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D-DIMER VARIABILITY WITH COMORBIDITIES AND MULTIMORBIDITIES DURING COVID-19 INFECTION

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Abstract

Coronavirus infection 2019 (COVID-19), a respiratory illness, is also linked to thrombotic disorders. The elevation of D-dimer is a prognostic biomarker for adverse outcomes in COVID-19. Nevertheless, the association between elevated D-dimer levels and different comorbidities and Multimorbidities lacks understanding. This study is designed to bridge this knowledge gap by focusing on this research side.

The study involved a cohort of 618 COVID-19 patients and explored the relationship of D-dimer level with different factors including age groups, comorbidities, medical interventions and disease outcomes. The mean D-dimer level at the time of hospitalization was 2664.08 ng/mL (2.7µg/mL), displaying significant variation (range: 96 to 12900 ng/mL). Old Age patients demonstrated a significant correlation (p=.000) with D-dimer levels, particularly elevated levels at the old age (≥65) group. A significant connection between D-dimer levels and comorbidities, including diabetes (p=.000), hypertension (p=.000), asthma (p=.003), ischemic heart disease (p=.000), and chronic kidney diseases (p=.000) and Tuberculosis (p=.001) revealed the occurrence of high coagulation activity due to these comorbidities. Furthermore, the elevated D-dimer was associated with high requirements of medical interventions including non-invasive ventilation (p=.000), mechanical ventilation (p=.000), and Intensive care unit admission (p=.000) with a high probability to cause deaths (p=.000). Cox regression analysis indicated a significant correlation of D-dimer levels with the duration of hospitalization in recovered COVID-19 patients (Chi-square = 32.839, df = 1, $p < .001$) as well as in deceased COVID-19 patients (Chi-square = 62.906, df = 1, $p < .001$). However, the hazard ratio for D-dimer level was found to be 1.000, representing no change in the hazard of duration of hospitalization with a one-unit increase in D-dimer values. In addition, logistic regression analysis revealed a significant association ($p < 0.001$) between elevated D-dimer levels at the time of admission increased likelihood of death. These findings provide crucial insights into the role of D-dimer in disease severity, prognosis, and personalized patient management strategies in the context of COVID-19.

In conclusion, this study underscores the intricate associations of D-dimer levels with comorbidities and multimorbidities ultimately affecting the medical interventions, and disease outcomes in COVID-19 patients.

Keywords: COVID-19, D-dimer, Comorbidities, multimorbidity, thrombotic disorders

1. Introduction

The emergence of Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a pulmonary inflammatory disease significantly affected by the underlying health condition of comorbidities and multimorbidity's [1], [2].

One intriguing aspect of COVID-19 is its association with thrombotic complications and coagulopathies, including the potentially life-threatening Disseminated Intravascular Coagulopathy (DIC) [3]–[5]. The underlying mechanisms behind these phenomena are intricate and multifaceted, likely involving the activation of the coagulation cascade due to viral presence or cytokine storms, as well as potential infections and organ dysfunction. Amid this complexity, the biomarker D-dimer, a byproduct of fibrin breakdown, has emerged as a possible indicator of coagulation abnormalities and thrombotic disorders [6].

Traditionally, a D-dimer value below 500ng/mL (0.5 μg/mL) is deemed within the normal range [7], [8] with levels varying based on the underlying health conditions. Notably, D-dimer levels have been correlated with the severity of COVID-19 patients. However, in the context of different comorbidities and multimorbidities in COVID-19 patients, D-dimer has garnered attention for its potential prognostic significance. Various studies have investigated the utility of D-dimer levels upon hospital admission as predictive markers of disease severity, offering intriguing insights into its potential clinical applications [9], [10].

This study aims to investigate D-dimer levels in COVID-19 patients with varying underlying health conditions and presents a compelling avenue of research aimed at unravelling the intricate relationship between coagulation abnormalities and comorbidities in the context of the disease. This study seeks to shed light on the potential association between different underlying health conditions, commonly referred to as comorbidities, and the coagulation status of individuals diagnosed with COVID-19.

