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Identifying susceptibility indexes to venous thrombosis in mortality rate of patients with COVID-19 pneumonia

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Abstract

Introduction: One of the most critical complications of Covid-19 is venous thrombosis. Factors such as hospitalization, catheterization, hypoxia, inflammation, immobilization, and infection can increase VTE incidence. Therefore, this study aims to explore VTE indices as a predictor of mortality rates.

Methods: This Cross-Sectional retrospective study was conducted in our center, in Tehran, from April 18, 2020, to December 19, 2020. The study sampling was census, so that all patients with Covid-19 diagnosis were admitted according to the inclusion criteria. In addition, a researcher-made checklist form is used to collect patient information, including demographic information, medical history, clinical symptoms of Covid-19, and medical test results.

Results: The present study was conducted on 406 patients with a diagnosis of Covid-19. This study's results indicate that the Padua index> four increases the death rate of Covid-19 by 2.32 times. Also, IBS index > 7 increases the death rate of Covid-19 by 5.41 times, and D-dimer> 1 increases the death rate of Covid-19 by 3.93 times in Covid-19 patients. The results indicated that the Padua index was significantly correlated with IBS and D-dimer indices among the dead patients. D-dimer> 1 increases Padua index > 4 by 3.51 and IBS index > 7 by 3.29 times and IBS>7 increases the odds of Padua index > 4 by 11.48 times.

Conclusion: Patients with Covid-19 pneumonia often experience elevated Padua index, IBS index, and D-dimer values affecting mortality rates. Medical staff should focus on preventing high mortality rates through prophylaxis.

Keywords: COVID-19, Mortality, Padua, D-dimer, Improve Bleeding Score

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Introduction

Vein thrombosis is a critical and potentially mortal disorder that generally complicates patients' course in hospital but may also affect individuals not hospitalized and otherwise healthy individuals [1]. Venous thromboembolism (VTE) is a disorder characterized by the formation of a blood clot, typically in the deep veins of the leg, groin, or arm, referred to as deep vein thrombosis (DVT), or by the clot's migration through the circulatory system, resulting in obstruction of the lungs, known as pulmonary embolism (PE). It has been determined that hospitalization for acute diseases, such as inflammatory bowel disease, pneumonia, rheumatoid arthritis, congestive respiratory failure, type 1 diabetes mellitus, or acute infection, increased risk of Venous Thromboembolism [2].

In the last few years, the world has been contending with a sickness known as COVID-19, initially detected in China in December 2019 (7,8). Covid-19 is most important cause of hospitalization over 4 years ago. so far, more than 770 million people worldwide have been infected, with over 6 million deaths reported [3]. Based on At the most estimates 5% of patients with COVID-19 are

severe or critical and require hospitalization in wards or intensive care units (ICU) [4]. Acute respiratory distress syndrome (ARDS) is an important complication with approximately 33% prevalence in hospitalized cases [5]. It has been found that one of the important complications of patients with Covid-19 is coagulation disorders [6]. Nevertheless, the etiology of thrombosis in these patients is still not evident [7]. However, hospitalization, catheterization, hypoxia, exceeding inflammation, immobilization, and acute infection could be feasible factors associated with a high incidence of thromboembolism [8-10]. Recent research has reported cumulative incidences of thrombotic events between 48% in their Intensive Care Units (ICUs) in patients with COVID-19 pneumonia [11].

Practical perceptions of hospitalized patients in ICU indicated that many patients have VTE symptoms [12-14]. Also, VTE symptom appears in severe and critical presentation of COVID-19 therefore VTE indices can predict mortality rate. Therefore, this study aimed to explore the significant predictors of mortality rate in patients with COVID-19 pneumonia due to venous thrombosis indexes

Method

Study design

This cross-sectional study was conducted Baqiyatallah Hospital in Tehran, Iran. There was performed from April 18, 2020, to December 19, 2020. Patients were hospitalized in three various Covid-19 dedicated units: Infectious and internal Disease units and ICU.

