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Prognostic factors for predicting severity and mortality in hospitalized COVID-19 patients

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Abstract

Background: Coronavirus disease 2019, COVID-19, has reached all the corners of the world and was declared by the WHO as a global pandemic and public health emergency of international concern on the January 31, 2020. Allocating quick and specific biomarkers to predict the disease severity upon admission to hospital became a crucial need. This study, therefore, aimed at exploring the relationship between laboratory results in COVID-19 patients admitted to hospital and the final outcome in these patients.

Methods: Retrospective analysis was performed on the medical records of 310 COVID-19-positive patients admitted to Uhod Hospital, the referral hospital in the area of Madinah, Kingdom of Saudi Arabia, between the April 13 and the July 29, 2020. The association of laboratory results with the survival/mortality outcomes was studied.

Results: It was demonstrated that lymphopenia, prolonged aPTT, high INR, high D. dimer and high CK are valuable prognostic predictors of the severity of the disease at early stages that can determine the outcome. Based on the results of the multiple logistic regression, the variables that are associated with death outcome are aPTT, HR, RR, ALT and CK level

Conclusion: It is proposed to perform these tests on admission to hospital for moderate to severe COVID-19 patients to improve the management of those cases and reduce mortality.

KEYWORDS
coagulation cascade, COVID-19, creatine kinase, hematocrit, lactate dehydrogenase, lymphopenia

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become an emergency concern due to its invasive and ambiguous nature. [1,2] Since the beginning of the pandemic in December 2019, it has infected 61.8 million cases and caused 1.4 million deaths as per the December 1, 2020, as reported by the World Health Organization. [3,4]

COVID-19 patients mostly present with fever, dyspnea and dry cough. However, in 8–15% of cases, depending on geographical and individual variations, it can lead to a severe illness requiring specialized management at intensive care units. [1] A number of COVID-19

patients may also develop acute respiratory distress syndrome which can occasionally progress to multiorgan failure and death. [5] The high infectivity nature of the SARS-CoV-2 virus and the inability to predict the severity of the infection at early stages of the disease led to increasing mortality rates. The hospitalization rate for COVID-19 ranges between 20.7 and 31.4% while a mortality rate of 3.4% was found to be higher than seasonal flu official rates, as reported by the WHO Director-General's opening remarks at the media briefing on COVID-19 on the March 11, 2020. Quick identification of patients who may, potentially, develop severe illness and require intensive care or mechanical ventilation is important for decreasing mortality rates of COVID-19. This will eventually improve the efficient utilization of health care resources which are already under strain worldwide due to the successive waves of this ongoing pandemic. [6]

Laboratory findings and chronic comorbidities are important to determine the diagnosis and prognosis of COVID-19. [7,8] The initial tests for COVID-19 patients are complete blood count (CBC), inflammatory and coagulation cascade parameters and other biochemical factors to determine the functionality of vital organs. [9] Vital signs at presentation represent an important indication of severity, used to decide on the therapeutic plan and to monitor patients who are at the risk of developing severe respiratory symptoms. [10] Analyzing laboratory findings of COVID-19 patients on admission to hospital can be used as an initial indicator of severity. [11] Investigation of these parameters can give an insight into the severity of disease and its possible outcomes. Therefore, laboratory findings and vital signs, together, can play a fundamental role in the diagnosis and prognosis of COVID-19 patients. [12] In the current study, clinical and laboratory data of 310 hospitalized COVID-19 cases were analyzed to assess the importance of laboratory findings and vital signs in predicting the final outcome of COVID-19 patients upon admission to hospital and to find possible biomarkers which can provide clinically important prognostic indicators of the progression of the disease at early stages.

