Original Article

Role of laboratory biomarkers in assessing the severity of COVID-19 disease. A cross-sectional study

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Abstract

Background: Corona virus disease 2019 (Covid-19) has high infectivity and mortality rate. Covid-19 patients can suddenly deteriorate and develop life threatening complications. Hence, there is a need to identify laboratory biomarkers in order to categorize high risk patients. The main purpose of the study is to investigate the role and correlation of laboratory parameters such as total leucocyte count (TLC), absolute lymphocyte count, platelet count, C-Reactive Proteins (CRP), serum ferritin, serum lactate dehydrogenase (LDH), serum procalcitonin and D-dimer in severe and non-severe Covid-19 patients. **Methodology:** This retrospective cross-sectional study was conducted at Latifa Women and Child Hospital in the UAE after obtaining ethical committee clearance. Based on the symptoms and the criteria by National Institute of Health, USA, 109 patients were divided into three groups: Non-severe with 75, severe with 18 and critical with 16 patients. Laboratory data of these patients were assessed through the electronic medical records (SALAMA). Statistical analysis was done using Statistical Packages for Social Sciences (SPSS) version 25.0 (SPSS/PC; SPSS-25.0, Chicago, USA). Laboratory test profiles were expressed as mean (SD). Independent 't' test and ANOVA were used to study the significance of means. *P* value less than 0.05 was considered significant. **Result:** Males were more severely affected than females. Severe and critically ill Covid-19 patients had a significantly higher TLC, serum LDH, ferritin and CRP and lower absolute lymphocyte count. PCT and D-dimer were significantly elevated in critical group. **Conclusion:** Along with clinical presentation and radiological findings, biochemical parameter may also be considered as important predictors for assessing severity in covid-19 patients.

Keywords: Covid-19, C-Reactive Proteins, Ferritin, LDH, PCT, severity

Introduction

The first confirmed case of Corona virus disease 2019 (COVID-19), caused by a novel virus, Severe Acute Respiratory Corona Virus -2 or SARS-CoV-2, was in December 2019. Since then, it has infiltrated into almost every country and spread rapidly affecting millions of people. Considering its high infectivity and a mortality rate of over 2%, the World Health Organization (WHO) declared COVID-19 as a pandemic in March 2020.[1,2] Usually, corona virus infections are mild and self-limiting but two different corona viruses have caused pandemics in the past: The Severe Acute Respiratory Syndrome (SARS) in 2002 and the Middle East Respiratory Syndrome (MERS) in 2012.[2,3] As the name of the virus suggests, it mainly affects the respiratory system and in severe cases, results in pneumonia and acute respiratory distress syndrome (ARDS). However, studies have reported that the mortality is higher in those with comorbidities such as hypertension, diabetes mellitus, pre-existing heart or renal disease and obesity.[4,5] Moreover, apart from respiratory complications; myositis, renal failure, disseminated intravascular

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coagulation (DIC) have also been reported to cause mortality in Covid-19 patients.[6-8] Therefore, early diagnosis and identification of severely affected Covid-19 patients is integral to provide treatment and reduce the mortality. Presently, the severity of a Covid-19 patient is based on clinical symptoms, presence of lung infiltrates and falling oxygen saturation and there are no validated biomarkers to predict the severity of the disease.[9,10] However, it has been reported that there has been sudden exacerbation of symptoms and rapid deterioration in the condition of about 6.5% of Covid-19 patients resulting in death, of about half of them.[11,12] Hence, there is a need to identify the serum biomarkers which can serve as early predictors for identification and timely management of potentially serious Covid-19 patient. In United Arab Emirates (UAE) the first case was reported in January 2020 following which there has been a rise in cases. However, data regarding the clinical manifestation, laboratory parameters and its correlation with severity of Covid-19 is lacking. Hence, we conducted this study with an aim to describe the epidemiology, clinical, laboratory and radiological manifestation in confirmed Covid-19 patients and investigate the correlation of laboratory parameters (total leucocyte count, absolute lymphocyte count, platelet count, CRP, serum ferritin, serum LDH, serum procalcitonin and D-dimer) in severe and non-severe Covid-19 patients. This would be the first published study regarding the biomarkers and severity of Covid-19 from the United Arab Emirates.

