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Assessment of Serum Electrolytes, Biochemical, and Inflammatory Markers in Predicting COVID-19 Severity in COPD Patients

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Abstract: Background: Chronic obstructive pulmonary disease (COPD) is the most prevalent long-term respiratory condition. Patients with COPD experience detrimental effects of COVID-19 infection. Objective: To figure out whether COPD is a risk factor influencing the progression of COVID-19 and to explore the clinical value of laboratory biomarkers to assess the severity of COVID-19 in patients with COPD comorbidity. Methods: In total, 1572 participants aged 35 to 70 years were enrolled to a tertiary hospital in Bangladesh between March 2022 and October 2022. Participants were categorized into four groups: (1) control, (2) COPD, (3) COVID-19, and (4) COVID-19 with COPD, and blood levels of clinical laboratory markers were assessed to analyze how these markers differ among the study groups. Results: COVID-19 patients with COPD had a significantly lower level of sodium (131.81 ± 2.8 mmol/L) and calcium (1.91 ± 0.28 mmol/L), and a significantly higher level of NT-proBNP (568.45 ± 207.40 pg/mL), bilirubin (1.34 ± 0.54 mg/dL), fibrinogen (577.27 ± 145.24 mg/dL), D-dimer (2.97 ± 2.25 µg/mL), C-reactive protein (71.08 ± 62.42 mg/L), interleukin-6 (166.47 ± 174.39 pg/mL), and procalcitonin (0.25 ± 0.30 ng/mL) compared to other study groups patients ($p < 0.0001$). In addition, the GOLD 4 group demonstrated significantly altered clinical parameters among COVID-19 patients with COPD. Furthermore, NT-proBNP, interleukin 6, D-dimer, C-reactive protein, and fibrinogen demonstrated excellent diagnostic performance in predicting disease severity among the COVID-19 patients with COPD, with a cut-off value of 511.2 pg/mL, 51.375 pg/mL, 1.645 µg/mL, 40.2 mg/L, and 510 mg/dL, respectively. Our results also indicate that inflammatory markers had significant positive correlations with the biochemical and coagulation markers in the COVID-19 patients suffering with COPD ($p < 0.0001$). Conclusions: NT-proBNP, interleukin 6, D-dimer, C-reactive protein, and fibrinogen are the most potential parameters for differentiating severe cases of COVID-19.

Keywords: COVID-19; COPD; clinical laboratory markers

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1. Introduction

The global pandemic of coronavirus disease 2019 (COVID-19), induced by the rapid transmission of a novel coronavirus strain named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), led to over 585 million infections and over 6.4 million deaths globally until 9 August 2022 [1,2]. Bangladesh is the second most afflicted nation in South Asia, following India, by the ongoing pandemic of COVID-19, with over 2 million confirmed cases and over 29 thousand deaths till 9 August 2022 [3]. Because the severity of the infection may vary from asymptomatic to symptoms comparable to the common cold to severe types of interstitial pneumonia requiring immediate medical treatment, it would be quite advantageous to understand the risk factors for critical clinical outcomes [4].

A prior comorbid disease was found in 77.5% of patients with COVID-19 in Bangladesh, which rose to 94.4% among those with severe disease [5]. Among the patients suffering from various comorbidities, those with chronic obstructive pulmonary disease (COPD) had the greatest hazard ratio (2.68) for intensive care unit admission, invasive ventilation, or mortality [6].

COPD is the most prevalent long-term respiratory condition. Globally, it is the third leading cause of mortality, claiming 3.23 million lives in 2019 [7]. Based on the criteria proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), approximately 12.5% of Bangladesh's population suffer from COPD [8]. Poor pulmonary reserve and small airways with over-expressed angiotensin-converting enzyme 2 (ACE-2) receptors in patients with COPD enhance the likelihood of adverse outcomes of COVID-19 infection [9]. Among severe COVID-19 cases, COPD has been proven to be an independent predictor of hospital admission, the need for intensive care, and mortality in multiple large, well-performed cohort studies worldwide [10,11]. In a retrospective research study conducted in China, COPD was the predominant causative factor of intensive care unit admission, invasive ventilation, or mortality among 1590 hospitalized COVID-19 patients [6]. On the contrary, a study in the United States reported that COPD accounted for only 5.4% of the 5700 patients hospitalized with COVID-19 [12].

Pre-existing COPD should be evaluated for its effect on the progression and severity of COVID-19. Males and older adults may be more vulnerable to COVID-19, which has a demographic profile resembling COPD. Furthermore, the symptoms of COVID-19 may be misinterpreted as those of COPD exacerbation. Fever, fatigue, shortness of breath, and cough were the most frequent symptoms encountered by COVID-19 patients admitted to hospitals, regardless of whether they had a concomitant condition, which might also be observed in COPD exacerbations with bacterial or viral infections [9,12]. As a result, physicians must conduct additional clinical laboratory testing to rule out COPD exacerbation from SARS-CoV-2 infection while evaluating signs or symptoms. While some research has been performed on the relationship between COPD and COVID-19, only a few studies have been implemented on the clinical and laboratory findings of COVID-19 with COPD comorbidity [9,13–15]. Even though it has already been established that chronic diseases such as COPD and others enhance morbidity and death from COVID-19, people of different ethnicities have been disproportionately impacted [16,17]. Some research has documented the clinical and laboratory characteristics of COVID-19 in the context of Bangladesh, but so far, the data concerning COVID-19 among COPD patients are still lacking [5].

To address this issue, we performed the present study to analyze the clinical and laboratory findings of the patients with concurrent COPD and COVID-19 infections to assist healthcare providers in treating and managing COVID-19 patients suffering with COPD. We believe that the outcomes of this study will contribute to a comprehensive understanding of risk assessment, symptom management, and therapeutic approaches for COVID-19 patients with COPD comorbidity.

