Al-Shajlawi M, Alsayed AR, Abazid H, Awajan D, AL-Imam A, Basheti I. Using laboratory parameters as predictors for the severity and mortality of COVID-19 in hospitalized patients. Pharmacy Practice 2022 Jul-Sep;20(3):2721.
https://doi.org/10.18549/PharmPract.2022.3.2721

Original Research

Using laboratory parameters as predictors for the severity and mortality of COVID-19 in hospitalized patients

Mustafa Al-Shajlawi, Ahmad R. Alsayed, Husam Abazid, Dima Awajan, Amniyah AL-Imam, Iman Basheti

Received (first version): 04-Aug-2022 Accepted: 30-Aug-2022 Published online: 09-Sep-2022

Abstract

Objective: The aim of this study was to explore association of initial laboratory parameters of hospitalized patients with COVID-19, with the severity and death incident. **Methods:** In this retrospective study, patients were classified based on mortality outcome (survivor and non-survivor) and disease severity (non-severe, severe, and critical). The initial laboratory data (within the first two days of hospital admission) were compared between these categories. **Results:** Of 362 COVID-19 patients hospitalized between January-2021 and May-2021, 39.0% were non-severe, 32.2% severe, and 28.7% critical. 77.3% were lived and 22.7% died in hospital. Non-survivors were significantly older than survivors. There was a statistically significant association between exceeding the cut-points of laboratory parameters and the severity of the disease or even death. These laboratory parameters included D-dimer, C-reactive protein, prothrombin time, ferritin, white blood cells, neutrophil count, aspartate aminotransferase, creatinine, blood urea nitrogen, lymphocyte count, and albumin. Also, exceeding the cut-points of these parameters showed high odds of death. The highest odds ratio was reported for albumin <3.5 g/dL (OR=14.318 [4.784-42.851], p<0.001). **Conclusion:** The cut-points of the laboratory parameters could effectively be used as predictors to assess the severity and risk of death to improve the management of COVID-19 patients.

Keywords: laboratory parameters; predictors; severity; mortality; COVID-19; hospitalized patients; Jordan

INTRODUCTION

In December 2019, Wuhan, a city in the Hubei Province of China, reported the first cases of coronavirus infectious disease-2019 (COVID-19), and became the center of the new pandemic outbreak.[1] The COVID-19 was caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[2]

The clinical spectrum of SARS-CoV-2 infection appears to be broad, from flu-like symptoms to multiple organ failure and death.[3] The classification of COVID-19 severity depends on the clinical manifestation, and the three severity levels of COVID-19 are non-severe, severe, and critical.[3,4] Patients with critical diseases are characterized by the development of acute respiratory distress syndrome (ARDS), sepsis, septic shock, organ failure, or the need for vasopressor therapy. Patients with severe disease are characterized by signs of pneumonia plus one of the following: SpO2 < 90% on room air, respiratory rate > 30 breaths per min, or severe respiratory distress. Non-severe patients are characterized by absence of any criteria for severe or critical patients.[3,4] People of any age may get infected with SARS-CoV-2, however, adults in their middle years and older are the most often affected, and older adults are more likely to develop severe disease. The median age of hospitalized patients with confirmed COVID-19 ranged from 49 to 56 years in several cohorts.[5-7]

The laboratory features of hospitalized patients with COVID-19 have also been associated with negative outcomes. These included an increased level of D-dimer, liver enzymes, lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, prothrombin time (PT), troponin, and decreased levels of lymphocyte and platelet count.[3,8-10] For instance, a study conducted in China on 138 hospitalized patients found that the non-survivors had a progressive decline in lymphocyte count and an increase in D-dimer over time, compared to survivors who had more stable levels.[6] Until now, there is no study conducted in Jordan with outcomes based on laboratory data of hospitalized patients with the aim to assess the severity of COVID-19. Also, there is lack of studies to use comprehensive laboratory parameters to predict both the COVID-19 severity

Mustafa AL-SHAJLAWI. MSc. Department of Clinical Pharmacy and Therapeutics, Faculty of Pharmacy, Applied Science Private University, Amman 11931-166, Jordan. Mustafanasri29@gmail.com
Ahmad R. ALSAYED*. PhD, MSc, PharmD. Department of Clinical Pharmacy and Therapeutics, Faculty of Pharmacy, Applied Science Private University, Amman 11931-166, Jordan. a_alsayed@asu.edu.jo; a.alsayed.phd@gmail.com
Husam ABAZID. PhD. Department of Clinical Pharmacy and Therapeutics, Faculty of Pharmacy, Applied Science Private University, Amman 11931-166, Jordan. h_abazid@asu.edu.jo
Dima AWAJAN. PharmD. Department of Clinical Pharmacy and Therapeutics, Faculty of Pharmacy, Applied Science Private University, Amman 11931-166, Jordan. d_awajan@asu.edu.jo
Amniyah AL-IMAM. Pharmacist. Al-Rayhan Medical Center, Amman, Jordan. umniyah96bassam@gmail.com
Iman BASHETI. PhD, BPharm. Department of Clinical Pharmacy and Therapeutics, Faculty of Pharmacy, Applied Science Private University, Amman 11931-166, Jordan. Dr_iman@asu.edu.jo

www.pharmacypractice.org (eISSN: 1886-3655 ISSN: 1885-642X)

and risk of death, and most of the previous studies used limited laboratory parameters with small sample size.

