Association between D-dimers and in-hospital all-cause mortality in COVID-19 patients at a tertiary hospital in South Africa: A retrospective study

J Matimba,[1] MB ChB, MMed (Int), FCP (SA); **T Ellis,**[1] MB ChB, MMed (Int), FRCP;
E S Grossman,[2] BSc Hons, MSc (Dent), PhD; **A Goolam Mahomed,**[3] MBB Ch, FCP (SA), FCCP

[1] *Department of Internal Medicine and Pharmacology, Faculty of Medicine and Health Sciences, Walter Sisulu University, Mthatha, and Livingstone Hospital, Gqeberha, South Africa*

[2] *Port Elizabeth and East London Health Resource Centre, Walter Sisulu University, Mthatha, South Africa*

[3] *Department of Internal Medicine, Faculty of Medicine and Health Sciences, Nelson Mandela University and Livingstone Hospital, Gqeberha, South Africa*

Corresponding author: *J Matimba (jmatimbaj@gmail.com)*

Background. The COVID-19 pandemic was caused by the SARS-CoV-2 virus. Many studies have shown that D-dimer levels were elevated in patients hospitalised for severe COVID-19, and that they served as a marker of poor prognosis with increased mortality in this subpopulation. There is a paucity of data on the prognostic value of D-dimer levels during the COVID-19 pandemic in the African population.

Objectives. To investigate the relationship between elevated D-dimer levels on admission and in-hospital mortality associated with COVID-19. The study also examined the sociodemographics of the study population, clinical characteristics, length of hospital stay and outcomes, stratified by D-dimer levels.

Methods. A retrospective observational review of COVID-19 patients admitted via acute medical admissions at Livingstone Tertiary Hospital, Gqeberha, South Africa, was conducted between 1 October 2020 and 30 September 2021, using the national COVID-19 hospital surveillance (DATCOV) database. D-dimer levels that were measured within 48 hours of admission and patient outcomes (discharge and in-hospital all-cause mortality) were analysed. Statistical significance was set at $p<0.05$.

Results. Of 423 patients with COVID-19, 267 (63.1%) had elevated D-dimer levels (>0.5 µg/mL) and 156 (36.9%) had normal D-dimer levels (≤0.5 µg/mL). Of the 267 with elevated D-dimer levels, 113 (42.3%) died during their hospital stay, whereas of the 156 with normal D-dimer levels, 38 (24.4%) died in hospital. D-dimer levels ≥1.1 µg/mL were associated with increased in-hospital all-cause mortality (odds ratio (OR) 2.717; $p<0.001$). Patients with D-dimer levels between 1.1 and 2 µg/mL were 2.3 times more likely to die in hospital compared with patients who had a normal D-dimer level (OR 2.311; $p=0.005$), and patients with D-dimer levels >2.0 µg/mL were three times more likely to die in hospital compared with patients with levels ≤0.5 µg/mL (OR 3.047; $p<0.001$). Apart from elevated D-dimer levels, age ≥70 years (OR 4.112; $p<0.001$), the presence of at least one comorbidity (OR 3.638; $p<0.001$), and specifically hypertension as a comorbidity (OR 3.224; $p<0.001$), were also found to be significantly associated with increased in-hospital COVID-19 mortality.

Conclusion. Elevated D-dimer levels on admission were associated with increased COVID-19 in-hospital all-cause mortality (OR 2.279; $p<0.001$).

Keywords. COVID-19, D-dimer, mortality.

Afr J Thoracic Crit Care Med 2025;31(4):e3320. https://doi.org/10.7196/AJTCCM.2025.v31i4.3320

Study synopsis

What the study adds. This study aimed to evaluate whether an elevated D-dimer level on admission was associated with in-hospital mortality in COVID-19 patients in Africa, specifically in the Eastern Cape region of South Africa.

Implications of the findings. D-dimers may be a helpful biomarker in risk stratification of COVID-19 patients. The study may stimulate further research and guidance in the management of future COVID-19 patients.

