Focusing on Asthma and Chronic Obstructive Pulmonary Disease with COVID-19

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Abstract

Introduction: We aimed to evaluate clinical and laboratory findings of hospitalized asthma and chronic obstructive pulmonary disease (COPD) patients with COVID-19 and demonstrate that they have different symptoms and/or laboratory results and outcomes than COVID-19 patients with comorbidity (CoV-com) and without comorbidity (CoV-alone).

Methodology: The data of the demographic, clinical, laboratory findings of hospitalized CoV-alone, asthma, COPD patients with COVID-19 (CoV-asthma, CoV-COPD, respectively), and CoV-com were analyzed.

Results: Out of 1082 patients hospitalized for COVID-19, 585 (54.1%) had CoV-alone, 40 (3.7%) had CoV-asthma, 46 (4.3%) had CoV-COPD and 411 (38%) had CoV-com. Cough, shortness of breath, fever and weakness were the most common four symptoms seen in all COVID-19 patients. Shortness of breath, myalgia, headache symptoms were more common in CoV-asthma than the other groups (p < 0.001, p < 0.01, p < 0.05 respectively). Sputum was more common in CoV-COPD than other groups (p < 0.01). COPD group most frequently had increased values, different from the other groups with CRP>5ng/mL in 91.3%, D-dimer > 0.05mg/dL in 89.1%, troponin > 0.014micg/L in %63.9, INR>1.15 in 52.2%, CK-MB>25U/L in 48.5%, PT>14s in 40.9% of patients (p < 0.05, p < 0.001, p < 0.001, p < 0.001, p < 0.05, p < 0.001, respectively). NT-ProBNP was found to have the highest AUC value and the best differentiating parameter for CoV-asthma from CoV-alone. Typical CT findings were present in 44.4% of CoV-alone, 57.5% of CoV-asthma, 28.3% of CoV-COPD and 38.9% of CoV-com groups. CoV-COPD and CoV-com patients died more frequently than other groups (17.8%, 18.5%).

Conclusions: CoV-asthma and CoV-COPD patients might have different symptoms and laboratory parameters than other COVID-19 patients which can guide the physicians.

Key words: Asthma; COPD; COVID-19 symptoms; biochemical parameters; RT-PCR; Chest CT.

J Infect Dev Ctries 2021; 15(10):1415-1425. doi:10.3855/jidc.14611

(Received 01 January 2021 – Accepted 13 June 2021)

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Introduction

During the coronavirus disease 2019 (COVID-19) pandemic, two major chronic respiratory diseases; asthma and chronic obstructive pulmonary disease (COPD) patients who had risk for COVID-19 were evaluated by various researchers [1,2]. According to a study performed in the UK, asthma was about 14.5% out of admitted 20133 COVID-19 cases and other chronic pulmonary diseases were 17.7% [3]. Richardson et al. [4] reported 9% asthma and 5.4% COPD comorbidity in 5700 hospitalized COVID-19 patients in US. On the contrary only 1.5% of the cases reported to have COPD in China [5]. Clinical data of COVID-19 patients with or without a comorbidity displayed fever, cough, fatigue, and shortness of breath when they were admitted to the hospitals [3-7]. Fever, cough, fatigue, and shortness of breath symptoms could also be seen in COPD or in asthma exacerbation with viral or bacterial infections [1,8]. Physicians need to perform other laboratory tests (real-time reverse transcriptase polymerase chain reaction (RT-PCR), hematological and biochemical analysis, radiological
examination) in order to evaluate signs or symptoms to distinguish the exacerbation of asthma and COPD from severe adult respiratory syndrome of coronavirus-2 (SARS CoV-2) infection. But the value of these tests and the differences of these tests from the COVID-19 cases without comorbidity (CoV-alone), in asthma and COPD patients with COVID-19 (CoV-asthma, CoV-COPD, respectively) were not fully studied.

Hematological and biochemical data of COVID-19 patients revealed that patients might have elevated or decreased parameters, usually depending on the comorbidity or the severity of the disease [9]. The detection of patients’ RNA with RT-PCR was needed for the accurate diagnosis of COVID-19. However, the sensitivity of the nasopharyngeal swabs varied from 45% to 67% depending on the days since symptom onset [10]. Yet, outside Wuhan, He et al. [11] found that RT-PCR and chest computed tomography (CT) results had comparable sensitivity. Chest CT was implied to offer the greatest sensitivity of up to 99% for detecting COVID-19 in a systematic review by Xu et al. [12].

The symptoms of COVID-19 patients could be confused with asthma and COPD exacerbation symptoms. False negative PCR results could be encountered to differentiate COVID-19 cases from asthma and COPD exacerbations. The differences of these groups’ laboratory parameters and symptoms in CoV-asthma and CoV-COPD patients from the CoV-alone and CoV-com were not studied in detail. The aim of this study was to evaluate the clinical and laboratory findings and outcome of CoV-asthma, CoV-COPD, CoV-alone and CoV-com and reveal the differences and similarities between groups to guide the physicians who provide care for asthma and COPD patients with COVID-19.