The aim of this study was to estimate the COVID-19 severity in patients diagnosed with COVID-19 living in Jordan, and outcome of the hospitalized patients using laboratory data within the first two days of hospital admission.

METHODS

Study design and participants

A retrospective cohort study included patients with confirmed COVID-19, and hospitalized at Prince Hamza hospital (PHH) in Amman, Jordan. The study was conducted between January 10, 2021 and May 30, 2021. Patients admitted for only one day or without initial laboratory data during the first two days of hospitalization were excluded from the study.

Ethical statement

The ethical approval was obtained from Applied Science Private University and the PHH ethical committee with an approval number 2020-PHA-24 and 6-11-2021-129 respectively.

Data collection

All data were extracted from the medical files by the research team. These data included age, gender, length of stay, comorbidities, treatment, laboratory data, and the clinical outcomes. SARS-CoV-2 detection was performed using real-time polymerase chain reaction (PCR), as outlined in details in previous recent studies.[11-13]

The classification of COVID-19 patients

There were two classifications for the patients in this study. The first classification was based on discharged status; survivor or non-survivor. The second classification was based on the severity of the disease (non-severe, severe, and critical), as shown in Table 1. This classification was based on the World Health Organization (WHO).[4] The baseline clinical characteristics was compared with different outcomes. These outcomes included survivor versus non-survivor, and non-severe versus severe versus critical.

Laboratory parameters

The initial laboratory values (i.e., documented within the first two days of hospital admission) were extracted from the medical files and uploaded into the SPSS template. These laboratory parameters included: platelet count, lymphocyte count, D-dimer, liver enzymes (AST and ALT, aspartate aminotransferase and alanine aminotransferase), C- reactive protein (CRP), blood urea nitrogen (BUN), creatinine, ferritin, procalcitonin, troponin I, prothrombin time (PT), neutrophil count, albumin, hemoglobin, and white blood cell (WBC).

The cut-points that was used for the different parameters were: D-dimer >1 mg/L; CRP >100 mg/L; ferritin >500 ng/ml; procalcitonin > 2.0 ng/mL; PT >12 sec; positive troponin; WBC >10 $\times 10^3/\mu$; neutrophil count > 7 $X10^9$/L; ALT >53 IU/L; AST >47 IU/L; creatinine > 104 µmol/L; BUN >8.9 mmol/L; platelet count <140 $\times 10^3/\mu$; albumin < 3.5 g/dL; lymphocyte count <0.8 $x10^9$/L; and hemoglobin <14 g/dL.

The cut-point values that were used for D-dimer, CRP, ferritin, and lymphocyte count were extrapolated from previous cohort studies that showed that these values may be associated with worsening outcomes.[5,6,8,14-16] The normal value of the PHH was used as a reference range to establish the cut-point values of the other laboratory parameters.

These initial laboratory parameters were compared with both the survival outcome and the severity classification of COVID-19 patients.

Statistical analysis

All data were analyzed using the Statistical Package for the Social Science (SPSS) version 24 (SPSS Inc., Chicago, IL, USA). As appropriate, the continuous variable was presented as mean (M) ± standard deviation (SD), or median (interquartile range [IQR]). The categorical variables were presented as frequency (%). Mann-Whitney U test, Kruskal-Wallis H test, and one-way ANOVA were used, as appropriate, to compare the age and length of stay (LOS) between survivor and non-survivor, and also to compare between the three different COVID-19 severity categories. The Chi-square test and Fisher exact tests were used to compare between the different categorical variables and survivor versus non-survivor categories, and also between the different categorical variables and the severity classification of COVID-19 patients. We chose the initial laboratory parameters that were significantly different between survivor and non-survivor patients and between non-severe, severe, and critical patients to calculate the odds ratio. A value of $P < 0.05$ was accepted as statistically significant.

Table 1. The classification of COVID-19 severity (adapted from the WHO[4])

Non-Severe	**Severe**	**Critical**
Patients without characteristics of severe and critical disease.	Patients characterized by signs of Pneumonia (fever, cough, dyspnea) with one of the following: • Respiratory rate >30. • Severe respiratory distress. • SpO2 < 90% on room air (RA.)	Patients characterized by one of the following: • ARDS. • Sepsis. • Septic shock. • Organ failure (ex, cardiac injury or acute kidney injury). • Need for mechanical ventilation (invasive or non-invasive) or vasopressor therapy.

ARDS- stands for acute respiratory distress syndrome. SpO_2- Peripheral oxygen saturation, an estimation of the oxygen saturation level.

RESULTS

Baseline characteristics

A total of 362 patients with COVID-19 who were hospitalized at PHH between January 10, 2021 and May 30, 2021 were included in this study. A total of 57 out of 419 (13.6%) cases were excluded due to either the unavailability of the initial laboratory parameters or the lack of the patient outcome. upon hospitalization. The median age (IQR) of the patients was 55 (22) years, 205 (56.6%) patients were males, and 157 (43.4%) patients were females (Table 2).

