



SEÇÃO: ORIGINAL ARTICLE

Evaluation of D-dimer as a predictor of severity, degree of pulmonary involvement and mortality in patients with COVID-19

Avaliação do D-dímero como preditor de gravidade, grau de envolvimento pulmonar e mortalidade em pacientes com COVID-19

Mofid Hosseinzadeh¹

orcid.org/0000-0002-3543-6627
mofdhosseinzadeh@ajums.ac.ir

Mandana Pouladzadeh¹

orcid.org/0000-0001-6251-6625
pouladzadeh_m@ajums.ac.ir

Amin Eftekhari²

orcid.org/0000-0003-1758-6303
eftekhari.a2016@ajums.ac.ir

Parastoo Moradi
Choghakabodi²

orcid.org/0000-0002-6263-5736
parastoomoradi40@yahoo.com

Alireza Sokooti³

orcid.org/0000-0001-8551-4681
sokoti.alireza33@ajums.ac.ir

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Abstract

Objective: To verify D-dimer values to predict disease severity, degree of lung involvement and mortality in patients with COVID-19.

Method: The D-dimer levels of 200 confirmed COVID-19 patients were prospectively measured in the Emergency Department of Razi Hospital of Ahvaz on the admission day, and its relations with the illness severity, computed tomography (CT) score, and mortality were assessed.

Results: D-dimer level > 1.04 µg/mL and ≤ 1.12 µg/mL could indicate severe illness and high grade of pulmonary involvement but low risk of death. The mortality rate in the patients with D-dimer level > 1.12 µg/mL (was significantly higher than its rate in those with D-dimer level ≤ 1.12 µg/mL (17.2% x 1.5%; P:0.02). An independent positive correlation was found between D-dimer and Chest CT score as well as the disease severity (OR: 1.84; 95%CI:1.38 - 2.45; P:0.0001).

Conclusion: D-dimer level > 1.12 µg/mL on the early stage of COVID-19 infection may independently predict the severe illness, high grade of pulmonary involvement, and high risk of death, indicating its beneficial role in timely management of critical patients.

Keywords: COVID-19, D-dimer, Disease Severity, Pulmonary involvement, Mortality.

Resumo

Objetivo: Verificar os valores do D-dímero para prever a gravidade da doença, o grau de envolvimento pulmonar e a mortalidade em pacientes com COVID-19.

Método: Os níveis de dímero D de 200 pacientes confirmados com COVID-19 foram medidos, prospectivamente, no Departamento de Emergência do Hospital Razi de Ahvaz, no dia da admissão, e suas relações com a gravidade da doença, escore de tomografia computadorizada (CT) e mortalidade foram avaliadas.

Resultados: Os níveis do D-dímero > 1.04 µg/mL e ≤ 1.12 µg/mL podem indicar doença grave e alto grau de envolvimento pulmonar, mas baixo risco de morte. A taxa de mortalidade nos pacientes com valor de D-dímero > 1.12 µg/mL foi significativamente maior do que naqueles com nível de D-dímero ≤ 1.12 µg/mL (17,2% x 1,5%; P:0,02). Foi encontrada uma correlação positiva independente entre o D-dímero e o escore de CT de tórax e a gravidade da doença (OR: 1,84; IC 95%:1,38 - 2,45; P:0,0001).

Conclusão: O nível do D-dímero > 1.12 µg/mL no estágio inicial da infecção por COVID-19 pode prever independentemente a doença grave, alto grau de envolvimento pulmonar e alto risco de morte, indicando seu papel benéfico no manejo oportuno de pacientes críticos.

Palavras-chave: COVID-19, D-dímero, Gravidade da doença, doença pulmonar, Mortalidade.

¹ Emergency Medicine Department, School of Medicine, Jundishapur University of Medical Sciences, Ahvaz, Iran.

² School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Khuzestan, Iran.

