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Clinical Characteristics among Patients with COVID-19: A Single-Center Experience from Medina, Saudi Arabia

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Abstract

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). To assess the effect of COVID-19 disease on hematology, coagulation profiles, renal and liver function over the course of the disease, the following laboratory tests were performed: WBCs per mm3, lymphocytes count, Platelet, D-dimmer, AST, Albumin, LDH, Ferritin, CRP, blood culture and viral loads. Patients were grouped according to their initial viral load (Group1: low viral load (L), Group 2: moderate viral load (I), and Group 3, high viral load (H)). The study population median age of the patients was 58 years, and 69% were male. Generally, all patients were admitted to the intensive care unit. Most of the patients (79.5%) had an intermediate viral load, 14.5% had a high viral load, and 5.7% had a low viral load. The Kusakal-Walli's test revealed a significant difference in the levels of white blood cells, lymphocytes, platelet, D-dimer, AST, CRP, and ferritin (p <0.0001). One hundred twenty-two isolates were recovered from 5362 blood cultures; where as 75% were multiple resistant to three classes of antibiotics and more. True bacteremia was most commonly caused by *Klebsiella pneumoniae* (45%), *Acinetobacter baumannii* (30%), and *C. albicans* (7%). The potential risk factors of advanced age, lymphopenia, D-dimer concentrations greater than 2µg/mL, and ferritin concentrations greater than 400ng/mL may assist clinicians to improve the management of the case and reduce mortality.

Keywords: COVID-19, SARS-CoV-2, Viral Load

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INTRODUCTION

The Covid disease 2019 (COVID-19), brought about by the novel severe acute respiratory syndrome (SARS-CoV-2), was first detailed in December 2019 in Wuhan, China, and has caused huge worldwide morbidity and mortality so far.[1] The outbreak of this infection progressed to an epidemic with over 528 million confirmed cases of positive COVID-19 and more than 6 million deaths were reported in worldwide. As of May 26, 2022, a total of 765,516 positive COVID-19 and 9138 deaths were reported in Saudi Arabia.[1,2] Most cases have been accounted for from the United States, in excess of 500,000 deaths in the U.S alone.[2] Most infected persons stay asymptomatic or show mild symptoms, yet others might require emergency care and hospitalization. Patients with signs and symptoms can include fever, cough, fatigue, shortness of breath, pink eye, headache, nausea, diarrhea, muscle aches, and loss of taste or smell.[3] The hospitalized patient population is usually high, and in-hospital mortality is on the rise.[3] Various cardiovascular risk factors have been connected to mortality, including hypertension, diabetes, obesity, and patient comorbidity.[4] The difficulty has been worsened by inadequate information on the new infection's epidemiological and clinical characteristics.[5]

The first case was accounted for in Madinah on March 2020, when a Saudi male with his spouse at the Alqatif was affirmed positive for COVID-19.[6] From that point forward, the Ministry of Health (MOH) has viewed the case in a serious way, isolating the patient and any contacts. The spreading of the virus was rapid and a few cases were accounted for in the same area because of a similar reason to the infection in the first case. With MERS Co-V in 2012, such a disease forces a huge burden on medical services professionals and governments.[7]

This study aimed to determine the impact of viral load (VL) on in-hospital mortality in patients with COVID-19 and to determine the rate of bacterial and viral co-diseases in patients admitted to the intensive care unit (ICU) for severe SARS-CoV-2 pneumonia as well as to distinguish the most often involved micro-organisms.

MATERIALS AND METHODS

Patient Population and Data Collection

This study included COVID-19 patients in the northwest region of the Kingdom of Saudi Arabian city of Madinah between March 18 to December 31, 2020. Ohud Hospital is a 250-bed facility that offers comprehensive care. The hospital has been transformed into an isolation center for Madinah region during the COVID-19 pandemic. A health care provider obtained a nasopharyngeal swab from suspected patients.

Data were extracted from Health Electronic Surveillance Network (HESN). HESN is a dashboard managed by MOH that enables the integration of infectious diseases and infection control, and public health. This system comprises polymerase chain reaction from nasopharyngeal swab and laboratory data and raw outcome data of COVID-19-positive patients from Madinah city.

Ethical Approval

Ethical approval was obtained from the Institutional Review Board of the Central Directorate of Health Affairs in Madinah, KSA, with approval Letter Number (IRB-92).

PCR Based Detection for SARS-CoV-2

Nasopharyngeal swabs were collected from all patients who presented to our emergency division with suspected COVID-19 infection. The nasopharyngeal samples collection was performed by Clinicians. The nasopharyngeal samples collection were quickly transferred to viral transport media and conveyed to the microbiology and molecular pathology research centers for additional examination.