Materials and Methods

Study design

This retrospective cross-sectional study was conducted at Latifa Women and Child Hospital (LWCH), a tertiary care center for Obstetrics and Gynecology in the UAE, which was converted to Covid-19 management center during the current pandemic. Institutional Ethical committee clearance (certificate no: DSREC-06/2020_12 dated 15th June 2020) was obtained before starting the study.

Study population

Selection of patients and sample size: Based on the inclusion and exclusion criteria, only patients above 18 years of age who tested positive using a nasopharyngeal swab test by RT-PCR were included in the study. Pediatric patients, Covid-19 pregnant females were excluded from the study. Data of 109 adult Covid-19 patients were analyzed through the electronic medical records (SALAMA) of the Hospital data base.

Classification of Covid-19 patients: Based on the symptoms and the criteria laid down by National Institute of Health, USA, the patients were divided into three groups: first, a non-severe disease group which included asymptomatic patients, patients with mild disease (patients with symptoms but no signs of viral pneumonia or hypoxia) and moderate disease (patients with pneumonia but SpO2 ≥94% at room air). The second group was a severe disease group which included patients with SpO2 <94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%. The third group was the critical disease group which included Covid-19 patients in Acute Respiratory Distress Syndrome (ARDS) or accompanied with sepsis, septic shock and multiple organ failure.[9,13]

Sample and Data collection: Vitals such as pulse, blood pressure and temperature along with Covid-19 related information such as comorbidities, mode of infection, symptoms, complications and prognosis in terms of discharge or mortality were recorded from the patient's data. Hematological assays such as total leucocyte count (TLC), absolute lymphocytes count, platelet counts were done on whole blood sample collected in an EDTA tube using Beckman DXS Coulter-800 fully automated analyzer.

For the determination of D-dimer, blood sample was collected in 3.2% Sodium Citrate containing tube and analyzed using Stago-compact Max Analyzer fully automated machine. Biochemical investigations were done on serum sample obtained by collecting a blood sample in a clot activator tube. Serum Lactate Dehydrogenase (LDH), C-Reactive Proteins (CRP) and serum procalcitonin were determined using COBAS-6000 fully automated analyzer. Serum ferritin levels were determined using Abbot Architect I – 2000. All the analyzers were calibrated and quality assurance was done using controls at two levels before performing the assays.

X-ray imaging**:** X-ray imaging was done using a mobile X-ray machine named SHIMADZ MOBILE DART EVOLUTION. Antero-posterior chest view was taken for all patients. Each lung was divided into three zones: upper, middle and lower. The upper zone extended from the lung apex to the superior hilar marking. The middle zone from superior hilar marking till the inferior hilar marking. The lower zone was the area between the inferior hilar marking up to the costophrenic sulcus. In total there were six zones. Opacity present in each zone was counted as 1 and absence was considered as 0. A score was given based on the total number of zones affected and type of opacity (whether ground glass opacity or reticular) present.

Statistical analysis: Data collected were analyzed using Statistical Packages for Social Sciences (SPSS) version 25.0 (SPSS/PC; SPSS-25.0, Chicago, USA). The categorical data were expressed as percentage. Laboratory test profiles were expressed as mean (SD). Significance of mean between males and females was studied using independent 't' test. For studying the significance of mean in the different groups of Covid-19 patients ANOVA was used. All graphs and figure were made using Microsoft Excel 2016 (Microsoft Corporation, Redmond, Washington, USA). *P* value less than 0.05 was considered significant.