Methodology

This study is a single center, retrospective and non-interventional, cross-sectional study focused on the clinical and laboratory data in real life conditions, aiming to observe the adult hospitalized COVID-19 patients, with and without comorbidity, with asthma and with COPD.

Ethical approval of this study was obtained by the Ethics Committee of the Medical Faculty of our University, (05/21/2020; No: 83045809-604.01.02-63860). The study was conducted between 22 May 2020 to 22 August 2020 with recovery of the first 1082 cases data of adult COVID-19 patients hospitalized in the University Hospital and met all inclusion and exclusion criteria.

Patients

The physicians collected all hospitalized patients’ data consecutively whose patient’s medical record to select the study patients and to avoid bias patients still hospitalized were excluded.

Admission criteria to hospital for COVID-19 cases in this time period were having CT findings suspicious for COVID-19 pneumonia with or without initial RT-PCR positivity finding with COVID-19 symptoms or having positive RT-PCR test with oxygen saturation rate below 90%. CoV-asthma, CoV-COPD, CoV-com and CoV-alone were included in the study. All patients were monitored by a specialist of pulmonary diseases and/or infectious diseases and/or internal medicine. The inclusion criteria were as follows:

- Age of COVID-19 diagnosis: ≥18 years hospitalized and discharged or died.
- Diagnosis of COVID-19 was validated via chest CT findings with PCR positivity or having positive RT-PCR test with oxygen saturation rate below 90%.
- Diagnosis of asthma was validated with a pulmonology specialist physician and with the historical diagnosis in the Governmental System with Global Initiative for Asthma (GINA) 2020 criteria (www.ginasthma.org).
- Diagnosis of COPD was validated with a pulmonology specialist physician and with the historical diagnosis in the Governmental System with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2021 criteria (www.goldcopd.org).
- Asthma and COPD patients with and without other comorbidities were enrolled.

Exclusion criteria were as follows:

- Patients still hospitalized but not yet discharged from the hospital were excluded.
- Patients with asthma and COPD hospitalized in the non-COVID part of the hospital or without PCR positivity or without typical COVID chest CT findings were excluded.

Procedures and measures

A “Case Report Form” was prepared by the authors. Data included the information written on patients’ routine medical records file. The collected previous and current medical history data were included: the referral information; socio-demographics (height, body weight, body mass index, education status and location of primary residence); etiology; medical history (reasons for application, concomitant diseases); risk factors (smoking, occupation); first diagnostic tests during admission to the hospital before COVID-19 treatment
including PCR, complete blood count (CBC), biochemical tests and CT; and the outcome.

Combined pharyngeal and nasopharyngeal swab samples were obtained for RT-PCR assay. All biochemical parameters, CBC and coagulation tests were measured at Central Biochemistry Laboratory of our Medical Faculty.

The chest CT examinations were reported in accordance with the Radiological Society of North America (RSNA) Consensus Statement on Reporting Chest CT Findings Related to COVID-19 [13].

Medical treatments for COVID-19 were initiated and proceeded with respect to our Ministry of Health guidelines. Underlying treatment of patients with asthma and COPD were written from the patients’ medical record and checked from the governmental system.

**Statistical analysis**

In the biostatistical analysis of the study, the criteria discussed were defined by mean, standard deviation, frequency, and percentage values. Chi-Square and Fisher exact tests were used to compare frequencies and percentages between the groups. For comparison of variable averages with normal distribution; “one-way analysis of variance” (One-Way ANOVA) in comparing more than two group averages and in order to interpret the differences between subgroups in variables with significant differences with ANOVA, the post-hoc “Scheffe” test was also used in binary comparisons of subgroups. If necessary, nonparametric “Kruskal-Wallis one-way analysis of variance” and post hoc Dunn's methods were used in appropriate experimental fictions (depending on the number of subjects and homogeneity control). In the study cases, receiver operating characteristic (ROC) curve analysis was used to investigate the performance of important criteria in determining disease diagnosis. A p-value below 0.05 was expressed as significant. All statistical analyses were carried out using the Statistical Product and Service Solutions (SPSS) v. 21.0 (IBM, Armonk, NY, USA) package program.

## Results

1136 COVID-19 patients were hospitalized in our hospital during the study time. 54 COVID-19 patients hospitalized who didn’t meet inclusion criteria were excluded. A total of 1082 newly diagnosed COVID-19 treatment-naïve adult patients with COVID-19 were included. The patients were categorized into four groups; COVID-19 patients without any comorbidities (N: 585), patients with comorbidities (N: 411), patients