2 | METHODS

2.1 | Patients and data collection

This study included COVID-19 patients with positive polymerase chain reaction (PCR) (310) admitted to Uhod Hospital, the referral hospital in the area of Madinah, western region of the Kingdom of Saudi Arabia between April 13 and July 29, 2020. Data were extracted retrospectively from the hospital information system by two groups and then cross-checked. Patients less than 18 years old were not included from the study. Data included sex, age, previous comorbidities, vital signs and laboratory results on admission including respiration rate (RR), heart rate (HR), mean arterial blood pressure (BP), oxygen saturation (SpO2), complete blood count (CBC), C-reactive protein (CRP), serum ferritin, alanine transaminase (ALT), aspartate transaminase (AST), serum creatinine, serum albumin, total bilirubin, direct bilirubin, lactate dehydrogenase, [13] creatine

kinase (CK), D-Dimer, international normalized ratio (INR) and activate partial thromboplastin time (aPTT). The modality of ventilation and the survival/death outcomes were also collected. Descriptive statistics for the variables was presented in the form of frequencies and percentages for categorical variables (lab tests and vital signs categories). Ethical approval was obtained from the institutional review board for research ethics, general directorate of health affairs in Madinah (H-03-M-084). Patients or their guardians provided written informed consent for the publication of patients' information in the present manuscript.

2.2 | Statistical analysis

Descriptive statistics for the variables were presented in the form of mean, standard deviation, median, quartiles. Multiple logistic regression was used to study the association between the death outcome and lab test results and vital signs while controlling for other variables. Variables were entered in the model in their numeric forms and were selected manually if the P-value for the simple logistic regression is <0.2. IBM SPSS version 26 for Windows software was used for the analysis. A P-value of < 0.05 was considered significant. In the multivariate analysis, the backward stepwise method was used to remove variables that are not significantly predicting mortality.

3 | RESULTS

3.1 | Demographic characteristics and comorbidities

This study included 310 COVID-19-positive patients admitted to hospital with respiratory symptoms ranging from mild, moderate, severe to critical (Table 1). The study did not include patients with no respiratory symptoms requiring only home isolation. The demographic data are presented in Table 1. The mean age of patients was 50.1 ± 16.3 years old, being 71.6% males and 28.4% females. Patients presented in 67.7 % of cases with comorbidities. The comorbidities were mainly diabetes mellitus (DM), hyperlipidemia and cardiovascular (CVS) diseases (Table 1).

3.2 | Vital signs and management plan

Patients with SpO2 of 93% or above were maintained at room air, while patients with SpO2 below 93% were on external oxygen support or invasive ventilation according to the severity of each case. Vital signs were taken on day 1 after admission to hospital and assigning oxygen support or mechanical ventilation according to need. The majority of patients maintained a normal heart rate (HR), respiratory rate (RR), mean arterial blood pressure (BP) and peripheral oxygen saturation (SpO_2) as shown in Table 2. Although fever was the presenting symptom in almost all patients, all temperatures were

TABLE 1 Demographic characteristics and comorbidities of COVID-19-positive patients

	Number	%
Gender		
F	88	28.4
M	222	71.6
Comorbidities		
DM	41	13.2
Hyperlipidemia	48	15.5
CVS diseases	50	16.1
Final outcome		
Died	22	7.1
Recovered	288	92.9
Severity		
Mild	157	50.7%
Moderate	51	16.5%
Severe	66	21.3%
Critical	36	11.6%

TABLE 2 Vital signs and modality of ventilation

	Number	%
Heart rate (HR)		
Low	4	1.5
Normal	220	83.7
High	39	14.8
Respiratory rate (RR)		
Normal	223	84.8
High	40	15.2
Mean arterial blood pressure (BP)		
Normal	216	81.8
High	48	18.2
Oxygen saturation (SpO2)		
Low	52	19.8
Normal	211	80.2
Modality of ventilation		
RA	120	45.6
NC	66	25.1
FM	40	15.2
NRBM	11	4.2
IV	26	9.9

Abbreviations: FM, Face mask; IV, invasive ventilation; NC, Nasal cannula; NRBM, Non-rebreather mask; RA, room air.

normal because patients were already on antipyretic medication shortly after admission.

All patients received a treatment regimen including anticoagulant, antiviral and antibiotics as per the MOH protocol at that time. Additional medications were given for chronic diseases including

antihyperlipidemic drugs (statins), antihypertensives and antidiabetic drugs. Antifungal drugs, corticosteroids, mucolytics, bronchodilators, antitussive drugs, multivitamins and other drugs were given according to the need of each patient. During the management plan, 54.4% of patients required supplemental oxygen either through nasal cannula (25.1%); Face mask (15.2%); non-rebreather mask (4.2%) or invasive ventilation (9.9%) (Table 2).