Results

Based on the inclusion and exclusion criteria, a total of 109 confirmed cases of Covid-19 were included in the study. 57 (52.3%) of the SARS-CoV-2 virus infected patients were males and 52 (47.7%) were females with a mean age ± SD of

44.52 ± 9.04 and 37.94 ± 9.38 respectively. Based on the National Institution of Health guidelines these patients were divided into three groups: A non-severe group consisting of asymptomatic, mild and moderate disease, a severe group and a critical group. As seen in Table 1, 75 Covid-19 patients were categorized as non-severe, 18 as severe and 16 as critical.

Vitals

As seen in Table 2, male patients had a significantly higher temperature, pulse rate, blood pressure and respiratory rate as compared to female patients ($P > 0.005$). The oxygen saturation was lower in male patients which was both clinically and statistically significant ($P = 0.009$).

With regards to the severity of Covid-19, it was observed that increase in the pulse rate and body temperature of severe and critical Covid-19 patients was significantly higher when compared to non-severe patients. However, the fall in the oxygen saturation and the increase in the respiratory rate was significant in the critically affected Covid-19 patients [Table 3].

Symptomatology

Of the 99 patients who showed symptoms, fever and cough were the two most common symptoms reported by over 50% of the patients. Over 50% of the severe and critical patients complained of breathlessness. Other fever related symptoms such as myalgia and headache were reported by few patients which has been summarized in Figure 1.

Comorbidities associated with Covid-19

Gender wise distribution revealed that 38 out of 57 males (66.7%) had comorbidities as compared to 27 out of 52 (52%) females. Diabetes mellitus was the most common comorbidity seen in 23.8% of the patients followed by hypertension in 19.2%. Other comorbid conditions present are summarized in Figure 2. Moreover 73.3% of critical patients had diabetes mellitus and hypertension as the two most common comorbid condition followed by cancer, obesity and cardiovascular accident [Figure 3].

Hematological, biochemical and radiological findings

The laboratory findings are summarized in Tables 2 and 3. The laboratory findings were deranged in both males and females. However, male patients had a significantly higher TLC count in comparison to females. Apart from this, various other parameters such as serum LDH, serum ferritin, D-dimer and CRP were higher in males which was both clinically and statistically significant [Table 2]. There was a statistically significant reduction in platelet count in males. Although there was reduction in the absolute lymphocytes count and increase in PCT in males, this was comparable in both the groups.

In order to study the significance of biochemical parameters in the three groups of Covid-19 patients, Analysis of Variance (ANOVA) followed by post hoc Tukey test was used. Severe and critically ill Covid-19 patients had a significantly higher TLC and lower absolute lymphocyte count as compared

Table 1: The distribution (%) of Covid-19 patients based on the severity

Group	Frequency		
	Males *n*=57	Females *n*=52	Total
Non-Severe	29 (50.8)	46 (88.5)	75 (68.8)
Asymptomatic	3 (5.3)	7 (13.8)	10 (9.2)
Mild	15 (26.3)	32 (61.5)	47 (43.1)
Moderate	11 (19.3)	7 (13.8)	18 (16.5)
Severe	15 (26.3)	3 (5.8)	18 (16.5)
Critical	13 (22.8)	3 (5.8)	16 (14.7)
Total	57	52	109 (100)

