Original Article

Clinical features and haematological parameters associated with COVID-19 severity among hospitalized patients: A retrospective observational study from Tribal Central India

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Abstract

Background: Reports describing demographics, clinical characteristics, hospital course, morbidity, and mortality in patients in the Indian setting have been published, but they are based on limited numbers of cases. The present study among the patients with known outcomes enabled us to better understand the disease process and progression of COVID-19 cases and to correlate the factors affecting the outcome. **Methods:** This was a record-based, retrospective observational study of patients admitted to COVID-19 Hospital. We have retrieved medical records for all the hospitalized patients with a laboratory confirmed COVID-19 diagnosis with a known outcome (discharged or died) between April 1, 2020 and February 28, 2021. The extracted data included basic demographics, signs and symptoms, duration of hospitalization, and laboratory parameters. Categorical variables were analysed using either the chisquare test or Fisher's exact test. The level of significance was set at $P < 0.05$. **Results:** The mean age of severe and moderate patients was 38.71 years, compared to 34.95 years for mild patients. No gender difference was observed for the severe/moderate, and mild cases. The mortality rate among severe/moderate cases was 11.6%, whereas it was 3.9% in mild patients. Laboratory parameters which were significantly ($p < 0.05$) raised among the dead compared to discharged patients included CT score, D-dimer, CRP, ALT, AST, and alkaline phosphatase. **Conclusion:** Clinical and laboratory characteristics reflect the pathophysiology of disease and thus help clinicians recognise the severity of medical illness. They also facilitate the creation of management protocols for clinical care that results in improvement in patient related outcomes.

Keywords: Clinical feature, COVID-19, disease outcome, haematological parameters, retrospective

Introduction

Coronavirus disease 2019 (COVID-19) is a viral sickness that mostly affects the respiratory tract. Before the Wuhan epidemic in China in December 2019, no one had heard of this disease. The two preceding coronavirus outbreaks were in 2003 with the severe acute respiratory syndrome-related coronavirus (SARS-CoV) infection and in 2012 with the Middle East Respiratory Coronavirus (MERS-CoV) epidemic.[1] In March 2020, the World Health Organization (WHO) labelled this disease a pandemic due to its global spread.

Fever, cough, dyspnea, and infiltrations in the chest are the most common symptoms of COVID-19 infection.[2,3] Even though the majority of the infections identified are not harmful, about

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15–20% of COVID-19 patients may develop a serious disease, such as respiratory failure, shock, or multiple organ dysfunction, necessitating admission to a critical care unit.[4,5]

According to the WHO, severe acute respiratory infection (SARI) is defined as an acute respiratory infection with a fever or temperature of 38°C or higher, cough, and starting within the last 10 days that necessitates hospitalisation.[6] In the midst of the current epidemic, all SARI patients should be screened for COVID-19 with a high index of suspicion. Using all COVID-19 patients as a denominator allows researchers to examine the clinical pattern in mild COVID-19 patients as well as moderate-to-severe COVID-19 patients.

The Indian Council of Medical Research (ICMR) published recommendations in March 2020 to investigate all patients with SARI for COVID-19.[7]

Many hospitals across the country were designated as COVID-19 hospitals for the management of COVID-19 confirmed or suspected cases. Our hospital was recognized as an official site for managing COVID-19 patients on March 27, 2020 when the disease started to occur in epidemic proportions in India. More than 400 beds were made dedicatedly available for COVID-19 confirmed or suspected cases. Each bed had an oxygen supply via a central oxygen circuit. Apart from this, all-available doctors from various departments were made 24 x 7 available as per the roster in the COVID-19 hospital. The confirmation of COVID-19 cases was done by the RT-PCR assays performed in the microbiology department. Multiple changes have been made since then in our infrastructure to accommodate the large inflow of cases [Figure 1].

Despite the swift spread and the rapidly increasing number of people affected, the complete clinical course of this disease is still unclear for Indian patients. Reports describing demographics, clinical characteristics, hospital course, morbidity, and mortality in patients in the Indian setting have been published, but they are based on limited numbers of cases.[8-10] The present study among the patients with known outcomes will enable family physicians and primary care physicians to better understand the disease process and progression of COVID-19 cases, and to correlate the factors affecting the outcome. This will help family physicians and primary care physicians in triaging the rapid rise of patients and streamlining resources for better management of cases with optimal efficiency and better outcomes in upcoming COVID-19 waves.