3.3 | The association between the vital signs at presentation and the outcome

Multiple logistic regression was used to study the association between the death outcome and vital signs at presentation while controlling for other variables. The variables that showed significant association (P-value < 0.05) are the heart rate (HR), respiratory rate (RR) and the peripheral O2 saturation (SpO2). Patients in the group who died showed higher HR, higher RR and lower SpO2 compared to those who survived with P-value of (0.001), (< 0.001) & (<0.001), respectively (Table 3).

3.4 | Predicting the prognostic value of the laboratory results

Multiple logistic regression was used to study the association between the death outcome and lab test results. The variables that showed statistically significant association (P-value < 0.05) are the lymphocytes count, CRP, aPTT, INR, D. dimer, ALT and CK. However, the other laboratory results abnormalities did not show statistically significant association with the outcome (Table 3).

3.4.1 | Prognostic value of CBC results

As shown in Table 3, patients who died had lower hematocrit (Ht), RBCs, hemoglobin (Hb), PLTs, WBCs, neutrophils and lymphocytic count as compared to those who recovered. Among those parameters, only the low lymphocytic count was significantly correlated with the death outcome with P-value less than (0.001).

Prognostic value of coagulation & inflammatory-related parameters results

A number of inflammatory and blood coagulation parameters were investigated, including CRP, serum ferritin, aPTT, INR and D-dimer. Prolonged aPTT, high INR, high D. dimer and high CRP showed a statistically significant correlation with morbidity as a final outcome with P-value of (0.004), (< 0.001), (0.017) & (0.004), respectively. Elevated ferritin showed no significant indication (Table 3).

Prognostic value of the biochemical parameters

A significant correlation was found between ALT, CK and the final outcome in COVID-19 patients. Patients who did not recover had

TABLE 3 Vital signs and laboratory results in the died and recovered groups

	Recovered						Died						P-value
	N	Mean	SD	Q1	Median	Q3	N	Mean	SD	Q1	Median	Q3	
Vital signs													
HR	243	86.9	14.6	78.0	86.0	94.0	20	99.2	16.1	88.0	97.0	107.8	**0.001****
RR	243	21.3	3.3	20.0	20.0	22.0	20	26.9	6.0	23.3	26.0	31.8	**<0.001****
SPO2	243	95.6	3.4	95.0	96.0	97.0	20	91.9	4.3	90.0	92.0	95.8	**<0.001****
Complete blood count													
RBC	224	4.8	0.8	4.3	4.9	5.3	22	4.7	0.7	4.2	4.7	5.0	0.557*
Ht	211	41.8	18.4	35.6	39.5	44.4	22	34.5	7.0	31.1	33.7	39.9	0.068*
HB	221	12.8	2.0	11.5	13.3	14.2	22	12.6	1.8	11.6	13.0	14.0	0.610*
PLT	224	243.6	94.8	182.5	229.7	284.1	22	213.9	75.5	163.2	186.8	255.5	0.078**
WBC	224	7.9	3.9	5.5	7.0	9.1	22	7.8	3.3	5.5	6.8	11.0	0.951*
Neutrophils 10^3/uL	231	5.7	3.6	3.4	4.6	6.7	22	6.5	2.8	4.2	5.5	9.2	0.261*
Lymphocytes 10^3/uL	230	1.5	0.9	0.9	1.3	1.9	22	1.0	0.8	0.5	0.8	1.1	**<0.001****
Coagulation and inflammatory-related parameters													
CRP	266	10.4	11.0	1.8	7.5	14.0	22	18.1	11.0	9.5	18.5	26.6	**0.004***
FERR	252	966.9	1109.8	266.0	647.0	1338.5	22	1090.4	744.4	591.0	967.0	1396.8	0.062**
aPTT	190	36.7	19.2	28.1	32.7	38.7	22	60.7	47.9	32.1	39.2	69.5	**0.004****
INR	189	1.2	0.2	1.1	1.1	1.2	22	1.4	0.4	1.2	1.3	1.4	**<0.001****
D. Dimer	231	2.8	5.8	0.7	1.0	2.4	22	4.7	6.0	1.0	1.9	6.5	**0.017****
Biochemical parameters													
Serum creatinine	228	123.9	209.4	58.6	72.5	98.6	22	84.0	41.0	59.7	74.9	92.6	0.880**
Serum albumin	230	29.8	5.8	26.0	30.0	33.5	22	27.5	5.3	24.4	28.0	29.2	0.076*
ALT U/L	238	54.3	78.4	22.0	33.0	58.3	22	28.0	12.2	19.3	26.5	34.5	**<0.001***
AST U/L	242	60.3	109.2	27.0	39.0	56.3	22	48.2	19.9	32.5	45.0	62.3	0.605*
Serum total bilirubin umol/L	236	11.8	8.6	7.0	10.0	13.4	22	11.6	5.6	7.0	11.0	13.8	0.697**
Serum direct bilirubin umol/L	217	3.6	3.8	1.8	2.7	3.8	21	3.6	2.9	1.7	3.0	4.5	0.732**
CK U/L	146	306.7	631.1	56.8	104.0	245.5	21	622.8	889.2	107.0	236.0	757.0	**0.009****
LDH	227	340.0	227.4	213.0	292.0	418.0	22	403.0	139.7	284.3	395.0	527.5	0.203*

