Journal of Taibah University Medical Sciences (2023) 18(5), 1089–1098

Taibah University

Journal of Taibah University Medical Sciences

www.sciencedirect.com

Original Article

Prognostic markers in patients with COVID-19 requiring intensive care support

Khalid A. Maghrabi, MRCP(UK) [a], Fatmah S. AlQahtany, MD [b], Hadeel AlOtair, MD [c], Mohannad K. Maghrabi, MD [d], Khalid AlSaleh, MD [e] and Tarek Owaidah, MD [f,g,*]

[a] *Department of Critical Care Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, KSA*
[b] *Department of Pathology, Hematopathology Unit, College of Medicine, King Saud University, King Saud University Medical City, Riyadh, KSA*
[c] *Department of Medicine, King Saud University, King Saud University Medical City, Riyadh, KSA*
[d] *Department of Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, KSA*
[e] *Department of Medicine, College of Medicine, King Saud University, Riyadh, KSA*
[f] *Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, KSA*
[g] *Alfaisal University, Riyadh, KSA*

Received 12 July 2022; revised 5 February 2023; accepted 27 February 2023; Available online 10 March 2023

المخلص

أهداف البحث: هدفت هذه الدراسة إلى تقييم مستويات معلمات الدم والتخثر المختلفة التي تم جمعها في نقاط زمنية مختلفة للتنبؤ بمضاعفات أو نتائج مرضى كوفيد-19 الذين تم إدخالهم في وحدة العناية المركزة.

طرق البحث: أجرينا دراسة استطلاعية متعددة المراكز في أقسام وحدة العناية المركزة، وأدرج 118 مريضا من كوفيد-19 تم قبولهم في وحدة العناية المركزة. تم جمع البيانات السريرية وعينات الدم من اختبارات الدم الروتينية واختبارات التخثر عند الدخول، وفي الأيام 3 و 7 و 14. كانت مقاييس النتائج الرئيسية هي متطلبات التدفق العالي للأكسجين، والتخثر، والوفيات لمدة 30 يوما.

النتائج: كان متوسط مدة الإقامة في وحدة العناية المركزة لمرضى عينة الدراسة 15.70 + 19 يوما بمتوسط 9. وقد تطول بشكل ملحوظ في المرضى المتعافين بمتوسط 28.20 + 29.90 يوما والمرضى الذين يعانون من تجلط الدم 34.40 + 39.60 يوما. تلقى ما مجموعه 113 (95.70٪) مريضا منع تخثر وقائي عند الدخول بأنظمة مختلفة، ومع ذلك، لوحظ تجلط الدم في أربعة (3.90٪) مرضى، لكن لم يمت أي منهم. كان هناك اتجاه تصاعدي في نتيجة الجلطات الدموية الوريدية بمرور الوقت من متوسط 5.10 + 2 في اليوم صفر إلى متوسط 6.40 + 2.80 في اليوم 14. ارتبطت درجة التخثر المنتشر داخل الأوعية بشكل كبير مع تجلط الدم. كان لدى 41.20 ٪ من المرضى في وحدة العناية المركزة درجة تخثر منتشر داخل الأوعية ≥4، وكان لدى 11.40 ٪ أقل من 4. ارتبط معدل الوفيات بشكل سلبي مع المرضى الذين عولجوا مع أوكسجين عالي التدفق، 9 (10.80٪)، وارتبط بشكل إيجابي مع المرضى الذين يستخدمون جهاز التنفس الصناعي، 16 (27.50٪). ارتبطت الزيادة في عدد خلايا الدم البيضاء (نسبة خطر التوزيع الفرعي: 0.91؛ فاصل الثقة 95٪: 0.80-1.0) وعدد العدلات (نسبة خطر التوزيع الفرعي: 1؛ فاصل الثقة 95٪: 1.01-1.05) بزيادة شدة المرض جنبا إلى جنب مع زيادة مستويات دي-دايمرز (نسبة مخاطر التوزيع الفرعي: 1.60 ؛ فاصل الثقة 95٪: 1.10-2.5).

الاستنتاجات: تعد مستويات دي-دايمر ومستويات التخثر المنتشر داخل الأوعية علامات تنبؤية قد تتنبأ بشدة المرض لدى مرضى كوفيد-19.

الكلمات المفتاحية: التخثر؛ علامات؛ العناية المركزة؛ كوفيد-19؛ المملكة العربية السعودية

Abstract

Objectives: Several hematological and immunological markers, particularly neutrophil count, predict the severity of COVID-19. This study aimed at assessing hematological and coagulation parameters at different time points, to predict the complications or outcomes of patients with COVID-19 admitted to the intensive care unit (ICU).

Methods: We conducted a prospective observational multicenter study in ICU departments. A total of 118 patients with COVID-19 admitted to the ICU were

* Corresponding address: Haematology and Transfusion Medicine, King Faisal Specialist Hospital, Alfaisal University, Centre of Excellence in Thrombosis and Hemostasis, P.O. Box 3354, Riyadh 11211, KSA.
E-mail: towaidah@kfshrc.edu.sa (T. Owaidah)

Peer review under responsibility of Taibah University.

Production and hosting by Elsevier

 https://doi.org/10.1016/j.jtumed.2023.02.013

included. Clinical data and blood samples from routine hematology and coagulation tests were collected at admission, and on days 3, 7, and 14. The main outcome measures were high-flow-O_2 requirement, thrombosis, and 30-day mortality.

Results: The venous thromboembolism score increased from a mean of 5.10 ± 2 on day 0 to 6.40 ± 2.80 on day 14 ($P = 0.0002$). The disseminated intravascular coagulation (DIC) score significantly correlated with thrombosis ($P = 0.031$). A total of 41.20% of patients in the ICU had a DIC score ≥4, and 11.40% had a score <4. Mortality was negatively associated with patients on high-flow O_2, 9 patients (10.80%) ($P = 0.040$), and positively associated with patients receiving ventilation, 16 patients (27.50%) ($P < 0.001$). An increase in white blood cell count (subdistribution hazard ratio (SHR): 0.91; 95% CI: 0.80−1) and neutrophil count (SHR: 1; 95% CI: 1.01−1.05) was associated with greater disease severity and D-dimer level (SHR: 1.60; 95% CI: 1.10 −2.5).