### Table 1. Sociodemographic data.

|                | CoV-alone | CoV-Asthma | CoV-COPD | CoV-Com | P value |
|----------------|-----------|------------|----------|---------|---------|
| N (%)          | 585 (54)  | 40 (3.7)   | 46 (4.3) | 411 (38) | 0.001***|
| Female N (%)   | 243 (41.5)| 29 (72.5)  | 15 (32.6)| 206 (50.1)|         |
| Male N (%)     | 342 (58.5)| 11 (27.5)  | 31 (67.4)| 205 (49.9)|         |
| Age (Year) (mean ± SD) | 51.8 ± 15.8 (cd***)| 56.1 ± 15.0 (c****)| 68.5 ± 9.7 (abd***)| 61.7 ± 15.8 (ac****)| 0.000***|
| ≥ 65y N (%)    | 110 (32.8)| 13 (32.5)  | 29 (63)  | 183 (44.5)| 0.000***|
| Occupation     | N (%)     | N (%)      | N (%)    | N (%)    |         |
| Unemployed     | 38 (20.5) | 0 (0.0)    | 4 (22.2) | 28 (19.6)|         |
| Office         | 13 (7.0)  | 1 (10.0)   | 0 (0.0)  | 5 (3.5)  |         |
| Health worker  | 18 (9.7)  | 2 (20.0)   | 0 (0.0)  | 14 (9.8) | 0.023*  |
| Self employed  | 61 (33.0) | 3 (30.0)   | 4 (22.2) | 47 (32.9)|         |
| House wife     | 27 (14.6) | 4 (40.0)   | 1 (5.6)  | 18 (12.6)|         |
| Retired        | 28 (15.1) | 0 (0.0)    | 9 (50.0) | 31 (21.7)|         |
| BMI (kg/m²)    | 27.5 ± 6.4| 28.9 ± 5.3 | 27.3 ± 3.5| 28.3 ± 6.4| 0.455   |
| BMI > 30 N (%) | 43 (24.9) | 12 (36.4)  | 6 (23.1) | 40 (34.5)|         |
| Smoking habit  | N (%)     | N (%)      | N (%)    | N (%)    |         |
| Non- smoker    | 124 (67.4)| 25 (62.5)  | 5 (12.8) | 80 (65.0)| 0.000***|
| Ex-smoker      | 42 (22.8) | 14 (35.0)  | 23 (59.0)| 35 (28.5)|         |
| Smoker         | 18 (9.8)  | 1 (2.5)    | 11 (28.2)| 8 (6.5)  |         |
| Comorbidity    | N (%)     | N (%)      | N (%)    | N (%)    |         |
| Hypertension   | 15 (37.5) | 23 (51.1)  | 218 (53.0)| 0.171   |
| Diabetes       | 13 (32.5) | 29 (64.4)  | 129 (31.4)| 0.000***|
| Cancer (last 2 years) | 2 (5.0) | 7 (15.6) | 63 (15.3) | 0.274 |
| Cardiac insuf  | 2 (5.0)   | 6 (13.3)   | 38 (9.2) | 0.417   |
| Other cardiac  | 4 (10.0)  | 11 (24.4)  | 65 (15.8)| 0.179   |
| Renal problem  | 0 (0.0)   | 6 (13.3)   | 41 (10.0)| 0.079   |
| Others         | 7 (17.5)  | 9 (20.0)   | 178 (43.3)| 0.000***|

In this table, the superscripts a, b, c and d show significant differences to study groups of CoV-alone, CoV-Asthma, CoV-COPD and CoV-com, respectively, and the following asterisks (*) notation show the significance level of the differences (*p < 0.05, **p < 0.01, ***p < 0.001) in one-way ANOVA result.
with COVID-19 and asthma (N: 40), and patients with COVID-19 and COPD (N: 46).

**Sociodemographic and clinical data**

Sociodemographic data of the patients’ groups were shown in Table 1. Only a female patient in the CoV-asthma group, at the age of 28, had no comorbidity, was neither obese nor a smoker.

Cough, shortness of breath, fever and weakness were most common four symptoms seen in all COVID-19 patients (Table 2).

**Hematological and biochemical laboratory results**

Hematological and biochemical laboratory parameters of the groups were shown in Table 3.

Hematologic parameters below or above the reference value of the groups at admission to hospital were shown in Table 4.

In CoV-alone patients, a positive moderate correlation was found between the hospitalization time and C-reactive protein (CRP) (r = 0.502, p < 0.001) and lactate dehydrogenase (LDH) levels (r = 0.505, p < 0.001). While there was a negative correlation between intensive care unit (ICU) length of stay and albumin (r = -0.432, p < 0.001), it was found that there was a positive correlation between ICU length of stay and N-terminal brain natriuretic peptide (NT-proBNP) (r = 0.462, p < 0.001), urea (r = 0.548, p < 0.001), CRP (r = 0.444, p < 0.001), LDH (r = 0.547, p < 0.001), and D-dimer levels (r = 0.435, p < 0.001).

In COVID-19 patients with comorbidities, only CRP levels were positively correlated with ICU length of stay (r = 0.484, p < 0.001).

In patients with CoV-COPD, a very strong positive correlation was found between ICU length of stay and NT-proBNP levels (r = 0.988, p < 0.01).

In CoV-asthma patients, SpO2 at first admission was negatively correlated with the hospitalization time (r = -0.573, p < 0.001), LDH levels (r = -0.447, p < 0.01) and ICU length of stay (r = -0.442, p < 0.01). ICU length of stay was also positively correlated with urea (r = 0.518, p < 0.001) and CRP levels (r = 0.654, p < 0.001) in these patients.