³ Department of Pathology, Razi Hospital, School of Medicine, Ahvaz, Khuzestan, Iran

INTRODUCTION

The growing coronavirus disease 2019 (COVID-19) pandemic has made worrying challenges for clinicians and people worldwide. So, timely diagnosis, hazard stratification, hospitalization, timely transferring of severe patients to the intensive care unit, using efficient treatments, and monitoring are vital procedures to help keep the maximum number of patients alive (1). Although clinical examination is an essential and useful diagnostic step, para-clinical examinations or laboratory assessment can provide significant information about the pathophysiology and pathobiology of disease as well as infection severity, which help the timely patient care management. Because COVID-19 is not merely a local respiratory infection but a multisystem disease involving a complex interaction of the inflammatory, immunological, and coagulative cascades. Tracking of significant changes in the potential biomarkers gives us the clues on how the virus affects the body organs and how the body reacts to it (2).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disrupts the healthy vascular endothelial barrier which leads to thrombosis and inflammation (3). As soon as platelets are activated, they recruit more platelets to crosslink with each other via fibrinogen. Then, proinflammatory cytokines and proangiogenic factors are secreted from platelets and induce leukocyte activation and extravasation. Such a coagulative cascade and escalating inflammation can eventually lead to thrombocytopenia as well as cytokine storm which in turn promotes thrombocytosis. In this process, macrophages procreate plasmin, through which the fibrin degradation product or D-dimers is produced; so, the abnormal extreme elevation of D-dimers is occurred in COVID-19 patients (3).

Recent COVID-19 related research has reported an elevated level of D-dimer, fibrinogen, and prolonged (PT) in the early stage of COVID-19 infection, denoting activation of thrombosis and coagulation pathways. Moreover, D-dimer levels increase in poor prognosis status. So, evaluating

the level of D-dimer from the early stage of the disease can be beneficial in timely controlling and managing of the disease (4). D-dimer, as an early marker, can be helpful for improving the management of COVID19 patients because the levels up to four times its normal on admission day ($\geq 2.0 \mu\text{g/ml}$) reported as a predictor of in-hospital mortality (5).

This prospective study is aimed at evaluating the potency of D-dimer in predicting the severity of illness, degree of pulmonary involvement, and mortality in COVID-19 patients at the admission day or the early stage of infection.

METHODS

Study design

In this prospective analytical study, 200 confirmed COVID-19 patients referred to the Emergency Department of Razi Hospital of Ahvaz from 8 April 2021 to 9 June 2021 were evaluated. This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran with Ethical Code: IR.AJUMS.REC.1399.737. The local institutional ethics committee of study center oversaw the proceedings and documentation.

Patients and laboratory measurements

Eligible voluntary patients (aged 18 years or elder) who showed the specified symptoms of COVID-19 and the positive results of SARS-CoV-2 real-time reverse transcription polymerase chain reaction test and computed tomography (CT) scan included into the study. But patients with non-completed documentation were excluded from the study.

Considering the statistician's idea and a sensitivity of 92.3% for the optimum cutoff value of D-dimer to predict in-hospital mortality reported in Zhang et al.'s study (5), the sample size was calculated using the following formula $l = 0.05$; $= 1.96$; d or accuracy of estimate $= 0.05$; $P = 0.923$:

$$N = \frac{Z^2 \alpha/2 \times P(1-P)}{d^2} = 110$$

By considering 10 - 20 % dropout rate, N= 121 cases or more.

The laboratory tests were done using standard kits (Merck KGaA, Darmstadt, Germany). Following blood sampling within 24 hours after admission, the routine laboratory tests (i.e., complete blood count and coagulation profile) were performed within two hours after blood sampling. D-dimer was measured on a coagulation analyzer Sysmex CS-5100 System™ (Siemens Healthcare Diagnostics, Erlangen, Germany) with a reference range of 0 - 0.5 µg/ml, and the intra-day and inter-day variability coefficients of 4.22% and 3.41%, respectively.

All COVID-19 patients were classified into three groups (i.e., patients with mild, moderate, and severe COVID-19 infection) based on the World Health Organization severity criteria explained in our previous study (6). Then, their demographic, clinical as well as laboratory characteristics were collected from medical records daily and recorded in data sheet for comparative analysis.

CT imaging and its analysis

The initial CT scan was performed for all patients at least five days after symptom onset. A 16-channel CT scanner (Canon Medical Aquilion CT system) with tube voltage 120 kV, current 50 mA; rotation time 0.5s, slice thickness 5 mm, and matrix 512 × 512 was applied. The scanning area was from the apex to the base of lung.

Our chest CT scan scoring system patterned from the total severity score system suggested by Mruk B et al. (7). Depend on the percentage of the lobe involvement, a range of 0 to 4 points was considered for each of the five lung lobes, and a total score was obtained by summing the scores of five lobe, which ranged from 0 - 20. CT severity scoring per each of the five lobes was as follows: 0, no involvement (0%); 1, minimal involvement (1 - 25%); 2, mild involvement (26 - 50%); 3, moderate involvement (51- 75%); and 4, severe involvement (76 - 100%).

