RESEARCH ARTICLE

Association of biochemical markers with COVID-19 severity in Pakistan

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Abstract

Objective: To evaluate demographics, biochemical markers and clinical features of patients suffering from coronavirus disease-2019.

Method: The cross-sectional study was conducted retrospectively at the Capital Hospital, Islamabad, and the Fauji Foundation Hospital, Rawalpindi, Pakistan, from October 08, 2021 to March 01, 2022 and comprised patients of either gender with coronavirus disease-2019 diagnosed on the basis of reverse transcriptase polymerase chain reaction. Patients' demographic, clinical and laboratory findings were obtained using patient charge sheets. Coronavirus disease-2019 was categorised as non-severe, severe and critical, according to the World Health Organisation criteria. Data was analysed using SPSS 26.

Results: Of the 431 patients, 91(21.1%) were men and 340(78.9%) were women. The overall mean age was 60.75±14.45 years. Of the total, 148(34.3%) had non-severe, 190(44.1%) severe and 93(21.6%) had critical condition at the time of admission. Hypertension 307(71.2%) and diabetes mellitus 249(57.8%) were the most common comorbidities, while fever 353(81.9%), shortness of breath 339(78.7%) and cough 302(70.1%) were the most common symptoms reported. Higher age was significantly associated with coronavirus disease-2019 severity (p<0.001). Among comorbidities, chronic kidney disease (p<0.001) and cancer (p=0.046), and, among signs and symptoms, shortness of breath (p=0.002) and chest pain (p=0.021), were significantly associated with coronavirus disease-2019 severity. Serum total bilirubin, alanine aminotransferase, urea and creatinine levels had significant association with disease severity (p<0.001). Total leukocyte count, neutrophil-to-lymphocyte ratio, prothrombin time, and plasma D-Dimer levels had significant association with disease severity (p<0.001). Serum ferritin, lactate dehydrogenase and interleukin-6 levels were also significantly associated with disease severity (p<0.05).

Conclusion: Assessment of biochemical markers was an excellent way to monitor disease progression in coronavirus disease-2019 patients.

Keywords: COVID-19, Diabetes, Severity, Hypertension, Clinical features. (JPMA 73: 1403; 2023)

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Introduction

Coronavirus disease-2019 (COVID-19) was an outbreak of the severe respiratory disease first reported in Wuhan, China.[1] The first incident of COVID-19 in Pakistan was reported in late February 2020.[2] The classic symptoms of patients suffering from COVID-19 include shortness of breath, fever, headache, cough and pneumonia. Further onset of the disease can result in respiratory failure because of the destruction of alveoli and can result even in death. COVID-19 exhibits various severity levels, varying from patient to patient. Severity status ranges from asymptomatic, non-severe and severe to critical. Severe infection may lead to death in many individuals, too. COVID-19 death risk is highly dependent on age and previous health conditions. Patients having age >65 years and chronic comorbidities, such as hypertension (HTN), cardiovascular disease (CVD), pulmonary illness, and diabetes mellitus (DM), are far more vulnerable to fatal and catastrophic disease outcomes.[3]

The main reason of COVID-19's mortality was multiple organ failure. Research suggests COVID-19 is associated with organ failure in around 33% of cases, with acute renal damage accounting for 37% of those cases. Impaired renal function can cause metabolite and toxin excretion to be obstructed in the body, compromising the body's electrolyte and acid-base balance. Furthermore, when renal function is substantially compromised, uraemia develops, posing a life-threatening situation. The importance of early detection of signs of renal damage and prompt, effective therapies in decreasing complications and enhancing prognosis cannot be overstated.[4]

COVID-19 pneumonia causes an abnormal coagulation profile, with a rise in D-Dimer and fibrin degradation products (FDPs) in particular. Severe acute respiratory syndrome coronavirus 2 (SARS-Cov2) causes the immune system to get activated, resulting in the virus being cleared.

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However, an increased number of inflammatory mediators are released in the body during this process of an overactive immune response, which damages microcirculation and activates blood coagulation cascades, producing coagulation profile derangement.[5] In intensive care units (ICUs), iron metabolism can undergo considerable changes that can be used to predict death. Serum ferritin has also recently been identified as one of the predictors of mortality in COVID-19 patients. Ferritin, through direct immuno-suppressive and pro-inflammatory actions, contributes to the cytokine storm and is a significant modulator of immune dysregulation, especially in extreme hyperferritinaemia.[6]

The SARS-Cov2 virus may cause cholangiocyte malfunction by binding to angiotensin-converting enzyme 2 (ACE2) on cholangiocytes, and result in systemic inflammatory response that leads to liver damage. A histological examination of liver biopsy specimens from a COVID-19 patient revealed moderate microvasicular steatosis and minor lobular and portal activity, suggesting that SARS-Cov2 may have caused the liver damage.[7]