NT-proBNP levels were found to be elevated in CoV-asthma patients rather than CoV-alone patients, and NT-proBNP were significant in differentiating CoV-asthma patients from CoV-alone patients according to ROC analysis. The NT-proBNP value higher than 1092.1 pg/mL indicates that the patient has CoV-asthma rather than COVID-19 alone, with 71% sensitivity and 87.50% specificity.

**PCR and Computed tomography (CT) findings**

At hospital admission PCR positivity rate of CoV-alone, CoV-asthma and CoV-COPD and CoV-com groups were 51.1%, 47.5%, 32.6% and 45.3%, respectively, in the total group positivity rate was 48%. The second PCR tests added very few positivity rates; +8.2% for CoV-alone, +5.0% for CoV-asthma, +8.7% for CoV-COPD and +9.0% for CoV-com group. For the total group, the added value is 8.4%.

CT findings at admission to hospital were shown in Table 5.

**Treatments and clinical outcomes**

COVID-19 treatment and clinical outcomes are shown in Table 6.

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**Table 2. Clinical Data Results at admission to hospital.**

| Symptoms N (%) | CoV-alone N:585 | CoV-asthma N:40 | CoV-COPD N: 46 | CoV-Com N:411 | P Value |
|---------------|----------------|----------------|---------------|---------------|---------|
| Fever and/or chills | N (%) | N (%) | N (%) | N (%) | N (%) |
| Cough | 215 (36.8) | 19 (47.5) | 17 (37.0) | 154 (37.5) | 0.604 |
| Shortness of breath | 131 (22.4) | 23 (57.5) | 20 (43.5) | 130 (31.6) | 0.004** |
| Weakness, fatigue | 109 (18.6) | 10 (25.0) | 11 (23.9) | 72 (17.5) | 0.523 |
| Sputum | 15 (2.6) | 5 (12.5) | 6 (13.0) | 18 (4.4) | 0.003** |
| Headache | 38 (6.5) | 5 (12.5) | 1 (2.2) | 13 (3.2) | 0.015* |
| Taste/smell disturb | 6 (1.0) | 1 (2.5) | 0 (0.0) | 5 (1.2) | 0.729 |
| Myalgia | 41 (7.0) | 9 (22.5) | 2 (4.3) | 27 (6.6) | 0.002** |
| Nasal congestion | 1 (0.2) | 0 (0.0) | 0 (0.0) | 3 (0.7) | 0.495 |
| Diarrhea / Vomiting | 40 (6.8) | 1 (2.5) | 2 (4.3) | 23 (5.6) | 0.596 |
| Pulse rate (mean±SD) | 88.5 ± 15.6 | 87.4 ± 15.2 | 90.8 ± 23.1 | 90.5 ± 21.7 | 0.060 |
| SBP (mean±SD) | 127.4 ± 10.3(4) | 127.3 ± 11.6(4) | 142.3 ± 5.2(4) | 128.5 ± 30.3 | 0.001*** |
| DBP (mean±SD) | 80.3 ± 5.2 | 78.0 ± 6.2 | 86.8 ± 8.7(4) | 73.7 ± 25.9(4) | 0.002** |

SBP: systolic blood pressure; DBP: diastolic blood pressure. In this table, the superscripts a, b, c and d show significant differences to study groups of CoV-alone, CoV-Asthma, CoV-COPD and CoV-com, respectively, and the following asterisks (*) notation show the significance level of the differences (*p<0.05, **p<0.01, ***p<0.001) in one-way ANOVA result.
### Table 3. Hematological and biochemical parameters of the subjects included in the study.