COVID-19 is a viral infectious disease caused by SARS-CoV-2, a novel betacoronavirus that has had a substantial impact on humankind,[1-3] resulting in both morbidity and mortality. As of January 2022, there had been over seven million deaths due to COVID-19 worldwide, of which just over 100 000 were in South Africa (SA).[4] A more comprehensive measure of the total impact of the COVID-19 pandemic on deaths is to look at excess deaths. According to the South African Medical Research Council report for the week ending 21 May 2022, Eastern Cape Province had the highest excess deaths, at 814 per 100 000 population.[5] Nationally, it is estimated that 85 - 95% of these excess

natural deaths were attributable to COVID-19. The remaining 5 - 15% were attributable to collateral damage due to health services being overwhelmed during surges in the pandemic.[5]

Several studies in America, Asia and Europe concluded that D-dimer elevation was associated with severe disease and poorer outcomes, including mortality.[3,6-8] In SA, a prospective study by Allwood *et al*.[9] at Tygerberg Hospital in Cape Town found that mortality of patients with COVID-19 admitted to the intensive care unit was associated with elevated D-dimer levels and a low standard bicarbonate ($HCO3^-$) level.

The D-dimer is a fibrin degradation product produced when plasmin cleaves cross-linked fibrin during the breakdown of a clot.[10,11] For D-dimers to be elevated, a clot must occur first. Elevated D-dimer levels were a hallmark of severe COVID-19 infection. The spectrum of the disease ranged from asymptomatic (World Health Organization (WHO) stage 1) to mild or moderate illness (stage 2), severe multisystemic inflammation (stage 3) and critical illness with endothelial damage and thrombosis (stage 4).[2,12-14] According to the WHO staging above, thrombosis was associated with the most severe stage 4 disease. While the pathophysiology of COVID-19 and the underlying mechanisms of its clinical manifestations remain unclear, evidence has emerged that an acquired prothrombotic state may have driven some complications associated with the COVID-19 syndrome.[10,15]

Numerous studies indicate that individuals hospitalised with severe COVID-19 often had elevated D-dimer levels, which may be linked to a higher mortality rate among these patients and could have served as a marker of poor prognosis. In a similar vein, this study aimed to explore whether higher admission D-dimer levels were associated with in-hospital mortality among COVID-19 patients in Africa, specifically in the Eastern Cape region of SA. The study also examined the sociodemographics of the study population, clinical characteristics, length of hospital stay and outcomes, stratified by D-dimer levels. The findings of this study will contribute to the existing body of knowledge on this topic.

Methods

Study design and setting

The study was a retrospective, observational record review of the first 423 consecutive COVID-19 acute medical admissions at Livingstone Tertiary Hospital, Gqeberha, between 1 October 2020 and 30 September 2021, using the national COVID-19 hospital surveillance (DATCOV) database. Livingstone Tertiary Hospital is a 512-bed facility that offers tertiary and regional healthcare services in the western region of Eastern Cape. The study period straddles the second and third waves of the COVID-19 pandemic in SA, with infections caused by the SARS-CoV-2 Beta variant (November 2020 - February 2021) and Delta variant (May - September 2021), respectively.[5]

Study population

All records of adults aged ≥18 years admitted via acute medical admissions between 1 October 2020 and 30 September 2021 with confirmed positive COVID-19 tests (polymerase chain reaction and/or rapid antigen test) were reviewed (Fig. 1). They included patients with a primary diagnosis of COVID-19 and those with incidental and comorbid COVID-19 infections. Only patients with D-dimer level results within 48 hours were included. The cut-off was set at 48 hours because prolonged hospitalisation in itself can lead to elevated D-dimer levels. Patients with untraceable or unrecorded results, as well as those with conditions that may result in elevated D-dimer levels (such as pregnancy, deep-vein thrombosis, pulmonary embolism, malignancy and gunshot wounds), were also excluded from the study (Fig. 1). The D-dimer levels were divided into four groups, 0 - 0.5 μg/mL, 0.6 - 1.0 μg/mL, 1.1 - 2.0 μg/mL and >2.0 μg/mL, and the number of patients who survived to discharge was determined. Different groups were necessary to compare our study with previous research that divided D-dimer levels into two[16-18] or three[19,20] groups, as well as to establish the D-dimer cut-off level above which the risk of mortality increases. Odds ratios (ORs) for the groups with elevated D-dimer levels were calculated relative to the group with normal D-dimer levels (≤0.5 μg/mL). D-dimer levels were measured on a Sysmex CS-2500 coagulation analyser (Siemens, Germany) in the National Health Laboratory Service laboratory at the hospital. The laboratory reference range for a normal D-dimer value was 0 - 0.5 μg/mL.

Ethical considerations

Ethical clearance for the study was obtained from the Faculty of Medicine and Health Sciences and the Biosafety Committee at Walter Sisulu University, Mthatha (ref. no. 034/2022). The Eastern Cape Department of Health and Livingstone Tertiary Hospital also approved the research.