2. Methodology

A retrospective study was conducted in two healthcare centers in Islamabad, Pakistan including the Pakistan Institute of Medical Sciences (PIMS), Hospital and Isolation Hospital & Infectious Treatment Center (IHITC) after getting ethical approval from the Institutional Review Board (IRB) of Quaid-i-Azam University, Islamabad. The required data of COViD-19 patients was obtained from the personal file record keeping in view of the strict ethical considerations to maintain the confidentiality of patients throughout the research process. The demographic information of patients including age and gender, previous comorbidities, D-dimer value of 1st and 3rd day of hospitalization was recorded. Furthermore, pre-existing comorbidities and multimorbidities, including hypertension (HTN), Diabetes mellitus (DM), Asthma, Chronic kidney disease (CKD), Ischemic heart disease (IHD) and Tuberculosis (TB), were documented based on medical records. Key disease outcomes, including duration of hospitalization, need for mechanical ventilation (MV), non-invasive ventilation (NIV), intensive care unit (ICU) admission, and final disease outcome (discharge or death), were also documented. All personally identifiable information was carefully removed during data collection and analysis to ensure compliance with data protection regulations.

2.1. Statistical analysis

The general characteristics were determined through descriptive statistics and frequency determination. The data of D-dimer in study population was not normally distributed; therefore, the non-parametric Kruskal-Wallis test was used to find out the differences in serum D-dimer levels across various age groups of the sample population. The non-parametric Mann-Whitney test was

performed to explore the association of D-dimer with different comorbidities in COVID-19 patients. To evaluate variations within various multimorbidities, one way ANOVA test which was performed on the D-dimer level of 1st and 3rd day of hospitalization in COVID-19 patients. Two independent samples t-test was used to find out the correlation between the D-dimer and bivariate variables including, the requirement of non-invasive ventilation, mechanical ventilation, ICU admission, and disease outcome (recovery or death). Cox regression analysis was employed to predict the association of D-dimer with duration of hospitalization in COVID-19 patients while logistic regression model was used to predict the D-dimer as predictor of death in COVID-19 patients.

3. Results

3.1. Descriptive Statistics and Baseline Characteristics

The research cohort consists of 618 individuals, comprising 62.6% males and 37.4% females. Notably, no children (≤14 years) were observed among the hospitalized subjects, while the predominant age group was old age (≥65 years), accounting for 38.3% of the cases and the remaining participants were distributed across various other age categories. Regarding comorbidities, 36.1% of the patients had no concurrent health conditions, while 27.8% presented with one, 23.6% with two, and 12.5% with three comorbidities. In terms of disease outcomes, 73.9% of the patients were discharged from the hospital after recovery, whereas 26.1% experienced fatal outcomes. **(Table 1).**

Table 1: Baseline Characteristics of COVID-19 Patients

Characteristics	Category	No. of patients (%)
	Total COVID-19 Patients	618 (100%)
Gender	Male	387 (62.6%)
	Female	231 (37.4%)
Age groups	Children (≤14 years)	0.0(0%)
	Young (15-24 years)	19 (3.1%)
	Adult (25-54 years)	207 (33.5%)
	Middle age (55-64 years)	155 (25.1%)
	Old age (≥65 years)	237 (38.3%)
No. of comorbidities	No Comorbidity	223 (36.1%)
	1 Comorbidity	172 (27.8%)
	2 Comorbidities	146 (23.6%)
	3 Comorbidities	77 (12.5%)
Disease outcome	Discharged after recovery	457 (73.9%)
	Death	161 (26.1%)

3.2. D-dimer as an inflammatory marker

The mean D-dimer value on the first day of hospitalization was 2664.08 ng/mL (SD= 3800.456) with a considerable variation (96 to 12900 ng/mL), suggesting diverse levels of fibrin degradation in COVID-19 patients. Analyzing the distribution of D-dimer values further, it was observed that 25% of the patients had D-dimer values below 243.00 ng/mL (25th percentile), while the median D-dimer value (50th percentile) was 564.50 ng/mL, signifying the central value of the D-dimer distribution. Moreover, 75% of the patients exhibited D-dimer values below 3736.25 ng/mL (75th percentile). Keeping in view the non-normality of D-dimer values, a non-parametric Mann-Whitney test was employed to compare the variations in D-dimer level between different age groups and comorbidities.

3.3. Fluctuations in the concentration of D-dimer in COVID-19 patients

3.3.1. Among different age groups: In young and adult age groups, no statistically significant difference was observed ($p = .254$). While in the pair of young and middle age groups, a significant variations ($p = .006$) was revealed. In the third comparison between young and old age groups, a significant difference ($p = .000$) was experienced in the central tendencies of D-dimer levels between these two age groups. These findings indicate that age has a significant influence on D-dimer levels in our study population of COVID-19 patients.