Procedure and patients

The patients were analyzed in the period of April 18, 2020, to December 19, 2020. According to the World health organization guidance, the data was collected from those diagnosed with covid-19 [15]. Moreover, a molecular laboratory test for SARS-COV-2 and radiological confirmation of Covid-19 infection was performed. The patient data was achieved by reviewing and analyzing historical medical records. The Iran National Committee approved this study for Ethics in Biomedical research. (IR.BMSU.REC.1399.302) The data variables were collected from medical records included; demographic, clinical variables, laboratory tests and radiologic foundations, foundation components for predicting venous thromboembolism, and predicting improving bleeding risk (Bleeding is the expulsion of blood. It may occur external or outside of the human body, as in the case of a cut or wound. It may also be internal, such as when there is a damage to an internal organ).

The Padua prediction score serves as a risk assessment model for predicting venous thromboembolism (VTE). The Padua score was computed based on the risk factor weights for each patient enrolled in the study. A cumulative score of ≥ 4 indicates a high risk of VTE, while a score of < 4 indicates a low risk [16].

The improved bleeding risk prediction score estimates the risk of bleeding among acutely ill hospitalized patients. [17] Thus, in the bleeding risk prediction, high risk is a cumulative score ≥ of 7 and a low risk of < 7 [17].

The usual thromboembolism was provided to patients whose Padua scores more than four points. For those with improving bleeding prediction scores, more than seven low intensive thromboprophylaxis was suggested.

Statistical analysis

Frequency tables were prepared as frequency indices (N (%)) for qualitative variables and mean and Standard deviation (SD) for quantitative variables. Univariate and multivariate logistic regression was used to determine the relationship between the variables with patients' mortality (dependent variable was Death/Survived), the odds ratio (OR), and 95% confidence interval (CI) were reported. In addition, adjusted P-value with Bonferroni correction for controlling Type I error too. The statistical analysis was executed with SPSS for Windows, version 21 (SPSS Inc., Chicago, Il., USA), Bonferroni correction for adjusted P-value perfumed with R software version 4.0.3 (stats package). In this study statistical significance level was considered 0.05.

Results

In the present study, 406 patients have confirmed Covid-19 in our center; this study has a mean age of 56.24 years with a SD of 14.81. they were ranging from 19 years old to 93 years old. Also, 30.8% of patients were women, and 69.2% were men. Body mass index (BMI) in 48.4% of patients was 25-30 and 46.1% in the range of 18.5 to 25. The baseline characteristics of the study population are summarized in table 1.

76.8% of the patients were discharged, and only 0.5% were readmitted. Computerized tomography (CT) scan results were positive (pulmonary involvement) among 85.0% of patients participating in this study.

Table 1. Summary of patients information.

		Total (N=406)		Survived (N=282)		Death (N=124)		P
		N	%	N	%	N	%	
Sex	**Male**	281	69.2	187	66.3	94	75.8	0.065 [1]
	Female	125	30.8	95	33.7	30	24.2	
BMI	**< 18.5**	7	1.8	3	1.1	4	3.3	0.464 [2]
	18.5 – 25	176	46.1	124	47.3	52	43.3	
	25 – 30	185	48.4	125	47.7	60	50.0	
	> 30	14	3.7	10	3.8	4	3.3	
CT-Result	**Negative**	61	15.0	51	18.1	10	8.1	0.009 [1]
	Positive	345	85.0	231	81.9	114	91.9	
		Mean(SD)	**Min-Max**	**Mean(SD)**	**Min-Max**	**Mean(SD)**	**Min-Max**	
Age		56.24(14.8)	19-93	53.26(14.3)	19-89	63.09(13.8)	28-93	0.001 [3]

1. Pearson Chi-Square, **2**. Fisher Exact Test, **3**. Independent Sample T-Test
N: Number, **%**: Percent, **BMI**: Body Mass Index, **SD**: Standard Deviation, **Min**: Minimum, **Max**: Maximum

Studies of the medical history of Covid-19 patients participating in this study showed that a history of hypertension by 1.97 times, lung disease by 2.17 times, Corticosteroid use by 3.14 times, active cancer by 98.38 times, having surgery by 16.81 times, and having angiography by 3.01 times increases the odds of death of Covid-19 patients (P <0.05). In addition, chest pain, headache, sore throat, diarrhea, and vomiting were among the symptoms of Covid-19 that had a significant effect on patient mortality. (Table 2)

Table 2. Summary of medical history information and Covid-19 symptoms.