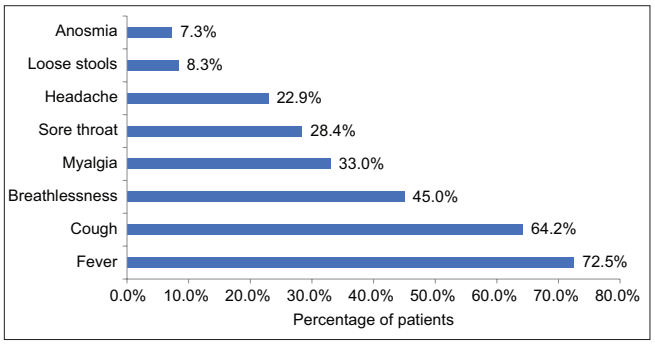

Figure 1: Figure showing the symptoms of Covid-19 patients

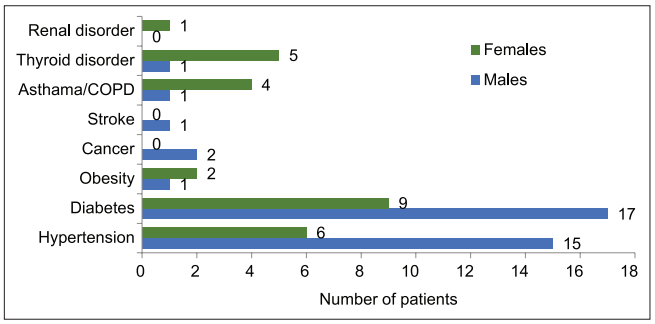

Figure 2: Figure showing the comorbidities in male and female Covid-19 patients

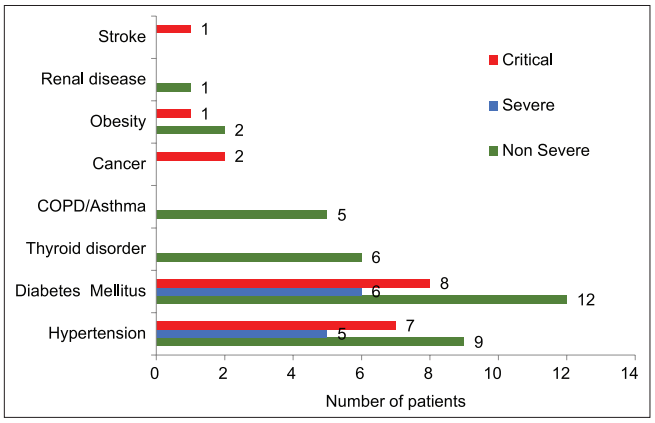

Figure 3: Figure showing the comorbidities in the Covid-19 patients

Table 2: The mean (S.D.) age, vital stats, hematological and biochemical laboratory profile of male and female Covid-19 patients

	Males (*n*=57)	Females (*n*=52)	*P*
Age in years	44.52 (9.041)	37.94 (9.382)	<0.001
Pulse	104.95 (17.407)	88.40 (10.73)	<0.001
Systolic BP	134.25 (17.818)	119.90 (11.00)	<0.001
Diastolic BP	83.65 (11.218)	75.69 (9.745)	<0.001
Respiratory rate	22.63 (13.352)	19.50 (2.804)	0.009
Oxygen saturation	91.93 (0.9012)	97.08 (3.174)	0.006
Temperature	38.31 (8.291)	37.371 (0.8306)	<0.001
Total leucocyte count (12-15 × 10^3 cells/μL)	11.7339 (5.31657)	7.136 (3.474)	<0.001
Absolute Lymphocyte count (1.0-3.0×10^3 cells/μL)	0.967 (0.703)	1.011 (0.316)	NS
Platelets (150-400 × 10^3 cells/μL)	204.66 (100.64)	251.25 (69.05)	0.006
LDH (105-222 U/L)	445.96 (247.60)	246.21 (124.13)	<0.001
Ferritin (10-150 ng/mL)	2461.207 (3575.05)	163.07 (199.65)	<0.001
D dimer (<0.5 mcg/ml FEU)	4.95 (8.81)	1.72 (4.05)	0.05
CRP (0-7 mg/L)	154.83 (157.16)	51.31 (75.42)	<0.001
PCT (<0.05 ng/ml)	3.74 (15.42)	0.84 (3.55)	NS

Table 3: A consolidated table showing the vitals, hematological, biochemical laboratory profile, Chest X-ray score and the prognostic outcome of Covid-19 patients