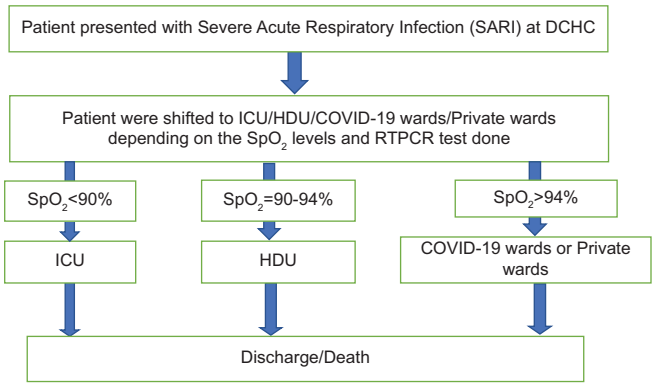

Figure 1: Care pathway of COVID-19 patients in DCH

Materials and Methods

Study design and population

This was a record-based, retrospective observational study of patients admitted to Hospital (more than 400 beds) that was designated as COVID-19 hospitals by the State Government. Over 1700 patients were admitted to the hospital in the first week of February 2021. We have retrieved electronic and paper based medical records for all the hospitalized patients with a laboratory confirmed COVID-19 diagnosis with a known outcome (discharged or died) between April 1, 2020 and February 28, 2021.

The inclusion criteria were: positive results on real-time reverse transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2); age >18 years (male and nonpregnant, nonlactating female); and closed cases with known outcome.

The government's testing guidelines were followed. Although most mild cases are now asked to quarantine at home, many with a positive RT-PCR were unable to quarantine and were admitted to the hospital at the time of this study. This study included mild as well as moderate and severe cases. All RT-PCR positive patients were subdivided into two groups, one with an oxygen saturation of >94% (the mild group) and the other with an oxygen saturation of <94% (the moderate to severe group).

Data Collection

The extracted data included basic demographics (age and gender), signs and symptoms (cough, fever, breathlessness, anosmia, headache, myalgia, pneumonia [chest pain, dyspnea, wheezing, lower chest wall in drawing, history of TB], gastroenteritis [nausea, vomiting, abdominal pain, diarrhea], ear pain, altered consciousness, and seizures), co-morbidities (diabetes, hypertension, asthma, COPD, chronic kidney disease [CKD] and Ischemic heart disease), Xraychest, mechanical ventilator requirements, duration of hospitalization, laboratory parameters (hemoglobin, total leukocyte counts, including neutrophil and lymphocyte percentage, platelet counts, serum urea, serum creatinine, serum Ddimer, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and total bilirubin values), CT score, and the outcome (dead/discharged). The study investigators checked the collected data independently. A separate, dedicated quality control abstractor (Deputy Registrar) reviewed records with missing data or with inconsistent values, and corrections were made as much as possible.

Statistical analysis

The primary end point was death or discharged alive. The collected data were processed using different cross-tabulations to analyze which characteristics are highly linked to mortality. Categorical variables were recorded as percentages and frequency. The continuous variables were recorded as mean and standard deviation. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired ttest, whereas the Mann–Whitney U test was used for variables that were not normally distributed. Categorical variables were analysed using either the chisquare test or Fisher's exact test. The level of significance was set at $P < 0.05$. SPSS 20.0 (IBM Corp., Armonk, NY, US) was used for all the calculations.

Ethical consideration

All ethical issues were followed during the study. No personal data were recorded. It was assured that all data collected was used only for the current study. The study was initiated after obtaining ethical approval from the Institutional Ethical and Review Board (IERB), GMC, Shahdol (Project ID: IERC/21/03/002, Date: June 06, 2021).

Results

Figure 2 shows that over 1700 patients were admitted to the hospital in the first week of February 2021, but only 746 patients' records were analyzed, and others were excluded due to lab report missing or incomplete, X-ray missing, clinical notes incomplete, etc., Table 1 shows that there was a statistically significant difference ($p < 0.05$) in the mean ages of severe and moderate patients (38.71 years) compared to mild patients (34.95 years). No gender difference was observed for the severe/moderate, and mild cases. Hypertension (171/746) was the most common comorbidity among the admitted patients, followed by diabetes mellitus (143/746). 36.3% of mild patients stayed for <5 days in the hospital, while 38.7% of severe and moderate patients stayed for <5 days. The mortality rate among severe and moderate cases was 11.6%, whereas it was 3.9% in mild patients.

