Original Article

Access this article online
Quick Response Code:

Website: www.jfcmonline.com
DOI: 10.4103/jfcm.jfcm_60_23

Risk factors associated with fatal thrombosis in hospitalized coronavirus disease 2019 (COVID-19) patients on anticoagulant therapy

Sholpan Kaliyeva, Yekaterina Yukhnevich, Zhanna Myasnikova, Natalya Simokhina, Nailya Dyussembaeva, Yuliya Bikbatyrova, Yelena Drobchenko[1], Torgin Sagadatova, Polina Semenikhina[2]

Abstract:

BACKGROUND: The purpose of this study was to determine the factors that increase the risk of fatal thrombotic events in hospitalized coronavirus disease 2019 (COVID-19) patients receiving standard therapy according to the National Clinical Practice Guidelines (National Guidelines).

MATERIALS AND METHODS: In this case–control study, cases included 83 adults with COVID-19 who had died from thrombosis and controls comprised 83 COVID-19 patients with comparable criteria who survived. Data was abstracted by reviewing the medical records of selected patients and analyzed using Statistica. Parametric and non-parametric tests, as appropriate, were used to compare continuos variables between cases and controls, whereas Chi-square test was employed to compare categorical variables. Odds ratio (OR) was also calculated to measure the strength of association of case status and various independent variables.

RESULTS: Fatal outcomes were higher in patients with chronic tubulointerstitial nephritis, (OR = 2.4, 95% CI 1.2–4.9); obesity, (OR = 2.1, 95% CI 0.5–8.6); and coronary heart disease (OR = 1.6, 95% CI 0.8–3.2). In the group with a D-dimer level from 250 to 1000 ng/ml, a statistically significant moderate positive correlation was found between the day of death and D-dimer level ($P = 0.026$). The lack of use of the PADUA Prediction Score for the risk of venous thromboembolism scale (PADUA Scale) and control of laboratory parameters (APTT and D-dimer) were associated with increased risk of fatal outcome. Overall, 19.2% cases and 8.4% of controls had no coagulation control; (OR = 2.6, 95% CI 1–6.7).

CONCLUSION: Chronic tubulointerstitial nephritis, obesity, and coronary heart disease were associatied with fatal thrombosis. A slight elevation of D-dimer level, lack of the PADUA Scale and laboratory monitoring in the management of hospitalized patients with COVID-19. was associated with an increased risk of thromboembolism.

Keywords:

Coronavirus disease 2019, risk factors, thrombosis

Departments of Clinical Pharmacology and Evidence-Based Medicine, [1]Informatics and Biostatistics and [2]Neurology, NCJSC Karaganda Medical University, Karaganda, Kazakhstan

Address for correspondence:
Dr. Yekaterina Yukhnevich, 100017, Gogolia Street 40, Karaganda, Kazakhstan.
E-mail: 3204229@gmail.com

Received: 17-03-2023
Revised: 22-07-2023
Accepted: 02-09-2023
Published: 13-10-2023

Introduction

The first case of coronavirus disease 2019 (COVID-19) was registered in the Republic of Kazakhstan on March 13, 2020. From March 2020 to October 2022, 1,394,714 laboratory-confirmed cases of infection were detected in the country; 1,380,159 people recovered, and 13,692 people died. The mortality level in Kazakhstan is comparable with worldwide data.[1,2]

How to cite this article: Kaliyeva S, Yukhnevich Y, Myasnikova Z, Simokhina N, Dyussembaeva N, Bikbatyrova Y, *et al*. Risk factors associated with fatal thrombosis in hospitalized coronavirus disease 2019 (COVID-19) patients on anticoagulant therapy. J Fam Community Med 2023;30:273-9.

The leading causes of death according to various studies were thrombosis and coagulopathy.[3] The main factors contributing to the poor outcomes in COVID-19 were associated with a higher degree of lung parenchymal lesions,[4] male gender, and comorbidity with respiratory, cardiology, and endocrinology diseases.[5]

Despite the development and implementation of the National Guidelines for patients with COVID-19 that unify evidence-based approaches to therapy, including anticoagulants, the desired results of treatment in some cases were still unreachable.

The aim of the research was, thus, to study the factors that increased the risk of fatal thrombotic events in hospitalized COVID-19 patients receiving standard therapy according to the National Guidelines.