*Independent sample t test was used; **Mann–Whitney U test was used.

Bold values are statistically significant $P < 0.05$.

higher CK as compared to those who recovered with *P*-value of (0.009). However, Patients who did not recover had lower ALT level as compared to those who recovered with *P*-value of (0.001). On the other hand, serum creatinine, serum albumin, AST, serum bilirubin and LDH did not significant association with the outcome (Table 3).

Multivariate analysis

In this model, the backward stepwise method was used to remove variables that are not significantly predicting mortality. Based on the results of the multiple logistic regression, the variables that are associated with death outcome are prothrombin, HR, RR, ALT and CK level with ORs of 1.02 and 1.06, 1.32, 0.92, 1.00, respectively (Table 4).

For each unit increase in the prothrombin level, the odds of death outcome increases by 1.02 multiplicatively, and for each unit increase in HR, the odds of death outcome increases by 1.06 multiplicatively. For each unit increase in the RR, the odds of death outcome increases by 1.32 multiplicatively, and for each unit increase in CK level, the odds of death outcome increases by 1.002. For each unit increase in the ALT level, the odds of death outcome decreases by 0.92 multiplicatively.

4 | DISCUSSION

The COVID-19 pandemic is a Public Health Emergency of International Concern (PHEIC) threatening the human health and wellbeing. Alertness at different levels is evidently needed to face this devastating pandemic. The critical situation caused by the pandemic imposes a great challenge in epidemiological, diagnostic, therapeutic and preventive research. The high infectivity nature of the disease and inability to assess the severity of the condition in the early stages of the infection led to a high mortality rate worldwide. The availability and validity of early predictors of severity is an inevitable need in hospitalized patients. In the current study, clinical and laboratory data of 310 COVID-19 confirmed cases admitted to the referral hospital in Madinah were analyzed to assess the importance of abnormal laboratory findings in COVID-19 final outcome.

Most patients demonstrated normal HR, RR, blood pressure and SpO2 after admission to hospital as patients were maintained in isolation rooms or in ICU on external oxygen supply according to

TABLE 4 Multiple logistic regression for variables associated with the mortality outcome

| | OR | *P*-value | 95% CI for OR | |
			Lower	Upper
aPTT	1.020	0.041	1.001	1.039
HR	1.061	0.012	1.013	1.111
RR	1.323	0.000	1.134	1.543
ALT U/L	0.922	0.003	0.874	0.972
CK U/L	1.002	0.019	1.000	1.003

the need of each patient. Elevated CRP, ferritin, LDH and ALT and decreased levels of albumin were prominent findings in most of the patients included in this study. On the other hand, more patients presented with normal CBC, coagulation profile, serum Cr, AST, total Bili and CK.

