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Original article

PREDICTABILITY OF D-DIMER LEVEL ON ADMISSION FOR HOSPITAL OUTCOMES IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA

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Abstract

The aim of this study was to evaluate the role of D-dimer as a biomarker in the assessment of COVID-19 prognosis in hospitalized patients.

Material and methods: A total of 117 patients with confirmed COVID-19 pneumonia between the age of 19 and 89 years (mean age 53) were admitted to the City General Hospital 8th September, Skopje, Macedonia. In all patients, a D-dimer test for coagulation profile and lactate dehydrogenase (LDH) for disease progression were performed on the day of admission. Patient demographic data, presence of comorbidities, severe symptoms, and radiological findings were determined for each patient. We calculated the National Early Warning Score (NEWS 2) for assessment of acute illness severity. The level of oxygen saturation (SpO_2) was also determined. Length of hospital stay and length of stay at home were filled later after hospitalization using medical records.

Results: Patients were classified according to D-dimer level into a low group (D-dimer ≤ 2 mcg/ml) and a high group (D-dimer ≥ 2 mcg/ml). Elevated D-dimer level was associated with severity, hypoxia, and lethal outcome. Patients with a high level of D-dimer had a higher NEWS 2 score, worsen radiological findings, and higher LDH. Patients with low levels of D-dimer stayed at home longer than those with higher D-dimer levels.

Conclusion: The D-dimer level is a useful marker in assessing the coagulation profile of patients with COVID-19 pneumonia regardless of the type of disease. Implementation of screening tools like the NEWS 2 score is also needed for better risk stratification on hospital admission.

Keywords: *D dimer, Covid-19 pneumonia, News2 score*

Introduction

Coronavirus primarily affects the respiratory tract and particularly the lungs[1]. Hospitalized patients are at high risk for fatal respiratory failure even in the absence of underlying comorbidities. Acute respiratory distress is one of the main complications associated with infection and death[2]. Another complication is abnormal coagulation[3]. Covid-19 pneumonia can affect coagulation and fibrinolysis in several ways. The virus may directly damage the endothelial cells and activate the coagulation cascade[4]. Vascular endothelin dysfunction due to the direct induce of virus results in thrombin activation, cleaving the fibrinogen into fibrin and fibrin into smaller pieces named D-dimer and systemic coagulopathy as a final outcome[5]. In addition, a severe type of COVID-19 is accompanied by an extremely marked increase in proinflammatory cytokines such as TNF, Il-1, IL-6. These cytokines may express the tissue factor and von Willebrand factor from endothelial cells and monocytes and can lead to further thrombosis events[6]. So, besides progressive pulmonary inflammation, local pulmonary intravascular coagulopathy and systemic activation of blood coagulation can also be present when the disease is progressive. Furthermore, recently it has been noted that in patients who had antiphospholipid antibodies coagulopathy starts in the lungs but only after it spreads into other organs[7]. Therefore, it is important to perform an evaluation of the coagulation profile in all patients at hospital admission in order to find those patients who are at risk. There are conventional tests such as prothrombin time, international normalized ratio, thrombin time, and activated partial thromboplastin time. Many studies confirm their inability to reflect the complexity of hemostatic impairment observed in COVID-19 patients[8]. Hence, international society of thrombosis and hemostasis recommends D-dimer as the most important test to be performed in patients with COVID-19[9]. Abnormal coagulation represented by a considerable elevation of D-dimer, ferritin, and fibrinogen degradation production, also adversely affects clinical outcomes: mortality, propagation, and length of hospital stay[10]. In the present study, we applied the D-dimer test in each patient on hospital admission in order to measure the level of D-dimer. We also applied the National Early Warning Score (NEWS 2) and we determined lactate dehydrogenase enzyme (LDH) in each patient at hospital admission. D-dimer is a useful marker in assessing the thrombotic pathology of COVID-19. We can measure D-dimer via analysis of a blood sample. The actual range for a normal population is 100-250 ng/ml. In COVID-19 pneumonia, Zhang *et al.*, reported an optimum cut-off value of D-dimer $\geq$ 2 mcg/ml within 24 hours of hospitalization[11]. NEWS2 score is an appropriately sensitive method for determining the degree of illness of a patient with COVID-19 pneumonia[12].

