malignancy are at higher risk of developing severe illness or succumbing to the disease [3], [4].Among the various laboratory findings observed in COVID-19 patients, elevated D-dimer levels have garnered considerable attention due to their association with disease severity and adverse outcomes [5], [6]. D-dimer, a fibrin degradation product, is produced during the activation of coagulation and subsequent fibrinolysis. Elevated levels of D-dimer are commonly observed in conditions involving thrombosis and systemic inflammation, making it a valuable biomarker in the clinical evaluation of COVID-19.3 Numerous studies have established a correlation between D-dimer levels and the severity of COVID-19. For instance, patients with D-dimer levels exceeding 1 µg/mL upon hospital admission had a significantly higher risk of mortality [7].

Patients requiring intensive care demonstrated higher median D-dimer levels (0.5 µg/mL) compared to those not requiring critical care [8]. These findings were further corroborated that identified a D-dimer cutoff value of 2.0 µg/mL, indicating the need for intensive monitoring in severe COVID-19 patients, even in the absence of overt clinical symptoms [9].The hypercoagulable state observed in severe COVID-19 is underpinned by complex pathophysiological mechanisms involving systemic inflammation, endothelial dysfunction, and activation of the coagulation cascade. Elevated levels of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), play a pivotal role in mediating these

processes [10]. TNF-α and IL-6 stimulate the expression of tissue factor (TF) on endothelial cells, monocytes, and platelets, which triggers the extrinsic coagulation pathway, leading to the rapid generation of thrombin. While thrombin formation is physiologically regulated by antithrombin, the overwhelming activation of coagulation in severe COVID-19 can exhaust inhibitory mechanisms, resulting in uncontrolled thrombinemia. Concurrently, fibrinogen polymerization into fibrin and its subsequent deposition in the microcirculation contribute to organ dysfunction and failure [10]. Additionally, the depletion of natural anticoagulants, such as antithrombin and protein C, exacerbates coagulopathy in COVID-19 patients. This is further complicated by reduced tissue factor pathway inhibitor (TFPI) levels, vascular leakage, and hepatic dysfunction, all of which are frequently observed in critically ill patients [10].

The clinical significance of D-dimer elevation extends beyond its role as a diagnostic marker; it has profound implications for predicting disease progression and patient outcomes. Several studies have highlighted the prognostic utility of D-dimer levels in stratifying COVID-19 patients based on their risk of adverse outcomes. For example, elevated D-dimer levels have been associated with increased risks of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, both of which are prevalent complications in hospitalized COVID-19 patients [6], [7], [9]. Moreover, a meta-analysis demonstrated that patients with significantly elevated D-dimer levels were more likely to experience severe disease progression and higher mortality rates [11]. These findings underscore the importance of incorporating D-dimer measurement into routine clinical assessments of COVID-19 patients, particularly those presenting with moderate to severe symptoms.At H. Adam Malik General Hospital in Medan, the evaluation of D-dimer levels in COVID-19 patients has provided valuable insights into the clinical management of the disease. The present study aimed to assess differences in D-dimer levels between patients with moderate and severe COVID-19 and to explore the relationship between these levels and various clinical parameters, including age, gender, comorbidities, ventilator use, severity of illness, and mortality rates. The findings of this study revealed that patients with severe COVID-19 exhibited significantly higher D-dimer levels compared to their moderate counterparts, consistent with previous research. Elevated D-dimer levels in severe cases reflect the heightened activation of coagulation and fibrinolysis, which are hallmarks of the hypercoagulable state induced by SARS-CoV-2 infection [5], [6] The prognostic value of D-dimer is particularly relevant in resource-limited settings, where early identification of high-risk patients is critical for optimizing resource allocation and improving patient outcomes.

In such contexts, the ability to predict disease severity and the need for intensive care based on D-dimer levels can facilitate timely interventions, such as anticoagulation therapy and close monitoring. Evidence suggests that anticoagulant prophylaxis may reduce the incidence of thromboembolic events and improve survival in COVID-19 patients with coagulopathy [6], [7]. This highlights the need for standardized protocols for D-dimer measurement and the establishment of consensus cutoff values to guide clinical decision-making in the management of COVID-19.In conclusion, the assessment of D-dimer levels provides a crucial window into the pathophysiological processes underlying COVID-19 and serves as a valuable tool for predicting disease severity and outcomes. As demonstrated in this study, significant differences in D-dimer levels between moderate and severe COVID-19 patients underscore the biomarker's role in identifying high-risk individuals and tailoring treatment strategies. Future research should focus on further elucidating the mechanisms driving D-dimer elevation in COVID-19 and exploring its potential as a therapeutic target. Additionally, studies investigating the interplay between D-dimer levels and other clinical and laboratory parameters could enhance our understanding of the disease and inform the development of comprehensive risk assessment models. As the pandemic continues to pose unprecedented challenges to global health, the integration of D-dimer assessment into routine clinical practice represents a critical step toward improving the care and outcomes of COVID-19 patients.