To perform qualitative RT-PCR, we utilized the Cobas SARS-CoV-2 qualitative assay (Emergency Use Authorization, Roche Diagnostics, and Basal, Switzerland) with the Cobas 6800/8800 gear (Roche).

The strategy depends on completely computerized sample preparation (nucleic acid extraction and purification), trailed by PCR intensification, and the detection of two SARS-CoV-2 target regions (Roche). We recognized samples with a Ct value of 25, 26-36, and 37

consecutively as having a high, moderate, or low VL. Assuming a linear relationship between Ct and target concentration, samples with a Ct value of 26 ought to have a VL of generally 2x 104. Our method has a detection limit of roughly 250 genome copies/mL (95% certainty).

Laboratory Procedures

All samples were collected by nurses utilizing laid-out phlebotomy methods. Blood was collected as follows: 8 mL in each blood culture bottle (aerobic and anaerobic), 5 mL in a plain tube for chemistry and serology, 2 mL in a purple K2-EDTA tube for complete blood counts, and 1.8 mL in a sodium citrate tube for coagulation profile and D-dimer.

All samples were transported to the lab in temperature-controlled bags maintained at a temperature of 15-25°C and handled on an average of 6 hours after collection, blood cultures were collected in BacT/ALERT FN Plus and BacT/ALERT FA Plus vials (bioMerieux; Marcy l'Etoile, France) and incubated for as long as 5 days in the oasis framework or until they signaled positive or negative. When the positive blood bottle was obtained, three drops of blood culture samples extracted, and inoculated onto blood agar, chocolate agar and MacConkey agar using a sterile syringe (Saudi Prepared Media Laboratory Company, Jeddah, KSA). All plates were incubated aerobically for 24-48h at 37°C. The Vitek II system (BioMerieu; Marcy-l'Etoile, France) used to identify and confirm Gram-positive cooci, Gram-negative rods, and yeast of clinical relevance. Antibiotic and antifungal testing was performed using the Vitek II system (BioMerieux). Antibiotic agents belonging to seven different classes were used, including penicillin, oxacillin, and ampicillin (beta-lactam), imipenem and meropenem (carbapenem), ciprofloxacin (fluoroquinolones), tigecycline (tetracyclines), gentamicin and amikacin (aminoglycosides), vancomycin (glycopeptides), colistin and trimethoprim/sulfamethoxazole (miscellaneous agents). Antifungal agent belonging to fourth classes were used, including fluconazole, voriconazole (azoles), flucytosine (antimetabolite), amphotericin B (polyene), caspofungin and micafungin (echinocandins).

RESULTS

The current study is a retrospective examination of the baseline characteristics and laboratory findings of 122 patients who tested positive for SARS-COV-19 on nasopharyngeal swabs in Ohud Hospital, Madinah, Saudi Arabia, between March and November of 2020. The mean age of patients was 58 years old, being 84 males (69%) and 38 females (31%), including 67 Saudi citizens and 55 non-Saudi citizens. Most of the patients (113, 92.6 %) were brought to the ICU due to severe clinical symptoms and the development of acute respiratory distress syndrome (ARDS), while nine patients were segregated for medical monitoring until they improved.

Prognostic Value of Hematology, Biochemistry, Coagulation and Inflammatory Related Results

A number of hematology, coagulation profiles, renal and liver function during the course of the disease, the following laboratory tests were performed: WBCs per mm3, lymphocytes count, Platelet, D-dimmer, AST, Albumin, LDH, Ferritin, CRP and viral loads (Table 1). The patients showed a variable range of median (IQR) hematology parameters, with the most demonstrated leukocytosis (>11/ mm3) (67, 54.9%), lymphocytopenia (<20%) (106, 86.9%), thrombocyte (>150) (54.9%) and an increased level of D-dimer above the reference range (2-8 µg/mL).

Additionally, the biochemistry results for AST, albumin, LDH, ferritin, and CRP were found to be variable amongst patients, with statistically significant differences in median (IQR) values in all tests except in ATS ($p \leq 0.0001$) (Table 1). Indeed, a significant proportion of patients had elevated median (IQR) LDH (>300) (98, 80.3%), median (IQR) albumin levels between 21-30 (61, 50%), median (IQR) serum ferritin levels higher than 400 ng/mL (104, 85%) and almost all patients (99.2%,122) had median (IQR) of CRP of 0.52 or above. Estimation of the Ct value of rRT-PCR for SARS-COV2 as a measure of VL in samples demonstrated low VL (Ct ≥37 cycles) in 7 patients, Intermediate VL (Ct 26-36 cycles) in 97 patients and elevated VL (Ct ≤25 cycle) for 18 patients.