		Survived (N=282)	Death (N=124)	Univariate	
		N (%)	N (%)	OR (95%CI)	P [1]
Disease History	**Hypertension**	101 (35.8%)	65 (52.4%)	1.97 (1.29 – 3.03)	0.002
	Diabetic	65 (23.0%)	39 (31.5%)	1.53 (0.96 – 2.45)	0.075
	Lung Disease	18 (6.4%)	16 (12.9%)	2.17 (1.07 – 4.42)	0.032
	Chemotherapy	4 (1.4%)	4 (3.2%)	2.32 (0.57 – 9.42)	0.240
	Corticosteroid	11 (3.9%)	14 (11.3%)	3.14 (1.38 – 7.12)	0.006
	Smoking	23 (8.2%)A	12 (9.7%)	1.21 (0.58 – 2.51)	0.615
	Active Cancer	2 (0.7%)	7 (5.6%)	8.38 (1.72 – 40.92)	0.009
	Surgery	1 (0.4%)	7 (5.6%)	16.81 (2.05 – 69.17)	0.010
	Trauma	4 (1.4%)	2 (1.6%)	1.14 (0.21 – 6.30)	0.881
	Heart Failure	10 (3.5%)	5 (4.0%)	1.14 (0.38 – 3.42)	0.801
	Coronary Heart Disease	2 (0.7%)	4 (3.2%)	4.67 (0.84 – 25.82)	0.078
	Stent	4 (1.4%)	1 (0.8%)	0.57 (0.06 – 5.11)	0.611
	CABG	17 (6.0%)	11 (8.9%)	1.52 (0.69 – 3.34)	0.301
	Angio	16 (5.7%)	19 (15.3%)	3.01 (1.49 – 6.07)	0.002
	Acute MI	1 (0.4%)	1 (0.8%)	2.29 (0.14 – 36.82)	0.560
	COPD	6 (2.1%)	6 (4.8%)	2.34 (0.74 – 7.41)	0.148
	Asthma	14 (5.0%)	10 (8.1%)	1.68 (0.73 – 3.89)	0.227
	ThromboProphylaxis	113 (40.2%)	46 (37.1%)	0.88 (0.57 – 1.36)	0.554

		Survived (N=282)	Death (N=124)	Univariate	
		N (%)	N (%)	OR (95%CI)	P [1]
Covid-19 Symptoms	**Cough**	180 (63.8%)	78 (62.9%)	0.96 (0.62 – 1.45)	0.858
	Weakness	84 (29.8%)	34 (27.4%)	0.89 (0.56 – 1.43)	0.628
	Chest Pain	118 (41.8%)	76 (61.3%)	2.20 (1.43 – 3.39)	0.001
	Headache	51 (18.1%)	35 (28.2%)	1.78 (1.08 – 2.92)	0.022
	Sore Throat	104 (36.9%)	28 (22.6%)	2.01 (1.23 – 3.26)	0.005
	Dizziness	13 (4.6%)	0 (0.0%)	-	-
	Diarrhea	16 (5.7%)	18 (14.5%)	2.82 (1.39 – 5.74)	0.004
	Vomiting	26 (9.2%)	22 (17.7%)	2.12 (1.15 – 3.92)	0.016
	Loss of taste or smell	43 (15.2%)	20 (16.1%)	1.07 (0.60 – 1.91)	0.821
	Myalgia	54 (19.1%)	34 (27.4%)	1.60 (0.97 – 2.61)	0.064
	Earache	1 (0.4%)	2 (1.6%)	4.61 (0.41 – 51.28)	0.214

1. Univariate Logistic Regression (Dependent Variable: Death/Survived)
OR: Odds Ratio, **95%CI**: 95% Confidence Interval, **P**: P-Value

Studies on the Padua index showed that more than 4 Padua index significantly increased the death rate of Covid-19 patients by 2.32 times (P =0.001). Studies related to the IBS index showed that more than 7 IBS index significantly increased the death rate of Covid-19 patients by 5.41 times (P =0.001), and more than 1 D-dimer index significantly increases the death rate of Covid-19 patients by 3.93 times (P =0.001) (Table 3).