Data source and collection

The study was a retrospective, observational record review of the national DATCOV database for COVID-19 patients admitted to Livingstone Tertiary Hospital between 1 October 2020 and 30 September 2021. At the onset of the COVID pandemic, there was no hospital surveillance system in place. The National Institute for Communicable Diseases (NICD) developed a DATCOV system for both public and private hospitals to report COVID cases. Our hospital reported to DATCOV on a daily basis. The first consecutive 423 patients were analysed according to the inclusion and exclusion criteria. Data collection sheets contained no patient identifiers, and data were entered into a password-protected computer.

Statistical analysis

The sample was described using descriptive statistics and frequency distributions. The study aimed to assess whether mortality (dependent variable) was predicted by categories of D-dimer level groups (independent variable) while controlling for specified comorbidities (asthma, cancer, chronic obstructive pulmonary disease, diabetes mellitus, HIV, hypertension and obesity). The relationship between independent and dependent variables was assessed using binary logistic regression. The likelihood of the event (non-survival/death) occurring was determined based on the independent variables. This method also allowed for the determination of ORs for each significant independent variable. ORs provide the likelihood (or odds) of a particular result (death) given a specific level of an independent variable. Cross-tabulations and χ^2 association tests were used to determine the level of association between categorical variables. The level of significance was set at $p<0.05$.

Results

Sociodemographics of the study population

The study population comprised 174 males (41.1%) and 249 females (58.9%). Their ages ranged from 18 to 97 years, with a mean (standard deviation) of 56.8 (14) years. Of the 423 patients, 186 (44%) were aged ≥60 years. Of these, 135 (72.6%) had elevated D-dimer levels (>0.5 µg/mL) and 51 (27.4%) had normal levels (≤0.5 µg/mL). Of the 81 patients aged ≥70 years, 68 (84.0%) had elevated D-dimer levels and 13 (16.0%) had normal levels, and of the 237 patients aged <60 years, 132 (55.7%) had elevated D-dimer levels and 105 (44.3%) had normal levels.

Clinical characteristics of the patients

Patients with at least one comorbidity accounted for 54.8% (*n*=232) of the patients available for final analysis, while those with no comorbidities comprised 45.2% (*n*=191). Of the 232 patients with comorbidities, 178 (76.7%) had hypertension and 105 (45.3%) had diabetes mellitus.

Length of hospital stay

Hospital stay ranged from <24 hours to 78 days. The mean length of stay was 7.01 days, with 30 patients (7.1%) having stayed in the hospital for <24 hours, 56 (13.2%) for a day, 124 (29.3%) for 2 - 3 days, 98 (23.2%) for 4 - 7 days, and 109 (25.8%) for 8 - 28 days. Only 6 patients (1.4%) stayed beyond 28 days.

D-dimer levels

Fig. 2 shows that 36.9% of the patients (*n*=156) had normal D-dimer levels (0 - 0.5 µg/mL), while 63.1% (*n*=267) had elevated levels. Of the groups with elevated D-dimer levels, the largest had levels >2 µg/mL (*n*=105; 39.3% of the patients with elevated levels) (Fig. 2).

Outcome

The outcomes for each D-dimer level group are summarised in Fig. 3. Among patients with elevated D-dimer levels, mortality was highest in those with D-dimer levels >2 µg/mL. Almost 50% of the patients with D-dimer levels >2 µg/mL died, whereas 24.4% of the patients with normal D-dimer levels died.

Of the 423 patients, 272 were discharged and 151 died, representing 64.3% and 35.7% of the cohort, respectively. The number of deaths in the group with normal D-dimer levels (0 - 0.5 µg/mL) was 38 (24.4%).