Table 2: Mann-Whitney tests Analysis to predict the association of D-dimer with different age groups

Age group comparison	Age group	N	Mean rank	Z	p (Asymp. sig. (2-tailed)
Young vs. Adult	Young	19	97.16	-1.141	.254
	Adult	207	115.00		
Young vs. Middle age	Young	19	57.45	-2.760	.006
	Middle age	155	91.18		
Young vs. Old age	Young	19	61.11	-4.124	.000
	Old age	237	133.90		

3.3.2. With different comorbidities:

No Comorbidity: In our investigation involving 618 COVID-19 patients, 223 of whom exhibited no comorbidities while 395 presented with comorbidities, the mean D-dimer concentration on the initial day of hospitalization was recorded as 2664.08 ng/mL (SD = 3800.456, Range = 96 to 12900) **(Table 3).** The Mann-Whitney test revealed a significant difference in D-dimer levels between patients without comorbidities (Mean Rank = 227.92) and those with comorbidities (Mean Rank = 355.56), U = 25849.500, Z = -8.540, p < .001. These findings suggest an association between comorbidities and variations in D-dimer levels, underscoring the importance of considering comorbidity status in risk assessment and clinical management.

Diabetes Mellitus: A significant difference in D-dimer level was observed between patients without diabetes (N=409, Mean Rank = 283.26) and those with diabetes (N=209, Mean Rank = 360.85), U = 32009.000, Z = -5.114, p < .001. These findings suggest an association between diabetes mellitus and variations in D-dimer levels, underscoring the importance of considering diabetes status in risk assessment and clinical management (**Table 3)**.

Hypertension: The Mann-Whitney test revealed a significant difference in D-dimer levels between patients without hypertension (N=358, Mean Rank = 287.13) and those with hypertension (N=260, Mean Rank = 340.30), U = 38533.000, Z = -3.656, p < .001. These results indicate a correlation between hypertension and fluctuations in D-dimer levels. This emphasizes the importance of factoring in hypertension status for both risk evaluation and clinical care strategies. **(Table 3)**.

Asthma: The patients without asthma (N=549, Mean Rank = 302.03) and those with asthma (N=69, Mean Rank = 368.90), revealed the significance differ. U = 14842.000, Z = -2.934, p = .003. These findings suggest an association between asthma and variations in D-dimer levels, underscoring the importance of considering asthma status in risk assessment and clinical management **(Table 3)**.

Ischemic Heart Disease: A significant difference in D-dimer levels between patients without IHD (N=516, Mean Rank = 298.27) and those with IHD (N=102, Mean Rank = 366.31), U = 20521.500, Z = -3.519, p < .001was observed. These findings recommend an association between ischemic heart disease and variations in D-dimer levels, highlighting the relevance of considering IHD status in risk assessment and clinical management **(Table 3).**

Chronic Kidney Disease (CKD): The Mann-Whitney test revealed a significant difference in D-dimer levels between patients without CKD (N=569, Mean Rank = 295.04) and those with CKD (N=49, Mean Rank = 477.38), U = 5714.500, Z = -6.863, p < .001. These findings suggest an association between chronic kidney disease and variations in D-dimer levels, highlighting the relevance of considering CKD status in risk assessment and clinical management **(Table 3)**.

Table 3: Association between D-dimer level and comorbidities analyzed by Mann-Whitney U test

Comorbidity	No/Yes	No of patients	%	Mean Rank D-dimer	Z	p (2-tailed)
No Comorbidity	No	223	36.1	227.92	-8.540	.000

Diabetes Mellitus (DM)	No	409	66.2	283.26	-5.114	.000
	Yes	209	37.4	360.85		
Hypertension (HTN)	No	358	57.9	287.13	-3.656	.000
	Yes	260	42.1	340.30		
Asthma	No	549	11.2	302.03	-2.934	.003
	Yes	69	88.8	368.90		
Ischemic heart disease (IHD)	No	516	83.5	298.27	-3.519	.000
	Yes	102	16.5	366.31		
Chronic kidney disease (CKD)	No	569	92.1	295.04	-6.863	.000
	Yes	49	7.9	477.38		
Tuberculosis (TB)	No	606	98.1	306.08	-3.391	.001
	Yes	12	1.9	482.46		

Tuberculosis (TB): A statistically significant difference in D-dimer levels was explored in patients without tuberculosis (N=606, Mean Rank = 306.08) and those with tuberculosis (N=12, Mean Rank = 482.46), U = 1560.500, Z = -3.391, p = 0.001. These results suggest an association between tuberculosis and variations in D-dimer levels, despite the low prevalence of tuberculosis in the study cohort. Further investigations with larger tuberculosis subgroups are warranted to explore this relationship more comprehensively **(Table 3)**.

