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ORIGINAL ARTICLE

EVALUATION OF D-DIMER LEVEL AS A BIOMARKER OF DISEASE SEVERITY AND MORTALITY IN PATIENTS WITH COVID-19

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Tetiana R. Kolotylo, Vasyl D. Moskaliuk, Borys V. Syrota, Iryna V. Balaniuk, Svitlana R. Melenko, Natalia V. Chernetska, Yuliia I. Boiko
BUKOVINIAN STATE MEDICAL UNIVERSITY, CHERNIVTSI, UKRAINE

ABSTRACT

The aim: To examine risk factors and evaluate the use of D-dimer as a biomarker of disease severity and mortality in patients with COVID-19.

Materials and methods: Data from a large NYU Langone Health system were analyzed to examine the prevalence of elevated D-dimer levels at first detection and the trend. A retrospective cohort study of 2,377 patients (NYU Langone Health) with severe COVID-19. Also we conducted a retrospective study based on the mortality database of 247 patients from COVID-19 at the Chernivtsi Regional Clinical Hospital.

Results: Patients with elevated baseline D-dimer were more likely to have critical illness than patients with normal D-dimer (43.9% vs. 18.5%). The frequency of adverse events increased with increasing D-dimer levels. Individuals with D-dimer >2000 ng/mL had the highest risk of critical illness (66.0%).

Conclusions: Thus, the level of D-dimer can be considered an important prognostic factor in COVID-19, as its level is elevated in the vast majority of patients with COVID-19 and correlates with a severe course and high mortality.

KEY WORDS: thrombosis, D-dimer, thromboembolism, coagulopathy, COVID-19

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INTRODUCTION

Numerous studies have shown that D-dimer is a valuable marker of coagulation activation and fibrinolysis. Normally, small amounts of D-dimer are detected in a healthy person due to the fact that approximately 2-3% of normally produced fibrinogen undergoes a continuous physiological cycle of fibrin formation and dissolution [1].

However, doctors in China, where the epidemic began, first reported that the level of D-dimer can be increased during COVID-19. A study of 191 patients with COVID-19 who were hospitalized in Wuhan in January 2020 at the start of the pandemic found that D-dimer levels were elevated in many of these patients, and the magnitude of the increase was greatest in those who died of the disease. A number of subsequent studies conducted around the world confirmed that D-dimer levels are elevated in those with severe COVID-19 and correlated with mortality rates [2].

In hospitalized patients with COVID-19, blood coagulation disorders, in particular, an increase in the level of D-dimer, fibrinogen, and an increase in prothrombin time are increasingly being detected [3].

Among adults admitted to the emergency department, the most common causes of elevated D-dimer levels are VTE (venous thromboembolism) and PE (pulmonary embolism). Previous studies in patients with community-acquired pneumonia (ACP) and chronic obstructive pulmonary disease (COPD) have shown that D-dimer levels are higher in severe cases and can be used as a prognostic biomarker [4].

However, the significance of D-dimer in patients with COVID-19 has not been fully investigated. We analyzed D-dimer levels in patient groups stratified by clinical severity, complications, and in-hospital death, and assessed the role of D-dimer as a biomarker of disease severity and clinical course.

THE AIM

The aim of the work is to examine risk factors and evaluate the use of D-dimer as a biomarker of disease severity and mortality in patients with COVID-19.

MATERIALS AND METHODS

We analyzed data from a large health care system at NYU Langone Health to examine the prevalence of elevated D-dimer levels at first detection and at baseline,