Parameter Mean (SD)	Non-severe (*n*=75)	Severe (*n*=18)	Critical (*n*=16)
Pulse	91.84 (8.76)	111.33 (18.11)*	105.44 (13.06)‡
Systolic BP	125.73 (14.16)	132.58 (18.16)	129.20 (23.90)
Diastolic BP	78.73 (10.38)	83.17 (12.39)	81.39 (13.39)
Respiratory rate	19.49 (3.38)	20.89 (4.42)	29.13 11.87)*
Oxygen saturation	97.41 (2.69)	93.53 (5.41)	80.33 (21.53)*
Temperature	37.52 (0.84)	38.66 (0.87)*	38.58 (0.85)*
Total WBC count (12-15 × 10^3 cells/μL)	7.59 (4.00)	12.26 (4.32)*	15.33 (4.48)*
Absolute Lymphocyte count (1.0-3.0 × 10^3 cells/μL)	1.13 (0.59)	0.65 (0.21)†	0.69 (0.27)§
Platelets (150-400 × 10^3 cells/μL)	237.99 (78.54)	209.66 (106.09)	193.43 (112.53)
LDH (105-222 U/L)	256.40 (127.53)	476.66 (157.87)*	615.87 (312.89)*
Ferritin (10-150 ng/mL)	381.28 (3.51)	4169.82 (4954.59)*	2148.85 (2823.98)‖
D dimer (<0.5 mcg/ml FEU)	1.30 (3.51)	2.56 (9.61)	9.61 (11.56)†
CRP (0-7 mg/L)	56.37 (105.63)	157.56 (106.13)**	277.48 (128.84)*
PCT (<0.05 ng/ml)	0.135 (0.19)	4.41 (10.19)	7.88 (24.58)¶
Outcome			
Recovered	75 (100%)	18 (100%)	12 (75.0%)
Prolonged stay	0	12 (66.7%)	13 (81.3%)
High flow oxygen	10 (13.3%)	17 (94.4%)	16 (100%)
Intubation	0	0	15 (93.8%)
Death	0	0	4 (25.0%)
Chest Xray score			
0	43 (57.3)	0	0
1	8 (10.7)	0	0
2	11 (14.7)	0	0
3	7 (9.3)	0	0
4	5 (6.7)	7 (38.9)	2 (12.5)
5	1 (1.3)	8 (44.5)	5 (31.2)
6	0	3 (16.6)	9 (56.3)

*P<0.001; †P=0.001; ‡P=0.004; §P=0.006; ‖P=0.032; ¶P=0.039, **P=0.002

to non-severe patients. Serum LDH levels, serum ferritin and CRP were also elevated in both severe and critical patients as compared to non-severe cases. PCT and D-dimer though elevated in both the severe and critical patients, statistical significance was seen only in the critical group on comparison with non-severe group. Although the platelet counts were decreased with severity of Covid-19 it was statistically not significant. Chest X-ray score was done for all Covid-19 positive patients. The reporting of X-ray was done independently by a radiologist and pulmonologist. For the purpose of scoring each lung area was divided into three zones: a superior zone from apex of the lungs up to the superior hilar marking; a middle zone from superior

hilar marking to inferior hilar marking; and a lower zone from inferior hilar marking up to the costophrenic sulcus. Each zone is given a binary score depending whether opacity is present (score 1) or absent (score 0).

In this study it was observed that 60.5% of the patients showed opacities in the lungs. While majority of the asymptomatic patients had a chest x-ray score of zero or less than three, severe and critical patients had greater chest involvement. Majority of the severe Covid-19 patients had four to five zones involved, whereas in case of critical patients 56% had all the six zones affected.

Course of treatment, complications and outcome

During the course of the treatment, high flow oxygen was given to 100% of critically ill patients, 93.3% (18/19) severely ill patients and only 13.3% (10/75) of non-severe cases. Amongst the critical patients (15/16) required intubation. Complications were mainly seen in the critical group with 4 deaths reported in them. Respiratory failure was seen in all four deceased patients. Multiorgan failure was associated in three of the four deaths.