2. Materials and Methods

2.1. Study Design and Participants

In total, 1364 Bangladeshi male and non-pregnant female adult patients aged 35 to 70 years and 208 age-matched healthy volunteers were recruited, irrespective of their race, religion, and socioeconomic background. All patients were admitted to Bangabandhu Sheikh Mujib Medical College Hospital in Faridpur district of Bangladesh from March 2022 and October 2022. Healthy volunteers and patients were assigned to the following groups: (1) control group (n = 208); (2) COPD group (n = 392): all patients were spirometry-tested and satisfied the diagnostic criteria for COPD (spirometry with a ratio of FEV1/FVC lower than 0.7 following bronchodilator treatment) [18]; (3) COVID-19 group (n = 410): all patients with confirmed COVID-19 infection (positive nasopharyngeal or throat swab samples by RT-PCR) [19,20]; (4) COVID-19 with COPD group (n = 562): all confirmed COPD patients with COVID-19 infection. Patients were excluded from the study if they

had a history of any respiratory problem or lung diseases, except COPD (e.g., chronic respiratory failure, asthma, bronchiectasis, pulmonary fibrosis, tuberculosis, and diffuse parenchymal lung disease, etc.). Patients on long-term oxygen therapy or suffering from any neurological disorder were also excluded from the study. Patients who received inhaled bronchodilators or immunosuppressive drugs, and unable to undergo spirometry were also excluded. In addition, patients were excluded who had liver disease, gout, or other serious comorbid diseases (e.g., major surgery, renal failure, malnutrition, malignancy, etc.). Demographic features of all the participants were collected via structured questionnaires and standard procedures.

2.2. Sample Preparation and Assay

A blood sample was collected and serum was prepared according to the standard laboratory procedure. On admission, laboratory markers including electrolyte profiles (e.g., sodium, potassium, chloride, calcium, magnesium, and bicarbonate), biochemical parameters (e.g., NT-proBNP, bilirubin, and uric acid), coagulation profiles (e.g., fibrinogen and D-dimer), and inflammatory markers (e.g., C-reactive protein, interleukin-6, and procalcitonin) were determined for each participant. All laboratory data were determined by automatic analyzers, including Dimension® EXL™ 200 Integrated Chemistry System (Siemens Healthineers, Erlangen, Germany), STA Compact Max® 3 (Diagnostica Stago, Inc., Asnières-sur-Seine, France), and ADVIA Centaur® XP Immunoassay System (Siemens Healthineers, Erlangen, Germany).

2.3. Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 26 (IBM Corporation, Armonk, New York, NY, USA) and GraphPad Prism software version 9.3.1 (GraphPad Software, San Diego, CA, USA). All markers were tested using receiver operating characteristic (ROC) curves to verify their potential to forecast disease outcome in subjects suffering from concurrent COPD and COVID-19 infection. Furthermore, Pearson correlation was employed to evaluate some important correlations between laboratory parameters in COVID-19 with COPD group patients. A two-sided p-value of less than 0.05 was deemed statistically significant for every analysis at a 95% confidence interval.

2.4. Ethics Approval and Consent to Participate

The research was authorized by the Ethics Committee of Bangabandhu Sheikh Mujib Medical College (code: BSMMC/2021/1666) and followed the ethical standards stated in the 1964 Declaration of Helsinki (PP 1964) [21]. Written consent was taken from all participants before recruiting them in the study.

3. Results

3.1. Sociodemographic Characteristics and Comorbidities of the Study Participants

The participants' socio-demographic characteristics and comorbid diseases are summarized in Table 1. Each group had a greater proportion of male participants than female, though the gender distribution did not show any statistically significant variation ($\chi^2 = 3.711$, $p = 0.2944$). Both the COPD group and the COVID-19 with COPD group exhibited a reduced body mass index (BMI) when compared to the control and the COVID-19 group ($p < 0.0001$). Meanwhile, participants in the COVID-19 with COPD group had a higher incidence of comorbidities than those in the other groups. Hypertension (39.9%), diabetes (23.0%), coronary artery disease (CAD) (12.6%), and stroke (6.4%) were the most frequently occurring comorbidities in COVID-19 patients with COPD.

Table 1. Socio-demographic characteristics and comorbid diseases of the study groups.

Variables	Control (n = 208)	COPD (n = 392)	COVID-19 (n = 410)	COVID-19 + COPD (n = 562)	F/χ^2	p Value
Age (years)	48.40 ± 9.30	50.35 ± 9.87	49.09 ± 9.12	51.94 ± 9.78	2.247	0.0828
BMI (kg/m^2)	24.02 ± 2.01	21.74 ± 2.51 [a]	24.26 ± 1.94 [b]	21.97 ± 2.59 [a,c]	25.53	<0.0001
Gender						
Male	113 (54.3%)	239 (61.0%)	226 (55.1%)	323 (57.5%)	3.711	0.2944
Female	95 (45.7%)	153 (39.0%)	184 (44.9%)	239 (42.5%)		
Residency status						
Rural	74 (35.6%)	246 (62.8%)	167 (40.7%)	360 (64.1%)	92.41	<0.0001
Urban	134 (64.4%)	146 (37.2%)	243 (59.3%)	202 (35.9%)		
Smoking status						
Never	149 (71.6%)	158 (40.3%)	281 (68.5%)	266 (47.3%)		
Current	43 (20.7%)	44 (11.2%)	87 (21.2%)	36 (6.4%)	261.2	<0.0001
Former	16 (7.7%)	190 (48.5%)	42 (10.3%)	260 (46.3%)		
Comorbidities						
Hypertension	23 (11.1%)	124 (31.6%)	107 (26.1%)	224 (39.9%)	64.40	<0.0001
Diabetes	14 (6.7%)	66 (16.8%)	58 (14.1%)	129 (23.0%)	32.06	<0.0001
CAD	3 (1.4%)	44 (11.2%)	27 (6.6%)	71 (12.6%)	28.13	<0.0001
Stroke	0 (0%)	22 (5.6%)	11 (2.7%)	36 (6.4%)	19.24	0.0002

Data are represented as frequencies and percentages (for categorical variables) or mean ± standard deviation (for continuous variables). The Chi-squared (χ^2) test for categorical variables and the one-way analysis of variance (ANOVA) test for continuous variables were used to compare variables statistically among the study groups. $p < 0.05$ was considered statistically significant at 95% confidence interval. [a] $p < 0.05$, in comparison to the control group; [b] $p < 0.05$, in comparison to the COPD group; [c] $p < 0.05$, in comparison to the COVID-19 group. BMI, body mass index; CAD, coronary artery disease.