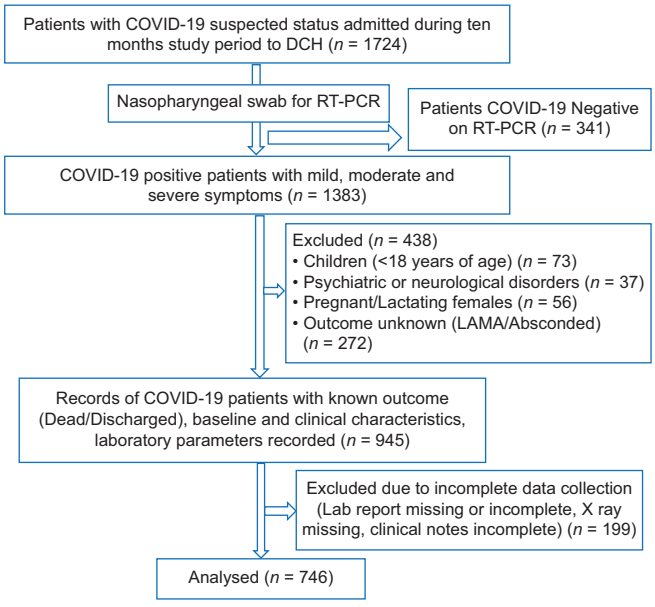

Figure 2: Consolidated Standards of Reporting Trials (CONSORT) flowsheet

The laboratory parameter analysis reflected that total leukocyte counts (/c.mm) were lowered in severe/moderate patients (11.69 ± 6.32) as compared to mild patients (13.65 ± 12.73) with a *P* value of < 0.05. Also, serum urea (mg/dL) levels were significantly raised ($p < 0.05$) in severe and moderate patients (28.08 ± 14.14) compared to mild patients (25.23 ± 8.48). Other laboratory parameters which were significantly ($p < 0.05$) raised among severe and moderate compared to mild patients included serum creatinine, total bilirubin, ALT, AST, and alkaline phosphatase [Table 2].

In the present study, we also compared the baseline, clinical, and laboratory characteristics with disease outcome among patients, that is, death vs discharged, and it was noticed that there was a statistically significant difference ($p < 0.05$) in the mean ages of deceased patients (45.10 years) vs discharged patients (33.10 years). No gender difference was observed for the dead and discharged patients. The duration of stay for <5 days was observed among 20.9% of dead patients, whereas 37.8% of discharged patients stayed in hospital for <5 days ($p < 0.05$). The laboratory parameters analysis reflected that total leukocyte counts (/c.mm) were lowered in deceased patients (11.02 ± 5.32) as compared to discharged patients (13.63 ± 8.61) with a *P* value of < 0.05. Also, serum urea (mg/dL) levels were significantly raised ($p < 0.05$) in dead patients (26.68 ± 11.90) compared to discharged patients (23.64 ± 6.49). Other laboratory parameters that were significantly ($p < 0.05$) raised among the deceased compared to discharged patients included CT score, D-dimer, CRP, ALT, AST, and alkaline phosphatase [Table 3].

Discussion

The COVID-19 epidemic is rapidly spreading over the world, putting a strain on healthcare systems. The unpredictable course of sickness, which can range from asymptomatic to severely ill with acute respiratory failure concerns, necessitates the gathering of sufficient evidence in order to evaluate the patient's condition swiftly and predict complications.

In the present study, it was found that male patients have a higher risk of experiencing the severity of COVID-19 compared to female patients. It was coherent with the studies done by Xu *et al.*, and Zhao *et al.*[11,12] An explanation for this can be that the male has weaker immunity because of genetic and hormonal factors and has shown higher mortality in several infectious diseases.[13]

In the present study, the mean age was 38.71 ± 13.62 years and 34.95 ± 16.73 years in patients with severe/moderate disease and mild disease, respectively, and it was comparable to studies

Table 1: Comparison of baseline and clinical characteristics with disease severity among study subjects (*n*=746)