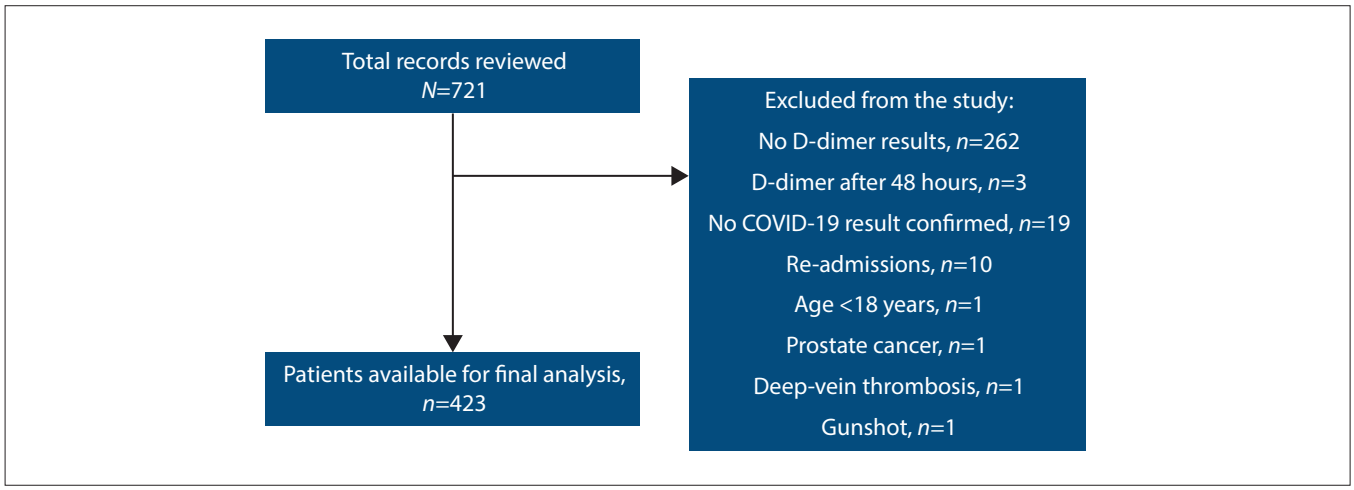

Fig. 1. Flow diagram showing systematic review of records and number of patients available for final analysis.

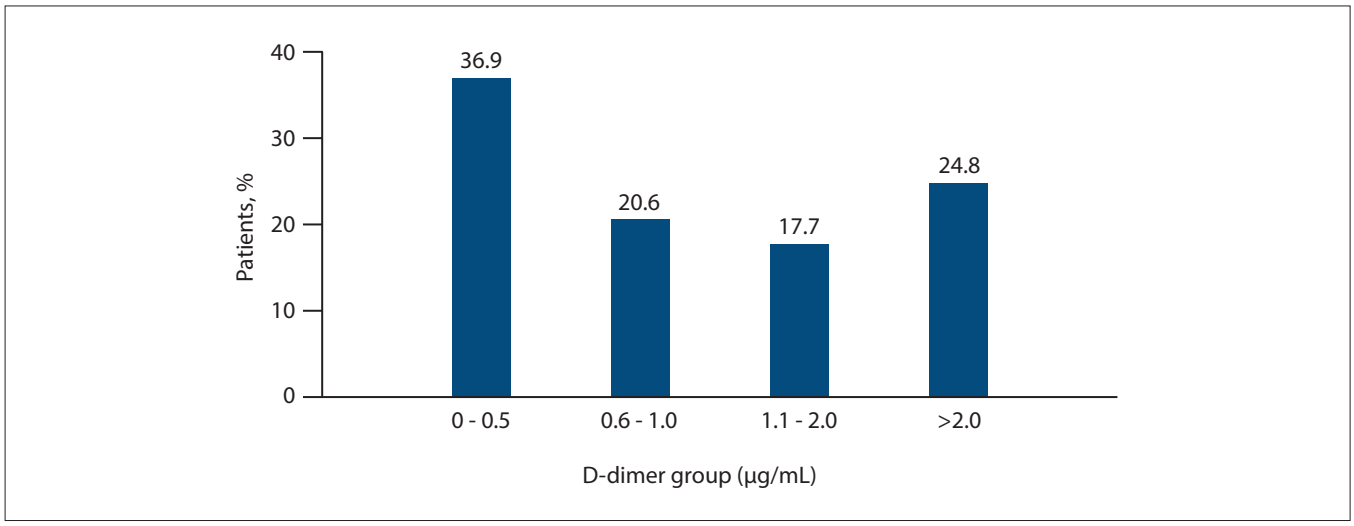

Fig. 2. Proportion of patients in each D-dimer level group.

Of the 267 patients with an elevated D-dimer level, 87 had a level of 0.6 - 1.0 µg/mL, of whom 58 (66.7%) were discharged and 29 33.3%) died. Of the 75 patients with D-dimer levels of 1.1 - 2.0 µg/mL, 43 (57.3%) were discharged and 32 (42.6%) died, and of the 105 patients with a D-dimer level >2 µg/mL, 53 (50.5%) were discharged and 52 (49.5%) died. Importantly, Fig. 4 shows a linear progression of how elevation in the D-dimer level increased the chances of death for each category.