Table 2. Baseline characteristics of COVID-19 patients based on the mortality status (N=362)

Characteristics	Total N=362	Survivor N=280 (77.3%)	Non-Survivor N=82 (22.7%)	P-Value
Age, median (IQR)	55 (22)	51 (23)	63 (19)	<0.001
Gender, n (%)				
Male	205 (56.6%)	155 (55.4%)	50 (61.0%)	0.367
Female	157 (43.4%)	125 (44.6%)	32 (39.0%)	
Comorbidity, n (%)				
Hypertension	121 (33.5%)	96 (34.4%)	25 (30.5%)	0.508
Diabetes	102 (28.2%)	78 (27.9%)	24 (29.3%)	0.803
IHD	16 (4.4%)	14 (5.0%)	2 (2.4%)	0.540
Other	(< 4.0%)			
Common symptoms, n (%)				
SOB	81 (22.4%)	74 (26.4%)	7 (8.5%)	<0.001
Dry cough	58 (16.0%)	55 (16.6%)	3 (3.7%)	<0.001
Fever	44 (12.2%)	40 (14.3%)	4 (4.9%)	0.022
Chest pain	31 (8.6%)	30 (10.7%)	1 (1.2%)	0.007
Headache	25 (6.9%)	23 (8.2%)	2 (2.4%)	0.070
Vomiting	23 (6.4%)	19 (6.8%)	4 (4.9%)	0.533
Sore throat	22 (6.1%)	21 (7.6%)	1 (1.2%)	0.035
Productive cough	21 (5.8%)	20 (7.2%)	1 (1.2%)	0.056
Diarrhea	21 (5.8%)	19 (6.8%)	2 (2.4%)	0.183
General fatigue	20 (5.5%)	18 (6.4%)	2 (2.4%)	0.269
Abdominal pain	15 (5.3%)	18 (6.5%)	1 (1.2%)	0.088
Loss of taste and smell	18 (5.0%)	17 (6.1%)	1 (1.2%)	0.087
Others	(< 5.0%)			
Treatment, n (%)				
Antibiotics	239 (66.0%)	205 (73.2%)	34 (41.5%)	<0.001
Vitamins	206 (56.9%)	192 (68.6%)	14 (17.1%)	<0.001
Anticoagulant	194 (53.6%)	163 (58.2%)	31 (37.8%)	0.001
Corticosteroids	174 (48.1%)	144 (51.4%)	30 (36.6%)	0.018
Oxygen therapy	144 (39.8%)	124 (44.3%)	20 (24.4%)	0.001
Antiplatelet	78 (21.5%)	63 (22.5%)	15 (18.3%)	0.415
Antiviral	34 (9.4%)	29 (10.4%)	5 (6.5%)	0.245
mAb (tocilizumab)	24 (6.6%)	15 (5.4%)	9 (11.0%)	0.072
Length of stay, median (IQR)	11 (12) days	10 (12) days	13 (11) days	0.282

The most common comorbidity was hypertension (33.5%), followed by diabetes (28.2%) and ischemic heart disease (IHD) (4.4%). The other comorbidity was less than 4.0%. Shortness of breath (SOB, 22.4%), dry cough (16.0%), and fever (12.2%) were the most common reported symptoms. The other symptoms (less than 10.0%) were chest pain (8.6%), headache (6.9%), vomiting (6.4%), sore throat (6.1%), productive cough (5.8%), diarrhea (5.8%), general fatigue (5.5%), abdominal pain (5.3%), and loss of taste and smell (5.0%) (Table 2).

A total of 82 (22.7%) patients died, and 280 (77.3%) patients survived the disease and were discharged from hospital. The comparison between survivor and non-survivor patients indicated that the non-survivor patients were older in age (p-value <0.001). In contrast, symptoms including SOB, dry cough, fever, chest pain, and sore throat were higher among survivors than non-survivor patients, with a significant difference. No significant difference in gender (P-value = 0.367) and comorbidities between the two groups was shown (Table 2).

The second comparison was based on disease severity, as shown in Table 3. Of 362 patients, 141 (39.0%) were classified as non-severe, 117 (32.2%) were severe, and 104 (28.7%) were critical. Data analysis showed a significant difference in age between the three groups (p-value <0.001). Also, some symptoms, including SOB, dry cough, headache, sore throat, general fatigue, abdominal pain, and loss of taste and smell were significantly different between the three groups. Gender (P-value = 0.906) and comorbidity were not significantly different between the three severity categories (Table 3).

Initial laboratory data

Laboratory analysis of the overall patients with COVID-19 showed that 58.0% exceeded the D-dimer cut-point and 53.8% exceeded the CRP cut-point (Table 4). Similarly, 83.8% and 6.4% of patients exceeded the cut-point value of PT, and troponin I, respectively. The cut-point values were exceeded for the other laboratory parameters, including ferritin in 25.0%, WBC in 36.9%, neutrophil count in 45.9%, ALT in 25.7%, AST in 38.4%, creatinine in 26.7%, BUN in 42.5%, and procalcitonin in 13.8%. Furthermore, 52.2%, 18.5%, 59.7%, and 68.6% of patients exceeded the cut-point values of lymphocyte count, platelet count, albumin, and hemoglobin, respectively (Table 4).

The comparison between survivor and non-survivor patients showed that there was a statistically significant association between exceeding the cut-point values of some laboratory parameters and death. These laboratory parameters include D-dimer, CRP, PT, ferritin, WBC, neutrophil count, AST, creatinine, BUN, lymphocyte count, and albumin (Table 4).