Table 1. Hematology, biochemistry, hormone serology and viral load results

Characteristic	Normal range	Count	Percent	P-value
Hematology WBC (median, IQR)				
<4.0		12	9.8	
4-11	4-11 10^3/uL	43	35.2	< 0.0001
>11		67	54.9	
Lymphocytes (median, IQR)				
<20%		106	86.9	
20-40%	20-40%	11	9.0	< 0.0001
>40%		5	4.1	
PLT (median, IQR)				
<50		15	12.3	
50-100	150-450 10^3/uL	20	16.4	< 0.0001
100-150		20	16.4	
>150		67	54.9	
D-Dimer (median, IQR)				
<0.5		1	0.8	
0.5-2	0-0.5 ug/mL	36	29.5	< 0.0001
2.01-8		68	55.7	
>9		17	13.9	
Biochemistry AST (median, IQR)				
<30		20	16.4	
30-60	0-40 U/L	39	32.0	0.091
60-100		29	23.8	
>100		34	27.9	
LDH (median, IQR)				
< 101		0	0.0	
101-150	135-225 U/L	1	0.8	< 0.0001
151-200		4	3.3	
201-300		19	15.6	
>300		98	80.3	
Albumin (median, IQR)				
< 15		7	5.7	
15-20	39-49 g/L	37	30.3	< 0.0001
21-30		61	50.0	
31-40		15	12.3	
>41		2	1.6	
Hormone Ferritin (median, IQR)				
<200		5	4.1	
201-400		13	10.7	
401-1000	13-150 ng/mL	39	32.0	< 0.0001
1001-2000		32	26.2	
>2000		33	27.0	
Serology				
C-reactive protein (median, IQR)				
<0.52		1	0.8	
0.52 – 10.99	0.1-0.8 mg/dL	65	53.3	< 0.0001
11 – 20		28	23.0	
>20		28	23.0	
Viral Load				
Group 1: low (ct ≥37)		7	5.75	
Group 2: intermediate (ct 26-36)	Negative < 40	97	79.5	< 0.0001
Group 3: High (ct ≤25)		18	14.75	

Table 2. Laboratory findings of patient with COVID-19 pneumonia

Parameters	Group (ct ≥37)			Group 2 (ct 26-36)			Group 3 (ct ≤25)			*P-value
	25th	50th (Median)	75th	25th	50th (Median)	75th	25th	50th (Median)	75th	
WBC	7.10	14.35	26.40	6.40	11.30	17.05	8.90	14.80	22.10	0.315
Lymph	3.325	6.15	18.825	3.85	6.60	14.65	6.80	8.01	13.30	0.396
PLT	139.0	186.5	260.0	93.5	154.0	286.0	90.0	158.0	201.0	0.514
D-dimer	1.285	2.55	5.65	1.725	3.10	5.795	2.70	3.30	5.99	0.324
AST	42.75	79.0	131.0	38.5	59.0	114.0	37.0	55.0	79.0	0.638
LDH	322.0	438.5	738.25	324.5	525.0	753.0	415.0	469.0	638.0	0.849
Albumin	18.0	25.3	29.25	18.0	23.0	28.0	18.0	21.0	26.0	0.478
Ferritin	383.0	783.0	2266.0	631.0	1250.0	2219.5	740.0	1102.0	1899.0	0.627
CRP	4.40	9.40	18.75	5.85	10.60	18.50	4.80	7.60	16.20	0.798

Data are 50th median and IQR. p values were collected by Kruskal–Walli's test.

Table 3. Summary of blood cultures identified by Bacetc Alert, stratified by SARS-CoV-2 status and months

Months	Total Blood culture	Contaminated Blood culture (Coagulase negative *Staphylococcus*)	Positive blood culture		
			Negative SARS-CoV	Positive SARS-CoV	Percent (%)
March	316	14 (4.4)	10	2	20%
April	598	26 (4.3)	17	14	82%
May	694	27 (3.8)	18	12	67%
June	756	32 (4.2)	13	10	77%
July	646	24 (3.7)	14	12	86%
August	652	18 (2.7)	33	27	81%
September	542	13 (2.3)	31	21	67%
October	562	11 (1.9)	14	14	100%
November	596	16 (2.6)	13	10	77%
Total	5362	181	163	122	75%