Conclusion: The venous thromboembolism score was significantly higher for patients who died than those who recovered. Furthermore, mechanical ventilation was associated with high mortality, whereas the risk of thrombosis and ICU admission correlated with high D-dimer values and DIC scores. Therefore, D-dimer levels and DIC scores are prognostic markers that may predict disease severity in patients with COVID-19.

Keywords: Coagulation; COVID-19; ICU; Markers; KSA

Introduction

An outbreak of acute pneumonia in Wuhan, China, in December 2019, due to a causative agent belonging to the Coronaviridae family of widely distributed RNA viruses, led to a global pandemic of Coronavirus Disease 2019 (COVID-19). The causative agent was a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, the virus has affected almost 280 million individuals, and caused nearly 5.4 million deaths worldwide.[1] In the KSA, 552,081 COVID-19 cases and 8869 deaths have been reported.[1,2]

The virus spreads rapidly among humans, and various factors may predict clinical outcomes, including chest X-ray/CT manifestations, respiratory rate, oxygen saturation, and blood leukocyte/lymphocyte count.[3] Patients with, rather than without, dyspnea, anorexia, and complications are more likely to require ICU admission.[4] Nonsurvivors tend to be older adults who are at higher risk of developing acute respiratory distress syndrome and are receiving invasive or noninvasive mechanical ventilation.[5] The reported mortality among critically ill patients is high, at ∼61.5% within 28 days.[5]

Several hematological and immunological markers, particularly neutrophil count, can help predict the severity of COVID-19.[6] Although patients with COVID-19 admitted to ICUs typically develop respiratory and digestive complications,[7,8] in some cases, coagulopathy has also been reported and associated with poor prognosis.[9] Disseminated intravascular coagulation (DIC) is characterized by systemic activation of blood coagulation that leads to fibrin generation and deposition, and the formation of microvascular thrombi in various organs, and has been associated with the COVID-19 survival rate. The DIC score is calculated by measurement of platelet count, D-dimer level, fibrinogen, and prothrombin time. A score ≥5 indicates overt DIC.[10] Tang et al. have reported that only 0.6% of survivors, compared with 71.4% of nonsurvivors, meet the criteria for DIC. Chen et al.[11] have also reported abnormal coagulation function, including attenuated prothrombin time (PT) in 30% of patients, elevated D-dimer level in 36% of patients, and prolonged activated partial thromboplastin time (aPTT) in 16% of patients. The levels of coagulation markers differ between patients with COVID-19 and patients with non-COVID-19 acute respiratory distress syndrome.[12] Heparin decreases mortality in patients with severe with COVID-19 meeting the sepsis-induced coagulopathy criteria or with markedly elevated D-dimer levels.[13] On the basis of standard coagulation markers, recent recommendations on coagulopathy management have been proposed by the International Society of Thrombosis and Hemostasis.[14]

In a multicenter Saudi study conducted on 636 patients with COVID-19, the risk of an arterial and venous thrombotic event (VTE) in ICU patients was higher than that in non-ICU patients. The rate of VTE was reported to be 0.19% in the non-ICU group and 10.3% in ICU patients. The rate of arterial events was 0.94% in non-ICU patients, compared with 8.4% in the ICU group. Elevated D-dimer level at baseline emerged as a predictor of thrombotic complications in patients with COVID-19. The study further suggested that intensifying anticoagulation in patients with COVID-19 beyond the standard of care should be pursued cautiously.[15] Nevertheless, in-hospital anticoagulation therapy is associated with a decrease in mortality and intubation among hospitalized patients with COVID-19.[16,17]

Various studies have reported changes in the expression patterns of hematological and coagulation markers in patients with COVID-19. However, further worldwide data are required to predict the precise roles of these markers in disease severity. This study aimed to assess the levels of multiple hematological and coagulation markers collected at different times to identify associations with complications or outcomes in patients with COVID-19 admitted to the ICU.

Materials and Methods

Study design and participants

This multicenter, prospective observational study was performed from April 2020 to July 2020, at two major

tertiary care centers (King Faisal Specialist and King Khalid University hospitals) in Riyadh, KSA, of both centers. In this cross-sectional study, 118 patients (≥18 years of age) admitted with laboratory-confirmed SARS-CoV-2 infection were included. Patients with COVID-19 who were transferred from other hospitals and patients who were already intubated at the start of the study were excluded. If a patient could not provide consent, electronic documented verbal informed consent was obtained from all study participants or their family members. Participants were allowed to withdraw at any time and have their collected samples destroyed if they had not already been analyzed.

Data collection

Demographic data, laboratory data, and vital parameters were collected via an electronic patient chart (CERNER). Patient privacy was maintained through data collection in a private electronic database. The collected data were entered into a password-protected database (REDCap) with access restricted to only the research team. Alphanumeric study IDs were assigned to each participant, thereby ensuring data confidentiality. Any links between the identifier and study code were deleted at the end of the study, and an anonymized dataset will be retained for at least 5 years after study completion, per Medical Research Council policy. Clinical data and outcomes were prospectively collected from the hospital's electronic medical records at admission, and days 3, 7, and 14. Comorbidities, including cancer, hyperlipidemia, hypertension, and diabetes, were defined according to the medical history. Body mass index (BMI) was measured after admission. Samples for special coagulation tests were collected at admission to the ICU unless they had been collected at admission to the hospital. VTE and DIC scores were calculated for all admitted patients at admission, and days 3, 7, and 14.

Laboratory analysis

Samples were collected at admission, and days 3, 7, and 14 for patients staying as long as 14 days. All patients had 10 cc of EDTA-treated blood, 10 cc of citrate-treated blood (at 3.2%), and 5 cc of sodium heparin-treated blood collected. CBC was tested on the EDTA samples with an automated SYSMEX XN-10 instrument (Sysmex Corporation, Kobe, Japan). Serum creatinine and C reactive protein were measured with a COBAS 601 automated chemistry analyzer (Roche Diagnostics, Basel, Switzerland).