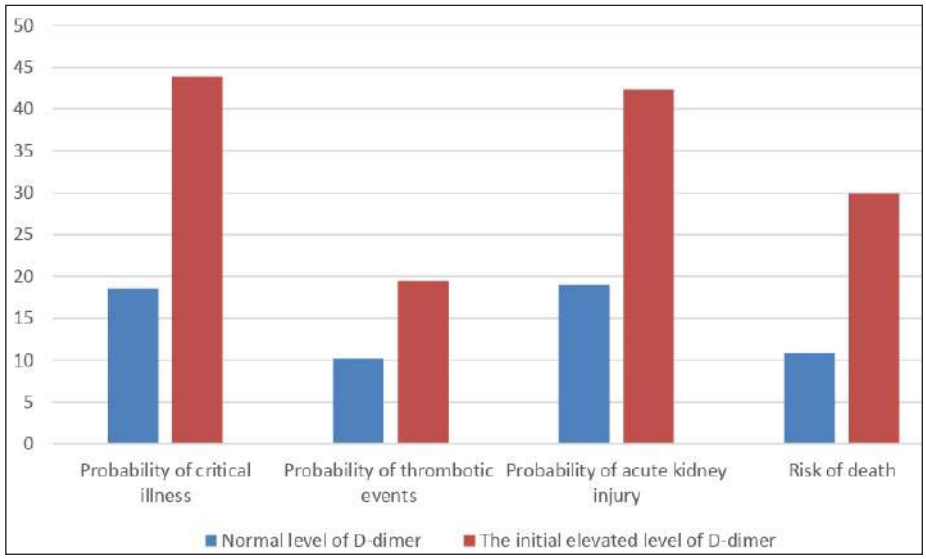

Fig. 1. The probability of developing serious conditions depending on the level of D-dimer

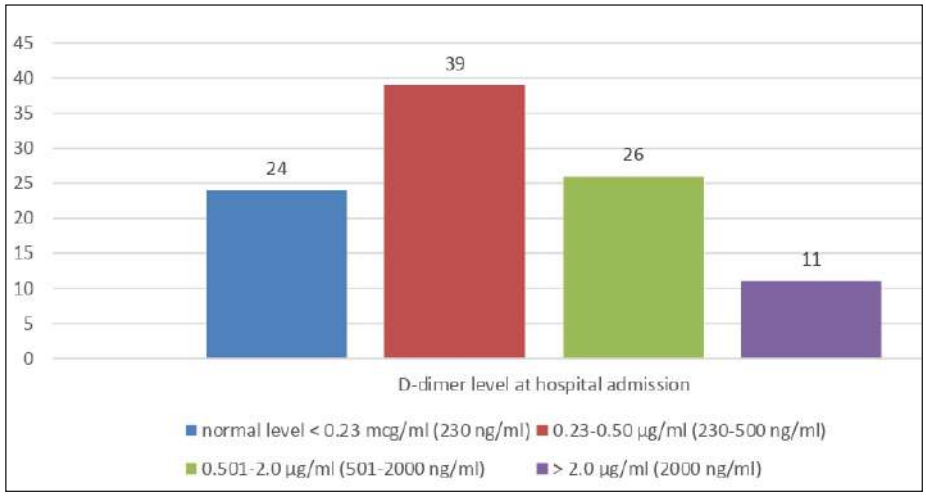

Fig. 2. The level of D-dimer at admission of patients to the hospital

and the association of the biomarker with thrombotic events, acute kidney injury, critical illness, and all-cause mortality. In a retrospective cohort study of 2,377 patients (NYU Langone Health) with severe COVID-19, 1,823 (76.0%) had elevated D-dimer above the laboratory upper limit of normal at hospital admission, 2,049 (86%) – an increase in the level of D-dimer during the period of hospitalization.

Also we conducted a retrospective study based on the mortality database of 247 patients from COVID-19 at the Chernivtsi Regional Clinical Hospital

RESULTS

In our analysis of clinical cases of patients with a diagnosis of COVID-19, elevation of D-dimer during hospitalization became a common phenomenon and was associated with both increased disease severity and in-hospital mortality. D-dimer can be synthesized only when the formation and degradation of cross-linked fibrin occurs, which is a global marker of activation of coagulation and fibrinolysis, and therefore reflects enhanced thrombotic activity [5]. Coagulation disorders such as hypercoagulability, thrombocytopenia, venous thrombosis, and disseminated intravascular coagulation (DIC) occur in approximately 60-70% of hospitalized patients. Autopsies showed that in nearly 58% of patients, the cause of death was pulmonary embolism or venous thrombosis, while CVD was reported in 70% of patients who died of COVID-19.