3.2. Clinical Manifestations among the Study Participants

Clinical manifestations among the study participants are shown in Table 2. Cough, fatigue, dizziness, sputum production, dyspnea, chest tightness, and wheeze were the most commonly occurring symptoms found in COPD patients. On the other hand, fever, cough, fatigue, smell or taste loss, abdominal pain, rhinorrhea, nasal congestion, sputum production, and dyspnea were the most frequently encountered clinical manifestations of the COVID-19 patients. In patients with concurrent COVID-19 and COPD, fever, cough, fatigue, dizziness, smell or taste loss, abdominal pain, diarrhea, sputum production, dyspnea, chest tightness, and wheeze were the more commonly observed symptoms as compared to those in either the COPD or the COVID-19 patients. The oxygen saturation level of less than 94% was more frequent among the COVID-19 patients with concurrent COPD than either the COPD or the COVID-19 patients.

Table 2. Clinical manifestations of the study participants.

Symptoms	COPD (n = 392)	COVID-19 (n = 410)	COVID-19 + COPD (n = 562)	χ^2	p Value
Fever (≥38.0 °C)	87 (22.2%)	398 (97.1%)	558 (99.3%)	901.0	<0.0001
Headache	124 (31.6%)	108 (26.3%)	159 (28.3%)	2.809	0.2455
Cough	225 (57.4%)	266 (64.9%)	403 (71.7%)	21.05	<0.0001
Fatigue	312 (79.6%)	211 (51.5%)	464 (82.6%)	129.0	<0.0001
Dizziness	269 (68.6%)	87 (21.2%)	412 (73.3%)	295.4	<0.0001
Nausea	14 (3.6%)	75 (18.3%)	107 (19.0%)	52.23	<0.0001
Vomiting	11 (2.8%)	43 (10.5%)	63 (11.2%)	23.52	<0.0001
Smell or taste loss	7 (1.8%)	275 (67.1%)	389 (69.2%)	495.1	<0.0001
Abdominal pain	0 (0%)	81 (19.8%)	173 (30.8%)	144.9	<0.0001
Diarrhea	0 (0%)	59 (14.4%)	158 (28.1%)	137.4	<0.0001
Rhinorrhea	0 (0%)	162 (39.5%)	194 (34.5%)	197.3	<0.0001
Nasal congestion	22 (5.6%)	81 (19.8%)	102 (18.1%)	38.68	<0.0001

Table 2. *Cont.*

Symptoms	COPD (n = 392)	COVID-19 (n = 410)	COVID-19 + COPD (n = 562)	χ^2	p Value
Sputum production	291(74.2%)	146 (35.6%)	424 (75.4%)	190.8	<0.0001
Sore throat	49 (12.5%)	83 (20.2%)	109 (19.4%)	10.22	0.0060
Hemoptysis	55 (14.0%)	11 (2.7%)	94 (16.7%)	47.96	<0.0001
Dyspnea	348 (88.8%)	162 (39.5%)	519 (92.3%)	410.0	<0.0001
Chest tightness	225 (57.4%)	77 (18.8%)	361 (64.2%)	213.1	<0.0001
Wheeze	334 (85.2%)	0 (0%)	503 (89.5%)	932.8	<0.0001
Peripheral edema	94 (24.0%)	0 (0%)	123 (21.9%)	111.7	<0.0001
Oxygen saturation (SpO_2) < 94%	218 (55.6%)	92 (22.4%)	353 (62.8%)	165.5	<0.0001

Data are represented as frequencies and percentages. Statistical comparison of categorical variables among study groups was performed using Chi-squared (χ^2) test. $p < 0.05$ was considered statistically significant at 95% confidence interval.

3.3. Clinical Laboratory Findings

3.3.1. Serum Electrolytes

The comparison of serum electrolyte levels between the study groups is shown in Figure 1. The serum sodium, potassium, chloride, calcium, magnesium, and bicarbonate levels in the control group were within the normal range, whereas these levels were significantly alerted in the other groups compared to the control group ($p < 0.0001$). Our results showed that serum sodium, potassium, chloride, calcium, and magnesium levels in the COVID-19 patients with COPD were significantly lower than in the COVID-19 patients ($p = 0.0009$, $p = 0.0001$, $p < 0.0001$, $p < 0.0001$, and $p < 0.0001$, respectively). The bicarbonate level in the COVID-19 patients with COPD was significantly higher compared to the COVID-19 patients and slightly lower compared to the COPD patients ($p < 0.0001$ and $p = 0.8530$, respectively). Interestingly, the serum chloride and magnesium levels were significantly lower in the COPD group than the COVID-19 with COPD group ($p < 0.0001$ and $p = 0.0004$, respectively).