3.4. Complex Interplay of D-dimer in COVID-19 Patients with comorbidities and multimorbidity

The one-way ANOVA was performed to determine the difference in D-dimer levels between 1st and 3rd days of hospitalization in COVID-19 patients with different comorbidities and multimorbidities. There was a significant difference in D-dimer levels on 1st day ($F(16, 601) = 13.629$, $p < 0.001$) and 3rd days ($F(16, 527) = 1.903$, $p = 0.018$) of hospitalization among the different groups of patients Furthermore, Post Hoc Tests (Tukey B method) identify the groups of patients which differed significantly from each other. For instance, those with DM, HTN, CKD and IHD had significantly higher D-dimer levels compared to other groups on both days. Additionally, individuals with Asthma, DM/IHD, TB & others, CKD, and No comorbidity had significantly different D-dimer levels on 3rd day of hospitalization. These results suggest that comorbidities may play a significant role in influencing D-dimer levels.

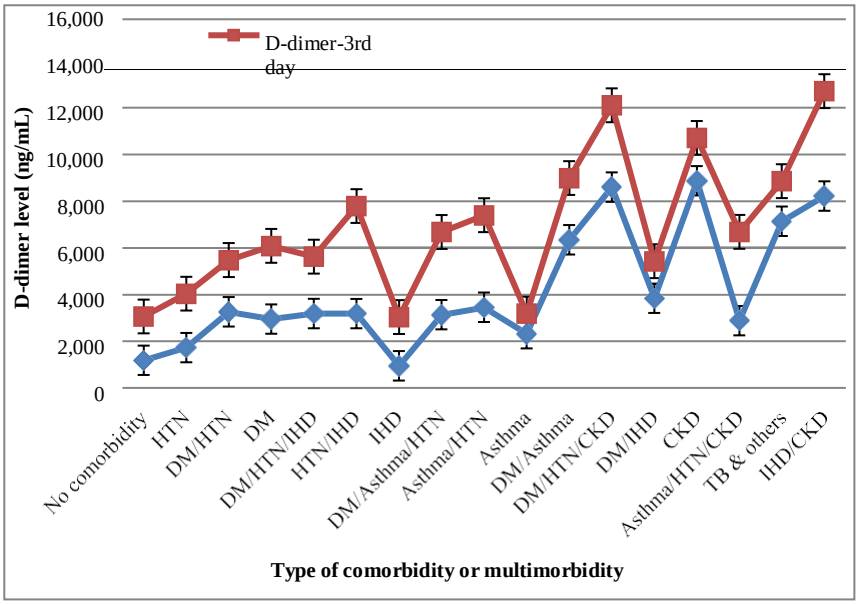


Figure 1: Mean value of D-dimer in comorbid and multimorbid COVID-19 patients (Abbreviations: HTN:hypertension, DM:Diabetes mellitus, IHD: Ischemic heart disease, CKD:Chronic kidney disease, TB:Tuberculosis)

3.5. Association of D-dimer with medical interventions

The Mann-Whitney U test was performed on the total sample population to find the association between D-dimer level and requirements for different medical interventions such as non-invasive ventilation, mechanical ventilation, ICU admission and ultimate disease outcomes.

Non-invasive ventilation: Patients who required non-invasive ventilation had significantly higher D-dimer levels compared to those who did not require it **(Table 4**). In a sample of 618 participants, the mean rank of D-dimer levels differ significantly between the two groups of patients (U = 26395.500, Z = -8.185, $p < 0.001$) who received non-invasive ventilation (N=220, Mean rank = 388.52) and those who did not (N=398, Mean rank = 265.82).

Table 4: Mann-Whitney U test analysis to determine the association of D-dimer with the requirements of medical interventions

Disease Variables	No/Yes	N	Mean rank	Z	p-value
Non-invasive ventilation	No	398	265.82	-8.185	.000
	Yes	220	388.52		
Mechanical ventilation	No	492	280.56	-7.968	.000
	Yes	126	422.51		
ICU admission	No	434	262.43	-10.072	.000
	Yes	184	420.53		
Disease outcome	Discharged	457	264.13	-10.650	.000
	Death	161	438.29		

Mechanical ventilation: A significant difference in D-dimer levels was observed (U = 16756.500, Z = -7.968, $p < 0.001$) between the two groups of patients who received mechanical ventilation (N= 126) and those who did not (N=492). Patients who received mechanical ventilation had significantly higher D-dimer levels (Mean rank = 422.51) compared to those who did not receive mechanical ventilation (Mean rank = 280.56) **(Table 4)**.

