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PROGNOSTIC VALUE OF D-DIMERS IN PATIENTS WITH COVID-19: NARRATIVE SYNTHESIS

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Keywords: *COVID-19, SARS-CoV-2, D-dimers, venous thromboembolism, biomarkers.*

Introduction. *Contemporary researchers have suggested and demonstrated the hypothesis that the elevated level of D-dimers, which is a valuable marker of coagulation and fibrinolysis activation, can predict the severity of COVID-19, pulmonary complications, and thromboembolic events before they occur.* ***Material and methods.*** *The bibliographic resources were analyzed and selected from databases such as PubMed, Hinari, SpringerLink, and Google Search using keywords such as "COVID-19," "SARS-CoV-2," "coronavirus," "D-dimers," "biomarkers," and "severity prediction," which were used in various combinations to maximize search efficiency. Therefore, the manuscript contains 51 representative articles for the purpose of this synthesis article.* ***Results.*** *The D-dimer levels are significantly higher in patients with severe forms of COVID-19 compared to those with non-severe forms, in patients with acute respiratory distress syndrome compared to those without acute respiratory distress syndrome, and in deceased patients compared to those who have survived. D-dimers positively correlate with the degree of severity and the increased risk of progression to severe disease, inversely proportional to the survival rate. They can predict prognosis, determine therapeutic strategies, prevent complications, positively influence the disease's course, and monitor the prognosis.* ***Conclusions.*** *D-dimers should be used as a pre-radiographic screening tool as early as possible after admission and as an indicator for risk stratification of venous thromboembolism in hospitalized patients with COVID-19. Based on the increase in D-dimer levels, adjusting therapeutic doses of anticoagulants is more beneficial for patients compared to administering prophylactic doses.*

Cuvinte-cheie: *COVID-19, SARS-CoV-2, D-dimeri, tromboembolism venos, biomarkeri.*

VALOAREA PROGNOSTICĂ A D-DIMERILOR LA PACIENȚII CU COVID-19: SINTEZĂ NARATIVĂ

Introducere. *Cercetătorii contemporani au sugerat și demonstrat ipoteza că nivelul crescut al D-dimerilor, care este un marker valoros de activare a coagulării și fibrinolizei, pot prezice severitatea bolii COVID-19, complicațiile pulmonare și evenimentele tromboembolice înainte ca acestea să survină.* ***Material și metode.*** *Resursele bibliografice au fost analizate și selectate din bazele de date PubMed, Hinari, SpringerLink și Google Search după cuvintele-cheie: „COVID-19", „SARS-CoV-2", „coronavirus", „D-dimeri", „biomarkeri", „predicția severității", care au fost folosite în diferite combinații pentru a maximiza randamentul căutării. Astfel, cuprinsul manuscrisului include 51 de articole reprezentative pentru scopul acestui articol de sinteză.* ***Rezultate.*** *Valoarea D-dimerilor este semnificativ mai mare la pacienții cu forme severe de COVID-19, comparativ cu cei cu forme non-severe, la pacienții cu sindrom de detresă respiratorie acută, comparativ cu cei fără sindrom de detresă respiratorie acută, la pacienții decedați, comparativ cu cei care au supraviețuit. D-dimerii corelează pozitiv cu gradul de severitate și riscul crescut de progresare la forma severă a maladiei, invers proporțional cu rata de supraviețuire, pot prezice prognosticul, determinarea strategiilor terapeutice, prevenirea complicațiilor, influențarea pozitivă a evoluției maladiei și supravegherea prognosticului.* ***Concluzii.*** *D-dimerii trebuie utilizați ca instrument de screening pre-radiografic cât mai precoce după internare și ca indicator de stratificare a riscului de tromboembolism venos pentru pacienții internați cu COVID-19. În baza creșterii D-dimerilor, ajustarea dozelor terapeutice de anticoagulante este mai benefică pentru pacienți, comparativ cu administrarea dozelor profilactice.*

INTRODUCTION

Since December 2019, a new coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been declared responsible for triggering the epidemic of coronavirus disease 2019 (COVID-19), which rapidly spread worldwide. Consequently, on March 11, 2020, the World Health Organization declared a global public health emergency – a state of pandemic (1, 2, 3). The clinical presentation of COVID-19 varies from asymptomatic and mild forms to severe and critical cases that progress rapidly, causing serious and fatal complications requiring admission to the intensive care unit (ICU) (1, 3, 4-9). The overall mortality rates for patients with COVID-19 range from 1.5% to 9.8% (10, 11), while mortality rates for patients admitted to the ICU range from 26% to 61.5% (4, 6, 9, 12).