| Variables               | CoV-alone | CoV-Asthma | CoV-COPD | CoV-Com | P      |
|-------------------------|-----------|------------|----------|---------|--------|
| SpO₂ (%) (FM)           | 94.1      | 94.26      | 92.57    | 6.50    | 0.236  |
| SpO₂ (%) (LM)           | 91.83***   | 91.00      | 88.16**  | 9.16    | 0.000***|
| WBC (10⁹/L)             | 7.26***    | 8.69       | 10.60*** | 5.12    | 0.000***|
| RBC (10⁹/L)             | 4.67***    | 4.54       | 4.12***  | 0.79    | 0.001***|
| HGB (g/dL)              | 13.32***   | 12.78      | 11.62*** | 2.12    | 0.000***|
| Hct (%)                 | 38.98***   | 38.64      | 35.45*** | 6.21    | 0.000***|
| PLT (10⁹/L)             | 219.04***  | 85.53      | 277.01***| 163.00  | 0.000***|
| Neut (%)                | 4.74***    | 4.79**     | 7.94***  | 4.18    | 0.000***|
| Lymph (%)               | 1.50       | 1.34       | 1.42     | 0.77    | 0.000***|
| Mono (%)                | 0.58***    | 0.34       | 0.26     | 1.06*** | 0.158***|
| EOS (%)                 | 0.07       | 0.21       | 0.08     | 0.09    | 0.012***|
| NLR                     | 4.47***    | 4.24       | 8.09***  | 7.25    | 0.000***|
| PLR                     | 180.13***  | 112.55     | 242.08** | 161.53  | 0.000***|
| Glucose (mg/dL)         | 119.99***  | 120.79     | 135.75   | 60.82   | 0.000***|
| Urea (mg/dL)            | 32.29***   | 22.31      | 56.39*** | 4.86    | 0.000***|
| Creatinine (mg/dL)      | 0.96***    | 0.92       | 1.40     | 1.08    | 0.001***|
| Total Protein (g/dL)    | 7.16       | 7.13       | 6.82     | 0.78    | 0.000***|
| Albumin (g/dL)          | 4.13***    | 4.10*      | 3.66***  | 0.61    | 0.000***|
| Tot. Bilirubin (mg/dL)  | 0.56       | 0.41       | 0.58     | 0.48    | 0.000***|
| Direct Bilirubin (mg/dL)| 0.23       | 0.14       | 0.25     | 0.35    | 0.000***|
| Uric Acid (mg/dL)       | 4.73***    | 4.81*      | 6.21***  | 0.51    | 0.000***|
| CRP (mg/L)              | 48.94***   | 45.47      | 77.44    | 81.42   | 0.000***|
| Na (mmol/L)             | 137.67     | 138.16     | 135.89   | 6.92    | 0.000***|
| K (mmol/L)              | 4.34***    | 4.41       | 4.75***  | 0.75    | 0.000***|
| Cl (mmol/L)             | 99.00      | 99.34      | 97.84    | 7.41    | 0.000***|
| Ca (mg/dL)              | 8.92       | 9.03       | 8.80     | 0.62    | 0.000***|
| AST (U/L)               | 34.07      | 33.63      | 49.60    | 77.62   | 0.000***|
| ALT (U/L)               | 32.70      | 39.25      | 34.45    | 60.45   | 0.000***|
| LDH (U/L)               | 278.25***  | 298.03     | 314.48   | 188.73  | 0.000***|
| GGT (U/L)               | 46.00      | 29.81      | 59.63    | 82.19   | 0.000***|
| CK (U/L)                | 192.48     | 221.16     | 148.64   | 198.21  | 0.000***|
| CK-MB (U/L)             | 28.72      | 33.59      | 36.30    | 25.75   | 0.000***|
| Ferritin (mg/ml) (FM)   | 389.83***  | 355.94     | 423.64   | 624.83***| 0.000***|
| Troponin T (µg/L)       | 0.03       | 0.03       | 0.06     | 0.15    | 0.000***|
| PT (s)                  | 13.25***   | 13.12      | 14.72    | 4.04    | 0.000***|
| PT activity (%)         | 85.41***   | 15.65      | 75.33*   | 21.26   | 0.000***|
| INR                     | 1.11*      | 1.00       | 1.24     | 0.35    | 0.000***|
| APTT (s)                | 25.29**    | 25.30      | 27.46    | 4.84    | 0.000***|
| Fibrinogen (mg/ml) (FM) | 458.35     | 461.23     | 478.52   | 173.05  | 0.000***|
| D-Dimer (mg/ml) (FM)    | 1.87**     | 5.25       | 3.22***  | 5.03    | 0.000***|
| Pro-BNP (pg/mL)         | 2302.26    | 11306.6    | 13923.7  | 6748.71 | 0.000***|
| Urea (mg/dL)            | 42.26***   | 35.33      | 74.64    | 74.17***| 0.000***|
| Creatinine (mg/dL) (HM) | 1.11***    | 25.59      | 1.72***  | 1.62    | 0.000***|
| CRP (mg/L)              | 75.46***   | 85.52      | 97.84    | 118.99***| 0.000***|
| LDH (U/L)               | 395.27***  | 210.77     | 347.12   | 580.12***| 0.000***|
| Ferritin (mg/ml) (HM)   | 550.29***  | 632.13     | 597.84   | 2512.25 | 0.000***|
| Fibrinogen (mg/ml) (HM) | 556.25     | 626.36     | 588.09   | 188.72  | 0.000***|
| D-Dimer (mg/ml) (HM)    | 3.84***    | 6.34       | 7.98***  | 12.70   | 0.000***|

WBC: white blood cell; RBC: red blood cell; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; CK-MB: creatine kinase-MB; CRP: C-reactive protein; LDH: lactate dehydrogenase; GGT: gamma-glutamyl transferase; TIBC: Total iron binding capacity; NT-proBNP: N-terminal pro-Brain natriuretic peptide; Na: sodium; K: potassium; Cl: chlorine; Ca: calcium; RBC: red blood cell; Hb: haemoglobin; EOS: eosinophil; NLR: Neutrophil - lymphocyte ratio; PLT: Platelet; PLR: Platelet-lymphocyte ratio; MLR: monocyte-lymphocyte ratio; FPR: fibrinogen-platelet ratio; FNR: fibrinogen-neutrophil ratio; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio; FM: First measurement; LM: Lowest measurement; HM: Highest measurement. In this table, the superscripts a, b, c and d show significant differences to study groups of CoV-alone, CoV-Asthma, CoV-COPD and CoV-com, respectively, and the following asterisks (*) notation show the significance level of the differences (*p < 0.05, **p < 0.01, ***p < 0.001) in one-way ANOVA result.
### Table 4. Hematologic parameters below or above the reference value of the groups at admission to hospital.