Increased levels of interleukin-6 (IL-6) are detected in more than half of individuals with COVID-19, and it is one of the key mediators of inflammatory and immunological responses triggered by infection or damage. In COVID-19 patients, IL-6 levels appear to be associated with an inflammatory response, respiratory failure, need for mechanical ventilation and/or intubation, and mortality.[8]

The widely recognised unusual laboratory discoveries in COVID-19 cases are the expanded degrees of lactate dehydrogenase (LDH), serum glutamate pyruvate transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT). Increased creatinine and phosphocreatine kinase demonstrated that the tracheobronchial tree is the primary target of the COVID-19 attack and LDH is a significant indicator of lung damage.[9]

Diagnostic tests are meant to investigate the overall condition of the infection. For quick and reliable molecular diagnosis of COVID-19, a correct respiratory tract sample from the right anatomic position at the right time must be collected. The molecular test for diagnosing COVID-19 infection is the reverse transcriptase polymerase chain reaction (RT-PCR).[10]

The current study was planned to evaluate demographics, biochemical markers and clinical features of COVID-19 patients.

Subjects and Methods

The cross-sectional study was conducted retrospectively at a tertiary care Capital Hospital, Islamabad, and the Fauji Foundation Hospital, Rawalpindi, Pakistan, from October 08, 2021 to March 01, 2022. After approval from the institutional ethics review committee, the sample size was calculated using OpenEpi calculator on 7th of August 2021[11] while keeping confidence interval (CI) 97% and margin of error 5% with an hypothesized frequency of outcome factor in the population (p) 35.3%.[12,13]

All COVID-19 in-patients diagnosed on the basis RT-PCR were included, while patients who were discharged without adequate laboratory investigations were excluded.

After informed consent, data was collected using a predesigned, structured, content validated questionnaire. Questionnaire was in English language and the researchers explained it to the patients when needed. The simple random sampling technique was used. Patients were categorized into non-severe, severe, and critical categories as per the World Health Organisation (WHO) criteria.[14] Patients having no signs of severe or critical disease were categorised as non-severe; those with oxygen saturation (SpO_2) <90% on room air, showing signs of pneumonia, or having symptoms of severe respiratory distress were categorised as severe cases; and patients requiring life-sustaining treatment or having acute respiratory distress syndrome (ARDS), sepsis or septic shock were categorised as critical.

As part of the baseline metabolic profile, COVID-19 patients' peripheral venous blood samples were drawn upon admission, placed in serum separating gel tubes, sodium citrate and ethylenediaminetetraacetic (EDTA) acid tubes. Liver function tests (LFTs), renal function tests (RFTs) and LDH levels were carried out on Selectra Pro S (Elitech, France) fully automated chemistry analyser, while electrolytes were determined by EasyLyte (Medica, United States). Complete blood count (CBC) was measured using Sysmex KX-21 (Sysmex, Japan) haematology analyser. Coagulation profile, including fibrinogen degradation product (FDP; D-Dimer), prothrombin time (PT) and activated partial thromboplastin time (APTT), were measured using CA-02C coagulometer (MRC, United Kingdom). Interleukin-6 (IL-6) levels were determined by double antibody sandwich enzyme-linked immunosorbent assay (ELISA) kit (Thermo Fischer, USA).

Data was analysed during March 2022 using SPSS 26. Continuous/numerical variables were described as mean±standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Chi-square test, and analysis of variance (ANOVA) were employed as appropriate. $P<0.05$ was considered statistically significant.

Results

Of the 431 patients, 91(21.1%) were men and 340(78.9%) were women. The overall mean age was 60.75±14.45 years. Of the total, 148(34.3%) had non-severe, 190(44.1%) severe and 93(21.6%) had critical condition at the time of admission. Higher age was significantly associated with disease severity (p<0.001). HTN 307(71.2%) and DM 249(57.8%) were the most common comorbidities. Among the comorbidities, chronic kidney disease (CKD) (p<0.001) and cancer (p=0.046) were significantly associated with COVID-19 severity (Table 1).

Fever 353(81.9%), shortness of breath 339(78.7%) and cough 302(70.1%) were the most common symptoms reported. Among all the symptoms, shortness of breath (p=0.002) and chest pain (p=0.021) were significantly associated with disease severity (Table 2).

Table-1: Demographic characteristics of coronavirus disease-2019 (COVID-19) patients.