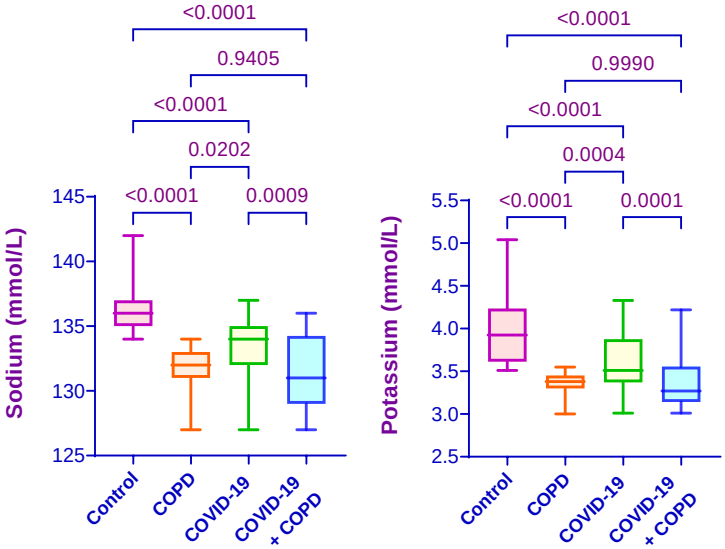


Figure 1. *Cont.*

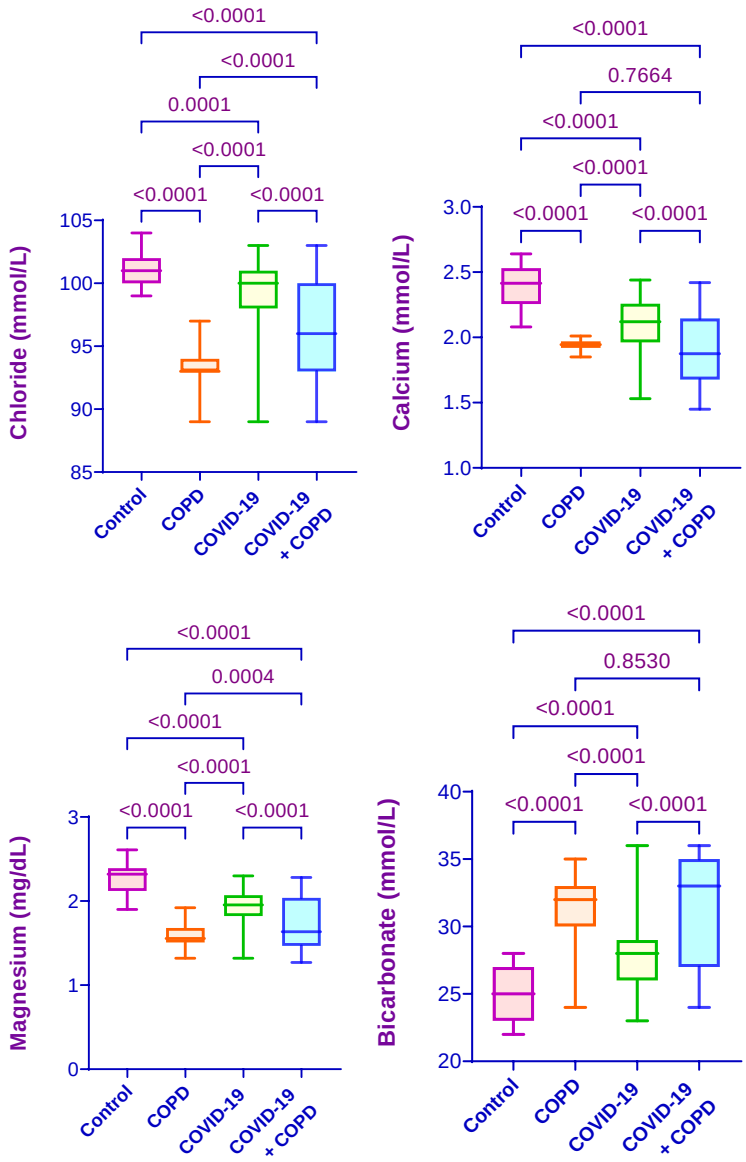


Figure 1. Comparison of serum electrolytes between study groups. Statistical comparison of variables among study groups was performed using one-way analysis of variance (ANOVA) followed by Tukey's test. $p < 0.05$ was considered statistically significant at 95% confidence interval.

3.3.2. Serum Biochemical Parameters

The comparison of serum biochemical markers between the study groups is shown in Figure 2. Among the biochemical parameters, we assessed NT-proBNP as a cardiovascular biomarker, bilirubin as a hepatic biomarker, and uric acid as a renal biomarker to investigate heart, liver, and kidney function. The NT-proBNP, bilirubin, and uric acid levels in the control group were within the normal range, whereas these levels were significantly alerted in the other groups compared to the control group ($p < 0.0001$). Our results also show that the levels of NT-proBNP and bilirubin were higher in the COVID-19 with COPD group compared to both the COPD ($p = 0.0106$ and $p = 0.9983$, respectively) and the COVID-19 group ($p < 0.0001$ and $p < 0.0001$, respectively). In contrast, the uric acid level was higher in the COPD group and lower in the COVID-19 group as compared to the COVID-19 with COPD group ($p < 0.0001$ and $p < 0.0001$, respectively).