Statistical analysis

IBM SPSS Statistics 26 was used for statistical analysis. Categorical and continuous variables

presented as frequency or percentages and the mean±standard deviation (SD), respectively. Based on the results of Kolmogorov-Smirnov test, the normality hypothesis was rejected for white blood count (WBC), polymorphonuclear (PMN) count, lymphocyte count, platelet count, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), D-dimer, and CT scan score, but the normality hypothesis and homogeneity of variances were only confirmed for age and hemoglobin. So, only these two markers were evaluated by ANOVA model while others were examined by Kruskal Wallis test. Subsequently, a Bonferroni adjusted Kruskal-Wallis test for several variables was used for multiple pairwise comparisons between three groups of COVID-19 patients. Association of D-dimer level with Chest CT score and disease severity was evaluated through multivariate linear and/or logistic regression analysis. The optimal D-dimer cutoff point were detected by receiver operator characteristic (ROC) curve to determine the efficacy of D-dimer level in identifying the survival probability as well as the disease severity in COVID-19 patients. A P-value <0.05 considered a definition of significances.

RESULTS

A total of 200 COVID-19 patients were assessed and no case was excluded or withdrawn from the study. Respectively, 110 (55%) men and 90 (45%) women with mean age 57.2±15.5 and 56.7±15.1 years were analyzed. The demographic, clinical as well as laboratory characteristics of all patients were detailed in **Table 1**. Fever (70.5%), shortness of breath (64%), dry cough (61.5%), fatigue (52.0%), and myalgia (41.5%) were the most common clinical symptoms, respectively.

No statistically significant difference was found between three groups of patients in terms of age, gender, underlying diseases, and hemoglobin level. All mean pairs of age and hemoglobin level were similar in three groups, meaning that there was no transitivity property in relationship between severity of infection and the mean age and hemoglobin level. A significant difference in

the median levels of WBC, PMN, Lymphocytes, PT, PTT, INR, D-dimer, and CT scan score was found between three studied groups which affected

by the severity of the infection. But there was no significant difference in the median level of platelets between three groups (**Table 1**).

TABLE 1 – Comparison of demographic, clinical, and para-clinical characteristics between three COVID-19 groups stratified based on the disease severity.

Groups	Severe	Moderate	Mild	Total	P
Variables	68 (34%)	114 (57%)	18 (9%)	200	
Male, n (%)	42(61.8)	58(50.9)	10(55.6)	110(55.0)	0.36*
Age (Year), mean±SD					
Male	60.8±15.5	54.3±14.9	58.8±16.9	57.2±15.5	0.08†
Female	58.8±15.2	55.5±15.5	58.1±12.7	56.7±15.1	
Underlying disease, n (%)	39 (57.4)	68 (59.6)	10 (55.6)	117 (58.5)	0.36*
Clinical signs, n (%)					
Fever	47(69.0)	81(71.0)	13(72.3)	141(70.5)	0.94*
Dry cough	42(61.8)	71(62.3)	10(55.6)	123(61.5)	0.86*
Sputum production	16(23.5)	20(17.5)	6(33.4)	42(21.0)	0.84*
Fatigue	36(53.0)	60(52.6)	8(44.4)	104(52.0)	0.79*
Myalgia	24(35.3)	53(46.5)	6(33.3)	83(41.5)	0.25*
Shortness of breath	47(69.1)	71(62.3)	10(55.6)	128(60.0)	0.96*
Headache	17(25.0)	27(23.7)	4(22.2)	48(24.0)	0.96*
Diarrhea	6(8.8)	20(17.5)	3(16.7)	29(14.5)	0.84*
Nausea	8(11.8)	35(30.7)	5(27.8)	48(24.0)	0.20*
Bellyache	11(16.2)	18(15.8)	2(11.1)	31(15.5)	0.52*
Laboratory markers					
WBC (cells/ μ L) [§]	9150(6900-11800)	7620(5700- 9350)	7950(7125-8775)	8100(6125-10200)	0.003†
PMN (cells/ μ L) [§]	7890(5639-9971)	6037(4550-7207)	6012(5747-7004)	6367(4876-8348)	0.0001†
Lymphocyte (cells/ μ L) [§]	836.8(553.4-1109)	1101(814.1-1678)	1102(842.9-1549)	1000.6(713.2-1413)	0.0001†
Platelet (cells/ μ L) [§]	205.5(156-296)	228 (176-293.3)	269.5(209-337)	224.5(167.3-295.8)	0.06†
PT (s) [§]	13 (13-14)	13(12-13)	13(12-13)	13(12-13)	0.0004†
PTT (s) [§]	35.5(30-42)	32(30-38)	34(30-38)	33.5(30-38.7)	0.02†
INR [§]	1.2(1-1.3)	1.2(1-1.2)	1.1(1-1.2)	1.2(1-1.2)	0.007†
D-dimer (μ g/mL) [§]	1.3(0.56-2.8)	0.70(0.32-0.92)	0.87(0.56-1.07)	0.8(0.4-1.4)	0.0001†
CT scan (score) [§]	8.5(7-11)	5(4-7)	3(2.7-4)	5(4-8)	0.0001†
Hemoglobin (g/dL) [§]	12.5±1.9	12.9±1.9	12.7±1.4	12.8±1.8	0.31†
Died, n (%)	8 (11.8)	5 (4.4)	0	13 (6.5)	0.52*