The samples for coagulation tests were centrifuged within 2 h after collection and divided into aliquots for testing of coagulation markers including PT/INR, aPTT, D-dimer level, and fibrinogen (FIB) at all four time points. Antithrombin III (AT), protein C (PC), protein S (PS), von Willebrand factor antigen (vWFAg), and factor VIII (FVIII) activity testing was performed with a STAR Max® instrument (Diagnostica Stago, Marseille, France) after patient admission to the hospital.

The VTE and DIC scores were calculated for all admitted patients at admission, and days 3, 7, and 14. Mortality was defined as the number of deaths among all participants and is reported as a percentage.

Statistical analysis

Categorical data are presented as numerical values and percentages. Normally distributed data were analyzed by with a two-tailed unpaired Student t-test. The significance threshold was set at $P < 0.05$. A receiver operating characteristic (ROC) curve was plotted to build a prediction model assessing the prognostic value of demographics and laboratory findings in predicting 30-day mortality in hospitalized patients with COVID-19. All data analysis was performed in SPSS version v23 (IBM Corp, Armonk, NY, USA). The main biological markers (CRP, fibrinogen, D-dimer, FVIII, vWFAg, and FVIII/vWFAg) were compared according to patient admission type and oxygen requirements at admission through analysis of the means. We assessed the association of biological markers measured at ICU admission with an increase in oxygen requirement, thrombotic events, and all-cause mortality within 30 days after admission.

Abbreviations

COVID-19, Coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; DIC, disseminated intravascular coagulation; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; aPTT, activated partial thromboplastin time; FIB, fibrinogen; AT, antithrombin III; PC, protein C; PS, protein S; vWFAg, von Willebrand factor antigen; FVIII, factor VIII; Hb, hemoglobin; CRP, C reactive protein; VTE, venous thrombotic event; BMI, body mass index; LMWH, low molecular weight heparin; UFH, unfractionated heparin; SHR, subdistribution hazard ratio; CPAP, continuous positive airway pressure; Fib, fibrinogen.

Results

Our cohort comprised 118 patients: 68 men (57.60%) and 50 (42.40%) women. The mean age of our cohort was 58.20 ± 15.80 years, and the median was 60 years. The mean BMI was 31.40 ± 7.20, and the median was 29.90. Table 1 shows the basic descriptive statistics as overall mean and variance for continuous variables, and as percentages for categorical variables.

Demographics and risk factors

The BMI was significantly higher in the women 33.70 ± 7.70 (*P*-value 0.0025) (Table 2). Six (5.1%) patients had cancer (three women and three men). The cohort's mean length of ICU stay was 15.70 ± 19 days, and the median was 9 days. Length of stay was significantly prolonged in recovered patients, with a mean of 28.20 ± 29.90 days ($P = 0.0022$), and patients with thrombosis, with a mean of 34.40 ± 39.60 days ($P = 0.024$). Patients with hypoxia and an oxygen saturation less than 93% at rest or the presence of pneumonia did not require ICU admission, and patients with an arterial oxygen partial pressure to fractional inspiratory oxygen ratio (PaO_2/FiO_2) <300 required ICU admission. The length of ICU stay was also positively associated with oxygen requirements ($P = 0.0076$): patients

Table 1: Basic descriptive statistics of the cohort.

Characteristics	N	Mean ± SD, median
Age	118	58.20 ± 15.80, 60
BMI	118	31.40 ± 7.20, 29.90
Length of stay	118	15.70 ± 19, 9
AT	118	93.10 ± 15.60, 94.50
PC	118	0.87 ± 0.84, 0.87
PS	118	0.73 ± 0.16, 0.70
vWFAg	118	0.98 ± 0.717, 0.80
FVIII	118	0.91 ± 0.82, 0.80
FVIII/vWFAg	118	1 ± 0.15, 1
CBC		
WBC	118	8.4 ± 5.30, 6.79
Hb	118	12 ± 2.30, 12.30
Platelets	118	215 ± 108, 196.50
Neut Abs.	118	6.90 ± 7.80, 4.90
Lym. Abs.	118	1.20 ± 1.50, 0.90
Mono Abs.	118	0.58 ± 0.10, 0.40
INR	118	1.17 ± 0.33, 1.10
PT	118	15.90 ± 4.30, 14.90
PTT	118	40.20 ± 11, 38.20
D-dimer	118	2.10 ± 3.70, 1
Fib	118	5.20 ± 1.60, 5.40
CRP	118	119.60 ± 101, 94.50
Creatinine	118	125 ± 119.80, 80
Characteristics	N	Values (%)
Risk factors		
All risk factors	118	105 (89%)
Hypertension	118	65 (55.1%)
Diabetes	118	67 (56.8%)
Cancer	118	6 (5.1%)
Hyperlipidemia	118	28 (23.7%)
Other comorbidities	118	69 (58.5%)
Previous VTE	118	4 (3.4%)
No ICU intervention	118	15 (12.7%)
ICU intervention (O_2 requirements)	118	103 (87.3%)
High flow O_2	118	83 (70.3%)
CPAP	118	10 (8.5%)
Ventilator	118	58 (49.2%)
Mortality	118	18 (15.3%)

BMI, Body mass index; AT, antithrombin III; PC, protein C; PS, protein S; vWFAg, von Willebrand factor antigen; FVIII, factor VIII; Hb, hemoglobin; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; CRP, C reactive protein.

requiring oxygen-based intervention stayed longer, for 17.70 ± 19.70 days.

The studied risk factors, such as hypertension, diabetes, hyperlipidemia, and cancer, were observed in all patients with thrombosis, resulting in 83.3% mortality.

ICU interventions

Thirty-eight (32.20%) patients were admitted to the ICU and kept under observation but did not require intervention. Thrombosis was reported in four patients; however, none died. Mortality was negatively associated with high flow O_2 (fewer patients died due to high flow O_2), 9 patients (10.80%) ($P = 0.040$). Mortality was significantly associated with patients on a ventilator, and more patients died on ventilatory support, 16 patients (27.50%) ($P < 0.001$).