One of the strategic elements that need to be undertaken in defining the management of treatment for patients with COVID-19 is the early identification of factors that may progress to more severe forms of the disease and those that require specific interventions or treatments (13). Based on the pathophysiology of severe COVID-19, which involves a hyperinflammatory state, a cascade of hypercoagulation, and multiorgan dysfunction, several biomarkers that represent each of these conditions could be useful as key predictive values for COVID-19. In this context, defining early and efficient predictors for patient outcome prognosis holds substantial clinical significance for risk stratification, severity prediction, management of patients with COVID-19, and prevention of serious complications. In emergency situations, risk stratification is as important as diagnosis, especially if testing all patients suspected of having COVID-19 is not possible (1, 8, 10, 14-20).

COVID-19 causes serious thromboembolic complications in patients with severe forms of the disease (7, 21). COVID-19-related mortality is largely associated with hypercoagulability and an increased risk of venous thromboembolism (VTE), leading to thrombo-inflammation in severe cases. Therefore, coagulation biomarkers can indicate disease severity, mortality, and contribute to patient triage, therapeutic strategies, and close monitoring of prognosis (5, 8, 21-27).

Excessive inflammation, platelet activation, endothelial dysfunction, and stasis play a significant role in the development of thrombotic complications (10, 17). Coagulation abnormalities such as hypercoagulability, thrombocytopenia, venous thrombosis, and disseminated intravascular coagulation have been observed in approximately 60-70% of hospitalized patients with COVID-19. Autopsies have shown that pulmonary embolism or venous thrombosis was the cause of death in about 58% of patients, while disseminated intravascular coagulation was reported in 70% of patients (28).

Researchers have suggested that the increased level of D-dimers (DD), which is a valuable marker of coagulation and fibrinolysis activation, can predict disease severity, pulmonary complications, and thromboembolic events before they occur (29-32). DD are degradation products of reticulated fibrin, a substance that is part of fibrin clots. Its presence itself implies venous thromboembolism (pulmonary embolism and deep vein thrombosis). DD are a marker of active coagulation, fibrinolytic events, and thrombotic activity, with elevated values in patients with vascular thrombosis caused by severe trauma, inflammatory and infectious conditions, pregnancy, inflammation, cancer, etc. Several studies have highlighted the correlation between elevated DD levels, especially their gradual increase during the course of the disease, with the severity and adverse outcomes of COVID-19. DD levels correlate with the severity of COVID-19, thrombotic activity, and mortality rates in these patients (2, 3, 16, 22, 27, 29, 31, 32, 33). The DD level significantly increases concomitantly with the increasing severity of clinical manifestations and with the findings of computed tomography investigations of COVID-19 (19, 32, 34).

Thus, elevated levels of D-dimers reflect significant activation of the coagulation cascade, which, in turn, can trigger acute coronary syndrome and pulmonary embolism with its full spectrum of clinical manifestations (1). However, the prognostic value of D-dimers, determined upon admission, in predicting disease severity, mortality, and thromboembolic events in COVID-19, has not been fully elucidated due to small cohorts and heterogeneity among studies (14, 17, 22, 27, 30, 35, 36).

In the context of the aforementioned points and considering that the clinical and laboratory characteristics associated with SARS-CoV-2 infection

are not fully elucidated (37), the *aim* of this narrative synthesis is to summarize the analysis and clinical significance of elevated D-dimer levels, their prognostic role, and their association with severity, adverse outcomes, thromboembolic events, and mortality in patients with COVID-19.

MATERIAL AND METHODS

The bibliographic resources were analyzed and selected from databases such as *PubMed, Hinari, SpringerLink*, and *Google Search* using keywords: "COVID-19," "SARS-CoV-2," "coronavirus," "D-dimers," "biomarkers," and "severity prediction"; which were used in various combinations to maximize search efficiency.