Intensive Care Unit (ICU) Admission: Patients who had ICU admission had significantly higher D-dimer levels compared to those who did not have ICU admission**.** The results showed a significant difference (U = 19499.000, Z = -10.072, $p < 0.001$) between two groups of patients: those who had ICU admission (N=184, Mean rank = 420.53) and those who did not (N=434, Mean rank = 262.43). **(Table 4)**.

Disease outcomes: Patients who experienced death (N=161, Mean rank = 438.29) had significantly higher D-dimer levels compared to those who were discharged from hospital after recovery (N=457, Mean rank = 264.13) (U = 16053.000, Z = -10.650, $p < 0.001$) (**Table 4)**.

3.6. Cox regression analysis: D-dimer as predictors of length of hospitalization in COVID-19 patients

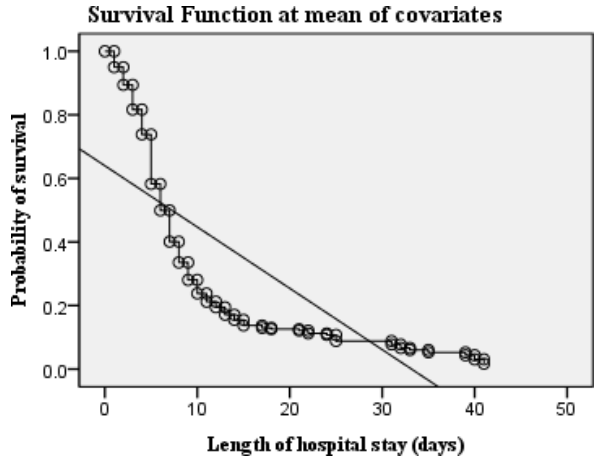
Cox regression analysis: D-dimer as predictors of length of hospitalization in COVID-19 patients

The Cox regression analysis was conducted to examine the relationship between D-dimer values and the length of hospital stay in COVID patients. Two separate analyses were performed based on the disease outcome (discharge and death).

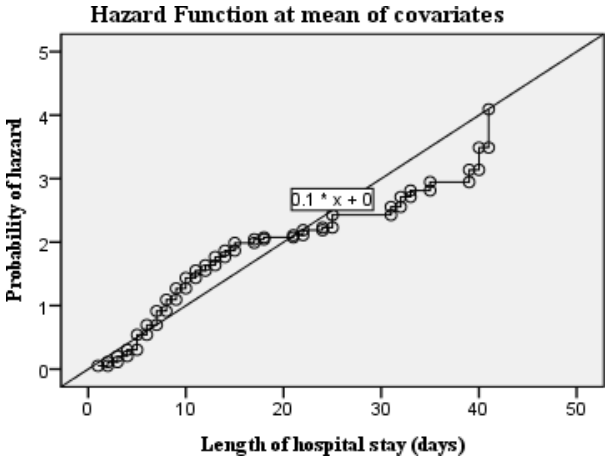
The Cox regression model indicated a significant association between D-dimer values and the length of hospital stay for patients who were discharged (Chi-square = 32.839, df = 1, $p < .001$). The hazard ratio for D-dimer was 1.000, indicating no change in the hazard of hospital stay length with a one-unit increase in D-dimer values (B = .000, SE = .000, Wald = 27.020, df = 1, $p < .001$). The covariate mean for D-dimer was 2669.102.

Similarly, for patients who experienced death, the Cox regression analysis showed a significant association between D-dimer values and the length of hospital stay (Chi-square = 62.906, df = 1, $p < .001$). The hazard ratio for D-dimer was 1.000, indicating no change in the hazard of hospital stay