CT, computed tomography; INR, International normalized ratio; IQR, interquartile range; PMN, Polymorphonuclear; PT, prothrombin time; PTT, partial thromboplastin time; SD, standard deviation; WBC, white blood count. *chi-square test; †One-Way ANOVA; ‡Kruskal-Wallis test; § median(IQR).

The median level of WBC in severe COVID-19 patients was significantly higher than its level in patients with moderate infection ($p= 0.002$). But no statistically significant difference was observed between patients with moderate infection and those with mild infection. The

median level of PMN in severe COVID-19 patients was significantly higher than its level in patients with moderate infection and/or mild infection ($p= 0.0001$). But the median level of PMN in patients with moderate infection was almost close to its level in patients with mild infection.

The median level of lymphocytes in severe COVID-19 patients was significantly lower than its level in patients with moderate infection and/or mild infection ($p= 0.0001$). The prothrombin time in severe COVID-19 patients was significantly longer than its time in patients with moderate infection and/or mild infection ($p= 0.0004$). The PTT in severe COVID-19 patients was significantly longer than its time in patients with moderate infection ($p= 0.02$) while PTT in patients with moderate infection was almost close to its time in patients with mild infection. INR in patients with severe infection was longer than that of the patients with mild infection ($P= 0.007$); but no statistically significant difference in INR was observed between patients with severe infection and those with moderate infection.

The median level of D-dimer in severe COVID-19 patients was significantly higher than its level in patients with moderate infection and/or mild infection ($p= 0.0001$). However, no significant difference in the level of D-dimer was observed between patients with moderate infection and those with mild infection.

Association of D-dimer level with disease severity-related biomarkers

Another Bonferroni adjusted Kruskal Wallis analysis was done to precisely detect the association between D-dimer level and disease severity-related biomarkers based on D-dimer level $> 1.04 \mu\text{g/mL}$ and ≤ 1.04 as patient classifier variable. Our results showed that WBC, PMN, PT, and INR were significantly associated with D-dimer level ($P<0.05$). But, D-dimer level showed not any notable correlation with lymphocytes count, platelets, and PTT, i.e., the median levels of WBC, PMN, PT, and INR in patients with D-dimer level $> 1.04 \mu\text{g/mL}$ were significantly higher than their median levels in those patients with D-dimer level $\leq 1.04 \mu\text{g/mL}$.

Association of D-dimer level with Chest CT score, Disease Severity, and Survival probability

After 4-weeks follow-up of 200 COVID-19 patients, 13 (6.5%) patients had died. The D-dimer level with an area below the curve of 76% and a cut-off point of $1.12 \mu\text{g/mL}$ showed a good efficacy in identifying the survival probability (95%CI: 0.62 to 0.89; specificity: 71.6%, sensitivity: 84.6%; $P: 0.001$) (**Figure 1**). The survival probability in the patients with D-dimer level $> 1.12 \mu\text{g/mL}$ was significantly lower than its probability in those with D-dimer level $\leq 1.12 \mu\text{g/mL}$ ($82.8\% \times 98.5\%$; $P: 0.02$), and vice versa for mortality rate. Also, D-dimer level $> 1.04 \mu\text{g/mL}$ and $\leq 1.04 \mu\text{g/mL}$ could truly determine almost 60% of severe patients and 80% of non-severe cases in the studied population, respectively (**Figure 2**). D-dimer level $> 1.04 \mu\text{g/mL}$ and $\leq 1.12 \mu\text{g/mL}$ could indicate severe illness and high grade of pulmonary involvement but low risk of death.