Material and methods

We enrolled 117 patients with confirmed COVID-19 referred to the City General Hospital 8th September in Skopje, Macedonia aged 19 to 89 years. Confirmed cases were defined as those with epidemiological history and microbiological evidence (respiratory specimens positive for SARS-Cov-2 by real-time reversed transcription-polymerase chain reaction - PCR assay) and clinical symptoms of COVID-19 like pneumonia. Patients were analyzed at hospital admission for demographic data (age, gender), presence of comorbidities (coded as with or without comorbidities), and severe symptoms like shortness of breath and severe general condition (coded as with or without certain symptoms). All patients underwent chest radiology within 24 hours of admission. Radiological findings were described as normal, pattern, and opacity. NEWS2 score on admission, level of blood saturation ($SpO_{2)}$ on admission, D-dimer on admission, and LDH on admission was also determined for each patient. SpO_2 was measured by a pulse oximeter put on the pointer finger on the day of admission. The NEWS2 score for assessment of acute illness severity was calculated on the following parameters: respiratory rate, oxygen saturation (SpO_2), need for supplemental oxygen, pulse rate, level of consciousness, and temperature. An online calculator by Gary B. Smith was used for the

calculation of the scores of NEWS 2[13]. D-dimer test for coagulation profile and LDH level for each patient was performed using a blood sample from the peripheral vein. The D-dimer level was tested using an immunoturbidimetric assay with a reference range of 0-0.500 mg/L. Blood samples of 5 ml peripheral blood were collected in silicone-coated glass tubes with a 3.2% (0.109 M) sodium citrate anticoagulant. Immediately after collection, whole blood D-dimer analyzer samples were centrifuged at room temperature at 3500 times gravity for 10 minutes. Patients were classified according to D-dimer level into low D-dimer group (≤ 2 mcg/ml) and high D-dimer group (≥ 2 mcg/ml). Patients were classified according to the novel coronavirus pneumonia diagnosis and treatment guideline (6th edition) by the National Health Commission of China in correlation to clinical severity into the following groups: mild, moderate, severe, and critically ill[19]. Severe and critically ill groups were merged into one group (severe group). Length of hospital stay and length of stay at home were filled later after hospitalization using medical records. Length of hospital stay was the average number of days that, patients spend in the hospital. The length of stay at home was an average number of days from the beginning of the symptoms to the day of admission.

Results

A total number of 117 patients with COVID-19 pneumonia (mean age 58.07 ± 14.43 for low D-dimer group and 57.71 ± 14.14 for high D-dimer group) were enrolled in the study. Patient characteristics according to D-dimer level are shown in Table 1. There was no difference between the two D-dimer groups according to age (t=0.137, p=0.892), gender (χ^2=0.069, p=0.792), and presence of comorbidities (χ^2=0.115, p=0.735). Certain symptoms (shortness of breath, severe general condition) and clinical data (type of disease, length of hospital stay, length of stay at home, and lethal outcome) were tested and significant associations are shown in Table 2. The frequency of patients with a high concentration of D-dimer (above 2 mcg/ml) was significantly higher in the subgroup with severe disease (85.1%) than in the subgroups with moderate (41.4%) and mild (14.6%) disease (χ^2=44.54, p<0.001). The shortness of breath (15.5% *vs.* 3.4%, χ^2=5.05, p=0.025) and severe general condition (32.8% *vs.* 10.2%, χ^2=8.883, p=0.003) were significantly more frequent symptoms in patients with a high concentration of D-dimer than in patients with a low concentration of D-dimer. The length of stay at home before hospitalization was significantly longer in patients with a low concentration of D-dimer (6.12 ± 8.41 days) than in patients with a high concentration of D-dimer (3.84 ± 2.08 days) (t=2.01, p=0.048). The lethal outcome was significantly more frequent in patients with a high concentration of D-dimer than in patients with a low concentration of D-dimer (74.1% *vs.* 25.4%, χ^2=27.77, p<0.001). Table 3 shows the association between D-dimer and investigations on admission (NEWS score, Spo2, and LDH) and radiology findings retrospectively. The frequency of patients with a high concentration of D-dimer (above 2 mcg/ml) was significantly higher in the subgroup with opacities (63.8%) than in the subgroups with pattern (33.3%) and normal radiological findings (11.1%) (χ^2=15.002, p=0.001). The mean

Table 1. Patient demographic characteristics according to D-dimer level

	Low D-Dimers ≤ 2 mcg/ml (N=59)	**High D-Dimers ≥ 2 mcg/ml (N=58)**	**Statistics, *p* value**
Age (years) (mean ± SD)	58.07 ± 14.43	57.71± 14.14	*t*=0.137 *p*=0.892
Gender - n (%)			
Male (n=72)	37 (51.4)	35 (48.6)	χ^2=0.069,
Female (n=45)	22 (48.9)	23 (51.1)	*p*=0.792
With comorbidities - n (%)	40 (67.8)	41 (70.7)	χ^2=0.115, *p*=0.735