| Parameters        | CoV-alone | CoV-Asthma | CoV-COPD | CoV-Com | P     |
|-------------------|-----------|------------|----------|---------|-------|
|                   | Count     | %          | Count    | %        | Count  | %         | Count    | %         |       |
| NLR               | 570       | 98.4       | 40       | 100.0    | 46      | 100.0     | 397      | 97.3      | 0.323 |
| NLR>0.6           | 9         | 1.6        | 0        | 0.0      | 0       | 0.0       | 11       | 2.7       |       |
| PLR               | 484.92    | 86.5       | 36       | 90.0     | 33      | 71.7      | 334      | 81.9      | 0.015*|
| PLR<484.92        | 78        | 12.5       | 4        | 10.0     | 13      | 28.3      | 74       | 18.1      |       |
| PLR               | 44.57     | 7          | 1        | 2.5      | 1       | 2.2       | 15       | 3.7       | 0.083 |
| Glucose           | 148       | 51.9       | 18       | 47.4     | 16      | 38.1      | 55       | 29.7      | 0.000***|
| Urea<49 mg/dL     | 529       | 90.9       | 34       | 85.0     | 30      | 65.2      | 280      | 68.5      | 0.000***|
| Creatinine<1.2 mg/dL | 511          | 87.7      | 35     | 87.5     | 28      | 60.9     | 291      | 71.1      | 0.000***|
| NLR               | 7         | 12.5       | 5        | 12.5     | 18      | 39.1      | 118      | 28.9      |       |
| Total protein<8.3 g/dL | 275  | 97.9       | 35      | 97.2     | 40      | 97.6      | 177      | 97.8      | 0.995 |
| Albumin<5.2 g/dL  | 292       | 99.7       | 37      | 100.0    | 43      | 100.0     | 195      | 100.0     | 0.816 |
| T.bilirubin<1.2 mg/dL | 288       | 95.4       | 38      | 100.0    | 41      | 93.2      | 179      | 89.5      | 0.022*|
| D.bilirubin<0.3 mg/dL | 264       | 87.7       | 35      | 92.1     | 37      | 84.1      | 157      | 78.5      | 0.023*|
| Uric acid<7 mg/dL | 251       | 93.7       | 31      | 83.8     | 33      | 80.5      | 131      | 77.5      | 0.000***|
| AST<40 U/L        | 458       | 78.7       | 31      | 77.5     | 31      | 67.4      | 318      | 77.8      | 0.368 |
| ALT<41 U/L        | 124       | 21.3       | 9       | 22.5     | 15      | 32.6      | 91       | 22.2      |       |
| LDH<250 U/L       | 324       | 56.0       | 23      | 57.5     | 22      | 47.8      | 195      | 48.0      | 0.078 |
| GGT<60 U/L        | 216       | 80.6       | 31      | 86.1     | 29      | 76.3      | 134      | 76.1      | 0.466 |
| CK>190 U/L        | 204       | 82.6       | 28      | 82.4     | 30      | 83.3      | 136      | 86.1      | 0.819 |
| CK<190 U/L        | 43        | 17.4       | 6       | 17.6     | 6       | 16.7      | 22       | 13.9      |       |
| Ferritin<400 mg/L | 378       | 67.6       | 31      | 81.6     | 32      | 71.1      | 241      | 61.8      | 0.039*|
| Troponin<0.014 µg/L | 200      | 84.7       | 25      | 83.3     | 13      | 36.1      | 79       | 50.6      | 0.000***|
| PT<14 s           | 243       | 84.4       | 31      | 83.8     | 26      | 59.1      | 137      | 72.5      | 0.000***|
| INR<1.15          | 225       | 78.1       | 28      | 75.7     | 21      | 47.7      | 123      | 65.1      | 0.000***|
| APTT>32 s         | 274       | 95.1       | 37      | 100.0    | 37      | 84.1      | 164      | 87.2      | 0.001***|

**Note:** NLR: Neutrophil – lymphocyte ratio; PLR: Platelet-lymphocyte ratio; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; CK-MB: creatine kinase-MB; LDH: lactate dehydrogenase; GGT: gamma-glutamyl transpeptidase; PT: prothrombin time; APTT: activated partial thromboplastin time. The unit of these parameters are given in Table 3. *p<0.05; **p<0.01; ***p<0.001.
Length of stay in hospital and in intensive care unit (ICU) was remarkably higher in CoV-COPD group than the others ($p < 0.001, p < 0.01$ respectively).