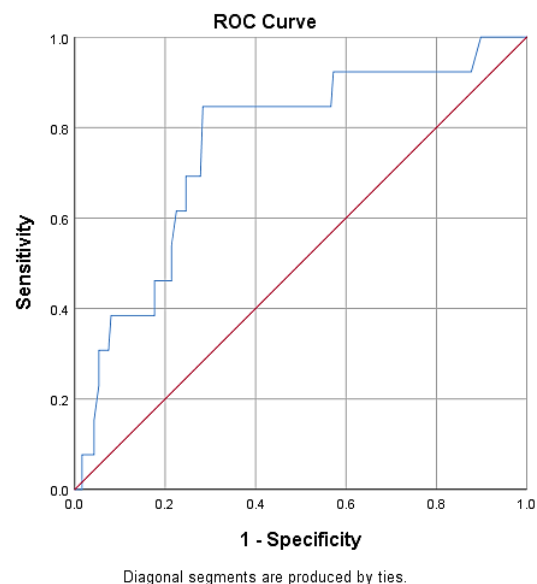


Figure 1 – The ROC Curve to determine the efficacy of D-dimer level in identifying the survival probability in COVID-19 patients. The sensitivity and the specificity of the cut-off point of $1.12 \mu\text{g/mL}$ were respectively 84.6 % and 71.6 % with AUC of 76% (95%CI: 0.62 - 0.89; $p=0.002$).

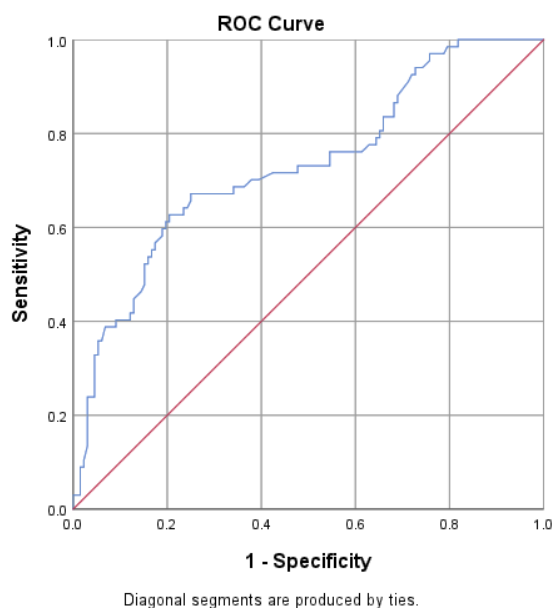


Figure 2 – The ROC Curve to determine the efficacy of D-dimer level in identifying the disease severity of COVID-19 patients. The sensitivity and the specificity of the cut-off point of $1.04 \mu\text{g}/\text{mL}$ were respectively 61.7 % and 79.5 % with AUC of 73 % (95%CI: 0.65 - 0.80; $p=0.0001$).

Based on the multivariate linear regression analysis of 200 COVID-19 patients, gender, underlying disease, WBC, PMN, Lymphocytes, PTT, and INR had not any significant association with Chest CT score ($P>0.05$); also, they were not confounders for the correlation between D-dimer and Chest CT score. But, D-dimer level, PT, and maybe age showed a significant relation with the Chest CT score ($P<0.05$). Also, the positive correlation between D-dimer and Chest CT score were not significantly changed by adding the age and PT, indicating these two markers were not confounders too.

Based on the multivariate logistic regression analysis for disease severity based on D-dimer level, age, and other significant biomarkers, none of the mentioned variables showed any significant correlation with disease severity, except D-dimer and lymphocyte count ($p<0.05$). However, variance inflation factor for lymphocyte count was greater than 5 (its cutoff value), and so, it was also deleted from the model. Conclusively, none of these variables were confounders for the correlation between D-dimer and disease

severity.