Table 3. Summary of the effects of Padua Score, Improve Bleeding Score, and D-dimeron recovery or deat.

		Survived (N=282)	Death (N=124)	Univariate		Multivariate	
		N (%)	N (%)	OR (95%CI)	P [1]	OR (95%CI)	P [2]
Padua Index	< 4	231 (81.9%)	82 (66.1%)	2.32 (1.44 – 3.75)	0.001	1.83 (1.08 – 3.07)	0.023
	>= 4	51 (18.1%)	42 (33.9%)				
Improve Bleeding Score	< 7	269 (96.8%)	105 (84.7%)	5.41 (2.37 – 12.34)	0.001	7.34 (3.05 – 17.65)	0.001
	>= 7	9 (3.2%)	19 (15.3%)				
D-dimer	< 1	179 (63.5%)	38 (30.6%)	3.93 (2.51 – 6.18)	0.001	3.99 (2.45 – 6.49)	0.001
	>= 1	103 (36.5%)	86 (69.4%)				

1. Univariate Logistic Regression
2. Multivariate Logistic Regression (Forward LR elimination) – Goodness of Fit with Hosmer and Lemeshow Test was confirmed (Chi-Square= 0.295 , P-value = 0.587)
OR: Odds Ratio, **95%CI**: 95% Confidence Interval, **P**: P-Value

The results show that all three variables simultaneously affect patient's mortality, so that more than 4 in the Padua index, and more than 7 in the IBS index, and more than 1 in the D-dimer index significantly increases the death rate in Covid-19 patients respectively by 1.83 (P=0.023), by 7.34 times (P=0.001), and by 3.99 times (P=0.001) (Table3). The distribution of mortality in patients is shown by each of the Padua index, IBS index, and D-dimer index in Figure1, which confirms the results of Table 3