II. METHODS

This observational study employs a cross-sectional design [12], [13] to assess differences in D-dimer levels among moderate and severe COVID-19 patients treated at H. Adam Malik General Hospital, Medan. Conducted from August to October 2021, the study involved collaboration between the Departments of

Clinical Pathology and Pulmonology at FK USU/RSUP H. Adam Malik. The accessible population included hospitalized COVID-19 patients who met inclusion criteria, such as willingness to participate, while excluding individuals with malignancy, trauma, severe infections like sepsis, or conditions such as disseminated intravascular coagulation (DIC) and deep vein thrombosis (DVT). Consecutive sampling was applied, targeting a calculated sample size of 36 subjects based on hypothesis testing for proportional differences. The primary variable, D-dimer, was measured quantitatively using an immuno-turbidimetric assay, with pre-analytical, analytical, and post-analytical phases standardized to ensure accuracy [14], [15]. D-dimer values were reported in ng/mL with a cutoff of <500 ng/mL, while samples exceeding 5000 ng/mL were diluted as needed. Ethical clearance was obtained from the Faculty of Medicine, USU, and written informed consent was collected from participants or their families.

Data analysis utilized SPSS software, employing ANOVA or Kruskal-Wallis tests based on data distribution, with p-values <0.05 considered significant [16], [17]. This study's operational definitions encompassed D-dimer as a fibrin degradation product, measured using a calibrated turbidimetric system, and COVID-19 severity categorized by clinical and laboratory findings. Quality control involved routine calibration and daily validation with TE Control reagents. Budget allocation included D-dimer testing (6,000,000 IDR), statistical analysis (500,000 IDR), stationery (500,000 IDR), and miscellaneous expenses (1,000,000 IDR), totaling 8,000,000 IDR. Data collection and analysis were conducted according to a predefined timeline, spanning proposal preparation, data collection, and analysis phases. The study flowchart illustrates the stepwise methodology, ensuring rigorous adherence to ethical and procedural standards to yield reliable insights into the relationship between D-dimer levels and COVID-19 severity. This comprehensive approach aims to inform clinical management and improve outcomes for hospitalized COVID-19 patients.

III. RESULT AND DISCUSSION

Result

Demographic Characteristics of Research Subjects

Table 1. Demographic Characteristics of Subjects

Demographic Characteristics	n = 36
Gender, n (%)	
Male	18 (50)
Female	18 (50)
Age, years	
Mean (SD)	50,92 (13,81)
Median (Min - Mak)	53 (20 – 79)
Comorbidities, n (%)	
Existing	25 (69,4)
None	11 (30,6)
Type of comorbidities, n (%)	
Asthma, DM, and Hypertension	1 (2,8)
CHF and Hypertension	1 (2,8)
DM	9 (25)
DM and Hypertension	2 (5,6)
TB	1 (2,8)
Hypertension	6 (16,7)
Hypotension	1 (2,8)
Ischemic Stroke	1 (2,8)
UAP	1 (2,8)
CHF	1 (2,8)
HHD	1 (2,8)
None	11 (30,6)
Breathing Apparatus, n (%)	
Ventilator	14 (38,9)
Non-Rebreather Mask	20 (55,6)
Non-Ventilator	2 (5,6)
Covid-19 Severity Level	

Severe	16 (44,4)
Moderate	20 (55,6)
Mortality, n (%)	
Yes	12 (33,3)
No	24 (66,7)