For targeted selection of bibliographic sources, the following filters were applied: full-text articles, articles in the English language, articles published between 2020-2022. After processing the identified information and according to the search criteria, 386 full-text articles were selected. After excluding records unrelated to the study's aim and reviewing the abstracts and full texts of the articles, 45 eligible original papers with different study designs, including editorials, narrative and systematic review articles, meta-analyses, case-control studies, and cohort studies, containing information about D-dimers in patients with COVID-19, were considered potentially relevant for the given synthesis.

According to the proposed aim and after careful evaluation and analysis of these sources, a total of 51 relevant publications were ultimately selected and included in the final bibliography of this manuscript. These publications were deemed representative of the materials published on the subject of this synthesis article.

The information from the publications included in the bibliography was gathered, classified, evaluated, and synthesized, highlighting the main aspects of the contemporary view regarding the role of D-dimers in patients with COVID-19, the correlation and prediction of clinical outcomes, severity, and prognosis of SARS-CoV-2 infection.

A primary objective was to minimize the risk of systematic errors (bias) in the study by conducting thorough searches in databases to identify a maximum number of relevant publications for the study's purpose. We evaluated only those studies that met valid criteria and applied strict exclusion criteria for article selection. We assessed both studies reporting optimistic data and research that did not highlight the benefit of D-dimer determinations in patients with COVID-19.

According to the requirements, additional sources of information were accessed to clarify specific and sophisticated concepts. Similar research, articles that did not align with the purpose of the study and were not available for full viewing, review articles, comments, and letters, case reports or case series, articles with insufficient information, articles lacking data on D-dimer concentrations, non-human studies, and studies on pediatric populations (<17 years) were excluded from the bibliography.

RESULTS

Coagulation dysfunction in patients with COVID-19 leads to the progression to severe form of the disease and fatal outcomes, and it is characterized by increased D-dimer levels and thromboembolic events (5, 22, 23). Several studies have assessed the association between initial D-dimer values and the severity or outcomes in patients with COVID-19.

A systematic review, conducted on 54 studies involving 1,022 COVID-19 patients, and two retrospective studies, including 343 and 182 patients respectively, with 13 and 34 in-hospital death cases, found a significantly higher mean D-dimer value at admission ($p<0.001$) in deceased patients (3.208-3.78 μg/mL) compared to survivors (0.79-1.067 μg/mL) (14, 32, 38). The authors calculated the optimal cutoff value determined at admission to predict in-hospital mortality – 1.5 μg/mL, with a sensitivity of 70.6% and specificity of 78.4%, and 2.0 μg/mL, with a sensitivity of 92.3% and specificity of 83.3% (14, 38).

A case-control study conducted on 248 COVID-19 patients found a significantly higher level of D-dimer in non-survivors compared to survivors (6.21 mg/L and 1.02 mg/L, $p<0.05$). D-dimer level >2.0 mg/L at admission was the only variable associated with increased odds of mortality (OR 10.17; $p<0.05$). D-dimer elevation (≥0.5 mg/L) was observed in 74.6% of patients. D-dimer level >2.14 mg/L predicted in-hospital mortality with a sensitivity of 88.2% and specificity of 71.3% (34).

A retrospective study of a cohort of 483 COVID-19 patients found that D-dimer elevation

(≥0.5 mg/mL) was observed in 80.1% of hospitalized patients and in 96% of cases that resulted in death. D-dimer level ≥2.01 mg/mL, with a sensitivity of 73.3% and specificity of 70.0%, was a significant predictor of subsequent mortality (HR 3.165; p<0.01). The median value of D-dimer among non-survivors was 6.34 mg/mL, while among survivors it was 0.94 mg/mL. Thus, a D-dimer value ≥2.01 mg/mL can effectively predict in-hospital mortality in patients with COVID-19 (39), and monitoring D-dimer during hospitalization is a better predictor of disease progression, severity, and mortality compared to D-dimer levels at admission (5, 39).

