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ASSOCIATION BETWEEN ADMISSION D-DIMER LEVELS AND MORTALITY IN COVID-19

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ABSTRACT

Background: It is possible that specific laboratory test results could indicate the likelihood of death from COVID-19. **Objective:** The main goal of this research was to figure out if measuring D-dimer levels could help forecast the likelihood of death for individuals suffering from COVID-19. **Methods:** A backward-looking study of a group of people based on observations, encompassing 317 individuals, was conducted utilizing existing data extracted from the health documents of COVID-19 inpatients. The concentration of D-dimer was acquired via patient's blood test results upon initial admittance to the medical facility. Following this, patients were divided into two categories: those who lived (comprising 252 individuals) and those who did not (consisting of 66 individuals), according to the end result. Proportions and central values were assessed employing Kolmogorov-Smirnov. Logistic regression was applied to ascertain if there exists a noteworthy disparity in D-dimer concentrations among different mortality statuses. **Results:** The cohort that did not survive showed a notably elevated presence of D-dimer (Odds Ratio 6.480 ;$p<0.001$). **Conclusion:** The starting assessment of D-dimer levels might be useful in spotting individuals who face increased vulnerability and help guide choices concerning critical care management.

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INTRODUCTION

The ailment recognized as Coronavirus Disease 2019 (COVID-19) signifies a communicable illness stemming from the virus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Given its nature as a systemic illness, COVID-19 showcases a wide array of clinical manifestations, spanning from symptoms that are only slight and resolve on their own to complications that pose a serious threat to life and carry an increased possibility of fatality.[1]

D-dimer arises from the disintegration of stabilized fibrin networks, a process initiated by plasmin's action in dissolving fibrin to eliminate blood-clotting agents.[2,3] D-dimer is very important in communicating the beginning of the blood clotting process and the later breaking down of fibrin.[2] Typically, D-dimer concentrations in serum are minimal, but heightened levels indicate the presence of thrombosis. Augmented thrombus development takes place within the bloodstreams of individuals afflicted with COVID-19, resulting in substantial thrombosis that precipitates widespread clotting within blood vessels, subsequently culminating in multi-organ dysfunction syndrome (MODS). Assessing D-dimer quantities proves valuable in pinpointing coagulation irregularities, enabling the prompt delivery of therapeutic interventions to diminish mortality risks.[4]

Following the height of the pandemic, both the frequency of SARS CoV-2 infections and the number of deaths linked to it have decreased.

The emergence of various Omicron subvariants, including BA.1, BA.2, BA.4/BA.5, XBB, BQ.1, EG.5, and JN.1, demonstrates their increased transmissibility, improved capacity to evade immune responses, and varying degrees of impact on individuals. Despite Omicron generally causing less

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severe illness than Delta, its rapid dissemination has placed significant strain on healthcare facilities and available resources.[5] This study aims to analyze the potential of D-dimer levels to predict the clinical outcome of COVID-19 patients, which are categorized based on clinical outcomes: survival or non- survival.[6] stud

METHODS

Research design and participants

This research employed a cross-sectional approach, carried out by reviewing past data collected from June to August 2021 at Wates Regional General Hospital, which is designated as a COVID-19 treatment center in Kulon Progo Regency. The entire group for this study consisted of every patient positively diagnosed with COVID-19 using real-time reverse transcription polymerase chain reaction (RT-PCR) testing and were admitted to the hospital during the defined period. The sampling process involved using a comprehensive method, incorporating all patients who met the requirements for inclusion and did not meet any conditions for exclusion.

To be considered for the study, participants had to be individuals over 18 years old who had a confirmed COVID-19 infection through RT-PCR testing. Additionally, they needed to possess comprehensive medical records, specifically including D-dimer measurements taken upon their arrival at the hospital, and they had to have been admitted to the hospital within the designated timeframe of the research. Conversely, individuals with a prior history of heart conditions, cerebrovascular events, thyroid disorders, blood-related illnesses such as immune thrombocytopenic purpura, aplastic anemia, or leukemia, liver problems, kidney problems, type 2 diabetes, high blood pressure, dengue hemorrhagic fever, any kind of cancer, recent surgical procedures or injuries, having undergone spleen removal, pregnancy, or those who had received a platelet transfusion less than a day before admission, were not eligible for participation.

Procedures

Subsequent to securing approval from the Research Ethics Committee of Wates General Hospital, designated under the reference number KEPK/035/RS/XII/2024, as well as the Faculty of Medicine at Ahmad Dahlan University, we obtained access to the healthcare records of patients who were hospitalized at Wates General Hospital as a result of contracting COVID-19. Information obtained from patient charts included personal details such as age and sex, along with results from lab tests. The lab results showed the amount of D-dimer present in each patient's blood sample. The concentrations of D-dimer were determined by employing the Ichroma™ II analyzer, utilizing a method of fluorescence immunoassay (with a normal range below 500 ng/mL).

The normal ranges corresponded to those utilized within the hospital's own testing facility. The biomedical test took place during the initial phase when patients were admitted and received care within the hospital.