Baseline and clinical characteristics	Disease severity Number (%)/Mean±SD		*P*
	Severe/Moderate (*n*=181)	Mild (*n*=565)	
Mean Age (in years)	38.71±13.62	34.95±16.73	*P*<0.05*
Age group			
<30 years (*n*=200)	52 (28.8)	148 (26.3)	*P*>0.05
30-40 years (*n*=215)	45 (25.0)	170 (30.0)	
41-50 years (*n*=184)	50 (27.5)	134 (23.7)	
>50 years (*n*=147)	34 (18.7)	113 (20.0)	
Gender			
Male (*n*=401)	104 (57.5)	297 (52.5)	*P*>0.05
Female (*n*=345)	77 (42.5)	268 (47.5)	
Any comorbidities			
Hypertension (*n*=171)	52 (28.7)	119 (21.1)	*P*>0.05
Diabetes mellitus (*n*=143)	34 (18.8)	109 (19.3)	
Asthma/COPD (*n*=35)	10 (5.5)	25 (4.4)	
Chronic kidney disease (*n*=28)	7 (3.9)	21 (3.7)	
Ischaemic heart disease (*n*=14)	2 (1.1)	12 (2.1)	
No (*n*=514)	119 (65.7)	395 (69.9)	
Signs and Symptoms			
Fever/Malaise (*n*=594)	149 (82.5)	445 (78.7)	*P*<0.001*
Shortness of breath (*n*=211)	41 (22.5)	170 (30.0)	
Chest pain (*n*=36)	4 (2.2)	32 (5.7)	
Cough (*n*=264)	59 (32.5)	205 (36.2)	
Sore throat (*n*=159)	25 (13.8)	134 (23.7)	
Nasal discharge (*n*=121)	36 (20.0)	85 (15.0)	
Anosmia (*n*=40)	2 (1.1)	38 (6.7)	
Ageusia (*n*=31)	1 (0.6)	30 (5.3)	
Myalgia (*n*=45)	4 (2.2)	41 (7.3)	
No (*n*=120)	6 (3.3)	114 (20.2)	
Days from onset of symptoms to admission			
<5 days (*n*=511)	109 (60.0)	402 (71.2)	*P*<0.001*
5-10 days (*n*=133)	27 (15.0)	106 (18.8)	
>10 days (*n*=102)	45 (25.0)	57 (10.0)	
Duration of hospital stay			
<5 days (*n*=275)	70 (38.7)	205 (36.3)	*P*>0.05
5-10 days (*n*=240)	57 (31.3)	183 (32.4)	
>10 days (*n*=231)	54 (30.0)	177 (31.3)	
Disease outcome			
Death (*n*=43)	21 (11.6)	22 (3.9)	*P*<0.001*
Discharge (*n*=703)	160 (88.4)	543 (96.1)	

*Statistically significant

done by Bhandari *et al.*, and Mohan *et al.*, in India but lower than that of other countries.[14-16] This is due in part to the increased population ageing in developed countries, where persons aged 65 years and older account for about half of the population, compared to only 10% in India.[16,17] Similar to studies by Bhandari *et al.*, and Rivera-Izquierdo *et al.*, older age was associated with a severe disease course in the present study.[14,16]

In the present study, the presence of at least one comorbidity was significantly higher among deceased patients (46.5%) compared to discharged patients (30.2%). In a study by Guan *et al.*,[18] patients having at least one comorbidity had a 2.38 times greater risk of severe illness than non-severe patients. The meta-analysis done by Kumar A *et al.*,[19] which included 33 studies (around 16,000 patients), found diabetes to be significantly associated with COVID-19 mortality with a pooled odds ratio of 1.9 (95% CI 1.37–2.64; $P < 0.01$).

In the present study, fever was more common among patients with severe or moderate disease (82.5%) compared to patients with mild disease (78.7%) at the time of presentation. According to Zhou *et al.*,[20] patients with fever had a 2.01 times greater risk of severe illness than non-severe patients. In the present study, 20.9% of deceased patients had a duration of stay <5 days, whereas 37.8% of discharged patients had a duration of stay <5 days and it was statistically significant ($p < 0.05$). But in contrast to that, a study by Bhandari *et al.*,[14] where the majority of patients had early mortality after admission to the hospital (within the initial three days) and the time to recovery/discharge varied from 5.4 to 7.6 days.