Numerous retrospective, prospective, cohort, and case-control studies, systematic reviews, and meta-analyses have reported an increased D-dimer level in a significant positive relationship with disease severity, composite outcome (including death, severe disease, ICU admission, and mechanical ventilation), VTE incidence, and mortality in patients with COVID-19 (1, 12, 15, 16, 21, 22, 24, 25, 26, 31, 34, 35, 40, 41). Elevated D-dimer levels within the first week of hospitalization in patients with COVID-19 have been associated with increased mortality and VTE incidence (20, 36, 40). The time for VTE screening in a patient is when the D-dimer level is three times higher than the upper limit of normal (0.5 μg/mL). In COVID-19 patients, a four-fold increase in the D-dimer level is a good predictor of mortality (32).

Uncontrolled inflammation combined with hypoxia and the direct cytotoxic effects of the virus on endothelial cells contribute to thromboembolic complications (12, 38, 42). Coagulation abnormalities are common in all severe infections and inflammations, but they occur more frequently and with a clinically severe prognosis in patients infected with SARS-CoV-2 (23).

SARS-CoV-2 typically induces a significant thrombo-inflammatory response in severe forms of COVID-19 with progressive diffuse pulmonary involvement (33). The most commonly cited reason in the literature for the increase in D-dimer levels includes viremia and the cytokine storm syndrome, with a significant rise in proinflammatory cytokines and inadequate control of anti-inflammatory factors, which dysregulate the coagulation cascade (38).

Mortality related to COVID-19, a prothrombotic condition, is largely associated with hypercoagulability and an increased risk of VTE, leading to thromboinflammation in severe cases (22, 23). For instance, according to data from a recent meta-analysis, the incidence of pulmonary embolism was estimated at 8% in the general population of patients with COVID-19 and at 17% in ICU-admitted patients (23). Coagulopathy occurs in 50% of patients who die from COVID-19 (42).

Therefore, coagulation biomarkers, including D-dimers, are positively associated with the severity of the disease and inversely proportional to survival. They can predict the prognosis and outcome of patients with COVID-19, including mortality. They contribute to patient triage, determination of therapeutic strategies, prevention of complications, positively influencing disease progression, and monitoring of prognosis (1, 2, 3, 22, 23, 28, 31, 34, 38).

D-dimer levels are higher in hospitalized patients with COVID-19 (36-43%) (8, 29). DD measured at admission serves as an accurate biomarker for predicting mortality in patients with COVID-19, with a specific normal value <0.5 μg/mL (21, 27, 34, 38, 43). DD level >1 μg/mL is considered a risk factor for mortality in hospitalized adult patients with COVID-19 (34). According to the results of multiple studies, a DD value at admission ≥2.38 μg/mL was associated with increased chances of mortality. Each 1 μg/mL increase in DD level at admission was associated with a 6% increase in the risk of all-cause mortality, an 8% increase in the risk of assisted ventilation, and an 8% increase in the risk of thromboembolism (44).

Therefore, elevated D-dimer levels at admission in patients with SARS-CoV-2 infection have been associated with an increased risk of escalation to severe form of the disease and death (2, 23, 28, 31, 38).

A systematic review and meta-analysis conducted on 12 studies involving 2,794 patients with COVID-19, including 596 (21.3%) patients with severe form and 2,198 (78.7%) patients with non-severe form of the disease, revealed that elevated D-dimer levels and low platelet count were more common in patients with severe condition (30). Increased DD level (OR: 5.67) and thrombocytopenia (OR: 3.61) predicted severe infection, enabling early identification and management of patients with negative outcomes. The elevated DD level and low platelet count may suggest the activation of systemic coagulation with secondary fi-

brinolysis and platelet consumption. This finding confirms the prothrombotic phenotype of SARS-CoV-2 infection, which is associated with disease severity (16, 30, 45).

The evaluation of three systematic reviews and meta-analyses conducted on 12-23 studies with a variable number of patients with COVID-19 included (7-4848) determined a significantly higher DD level in patients with COVID-19 compared to healthy individuals (2, 12, 34), in patients with severe forms of COVID-19 compared to those with non-severe forms (2, 6, 12, 18, 34), in patients with acute respiratory distress syndrome (ARDS) compared to those without ARDS, and in deceased ARDS patients compared to those who survived ($p<0.001$). Patients with COVID-19 treated with anticoagulants, due to the reversal of the procoagulant pattern, had lower mortality compared to untreated patients ($p<0.05$) (2, 12, 13, 34).