Table 3. Baseline characteristics of COVID-19 patients based on the disease severity (N=362)

Characteristics	Total N=362	Non-severe case N=141 (39.0%)	Severe case N=117 (32.2%)	Critical case N=104 (28.7%)	P-Value
***Age mean, (SD)**	55 (22)	46.65 (15.923)	55.61 (14.326)	62.54 (13.238)	<0.001
Gender, n (%)					
Male	205 (56.6%)	81 (57.4%)	67 (57.3%)	57 (54.8%)	0.906
Female	157 (43.4%)	60 (42.6%)	50 (42.7%)	47 (45.2%)	
Comorbidity, n (%)					
Hypertension	121 (33.5%)	43 (30.5%)	40 (34.2%)	38 (36.9%)	0.569
Diabetes	102 (28.2%)	36 (25.5%)	32 (27.4%)	34 (32.7%)	0.455
Ischemic heart disease	16 (4.4%)	5 (3.5%)	7 (6.0%)	4 (3.8%)	0.603
Other	(< 4.0%)				
Common symptoms, n (%)					
SOB	81 (22.4%)	19 (13.5%)	43 (36.8%)	19 (18.3%)	<0.001
Dry cough	58 (16.0%)	37 (26.2%)	15 (12.8%)	6 (5.8%)	<0.001
Fever	44 (12.2%)	16 (11.3%)	19 (16.2%)	9 (8.7%)	0.211
Chest pain	31 (8.6%)	11 (7.8%)	15 (12.8%)	5 (4.8%)	0.096
Headache	25 (6.9%)	14 (9.9%)	9 (7.7%)	2 (1.9%)	0.047
Vomiting	23 (6.4%)	9 (6.4%)	10 (8.5%)	4 (3.8%)	0.360
Sore throat	22 (6.1%)	19 (13.7%)	2 (1.7%)	1 (1.0%)	0.000
Productive cough	21 (5.8%)	13 (9.3%)	4 (3.4%)	4 (3.8%)	0.080
Diarrhea	21 (5.8%)	12 (8.5%)	5 (4.3%)	4 (3.8%)	0.210
General fatigue	20 (5.5%)	5 (3.5%)	12 (10.3%)	3 (2.9%)	0.024
Abdominal pain	19 (5.3%)	13 (9.3%)	2 (1.7%)	4 (3.8%)	0.019
Loss of taste and smell	18 (5.0%)	16 (11.3%)	1 (0.9%)	1 (1.0%)	<0.001
Others	(< 5.0%)				
Treatment, n (%)					
Antibiotics	239 (66.0%)	77 (54.6%)	107 (91.5%)	55 (52.9%)	<0.001
Vitamins	206 (56.9%)	104 (73.8%)	78 (66.7%)	24 (23.1%)	<0.001
Anticoagulant	194 (53.6%)	45 (31.9%)	99 (84.6%)	50 (48.1%)	<0.001
corticosteroids	174 (48.1%)	30 (21.3%)	98 (83.8%)	46 (44.2%)	<0.001
Oxygen therapy	144 (39.8%)	1 (0.7%)	106 (90.6%)	37 (35.6%)	<0.001
Antiplatelet	78 (21.5%)	24 (17.0%)	32 (27.4%)	22 (21.2%)	0.132
Antiviral	34 (9.4%)	7 (5.0%)	17 (14.5%)	10 (9.6%)	0.032
mAb (tocilizumab)	24 (6.6%)	1 (0.7%)	10 (8.5%)	13 (12.5%)	0.001
Length of stay, median (IQR)	11 (12) days	10 (3) days	17 (17) days	15 (16) days	<0.001

*Age was presented as median (IQR) for the total patients and mean (SD) for non-severe, severe, and critical patients.

The second comparison was based on disease severity: non-severe, severe, and critical (Table 5). Laboratory investigation of different disease severity showed a significant association between exceeding the cut-point values of some laboratory parameters and disease severity. These laboratory parameters were similar to what was mentioned in the previous comparison (i.e., survivor and non-survivor), which included D-dimer, CRP, PT, ferritin, WBC, neutrophil count, AST, creatinine, BUN, lymphocyte count, and albumin. Furthermore, this comparison also showed a significant association between exceeding the cut-point values and disease severity for ALT and hemoglobin (Table 5).

Treatment and clinical outcomes

Overall, 66.0% of patients received antibiotics, 56.9% received vitamins, 53.6% received anticoagulant, 48.1% received corticosteroids, 39.8% received oxygen therapy, 21.5% received antiplatelet, 9.4% received antiviral, and 6.6% received tocilizumab (Table 2). Of 362 patients, 82 (22.7%) patients died due to the infection, and 280 (77.3%) patients survived. The

Table 4. Initial laboratory findings for survivor and non-survivor patients (N=362)