Factors associated with mortality

Analysis of the sociodemographic characteristics showed that mortality was highest in patients ≥70 years of age. Of the 81 (19.1%) patients in this age group, 42 (51.9%) died and 39 (48.1%) were discharged.

Of the 423 patients, 232 (54.8%) had at least one comorbidity. Of these, 120 (28.4% of the total) were discharged, while 112 (26.5%) died. Of the 191 patients with no comorbidities (45.2%), 152 (35.9%) were discharged and 39 (9.2%) died.

Logistic regression

The binary logistic regression showed that patients aged 60 - 69 years were 3.2 times more likely to have a death outcome compared with patients aged <40 years (OR 3.215; $p<0.003$). The risk quadrupled in patients aged ≥70 years compared with those aged <40 years (OR 4.112; $p<0.001$).

It was found that patients with at least one comorbidity were 3.6 times more likely to have a death outcome compared with patients who did not have any comorbidities (OR 3.638; $p<0.001$).

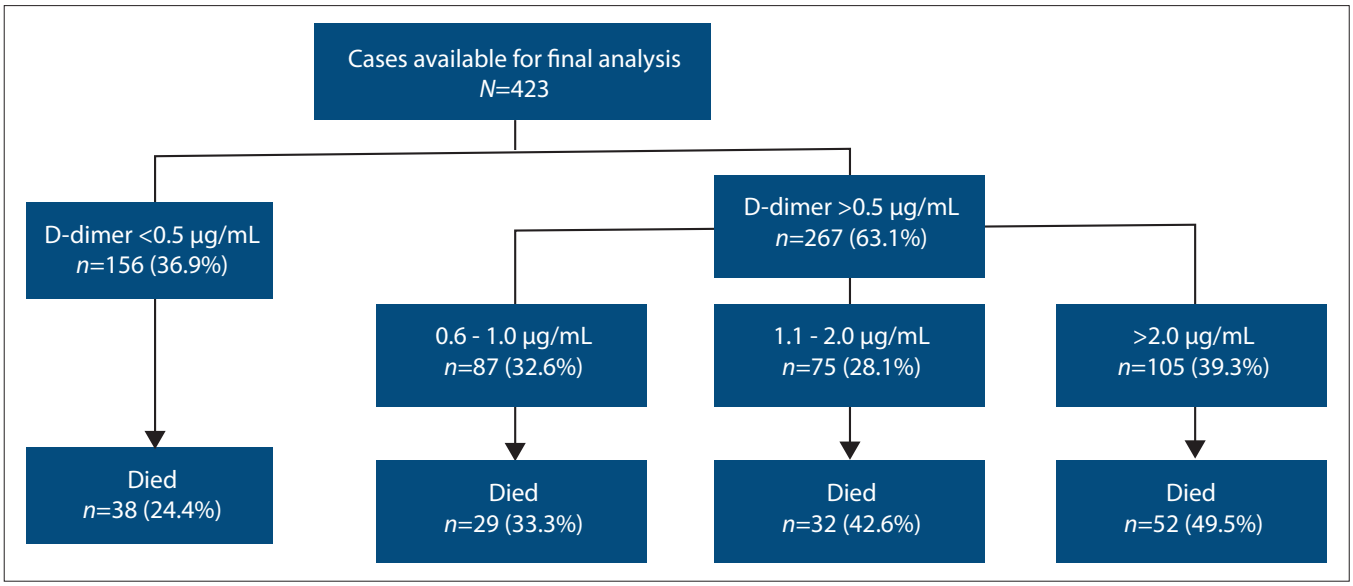

Fig. 3. Flow diagram illustrating outcome according to D-dimer level group.