Materials and Methods

In a retrospective case–control study, we analyzed 16,898 electronic medical records of adult patients with a positive polymerase chain reaction result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), who were hospitalized in regional medical institutions of the Karaganda region, Kazakhstan, from January to May 2021. The materials for this study were taken from the electronic Regional Integrated Health Information System, access to which was provided for the study of the quality of medical care for patients with COVID-19 in the Karaganda region. Ethical approval was obtained from the Institutional Ethics Committee vide Letter No. 66 dated 30/05/2022, with a waiver of informed consent since there was no direct involvement of human subjects in this study.

In our study of 16,898 medical records of patients who were treated according to the National Guidelines, 173 cases of patients with COVID-19 with a fatal outcome from various causes were selected. Eighty-three cases of these had fatal pulmonary embolism (verified through clinical autopsy) and were distributed for the case group. The remaining cases (90 cases) were not included because other causes of death were specified, and/or clinical autopsy results were not available; patients who died within 24 h of admission were also not included. For the control group, 83 cases of survived patients were selected according to the following comparable criteria: participants matching with cases on parameters of age (+ 2 years), gender, hospital/medical institution, the identical month of hospitalization, and the volume of lung tissue damage on computed tomography (CT) [Figure 1].

D-dimer was analyzed in both groups for assessment of the correlation between its level and fatal thrombosis. The D-dimer parameters from medical records in the case group were determined at the time of admission to the hospital, at the time of transfer to the intensive care unit (ICU), and at last measurement recorded before death; in the control group – at admission, at the time of transfer to the ICU, and at discharge from hospital. Depending on the level of D-dimer, all patients were divided into three groups: Group 1 – D-dimer <250 ng/ml, Group 2 – 250–1000 ng/ml, and Group 3 – 1000 and more ng/ml.

Data statistical processing was carried out using the descriptive statistics program Statistica 8.0 (StatSoft, Russia). Data were described as frequency (%) for categorical variables and mean (confidence interval [CI] 95%) for continuous variables. The parametric tests were used (Student's *t*-test and methods of correlation analysis), the nonparametric Mann–Whitney *U*–test was used to compare two independent samples, and the *Z*–test was used to compare categorical variables. The significance of differences in the compared parameters was determined starting from $P < 0.05$.

Results

All patients from the case and control groups received the standard therapy, including anticoagulants in accordance with the National Guidelines.[6]

In the case group, the mean age of patients was 69.2 years (CI 95% 66.7–71.7); in the control group, it was 68.2 years (CI 95% 66.0–70.4); no statistical differences were observed ($P = 0.566$). The gender distribution showed that men accounted for 43.3% and women for 56.6% of patients in both groups. The day of death of the case group patients was compared with the day of discharge of the control group patients. The mean hospital stays of patients in the case group was 10.2 days, and in the control group was 11.9 days [Table 1].

Multimorbidity was characteristic for many patients infected with SARS-CoV-2, leading us to evaluate the influence of comorbidity on an unfavorable outcome. The results showed that all patients in the case group and 96.4% ($n = 80$) of the control group had comorbidities. Moreover, the patients suffered from two or more concomitant diseases in 95.2% ($n = 79$) of cases in the group with fatal outcomes and in 80.7% ($n = 67$) in the control group. The most common were cardiovascular diseases: in the case group – 94% ($n = 78$), and in the control group – 90.4% ($n = 75$).

In both groups, there was a high prevalence of arterial hypertension (more than 60%) and coronary artery disease (more than 20%). Furthermore, our study revealed that a history of previous conditions associated with a high risk of thrombosis (acute coronary syndrome,