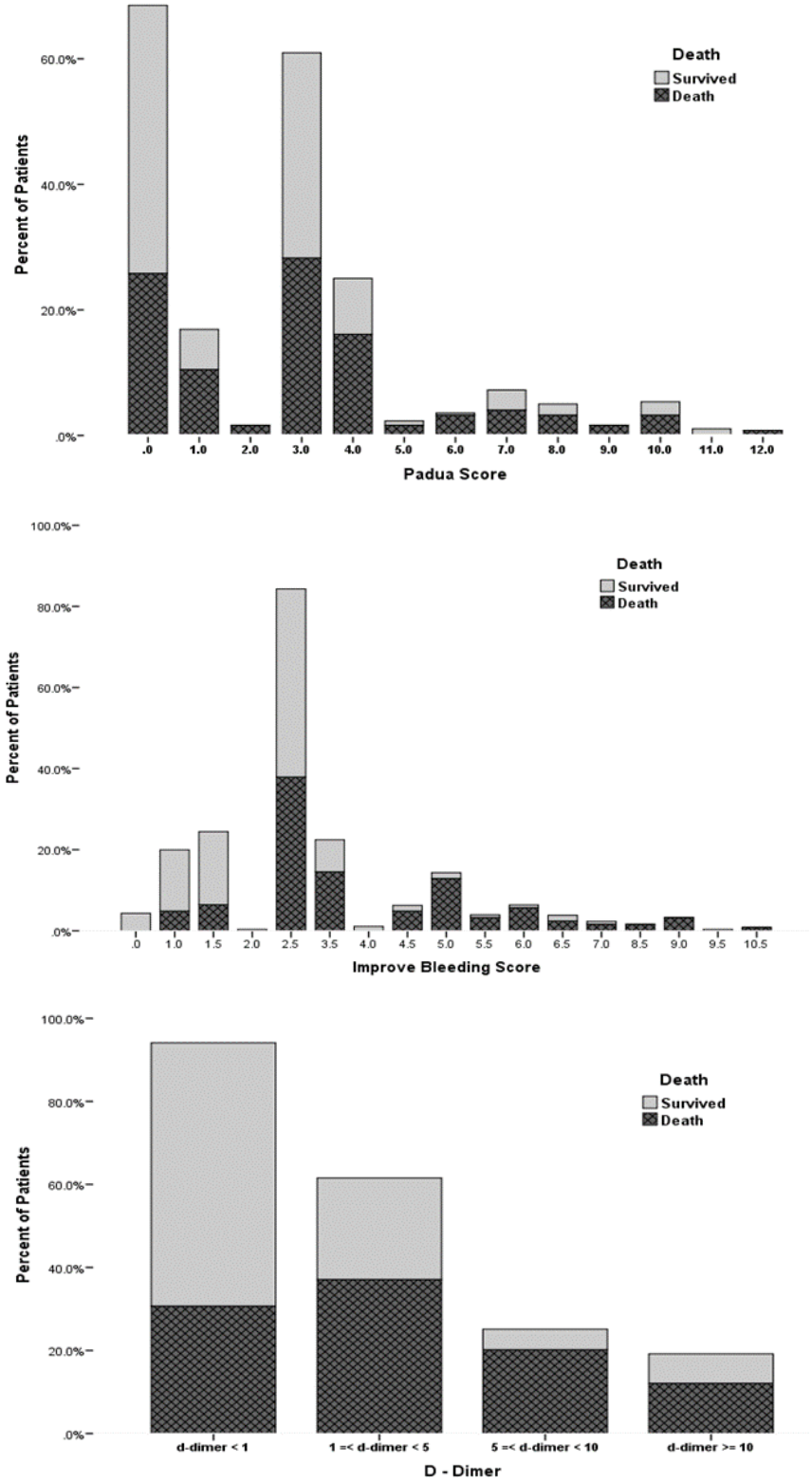

Figure 1. The distribution of patients mortality basis of Padua, Improve Bleeding Score, and D-dimer index.

Considering the effect of all these three indices of Padua index, IBS index, and D-dimer on death or recovery of patients who died and improved on the correlation between these three indices. The results showed that the Padua index in the expired patients had a significant relationship with and D-dimer indices ($P < 0.05$). Therefore, more than 1 D-dimer index increases the Padua index's odds being more than 4 by 3.51 times and the IBS index being more than 7 by 3.29 times. Also, more than 7 IBS index increases the odd Padua index being more than 4 by 11.48 times. (Table 4)

Table 4. Summary of the results of the correlation between Improve Bleeding Score, Pauda Score, and D-dimer.

Padua - D-dimer		D-dimer < 1	D-dimer >= 1	OR (95%CI)	P [1]
		N(%)	N(%)		
Survived	Padua < 4	155 (85.2%)	76 (76.0%)	2.30 (1.02 – 5.14)	0.016
	Padua >= 4	27 (14.8%)	24 (24.0%)		
Death	Padua < 4	32 (84.2%)	50 (58.1%)	3.51 (1.07 – 13.77)	0.014
	Padua >= 4	6 (15.8%)	36 (41.9%)		
IBS - D-dimer		**D-dimer < 1**	**D-dimer >= 1**	**OR (95%CI)**	**P [1]**
		N(%)	**N(%)**		
Survived	IBS < 7	172 (97.2%)	97 (96.0%)	1.43 (0.24 – 8.23)	0.999
	IBS >= 7	5 (2.8%)	4 (4.0%)		
Death	IBS < 7	78 (90.7%)	27 (71.1%)	3.29 (1.05-14.92)	0.007
	IBS >= 7	8 (9.3%)	11 (28.9%)		
Padua - IBS		**IBS < 7**	**IBS >= 7**	**OR (95%CI)**	**P [1]**
		N(%)	**N(%)**		
Survived	Padua < 4	223 (82.9%)	5 (55.6%)	3.72 (0.66 – 22.94)	0.100
	Padua >= 4	46 (17.1%)	4 (44.4%)		
Death	Padua < 4	18 (94.7%)	64 (61.0%)	11.48 (3.51 – 36.67)	0.038
	Padua >= 4	1 (5.3%)	41 (39.0%)		

1. Univariate Logistic Regression with adj. P-value (Bonferroni Correction)
IBS: Improve Bleeding Score, **OR**: Odds Ratio, **95%CI**: 95% Confidence Interval, **P**: P-Value

According to Table 4, further surveys were performed on patients who died of Covid-19 and Padua and IBS indicators. The results showed that among the dead patients, the D-dimer index was significantly associated with age more than70 years, Thrombophilia, and previous VTE of Padua indices (P <0.05). In addition, the results also show that the D-dimer index was significantly associated with age over 85 years and current cancer of IBS indices (P <0.05).