Discussion

Covid-19 is a major health concern affecting over 65 million of the world population, and unfortunately, leaving over 1.5 million of them dead.[14] With exponentially increasing cases being reported daily, no prediction seems to be enough to forecast the total devastation this disease will have in terms of morbidity and mortality. Being a novel disease, which was first reported in December 2019, not much is known regarding its pathophysiological basis and progression. Compared to seasonal flu, Covid-19 has a longer incubation period, of 2 to 15 days, and is more contagious. Once infected, the patient may be either asymptomatic or develop with flu-like symptoms such as fatigue, myalgia, cough, shortness of breath and fever or may be asymptomatic. However, some patients may develop severe pneumonia or complication such as ARDS, myocarditis, septic shock, venous thromboembolism and multi-organ failure.[15,16]

To worsen the situation, there is no definite treatment available and the ability of the virus to mutate, further aggravates the concern. Therefore, in the absence of a definite drug to treat Covid-19, the first step is to isolate the patients in order to prevent further transmission. The management is mainly supportive and focusses on preventing respiratory failure and other life-threatening complications.[17] However, some Covid-19 patients have been reported to rapidly progress from moderate to severe or critical state which is associated with poor prognosis.[12,18] It is in this view that there is a need to identify these patients early. Laboratory investigation plays an important role in management of any disease as it helps not just in diagnosis but also to predict the outcome of the disease. Hence biochemical markers could play an important role it identifying and classifying high risk Covid-19 patients.

In this study we observed that male patients were more seriously affected than females. Although the prevalence of Covid-19 in males and females are the same, Jin *et al.*,[18] in their preliminary case series study concluded that male patients had higher mortality.

Similarly, in this study we observed that almost 50% (28/57) of the affected males were either severely or critically affected in comparison to 11% (6/52) in females [Table 1]. Even though both male and female patients had an over-all deranged vital stat, the male patients had a significantly higher pulse rate ($P < 0.001$), respiratory rate ($P = 0.009$) and temperature ($P < 0.001$) and lower oxygen saturation ($P < 0.001$) as compared to the females [Table 2]. Also, the hematological and biochemical laboratory findings were deranged in both the genders but showed greater degree of derangement in males [Table 2]. The presence of comorbidities in particularly diabetes mellitus and hypertension was higher in males [Figure 2]. All these findings substantiate that males are more severely affected. Various reasons are hypothesized for a male predilection which includes occupation, lifestyle habits smoking and alcohol intake, presence of comorbidities.[19] Genetic predisposition may also play a role as previous studies have reported higher circulatory ACE2 levels in males than in females and also in diabetics and hypertensives.[20]

In our study about 60% of Covid-19 patients had co-morbidities of which diabetes mellitus and hypertension were the most common across all the three groups. This was in accordance with a meta-analysis by Emami *et al.*,[21] which reported diabetes mellitus, hypertension and cardiovascular disease to be most prevalent co-morbidity with covid-19. This is probably due to the fact that the mentioned three condition the common non-communicable diseases present among the population. Moreover, dysregulation of ACE2 in diabetes mellitus and higher circulatory ACE2 in diabetes and hypertensive patients predisposes them for higher incidence and severe Covid-19.[22]

In this study, the hematological indices showed a significantly higher total leucocyte count and a reduced absolute lymphocyte count in both severe and critical patients in comparison to non-severe patients [Table 3]. In accordance to our study, many studies have reported lymphopenia to be commonly associated with increased severity of Covid-19.[22-24]

However, on the contrary, they also reported a lower total leucocyte count in covid-19 patients. This could be because they had not categorized the Covid-19 patients as severe and critical. There are studies which have reported leukocytosis to be associated with Covid-19 particularly in severe cases. Zhao *et al.*,[25] in their retrospective study found that 52 patients had high total leucocyte count along with lymphopenia. Most of these patients were either elderly or had some other associated diseases. This increase in leucocytes is due to the increase in the neutrophils. This rise is due to the increased inflammatory state and cytokine storm. resulting in increased levels of inflammatory mediators such as interleukins (IL) and tumor

necrosis factor – α (TNF-α) which induced the apoptosis of lymphocyte resulting in lymphopenia.[26,27]