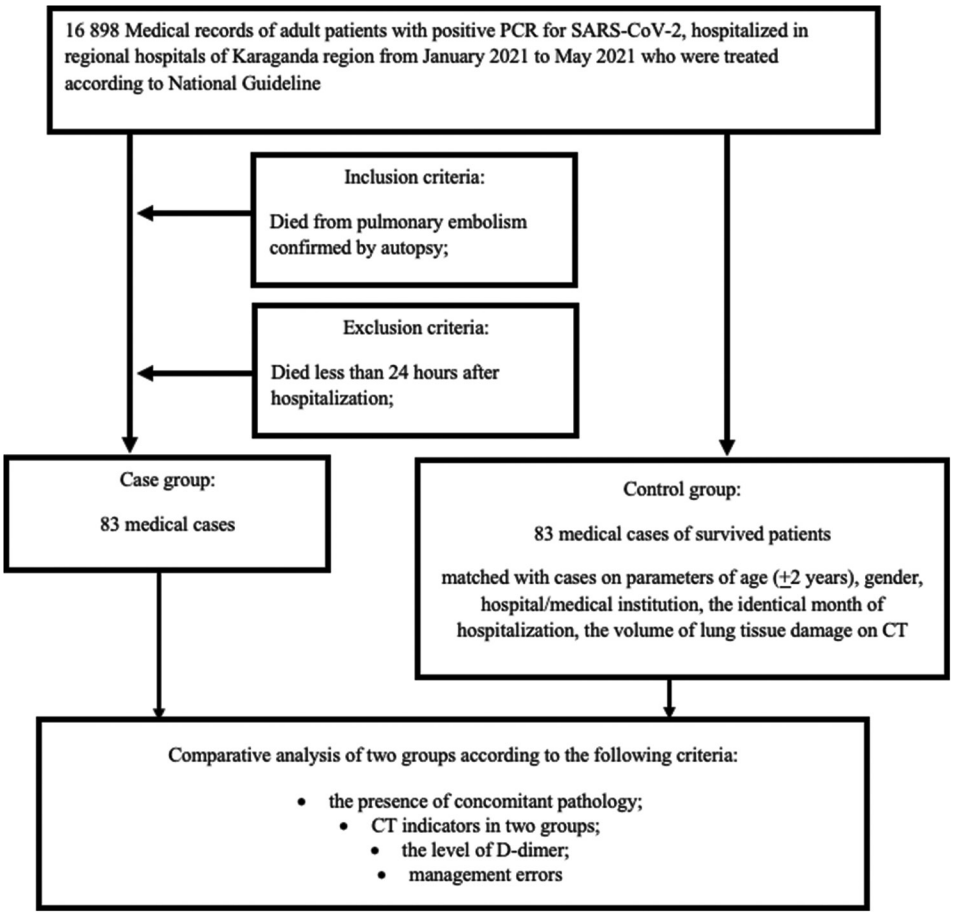

Figure 1: Overview of the study

Table 1: Characteristics of COVID-19 patients with fatal outcomes by pulmonary embolism case status, Karaganda region, Kazakhstan 2021

Variables	Pulmonary embolism		*P*-value
	Yes *N* (%)	No *N* (%)	
Age (years), mean	69.2	68.2	0.566
Males	36 (43.3)	36 (43.3)	
Females	47 (56.6)	47 (56.6)	
Average hospital stay (days)	10.2	11.9	0.0113
Concomitant diseases			
Arterial hypertension	51 (61.4)	52 (62.6)	0.873
Coronary artery disease	24 (28.9)	17 (20.5)	0.208
Diabetes mellitus	22 (26.5)	30 (36.1)	0.181
Obesity	6 (7.2)	3 (3.6)	0.304
Chronic tubulointerstitial nephritis	32 (38.5)	17 (20.5)	0.011

ischemic stroke, and stenting) in the year before hospitalization was a predictor of lethal outcome in patients with COVID-19 (OR = 7.4, CI 95% 2–26). Thus, in the case group, previous thrombosis was detected in 21.7% (n = 18) of patients, and in the control group only in 3.7% (n = 3, P = 0.001).

In the second place in terms of frequency in both groups was endocrine diseases, (more than 50%), particularly, type 2 diabetes mellitus and obesity. The third in frequency in both groups was chronic tubulointerstitial nephritis: 38.5% (n = 32) in the case group and 20.5% (n = 17) in the control group (P = 0.011).

On calculating the relationship between comorbidities and the likelihood of a fatal outcome, it was found that the probability of a fatal outcome was higher in patients with chronic tubulointerstitial nephritis, OR = 2.4 (CI 95% 1.2–4.9), obesity, OR = 2.1 (CI 95% 0.5–8.6), and coronary heart disease, OR = 1.6 (CI 95% 0.8–3.2).

The distribution of degrees of lung tissue lesion according to CT[7] in the case and control groups is shown in Figure 2. In the case group, 25.9% of patients had CT3, and 54.3% had CT4, while in the control group, 40.2% of patients had CT2 and 37.8% had CT3. The OR between the case group and the control group clearly showed that the risk of death was 4.88 times higher in patients with extensive lesions of the lung tissue according to CT (P < 0.05).