Discussion

This study found that increasing the Padua, IBS and D-dimer indices are effective in mortality in patients with Covid-19. Such a way that is increasing these indicators' level increases the odds of death of these patients. Also, according to this study's results, it was found that the Padua index is significantly correlated with both IBS and D-dimer indices in dead patients with Covid-19. Therefore, according to our studies' results, thrombosis is widespread in patients with Covid-19 and affects these patients' mortality. Furthermore, this study's results are confirmed by several other similar studies that have been performed in this field [18-21]. However, in this study, we examined the effect of pneumonia caused by Covid-19 and the occurrence of thrombosis.

According to research of Regina et al. in Italian cohort study was mentioned that its about 90% of internal medicine patients are in risk of VTE, IBS>7 and Padua score>4 can increase risk of mortality in internal medicine patients [22]. Similar to our results in a prospective study designed by Vardi et al. in 2013 positive Padua score increases significantly risk of mortality in patients with severe septic condition [23].

A study conducted by Huertas et al. demonstrates the early pathogenesis in COVID-19 pneumonia specified by a rampant endothelialitis affecting multiple organ systems. Viral inclusion bodies are considered within endothelial cells accompanied by apoptosis, inflammatory cell infiltration and microvascular thrombosis [24]. However, it is not yet known exactly what causes this disorder in patients with COVID-19.

According to research of Zeng et al. in cohort study was mentioned that COVID-19 patients with PPS=>4 have more comorbidities and a higher White Blood Cells (WBC) count, and a lower lymphocytes and platelets count than patients with PPS=<4. They also have a higher level of inflammatory markers. These patients (PPS=>4) have a significantly higher levels of PT, D-dimer, and fibrinogen. As greater PPS indicates a greater prevalence of co-morbidities and VTE risk assessment, mortality was considerably elevated compared to the VTE low-risk group. The PPS in critically ill patients was higher than that in severely ill ones [25]. Arpaia et al. examined patients that hospitalized at internal medicine unit. The findings suggest that when PSS is greater than or equal to 4, the predicted probability of early death rises. Similarly, a higher or equal IMPROVE bleeding score of 7 is associated with an increased predicted probability of early death [26]. Depietri et al. Found that, 48% of patients exhibited an increased risk of venous thromboembolism (VTE) with a score of PPS ≥ 4. Additionally, 13% of patients demonstrated an elevated hemorrhagic risk, indicated by an IBS ≥ 7. Only 6% of patients presented both heightened thrombotic and hemorrhagic risks, characterized by PPS ≥ 4 and IBS ≥ 7, respectively. The most significant baseline clinical features of hospitalized patients included acute infective disease, reduced mobility, acute heart or respiratory failure, and varying degrees of renal failure. [27]. In another study, Haixia Zhou et al. examined medical inpatients identified as having VTE. This study indicates that the risk of VTE increases almost linearly with cumulative PPS, following adjustments for VTE prophylaxis use [28]. However, PPS demonstrated inefficiency in identifying individuals at risk for VTE, while it accurately identified those at risk for mortality.