Discussion

Our findings showed that the levels of D-dimer in severe patients was significantly higher than its levels in moderately and/or mildly infected patients; also, its median level among died patients was about twofold higher than survivors, which confirms the results of previous studies (5, 8, 9). Zhang et al reported that D-dimer level higher than $2.0 \mu\text{g}/\text{mL}$ was an independent predictor of death in COVID-19 patients (5). Similarly, Guan et al and Ning T et al found a significant elevated D-dimer in died COVID-19 patients compared with survivors (5, 8). However, the median D-dimer level in died patients of our geographic region ($1.55 \mu\text{g}/\text{mL}$) was somewhat less than its level in China, which may be affected by different sample size and or various demographic and genetic characteristics of people from different regions. Nevertheless, the range of D-dimer level in non-survivors ($> 1 \mu\text{g}/\text{mL}$) in Fei Zhou et al's study in China (9) was near to the mortality-related D-dimer range of our study, which more highlighted the role of sample size, because their sample size ($n= 191$) was almost similar to our sample size.

In this prospective research, the predictive potential of D-dimer was evaluated through finding the association of D-dimer levels at the early stage of infection with the severity of illness, the degree of pulmonary involvement, and mortality rate in COVID-19 patients. In this regard, our results showed that D-dimer level can independently predict the degree of pulmonary involvement as well as the disease severity; however, the sensitivity of the cut-off point of $1.04 \mu\text{g}/\text{mL}$ to identify severely infected patients was partially low. Zhang et al demonstrated that patients with D-dimer levels $\geq 2.0 \mu\text{g}/\text{mL}$ were in a critical condition with a higher rate of underlying disease, lower level of lymphocyte, hemoglobin, platelet count, and higher level of neutrophil, c-reaction protein, and PT in comparing with those with D-dimer levels $< 2.0 \mu\text{g}/\text{mL}$ (5). Our findings confirmed Zhang et al's reports, yet

the severity of infection as well as the elevated level of D-dimer in our study population were not correlated with gender, age range, underlying diseases, and hemoglobin level. Nevertheless, D-dimer level greater than 1.04 µg/mL on admission day was significantly associated with the higher levels of WBC, PMN, CT scan score, and prolonged PT and INR, implying the warning role of D-dimer for patients' critical conditions.

SARS-CoV-2 infection can lead to an elevation of D-dimer through inducing the dysfunction of endothelial cells, thrombosis, hypoxia-inducible thrombosis, and a hypercoagulative and inflammation status (3, 10, 11). Although underlying diseases and elder ages were risk factors of hypercoagulation (5), our results have not shown any association between high level of D-dimer with underlying diseases and/or elder age. Also, our findings indicated a simultaneous increase in the degree of pulmonary involvement and D-dimer level at the early stage of severe COVID-19 infection confirming a micro-thrombosis formation in pulmonary small vessels (9).

Study Strengths and Limitations

Despite the previous retrospective studies, our prospective research can precisely detect whether there is a causal association between D-dimer and outcomes or not. Also, identifying the exact relationship between the D-dimer and the degree of pulmonary involvement or chest CT scan score is one of our novel findings. Our study also met a few limitations. The absence of assessment for stressful conditions and medical intervention during hospitalization (as the probable confounder risk factors) may make doubts in definitive conclusion about the predictive role of D-dimer; so, further researches are recommended to prove their probable effects.

Conclusion

A few recent reports have pointed to the hemostatic abnormalities and remarkable elevated D-dimer levels in non-survivors with COVID-19. Our findings suggested that D-dimer

level > 1.04 µg/mL on the early stage of COVID-19 infection can independently predict the severe illness and high grade of pulmonary involvement but low risk of death. Also, D-dimer level > 1.12 µg/mL can predict in-hospital mortality, indicating its beneficial role in timely management of critical patients with COVID-19.

Notes

This study is part of the result of a Doctor of Medicine (M.D) thesis in the Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, by one of the authors (AE), entitle "Association between disease severity and D-dimer levels in patients with COVID_19 referring to the emergency department of Razi Hospital in Ahvaz, southwestern Iran", presented in August 2021.

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Conflicts of interest disclosure

The authors declare no competing interests relevant to the content of this study.

Authors' contributions.

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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Minicurriculum

Mofid Hosseinzadeh: MD-PhD in Emergency medicine from Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; assistant professor at the Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Mandana Pouladzadeh: MD-PhD in Emergency medicine from Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; assistant professor at the Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Amin Eftekhari: graduated MD student from Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Parastoo Moradi Choghakabodi: DVM from Shahid Chamran University of Ahvaz (Jundi Shapur); MD Senior Clinical Investigator at Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Alireza Sokooti: MD-PhD of clinical pathology from Department of Pathology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; working at Razi Hospital

Mailing Address

Parastoo Moradi Choghakabodi

parastoomoradi40@yahoo.com

Address: School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Golestan Blv. Ahvaz, Iran. Zip Code: 61357- 15794.

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