Numerous studies have also demonstrated an association between a trend in D-dimer levels and disease progression in COVID-19. Initial studies equated elevated D-dimer levels with CVD, but scientific studies have shown that coagulopathy associated with COVID-19 is a unique form. Innate immune response and endothelial damage contribute to coagulopathy associated with COVID-19. There is increasing evidence for an inflammatory component of coagulopathy associated with COVID-19, with one study even showing that an elevated white blood cell count during hospitalization is an independent predictor of VTE. Proposed contributing factors include endothelial damage, cytokine storm, complement activation, especially the alterna-

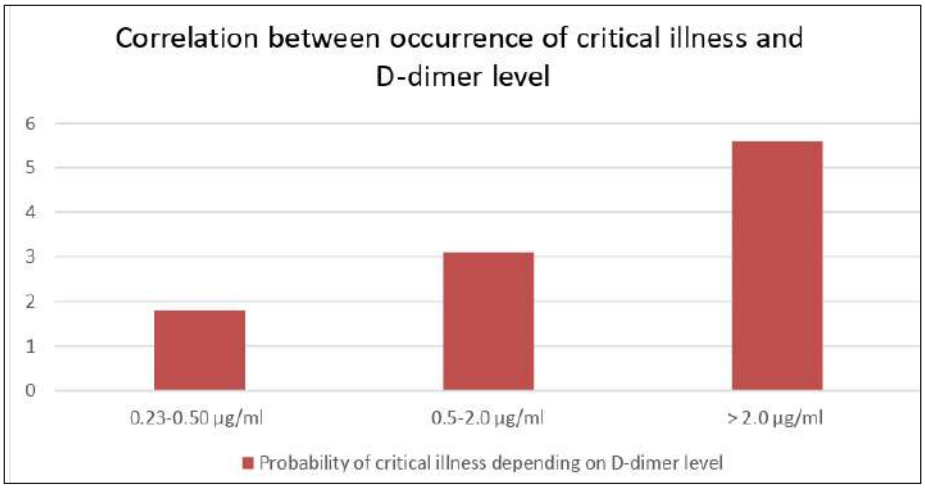

Fig. 3. The probability of a critical illness depending on the level of D-dimer

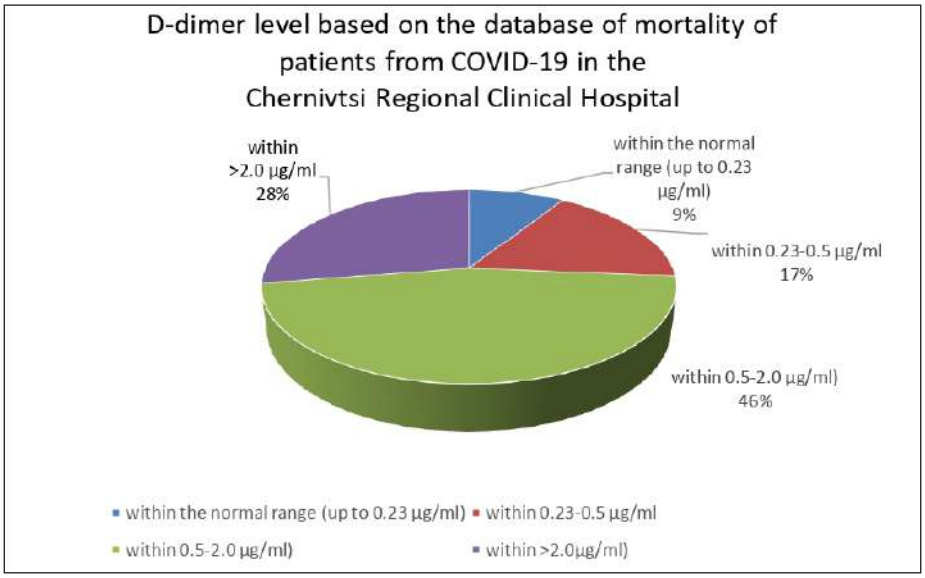

Fig. 4. D-dimer level in patients with COVID-19

tive pathway, which induces a hypercoagulable state and the formation of neutrophil extracellular traps [6].