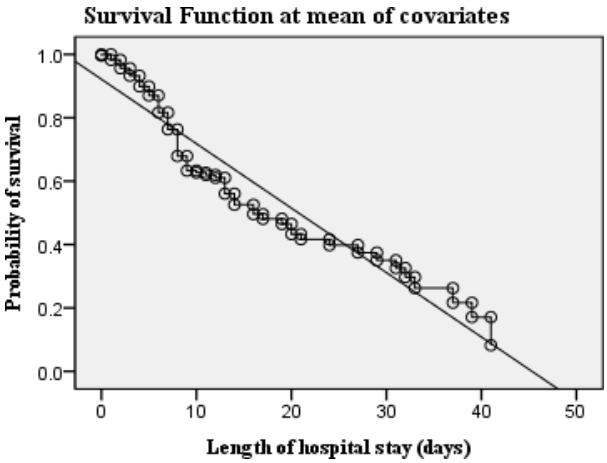
length with a one-unit increase in D-dimer values (B = .000, SE = .000, Wald = 70.554, df = 1, p < .001). The covariate mean for D-dimer was 2664.083. In both groups, the Cox regression model showed that D-dimer values were not predictive of the length of hospital stay. It should be noted that the results are based on the available data, with a proportion of censored cases for both discharged and death groups.



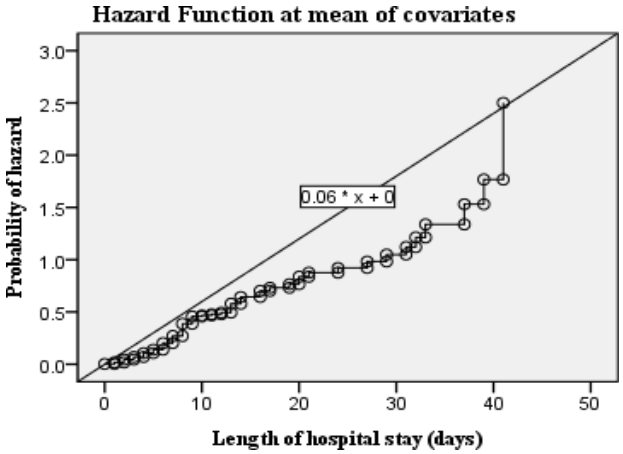
A:Probablity of survival in recovered patients



B:Probablity of hazard in recovered patients



C: Probability of survival in deceased patients



D: Probability of hazard in deceased patients

Figure 2: Cox Regression Analysis model to predict the probability of survival and hazard in recovered and deceased COVID-19 patients

3.7. Logistic Regression Analysis: D-dimer as predictors of death

The logistic regression analysis aimed to explore the potential of D-dimer as a death predictor in COVID-19 patients. At the initial stage, designated as Step 0, the model exhibited a proficient prediction accuracy of 73.9%, accompanied by a constant coefficient of -1.043. Progressing to Step 1, where the "Method = Enter" approach was employed, the model demonstrated statistical significance (Chi-square = 174.227, p < 0.001). Notably, the model's explanatory capacity was reflected by the Cox & Snell R-Square (0.246) and Nagelkerke R-Square (0.360) values. Within Step 1, the introduction of the predictor "D-dimer_day1" yielded a statistically significant impact (p < 0.001). The odds ratio of 1.027 indicated that a unit increase in "D-dimer_day1" was associated with a 2.7% rise in the odds of death occurrence. The 95% confidence interval ranged from 1.022 to 1.033. The Correlation Matrix analysis revealed a negative correlation coefficient of -0.942 between "D-dimer_day1" and the constant.

In summary, the logistic regression analysis underscored the significant predictive role of "D-dimer at day 1 of hospitalization" in forecasting COVID-19 patient mortality. Elevated values of the predictor were linked with an increased likelihood of death, thereby facilitating the identification of patients at higher risk.

4. Discussion

The presented research investigated the role of D-dimer levels in COVID-19 patients in relation to age groups, comorbidities, disease outcomes, and medical interventions. It provides compelling evidence of the multifaceted role of D-dimer levels in COVID-19 patients, reflecting its direct correlation with underlying health conditions, age, medical interventions and disease outcomes. Prior research studies have consistently affirmed the link between age, comorbidities and increased D-dimer levels [9], [11]–[13].

The observed positive correlation can be attributed to the physiological changes associated with ageing and comorbidities including increased vascular dysfunction, chronic inflammation, oxidative stress and alterations in coagulation dynamics, which collectively contribute to higher fibrin turnover and subsequent D-dimer production [11], [14]–[16]. The presence of comorbidities creates a chronic inflammatory state and endothelial dysfunction, creating an environment conducive to coagulation abnormalities. Diabetes mellitus, hypertension, asthma, ischemic heart disease, and chronic kidney diseases and tuberculosis were individually associated with elevated D-dimer levels. The low prevalence of tuberculosis limited the scope of the study, emphasizing the need for further investigation with larger subgroups. Furthermore, the prevalence of more than one comorbidity/multimorbidity further enhances the plasma D-dimer level in COVID-19 patients.