Table 2: Comparison of laboratory characteristics with disease severity among study subjects (*n*=746)

Laboratory characteristics	Disease severity Number (%)/Mean±SD		*P*
	Severe/Moderate (*n*=181)	Mild (*n*=565)	
CT score	22.72±4.88	22.98±5.20	*P*>0.05
Hemoglobin (gms%)	11.40±2.40	11.14±6.89	*P*>0.05
Total RBC count (mill/c.mm)	4.27±1.01	4.06±1.06	*P*<0.05*
Total leukocyte counts (/c.mm)	11.69±6.32	13.65±12.73	*P*<0.05*
Neutrophils (%)	79.21±11.29	74.46±14.18	*P*<0.001*
Lymphocytes (%)	13.18±8.06	15.26±12.25	*P*<0.05*
Monocyte (%)	2.06±1.32	2.53±1.98	*P*<0.05*
Neutrophil lymphocyte ratio	25.71±17.78	15.6±14.44	*P*<0.001*
Lymphocyte monocyte ratio	1.48±0.89	3.91±1.27	*P*<0.001*
Total Platelet counts (lacs/c.mm)	2.69±1.46	2.66±1.58	*P*>0.05
D-dimer (µg/mL)	1.65±2.08	1.69±2.17	*P*>0.05
CRP (mg/L)	21.42±40.04	19.57±34.61	*P*>0.05
Serum Urea (mg/dL)	28.08±14.14	25.23±8.48	*P*<0.05*
Serum Creatinine (mg/dL)	1.18±0.55	1.08±0.20	*P*<0.001*
Serum Total Bilirubin (mg/dL)	0.66±0.51	0.58±0.29	*P*<0.05*
Serum Direct Bilirubin (mg/dL)	0.40±0.29	0.32±0.13	*P*<0.001*
Serum Indirect Bilirubin (mg/dL)	0.26±0.22	0.26±0.16	*P*>0.05
Serum ALT (IU/L)	54.56±52.22	45.50±38.12	*P*<0.05*
Serum AST (IU/L)	54.10±47.68	38.08±27.46	*P*<0.001*
Serum Alkaline phosphatase (IU/L)	244.64±106.93	187.46±70.00	*P*<0.001*

*Statistically significant

In India, the number of cases of COVID-19 is escalating, but the mortality has remained at a lower level than in other countries with almost similar numbers of COVID-19 infections. In the present study, mortality was found to be 5.8% (43/746), which is remarkably lower than that of developed countries.[16] One of the rationales for lower mortality in India was believed to be India's stringent nationwide lockdown, supported by the findings of a study which reported that most Indians had a favourable attitude and practises toward lockdown restrictions.[21] So it could be one of the reasons for comparatively lower deaths in India. Also, it can be seen that recent loosening of restrictions in India and the migration of people has led to a rise in the number of reported infections and deaths.[22]

In the present study, lymphocyte count was decreased in the COVID-19 patients (severe/moderate cases: 13.18 ± 8.06 vs mild cases: 15.26 ± 12.25), and it was significantly associated with the severity of disease ($p < 0.05$). These findings were consistent with the studies done by Huang *et al.*, and Patel *et al.*[23,24] One hypothesis is that lymphocytes express the SARS-CoV-2 receptor ACE2 and hence are directly attacked and consumed by the virus.[25] Another theory is that high levels of proinflammatory cytokines like tumour necrosis factor (TNF) and IL-6 in COVID-19 patients cause lymphocyte apoptosis.[26] Therefore, lymphopenia inhibits the body's innate immune system, leading to exacerbations of COVID-19 patients and poor outcomes.

CRP is a non-specific acute phase reactant induced by IL-6 in the liver. Elevated CRP levels are directly correlated with level of inflammation and disease severity.[27] In the present study, CRP levels were elevated with the increased disease severity (severe/moderate cases: 21.42 ± 40.04 vs mild cases 19.57 ± 34.61) and poor disease outcome (deceased: 1.82 ± 2.21 vs discharged: 1.08 ± 1.69; $P < 0.05$) and it was in coherence with the studies done by Liu *et al.*, and Qin *et al.*[28,29]

It was found in the present study that elevated D-dimer levels were significantly associated with an increased risk of poor outcomes (deceased: 22.49 ± 37.58 vs discharged: 15.67 ± 26.68; $P < 0.05$) among COVID-19 patients. The increased inflammatory response in COVID-19 and hypoxia due to severe pneumonia eventually led to the activation of coagulation and fibrinolysis, followed by a hypercoagulable state causing DIC and multi-organ dysfunction.[30]

The present study found that liver function tests were significantly deranged with the increased severity of disease ($p < 0.05$). In a study done by Cai *et al.*,[31] 76.3% of COVID-19 patients had abnormal liver tests (ALT, AST, AP, and total bilirubin) and in COVID-19 the ALT and AST levels are transiently increased and the mechanism through which liver dysfunction occurs is most likely through secondary liver damage rather than a direct insult.