In another study conducted by Iba et al., it was found that Patients with Covid-19 exhibit a heightened risk of thrombotic complications. Coagulation disorders may lead to the worsening of a patient's condition as well as elevate the mortality rate.[29]. Cattaneo et al. also studied 184 Covid-19 patients in ICUs. The incidence rate of thrombotic events was determined to be 31%, with 27% diagnosed as venous thromboembolism (VTE) and 3.7% identified as arterial thrombi inside the systemic circulation. This investigation demonstrated that Covid-19 may lead to coagulation abnormalities in both the venous and arterial systems [30]. Flegal et al. reported that 533 out of 3,334 hospitalized Covid-19 patients (16.0%), the majority of whom were administered low-dose anticoagulants for prophylaxis, experienced thrombotic events, with several patients suffering from multiple thromboembolic episodes. Venous thromboembolism was observed in 207 cases (6.2%), while arterial thromboembolism occurred in 365 cases (11.1%).[31]. In China, massive clinical research showed that 46.4% of Covid-19 cases had a raised d-dimer, while the proportion was even higher in ICU patients (59.6%) [32]. Also Goshua et al. found that COVID-19 ICU patients had significantly greater d-dimer levels than non-ICU patients, exceeding the usual reference range.[33]. A recent study indicated a positive correlation between d-dimer levels and mortality in Covid-19 patients who did not receive heparin [34]. Zhang et al. found that the level of d-dimer (>2.0 mg/L) could predict the patient's mortality with 92.3% sensitivity and 83.3% specificity [35]. A research conducted by Demelo-Rodríguez et al. In patients admitted with COVID-19 pneumonia and elevated D-dimer levels, the incidence of asymptomatic deep vein thrombosis (DVT) was comparable to that reported in other studies. Elevated cut-off levels may be necessary for D-dimer assessment in the diagnosis of DVT among COVID-19 patients [36].

In contrast, some studies have stated that no significant difference in platelet count existed between the severe Covid-19 patients and moderate patients [37,38]. Recently, a study also indicated that the platelet count in Covid-19 patients with DVT was not significantly different from those without DVT [39]. However, some cases stated a raised platelet count in severe Covid-19 patients. This event was considered the over-activation of platelets resulting from the over-production of pro-inflammatory factors and forming a cytokine storm [40,41].

Therefore, these Indicators can vary with each individual, and the specific correlation between them and Covid-19 needs more research to reveal.

Limitation

One of the limitations of this study is diagnosing covid-19 disease in patients at the beginning of the study, which slowed down the study process due to the lack of laboratory tools.

Conclusion

A thrombosis is a joint event in patients with Covid-19 pneumonia. Padua index, IBS index, and D-dimer values are elevated in most of these patients and increasing the level of these indicators directly affects these patients' mortality rate. On the other hand, the Padua index has a significant correlation with IBS and D-dimer indices. Therefore, increasing either IBS or D-dimer indices increases the Padua index and ultimately increases the patients' odds of death. Therefore, the medical staff, especially physicians, should pay special attention to increasing the mentioned indicators and preventing high mortality in these patients by using prophylaxis.

Highlights

What Is Already Known?

The association between coagulation abnormalities and adverse outcomes in patients with severe coronavirus disease 2019 (COVID-19) has been well documented. Elevated D-dimer levels, increased thrombotic risk as assessed by the Padua Prediction Score, and bleeding risk evaluated via the Improve Bleeding Score (IBS) have all been linked to higher mortality rates in hospitalized patients.

What Does This Study Add?

This study provides further evidence that elevated Padua index (>4), IBS (>7), and D-dimer levels (>1 mg/L) are significantly associated with increased mortality in patients with COVID-19 pneumonia. It also demonstrates a strong intercorrelation among these indices, particularly showing that elevated D-dimer levels increase the likelihood of high Padua and IBS scores, which in turn amplify mortality risk.

Authors' Contributions

Concept and Design: Maryam Moshkani farahani
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Manuscript editing and review: Mostafa Eslamimahmoudabadi, Mohammadhosein Ranjkesh

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Conflicts of Interest Disclosures

The author's None declared.

Consent For Publication

All authors expressed explicit consent for the publication of this manuscript.

Ethics approval

IBS *Improve Bleeding Score*
Padua *Preoperative Aspects and Dimensions Used for an Anatomical*
CT *Computerized tomography*
BMI *Body mass index*
VTE *Venous Thromboembolism*
ICU *Intensive Care Units*
SD *Standard Deviation*
OR *Odds Ratio*
95% CI *95% Confidence Interval*

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The present study has no Funding resources.

The extent of AI use

I did not use artificial intelligence

Availability of data and materials

All study-related information is stored in secure folders with restricted access. Furthermore, electronic data files are maintained within a file system that restricts access to authorized researchers and data managers. The dataset can be obtained from the corresponding author at the Baqiyatallah Atherosclerosis Research Center.

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