Laboratory Findings of COVID-19 Patients Based on their Initial VL

Another approach used to analyze the data was by comparing the laboratory parameters between COVID-19 patients according to the results of the initial VL (Group1: low VL (L), Group 2: moderate VL (I), and Group 3, high VL (H)). Analysis of the median (IQR) WBC count revealed leukocytosis in all the three groups (14.3, 11.3, and 14.8, respectively), with no noticeable statistical difference. A comparison of the median lymphocyte count demonstrated moderate lymphocytosis, and the levels were comparable between patient groups, although it is slightly higher in group 3 (L:6.15, I= 6.6 and H=8.01, respectively), with no statistically significant differences. Regarding platelets, normal counts were detected in all patient groups (L=186.5, I=154, and H=158, respectively), with no appreciable statistical difference. All patients had a median D-dimer level more than the normal range, which was more prominent in group 3 patients (L=2.55, I=3.1, and H= 3.3, respectively). Regarding biochemistry tests, the study revealed that all patient groups had elevated median levels of AST, LDH, ferritin, and CRP. In contrast, the median albumin was slightly decreased, despite the absence of significant statistical differences in tests values between patient groups were observed (Table 2).

Microbiological Results of COVID-19 Patients

Altogether, 5362 blood cultures were performed between the eighteenth of March and November 2020, representing a 52.8% increase from April. Patients infected with SARS-

Table 4. Antibacterial susceptibility pattern of bacteria isolated from inpatients

Resistant organism	Sensitive only antibiotic	No. of isolates
MDR *Klebsiella pneumoniae*	Colistin and tigecycline	55
MDR *Acinetobacter baumannii*	Colistin and tigecycline	37
ESBL *E. coli, Citrobacter* spp., *Enterobacter* spp.	Gentamicin, amikacin, imipenem, colistin and tigecycline	4
Stenotrophmonas maltophilia	Cotrimoxazole	3
C. albicans	Fluconazole, voriconazole, amphotericin B and caspofungin	8
Non-albicans	Voriconazole, caspofungin, and amphotericin B	6
MSSA	Oxacillin, gentamicin, linezolid and vancomycin	6
E. faecalis	Gentamicin, imipenem and vancomycin	3

MDR; Multi Drug Resistant, ESBL; Extended Spectrum Beta Lactamase, MSSA; Methicillin Sensitive *Staphylococcus aureus.*

CoV-2 represented the majority of the increased blood cultures orders. Eminently, the increased ordering among COVID-19 patients was not completely because of continued ordering, as 50% of COVID-19 patients had in excess of two blood culture sets drawn (peripheral and central line), while blood cultures were ordered for 75% of COVID-19 positive patients (Table 3).

Among patients with positive blood cultures, COVID-19 patients had increased coagulase-negative *staphylococcus* of cultures that probably addressed infection with typical skin flora than any remaining groups (Table 4). Coagulase-negative *Staphylococcus* species represented 3.3% of all positive cultures among COVID-19 patients contrasted with 5.3% among patients that tested negative and positive for SARS-CoV-2. The most widely recognized causes of true bacteremia among COVID-19 patients were *Klebsiella pneumoniae* (45%), *Acinetobacter baumannii* (30%), and *C. albicans* (7%).

Fifty-five *Acinetobacter baumannii* strains were isolated and were susceptible to colistin + tigecycline. Thirty-seven of *Klebsiella pneumoniae* strains were susceptible only to colistin + tigecycline.

Methicillin Sensitive *Staphylococcus aureus* (MSSA) to oxacillin was exhibited by all 6 (100%) isolates, this was confirmed by cefoxitin screening, where all isolates sensitive to oxacillin were negative for cefoxitin screening test. Eight of *Candida albicans* strains were susceptible to fluconazole, voriconazole, amphotericin B and caspofungin and six non-albicans were susceptible to Voriconazole, caspofungin, and amphotericin B.