These Comorbidities and multimorbidities exhibit an exaggerated immune response, leading to a cytokine storm. This hyper inflammation can trigger endothelial dysfunction and damage, promoting the activation of coagulation pathways and subsequent D-dimer release. Underlying health conditions like hypertension, diabetes, and cardiovascular diseases can lead to endothelial dysfunction. Damaged endothelial cells are more prone to thrombosis and clot formation, resulting in the release of D-dimer fragments as fibrin clots are degraded [17]–[19].

Certain comorbidities, such as obesity and metabolic syndrome, can induce a procoagulant state characterized by increased levels of prothrombotic factors and decreased levels of anticoagulant factors. This imbalance can enhance clot formation and fibrinolysis, contributing to elevated D-dimer concentrations [20]. In addition, Comorbid conditions may interfere with the fibrinolytic system's ability to effectively break down fibrin clots. This impairment leads to the accumulation of fibrin fragments, including D-dimer, in circulation. Sometimes, small microthrombi are developed in small blood vessels. This microthrombi can contribute to the consumption of clotting factors, leading to D-dimer release as the clots are degraded [21].

Conditions like hypertension, diabetes, and cardiovascular diseases can lead to platelet activation and aggregation. Aggregated platelets can trigger the coagulation cascade, ultimately leading to D-dimer generation [22]. In addition, multi-organ involvement in COVID-19 can lead to organ dysfunction, including liver and kidney impairment. These dysfunctions can impact the clearance of clotting factors and fibrin degradation products, leading to elevated D-dimer levels [23], [24]. Chronic diseases can trigger angiogenesis and tissue remodeling, which may result in altered coagulation pathways and an increased release of D-dimer as part of the fibrinolytic process [25].

The study's outcomes emphasize the intricate relationship between D-dimer levels, underlying health conditions, age, and clinical outcomes in COVID-19 patients. The positive associations observed highlight the need for a comprehensive understanding of the interplay between systemic inflammation, coagulation dysfunction, and disease severity.

5. Conclusion

This study contributes significantly to our knowledge of the intricate coagulation abnormalities seen in COVID-19 patients, providing valuable insights into the potential mechanisms underlying the observed associations and reinforcing the importance of monitoring D-dimer levels as part of the

management strategy for these patients. Moreover, the demonstrated prognostic value of D-dimer levels emphasizes its potential as a readily available and informative biomarker for risk assessment and clinical management in the context of COVID-19.

6. Future Perspective

The study's findings suggest future research avenues to enhance our understanding of the intricate link between D-dimer levels, underlying health conditions, age, and COVID-19 outcomes. Mechanistic investigations into coagulation dysregulation, longitudinal studies tracking D-dimer dynamics, intervention trials targeting coagulation abnormalities, and the integration of D-dimer in risk prediction models are potential directions.

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Institutional Review Board Statement: The retrospective study was approved by the institutional review board of Quaid-i-Azam University, Islamabad, Pakistan.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