Laboratory findings	Cut-point	Missing data	Total*	Survivor N=280 (77.3%)	Non-Survivor N=82 (22.7%)	P-Value
D-dimer	>1 mg/L	124 (34.3%)	138 (58.0%)	86 (48.3%)	52 (86.7%)	<0.001
CRP	>100 mg/L	46 (12.7%)	170 (53.8%)	106 (45.1%)	64 (79.0%)	<0.001
PT	>12 sec	71 (19.6%)	244 (83.8%)	172 (81.1%)	72 (91.1%)	0.039
Troponin	Positive	222 (61.3%)	9 (6.4%)	4 (4.4%)	5 (10.2%)	0.277
Ferritin	>500 ng/ml	314 (86.7%)	12 (25.0%)	9 (20.5%)	3 (75.0%)	0.043
WBC	>10 ×10^3/µL	12 (3.3%)	129 (36.9%)	76 (28.4%)	53 (64.6%)	<0.001
Neutrophil count	> 7 X10^9/L	24 (6.6%)	155 (45.9%)	90 (34.9%)	65 (81.3%)	<0.001
ALT	>53 IU/L	31 (8.6%)	85 (25.7%)	60 (24.0%)	25 (30.9%)	0.219
AST	>47 IU/L	34 (9.4%)	126 (38.4%)	77 (31.2%)	49 (60.5%)	<0.001
Creatinine	> 104 µmol/L	17 (4.7%)	92 (26.7%)	59 (22.4%)	33 (40.2%)	0.001
BUN	>8.9 mmol/L	30 (8.3%)	141 (42.5%)	77 (30.8%)	64 (78.0%)	<0.001
Procalcitonin	> 2.0 ng/mL	333 (92.0%)	4 (13.8%)	3 (15.0%)	1 (11.1%)	1.00
Lymphocyte count	<0.8 x10^9/L	23 (6.4%)	177 (52.2%)	113 (44.0%)	64 (78.0%)	<0.001
Platelet count	<140 × 10^3/µL	16 (4.4%)	64 (18.5%)	46 (17.4%)	18 (22.0%)	0.356
Albumin	< 3.5 g/dL	213 (58.8%)	89 (59.7%)	44 (44.0%)	45 (91.8%)	<0.001
Hemoglobin	<14 g/dL	12 (3.3%)	240 (68.6%)	178 (66.4%)	62 (75.6%)	0.117

*Represents all patients with reported laboratory parameter and achieved the cut-point. PT= prothrombin time. WBC= White blood cells. ALT= alanine aminotransferase. AST= aspartate transferase. BUN= blood urea nitrogen.

Table 5. Initial Laboratory findings based on the disease severity (N=362)

Laboratory findings	Cut-point	Missing data	Total*	Non severe case N=141 (39.0%)	Severe case N=117 (32.2%)	Critical case N=104 (28.7%)	P-Value
D-dimer	>1 mg/L	124 (34.3%)	138 (58.0%)	19 (24.1%)	50 (63.3%)	69 (86.3%)	<0.001
CRP	>100 mg/L	46 (12.7%)	170 (53.8%)	17 (16.7%)	76 (67.9%)	77 (75.5%)	<0.001
PT	>12 sec	71 (19.6%)	244 (83.8%)	67 (73.6%)	84 (84.8%)	93 (92.1%)	0.002
Troponin	Positive	222 (61.3%)	9 (6.4%)	0 (0.0%)	2 (3.8%)	7 (10.8%)	0.123
Ferritin	>500 ng/ml	314 (86.7%)	12 (25.0%)	6 (15.8%)	1 (25.0%)	5 (83.3%)	0.002
WBC	>10 ×10^3/µL	12 (3.3%)	129 (36.9%)	17 (12.7%)	48 (42.9%)	64 (61.5%)	<0.001
Neutrophil count	> 7 X10^9/L	24 (6.6%)	155 (45.9%)	17 (13.4%)	60 (55.0%)	78 (76.5%)	<0.001
ALT	>53 IU/L	31(8.6%)	85 (25.7%)	16 (13.6%)	39 (35.5%)	30 (29.1%)	<0.001
AST	>47 IU/L	34 (9.4%)	126 (38.4%)	21 (18.3%)	49 (44.5%)	56 (54.4%)	<0.001
creatinine	> 104 µmol/L	17 (4.7%)	92 (26.7%)	29 (22.8%)	23 (20.2%)	40 (38.5%)	0.004
BUN	>8.9 mmol/L	30 (8.3%)	141 (42.5%)	22 (18.5%)	43 (39.4%)	76 (73.1%)	<0.001
Procalcitonin	> 2.0 ng/mL	333 (92.0%)	4 (13.8%)	2 (20.0%)	1 (11.1%)	1 (10.0%)	0.779
Lymphocyte count	<0.8 x10^9/L	23 (6.4%)	177 (52.2%)	18 (14.3%)	80 (73.4%)	79 (76.0%)	<0.001
Platelet count	<140 × 10^3/µL	16 (4.4%)	64 (18.5%)	19 (14.7%)	22 (19.5%)	23 (22.1%)	0.335
Albumin	< 3.5 g/dL	213 (58.8%)	89 (59.7%)	12 (22.2%)	22 (64.7%)	55 (90.2%)	<0.001
Hemoglobin	<14 g/dL	12 (3.3%)	240 (68.6%)	76 (57.1%)	83 (73.5%)	81 (77.9%)	0.001

*Represents all patients with reported laboratory parameter and achieved the cut-point. PT= prothrombin time. WBC= White blood cells. ALT= alanine aminotransferase. AST= aspartate transferase. BUN= blood urea nitrogen.

median (IQR) length of stay of all patients in the hospital was 11 (12) days.

There was a significant difference between survivor and non-survivor patients in the usage of antibiotics, vitamins, anticoagulants, corticosteroids, and oxygen therapy. The median days from hospital admission until death documentation were 13 days, whereas until discharge was 10 days for the survivor group (Table 2).

In terms of disease severity (Table 3), there was a significant difference in the usage of antibiotics, vitamins, anticoagulants,

corticosteroids, oxygen therapy, and tocilizumab between non-severe, severe, and critical patients. The median length of stay of non-severe, severe, and critical patients was 10 days, 17 days, and 15 days, respectively, with a significant difference between the three groups (p-value <0.001).