Data analysis

The Kolmogorov-Smirnov test was utilized to determine if the gathered information adhered to a typical distribution. The Pearson correlation test was conducted to ascertain the correlation of D-dimer measurements inside datasets that presented a typical distribution arrangement.

The whole of the analyses were carried out making use of IBM SPSS for Windows, release 26.0 (IBM Corp., Armonk, NY, U. S. A.) by means of a level of significance of $\alpha = 0.05$ and also a confidence interval of 95%.

RESULTS AND DISCUSSION

This investigation involved 317 individuals diagnosed with COVID-19, encompassing 252 who recovered and 66 who did not survive. The attributes of the participants are detailed in Table 1. A majority of the participants were women (52.4%), with an average age of 53.74 years. Elevated D-dimer levels were observed in the majority of participants (63.5%).

Table 1. Demographic characteristics of the subjects

Variable	f (%)	Mean (SD)
Gender		
Male	151 (47,6%)	
Female	166 (52.4%)	
Age (year)		53.74(16.11)
D-dimer level (ng/mL)		
Normal	78 (24.6%)	
Increased	239 (75.4%)	

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COVID-19 affects men and women at similar rates, yet men face a higher risk of death from the disease. This observation has sparked speculation about whether female sex hormones provide some protection from severe health outcomes. Sex hormone receptors are found extensively throughout the body, appearing in nearly all tissues and organs, and they perform roles beyond reproduction. When experiencing acute SARS-CoV-2 infection, males and females display many notable differences in clinical symptoms and immune responses; females showed reduced inflammation severity, higher counts of lymphocyte cells, and more rapid immune reactions.[7]

Multiple investigations have yielded differing results. The study by Alsan et al., which included 5,198 participants, revealed that men experienced COVID-19 at a rate four times greater than women.[8] Pijls et al. came to a comparable judgement after examining 229 research involving more than 10 million individuals, revealing that males had a higher chance of contracting COVID-19 than females, with a relative risk (RR) of 1.14 (95% CI 1.07-1.21).[9] This increased vulnerability to infection in males could be explained by greater ACE2 receptor expression in organs such as the lungs and heart. Conversely, estrogen lowers ACE2 levels in females, who also benefit from possessing two X chromosomes containing essential immunological genes such as TLR-7, TLR-8, and CD-40L, which enables a quicker immune response.[10]

Table 2. D-dimer level in COVID-19 patients

Variable	Mean (SD)
D-dimer level (ng/mL)	2303.64 (3093.81)

In this investigation, the mean D-dimer measurements reached 2303. 64 ng/mL, accompanied by a standard deviation of 3093. 81 ng/mL, displaying a spectrum from a lowest point of 105 ng/mL to a highest point going beyond 10000 ng/mL. As indicated in Table 2, the mean D-dimer concentration in this study goes beyond the typical threshold of below 500 ng/mL and goes beyond the investigation carried out by Nugraha et al., which revealed that individuals impacted by COVID-19 exhibited moderately increased D-dimer concentrations, with an average standing at 1,180.51 ng/mL and a distribution spanning 198 to 4,037 ng/mL.[11]

Al Mutair and colleagues found that in individuals infected with COVID-19, D-dimer levels increased, and this increase was more significant in patients experiencing moderate symptoms compared to those with milder symptoms (570 mg/L compared to 690 mg/L).[11] Elevated levels of D-dimer were found to be associated with the emergence of coagulopathy, which is related to the basic ways COVID-19 affects the body.[11] The rise in D-dimer initiates thrombotic problems due to the overactivation of the processes involved in coagulation. The extensive inflammatory response triggered by a viral infection has the ability to bring.[13]

Table 3. Comparison of D-dimer levels based on Clinical Outcomes of Subjects

Variable	Group	Median (IQR)	Mean Rank	p-value
D-dimer (ng/mL)	Survive	734 (83-9867)	144.77	<0.001
	Death	1278 (133-9548)	213.13	

According to the Mann-Whitney U test analysis findings shown in table 3, a noteworthy disparity existed in D-dimer amounts between the patient groups who lived and those who did not. For the group that lived, the D-dimer level's median (IQR) was 734 (83-9867) pg/mL, but for the group that did not, it was 1278 (133-9548) pg/mL. The mean rank amount for the group that lived was 144.77, whereas it was 213.13 for the deadth group, with a p value of less than 0.001. According to these results, D-dimer amounts were noticeably greater in individuals who passed away than in those who lived. These data imply that higher D-dimer amounts may worsen the patient's health and raise the possibility of deatThe outcomes derived from the investigation in this work are consistent with the research performed by Gungor and colleagues, who established that increased D-dimer amounts, assessed at the point of hospital admission, demonstrate a clear link with the severity of lung swelling due to COVID-19 and could potentially anticipate mortality percentages among patients who are hospitalized for care. Across thirty-nine investigations, data on D-dimer quantities were presented for 5750 patients experiencing non-severe conditions and 2063 patients with severe conditions,