Underlying treatment of asthma group at admission to hospital consisted of 25 patients (62%) on inhaled corticosteroid (ICS)/long-acting β2-agonist (LABA) (one of them also received one biologic or placebo), 5 patients (12.5%) on ICS and as needed short acting β2 agonist (SABA) and 10 patients (25%) on as needed SABA. COPD patients underlying treatments were very different than asthma; 15 (30.6%) used LABA/long-acting muscarinic antagonist (LAMA), 7 (15.2%) used ICS/LABA, 10 (21.7%) used ICS/LABA/LAMA, 5 (10.9%) SABA/short acting muscarinic antagonists (SAMA) and 10 (30.6%) LAMA.

**Discussion**

The results revealed that 3.7% of hospitalized COVID-19 adult patients were asthma patients and 4.3% were COPD patients. Cough was the one most common of the three symptoms seen in all groups. Shortness of breath was the most common symptom for CoV-asthma and CoV-COPD groups. The augmentation of these symptoms might be in asthma and COPD exacerbations. COPD group had most frequently increased CRP, D-dimer, troponin, INR, CK-MB and PT values than the reference range and different than the other groups ($p < 0.05, p < 0.01, p < 0.001, p < 0.001, p < 0.05, p < 0.01$ respectively). NT-proBNP was found to have the highest AUC value and the best differentiating parameter for CoV-asthma from CoV-alone. PCR positivity is gold standard but may not be positive in half of the COVID-19 patients. Different CT patterns and worst outcome seen in CoV-COPD were also important findings of our study.

**Sociodemographic and clinical data**

Mean age was over 50 in all groups. But CoV-COPD group had a higher mean age, higher smoking rate and contained a higher male percentage than the

| Table 5. Computed Tomography Findings at admission to hospital*. |
|---------------------------------------------------------------|
| N (%)  | CoV-alone | CoV-Asthma | CoV- COPD | CoV-Com | p value |
| Multi focal N (%) | 347 (76.9) | 26 (81.3) | 20 (76.9) | 225 (77.3) | 0.991 |
| Ground glass opacities | 377 (97.4) | 27 (96.4) | 22 (100.0) | 244 (98.8) | 0.533 |
| Crazy paving pattern | 180 (46.5) | 15 (55.6) | 12 (54.5) | 131 (53.0) | 0.356 |
| Consolidation | 201 (51.9) | 10 (37.0) | 8 (36.4) | 169 (68.4) | 0.000** |
| Halo sign | 156 (40.3) | 10 (37.0) | 7 (31.8) | 98 (39.8) | 0.870 |
| Reverse halo sign | 60 (15.5) | 4 (14.8) | 1 (4.5) | 47 (19.0) | 0.287 |
| Pleural effusion | 34 (8.8) | 1 (3.7) | 5 (22.7) | 48 (19.4) | 0.000** |
| Lymphadenopathy | 45 (11.6) | 4 (14.8) | 8 (36.4) | 76 (30.8) | 0.000** |
| Tromboembolism | 4 (1.0) | 0 (0.0) | 0 (0.0) | 1 (0.4) | 0.916 |
| Emphysema | 48 (12.5) | 2 (7.4) | 9 (40.9) | 45 (18.4) | 0.000** |
| Typical COVID* | 260 (44.4) | 23 (57.5) | 13 (28.3) | 160 (38.9) | 0.000*** |

*Only patients having CT in the hospital system were analyzed by two radiology specialists. **Typical COVID CT sign; Multifocal GGO of rounded morphology with or without consolidation or visible intra lobular lines (“crazy-paving”), reverse halo sign or other findings of organizing pneumonia (20). *p < 0.05, **p < 0.01, ***p < 0.001.

| Table 6. COVID-19 treatment and clinical outcomes. |
|-------------------------------------------------|
| COVID treatment and outcome N (%) | CoV-alone N: 585 | CoV-Asthma N: 40 | CoV- COPD N:46 | CoV-Com N:411 | p value |
| Hydroxychloroquine | 473 (81.0) | 33 (82.5) | 40 (88.9) | 336 (81.8) | 0.623 |
| Ritonavir+Lopinavir | 26 (4.5) | 1 (2.5) | 1 (2.2) | 18 (4.4) | 0.842 |
| Oseltanivir | 280 (47.9) | 27 (67.5) | 19 (42.2) | 224 (54.5) | 0.019* |
| Favipiravir | 277 (47.4) | 20 (50.0) | 28 (62.2) | 222 (54.0) | 0.082 |
| Tocilizumab | 66 (11.3) | 7 (17.5) | 6 (13.3) | 41 (10.0) | 0.487 |
| Systemic Corticosteroid | 24 (4.1) | 3 (7.5) | 4 (8.9) | 49 (11.9) | 0.000*** |
| Azithromycin | 344 (58.9) | 30 (75.0) | 26 (57.8) | 258 (62.8) | 0.164 |
| Enoxaparin | 373 (63.9) | 29 (72.5) | 36 (80.0) | 293 (71.3) | 0.020* |
| Nasal O2 | 311 (53.3) | 30 (75.0) | 34 (75.6) | 247 (60.1) | 0.001*** |
| O2 with reservoir | 12 (2.1) | 3 (7.5) | 3 (6.7) | 20 (4.9) | 0.492* |
| High flow O2 | 7 (1.2) | 1 (2.5) | 0 (0.0) | 5 (1.2) | 0.774 |
| Intensive care unit admission | 47 (8.0) | 6 (15.0) | 13 (28.9) | 102 (24.8) | 0.000*** |
| Intubation | 17 (2.9) | 2 (5.0) | 8 (17.8) | 41 (10.0) | 0.000*** |
| Home discharged | 535 (91.6) | 33 (86.8) | 30 (64.4) | 301 (73.2) | 0.000*** |
| Other unit discharged | 26 (4.5) | 4 (10.5) | 8 (17.8) | 34 (8.3) | 0.000*** |
| Death | 23 (3.9) | 1 (2.6) | 8 (17.8) | 76 (18.5) | 0.000*** |