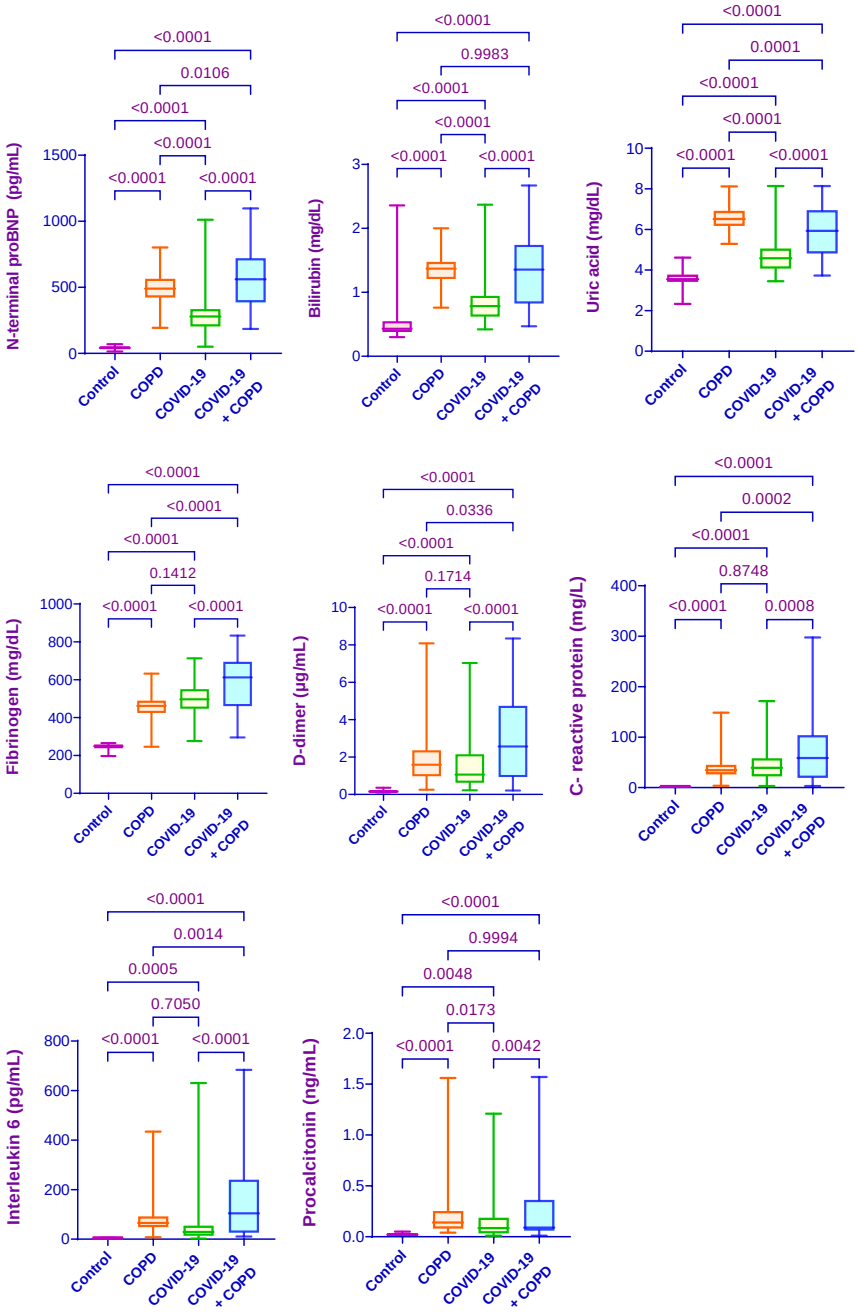


Figure 2. Comparison of serum biochemical markers between the study groups. Statistical comparison of variables among study groups was performed using one-way analysis of variance (ANOVA) followed by Tukey's test. $p < 0.05$ was considered statistically significant at 95% confidence interval.

Except for participants of the control group, the level of coagulation and inflammatory markers exceeded the reference range to varying degrees among the participants of all three patient groups. The levels of fibrinogen and D-dimer were higher in the COVID-19 with COPD group than either the COVID-19 group ($p < 0.001$ and $p < 0.001$ respectively) or the COPD group ($p < 0.001$ and $p = 0.0336$, respectively). Among the inflammatory markers, the levels of serum C-reactive protein and interleukin-6 levels were significantly higher in the COVID-19 with COPD group compared to both the COPD group ($p = 0.0002$ and $p = 0.0014$, respectively) and the COVID-19 group ($p = 0.0008$ and $p < 0.0001$, respectively). In contrast, the serum procalcitonin level was slightly increased in the COVID-19 with COPD group as compared to the COPD group ($p = 0.994$), but significantly increased when compared with the COVID-19 group ($p = 0.0042$).

To compare the biomarker status of patients with concurrent COVID-19 and COPD, we categorized them based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) system. Specifically, we grouped 237 patients with FEV1 of greater than or equal to 80% into GOLD 1, 185 patients with FEV1 less than 80% but greater than or equal to 50% into GOLD 2, 89 patients with FEV1 less than 50% but greater than or equal to 30% into GOLD 3, and 51 patients with FEV1 less than 30% into GOLD 4. Table 3 depicts clinical parameters for patients with concurrent COVID-19 and COPD categorized according to the GOLD system.

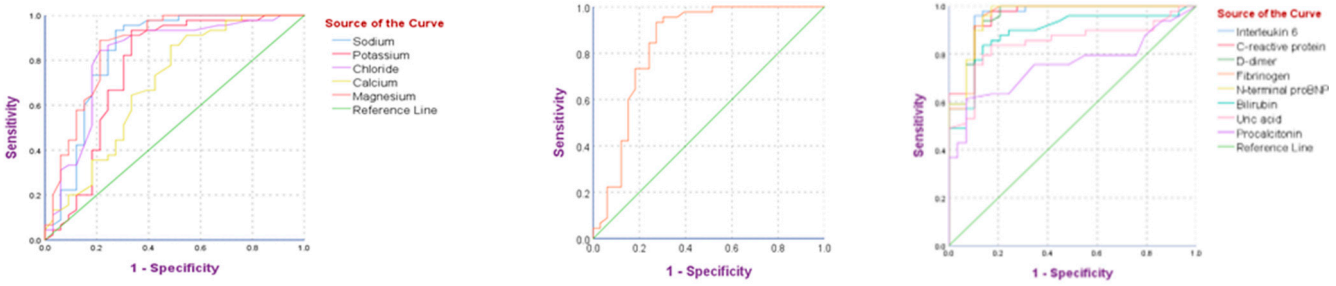
Table 3. Comparative analysis of clinical parameters among concurrent COVID-19 and COPD patients.

Clinical Parameters	GOLD-1 (n = 237)	GOLD-2 (n = 185)	GOLD-3 (n = 89)	GOLD-4 (n = 51)	p Value
Sodium	134.68 ± 0.81	130.39 ± 0.76 [a]	129.75 ± 1.32 [a,b]	128.44 ± 1.93 [a,b,c]	<0.0001
Potassium	3.63 ± 1.09	3.19 ± 1.20 [a]	3.09 ± 0.68 [a]	3.03 ± 0.53 [a,b]	<0.0001
Chloride	100.32 ± 2.06	95.17 ± 1.97 [a]	92.46 ± 4.14 [a,b]	90.11 ± 2.32 [a,b,c]	<0.0001
Calcium	2.15 ± 0.58	1.90 ± 0.23 [a]	1.59 ± 0.81 [a,b]	1.57 ± 0.70 [a,b]	<0.0001
Magnesium	2.05 ± 0.73	1.62 ± 0.42 [a]	1.41 ± 0.67 [a,b]	1.36 ± 0.33 [a,b]	<0.0001
Bicarbonate	27.98 ± 1.97	33.02 ± 2.35 [a]	34.58 ± 1.04 [a,b]	35.33 ± 0.17 [a,b]	<0.0001
NT-proBNP	352.06 ± 83.40	535.58 ± 121.18 [a]	774.08 ± 98.27 [a,b]	933.68 ± 157.53 [a,b,c]	<0.0001
Bilirubin	0.87 ± 0.25	1.57 ± 0.38 [a]	1.86 ± 0.64 [a,b]	2.33 ± 0.15 [a,b,c]	<0.0001
Uric acid	4.78 ± 1.15	6.20 ± 0.54 [a]	7.11 ± 0.85 [a,b]	7.84 ± 1.07 [a,b,c]	<0.0001
Fibrinogen	434.83 ± 164.24	642.03 ± 115.30 [a]	720.64 ± 172.92 [a,b]	792.01 ± 217.67 [a,b]	<0.0001
D-dimer	0.89 ± 1.72	3.14 ± 2.05 [a]	5.51 ± 1.47 [a,b]	7.45 ± 2.96 [a,b,c]	<0.0001
C-reactive protein	29.88 ± 26.11	74.67 ± 76.09 [a]	122.67 ± 75.42 [a,b]	218.48 ± 85. 64 [a,b,c]	<0.0001
Interleukin-6	41.83 ± 29.51	145.86 ± 78.94 [a]	357.38 ± 103.47 [a,b]	568.07 ± 142.63 [a,b,c]	<0.0001
Procalcitonin	0.04903 ± 0.04	0.1779 ± 0.09 [a]	0.5233 ± 0.13 [a,b]	0.9971 ± 0.32 [a,b,c]	<0.0001