Six large-scale systematic reviews and meta-analyses, conducted on 6-75 studies with 1,329-17,052 hospitalized patients with COVID-19, revealed that an increase in DD level was associated with a 2-3 times higher risk of poor composite outcome (including mortality, severe COVID-19, ARDS, ICU admission, and mechanical ventilation), a 2-fold higher risk of developing severe COVID-19, and a 4-fold higher risk of mortality (11, 24, 35, 43, 46, 47). Subgroup analysis showed that the elevated DD level was associated with increased mortality: 21% versus 4.9% ($p<0.001$), RR 4.11-4.77 ($p<0.001$) (27, 35, 47); OR 28.14 ($p<0.001$) (13, 27, 35, 48). The elevated DD level was also associated with severe COVID-19: 40.74% versus 21.98% ($p<0.001$), RR 2.04-2.42 ($p<0.001$) (13, 35, 47, 48). The DD level was higher in the severe/non-survivor group compared to the non-severe/survivor group (2.9 and 0.8 mg/dL, respectively; $p<0.001$) (48).

The results of a systematic review and meta-analysis were based on 39 studies reporting DD levels in 5,750 non-severe patients and 2,063 severe patients, and 16 studies reporting DD levels in 2,783 survivors and 697 non-survivors. DD levels were significantly higher in patients with severe clinical status compared to those with non-severe forms of COVID-19, and in non-survivors compared to survivors. DD levels above the upper limit of normal were associated with a higher risk of severity (RR: 1.58; $p<0.0001$) and mortality (RR: 1.82; $p<0.0001$). The authors concluded that elevated DD levels determined at admission correlate significantly with the severity of COVID-19 and can predict mortality in hospitalized patients, thus they should be used for risk stratification in COVID-19 patients (17). Another systematic review and meta-analysis involving 6 original studies and a total of 1,355 hospitalized patients with moderate to critical COVID-19 confirmed these results – DD level is significantly associated with the risk of mortality in COVID-19 patients. The average DD value was higher in non-survivors compared to survivors (49).

According to the results of four meta-analyses published in 2020 and 2021, the sensitivity of the prognostic performance of DD for severity, mortality, and VTE in patients with COVID-19 was 55-77%, 64-75%, and 90% respectively, while the specificity was 56-71%, 66-83%, and 60% respectively. DD is considered a global marker of hemostasis activation and can predict severe and fatal outcomes in COVID-19 patients with moderate sensitivity and specificity. It can diagnose VTE with high sensitivity and low specificity. The authors recommend the use of this marker as a pre-radiographic screening tool, risk stratification indicator for VTE, and routine investigation after anticoagulant therapy for hospitalized patients with COVID-19 (2, 12, 22, 29).

DISCUSSIONS

DD is an independent prognostic marker. Higher DD levels in patients with COVID-19 are significantly associated with the risk of disease progression, severity of the condition, composite outcome, and mortality risk (12). These meta-analyses recommend the rapid assessment of DD for predicting adverse outcomes in COVID-19 (2, 12, 22, 29).

Patients with severe forms of COVID-19 have a higher risk of hypercoagulability, and deceased patients show significantly higher DD levels, reflecting a state of hypercoagulability. These findings suggest that higher DD levels in patients with COVID-19 may indicate coagulopathy and thrombotic risk (12, 48, 50).

Although the DD levels at admission and their trends during hospitalization are associated with outcomes in COVID-19, DD has limited performance characteristics as prognostic tests when analyzed separately (44).

A systematic review and meta-analysis conducted on 12 studies with 3,343 patients, including 2,801 patients with COVID-19 (967 patients with severe form of the disease), revealed that the pooled results of all studies showed significantly higher DD concentrations in patients with more severe COVID-19 compared to patients with non-severe condition and the overall COVID-19 patients (29). There are correlations between the severity of COVID-19, severe increase in DD levels, and the increased rate of complications and final outcomes (2).

Therefore, DD should be used as a pre-radiographic screening tool as early as possible after admission, as a risk stratification indicator for VTE, and as a routine investigation after anticoagulant therapy for hospitalized patients with COVID-19. Based on the increase in DD levels, adjusting therapeutic doses of anticoagulants becomes more beneficial for patients compared to prophylactic doses (22).