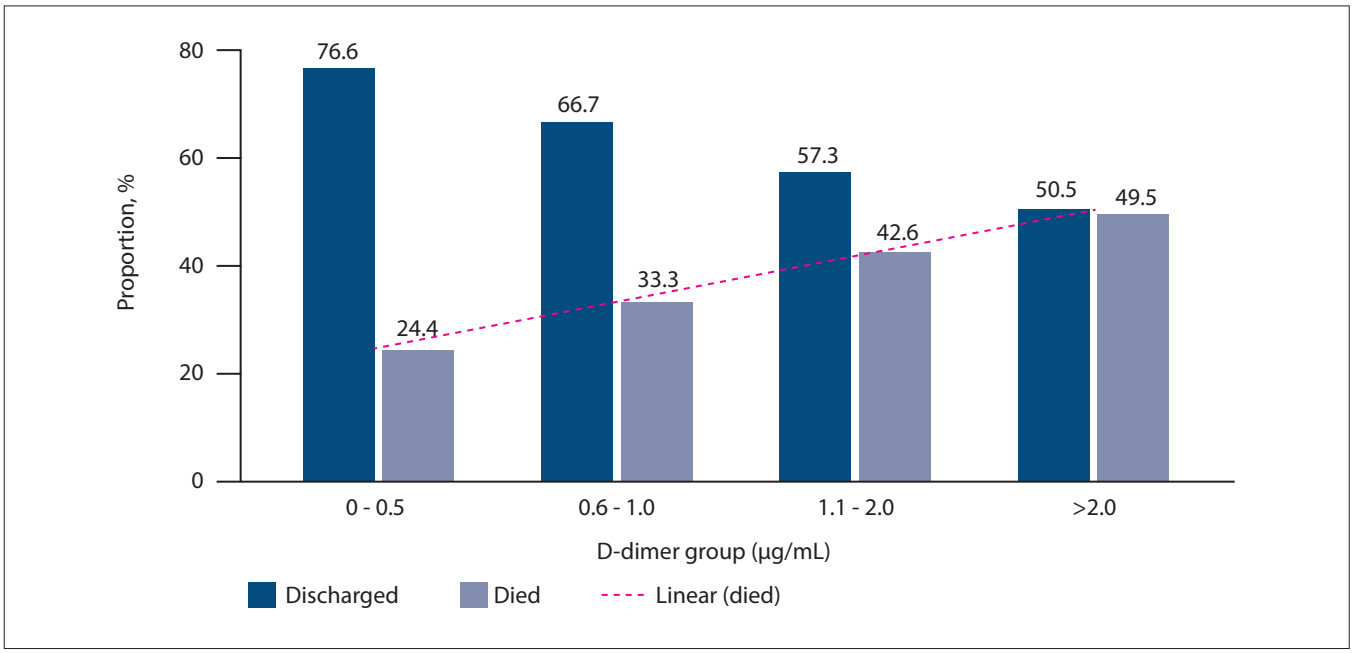

Fig. 4. Outcome according to D-dimer level group.

With regard to individual comorbidities, patients with hypertension were 3.2 times more likely to have a death outcome compared with patients who did not have hypertension (OR 3.224; $p<0.001$).

D-dimer levels and mortality

The D-dimer groups were re-coded into two summarised categories: normal D-dimer level (0 - 0.5 µg/mL) and elevated D-dimer level (>0.5 µg/mL). It was found that patients with elevated D-dimer levels were 2.2 times more likely to have a death outcome compared with patients who had normal D-dimer levels (OR 2.279; $p<0.001$).

Table 1 shows that the likelihood of dying of COVID-19 increased with an increase in D-dimer levels.

Discussion

The results of this study conducted in Eastern Cape, SA, were similar to international studies demonstrating that patients with elevated D-dimer levels had a significantly higher risk of death compared with those with normal D-dimer levels, and that elevated D-dimer levels can effectively predict in-hospital mortality in patients with COVID-19.[18,21] Patients with D-dimer levels >0.5 µg/mL were 2.3 times more likely to die than those with normal levels (OR 2.279; $p<0.001$). This increase becomes even more significant for D-dimer levels >2 µg/mL (four times the upper limit of normal), as the likelihood of death rises to three times that of individuals with normal levels (crude OR 3.047, adjusted OR 2.836; $p<0.001$). The rise occurs because COVID-19 is associated with a hypercoagulable state, microthrombi and endothelial injury, which increase D-dimer levels, particularly in patients in WHO classes 3 and 4. D-dimers serve as an indicator of fibrin degradation, which is pertinent to both venous thromboembolism and the systemic inflammatory response observed in severe COVID-19.

The study also demonstrated that D-dimer levels are often elevated in individuals with COVID-19 and that levels ≥1.1 µg/mL were the strongest predictor of in-hospital mortality related to COVID-19 infection. This observation aligns with findings from various international and local studies. Chilimuri *et al.*[1] reported similar findings, with admission D-dimer levels >1 µg/mL effectively predicting death outcomes (OR 3.16; 95% confidence interval (CI) 1.75 - 5.73; $p<0.0001$). The D-dimer level above which mortality increases could have been determined using D-dimer as a continuous variable. However, most studies in the literature have used categorical values,[3,16,18] hence our selection of D-dimer level categories.