Characteristics	Non-Severe	Severe	Critical	Total	*p*-value
	n(%)	n(%)	n(%)	n(%)	
	148 (34.3)	190 (44.1)	93 (21.6)	431 (100)	
Gender					0.036*
Males	36 (24.3)	40 (21.1)	15 (16.1)	91 (21.1)	0.021*
Females	112 (75.7)	150 (78.9)	78 (83.9)	340 (78.9)	
Mean Age (years)	57.63±14.65	60.14±13.91	66.96±13.44	60.75±14.45	<0.001
Hypertension	99 (66.9)	133 (70)	75 (80.6)	307 (71.2)	0.063
Diabetes Mellitus	83 (56.1)	110 (57.9)	56 (60.2)	249 (57.8)	0.818
CKD	4 (2.7)	12 (6.3)	15 (16.1)	31 (7.2)	<0.001
Hepatitis C	5 (3.4)	8 (4.2)	2 (2.2)	15 (3.5)	0.672
Asthma	17 (11.5)	18 (9.5)	9 (9.7)	44 (10.2)	0.817
COPD	2 (1.4)	3 (1.6)	2 (2.2)	7 (1.6)	0.89
Stroke	3 (2.0)	6 (3.2)	1 (1.0)	10 (2.3)	0.527
Allergy	8 (5.4)	7 (3.7)	2 (2.2)	17 (3.9)	0.437
Cancer	0 (0)	8 (4.2)	3 (3.2)	11 (2.6)	0.046*
Tuberculosis	2 (1.4)	5 (2.6)	3 (3.2)	10 (2.3)	0.597

* Statistically significant at p<0.05. SD: Standard deviation, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease.

Table-2: Association of signs and symptoms with coronavirus disease-2019 (COVID-19) severity.

Parameters	Non-Severe	Severe	Critical	Total	*p*-value
	n(%)	n(%)	n(%)	n(%)	
Cough	103 (69.6)	132 (69.5)	67 (72)	302 (70.1)	0.895
Shortness of breath	103 (69.6)	154 (81.0)	82 (88.2)	339 (78.7)	0.002*
Flu	10 (6.8)	10 (52.6)	5 (5.4)	25 (5.8)	0.827
Fever	125 (84.4)	150 (78.9)	78 (83.9)	353 (81.9)	0.365
Sore throat	6 (4.1)	9 (4.7)	2 (2.2)	17 (3.9)	0.574
Diarrhoea	9 (6.1)	8 (4.2)	2 (2.2)	19 (4.4)	0.346
Chest Pain	5 (3.4)	22 (11.6)	7 (7.5)	34 (7.9)	0.021**
Vomiting	10 (6.8)	17 (8.9)	3 (3.2)	30 (7)	0.205
Body ache	15 (10.1)	19 (10)	4 (4.3)	38 (8.8)	0.222
Abdominal Pain	7 (4.7)	12 (6.3)	4 (4.3)	23 (5.3)	0.717
Weakness	9 (4.7)	10 (52.6)	4 (4.3)	23 (5.3)	0.835
Anorexia	9 (4.7)	14 (7.4)	8 (8.6)	31 (7.2)	0.756
Headache	6 (4.1)	5 (2.6)	6 (6.5)	17 (3.9)	0.299
Constipation	0 (0)	4 (2.1)	0 (0)	4 (0.9)	0.077

* Statistically significant at p<0.01; ** Statistically significant at p<0.05

Among other markers, serum total bilirubin, alanine aminotransferase (ALT), urea and creatinine levels had significant association with disease severity (p<0.001). Total leukocyte count (TLC), neutrophil-to-lymphocyte ratio (NLR), PT, and plasma D-Dimer levels had significant association with disease severity (p<0.001). Serum ferritin, LDH and IL-6 levels were also significantly associated with disease severity (p<0.05) (Table 3).

Discussion

In a population, the percentage of immunocompromised people is associated with age structure of that population, which appears to be a substantial risk factor for COVID-19 severity and consequences. Compared to adults, children are less likely to have severe COVID-19. Men and women may be affected differently by the infectious disease. Women are more likely than men to suffer from a variety of inflammatory and autoimmune disorders, both non-specific and specific. These findings may be explained by the immune-modulating effect of sex hormones.[15] In the current study, patients' age was strongly associated with COVID-19 severity, and most of the participants were women. According to Gallo et al., older age significantly predicts disease severity.[16] The current study found that NTH and DM were the most common comorbidities. In a similar study of 85 participants, shortness of breath was found in 50(58.8%), HTN 32(37.6%) and DM 19(22.4%) patients.[17]

LFTs are used to diagnose liver disease or damage. Saini et al. observed raised liver enzyme levels (ALT) in a majority of patients.[18] The current study reported significantly elevated ALT levels. RFTs are performed to assess kidney function. In COVID-19 patients, elevated values are associated with kidney dysfunction. In the current study, raised levels of urea and creatinine were also significantly associated with severity of the disease. According to Iftikhar et al., COVID-19 patients showed signs of renal dysfunction mirrored by a raised level of urea and creatinine in blood.[19] Infection or inflammation induces bone marrow to produce more white blood cells (WBCs), releasing them into the blood, resulting in the raised count. In the current study, TLC and NLR were significantly associated with disease severity. D-Dimer is a degradation product of fibrin that circulates in the blood, and this test is used to look for a blood clot. D-Dimer had a significant association with disease severity. These results are in line with those of an earlier study.[20]

Ferritin can be used to detect liver damage, significant disease, and therapy outcomes. Ferritin is an acute-phase protein that can be released from hepatocytes that have been damaged. Hyper-ferritinaemia can be

Table-3: Biochemical features of the patients.