Data are represented as mean ± standard deviation. The one-way analysis of variance (ANOVA) followed by Tukey's HSD test was used to compare variables statistically among the study groups. $p < 0.05$ was considered statistically significant at 95% confidence interval. NT-proBNP, N-terminal pro-brain natriuretic peptide. Note: [a] $p < 0.05$, in comparison to control group; [b] $p < 0.05$, in comparison to COPD group; [c] $p < 0.05$, in comparison to COVID-19 group.

3.3.3. Risk Factors Predicting Disease Severity in Subjects with Concurrent COIVD-19 and COPD

COVID-19 patients with concurrent COPD showing SpO_2 < 94% were assessed to have a severe illness, while those with $SpO_2 \geq 94\%$ were regarded to have a non-severe disease [22]. The area under the curve (AUC) of the receiver operating characteristics (ROC) curve was used to analyze the effectiveness of laboratory tests in differentiating the severity of COVID-19 with COPD comorbidity among the study subjects. The ROC curves of clinical parameters in predicting overall poor prognosis and severe progression are depicted in Figure 3, and the data derived from the ROC curve are provided in Table 4.



(**a**) (**b**) (**c**)

Figure 3. ROC curves demonstrate the comparative prediction accuracy of significant indicators. The area under the curve for sodium, potassium, chloride, calcium, magnesium (**a**), bicarbonate (**b**), and interleukin-6, C-reactive protein, D-dimer, fibrinogen, NT-proBNP, bilirubin, uric acid, and procalcitonin (**c**) were assessed to anticipate disease severity in COVID-19 patients with COPD.

Table 4. Recommended cutoff values of clinical parameters derived from ROC curve analysis for the prediction of severely progressed COVID-19 with concurrent COPD.

Clinical Parameters	AUC	Std. Error	*p* Value	95% Confidence Interval		Cutoff Value	Sensitivity	Specificity
				Lower Bound	Upper Bound			
Na^+	0.838	0.053	<0.001	0.734	0.941	132.5	94.3%	74.5%
K^+	0.763	0.062	<0.001	0.64	0.885	3.43	94.4%	66.1%
Cl^-	0.819	0.053	<0.001	0.714	0.924	96.5	84.8%	78.4%
Ca^{++}	0.693	0.063	<0.004	0.57	0.817	1.96	86.7%	51.2%
Mg^{++}	0.861	0.046	<0.001	0.77	0.951	1.67	88.6%	78.6%
HCO_3^-	0.838	0.053	<0.001	0.734	0.941	29.5	93.3%	72.3%
Interleukin-6	0.958	0.022	<0.001	0.915	1	51.375	95.9%	89.7%
C-reactive protein	0.954	0.023	<0.001	0.909	0.999	40.2	91.8%	89.7%
D-dimer	0.955	0.023	<0.001	0.909	1	1.645	93.9%	86.2%
Fibrinogen	0.954	0.025	<0.001	0.905	1	510	95.9%	86.2%
NT-proBNP	0.959	0.022	<0.001	0.916	1	511.2	89.8%	89.7%
Bilirubin	0.888	0.039	<0.001	0.812	0.964	1.1	83.7%	86.2%
Uric acid	0.847	0.045	<0.001	0.759	0.935	5.16	83.7%	82.8%
Procalcitonin	0.754	0.054	<0.001	0.647	0.860	0.085	75.5%	65.5%

$p < 0.05$ was considered statistically significant at 95% confidence interval. AUC, area under the curve; Ca^{++}, calcium; Cl^-, chloride; HCO_3^-, bicarbonate; K^+, potassium; Mg^{++}, magnesium; Na^+, sodium; NT-proBNP, N-terminal pro-brain natriuretic peptide; ROC, receiver operating characteristics.

Based on the results of ROC analysis, NT-proBNP, interleukin-6, D-dimer, C-reactive protein, and fibrinogen demonstrated excellent diagnostic performance, while bilirubin, magnesium, uric acid, sodium, bicarbonate, and chloride revealed good clinical utility. In contrast, potassium and procalcitonin showed reasonable diagnostic accuracy, and calcium displayed poor predictive accuracy.

3.3.4. Associations among Clinical Laboratory Markers in COVID-19 Subjects with and without COPD

Aberrant inflammatory cell activity and abnormal cytokine elevations are hallmarks of COPD [23]. Enhanced cytokine release is also linked to COVID-19-induced systemic inflammation [24]. It has been reported that both interleukin-6 and C-reactive protein are profoundly linked to the severity of COVID-19 infection in subjects with and without COPD [25]. According to our ROC analysis, interleukin-6 and C-reactive protein demonstrated excellent diagnostic efficacy in predicting COVID-19 disease severity in subjects with COPD. Therefore, we analyzed the correlation of interleukin-6 and C-reactive protein with other biochemical markers in the COVID-19 patients with COPD. Our results demonstrate that interleukin-6 is positively correlated with NT-proBNP (r = 0.8692, $p < 0.0001$), bilirubin (r = 0.9170, $p < 0.0001$), uric acid (r = 0.9044, $p < 0.0001$), fibrinogen (r = 0.8601, $p < 0.0001$), D-dimer (r = 0.9519, $p < 0.0001$), C-reactive protein (r = 0.9535, $p < 0.0001$), and procalcitonin (r = 0.8494, $p < 0.0001$). Similarly, C-reactive protein is also positively correlated with NT-proBNP (r = 0.8962, $p < 0.0001$), bilirubin (r = 0.9171, $p < 0.0001$), uric acid (r = 0.9175, $p < 0.0001$), fibrinogen (r = 0.8856, $p < 0.0001$), D-dimer (r = 0.9400, $p < 0.0001$), IL-6 (r = 0.9535, $p < 0.0001$), and procalcitonin (r = 0.7836, $p < 0.0001$) in the COVID-19 patients suffering with concurrent COPD (Table 5).