Risk of mortality

Odds of in-hospital death were calculated for laboratory parameters that significantly differed between survivor and non-survivor patients and between non-severe, severe, and critical patients (Table 6).

Odds of in-hospital death were higher among patients with albumin < 3.5 g/dL (OR 14.318 [4.784-42.851], p-value <0.001), ferritin >500 ng/ml (OR 11.667 [1.081-125.902], p-value 0.043), neutrophil count > 7 X10^9/L (OR 8.089 [4.634-14.992], p-value <0.001), and BUN >8.9 mmol/L (OR 7.988 [4.438-14.380], p-value <0.001). Similarly, D-dimer >1 mg/L (OR 6.953 [3.123-15.480], p-value <0.001), WBC >10 ×10^3/µL (OR 4.617 [2.732-7.804], p-value <0.001), CRP >100 mg/L (OR 4.582 [2.531-8.292], p-value <0.001), and lymphocyte count <0.8 x10^9/L (OR 4.531 [2.542-8.076], p-value <0.001). AST >47 IU/L (OR 3.381 [2.009-5.689], p-value <0.001), creatinine > 104 µmol/L (OR 2.329 [1.373-3.948], p-value 0.001), and PT >12 sec (OR 2.392 [1.024-5.590], p-value 0.039) were also associated with higher rate of death (Table 6).

Table 6. The risk factors associated with higher death rate in hospital for COVID-19 patients

Parameters	OR (95% CI)	p-value
Albumin < 3.5 g/dL	14.318 (4.784-42.851)	<0.001
Ferritin >500 ng/ml	11.667 (1.081-125.902)	0.043
Neutrophil count > 7 X10^9/L	8.089 (4.634-14.992)	<0.001
Blood urea nitrogen >8.9 mmol/L	7.988 (4.438-14.380)	<0.001
D-dimer >1 mg/L	6.953 (3.123-15.480)	<0.001
WBC >10 ×10^3/µL	4.617 (2.732-7.804)	<0.001
C-reactive protein >100 mg/L	4.582 (2.531-8.292)	<0.001
Lymphocyte count <0.8 x10^9/L	4.531 (2.542-8.076)	<0.001
AST >47 IU/L	3.381 (2.009-5.689)	<0.001
Creatinine > 104 µmol/L	2.329 (1.373-3.948)	0.001
Prothrombin time >12 sec	2.392 (1.024-5.590)	0.039

WBC= white blood cell. AST= aspartate transferase

DISCUSSION

The present study is the first to explore the association of baseline clinical characteristics and initial laboratory parameters with worsening outcomes and even death in COVID-19 patients living in Jordan. This study revealed the initial laboratory data (within the first two days of hospital admission) between survivor and non-survivor patients and between non-severe, severe, and critical COVID-19 patients.

The non-survivor patients had a higher frequency of exceeding the estimated laboratory cut-points at the time of hospital admission. These parameters included D-dimer, CRP, PT, ferritin, WBC, neutrophil count, AST, creatinine, BUN, lymphocyte, and albumin. Similarly, these abnormal initial laboratory parameters were higher in prevalence in critical patients, followed by severe and non-severe patients with significant differences. Exceeding ALT and hemoglobin cut-points were not significantly different between survivor and non-survivor, but the second comparison (i.e., between the different severity categories) showed significant differences.

Previous studies showed that the levels of D-dimer, CRP, PT, ferritin, WBC, creatinine, lymphocyte, albumin, and BUN were significantly different between non-survivor and survivor patients.[8,16] Findings of this study are consistent with those of previous studies. Among non-survivor patients, 86.7% had D-dimer >1 µg/ml, 79.0% had CRP >100 mg/L, 91.1% had PT >12 sec, 75.0% had ferritin >500 ng/ml, 64.6% had WBC >10 ×10^3/µl, 40.2% had creatinine > 104 µmol/L, 78.0% had BUN > 8.9 mmol/L, 78.0% had lymphocyte count <0.8 x10^9/L, and 91.8% had albumin < 3.5 g/dL. In addition, in this study neutrophil count > 7 X10^9/L was reported in 81.3% of non-survivor patients and AST >47 IU/L was reported in 60.5% of patients. Moreover, low hemoglobin (<14 g/dL) was not significantly different between survivor and non-survivor patients, but in the second comparison, there was a significant difference which is consistent with Liu and co-workers findings.[17]

The odds of in-hospital death were calculated for initial laboratory parameters that were significantly different in both comparisons. Odds of in-hospital death were higher among patients who had exceeded cut-point values of lymphocyte count, albumin, D-dimer, CRP, PT, ferritin, WBC, neutrophil count, AST, creatinine, and BUN.

This study established a cut-point value of >1 mg/L and >100 mg/L for D-dimer and CRP, respectively. 86.7% of non-survivors exceeded the cut-point value of D-dimer, and 79.0% of patients exceeded the cut-point value of CRP. Furthermore, there were significant differences between non-severe, severe, and critical patients in the incidence of exceeding the cut-point value. According to a previous study, the level of D-dimer was significantly higher among non-survivor patients with a median (IQR) of 5.2 mg/L (1.5-21.1).[8] Patients with the critical disease had higher D-dimer followed by severe and moderate patients.[3] Moreover, CRP levels were significantly different between moderate, severe, and critical patients and the median level was 92.79 mg/L for patients with the critical disease.[3]

The PT was significantly higher in non-survivor patients than in survivors in a previous study.[8] Also, this parameter showed a significant difference in the levels between moderate, severe, and critical patients, with a higher level among patients with the critical disease.[3] In this study, non-survivor patients and patients with critical disease had a higher incidence of exceeding the cut-point value of PT.