In this study, it was found that low lymphocyte count was associated with death as a final outcome. These results are in agreement with previous studies where lymphopenia was shown to be more frequently encountered in severe cases. [14–16] Remarkably, lymphopenia was a prevailing feature in SARS infections. [17] Viral-mediated bone marrow suppression or immune-mediated lymphocytes destruction can be suggested as causes of lymphopenia in COVID-19 patients. As in SARS-COV-1, SARS-COV-2 might have similar properties, in addition to cytokine-mediated lymphocytes destruction, in inducing lymphopenia. [18–21] According to our results and previous studies, it is sensible to consider lymphopenia as a predictor for the development of severe illness at early stages of the disease. On the other hand, the results from the current study did not find a prognostic value for leukocytosis, neutrophilia or thrombocytopenia as presented in some previous series. [14,22]

The prognostic significance of laboratory tests was not limited to the CBC data, as increased aPTT, INR and D. dimer showed a significant prognostic value in our hands. It was found that patients who did not survive demonstrated prolonged aPTT and higher INR and D. dimer upon admission to hospital, when compared to the recovered group. Marked inflammation and hypoxia during COVID-19 infection can lead to coagulation abnormalities resulting from the activation of the coagulation cascade and the consumption of coagulation factors in a phenomenon known as COVID-19 associated coagulopathy. [23] The exact mechanism of this phenomenon is not clear yet, however, endothelial damage in COVID-19 infection was shown to trigger platelet aggregation and consumption with subsequent microvascular thrombosis. [22,24,25] Coagulopathy, defined as spontaneous prolongation of prothrombin time (PT) > 3s or an activated partial thromboplastin time (aPTT) > 5s, was reported as an independent predictor of thrombotic complications. [23] In our results, patients in the non-survivors group demonstrated prolonged aPTT, a finding which comes in agreement with a previous retrospective analysis. [26] Additionally, elevated D-dimer and prolonged INR showed significant association with the mortality outcome as shown in other previous studies. [26]

Among the biochemical parameters analyzed in this study, elevation of CK showed positive association with the severity of the disease and death. Creatine kinase (CK) is an essential enzyme to intracellular energy transport and muscle contraction. [27–29] CK is mainly found in cardiac and skeletal muscles, brain, lungs and GIT and is released in different pathological conditions of these tissues. [30] Regarding serum CK levels in COVID-19 patients, our results are in agreement with the results of two meta-analysis studies that demonstrated the positive correlation between elevated serum CK levels and the severity of COVID-19. [31,32]

In the current study, LDH levels were higher in patients who died as compared to patients who recovered, however it did not show

significant statistical association to the outcome. LDH is known to increase in the early stage of myocardial infarction and in hemolytic states. High serum LDH is used as a negative prognostic biomarker in those conditions. The levels of LDH were shown to be elevated in different inflammatory conditions, e.g., infections, malignancies and sepsis. [33] In addition, LDH was suggested as a potential marker of vascular permeability in immune-mediated lung injury. [33] Previously, Yuan et al. also found a direct correlation between the decay of serum LDH and CK levels with viral mRNA elimination. [34] Also, the meta-analysis results from Szarpak et al. (2020) suggested that LDH level can be used as a COVID-19 severity marker and is a predictor of survival. [33]

Finally, higher percentage of patients who recovered had high ALT levels as compared to those who did not recover. This finding, however, is in contrast with some previous studies showing that high ALT was a negative prognostic biomarker in COVID-19. This may indicate a virus-mediated liver injury and the emergence of severe disease due to the injury of other non-pulmonary organs. [35] Collectively, estimating the mortality rate from the total number of hospitalized cases demonstrated that most COVID-19 patients recover; however, the increasing number of global deaths necessitates finding a rapid, cheap and easily detectable biomarker to predict the severity of the condition as early as possible. Our data demonstrated that lymphopenia, prolonged aPTT, high INR, high D. dimer and high CK are valuable prognostic predictors of the severity of the disease at early stages. Based on the results of the multiple logistic regression, the variables that are associated with death outcome are aPTT, HR, RR, ALT and CK level

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