Source: Primary Data Processed, 2024

From Table 1. This study involved 36 hospitalized COVID-19 patients at RSUP Haji Adam Malik Medan who met the inclusion criteria. The characteristics of the study subjects are summarized as follows: the gender distribution was balanced, with 18 male participants (50%). The mean age was 50.92 years, with the youngest patient aged 20 years and the oldest aged 79 years. Among the subjects, 25 individuals (69.4%) had comorbidities, with diabetes mellitus (DM) being the most prevalent comorbidity, affecting 9 patients (25%), followed by hypertension in 6 patients (16.7%). Additionally, 14 patients (38.9%) required ventilator support during their treatment. Regarding the severity of COVID-19, 16 patients (44.4%) were classified as having a severe degree of illness, while 20 patients (55.6%) were classified as moderate. The study also reported that 12 patients (33.3%) succumbed to the disease. These findings highlight the significant burden of comorbidities such as DM and hypertension among hospitalized COVID-19 patients, which may contribute to disease progression and poor outcomes. The high percentage of patients requiring ventilator support further underscores the severity of respiratory complications in this population. The mortality rate of 33.3% reflects the serious impact of COVID-19 on hospitalized patients, particularly those with severe disease. This demographic and clinical profile provides crucial insights into the characteristics and outcomes of COVID-19 patients treated in a tertiary care hospital setting, emphasizing the need for effective management strategies tailored to high-risk populations.

Difference and mean of D Dimer Value Based on Covid-19 Severity Degree

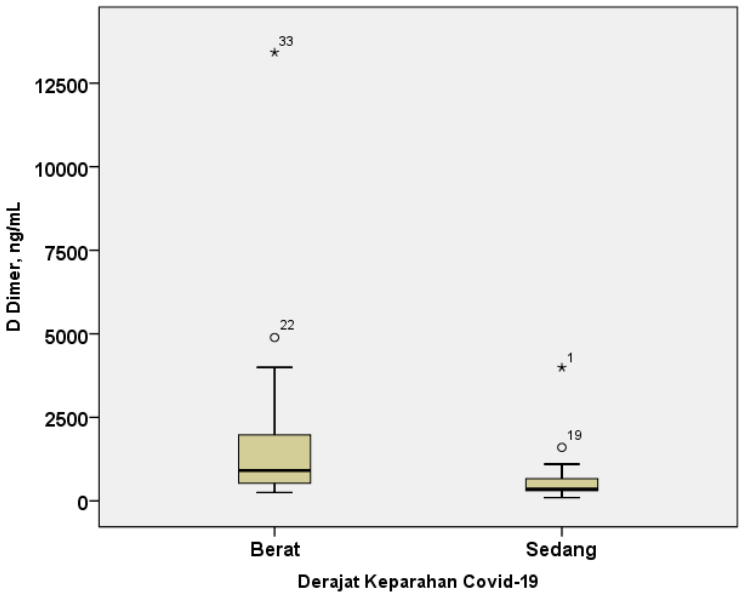
Table 2. Differences in D Dimer Levels Based on the Degree of Covid-19 Severity

	Derajat Berat (n = 16)	**Derajat Sedang (n = 20)**	**p**
D Dimer, ng/mL			
Rerata (SD)	2145,81 (32,81,66)	667,05 (859,43)	0,008[a]
Median (Min – Mak)	909 (250-13420)	352,5 (100 – 3990)	

**Mann Whitney Test*

Source: Primary Data Processed, 2024

Fig 1. Boxplot Graph of D Dimer Value Based on The Severity of Covid-19 Infection



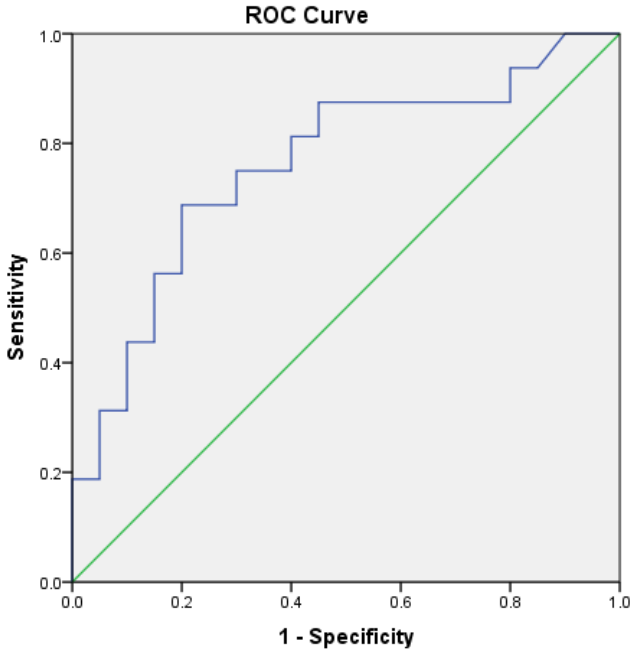
From Table 2. presents fibrinogen and D-dimer values in COVID-19 patients with severe and moderate disease severity. In patients with severe COVID-19, the average D-dimer level was significantly elevated, reaching 2145.81 ng/mL, with a range from 250 ng/mL to a maximum of 13,420 ng/mL. This