We analyzed the relationship between D-dimer and the development of thromboembolism since there was

evidence of the significance of this indicator in assessing the risk of death.[8-10] Determination of the D-dimer level was carried out in 79 patients of the case group and 80 patients of the control group [Table 2].

Analysis of the D-dimer values showed that 88.6% (n = 70) of the case group and 66.2% (n = 53) of the control had an abnormal D-dimer level at the time of hospitalization. D-dimer over 1000 ng/ml was detected in 49.8% (n = 39) of patients of the case group versus 17.5% (n = 14) of the control group; D-dimer level from 250 to 1000 ng/ml in 39.2% of patients (n = 31) in the case group versus 48.8% (n = 39) in the control group; and D-dimer of level less than 250 ng/ml was detected in 11.4% of patients (n = 9) in the case group and 33.8% of patients (n = 27) in the control group.

A correlation analysis was done between the D-dimer level and the day of death for the case group and the average hospital stay for the control group. On evaluating the relationship between the day of death of the patients in the case group and the level of D-dimer on admission to the ICU, it was found that in the group with a D-dimer level of 250–1000 ng/ml, a statistically significant moderate positive correlation was found between the day of death and D-dimer level (P = 0.026); in the remaining groups, no relationship was found between the day of death and the level of D-dimer.

The next stage of the analysis was an assessment of management errors of patients according to the medical records. As a result of a retrospective clinical assessment, the following differences were revealed in the patients' management [Figure 3].

The most significant proportion of management errors was associated with the lack of use of thrombosis risk assessment with the PADUA Scale and the monitoring of laboratory parameters, late patients transfer to the ICU, and absence of CT control.

According to the International Recommendations and the National Guidelines,[6] the routine use of the PADUA Scale is recommended to define the appropriate tactics of anticoagulant therapy. In our study, the most commonly found error in patient management was the omission of the PADUA Score by doctors; in the case group, this error was noted in 80.7% (n = 67) of cases, and in the control group in 81.9% (n = 68). Table 3 presents data on the assessment of the use of the PADUA Scale in groups.

The PADUA Scale was used for 19.3% (n = 16) of patients in the case group and for 18.1% (n = 15) in the control group. It should be noted that in the case group, 14.5% (n = 12) of the situations were assessed incorrectly by the doctors, while in the control group, this problem was confirmed for 2.4% (n = 2) of cases.

The second most commonly detected error was the lack of thrombosis risk control with laboratory tests: coagulogram, in general, as well as APTT and D-dimer. Figure 4 presents a frequency analysis of defects associated with the absence of laboratory parameters monitoring in COVID-19 patients.

Thus, the lack of APTT control during anticoagulant therapy was recorded in 31.3% (n = 26) in the case group versus 8.4% (n = 7) in the control group. There was no dynamic control of D-dimer to assess the severity of the patients' condition in 19.2% (n = 16) in the case group and in 13.2% (n = 11) of the control group. Overall, 19.2% (n = 16) of the case group and 8.4% (n = 7) of the control group had no coagulation

Table 2: D-dimer levels in COVID-19 patients with fatal outcomes by pulmonary embolism case status, Karaganda region, Kazakhstan 2021

D-dimer value (ng/mL)	Pulmonary embolism		*P*-value
	Yes *N* (%)	No *N* (%)	
<250	9 (11.4)	27 (33.8)	0.001
250–1000	31 (39.2)	39 (48.7)	0.209
>1000	39 (49.4)	14 (17.5)	<0.001

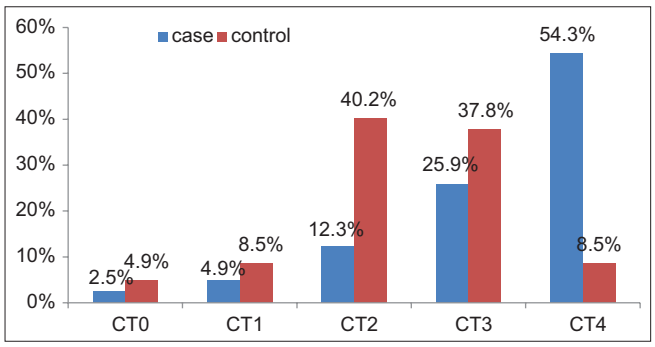

Figure 2: The distribution of degrees of lung tissue lesion according to computed tomography in the groups