A prospective study in SA by Allwood *et al.*[9] also concluded that elevated D-dimer levels were associated with an increased risk of death (hazard ratio (HR) 1.05; 95% CI 1.00 - 1.11) and that D-dimer levels were higher among patients who died compared with those who survived (median (interquartile range) 1.51 (0.65 - 4.86) µg/mL v. 0.41 (0.24 - 0.95) µg/mL; $p<0.001$). Whereas Allwood *et al.*[9] compared the number of people who died with elevated D-dimer levels (HR) with those with normal D-dimer levels, our study demonstrated the odds of dying in hospital for patients with elevated D-dimer levels (OR). Adjusted ORs were used to provide a more precise evaluation of the relationship between D-dimer level and in-hospital mortality, while controlling for other potential confounders.

Besides elevated D-dimers, the following factors were significant predictors of in-hospital all-cause mortality: increasing age, at least one comorbidity, and hypertension, all of which were independent of D-dimer level. International studies, such as a study in the USA,[1] had similar findings.

Study limitations

The nature of this study, which was retrospective and conducted at a single centre, may introduce selection bias. Although all eligible patients were included, some were excluded owing to lack of D-dimer results at the time of admission. There were various reasons for unavailability of D-dimer results, including 'it was not done', 'the wrong tube was used', 'underfilled', 'clotted blood', 'no date on the specimen', and 'too old'. Attempts were made to address some of these challenges by including specimens taken up to 48 hours after arrival. Obesity may have been under-reported, as most patients were likely to have been too unwell to stand for weight and height measurements. Furthermore, staff may have been overwhelmed by the massive influx of patients, resulting in the omission of weight and height measurements, even for those who were able to stand. Another limitation is that only the D-dimer level was examined in this study, while many factors can influence mortality, including the severity of illness, treatments received, and the time taken to seek medical attention. Furthermore, normal D-dimer levels tend to increase with age. Using adjusted ORs aimed to address this limitation by assessing the relationship between D-dimers and COVID-19 mortality while controlling for all other factors.

Conclusion

Elevated D-dimer levels on admission were associated with increased in-hospital all-cause mortality from COVID-19. The findings of this article are especially significant in resource-limited settings, as they suggest that resource allocation during the COVID-19 pandemic could depend on a relatively simple blood test, specifically the D-dimer. The research should probably be extended to other respiratory pathogens, as the number of COVID-19 infections has dramatically decreased worldwide. Nonetheless, the article has value, particularly in view of the paucity of local African research information.

Finally, COVID-19 patients with comorbidities, especially hypertension, should be prioritised for intensive treatment, as they tend to have a poorer prognosis.

Table 1. Elevated D-dimer level groups with crude and adjusted ORs

D-dimer level group (µg/mL)	Crude OR (95% CI)	Adjusted OR (95% CI)	*p*-value
0.6 - 1.0	1.553 (0.872 - 2.763)	1.369 (0.743 - 2.521)	0.313
1.1 - 2.0	2.311 (1.287 - 4.151)	2.302 (1.230 - 4.307)	0.009
>2.0	3.047 (1.795 - 5.172)	2.836 (1.616 - 4.976)	<0.001

OR = odds ratio; CI = confidence interval.

Data availability. The data sets generated and analysed during this study are available from the corresponding author (JM) on reasonable request.

Declaration. The research for this study was done in partial fulfilment of the requirements for JM's MMed (Internal Medicine) degree at Walter Sisulu University. AGM is a member of the editorial board

Acknowledgements. JM thanks the NICD for providing access to the DATCOV database. He is particularly grateful to Carmen Stindt, Director and Chief Statistical Consultant at Eversci in Gqeberha, for her valuable statistical input.

Author contributions. JM: principal investigator, responsible for conceptualisation, collecting data, and writing the article. TE: supervisor of the MMed, oversaw the review, provided comments, and guided drafts of the manuscript. ESG: responsible for guiding initial research and commenting on manuscript drafts. AGM: instrumental in harvesting the article from the dissertation and commenting on previous drafts of the manuscript.

Funding. None.

Conflicts of interest. None.