contrasts sharply with the moderate severity group, where the mean D-dimer level was markedly lower at 667.05 ng/mL (SD = 859.43 ng/mL), with values ranging from a minimum of 100 ng/mL to a maximum of 3990 ng/mL. Statistical analysis using the Mann-Whitney test confirmed a significant difference in D-dimer levels between the two groups (p = 0.008). These findings highlight the correlation between the severity of COVID-19 and elevated D-dimer levels, which serve as a biomarker for hypercoagulability and inflammation. Higher D-dimer levels in severe cases indicate a greater degree of thrombin generation and fibrinolytic activity, reflecting the systemic procoagulant state associated with severe COVID-19. This elevation is consistent with the increased risk of complications such as venous thromboembolism, disseminated intravascular coagulation, and poor clinical outcomes in patients with severe disease. The significant disparity in D-dimer levels underscores its potential role as a prognostic marker for disease severity and a guide for tailored therapeutic interventions. These results emphasize the importance of routine D-dimer monitoring in COVID-19 patients to predict disease progression and inform management strategies effectively.

Ability of D Dimer as a Predictor of Covid-19 Disease Severity

The analysis using the ROC curve (Figure 2) revealed that the area under the curve (AUC) for D-dimer levels in predicting the severity of COVID-19 was 76.1%, with a p-value of 0.008 and a 95% confidence interval (CI) ranging from 59.8% to 92.4%. These results indicate that D-dimer levels can be utilized as a moderate predictor of COVID-19 disease severity (AUC >70% - 80%). Based on the line graph in Figure 4.2, a cut-off value of 2510 ng/mL was established for D-dimer levels to predict the severity of COVID-19. This cut-off value highlights the clinical utility of D-dimer as a biomarker for identifying patients at risk of severe disease progression. Elevated D-dimer levels above this threshold may signal a hypercoagulable state and increased thrombotic complications, often observed in severe COVID-19 cases. This finding supports the integration of D-dimer level assessment into routine clinical practice to enhance early risk stratification and guide therapeutic decision-making for COVID-19 patients.

Fig 2. ROC Curve of D Dimer Value as a predictor of Covid-19 disease severity



Discussion

This study utilized a cross-sectional design to evaluate differences in D-dimer levels among patients with mild, moderate, and severe degrees of COVID-19 treated at the Department of Clinical Pathology and Pulmonology at FK USU/RSUP H. Adam Malik Medan. Patient sampling was conducted consecutively between August and October 202 of the 36 patients included, the average age of participants was relatively high, consistent with Crimmins' research, which highlighted a correlation between age and increased

susceptibility to COVID-19. Older individuals are more vulnerable to the disease due to immunosenescence, marked by reduced availability of naive T cells and altered CD4/CD8 T cell ratios, diminishing the body's ability to combat novel pathogens like SARS-CoV-2. In Crimmins' multicenter study, mortality rates increased sharply after the age of 50, with the highest rates observed among the elderly population [1]. Most patients in this study presented with comorbidities, predominantly diabetes mellitus (DM) and hypertension (HT), which align with findings revealed that HT and DM heightened the risk of severe COVID-19 by 2.54 and 1.70 times [18]. The underlying mechanisms remain unclear but are hypothesized to involve variations in innate immunity and treatment history [2]. Laboratory analyses showed that elevated D-dimer levels were consistently observed across respondents, suggesting hyperinflammatory and procoagulant states associated with severe COVID-19. Elevated D-dimer levels (>1.0 µg/mL) have been established as significant indicators of mortality, while levels exceeding 1.5 µg/mL are predictive of venous thromboembolism (VTE) with 85% sensitivity and 88.5% specificity [3], [4], [19].