In a previous study, the odds of in-hospital death were higher among patients with elevated D-dimer and PT.[8] Findings of this study showed that the odds of in-hospital death were significantly higher among patients with D-dimer >1 mg/L, PT

>12 sec, and CRP >100 mg/L.

This study showed that 75.0% of non-survivor patients exceeded the cut-point value of ferritin and 64.6% exceeded the cut-point value of WBC. Ferritin and WBC were significantly higher in non-survivor patients than in survivor patients in a previous study.[8] The median (IQR) of ferritin and WBC among non-survivor patients was 9.8 $\times 10^3/\mu L$ (6.9–13·9) and 1435.3 ng/ml (728.9–2000.0), respectively.[8]

Certain parameters were associated with higher rates of death. In a previous study, the level of neutrophil count in non-survivor patients continued to increase until death occurred.[5] AST level was higher than >40 U/liter in 39.4% of severe patients.[14] Creatinine levels were significantly different between survivor and non-survivor patients.[16] This study showed that among non-survivor patients, 81.3% exceeded the cut-point value of neutrophil count, 60.5% exceeded the cut-point value of AST, and 40.2% exceeded the cut-point value of creatinine. Furthermore, patients with critical disease had a higher incidence of exceeding the cut-point value than severe and non-severe patients.

The odds of in-hospital death were shown to be higher among patients with elevated ferritin, WBC, neutrophil count, AST, and creatinine in a previous study.[8] In this study, the odds of in-hospital death were also higher among patients that exceeded cut-point value of with ferritin (>500 ng/ml), WBC (>10 $\times 10^3/\mu L$), neutrophil count (> 7 $X10^9/L$), AST (>47 IU/L), and creatinine (> 104 µmol/L).

As for the BUN levels, results of a previous study indicated that they were significantly different between patients who died and those who were discharged.[16] In addition, ICU patients had higher BUN levels than non-ICU patients.[6] Findings of this study showed that 78.0% of non-survivor patients exceeded the cut-point value (>8.9 mmol/L), and critical patients had a higher frequency of exceeding the cut-point value, followed by severe and non-severe patients.

The lymphocyte count and albumin were lower in a previous study in non-survivor than in survivor patients.[8] The incidence of lymphocytopenia was higher in severe than in non-severe patients.[14] In a recent study, albumin level was lower in patients with critical disease than in severe and moderate disease.[17] The current study showed that among non-survivor patients, 78.0% exceeded the lymphocyte cut-point (<0.8 $x10^9/L$), and 97.8% exceeded the albumin cut-point (< 3.5 g/dL). Furthermore, patients with critical disease significantly exceeded the cut-point value of lymphocyte and albumin more than severe and non-severe patients. Odds of in-hospital death were higher among patients with lymphocytopenia.[8] A similar finding was observed among patients in this study. In addition, patients who exceeded BUN and albumin cut-point also had higher odds of death.

Previously, Zhang et al. and Zhou et al. showed that the median age of patients who survived and did not survive COVID-19 was 54 years and 56 years, respectively.[8,18] In addition, non-survivor patients were older than survivors.[8,18] Similarly, in this study, the median age of survivor patients was 55 years, and non-survivor patients were older in age than survivor patients (P-value <0.001). Results of this study also showed that critical patients were significantly older than the severe, followed by the non-severe patients (P-value <0.001). This result provides further support for the hypothesis that older age was associated with worsening outcomes in COVDI-19 patients. Other findings showed no significant difference in gender between non-survivor and survivor patients, and between non-severe, severe, and critical patients, which is consistent with previous studies.[8,17] A possible explanation for this might be that the gender is not a risk factor for disease severity or even death.

In this study, the most common comorbidities among patients were hypertension (33.5%), diabetes (28.2%), and IHD (4.4%). This finding is consistent with previous studies.[8,18] However, this study has been unable to demonstrate a significant difference in comorbidities between survivor and non-survivor patients, and between non-severe, severe, and critical patients. Regarding the symptoms of patients in this study, SOB (22.4%), dry cough (16.0%), and fever (12.2%) were the most common reported symptoms. This is relatively similar to previous studies.[12,18] The difference in frequency and order of symptoms explained the difficulty to diagnose patients with COVID-19 based on the clinical manifestations alone. Previous studies showed that antibiotics, antiviral, and corticosteroids were the most common treatments used for COVID-19 patients.[8,18]

In this study, antibiotics (66.0%), vitamins (56.9%), anticoagulants (53.6%), and corticosteroids (48.1%) were the most commonly used treatment. Our findings are consistent with the previous mentioned studies on the usage of antibiotics and corticosteroids. In contrast, only 9.4% of patients, in our study, received antiviral agents. These differences in treatment reflect the missing of a specific agent for COVID-19. Moreover, the lack of specific effective agents for COVID-19 and continuing usage of antibiotic and antiviral agents increase the possibility of gut microbiota imbalance (dysbiosis) and other negative consequences among COVID-19 patients.[19,20]

In this study, the length of hospital stay was 12 days for all patients; 10 days for the survivor patients, and 13 days for the non-survivor patients, which is lower than that reported in a previous study.[8] The mortality rate (22.7%) was lower in this study as compared to other previous studies.[8,16]

This study has some limitations. First, it was a retrospective study, so not all laboratory tests were performed for all of the included patients. Missing values were mainly found for procalcitonin, ferritin, troponin I, and albumin assessments. These missing variables could have resulted in a better insight into the findings of this study. Also, the data of this study come from a single-center in Jordan, and further multi-center studies are called for to validate the findings presented. However, this is the first study, with a higher sample size than previous studies, to use comprehensive laboratory parameters to predict both the COVID-19 severity and risk of death. Furthermore, symptoms, disease severity and risk of death after SARS-

CoV-2 infection are influenced by the vaccination's status of the patients. However, due to the retrospective nature of this study, this information was not available for all of the patients.