It is currently known that acute lung injury in COVID-19 is associated with an increased frequency of thromboembolic events, which is a consequence of an imbalance between procoagulation factors and natural inhibitors of blood coagulation, cessation of fibrinolysis, endothelial damage, and the inflammatory process. It has been established that PE can be detected in 20-30% of patients with an acute course of COVID-19 [7].

D-dimer testing during hospitalization is routinely used in patients with COVID-19 in the healthcare system. The upper limit of normal for D-dimer analysis is 0.23 µg/ml (230 ng/ml). Currently, it is known that D-dimer can be not only a marker of hypercoagulation and prothrombotic state, but also participate in the pathogenesis of the disease. Fibrin breakdown products cause acute pulmonary dysfunction and have a direct procoagulant effect [8].

The D-dimer level is positively correlated with disease severity and inversely proportional to survival. Some case series report D-dimer values > 3 mg/L in 85% of patients who died after COVID-19, others D-dimer values > 1 mg/L in 81% of patients who died after COVID-19, and only 24% of surviving patients had a D-dimer level > 1 mg/l.

In early retrospective cohort studies of patients with COVID-19 in Wuhan, China, abnormalities in coagulation parameters including elevated D-dimer and prothrombin time were found. These coagulation changes were predictive of high mortality, with 15 of 22 (71.4%) failing International Society of Thrombosis and Haemostasis (ISTH) criteria for disseminated intravascular coagulation (DVT) compared with only 1 of 162 (0.6), which were confirmed in an early study [8]. By March 2020, the ISTH published an algorithm for the recognition and treatment of "Coagulopathy in COVID-19". Markers of coagulation disorders in COVID-19 currently being investigated include D-dimer levels, platelet count, von Willebrand factor (VWF), factor VIII, thromboelastography (TEG), lupus anticoagulant (LAC), antiphospholipid antibodies (APL), and fibrinogen [9].

In addition to abnormalities in laboratory markers of coagulation, COVID-19 infection has been associated with both venous and arterial thrombosis. Autopsy studies of patients with COVID-19 have shown both macro- and microvascular thrombosis. The SARS-Cov2 virus uses angiotensin-converting enzyme-2 (ACE-2) as its main receptor; this membrane protein is expressed in blood vessels, lungs, heart, kidney, and many other tissues. It has been hypothesized that the binding of SARS-CoV-2 to ACE-2 leads to a local and systemic inflammatory response, endothelial damage, and an imbalance of pro- and anticoagulant signals, leading to macro- and microvascular thrombosis [9].

During SARS-COV-2 infection, dysregulation of coagulation/anticoagulation cascades, increased viral replication and immune mechanism can be explained by an abnormal blood coagulation system, which includes both cellular and protein components. Considering the endothelial aggression and prothrombotic mechanisms caused by SARS-CoV-2, as well as the statistical results of the studies, we can say that the increased value of D-dimers can be prognostic for abnormal functional parameters of the liver and the severe course of the disease.

Presumably, elevated D-dimer represents a state of hyperfibrinolysis and increased inflammatory burden caused by SARS-COV-2 infection. In our logistic regression model to assess risk factors associated with mortality, systemic anticoagulation was not examined in detail. However, in a recent study that included 2,773 hospitalized patients with COVID-19, experts found that taking a therapeutic dose of anticoagulants was associated with a reduced risk of death, especially among patients who required mechanical ventilation.

The pathophysiology of coagulopathy associated with COVID-19 is an important factor in the appropriate treatment and monitoring of these complications. Experts emphasize the importance of diagnosis and treatment of coagulation disorders in COVID-19 to improve the outcomes of treatment of patients with COVID-19 with thromboembolic complications. Prolonged elevation of D-dimer may predict persistent ventilation-perfusion mismatch due to macro- and/or microthrombi and persistent inflammatory lung injury. Thus, elevated D-dimer levels may not only be a consequence of COVID-19, but also an associated comorbidity [10].