Table 5. Correlation of interleukin 6 and C-reactive protein with other clinical parameters in the COVID-19 patients with COPD.

Clinical Parameters	Pearson r	*p* Value
Interleukin 6 and NT-proBNP	0.8692	<0.0001
Interleukin 6 and bilirubin	0.9170	<0.0001
Interleukin 6 and uric acid	0.9044	<0.0001
Interleukin 6 and fibrinogen	0.8601	<0.0001
Interleukin 6 and D-dimer	0.9519	<0.0001
Interleukin 6 and C-reactive protein	0.9535	<0.0001
Interleukin 6 and procalcitonin	0.8494	<0.0001
C-reactive protein and NT-proBNP	0.8962	<0.0001
C-reactive protein and bilirubin	0.9171	<0.0001
C-reactive protein and uric acid	0.9175	<0.0001
C-reactive protein and fibrinogen	0.8856	<0.0001
C-reactive protein and D-dimer	0.9400	<0.0001
C-reactive protein and procalcitonin	0.7836	<0.0001

Pearson's linear correlation assay was performed. $p < 0.05$ was considered statistically significant. NT-proBNP, N-terminal pro-brain natriuretic peptide; r, Pearson's linear correlation coefficient.

4. Discussion

In the present study, we assessed the clinical value of serum electrolytes, biochemical, coagulation, and inflammatory markers in predicting the progression and severity of COVID-19 with concurrent COPD in Bangladeshi patients. Our results showed that serum sodium, potassium, and chloride levels in the COVID-19-patients with COPD were significantly lower than in the COVID-19 patients. Similar results were observed by Wu et al., though the differences were not significant in their study [14]. Another study by Gemicioglu et al. showed that the serum sodium and chloride levels were not significantly decreased in the COVID-19 patients with COPD compared to the COVID-19 patients, while the potassium level was significantly lower [15]. Our study also revealed that the COVID-19 patients with COPD had a significantly lower calcium level than the COVID-19 patients. This finding is congruent with that of Gemicioglu et al. [15]. The COVID-19 patients with COPD also had a significantly lower magnesium level than the COVID-19 patients but it was significantly higher than the COPD patients. The bicarbonate level in the COVID-19 patients with COPD was significantly higher compared to the COVID-19 patients but only slightly higher compared to the COPD patients.

Using ROC analysis, we investigated the diagnostic performance of electrolyte components for predicting COVID-19 disease severity. The AUC for electrolyte components varied between 0.693 and 0.861. We established cut-off values for sodium, potassium, chloride, calcium, magnesium, and bicarbonate as 132.5 mmol/L, 3.43 mmol/L, 96.5 mmol/L, 1.96 mmol/L, 1.67 mg/dL, and 29.5 mmol/L, respectively, as a predictor of severity in COVID-19 patients with COPD. Sadiq et al. and Sun JK et al. determined a cut-off value of 136.9 mmol/L for sodium and 2.035 mmol/L for calcium, respectively, in COVID-19 anticipated severity [26,27]. According to Chalela et al., a sodium level of less than 129.7 mmol/L had the greatest prognostic validity for mortality during COPD exacerbation [28]. Gumus et al. identified a magnesium cut-off value of 2.26 mg/dL as a significant indicator of recurrent COPD exacerbations [29].

Elevated NT-proBNP peptides have been linked to concurrent cardiac dysfunction in COVID-19 patients [30,31]. In our study, the serum NT-proBNP level in the COVID-19 with COPD group was significantly elevated compared to either the COVID-19 or COPD patients. Several studies revealed that elevated NT-proBNP levels in COVID-19 and COPD patients are related to an increased requirement for intensive care and a greater incidence of death [32–34]. In the current study, NT-proBNP demonstrated excellent diagnostic performance, with a cut-off value of 511.2 pg/mL for predicting severity in the COVID-19 patients with COPD based on the results of the ROC analysis. NT-proBNP was shown to be the best predictor for COVID-19 mortality in the hospital by Zwaenepoel et al., Gao

et al., and Wang et al., with the cutoff value of 415.5 pg/mL [35], 86.4 pg/mL [36], and 300 pg/mL [37], respectively. On the other hand, according to Wang et al. and Gehan et al., the best cutoff values for NT-proBNP were 935.0 ng/L [38] and 200 pmol/L [39], respectively, for assessing left ventricular dysfunction in COPD patients experiencing an acute exacerbation.

Bilirubin and uric acid are potential biomarkers for the interpretation of abnormalities in liver function and renal dysfunction, respectively [40,41]. In our study, the COVID-19 with COPD group patients showed a higher serum bilirubin concentration than either the COVID-19 or the COPD group patients, with the difference being significant only for the COVID-19 group patients but not for the COPD group patients; whereas the COVID-19 with COPD group patients had a uric acid level that was significantly greater than the COVID-19 group patients but significantly lower than the COPD group patients. These findings are congruent with those of previous reports by Wu et al. and Gemicioglu et al. [14,15]. In the present study, cut-off values of 1.1 mg/dL for bilirubin and 5.16 mg/dL for uric acid were shown to be useful in predicting the severity of the COVID-19 patients with COPD. Araç et al. and Koseki et al. revealed that bilirubin and uric acid levels exceeding 0.5 mg/dL and 3.7 mg/dL, respectively, were related to poor prognosis, including fatality in patients with COVID-19 [42,43]. Tian et al. and Bartziokas et al. reported that cutoff values of 15.07 µmol/L of total bilirubin and 6.9 mg/dL of uric acid were relevant for the assessment of mortality and impending COPD exacerbations [44,45].