DIC score

A DIC score ≥4 was found in 58% of patients. Thrombosis was observed in 3.8% of these patients. The DIC score was significantly correlated with thrombosis ($P = 0.031$). However, the risk of ICU admission was significantly associated with the DIC score ($P < 0.001$). A total of 41.20% of patients in the ICU had a DIC score ≥4, and 11.4% had a score <4.

Beyond older age and having an ICU visit, presentation with comorbid conditions, particularly diabetes and malignancy, higher COVID-19 stage, DIC scores ≥4, higher VTE score, D-dimer level, platelet count below 140×10^9/L, and higher fibrinogen, was significantly associated with mortality. The incidence of thrombosis was significantly associated with ICU admission. Higher DIC and VTE scores, D-dimer level, BMI, COVID-19 stage, platelets $>450 \times 10^9$/L, old age with comorbid conditions, and being symptomatic at admission were significantly associated with an ICU stay.

Thrombosis: prophylaxis and management

The VTE score was calculated at admission, and on days 3, 7, and 14. The mean VTE score significantly increased from the day of admission to day 14, from 5.10 ± 2 to 6.40 ± 2.80 ($P = 0.0002$). The VTE score was significantly higher for patients who died (8.20 ± 2) than for recovered patients (6 ± 2.80) ($P = 0.027$).

A total of 113 (95.70%) patients received prophylactic anticoagulation after admission with different regimens. The type of anticoagulant was low molecular weight heparin (LMWH) in 83 patients (72.80%), of whom 59 (71%) received 40 mg daily, and 24 (28.90%) received 40 mg BID. Unfractionated heparin (UFH) was given to 30 patients (26.30%) at a median dose of 5000 IU, and two patients (6.60%) had thrombosis. Prophylaxis with UFH was significantly higher among the patients who died (10; 58.8%) than patients who recovered (20; 20.60%) ($P = 0.001$). We found no significant correlation between mortality and a dose of LMWH once daily or twice daily ($P = 0.980$).

Four patients had thrombosis: two had pulmonary embolism, one had a thrombosed vessel in the brain, and one had thrombosis of the portal vein extending to the proximal superior mesenteric vein. Two patients received a therapeutic dose of LMWH (1 mg/kg, BID), whereas two received UFH at a therapeutic dose.

Table 3 shows VTE prophylaxis and thrombosis variables, comparing the mean and proportion for sex, outcome, and thrombosis. VTE prophylaxis was given to all patients except four (3.30%). DIC scores were measured for all patients, and a score >4 was found in 83% of patients, whereas 18 patients (100%) died, and 4 (80%) had thrombosis.

Although the number of patients with thrombosis was low (4; 3.40%), all such patients were kept under observation in the ICU but did not receive intervention.

Table 2: Basic descriptive statistics analysis of demographics and risks, with comparison of the mean according to sex, outcome, and thrombosis.

Variable	Female	*P*	Mortality	*P*	Throm	*P*	O_2	*P*
Age	56.40 ± 16.90	0.300	62 ± 14.21	0.260	47.80 ± 13.40	0.130	58.70 ± 16.30	0.377
BMI	33.70 ± 7.70	**0.0025***	29.80 ± 7.90	0.340	30.80 ± 7.20	0.870	31.20 ± 6.90	0.560
Length of ICU stay	14.90 ± 15.40	0.680	13.50 ± 15.50	**0.0022***	34.40 ± 39.60	**0.024***	17.70 ± 19.70	**0.0076***
All risk factors	45 (43%)	0.760	10 (83.30%)	0.406	5 (100%)	0.421	92 (87.60%)	0.750
Hypertension	30 (46%)	0.350	10 (55.60%)	0.965	1 (20%)	0.107	58 (89.20%)	0.480
Diabetes	27 (40.30%)	0.600	12 (66.70%)	0.380	3 (60%)	0.882	61 (91%)	0.160
Cancer	3 (50%)	0.700	2 (11.10%)	0.700	0 (0%)	0.600	6 (100%)	0.337
Previous VTE	0 (0%)	0.081	2 (11.10%)	**0.049***	0 (0%)	0.669	4 (100%)	0.430
Hyperlipidemia	15 (53.60%)	0.170	5 (27.80%)	0.670	1 (20%)	0.840	23 (82.14%)	0.340
Other comorbidities	32 (46.40%)	0.290	9 (50%)	0.428	4 (80%)	0.318	62 (89.80%)	0.320
No ICU intervention	7 (46.70%)	0.700	0 (15.80%)	0.0790	0 (0%)	0.380	–	–
ICU intervention	43 (41.70%)	0.700	18 (17.50%)	0.0790	4 (4.2%)	0.380	–	–
High flow O_2	36 (72%)	0.700	9 (50%)	**0.040***	3 (60%)	0.650	–	–
Ventilator	23 (46%)	0.550	16 (88.90%)	**<0.001***	3 (60%)	0.620	–	–
CPAP	5 (10%)	0.600	0 (0)	0.161	0 (10%)	0.487	–	–

*$P < 0.05$, significant difference.
VTE: venous thrombotic event; CPAP, continuous positive airway pressure.

Table 3: SHR and corresponding *P*-values for oxygen requirement, mortality, and thrombosis for clinical variables at admission.

Variables	SHR (O_2+ve)	$P > z$	95% CI	SHR (Mor.)	$P > z$	95% CI	SHR (Th+ve)	$P > z$	95% CI
WBC	0.91	0.03	0.80–1	1.00	0.410	0.90–1.20	0.60	0.500	0–2
Hb	0.99	0.95	0.90–1.10	0.50	0.001	0.30–0.70	1.90	0.080	1–4
Platelet	1.0	0.46	0.90–1	0.99	0.060	0.98–1	1.00	0.700	0.90–1
Neut Abs	1.0	0.00	1.011.05	1.01	0.850	0.90–1.10	0.70	0.170	0.40–1.10
Lym Abs	0.93	0.78	0.60–1.50	1.13	0.880	0.20–5.90	7.30	0.250	0.20–2.30
Mono Abs	1.29	0.32	0.80–2.20	1.68	0.560	0.30–9.70	0.00	0.250	0.40–6.40
D-dimer	1.0	0.77	0.90–1.05	0.64	0.010	0.40–0.90	1.60	0.010*	1.10–2.50
CRP	0.99	0.74	0.90–1						
Creatinine	0.99	0.22	0.90–1	1.00	0.450	0.90–1	1.00	<0.010*	1–1.01
Fib	1.13	0.21	0.90–1.30	1.34	0.180	0.80–2	0.20	<0.010*	0.07–0.60
FVIII	1.71	0.25	0.7–4.30	0.46	0.840	0.90–2.10	0.14	0.490	0.30–7
vWFAg	1.29	0.28	0.8–2.10	0.02	0.280	0.20–1	11.6	0.046*	1–1.30

*$P < 0.05$, significant difference.
Fib, Fibrinogen; vWFAg, von Willebrand factor antigen.