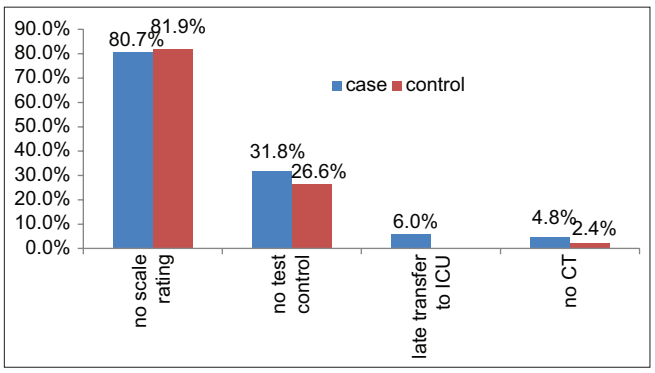

Figure 3: Frequency analysis of identified errors in the management of patients with COVID-19

Table 3: Frequency of venous thromboembolism risk assessment using the PADUA Prediction Score (*n*=83)

Scale assessment in the hospital	Pulmonary embolism		*P*-value
	Yes *N* (%)	No *N* (%)	
Not performed	67 (80.7)	68 (81.9)	0.842
Performed incorrectly	12 (14.5)	2 (2.4)	0.005
Performed correctly	4 (4.8)	13 (15.7)	0.021

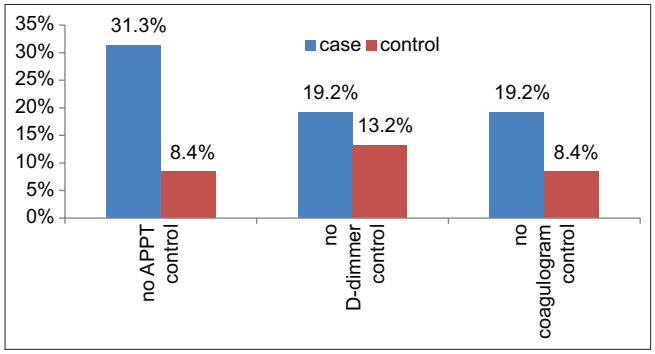

Figure 4: Frequency analysis of identified errors in the management of patients with COVID-19

control. However, the relationship between this defect and the development of the lethal outcome was weak, OR = 2.6 (CI 95% 1–6.7).

An analysis of the timing of transfer to the ICU showed a delay in the case group. The average delay was 6 h after the deterioration of the patient's condition, while in the control group, no such cases were detected. A total of 6% ($n = 5$) of such cases were identified in the case group.

Furthermore, in both groups, the lack of CT control of the disease progression was observed in 4.8% ($n = 4$) in the case group versus 2.4% ($n = 2$) in the control group.

Discussion

Previous studies assert that approximately 50% of patients infected with SARS-CoV-2 had multimorbidity, while its frequency increased to 72% for severe COVID-19 cases.[7,11] Cardiovascular diseases, obesity, and diabetes mellitus, often recorded in patients with COVID-19,[12-14] were also detected in our research. However, the correlation between the death from thromboembolism and obesity ($P = 0.304$) and coronary heart disease ($P = 0.208$) was insignificant.

Nonetheless, in our study, the history of acute coronary syndrome, ischemic stroke, and stenting within a year before hospitalization was a predictor of death in patients with COVID-19 (OR = 7.4, CI 95% 2–26). These results correspond with previous studies on the relationship of concomitant noninfectious diseases and death resulting from thrombosis.[15,16]

Other authors note that kidney disease also independently correlates with a higher risk of death from thrombosis.[17] In our research, a similar correlation was confirmed between the death from thromboembolism and the presence of chronic tubulointerstitial nephritis ($P = 0.011$).

The results of this study also correlate with worldwide data about the degree of lung injury on CT and the development of venous thromboembolic complications, which confirms that a bigger volume of lung injury causes a higher risk of death, regardless of age, the presence of comorbidities, and other risk factors.[18-21] Our study determined the risk of death from thromboembolic complications as 4.88 times higher in patients with extensive lesions of the lung tissue according to CT ($P < 0.05$).