Cardiovascular disease is the most common co-morbid condition and the second most prevalent reason for mortality for COPD patients, following respiratory failure [46]. Additionally, COVID-19 patients showed altered hemostasis with an increased tendency toward hypercoagulability [47]. The present study found significantly higher levels of plasma fibrinogen and D-dimer in the COVID-19 patients with COPD compared to the COVID-19 patients. These findings align with those of Gemicioglu et al., although the differences in their study were not statistically significant [15]. Another study by Wu et al. reported that the COVID-19 patients with COPD had a substantially greater portion of elevated D-dimer compared to the COVID-19 patients (65.9% vs. 29.3%) [14]. In our study, the ROC analysis revealed that fibrinogen and D-dimer have excellent diagnostic effectiveness for projecting aggravation in COVID-19 patients with COPD, with the cut-off values of 510 mg/dL and 1.645 µg/mL, respectively. Micco et al., Sui et al., and Murat et al. stated that cut-off values of 617 mg/dL [48], 528 mg/dL [49], and 546 mg/dL [50] for fibrinogen could be used to ascertain individuals with the pathologically severe type of COVID-19 upon emergency unit admission. In contrast, Mohan et al. proposed a cut-off value of 358 mg/dL for fibrinogen to assess the severity and acute exacerbation of COPD [51].

An elevated level of inflammatory biomarkers triggers a hyperinflammatory response in the host, resulting in a cytokine storm and eventually the severe pathophysiology of COPD and COVID-19 [24,52]. In our study, interleukin-6, C-reactive protein, and procalcitonin were significantly higher in the COVID-19 with COPD group patients than in the other groups. Wu et al. reported that 95.3% of the COVID-19 with COPD group had elevated C-reactive protein levels, compared to 82.4% of the COVID-19 group [14]. According to Aziz et al. and Chen et al., COVID-19 advancement has been linked to higher levels of interleukin-6 in critically and severely sick individuals [53,54]. COPD patients have higher levels of interleukin-6 and C-reactive protein in their peripheral blood circulation [55–57].

ROC analysis in our study revealed that interleukin-6 and C-reactive protein showed excellent prognostic effectiveness for projecting severity among patients who were suffering concurrently from COPD and COVID-19, with a cut-off value of 51.375 pg/mL and 40.2 mg/L, respectively. Findings from the studies of Herold et al., Wang et al., Luo et al., and Prasetya et al. noted a cutoff value of 80 pg/mL for interleukin-6 [58] and 64.79 mg/L [25], 41.4 mg/L [59], and 47 mg/L [60] for C-reactive protein, which were connected to an enhanced incidence of disease progression in COVID-19. On the contrary, the

recommended cut-off values of 25.7 mg/L [61] and 11.86 mg/L [62] for C-reactive protein by Demirtaş et al. and Pancirov et al., respectively, and 14.03 pg/mL [63] for interleukin-6 by Huang et al. were reported to predict pathogenicity in patients with stable and acute exacerbations of COPD.

In the present study, C-reactive protein and interleukin-6 levels were shown to have a significant positive association with NT-proBNP, bilirubin, fibrinogen, D-dimer, and procalcitonin levels in the COVID-19 with COPD group patients. The findings of Wang et al., Debi et al., and Caro-Codón et al. indicated a significant positive correlation of C-reactive protein with D-dimer, fibrinogen, and NT-proBNP in COVID-19 patients [64–66]. Kesmez Can et al. and Avila-Nava et al. found a significant positive correlation of interleukin-6 with bilirubin, fibrinogen, D-dimer, procalcitonin, and C-reactive protein in COVID-19 infection [67–70]. Recent studies by Wu et al. demonstrated that 75.7% of the COVID-19 patients with COPD and 67.5% of the COVID-19 patients among the participants had a procalcitonin level of $\geq$0.5 ng/mL, although the difference was not statistically significant [14]. Based on our ROC analysis, a procalcitonin cut-off value of 0.085 ng/mL was found to be beneficial in assessing the severity of COPD in individuals infected with COVID-19. To evaluate the diagnostic accuracy and foretell prognosis in patients with COVID-19, Liu et al. recommend a cut-off of 0.07 ng/mL for procalcitonin in serum [24]. Ergan et al. showed that a procalcitonin level of less than 0.25 ng/mL at admission and throughout follow-up indicates the exclusion of a bacterial etiology for COPD exacerbation [71].

In patients with concurrent COVID-19 and COPD, serum levels of sodium, potassium, chloride, calcium, and magnesium were significantly lower in the GOLD 4 group compared to other GOLD groups. The levels of bicarbonate, NT-proBNP, bilirubin, fibrinogen, D-dimer, C-reactive protein, interleukin-6, and procalcitonin were significantly higher in GOLD 4 than in the other three GOLD groups of concomitant COVID-19 patients with COPD.

In this research, there were two limitations to note. Our research was based on a single-center study. A multicenter approach may allow for a more comprehensive assessment of the clinical characteristics of COVID-19 patients with preexisting COPD comorbidity. This study did not include any subsequent follow-up information. Therefore, large-scale prospective cohort studies are required to assess the effect of post-COVID-19 infection impairment in COPD patients.

5. Conclusions

The present study showed that preexisting COPD is related to the progression and poor outcomes of COVID-19. Patients with concurrent COPD and COVID-19 showed more pronounced alterations in the levels of sodium, calcium, NT-proBNP, bilirubin, fibrinogen, D-dimer, interleukin-6, C-reactive protein, and procalcitonin. Our results suggest that NT-proBNP, interleukin 6, D-dimer, C-reactive protein, and fibrinogen have the most potential as parameters for differentiating severe cases of COVID-19 with concurrent COPD. These findings would be beneficial for the physicians to understand the clinical value of laboratory biomarkers to assess the severity of COVID-19 with COPD comorbidity and, subsequently, to develop and implement an effective therapeutic approach for the management of these patients.

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