With respect to thrombocytes no clinical or statistical significance was seen. This was in accordance to the finding reported by Ferrari *et al.*[28]

In addition to the cytokine storm, viral proteins also increase the production of acute phase reactants such as CRP, ferritin and procalcitonin. We found that all the three markers were significantly elevated in severe cases. Similar findings were reported in many other studies.[29-31] CRP, a member of the pentraxin group of proteins, has a half-life of 19 hours and is found to be increased by many folds during inflammation and tissue necrosis.[32] Huang *et al.*,[29] in their meta-analysis reported that CRP was a consistent finding in severe Covid-19 but were not associated with mortality. Recent studies have shown that CRP can be used to monitor the progression and improvement in covid-19 patients.[33,34]

Ferritin has been identified as one of the key mediators of immune dysregulation and contributes to cytokine storm. Moreover, elevated serum ferritin levels also indicate ongoing inflammatory response as the macrophages in the lung parenchyma may increase its synthesis and release. Another reason for the increased ferritin levels could be due to hemophagocytic lymphohistocytosis (HLH) in severely and critically ill patients which is associated with poor prognosis.[34] In the absence of bacterial infection, an elevated procalcitonin points toward severe inflammatory condition and release of pro-inflammatory cytokines.

Lippi *et al.*,[35] in their meta-analysis reported that Covid-19 patients with increased PCT were five times at a higher risk to develop severe infection. LDH is an isoenzyme present in almost all the cells. LDH-3 is found in the lung tissue. Therefore, higher levels of LDH in severe and critical patients points to a greater damage to pneumocytes. Disseminated intravascular coagulation (DIC) has been reported to be a cause of death in Covid-19 across various studies.[6,23] Xiong *et al.*,[36] in their meta-analysis reported that prothrombin time (PT) and D-dimer levels were significantly elevated in severe COVID-19 patients. This increase in D-dimer points towards DIC which was a common entity found in deceased COVID-19 patients. Fibrin clots are formed in response to viral infections which provides protection against the virus. Therefore, there is a possibility that a severe COVID-19 infection may induce fibrinolysis which is a cause of DIC.[36,37] In a study done by Tang *et al.*[6] On 183 COVID 19 positive patients, 71.4% of the non survivors had overt DIC compared to 0.6% in survivors.. In another study on 201 COVID-19 positive patients, high D-dimer and PT was observed in patient who developed ARDS. 52.8% who died had elevated D-dimer levels compared to those who recovered.[38]

There were some limitations in our study. First, it was a retrospective study and data were obtained from the records of the patients. Second, it was carried out only at one center and our sample size was limited to the duration of the study. Further studies may be required to extrapolate the findings to a larger population.

Laboratory biomarkers such as TLC, serum ferritin, serum CRP, LDH, procalcitonin and D-dimer are all deranged in severe and critical Covid-19. Therefore, along with clinical symptoms and radiological findings, these parameters can also prove to be useful in categorizing these patients.

Conclusion

Based on the finding of the study we conclude that males are more vulnerable to develop severe form of Covid-19. Also, increased total leucocyte count with decreased absolute lymphocytes is associated with severe and critical Covid-19. Acute phase proteins such as CRP, ferritin and procalcitonin are elevated in Covid-19. Their increase was greater in severe and critical cases hence playing an important role in cytokine storm. Rising serum LDH and D-dimer levels may be used as a marker to assess the damage to the lung tissues and identify the patients at risk to develop complications respectively. Therefore, along with clinical presentation and radiological findings, biochemical parameter may also be considered as important predictors for assessing severity in covid-19 patients.

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Conflicts of interest

There are no conflicts of interest.

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