Table 2. Certain symptoms and clinical data according to D-dimer level

	Low D-Dimers ≤ 2 mcg/ml (N=59)	**High D-Dimers ≥ 2 mcg/ml (N=58)**	**Statistics, *p* value**
Type of disease - n (%)			
1 Mild (n=41)	35 (85.4)	6 (14.6)	χ^2=44.54,
2 Moderate (n=29)	17 (58.6)	12 (41.4)	*p*<0.001
3 Severe (n=47)	7 (14.9)	40 (85.1)	
Shortness of breath - n (%)	2 (3.4)	9 (15.5)	χ^2=5.05, *p*=0.025
Severe general condition - n (%)	6 (10.2)	19 (32.8)	χ^2=8.883, *p*=0.003
Lethal outcome - n (%)	15 (25.4)	43 (74.1)	χ^2=27.77, *p*<0.001
Length of hospital stay (days) (mean ± SD)	12.12 ± 8.22	13.95 ± 8.85	*t*=-1.16, *p*=0.249
Length of stay at home before hospitalization (days) (mean ± SD)	6.12 ± 8.41	3.84 ± 2.08	*t*=2.01, *p*=0.048

Table 3. Investigations on admission according to D-dimer level

	Low D-Dimers ≤ 2 mcg/ml (N=59)	**High D-Dimers ≥ 2 mcg/ml (N=58)**	**Statistics, *p* value**
Radiological findings - n (%)			
1 Normal (n=9)	8 (88.9)	1 (11.1)	χ^2=15.002,
2 Pattern (n=39)	26 (66.7)	13 (33.3)	*p*=0.001
3 Opacity (n=69)	25 (36.2)	44 (63.8)	
NEWS score (mean ± SD)	4.25 ± 2.39	6.19 ± 2.06	*t*=-4.685 *p*<0.001
LDH mg/L (mean ± SD)	326.95 ± 186.71	562.74 ± 246.18	*t*=-5.83 *p*<0.001
O_2 Saturation (mean ± SD) (%)	85.85 ± 14.5	64.38 ± 23.59	*t*=5.92 *p*<0.001

NEWS 2 score was significantly higher in patients with a high concentration of D-dimer (6.19 ± 2.06) than in patients with a low concentration of D-dimer (4.25 ± 2.39) (t=-4.685, p<0.001). The mean LDH level was similarly higher in patients with a high concentration of D-dimer (562.74 ± 246.18 *vs.* 326.95 ± 186.71) (t=-5.83, p<0.001). On the contrary, the mean O_2 saturation was higher in patients with a low concentration of D-dimer (85.85 ± 14.5 *vs.* 64.38 ± 23.59) (t=5.92, p<0.001).

Discussion

Elevated D-dimer is a common finding at hospital admission even in the absence of clinically relevant microthrombi[14]. Men are well known to become infected more frequently than women and the elderly, and patients with comorbidities are more likely to develop more severe disease and poor outcomes consequently[15]. Our study also found that males had a higher D-dimer and an increased risk of lethal outcomes when infected. However, we noticed that the median age and existence of comorbidities between the two groups, low and high, were almost identical. Some studies demonstrated that coagulopathy measured as D-dimer level was associated with an increased risk of developing severe pneumonia in COVID-19 and poor prognosis[16]. The reported incidence of a severe type of disease in patients with elevated D-dimer in our study was 40% compared to 7 patients in the low D-dimer group. Furthermore, among patients with elevated D-dimer, LDH was higher than that in lower D-dimer. LDH is an intracellular enzyme released when lung damage exists like in severe

infection[17]. This may explain the correlation between LDH and the severe type of the disease and the probability of dying when the disease becomes severe. A possible explanation for survival in the high group is a type of disease. Among the different types of COVID-19, coagulopathy more often occurs in the severe form[18]. But, as we have already mentioned coagulopathy may be present even in the mild form, before the presentation of any other severe respiratory symptoms and without typical ground-glass opacities on the chest x-ray findings. We did not divide the high group into subgroups: death and survival subgroup to determine the exact difference. We applied the NEWS 2 score for the evaluation of vital parameters in patients with the aim to evaluate the compensatory mechanism. In our study, NEWS 2 score was similarly higher among patients with elevated D-dimer than patients with a low level of D-dimer. Furthermore, we found a positive association between shortness of breath, opacities, and oxygen saturation with elevated D-dimer. This suggests that thrombotic events represented with an elevated level of D-dimer can affect the lungs immediately after the inflammation sets in. In our study, the high group stayed at home shorter compared to those who were with a low level of D-dimer.

Conclusion

D-dimer is a useful marker in assessing the thrombotic pathology of COVID 19 regardless of the type of disease. D-dimer can predict severe and fatal outcomes in COVID-19 patients. It is suitable to employ this indicator as a screening tool as well as a routine investigation test in all patients with COVID-19. Implementation for an initial assessment for cardiovascular compensation is also needed for better risk stratification on hospital admission.

Conflict of interest statement. None declared.

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