Table 4: Comparison of coagulation markers, and laboratory findings at admission, and days 3, 7, and 14.

Variable	Adm.	Day 3	*P*	Day 7	*P*	Day 14	*P*
WBC	8.40 ± 5.40	7.30 ± 4.30	**0.0051***	8.70 ± 5.10	0.570	9.50 ± 5.60	0.200
Hb	108 ± 41	102 ± 39.30	**0.0002***	98.90 ± 40.20	**0.0001***	101.40 ± 31.30	**0.0008***
Platelet	216 ± 102	239 ± 106	**0.0002***	292 ± 143	**<0.001***	270 ± 120	**0.0018***
Neut Abs	7.50 ± 9.90	6.30 ± 6.50	0.420	7.02 ± 5.30	0.780	7.40 ± 4.50	0.500
Lym Abs	1.30 ± 1.70	1.10 ± 0.80	0.540	1.10 ± 0.64	0.770	1.80 ± 2.20	0.052
Mono Abs	0.70 ± 1.40	0.40 ± 0.25	0.210	0.50 ± 0.30	0.700	0.70 ± 0.80	0.056
INR	1.20 ± 0.30	1.20 ± 0.28	0.430	1.21 ± 0.40	0.400	1.30 ± 0.40	0.360
PT	16 ± 4.50	16.40 ± 3.30	0.330	16.40 ± 4.60	0.500	17.20 ± 4.50	0.600
PTT	40.40 ± 11.40	44.20 ± 14.60	**0.020***	46.70 ± 20	**0.0082***	48.40 ± 20.70	**0.0172***
D-dimer	3.50 ± 12.20	2.20 ± 2.80	0.300	3.70 ± 4.60	**0.0086***	3.20 ± 3.57	0.570
CRP	129 ± 100	105 ± 92	**0.027***	47 ± 71	**<0.001***	30 ± 64	**<0.001***
Creatinine	127 ± 121	127 ± 123	0.930	136 ± 133	0.460	128 ± 128	0.530
Fib	5.20 ± 1.60	5.40 ± 1.60	0.340	4.70 ± 1.60	0.061	3.40 ± 1.50	**0.0001***

*$P < 0.05$, significant difference.
Hb, hemoglobin; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; CRP, C reactive protein.

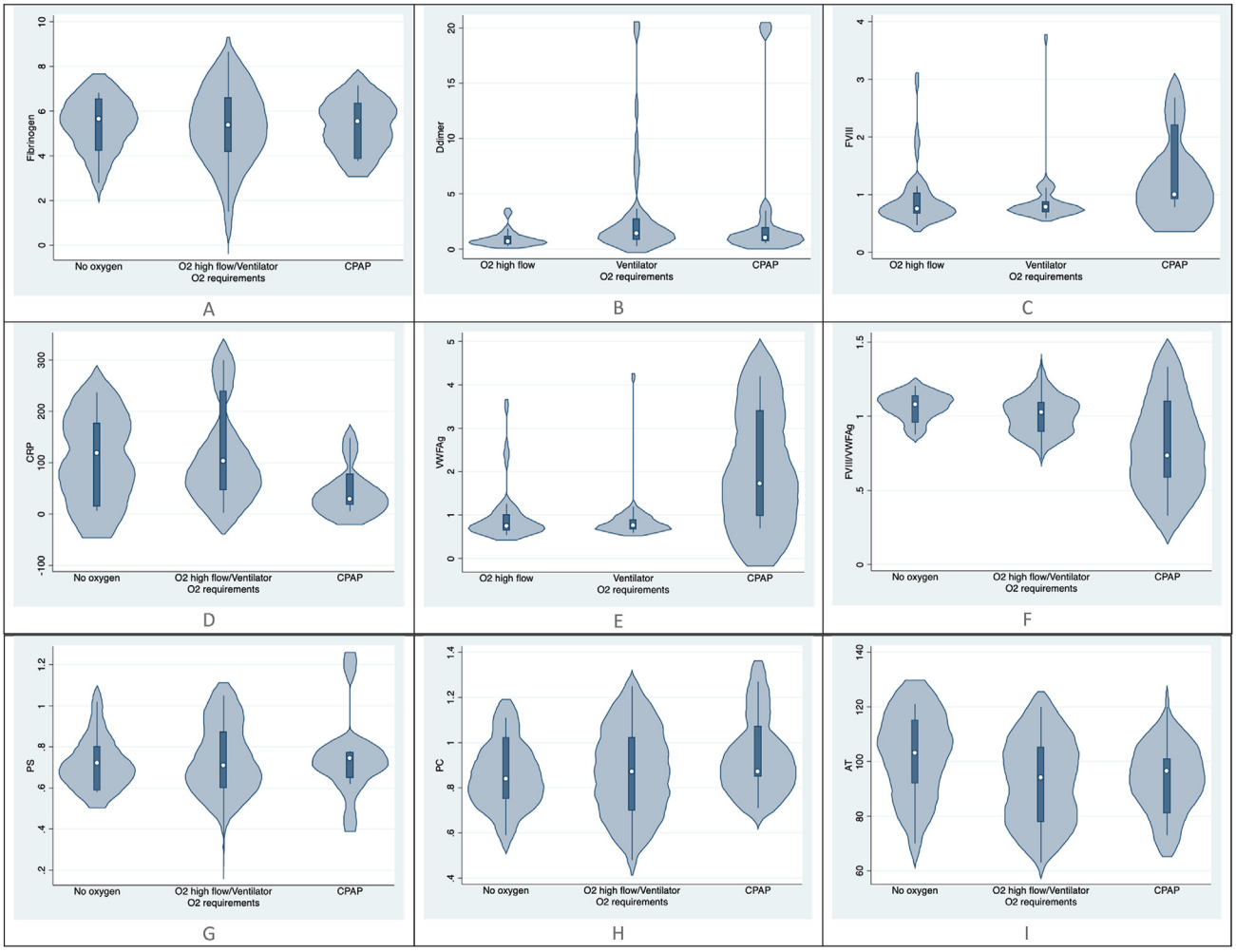

Figure 1: Violin plot showing high oxygen requirement variables with respect to baseline values of the main biomarkers. A) Fibrinogen, B) D-dimer, C) FVIII, D) CRP, E) vWFAg, F) FVIII/vWFAg, G) PS, H) PC, and I) AT.