COVID-19 infection is associated with microvascular inflammation and thrombosis,[22,23] which is reflected by an increase in inflammation markers and D-dimer.[24] A study by Nadeem *et al*., stated that the level of D-dimer is one of the factors affecting 28-day survival,[8] and some other researchers have presented similar results.[25,26] A multivariate analysis conducted by Chinese scientists showed that D-dimer levels >1 μg/L during hospitalization correlated with higher mortality.[27,28] The results of our study confirmed that a D-dimer level higher than 1000 ng/ml increased the risk of thromboembolism by 4.56 times. There was also a statistically significant positive relationship of moderate strength between the day of death and the level of D-dimer in the group with a D-dimer of 250–1000 ng/ml ($P = 0.026$).

There were errors in the management of patients, particularly, the lack of control of laboratory tests: coagulogram, in general, as well as APTT and D-dimer in both groups. The absence of a coagulogram was observed in 19.2% ($n = 16$) of patients in the case group and 8.4% ($n = 7$) of patients in the control group. The lack of APTT control was detected in 31.3% ($n = 26$) of the case group and 8.4% ($n = 7$) of the control group. Furthermore, it was revealed that 19.2% ($n = 16$) of the case group and 13.2% ($n = 11$) of the control group had no D-dimer control. Although the inattention of the doctors to the assessment of the level of D-dimer is disquieting, our study revealed no association between a lack of D-dimer control and mortality (OR = 1.6, CI 95% 0.7–3.6).[29]

However, an analysis of patient management errors, including an assessment of the CT control, the timing of patients transfer to the ICU, and the use of the PADUA Scale, revealed that the numbers for all the listed indicators in both groups were comparably low, except for the last. In the case group, the PADUA Scale was not used in 80.7% ($n = 67$) of cases, while

in the control group, this number was 81.9% (n = 68). It was striking that in 14.5% (n = 12) of cases in the case group and 2.4% (n = 2) in the control group, the interpretation of the PADUA Scale was carried out incorrectly ($P < 0.005$). This study revealed that there was little application of the PADUA Scale by the doctors, although the National Guidelines included evidence-based recommendations for assessing the risk of thromboembolism using valid scales[30,31] directly after the international data on the development of endotheliopathy, hyperactivity of the coagulation cascade, and micro-macro thrombosis with COVID-19 were made known.

There are limitations in the data obtained in our study, since in any retrospective study, there could be distortions and the lack of clear entries in the electronic medical records of patients.

Conclusion

The results of our study confirm once again the global data on the influence of such factors as comorbidity, high degree of lung tissue lesion, and D-dimer level on predicting the risk of death as a result of thromboembolism in COVID-19.

We found that chronic tubulointerstitial nephritis as well as a history of conditions associated with a high risk of thrombosis in the year before hospitalization was associated with a higher incidence of death from thromboembolism. Furthermore, a slight elevation of D-dimer level was associated with an increased risk of thromboembolism. However, these factors, unlike the management errors observed in our study, cannot be modified. The use of the PADUA Scale, regular instrumental and laboratory monitoring, and timely correction of patient management contribute to the survival from COVID-19. Therefore, it is critically important for practitioners not to simply rely on their own clinical experience, but to use the current prediction methods according to the guidelines.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Coronovirus Disease 2019 (COVID-19). Symptoms, Diagnosis, Treatment. BMJ Best Practice. Available from: https://www.bestpractice.bmj.com/topics/ru-ru/3000201. [Last accessed on 2022 Sep 05, Last updated on 2022 Jul 08].
2. Coronavirus in Kazakhstan – Statistics. Available from: https://www.coronavirus2020.kz/. [Last accessed on 2022 Sep 05, Last updated on 2023 Jul 21].
3. Makatsariya AD, Slukhanchuk EV, Bitsadze VO, Khizroeva JK, Tretyakova MV, Shkoda AS, *et al.* Thrombotic storm, hemostasis disorders and thromboinflammation in COVID-19. Obstet Gynecol Reprod 2021;15:499-514.
4. Morozov SP, Gombolevskiy VA, Chernina VY, Blokhin IA, Mokienko OA, Vladzimirskiy AV, *et al.* Prediction of lethal outcomes in COVID-19 cases based on the results chest computed tomography. Tuberc Lung Dis 2020;98:7-14.
5. Milota T, Sobotkova M, Smetanova J, Bloomfield M, Vydlakova J, Chovancova Z, *et al.* Risk factors for severe COVID-19 and hospital admission in patients with inborn errors of immunity – Results from a multicenter nationwide study. Front Immunol 2022;13:835770.
6. Coronavirus Infection in Adults (6th Edition of 25.07.2022) > Clinical Protocols MH RK – 2022 Kazakhstan. Available from: https://www.diseases.medelement.com/disease/coronavirus-infection-covid-19-in-adults-6-revision-kp-rk-2022/17238. [Last accessed on 2022 Aug 01].
7. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
8. Nadeem I, Anwar A, Jordon L, Mahdi N, Rasool MU, Dakin J, *et al.* Relationship of D-dimer and prediction of pulmonary embolism in hospitalized COVID-19 patients: A multicenter study. Future Microbiol 2021;16:863-70.
9. Gómez CA, Sun CK, Tsai IT, Chang YP, Lin MC, Hung IY, *et al.* Mortality and risk factors associated with pulmonary embolism in coronavirus disease 2019 patients: A systematic review and meta-analysis. Sci Rep 2021;11:16025.
10. Hilda F, Liana P, Nurtjahyo A, Hudari H, Sari NP, Umar TP, *et al.* D-Dimer as a sensitive biomarker of survival rate in patients with COVID-19. Eurasian J Med 2022;54:219-24.
11. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Medicine [Internet]. 2020;46:846-8. Available from: https://pubmed.ncbi.nlm.nih.gov/32125452/.
12. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, *et al.* Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. Eur Respir J 2020;55:2000547.
13. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323:1775-6.
14. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, *et al.* Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;323:2052-9.
15. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395:1054-62.
16. Chen R, Liang W, Jiang M, Guan W, Zhan C, Wang T, *et al.* Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. Chest 2020;158:97-105.
17. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
18. Zakariaee SS, Salmanipour H, Naderi N, Kazemi-Arpanahi H, Shanbehzadeh M. Association of chest CT severity score with mortality of COVID-19 patients: A systematic review and meta-analysis. Clin Transl Imaging 2022;10:663-76.
19. Kampouri E, Filippidis P, Viala B, Méan M, Pantet O,