The pathophysiological elevation of D-dimer in COVID-19 patients is triggered by tissue factor (TF)-mediated thrombin generation. TF is expressed on endothelial cells, monocytes, and platelets in response to toxins and cytokines like tumor necrosis factor (TNF)-α and interleukin (IL)-6, the latter being closely associated with severe COVID-19 complications. While antithrombin typically inhibits thrombin formation, rapid thrombin generation may overwhelm this regulatory pathway, leading to thrombinemia. Thrombin converts fibrinogen into fibrin clots that accumulate in the microcirculation, potentially causing organ dysfunction [20]. Concurrently, the fibrinolytic system becomes activated to limit clot formation, enzymatically degrading fibrin into D-dimer, a specific marker of fibrinolysis used to diagnose conditions like pulmonary embolism, disseminated intravascular coagulation (DIC), or deep vein thrombosis (DVT) [21]. This study demonstrated significant differences in D-dimer levels between moderate and severe COVID-19 patients. Patients with severe disease exhibited substantially higher mean D-dimer levels, corroborating findings by Düz et al., whose meta-analysis of 12 studies consistently reported elevated D-dimer levels in severe cases. Researchers have observed widespread thromboembolic events in autopsy reports, histopathological series, and clinical cases, supporting the notion that COVID-19 is a prothrombotic disease. Virchow's triad, encompassing vascular endothelium abnormalities, altered blood flow, and platelet dysfunction, explains the thrombotic phenomena observed in COVID-19. Activation of the renin-angiotensin-aldosterone system (RAAS), increased plasminogen activator inhibitor-1 (PAI-1), and systemic immune responses from activated platelets contribute to thrombogenesis [22].

D-dimer levels serve as a critical marker for hypercoagulability, with higher levels indicating greater susceptibility to thrombosis. Approximately 43.5% of COVID-19 patients exhibit elevated D-dimer levels during the early stages of infection, and 64.3% show increased fibrinogen levels [23]. Elevated D-dimer levels (three to four times above baseline) warrant hospitalization, even in asymptomatic cases, due to the heightened risk of thrombosis [24]. This hypercoagulable state underscores the need for vigilance in managing COVID-19 patients with elevated D-dimer levels to mitigate complications [3]. The discrimination performance of D-dimer levels in predicting COVID-19 severity was moderate in this study, with an area under the curve (AUC) value of 76.1% (95% CI: 59.8%-92.4%). The study established a D-dimer cutoff of 2510 ng/mL to predict severe disease. This value differs from previous studies, a cutoff of 0.8 µg/mL, and Suastika et al., who found a cutoff of 1500 mg/mL. These variations may arise from differences in study objectives, sample selection, methodologies, and measurement units [25]. Additionally, research indicates that elevated D-dimer levels are strongly associated with adverse clinical outcomes, including acute respiratory distress syndrome (ARDS), the need for intensive care, and mortality. Studies highlight that elevated D-dimer levels should prompt early therapeutic interventions, such as anticoagulation, to prevent complications like VTE and improve survival rates. In a meta-analysis, D-dimer levels were identified as a reliable prognostic marker for stratifying COVID-19 patients by risk, guiding resource allocation and clinical decision-making [21]–[23].

Understanding the mechanisms underlying D-dimer elevation in COVID-19 patients is essential for effective clinical management. TF-mediated thrombin generation, fibrin deposition in microcirculation, and dysregulated fibrinolysis are pivotal processes in the pathogenesis of COVID-19-associated coagulopathy.

These mechanisms highlight the importance of incorporating D-dimer monitoring into routine clinical assessments, particularly for moderate-to-severe cases. The study findings reinforce the role of D-dimer as a biomarker for hypercoagulability, aiding in early identification of high-risk patients and informing treatment strategies. Monitoring and managing D-dimer levels can significantly enhance patient outcomes and reduce mortality in severe COVID-19 cases. In conclusion, this study underscores the critical role of D-dimer as both a diagnostic and prognostic marker in COVID-19. Elevated D-dimer levels reflect a hypercoagulable state that is associated with disease severity and adverse clinical outcomes. Further research is needed to standardize D-dimer cutoff values and explore the underlying mechanisms to optimize therapeutic approaches and improve survival rates in COVID-19 patients.