Respiratory support variables and mortality

The percentage of high flow O_2 was significantly higher in recovered patients (85; 82.50%) than patients who died (18; 17.50%) ($P = 0.090$) (Table 2). Mortality was significantly higher in patients on a ventilator (16; 88.9%) than not on a ventilator ($P < 0.001$).

Laboratory data

The subdistribution hazard ratio (SHR)[18] for laboratory variables with respect to oxygen requirements, thrombosis, and mortality is shown in Table 3. Patients requiring high flow oxygen had significantly higher WBC levels (SHR: 0.91; 95% CI: 0.80−1). Patients who died had significantly lower Hb levels (SHR, 0.50; 95% CI: 0.30−0.70). Patients with higher oxygen requirements had significantly higher neutrophil counts (SHR, 1; 95% CI: 1.01−1.05). Patients with thrombosis had higher D-dimer values (SHR 1.60; 95% CI: 1.10−2.50).

Comparison from admission to day 14 of the mean test for coagulation markers and laboratory results, we explored increasing or decreasing trends (Table 4). WBC increased from admission (8.4 ± 5.40 to 9.50 ± 5.60). A significant decrease in hemoglobin was observed, from 108 ± 41 to 101.40 ± 31.30 ($P = 0.0008$). The mean platelet count significantly increased from 216 ± 102 at admission to 270 ± 120 ($P = 0.0018$). A significant rise was observed in the mean PTT, from 40.40 ± 11.40, to 48.40 ± 20.70 ($P = 0.0172$). CRP showed a declining mean trend across all readings, from an admission value of 129 ± 100 to 30 ± 64 ($P < 0.001$). The D-dimer value decreased from 3.50 ± 12.20 to 3.20 ± 3.50, whereas the FIB decreased significantly from 5.20 ± 1.60 to 3.40 ± 1.50 ($P = 0.0001$).

Figure 1 shows a violin plot of associations of high oxygen requirement variables with FIB, D-dimer, FVIII, CRP, vWFAg, the ratio of vWFAg and FVIII, PS, PC, and AT. No association was observed with AT, PS, D-dimer, and FIB among these variables. An association between high-flow oxygen and CPAP was found with CRP ($P = 0.030$), vWFAg ($P < 0.010$), FVIII ($P = 0.0018$), and the FVIII/vWFAg ratio ($P = 0.0002$). Figure 2 shows ROC curves for D-dimer, CRP, and creatinine.

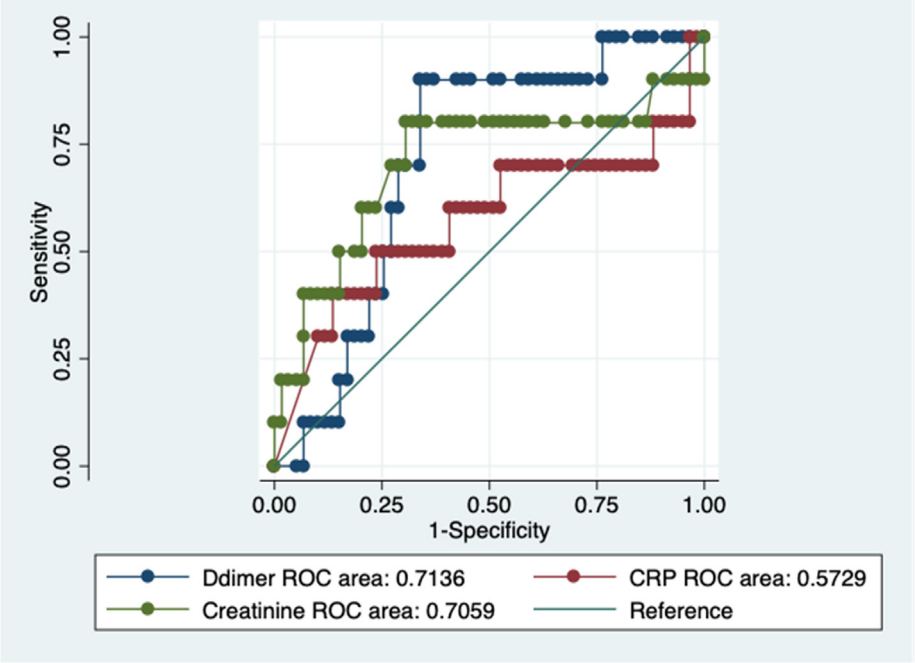

Figure 2: ROC curves for D-dimer, CRP, and creatinine.

Discussion

The number of COVID-19 cases and associated mortality have risen worldwide.[19] In severely ill patients, multiple-organ failure, usually following respiratory failure, is attributed to coagulopathy and thromboembolic events.[3,20,21] Coagulation abnormalities in patients with COVID-19 differ from the usual sepsis-induced DIC and can help predict disease prognosis.[22]

Men and older people tend to be overrepresented among patients with COVID-19 with severe disease and ICU admission.[23–25] Obesity is a major risk factor for poor disease outcomes and mortality among patients with COVID-19.[26,27] The mean BMI score of our ICU admitted participants indicated increased presentation of severe COVID-19 among obese patients. Additionally, diabetes and hypertension are important risk factors for ICU admission and have been reported as comorbidities in patients with COVID-19.[28–30] More than 50% of patients had one or both of these non-communicable diseases in our cohort.