A D-dimer level >2590 ng/mL was associated with a 17-fold increase in the adjusted risk of pulmonary embolism, and the absence of any anticoagulant therapy was associated with a 4-fold increase in the risk of pulmonary embolism in patients with severe COVID-19 (oxygen saturation measured by pulse oximetry SpO_2 ≤93% in room air, respiratory rate ≥30 breaths/min, or rapid clinical deterioration) (51).

It is confirmed that severe COVID-19 is associated with cascades of inflammatory mediators, and the evaluation of these markers allows for early identification or even prediction of disease progression. It is well known that C-reactive protein is an acute-phase protein and an active regulator of innate immunity, serving as a predictive proinflammatory biomarker for the need of mechanical ventilation and escalation of treatment in uncontrolled inflammation in SARS-CoV-2 viral infection (38).

Therefore, early identification of variables associated with poor outcomes in patients with COVID-19 can be useful for planning more appropriate preventive treatment, reducing the risk of developing ARDS and ICU admission, improving survival, and optimizing the allocation of healthcare resources, which can be highly limited in some countries. Additionally, ambulatory patients presenting one or more of these characteristics can be promptly hospitalized for enhanced management (16, 30).

Furthermore, the assessment of DD concentration and its correlation with inflammatory markers and the severity of COVID-19 has found that the median value of DD was three times higher in patients with severe forms of COVID-19 compared to those with mild forms of the disease (1870 mg/L versus 630 mg/L, respectively). A weak but significant positive correlation was observed between DD and CRP ($r=0.327$; $p<0.001$). The combination of CRP value of 72.65 mg/L and DD value of 1250 mg/L can be used as a marker of COVID-19 severity with moderate accuracy (42).

Therefore, based on the aforementioned information, it is evident that COVID-19 is a prothrombotic condition, and coagulopathy is a significant complication in such patients, closely associated with clinical outcomes. DD indicates hypercoagulability and is directly associated with the severity of COVID-19. Furthermore, DD can be used as an early and reliable prognostic biomarker to predict mortality in patients with COVID-19 at the time of hospitalization. They facilitate a personalized and effective clinical management process, including anticoagulation strategies, which could significantly reduce the mortality rate (3, 12, 22, 24, 29, 34, 44, 45, 48, 49).

The determination of DD is a widely available laboratory test, feasible in patients with COVID-19 (16, 17, 24, 38, 49). However, there are also sources of heterogeneity, including age, comorbidity rates, average length of hospitalization, criteria for excluding conditions that increase DD levels (such as pregnancy, cancer, post-trauma state, and surgery), and the timing of DD measurement. Furthermore, the lack of association between DD levels and mortality indicates that anticoagulant treatment may lead to a decrease in the number of deaths (22, 45). Confirmation of these results requires further studies, particularly on a global scale, to determine the specific key value of this laboratory biomarker (6, 18).

CONCLUSIONS

1. COVID-19 is a prothrombotic, procoagulant condition, and coagulopathy is a common complication in such patients closely associated with clinical outcomes. In the majority of cases, D-dimer levels

are elevated and indicate hypercoagulability that is directly proportional to the severity of COVID-19.

2. D-dimers are positively associated with the degree of severity and increased risk of progression to a severe form of the disease. They correlate inversely with survival and can predict the prognosis and outcome of patients with COVID-19. D-dimers contribute to patient triage, determining therapeutic strategies, preventing complications, positively influencing the course of the disease, and monitoring prognosis.
3. The level of D-dimers is significantly higher in patients with COVID-19 compared to healthy individuals, in patients with severe forms of COVID-19 compared to those with non-severe forms, in patients with ARDS compared to those without ARDS, and in deceased patients compared to those who have survived.
4. D-dimers should be used as a pre-radiographic screening tool as early as possible after admission, as an indicator for stratifying the risk of venous thromboembolism, and as a routine investigation after anticoagulant therapy for hospitalized patients with COVID-19. Based on the increase in D-dimers, adjusting therapeutic doses of anticoagulants is more beneficial for patients compared to administering prophylactic doses.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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