IV. CONCLUSION

Based on the results of data analysis obtained, this study concludes that age above 50 years dominates as a characteristic of COVID-19 patients treated at H. Adam Malik Hospital Medan, with an almost equal proportion of male and female gender. The most common comorbidities found were diabetes mellitus (DM) and hypertension (HT). The mean D-dimer level in treated COVID-19 patients was 1324.28 ng/mL, showing a significant increase. In addition, there was a significant difference between the D-dimer levels of COVID-19 patients with moderate and severe degrees treated at H. Adam Malik Hospital Medan. Based on these findings, it is recommended to conduct further research by taking into account other variables that may play a role in the thrombosis process, such as systemic inflammation, coagulation disorders, or the influence of therapy received by patients, so that the resulting analysis is more accurate and comprehensive. In addition, it is important to standardize laboratory examination methods to determine the specific D-dimer consensus value in COVID-19 cases, so that it can be used as a more reliable diagnostic and prognostic parameter. This study is expected to be the basis for developing clinical strategies in managing COVID-19 patients, especially in diagnosing and monitoring thrombosis complications that often occur in patients with severe conditions.

V. ACKNOLEDGMENTS

We would like to express our deepest gratitude to the Department of Clinical Pathology and the Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of North Sumatera, and H. Adam Malik General Hospital, Medan, for their invaluable support and collaboration throughout the course of this research. Special thanks are extended to all the medical staff and healthcare workers who facilitated data collection and patient care during this study. Their dedication and commitment, particularly during the challenges posed by the COVID-19 pandemic, have been truly inspiring. We also acknowledge the contribution of the patients and their families, whose participation made this study possible. Your cooperation and willingness to contribute to the advancement of medical knowledge are deeply appreciated. Finally, we are grateful to our mentors and colleagues, especially Dr. Jelita Siregar and Prof. Noni Novisari Soeroso, for their guidance, expertise, and constructive feedback that greatly enriched this study. This work would not have been possible without the combined efforts and encouragement from all involved. Thank you for your continued support and contributions.

REFERENCES

[1] Y.-R. Guo *et al.*, “The Origin, Transmission and Clinical Therapies On Coronavirus Disease 2019 (COVID-19) Outbreak – An Update On The Status,” *Mil. Med. Res.*, vol. 7, no. 1, p. 11, Dec. 2020, doi: 10.1186/s40779-020-00240-0.

[2] World Health Organization, “WHO Director-General’s Opening Remarks at The Media Briefing on COVID-19 - 11 March 2020,” *WHO*, 2020. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (accessed Jan. 06, 2025).

[3] W. Cao and T. Li, “COVID-19: Towards Understanding of Pathogenesis,” *Cell Res.*, vol. 30, no. 5, pp. 367–369, May 2020, doi: 10.1038/s41422-020-0327-4.

[4] F. Di Gennaro *et al.*, “Coronavirus Diseases (COVID-19) Current Status and Future Perspectives: A Narrative Review,” ***Int. J. Environ. Res. Public Health*****,** vol. 17, no. 8, p. 2690, Apr. 2020, doi: 10.3390/ijerph17082690.

[5] S. Zaim, J. H. Chong, V. Sankaranarayanan, and A. Harky, "COVID-19 and Multiorgan Response," *Curr. Probl. Cardiol.*, vol. 45, no. 8, p. 100618, Aug. 2020, doi: 10.1016/j.cpcardiol.2020.100618.

[6] S. H. Nile, A. Nile, J. Qiu, L. Li, X. Jia, and G. Kai, "COVID-19: Pathogenesis, Cytokine Storm and Therapeutic Potential of Interferons," *Cytokine Growth Factor Rev.*, vol. 53, pp. 66–70, Jun. 2020, doi: 10.1016/j.cytogfr.2020.05.002.

[7] Y. Yao *et al.*, "D-Dimer as A Biomarker For Disease Severity and Mortality In COVID-19 Patients: A Case Control Study**," *J. Intensive Care***,** vol. 8, no. 1, p. 49, Dec. 2020, doi: 10.1186/s40560-020-00466-z.

[8] T. Zhang, Q. Wu, and Z. Zhang, "Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak," *Curr. Biol.*, vol. 30, no. 7, pp. 1346-1351.e2, Apr. 2020, doi: 10.1016/j.cub.2020.03.022.

[9] M. Marietta *et al.*, "COVID-19 and Haemostasis: A Position Paper From Italian Society On Thrombosis and Haemostasis (SISET)," *Blood Transfus.*, vol. 18, no. 3, pp. 167–169, May 2020, doi: 10.2450/2020.0083-20.