In present study, it was found that creatinine levels increase with the increased severity of disease ($p < 0.05$). In a prospective cohort study done in 701 COVID-19 patients, it was found that during hospitalisation, the incidence of acute kidney injury and death was significantly higher in patients with elevated baseline serum creatinine levels than in patients with normal baseline values. The mechanism by which this takes place is speculated to be through hematogenous spread and accumulation of the virus in the kidney, causing renal cell necrosis.[32]

The variety of clinical characteristics and laboratory results reported in this study provide valuable vision into disease severity

Table 3: Comparison of baseline, clinical, and laboratory characteristics with disease mortality among study subjects (*n*=746)

Baseline, clinical, and laboratory characteristics	Disease outcome Number (%)/Mean±SD		*P*
	Death (*n*=43)	Discharged (*n*=703)	
Mean Age (in years)	45.10±21.40	33.10±32.05	*P*<0.05*
Gender			
Male (*n*=401)	24 (55.8)	377 (53.6)	*P*>0.05
Female (*n*=345)	19 (44.2)	326 (46.4)	
Any comorbidities			
Yes (*n*=232)	20 (46.5)	212 (30.2)	*P*<0.05*
No (*n*=514)	23 (53.5)	491 (69.8)	
Signs and Symptoms			
Yes (*n*=626)	39 (90.7)	587 (83.5)	*P*>0.05
No (*n*=120)	4 (9.3)	116 (16.5)	
Days from onset of symptoms to admission			
<5 days (*n*=511)	18 (41.9)	493 (70.1)	*P*<0.001*
5 or more days (*n*=235)	25 (58.1)	210 (29.9)	
Duration of hospital stay			
<5 days (*n*=275)	9 (20.9)	266 (37.8)	*P*<0.05*
5 or more days (*n*=471)	34 (79.1)	437 (62.2)	
CT score	20.63±6.56	22.67±4.18	*P*<0.05*
Hemoglobin (gms%)	11.24±2.74	11.88±5.32	*P*>0.05
Total RBC count (mill/c.mm)	4.17±1.20	3.96±1.19	*P*>0.05
Total leukocyte counts (/c.mm)	11.02±5.32	13.63±8.61	*P*<0.05*
Total Platelet counts (lacs/c.mm)	1.49±1.78	2.76±1.82	*P*<0.001*
D-dimer (µg/mL)	22.49±37.58	15.67±26.68	*P*<0.05*
CRP (mg/L)	1.82±2.21	1.08±1.69	*P*<0.05*
Serum Urea (mg/dL)	26.68±11.90	23.64±6.49	*P*<0.05*
Serum Creatinine (mg/dL)	1.12±0.45	1.06±0.19	*P*>0.05
Serum Total Bilirubin (mg/dL)	0.67±0.62	0.62±0.33	*P*>0.05
Serum Direct Bilirubin (mg/dL)	0.55±0.24	0.37±0.89	*P*>0.05
Serum Indirect Bilirubin (mg/dL)	0.16±0.52	0.24±0.83	*P*>0.05
Serum ALT (IU/L)	57.21±46.17	44.18±37.85	*P*<0.05*
Serum AST (IU/L)	46.54±40.20	36.54±26.85	*P*<0.05*
Serum Alkaline phosphatase (IU/L)	241.64±175.47	205.84±56.46	*P*<0.001*

*Statistically significant

early predictors. These should be under the horizons of not just doctors at tertiary care centres, but they should also expand their horizons to include primary care physicians in order to diagnose a suspected case of SARI in a timely manner and direct patients to the suggested management required.

To summarize, in the present study we compared the baseline, clinical, and laboratory characteristics with disease outcome among patients, and it was observed that increased age, shorter duration of hospital stay, lower total leukocyte, raised serum urea, CT score, D-dimer, CRP, ALT, AST, and alkaline phosphatase were significantly related to higher mortality.

Conclusion

Clinical and laboratory characteristics reflect the pathophysiology of disease and thus help clinicians recognise the severity of medical illness. They also facilitate the creation of management protocols for clinical care that results in improvement in patient related outcomes. These characteristics will be helpful in differentiating severely ill patients and will allow for the appropriate allocation of healthcare resources. The use of these characteristics in understanding COVID-19 may also help to prevent virus-induced acute inflammatory response complications such as acute hypoxemic respiratory failure and multiorgan dysfunction, including acute cardiac, hepatic, and renal injury in affected patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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