1. Chilimuri S, Sun H, Alemam A, et al. Predictors of mortality in adults admitted with COVID-19: Retrospective cohort study from New York City. West J Emerg Med 2020;21(4):779-784. https://doi.org/10.5811/westjem.2020.6.47919
2. Shah S, Shah K, Patel SB, et al. Elevated D-dimer levels are associated with increased risk of mortality in coronavirus disease 2019: A systematic review and meta-analysis. Cardiol Rev 2020;28(6):295-302. https://doi.org/10.1097/CRD.0000000000000330
3. Yao Y, Cao J, Wang Q, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case-control study. J Intensive Care 2020;8:49. https://doi.org/10.1186/s40560-020-00466-z
4. World Health Organization. WHO COVID-19 dashboard. https://covid19.who.int (accessed 30 January 2022).
5. South African Medical Research Council. Report on weekly deaths in South Africa. 2022. https://www.samrc.ac.za/reports/report-weekly-deaths-south-africa (accessed 27 May 2022).
6. Shi L, Wang Y, Wang YD, Duan GC, Yang HY. D-dimer is associated with the risk of mortality in coronavirus disease 2019 patients. Eur Rev Med Pharmacol Sci 2020;24(16):8576-8579. https://doi.org/10.26355/eurrev_202008_22655
7. Soni M, Gopalakrishnan R, Vaishya R, Prabu P. D-dimer level is a useful predictor for mortality in patients with COVID-19: Analysis of 483 cases. Diabetes Metab Syndr 2020;14(6):2245-2249. https://doi.org/10.1016/j.dsx.2020.11.007
8. Nugroho J, Wardhana A, Maghfirah I, et al. Relationship of D-dimer with severity and mortality in SARS-CoV-2 patients: A meta-analysis. Int J Lab Haematol 2021;43(1):110-115. https://doi.org/10.1111/ijlh.13336
9. Allwood BW, Koegelenberg CF, Ngah VD, et al. COVID-19 Research Response Collaboration. Predicting COVID-19 outcomes from clinical and laboratory parameters in an intensive care facility during the second wave of the pandemic in South Africa. IJID Reg 2022;3:242-247. https://doi.org/10.1016/j.ijregi.2022.03.024
10. Martín-Rojas RM, Pérez-Rus G, Delgado-Pinos VE, et al. COVID-19 coagulopathy: An in-depth analysis of the coagulation system. Eur J Haematol 2020;105(6):741-750. https://doi.org/10.1111/ejh.13501
11. Cabrera-Garcia D, Miltiades A, Yim P, et al. Plasma biomarkers associated with survival and thrombosis in hospitalised COVID-19 patients. Int J Hematol 2022;116(6):937-946. https://doi.org/10.1007/s12185-022-03437-2
12. Cordon-Cardo C, Pujadas E, Wajnberg A, et al. COVID-19: Staging of a new disease. Cancer Cell 2020;38(5):594-597. https://doi.org/10.1016/j.ccell.2020.10.006
13. Huang Y, Lyu X, Li D, et al. A cohort study of 676 patients indicates that D-dimer is a critical risk factor for the mortality of COVID-19. PLoS ONE 2020;15(11):e0242045. https://doi.org/10.1371/journal.pone.0242045
14. Bansal A, Singh AD, Jain V, et al. The association of D-dimers with mortality, intensive care unit admission or acute respiratory distress syndrome in patients hospitalized with coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Heart Lung 2021;50(1):9-12. https://doi.org/10.1016/j.hrtlng.2020.08.024
15. Naymagon L, Zubizarreta N, Feld J, et al. Admission D-dimer levels, D-dimer trends, and outcomes in COVID-19. Thromb Res 2020;196:99-105. https://doi.org/10.1016/j.thromres.2020.08.032
16. Oualim S, Abdeladim S, Ouarradi AE, et al. Elevated levels of D-dimer in patients with COVID-19: Prognosis value. Pan Afr Med J 2020;35(Suppl 2):105. https://doi.org/10.11604/pamj.supp.2020.35.2.24692
17. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: A prospective cohort study. Eur Respir J 2020;55(5):2000524. https://doi.org/10.1183/13993003.00524-2020
18. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with COVID-19. J Thromb Haemost 2020;18(6):1324-1329. https://doi.org/10.1111/jth.14859
19. Giacomelli A, Ridolfo AL, Milazzo L, et al. 30-day mortality in patients hospitalised with COVID-19 during the first wave of the Italian epidemic: A prospective cohort study. Pharmacol Res 2020;158:104931. https://doi.org/10.1016/j.phrs.2020.104931
20. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395(10229):1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3
21. Hodges G, Pallisgaard J, Schjerning Olsen AM, et al. Association between biomarkers and COVID-19 severity and mortality: A nationwide Danish cohort study. BMJ Open 2020;10(12):e041295. https://doi.org/10.1136/bmjopen-2020-041295

Received 26 March 2025. Accepted 15 September 2025. Published 19 December 2025.