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while sixteen investigations delivered data on D-dimer quantities for 2783 patients who recovered and 697 patients who did not survive. A substantial increase in D-dimer amounts was seen among patients presenting with severe clinical conditions (WMD: 0.45 mg/L, 95% CI: 0.34–0.56; $p < 0.0001$). D-dimer amounts were considerably elevated in patients who did not survive when contrasted with those who did (WMD: 5.32 mg/L, 95% CI: 3.90–6.73; $p < 0.0001$). D-dimer amounts that surpassed the highest standard threshold (ULN) correlated with a heightened probability of severe illness (RR: 1.58, 95% CI: 1.25–2.00; $p < 0.0001$) and death (RR: 1.82, 95% CI: 1.40–2.37; $p < 0.0001$).[14]

Based upon this information, the existing study by Lee (2025) posits that when individuals are hospitalized with COVID-19, it can lead to elevated D-dimer levels; moreover, these levels might help assess the likelihood of death and the emergence of venous thromboembolism. The most effective threshold for peak D-dimer in forecasting mortality stood at 2004, which resulted in a sensitivity of 71.0% and a specificity of 77.9%.[15]

Table 4. Result of Binary Logistic Regression Analysis.

Variabel	OR	95% C.I. for Exp (B)		sig
		Lower	Upper	
D-dimer	6.480	2.275	18.460	<0.001

Based on the binary logistic regression analysis results presented in table 4, the D-dimer levels demonstrated a noteworthy statistical correlation to the observed clinical results, reflected by an odds ratio (OR) of 6.480 (95% CI: 2.275-18.460; $p = <0.001$). This suggests that individuals exhibiting elevated D-dimer levels face a risk that is 6.48 times higher for experiencing specific clinical results when contrasted with individuals who have lower D-dimer levels.

The findings imply that individuals with Covid 19 who require hospitalization exhibit higher concentrations of D-dimer, and these concentrations can be used as an indicator to forecast mortality. Valerio et al.'s research publication scrutinized the peak D-dimer measurements throughout each patient's hospital stay, revealing that elevated D-dimer concentrations were identified among individuals who did not survive when contrasted against those who did, similar to our study.[16]

Yao et al.'s case-control research indicated that a D-dimer concentration surpassing 2140 ng/mL could forecast mortality during a hospital stay, exhibiting a sensitivity rate of 88.2% alongside a specificity rate of 71.3%.[17] Zhang along with his team conducted a separate investigation that yielded analogous findings; they concluded that a D-dimer concentration of 2000 ng/mL served as the optimal cutoff point for forecasting mortality during a hospital stay, exhibiting a sensitivity of 92.3% and a specificity of 83.3%.[18] Soni accompanied by a team of scientists noted that D-dimer readings demonstrated the greatest C-index among the coagulation parameters analyzed, implying their potential to anticipate mortality in Covid 19 patients throughout their hospitalization.[19] As stated by Li and co-workers, elevated D-dimer levels were identified as an independent predictor of death resulting from Covid 19.

When individuals initially show signs of a Covid-19 infection, it's quite rare to observe irregularities in their prothrombin time, partial thromboplastin time, or the number of platelets. Increased amounts of D-dimer and fibrinogen, pointing towards widespread clotting within blood vessels, could show up roughly one to two weeks after symptoms first arise, or otherwise, four to ten days after a patient is admitted to a healthcare facility. The existence of higher than normal D-dimer quantities is linked to the forming of issues with blood coagulation as part of how COVID-19 impacts the body.

This blood clotting dysfunction leads to higher D-dimer concentrations as a consequence of amplified thrombin creation and fibrin breakdown. The rise in D-dimer can also be attributed to lung damage caused directly by COVID-19, serving as an additional contributing factor. When the lungs are acutely injured, fibrin accumulates within the air sacs, prompting the cells lining these sacs to generate urokinase, which reduces fibrin buildup by transforming plasminogen into plasmin and consequently dissolving fibrin clots. The extent of lung damage corresponds directly with how severe the illness is, which in turn will elevate D-dimer readings.[20,21] The SARS-CoV-2 virus attaches itself to ACE2 and initiates harm to the endothelium. Injury to the endothelium leads to the discharge of tissue elements and sets off the process of the coagulation sequence, noticeable by an elevated presence of D-dimer.

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These irregularities appear to be connected with a greater need for breathing machines, entrance into critical care units, and mortality.[22] Even though there is not enough proof to suggest checking blood and clotting measures, blood-clotting tests are commonly tracked in individuals with Covid 19, particularly when the pandemic was at its worst. Roughly 20–50% of patients in the hospital show blood-related changes in blood-clotting tests. [22,23] Clotting issues were observed to happen in as many as one-third of individuals with Covid 19, with lung blood clots being the most frequent problem.[24]

CONCLUSION

Based on the results of this study, it can be concluded that D-dimer levels have statistically significant associations with COVID-19 patient clinical outcomes, so that it can be categorized as an independent predictor of mortality risk. According to our research, individuals with Covid-19 who require hospitalization exhibit heightened D-dimer concentrations, and these concentrations might function as a predictive factor for death.

ETHICAL APPROVAL

This research received approval from the Research Ethics Committee of the Faculty of Medicine, Ahmad Dahlan University and Wates General Hospital with reference number KEPK/035/RS/XII/2024.

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