The results of patients at the time of hospitalization with an elevated D-dimer level were correlated with the following conditions: 45.0% of patients were in critical condition, 20.0% – with thrombosis, and 43.0% – with acute kidney injury. Individuals without elevated D-dimer at presentation were more likely to be discharged without developing severe conditions. Patients with elevated baseline D-dimer were more likely than patients with normal D-dimer to have critical illness (43.9% vs. 18.5%), any thrombotic event (19.4% vs. 10.2%); acute kidney injury (42.4% vs. 19.0%) and death (29.9% vs. 10.8%) (Figure 1).

It is currently known that the frequency of adverse events increased with increasing D-dimer levels. Individuals with D-dimer >2000 ng/mL had the highest risk of critical illness (66.0%), thrombosis (37.8%), acute kidney injury (58.3%), and death (47.0%). D-dimer was 387 (25-75th percentile), and 1823 (76.0%) patients had elevated D-dimer (>230 ng/ml). Median peak D-dimer was 767 (25th–75th percentile), and 2049 (86.0%) had elevated D-dimer >230 ng/mL at some point during hospitalization. Compared with patients with normal baseline D-dimer, patients with elevated baseline D-dimer were older (mean age 65) and had a lower body mass index (28.8). Among patients with elevated D-dimer, comorbidities were more common, including hypertension (63.5%), hyperlipidemia (44.2%), coronary heart disease (23.4%), and chronic kidney disease (23.0%) [8]. According to the results of studies, at admission, 1823 (76.0%) patients had elevated D-dimer (> 0.23 μg/ml (230 ng/ml)); 932 (39.0%) – in the range of 0.23-0.50 μg/ml (230-500 ng/ml), 628 (26.0%) – 0.501-2.0 μg/ml (501-2000 ng /ml), and 263 (11.0%) – > 2.0 μg/ml (2000 ng/ml) (Figure 2).

Of the total studied population, 899 (37.8%) patients had a critical illness (admitted to the intensive care unit), 620 (26.1%) needed mechanical ventilation, 410 (17.2%) had thrombotic events (DVT, PE, heart attack myocardial, ischemic stroke)) and 871 (36.8%) had acute kidney injury (AKI). Considering all these serious adverse clinical outcomes of COVID-19, patients with elevated D-dimer (> 0.23 μg/mL (230 ng/mL)) at the time of hospitalization were more likely to be affected than those with normal D-dimer (< 0.23 μg/ml (230 ng/ml)). For example, 43.9% of patients with elevated D-dimer at hospitalization compared with 18.5% of patients with normal D-dimer at hospitalization developed critical illness. Similarly, patients with elevated D-dimer on admission were more likely to require mechanical ventilation compared to patients with normal D-dimer levels (29.9% vs. 13.9%), and were more likely to suffer from APN (42.4% vs. 19.0%) and from thrombosis (19.4% versus 10.2). %).

It was found that the magnitude of the D-dimer increase upon admission to the hospital is independently associated with the risk of serious clinical consequences. After controlling for age, sex, ethnicity, defined list of comorbidities, and prescribed treatment, critical illness was 1.8 times higher if D-dimer was in the range of 0.23-0.50 μg/ml (230- 500 ng/ml) than normal (< 0.23

μg/ml (230 ng/ml)), 3.1 times more likely if D-dimer was in the range of 0.5-2.0 μg/ml (500-2000 ng/ml) and 5.6 times more likely if D-dimer at admission was > 2.0 μg/ml (2000 ng/ml) (Figure 3).