CONCLUSIONS

The current study adds substantial value to the current literature with regards to estimating the COVID-19 severity in patients diagnosed with COVID-19 using laboratory data within the first two days of hospital admission. Results suggest that D-dimer >1 mg/L, CRP >100 mg/L, PT >12 sec, ferritin >500 ng/ml, WBC >10 $\times 10^3/\mu L$, neutrophil count > 7 $X10^9/L$, AST >47 IU/L, creatinine > 104 µmol/L, BUN >8.9 mmol/L, lymphocyte count <0.8 $x10^9/L$, and albumin < 3.5 g/dL are associated with worsening outcomes and even death for COVID-19 patients. Therefore, these cut-point values could effectively be used to predict the severity and risk of death at an early stage of hospital admission to improve the management of patients with COVID-19.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

ACKNOWLEDGMENTS

We would like to thank every member in PHH for the approval and the facilities they provide to get this work finished successfully. Also, we would like to thank Dr Firas Elhaji and Dr Abdelqader Al-Bawab for their feedback.

FUNDING

Authors received no specific funding for this work.

References

1. Park M, Cook AR, Lim JT, et al. A Systematic Review of COVID-19 Epidemiology Based on Current Evidence. 2020;9(4):967. https://doi.org/10.3390/jcm9040967
2. Viruses CSGotICoTo. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nature Microbiology. 2020;5(4):536-544. https://doi.org/10.1038/s41564-020-0695-z
3. Liao D, Zhou F, Luo L, et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. The Lancet. Haematology. 2020;7(9):e671-e678. https://doi.org/10.1016/S2352-3026(20)30217-9
4. WHO. Living guidance for clinical management of COVID-19. Vol March 1, 2022. World Health Organization (WHO). 2021.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020;395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5
6. Wang D, Hu B, Hu C, 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
7. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet (London, England). 2020;395(10223):507-513. https://doi.org/10.1016/S0140-6736(20)30211-7
8. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England). 2020;395(10229):1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3
9. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiology. 2020;5(7):802-810. https://doi.org/10.1001/jamacardio.2020.0950
10. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Internal Medicine. 2020;180(7):934-943. https://doi.org/10.1001/jamainternmed.2020.0994
11. Alsayed A, Talib W, Al-Dulaimi A, et al. The first detection of Pneumocystis jirovecii in asthmatic patients post COVID-19 in Jordan. Bosn J Basic Med Sci. 2022. https://doi.org/10.17305/bjbms.2022.7335
12. Al-Dulaimi A, Alsayed A, Maqbali M, et al. Investigating the human rhinovirus co-infection in patients with asthma exacerbations and COVID-19. Pharmacy Practice. 2022;20(2):2665. https://doi.org/10.18549/PharmPract.2022.2.2665
13. Alsayed A, Al-Doori A, Al-Dulaimi A, et al. Influences of bovine colostrum on nasal swab microbiome and viral upper respiratory tract infections - A case report. Respiratory Medicine Case Reports. 2020;31:101189. https://doi.org/10.1016/j.rmcr.2020.101189
14. Guan W-j, Ni Z-y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. 2020;382(19):1708-1720. https://doi.org/10.1056/NEJMc2005203
15. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. Jama. 2020;323(13):1239-1242. https://doi.org/10.1001/jama.2020.2648
16. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients

from Wuhan, China. Intensive Care Medicine. 2020;46(5):846-848. https://doi.org/10.1007/s00134-020-05991-x
17. Liu X-q, Xue S, Xu J-b, et al. Clinical characteristics and related risk factors of disease severity in 101 COVID-19 patients hospitalized in Wuhan, China. Acta Pharmacologica Sinica. 2022;43(1):64-75. https://doi.org/10.1038/s41401-021-00627-2
18. Zhang X-B, Hu L, Ming Q, et al. Risk factors for mortality of coronavirus disease-2019 (COVID-19) patients in two centers of Hubei province, China: A retrospective analysis. PloS One. 2021;16(1):e0246030. https://doi.org/10.1371/journal.pone.0246030
19. Kaźmierczak-Siedlecka K, Vitale E, Makarewicz W. COVID-19 - gastrointestinal and gut microbiota-related aspects. European Review for Medical and Pharmacological Sciences. 2020;24(20):10853-10859. https://doi.org/10.26355/eurrev_202010_23448
20. Alsayed A, El Hajji FD, Al-Najjar MA, et al. Patterns of antibiotic use, knowledge, and perceptions among different population categories: A comprehensive study based in Arabic countries. Saudi Pharmaceutical Journal. 2022;30(3):317-328. https://doi.org/10.1016/j.jsps.2022.01.013