DISCUSSION

COVID-19 clinical manifestations range from asymptomatic to severe respiratory disease.[1] The percentages of the most common characteristics upon arrival in our study were generally higher than those reported in other studies from China and New York City; dyspnea appeared to be the most prevalent symptom, followed by fever and cough.[8,9]

This study aimed to describe the laboratory parameters of 122 confirmed patients at Ohud hospital in Madinah, Saudi Arabia. COVID-19 was frequently found to infect the median aged, and these finding are consistent with previously reports that indicated the median age of infection was 58 years.[10,11]

The study found that more significant proportion of males (69%) than females (31%) as having the infection, which confirms previous findings by Chen et al and Xia et al.[11,12] Whereas other studies showed that men are more likely than women to be infected this regard,[6,13] decreased sex hormones and an X chromosome, both of which are required for innate and adaptive immunity thereby Women's less infection by COVID-19.[11,12]

In terms of hematological parameters, it is critical to estimate white blood cells counts to predict the outcomes of COVID-19 infection.[14] Leukocytosis (54.9%) was detected in our results, along with lymphopenia (86.9%) and a normal thrombocyte limit (55%). Similarly, Jin et al. demonstrated that, the total number of leukocytes was normal or decreased during the early stage

of the disease, while the lymphocyte count was decreased.[14] Recent reports indicated that COVID-19 is associated with increased neutrophils and decreased lymphocyte counts.[15,16] According to some studies, a significant reduction in the total number of lymphocytes indicates that coronaviruses disrupt many immune cells and impair cellular immune function.[17,18]

Additionally, we revealed that AST and LDH levels were statically significantly elevated in patients with COVID-19 infection. Research data suggest that SARS-CoV-2 may cause damage to liver and myocardium tissues, resulting in elevated AST and LDH levels in critically ill patients.[11] MacIntyre et al. demonstrated that elevated LDH levels in SARS correlate with tissue necrosis caused by immune hyperactivity and thus with poor outcomes.[19] Therefore, monitoring LDH levels and other cardiac and liver enzymes may assist predicting of severe COVID-19 infection in patients.[20]

D-dimer, ferritin, and CRP levels were basic in identifying bacterial infection in the lungs and may assist with assessing patients' immune status.[21] The presence of that COVID-19 disease could make sense of the increased D-dimer concentration noticed in this review. Similarly, studies have established that an elevated D-dimer concentration is a standard element of COVID-19 infections, especially in severe cases.[21-23] Be that as it may, in our review, we underscored the significance of blood culture in this specific setting. The utilization of dexamethasone and antivirals to treat severe COVID-19 infection may fundamentally expand the risk of secondary bacterial infections.[13]

Therefore, we cannot try not to perform the necessary methodology to securely diagnose bacteremia during the care of COVID-19 patients while additionally attempting to avoid it unnecessarily. Concerning microbiological results, the pandemic time frame saw an expansion in the amount of bacteremia each persistent day in ICU, representing a 52.8% increment from April. We likewise tracked down infection in 3.3% of all positive blood cultures got from COVID-19 patients. Past investigations have examined the rate of bacteremia and blood culture infection in a hospital in Spain, the United States, and Sweden and found that the general infection rate was higher than 8.4%.[16-18]

Our findings indicated that 5.3% of all patients developed bacterial co-infection, slightly more than Chen et al. estimate (1%).[14] It was previously believed that bacterial complications manifested themselves later in virus infection. Chen et al.[14] study was conducted in the outbreak's early stages and thus likely underestimated the rate of bacterial co-infection. Additionally, the severity of COVID-19 affects the occurrence of secondary bacterial infections. All 122 patients in this study were critically ill and received mechanical ventilation prior to getting secondary bacterial infections.

Gram-negative bacilli, such as *K. pneumoniae, A. baumannii, E. coli, Citrobacter* spp., *Enterobacter* spp., and *S. maltophilia*, were the most common cause of co-infection. Studies on bacterial co-infection in influenza had demonstrated that patients admitted to ICU and requiring mechanical ventilation were at increased risk of developing this complication.[19] *Candida albicans* and non-albicans most frequently caused co-infection. However, Methicillin Sensitive *Staphylococcus aureus* (MSSA) and *E. faecalis* were the most frequently identified organisms in patients with influenza,[19-21] typically occurring during the disease's early stages.

It is important that nosocomial clone dissemination of multidrug-resistant organisms, *A. baumannii* and *K. pneumoniae* was viewed as the most widely recognized reasons for bacterial infection, representing 75% of cases, and was viewed as emphatically connected with mortality.[22] Furthermore, our past reviews revealed a long-term nosocomial predominance of carbapenem-safe *A. baumannii* and *K. pneumoniae* on the hospital's fundamental campus[22,23] suggesting conceivable environmental colonization. Therefore, strict tidiness and sanitization of the hospital environment are basic parts of managing critically sick COVID-19 patients.

This study showed that an elevated inflammatory marker (ferritin and CRP), an elevated coagulation profile (D-dimer), and decreased hematological value (lymphocyte count) were associated with a poor outcome in COVID-19.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of the General Directorate of Health Affairs in Madinah, KSA, with reference number IRB-92.

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