In addition, we conducted a retrospective study based on the database of mortality of patients from COVID-19 in the Chernivtsi Regional Clinical Hospital. It was established that the elevated level of D-dimer was noted in 225 out of 247 patients with coronavirus disease, which is 91.0%. It was found that in all patients the level of D-dimer varied in the range: within the normal range (< 0.23 μg/ml (230 ng/ml)) – in 22 people (8.9%); 0.23-0.50 μg/ml (230-500 ng/ml) – in 43 people (17.4%); in the range of 0.5-2.0 μg/ml (500-2000 ng/ml) – in 114 people (46.2%); and more than 2.0 μg/ml (2000 ng/ml) in 68 people (27.5%) (Figure 4).

Thus, the results of D-dimer studies should be used as a biomarker to assess clinical outcomes in patients with COVID-19. It is worth noting that the obtained data indicate a connection between the levels of D-dimer and the severity of the disease and mortality, which is also confirmed by the data of other scientists.

DISCUSSION

When assessing the trajectory of D-dimer elevation during COVID-19, it was found that D-dimer levels continued to rise after hospitalization, reaching a maximum level around day 5 before gradually plateauing at a level below the peak but greater than, than the level at hospitalization. Median D-dimer for the entire study population at admission was 0.387 mcg/mL (387 ng/mL) (25th-75th percentile range: 0.237-0.713 mcg/mL (237-713 ng/mL)) compared with a median peak of 0.767 μg/mL (767 ng/mL) (25th-75th percentile: 0.328-3.372 μg/mL (328-3372 ng/mL)) after approximately 5 days. The results of the study demonstrate that the magnitude of the peak D-dimer level, as well as the magnitude of the D-dimer level at hospitalization, correlates with the risk of an adverse clinical course. It was found that of the total study population, 301 (12.7%) patients had a peak D-dimer level > 10.0 μg/ml (10,000 ng/ml). This group of patients with the highest peak D-dimer levels had the highest incidence of serious clinical outcomes during hospitalization: 86.0% had critical illness requiring admission to the intensive care unit; 71.0% required mechanical ventilation; 81.0% – had GPN; and 39.0% had a thrombotic event.

In addition to the association between D-dimer levels and adverse clinical outcomes, we also examined the relationship between D-dimer levels at admission and the final outcome for patients with COVID-19: death or recovery.

The data we received also confirm the research of other scientists. A retrospective study by W.J. Guan et al. (2020) (n=1099) established a relationship between the severity of the course of COVID-19 and a high level of D-dimer. The level of D-dimer ≥0.5 mg/l was noted in 46.4% of patients, and 60% of them developed severe manifestations of the disease [11]. Another retrospective study (n=183) found that the level of D-dimer in patients with a severe course of the disease is almost 3.5 times higher than in patients with a mild or moderate course [12]. In addition, it is noted that D-dimer is a marker of fibrin deposition in the lungs. The experience of Spanish doctors established that patients with high levels of D-dimer and C-reactive protein more often required hospitalization and transfer to artificial lung ventilation [13].

CONCLUSIONS

D-dimer level is an important tool for early triage and monitoring of patients with COVID-19, a prognostic marker of severe course and death due to SARS-CoV-2 coronavirus disease. D-dimer levels were independently associated with a higher risk of critical illness, thrombosis, acute kidney injury, and all-cause mortality among patients with COVID-19.

Thus, the level of D-dimer can be considered an important prognostic factor in COVID-19, which correlates with a severe course and high mortality.

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ORCID and contributionship:
Tetiana R. Kolotylo: 0000-0002-0821-7904 [B,D-F]
Vasyl D. Moskaliuk: 0000-0002-4104-8153 [A,B,D-F]
Borys V. Syrota: 0000-0002-2654-5602 [A,B,D]
Iryna V. Balaniuk: 0000-0003-1146-4065 [B-D]
Svitlana R. Melenko: 0000-0003-4920-5843 [C,D]
Natalia V. Chernetska: 0000-0002-5156-1313 [B,D]
Yuliia I. Boiko: 0000-0001-6542-6844 [B-D]

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The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Tetiana R. Kolotylo
Bukovinian State Medical University
2 Teatralna Square, 58002 Chernivtsi, Ukraine
tel: +380664669273
e-mail: taniakolotylo15@gmail.com

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