References

[1] A. Catalano et al., "Multimorbidity and SARS-CoV-2–Related Outcomes: Analysis of a Cohort of Italian Patients," JMIR Public Heal. Surveill., vol. 9, no. 1, p. e41404, 2023.
[2] Y. V Chudasama et al., "Patterns of multimorbidity and risk of severe SARS-CoV-2 infection: an observational study in the UK," BMC Infect. Dis., vol. 21, no. 1, pp. 1–12, 2021.
[3] F. A. Klok et al., "Incidence of thrombotic complications in critically ill ICU patients with COVID-19," Thromb. Res., vol. 191, pp. 145–147, 2020.
[4] I. Tusheva, K. Damevska, I. Dimitrovska, Z. Markovska, and L. Malinovska-Nikolovska, "Unilateral livedo reticularis in a COVID-19 patient: Case with fatal outcome," JAAD Case Reports, vol. 7, pp. 120–121, 2021.
[5] F. Rongioletti and V. Caputo, "COVID-19-Related Cutaneous Manifestations," New Emerg. Entities Dermatology Dermatopathol., pp. 287–311, 2021.
[6] S. Rashid, A. Zulfiqar, A. A. Sattar, M. Rizwan, W. Ali, and A. Ilyas, "Platelets and D-dimer as the Biomarkers for COVID-19: Platelets and D-dimers as Biomarkers for COVID-19," Pakistan Biomed. J., vol. 4, no. 2, pp. 103–106, 2021.
[7] R. Yu and M. Ferri, "An unusual cause of pulmonary nodules in the emergency department," Case Rep. Emerg. Med., vol. 2015, 2015.
[8] P. Zubiate Orzanco et al., "Fiber-based early diagnosis of venous thromboembolic disease by label-free D-dimer detection," Biosens. Bioelectron. X 2 2019 100026, 2019.
[9] F. Alzoughool, L. Alanagreh, S. Abumweis, and M. Atoum, "Cerebrovascular comorbidity, high blood levels of C-reactive protein and D-dimer are associated with disease outcomes in COVID-19 patients," Clin. Hemorheol. Microcirc., vol. 77, no. 3, pp. 311–322, 2021.
[10] H. Zhan et al., "Diagnostic value of D-dimer in COVID-19: a meta-analysis and meta-regression," Clin. Appl. Thromb., vol. 27, p. 10760296211010976, 2021.
[11] L. Zhang et al., "D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19," J. Thromb. Haemost., vol. 18, no. 6, pp. 1324–1329, 2020.
[12] X. He et al., "The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients," Sci. Rep., vol. 11, no. 1, p. 1830, 2021.
[13] H. Debi, Z. T. Itu, M. T. Amin, F. Hussain, and M. S. Hossain, "Association of serum C-reactive protein (CRP) and D-dimer concentration on the severity of COVID-19 cases with or without diabetes: a systematic review and meta-analysis," Expert Rev. Endocrinol. Metab., vol. 17, no. 1, pp. 83–93, 2022.

[14] G. Lippi, F. Mullier, and E. J. Favaloro, "D-dimer: old dogmas, new (COVID-19) tricks," Clin. Chem. Lab. Med., vol. 61, no. 5, pp. 841–850, 2023.
[15] L. Roncon, M. Zuin, and P. Zonzin, "Age-adjusted D-dimer cut-off levels to rule out venous thromboembolism in COVID-19 patients," Thromb. Res., vol. 190, p. 102, 2020.
[16] A. Alsrhani, A. Alshomar, A. Y. Elderdery, Z. Rasheed, and A. Farhana, "Diagnosis and Stratification of COVID-19 Infections Using Differential Plasma Levels of D-Dimer: A Two-Center Study from Saudi Arabia," Microbiol. Res. (Pavia)., vol. 14, no. 1, pp. 67–76, 2023.
[17] I. Hashim Ibrahim Elbashir, H. Kamal Ali Mohamed, M. E. Adam Essa, and A. Seri, "Comparison between D-dimer levels in diabetic and non-diabetic positive COVID-19 adult patients: A hospital-based study," Endocrinol. Diabetes Metab., vol. 5, no. 4, p. e349, 2022.
[18] E. Manalu, J. Josafat, and D. E. J. Luhulima, "D-Dimer Levels in Covid-19 Patients with Moderate and Severe Symptoms," Int. J. Heal. Sci. Res., vol. 13, no. 2, pp. 210–216, 2023.
[19] S. Patil, S. Khule, and S. Toshniwal, "Role of D-Dimer in assessing severity, monitoring, and predicating outcome in COVID-19 pneumonia: A single center study," Glob J Heal. Sci Res, vol. 1, pp. 31–37, 2023.
[20] O.-Z. Akácsos-Szász et al., "Pathways of Coagulopathy and Inflammatory Response in SARS-CoV-2 Infection among Type 2 Diabetic Patients," Int. J. Mol. Sci., vol. 24, no. 5, p. 4319, 2023.
[21] A. Bonaventura et al., "Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19," Nat. Rev. Immunol., vol. 21, no. 5, pp. 319–329, 2021.
[22] M. Kannan, F. Ahmad, and R. Saxena, "Platelet activation markers in evaluation of thrombotic risk factors in various clinical settings," Blood Rev., vol. 37, p. 100583, 2019.
[23] S. Vinayagam and K. Sattu, "SARS-CoV-2 and coagulation disorders in different organs," Life Sci., vol. 260, p. 118431, 2020.
[24] W. Zhao, H. Li, J. Li, B. Xu, and J. Xu, "The mechanism of multiple organ dysfunction syndrome in patients with COVID-19," J. Med. Virol., vol. 94, no. 5, pp. 1886–1892, 2022.
[25] H. Lu et al., "Fibrinolysis regulation: A promising approach to promote osteogenesis," Tissue Eng. Part B Rev., vol. 28, no. 6, pp. 1192–1208, 2022.