Desgranges F, *et al*. Predicting venous thromboembolic events in patients with coronavirus disease 2019 requiring hospitalization: An observational retrospective study by the COVIDIC initiative in a Swiss university hospital. Biomed Res Int 2020;2020:9126148.
20. Charpentier E, Soulat G, Fayol A, Hernigou A, Livrozet M, Grand T, *et al*. Visual lung damage CT score at hospital admission of COVID-19 patients and 30-day mortality. Eur Radiol 2021;31:8354-63.
21. Zakariaee SS, Naderi N, Rezaee D. Prognostic accuracy of visual lung damage computed tomography score for mortality prediction in patients with COVID-19 pneumonia: A systematic review and meta-analysis. Egypt J Radiol Nucl Med 2022;5:64.
22. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, *et al.* Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res 2020;220:1-13.
23. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: Vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med 2020;46:1105-8.
24. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: A meta-analysis. Ther Adv Respir Dis 2020;14:1753466620937175.
25. Yu HH, Qin C, Chen M, Wang W, Tian DS. D-dimer level is associated with the severity of COVID-19. Thromb Res 2020;195:219-25.
26. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, *et al.* D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. J Intensive Care 2020;8:49.
27. Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, *et al*. Deep vein thrombosis in hospitalized patients with COVID-19 in Wuhan, China: Prevalence, risk factors, and outcome. Circulation 2020;142:114-28.
28. Cai C, Guo Y, You Y, Hu K, Cai F, Xie M, *et al.* Deep venous thrombosis in COVID-19 patients: A cohort analysis. Clin Appl Thromb Hemost 2020;26:1076029620982669.
29. Rashidpouraie R, Sharifi M, Mostaghim S. COVID-19 and medical error. J Iran Med Counc 2022;5:334-7.
30. Sjr M. Correlation between coagulation tests parameter with Padua prediction score in COVID-19 patients at general hospital of Prof. Dr. R. D. Kandou Manado. Int J Blood Res Disord 2022;9:079. Available from: https://www.clinmedjournals.org/articles/ijbrd/international-journal-of-blood-research-and-disorders-ijbrd-9-079.php?jid=ijbrd. [Last accessed on 2023 Jun 06].
31. Wei G, Yang G, Lu S, Shuang L. Validity of Padua forecast score table in assessment the risk of deep venous thrombosis of patients with corona virus disease 19. Chinese medicine 2020;07:981-3. Available from: https://www.pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/pt/czh-46. [Last accessed on 2022 01 Aug].