The length of hospital stay among patients with COVID-19 who die in the hospital is generally shorter than that among patients discharged alive.[31] In our cohort, the ICU stays were also longer for recovered patients. COVID-19 associated coagulopathy has prothrombotic characteristics with a high risk of VTE.[9,32,33] The rate of VTE in ICU patients ranges from 13% to 31%.[34,35] An increasing trend was observed in our cohort's VTE scores over time. The VTE score was significantly higher for patients who died than those patients who recovered. The individual patient-related risk factors and ICU-specific risk factors contribute to an increased risk of VTE in critically ill individuals.[34] These factors might have led to a surge in VTE events among ICU patients, which was directly associated with the length of ICU stay, and the highest scores were observed among the patients who died. Of the 118 patients, only 3.4% had thrombosis, and their mortality rate was 50%. The cumulative incidence of VTE increased during ICU admission. The incidence of VTE has been reported to be 59% in ICU patients, compared with 9.2% in patients admitted to the ICU on day 21 after hospital admission.[36] Another study has reported a rate of VTE in patients under intensive care of 10.30%, compared with 0.19% in the non-ICU group.

Of note, previous reports have indicated mixed findings regarding the efficacy and preferential use of prophylactic or therapeutic anticoagulation therapy.[37] Therefore, a precise treatment plan with anticoagulants must be individualized rather than protocolized.[37] In a meta-analysis of 21 studies, severe or fatal COVID-19 has been associated with elevated WBC and neutrophil counts, and diminished hemoglobin levels.[38] We observed similar findings. DIC scores >4 were found in 83% of patients. Tang et al. have reported that only 0.6% of survivors meet the DIC criteria, as compared with 71.4% of non-survivors.[9] Higher DIC scores in severely ill patients with COVID-19 suggest the existence of common coagulation pathways. An increase in D-dimer levels has been found to be the most pronounced change in coagulation parameters in patients with COVID-19.[9,33,39] Markedly elevated D-dimer levels at admission might predict more severe disease outcomes.[40] In our study, patients with thrombosis had higher D-dimer and lower fibrinogen values. The fibrinolytic system is responsible for breaking down the fibrin mesh after clot formation. D-dimers are a marker of activation of coagulation and fibrinolysis systems. An increase in D-dimer levels leads to a corresponding decrease in fibrinogen levels.[41]

vWFAg, platelet count, and PTT are coagulation markers that indicate increased clotting. Levels of these coagulation

markers increase in COVID-19.[42,43] All three coagulation markers were markedly elevated in our study cohort, particularly those with thrombosis. CRP levels, along with those of vWFAg and FVIII, and the FVIII/vWFAg ratio, were associated with greater high-flow oxygen, thereby suggesting links between these coagulation markers and the extent of respiratory support required. Elevated CRP levels at admission have been associated with a risk of high oxygen requirements during follow-up.[44] Anticoagulant therapy with LMWH has been associated with diminished mortality in patients with severe COVID-19 meeting sepsis-induced coagulopathy criteria or having markedly elevated D-dimer levels.[13] Our study suggests that LMWH is a better therapeutic option than UFH for critically ill patients with COVID-19. Ahmed et al. have suggested high-dose heparin for high-risk individuals.[45] No significant correlation between LMWH dosing frequency and mortality rates was observed in our study cohort.

The cumulative findings of our study were concordant with previously reported data. These findings suggest that assessment of coagulation markers may help predict overall disease course in patients with COVID-19 and facilitate timely administration of anticoagulants to decrease COVID-19 associated mortality.

Conclusion

The VTE score was significantly higher in patients who died than patients who recovered. Furthermore, mechanical ventilation was associated with high mortality, whereas the risk of thrombosis and ICU admission correlated with high D-dimer values and DIC scores. Therefore, D-dimer levels and DIC scores are prognostic markers that might predict disease severity in patients with COVID-19. That is, assessment of coagulation markers may help predict overall disease course in patients with COVID-19 and aid in timely administration of anticoagulants to decrease COVID-19 associated mortality.

Recommendations

On the basis of the data generated from our study and previously reported findings, we suggest that levels of coagulation markers must be assessed in early stage disease to prevent serious thrombotic complications that can lead to life-threatening complications. Prophylactic administration of anticoagulants, particularly LMWH, may help decrease disease complications, alleviate the burden on the health care system caused by prolonged hospital stays due to COVID-19 complications, and save lives in the COVID-19 pandemic.

Availability of data and materials

Data and materials will be provided on reasonable request to the corresponding author.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

The study was approved by the Institutional Review Board of King Faisal Specialist Hospital and Research Centre, KSA, under approval #RAC KFSHRC (2201086), approval date is May 2021.

Consent

All authors provided consent for publication.

Authors' contribution

TO and KM designed and developed the study. Both authors were responsible for the content and authenticity. FA and HO oversaw data collection and data entry. MM and KS performed the final review of the data and analysis. All authors were responsible for the direction of the study team and facilitation of the project plan. All authors made a significant contribution to the work reported, through the conception, study design, execution, data acquisition, analysis and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

References

1. Coronavirus update (Live) 2021 [updated 5th March, 2021; cited 2021 6th March]. Available from: https://www.worldometers.info/coronavirus/.
2. Organization WH. Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update 2021 [cited 2021 6th March]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/.
3. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. **N Engl J Med 2020**; 382(18): 1708–1720.
4. 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(11): 1061–1069.
5. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, 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(5): 475–481.
6. Elshazli RM, Toraih EA, Elgaml A, El-Mowafy M, El-Mesery M, Amin MN, et al. Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: a meta-analysis of 6320 patients. **PLoS One 2020**; 15(8):e0238160.
7. Glass WG, Subbarao K, Murphy B, Murphy PM. Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. **J Immunol 2004**; 173(6): 4030–4039.

8. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, et al. Fair allocation of scarce medical resources in the time of Covid-19. **N Engl J Med 2020**; 382(21): 2049–2055.
9. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. **J Thromb Haemostasis 2020**; 18(4): 844–847.
10. Taylor Jr FB, Toh C-H, Hoots KW, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. **Thromb Haemostasis 2001**; 86(11): 1327–1330.
11. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. **Lancet 2020**; 395(10223): 507–513.
12. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. **Intensive Care Med 2020**; 46(6): 1089–1098.
13. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. **J Thromb Haemostasis 2020**; 18(5): 1094–1099.
14. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. **J Thromb Haemostasis 2020**; 18(5): 1023–1026.
15. Al Raizah A, AlAskar A, Shaheen N, Aldosari K, Alnahdi M, Luhanga M, et al. High rate of bleeding and arterial thrombosis in COVID-19: Saudi multicenter study. **Thromb J 2021**; 19(1): 13.
16. Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno PR, Pujadas E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. **J Am Coll Cardiol 2020**; 76(16): 1815–1826.
17. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. **J Thromb Haemostasis 2020**; 18(7): 1743–1746.
18. Shrivasta SR, Shrivasta PS, Ramasamy J. Effective feedback: an indispensable tool for improvement in quality of medical education. **J Pedagogic Dev 2014**; 4(1): pp.12–20.
19. (WHO) WHO. WHO Coronavirus (COVID-19) Dashboard 2021 [cited 2021 16th April]. Available from: https://covid19.who.int/.
20. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. **Lancet Haematol 2020**; 7(6): e438.
21. Warkentin TE, Kaatz S. COVID-19 versus HIT hypercoagulability. **Thromb Res 2020**; 196: 38–51.
22. Anwar N, Tashfeen S, Akhtar F, Noor A, Khan SA, Omair A. Can disseminated intravascular coagulation scores predict mortality in COVID-19 patients? **J Taibah Univ Med Sci 2021**. https://doi.org/10.1016/j.jtumed.2021.03.002.
23. 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(11): 1061–1069. https://doi.org/10.1001/jama.2020.1585.
24. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. **BMJ 2020**: 368.
25. Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. **J Thromb Haemost 2020**; 18(6): 1469–1472. https://doi.org/10.1111/jth.14848.
26. Soeroto AY, Soetedjo NN, Purwiga A, Santoso P, Kulsum ID, Suryadinata H, et al. Effect of increased BMI and obesity on the outcome of COVID-19 adult patients: a systematic review and meta-analysis. **Diabetes Metab Syndr 2020**; 14(6): 1897–1904. https://doi.org/10.1016/j.dsx.2020.09.029.
27. Hussain A, Mahawar K, Xia Z, Yang W, El-Hasani S. Obesity and mortality of COVID-19. Meta-analysis. **Obes Res Clin Pract 2020**; 14(4): 295–300. https://doi.org/10.1016/j.orcp.2020.07.002.
28. Guan W-j, Liang W-h, Zhao Y, Liang H-r, Chen Z-s, Li Y-m, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. **Eur Respir J 2020**; 55(5).
29. Wang X, Fang J, Zhu Y, Chen L, Ding F, Zhou R, et al. Clinical characteristics of non-critically ill patients with novel coronavirus infection (COVID-19) in a Fangcang Hospital. **Clin Microbiol Infect 2020**; 26(8): 1063–1068. https://doi.org/10.1016/j.cmi.2020.03.032.
30. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. **N Engl J Med 2020**; 382(18): 1708–1720. https://doi.org/10.1056/NEJMoa2002032.
31. Rees EM, Nightingale ES, Jafari Y, Waterlow NR, Clifford S, Pearson CAB, et al. COVID-19 length of hospital stay: a systematic review and data synthesis. **BMC Med 2020**; 18(1): 270. https://doi.org/10.1186/s12916-020-01726-3.
32. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? **Eur Heart J 2020**; 41(19): 1858.
33. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. **J Thromb Haemostasis 2020**; 18(6): 1421–1424.
34. Minet C, Potton L, Bonadona A, Hamidfar-Roy R, Somohano CA, Lugosi M, et al. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. **Crit Care 2015**; 19(1): 1–9.
35. Malato A, Dentali F, Siragusa S, Fabbiano F, Kagoma Y, Boddi M, et al. The impact of deep vein thrombosis in critically ill patients: a meta-analysis of major clinical outcomes. **Blood Transfus 2015**; 13(4): 559.
36. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. **J Thromb Haemost 2020**; 18(8): 1995–2002. https://doi.org/10.1111/jth.14888.
37. Hasan SS, Radford S, Kow CS, Zaidi STR. Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: a systematic review and meta-analysis. **J Thromb Thrombolysis 2020**; 50(4): 814–821. https://doi.org/10.1007/s11239-020-02235-z.
38. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. **Clin Chem Lab Med 2020**; 58(7): 1021–1028. https://doi.org/10.1515/cclm-2020-0369.
39. Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of coronavirus disease 2019. **Crit Care Med 2020**; 48(9): 1358–1364.
40. 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(10229): 1054–1062. https://doi.org/10.1016/s0140-6736(20)30566-3.
41. Gaffney P. Breakdown products of fibrin and fibrinogen: molecular mechanisms and clinical implications. **J Clin Pathol Suppl (R Coll Pathol) 1980**; 14: 10.
42. Goshua G, Pine AB, Meizlish ML, Chang CH, Zhang H, Bahel P, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study.

Lancet Haematol 2020; 7(8): e575–e582. https://doi.org/10.1016/s2352-3026(20)30216-7.

43. Henry BM, De Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. **Clin Chem Lab Med 2020**; 58(7): 1021–1028.
44. Rauch A, Labreuche J, Lassalle F, Goutay J, Caplan M, Charbonnier L, et al. Coagulation biomarkers are independent predictors of increased oxygen requirements in COVID-19. **J Thromb Haemostasis 2020**; 18(11): 2942–2953.
45. Ahmed S, Zimba O, Gasparyan AY. Thrombosis in Coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad. **Clin Rheumatol 2020**; 39(9): 2529–2543. https://doi.org/10.1007/s10067-020-05275-1.

How to cite this article: Maghrabi KA, AlQahtany FS, AlOtair H, Maghrabi MK, AlSaleh K, Owaidah T. Prognostic markers in patients with COVID-19 requiring intensive care support. J Taibah Univ Med Sc 2023;18(5):1089–1098.