[10] M. Panigada *et al.*, "Hypercoagulability of COVID-19 Patients in Intensive Care Unit: A Report of Thromboelastography Findings and Other Parameters of Hemostasis," ***J. Thromb. Haemost.***, vol. 18, no. 7, pp. 1738–1742, Jul. 2020, doi: 10.1111/jth.14850.

[11] Y. Ryadi, S. S. Rahardjo, and B. Ichsan, "Meta-Analysis: The Effect of D-Dimer on Mortality in Patients with COVID-19," ***J. Epidemiol. Public Heal.***, vol. 7, no. 4, pp. 552–561, Oct. 2022, doi: 10.26911/jepublichealth.2022.07.04.11.

[12] Notoatmodjo, *Metode Penelitian Kesehatan*. Jakarta: Rineka Cipta, 2012.

[13] I. K. Swarjana, *Metode Penelitian Kesehatan*. Surabaya: Andi Offset, 2016.

[14] Y. Agnesia, S. W. Sari, H. Nu'man, D. W. Ramadhani, and Nopianto, *Buku Ajar Metode Penelitian Kesehatan*. Pekalongan: Penerbit NEM, 2023.

[15] I. A. Liberty, *Metode Penelitian Kesehatan*. Pekalongan: Penerbit NEM, 2024.

[16] V. W. Sujarweni, *SPSS untuk Penelitian*. Yogyakarta: Pustaka Baru Press, 2015.

[17] P. ldy Rochmat, *Analisis Statistik Ekonomi dan Bisnis dengan SPSS*. Yogyakarta: Fadilatama, 2016.

[18] D. Tascioglu, K. Yalta, and E. Yetkin, "Hypertension and Diabetes Mellitus in Patients with COVID 19: A Viewpoint on Mortality," *Cardiovasc. Endocrinol. Metab.*, vol. 9, no. 3, pp. 108–109, Jun. 2020, doi: 10.1097/XCE.0000000000000213.

[19] Z. Zheng *et al.*, "Risk Factors of Critical & Mortal COVID-19 Cases: A Systematic Literature Review and Meta-Analysis,**" *J. Infect.***,** vol. 81, no. 2, pp. 16–25, Aug. 2020, doi: 10.1016/j.jinf.2020.04.021.

[20] W. Guan *et al.*, "Comorbidity and its Impact on 1590 Patients with COVID-19 in China: A Nationwide Analysis," ***Eur. Respir. J.***, vol. 55, no. 5, p. 2000547, May 2020, doi: 10.1183/13993003.00547-2020.

[21] M. Levi, J. Thachil, T. Iba, and J. H. Levy, "Coagulation Abnormalities and Thrombosis in Patients with COVID-19," *Lancet Haematol.*, vol. 7, no. 6, pp. e438–e440, Jun. 2020, doi: 10.1016/S2352-3026(20)30145-9.

[22] B. M. Henry, J. Vikse, S. Benoit, E. J. Favaloro, and G. Lippi, "Hyperinflammation and Derangement of Renin-Angiotensin-Aldosterone System in COVID-19: A Novel Hypothesis For Clinically Suspected Hypercoagulopathy and Microvascular Immunothrombosis," *Clin. Chim. Acta*, vol. 507, pp. 167–173, Aug. 2020, doi: 10.1016/j.cca.2020.04.027.

[23] Y. Oussou, Z. Nadhil, and M. Cherti, "Acute Stroke in Young Patient: Also Think About Coronavirus ! (About a Case and a Review of the Literature)," ***Int. J. Adv. Res.***, vol. 9, no. 01, pp. 110–115, 2021, doi: 10.21474/ijar01/12282.

[24] D. Wichmann *et al.*, "Autopsy Findings and Venous Thromboembolism in Patients With COVID-19," *Ann. Intern. Med.*, vol. 173, no. 4, pp. 268–277, Aug. 2020, doi: 10.7326/M20-2003.

[25] A. Kollias, K. G. Kyriakoulis, E. Dimakakos, G. Poulakou, G. S. Stergiou, and K. Syrigos, "Thromboembolic Risk and Anticoagulant Therapy in COVID-19 Patients: Emerging Evidence and Call For Action,**" *Br. J. Haematol.***,** vol. 189, no. 5, pp. 846–847, Jun. 2020, doi: 10.1111/bjh.16727.