Parameters	Ref. Range	Non-Severe	Severe	Critical	Total	*p*-value
LFTs, mean (SD)						
T. Bil. (mg/dL)	0.1-1.2	0.61 (0.38)	0.75 (0.47)	1.17 (1.15)	0.79 (0.69)	<0.001
ALT (U/L)	10-40	39 (28)	51 (35)	91 (129)	56 (69)	<0.001
RFTs, mean (SD)						
Urea (mg/dL)	10-50	45 (45)	66 (51)	128 (83)	72 (65)	<0.001
Creatinine (mg/dL)	0.2-1.2	1.27 (1.20)	1.66 (2.07)	2.94 (3.27)	1.81 (2.25)	<0.001
Electrolytes, mean (SD)						
Sodium (mmol/L)	135-145	137 (3.9)	136 (4.7)	138 (6.6)	137 (4.9)	0.213
Potassium (mmol/L)	3.5-5.0	4.6 (3.6)	4.4 (0.6)	5.4 (7.6)	4.7 (4.1)	0.158
Chloride (mmol/L)	95-105	100 (4.5)	100 (7.1)	99 (6.3)	100 (6.1)	0.485
Haematology, mean (SD)						
TLC ($x10^3$/ul)	4.0-11.0	8.3 (3.4)	13.4 (5.7)	20.4 (7.3)	13.2 (7.0)	<0.001
N/L ratio	1.0-3.0	6.5 (6.7)	15.2 (19.0)	33.6 (27.3)	16.20 (20)	<0.001
Platelet Count ($x10^3$/l)	150-400	249 (96)	258 (109)	240 (135)	251 (111)	0.412
Coagulation, mean (SD)						
PT (seconds)	11-14	11 (1.3)	11 (1.5)	12 (2.6)	11 (1.8)	<0.001
APTT (seconds)	25-34	30 (4.2)	31 (7.1)	32 (4.3)	31 (5.7)	0.073
D-Dimer (ng/mL)	220-500	356 (417)	841 (1438)	1604 (2777)	839 (1681)	<0.001
Ferritin (ug/L)	11-336	329 (288)	729 (958)	1598 (2138)	779 (1275)	<0.001
LDH (U/L)	140-480	481 (248)	812 (386)	1434 (1052)	849 (677)	<0.001
Interleukin-6 (pg/mL)	0- 43	56 (93)	106 (236)	281 (548)	123 (303)	0.025*

* Statistically Significant at p<0.05; LFT: Liver function test, RFT: Renal function test, ALT: Alanine transaminase, ALP: Alkaline phosphatase, TLC: Total leukocyte count, N/L: Neutrophil-to-lymphocyte, PT: Prothrombin time, APTT: Activated partial thromboplastin time, LDH: Lactate dehydrogenase.

produced by a metabolic syndrome or reduced liver activity. Patients with abnormal ferritin levels in COVID-19 are at a higher risk of liver injury and severe illness. The current study reported elevated levels of ferritin in severe and critical COVID-19 patients with statistical significance. Similar results have been reported earlier.[21]

LDH having five isomers is found in almost all body cells, including liver, kidney, brain, heart and the muscles. LDH is involved in energy production and its increased levels in blood indicate damaged or diseased tissue. The current study found that LDH levels were significantly raised in COVID-19 patients. Lee et al. reported that LDH levels increase in several inflammatory processes, including ARDS, and it is a comprehensive marker of cell destruction and demise, and that LDH is broadly dispersed throughout the body.[22]

Elevated levels of IL-6 in the current study indicated a strong association with COVID-19 severity. Keddie et al. reported that IL-6 is a vigorous multifunctional inflammation mediating cytokine and is responsible for the COVID-19 cytokine storm.[23] Herold et al. stated that an IL-6 cut-off value of >80pg/ml during the disease phase was an indication of respiratory arrest, and all patients required intubation except one.[24]

Conclusion

In COVID-19 patients, disease progression and clinical outcome were associated with older age, female gender, underlying illness, persistent fever, impaired liver and renal functions, increased NLR, elevated D-Dimer, ferritin, LDH and high IL-6 expression.

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