*p < 0.05, **p < 0.01, ***p < 0.001.
other groups. Higher age, male gender and smoking were demonstrated as major risk factors in COVID-19 [7,9]. All patients in CoV-COPD group had at least one other comorbidity and more than half had diabetes and/or hypertension. These comorbidities were present for CoV-com group and also were demonstrated as major comorbidities of COVID-19 in other studies [4,5,7,9]. Having comorbidity or obesity or being smoker/ex-smoker and/or aging were present in 95.5% of the CoV-asthma group. Only one patient at the age of 28 who was female had no comorbidity, no obesity, no smoking but in regard to the underlying treatment it was revealed that she used salbutamol when needed. Using ICS might decrease the risk of COVID-19 as reported by Liu et al. [14].

The most common symptoms in admission to the hospital, in CoV-alone group were cough and fever, in CoV-asthma group were shortness of breath, cough and fever, in CoV-COPD group were shortness of breath and cough, in CoV-com group were cough, shortness of breath and fever in our study. These results demonstrate that the difficulty of diagnosis of COVID-19 in asthma and COPD patients as they usually had these symptoms when they were uncontrolled or had an exacerbation of their diseases. This problem has already been pointed [1,15]. For the differential diagnosis, performing PCR is important but may be negative at the first visit. Physicians should know if a patient has COVID-19 before performing spirometry or nebulized treatments or non-invasive ventilation that produces aerosols [15-17]. Higher levels of fatigue, myalgia and headache seen in our asthma patients may point to COVID-19 rather than asthma exacerbation and this must be evaluated with future research. The difference of sputum percentage seen in CoV-COPD patients from the other groups was clinically non-significant as it is one of the major symptoms of COPD. CoV-COPD patients had significantly lower level of SpO₂, higher level of SBP than the other groups. More severe disease and worse outcome in COPD and COVID-19 patients were also demonstrated in other studies [1,18].

**Hematological and biochemical findings**

Researchers demonstrate that COVID-19 patients have abnormalities in some hematological and biochemical parameters depending on the stage and severity of the diseases [19]. The worst outcome was seen in CoV-COPD group and had increased CRP, D-dimer, troponin, INR, CK-MB, and PT values than the reference range. Physicians who think that their COPD patient may have COVID-19 must ask for PCR and also request these biochemical parameters that may guide them as a diagnostic tool for COVID-19. Elevated levels of these biochemical results may warrant multiple PCR tests or thorax CT if the first PCR test remains negative.

We found that there was a positive correlation between ICU length of stay and NT-proBNP, urea, CRP, LDH, and D-dimer levels in CoV-alone patients. Fan et al. [20] identified LDH as a discriminator between ICU and non-ICU patients in their series of COVID-19 patients from Singapore. Increased LDH is common in COVID-19 patients in the ICU setting and indicates a poor outcome in other studies [20-22]. Liu et al [22] mentioned that COVID-19 patients with lymphopenia, higher urea, LDH at admission pointed poor outcomes, particularly for older patients and those with comorbid conditions. In the current study, unlike other groups, increased NT-proBNP levels are directly related to the increase in ICU and indicate a poor outcome in CoV-COPD patients. In CoV-com patients only CRP levels were positively correlated with ICU length of stay.

COVID-19 is a systemic infection with significant impacts on the hematopoietic system and hemostasis. Yang et al. [23] demonstrated that elevated age and neutrophil-lymphocyte ratio (NLR) can be considered as independent prognostic biomarkers for indicating the poor clinical outcomes in COVID-19 patients. Lymphopenia can be considered to be a cardinal laboratory sign, and is potentially prognostic [22,24]. Qin et al. [19] reported that there is an increase in NLR in patients with severe disease compared to those without. In the current study, we found that platelet, white blood cell count, monocytes, neutrophils, NLR, platelet-lymphocyte ratio (PLR) as inflammatory parameters were higher in CoV-COPD patients than CoV-alone patients. It was concluded that especially hematologic-inflammatory indices such as NLR and PLR might be useful markers for monitoring CoV-COPD patients.

Only 5% of CoV-asthma patients had cardiac insufficiency but NT-proBNP was found to have the highest AUC value and the best differentiating parameter for CoV-asthma from CoV-alone. This finding might guide physicians who provide care for asthma patients during the COVID-19 pandemic and must be evaluated in further research.

**PCR and CT findings**

Our initial PCR positivity rate was lower than other researchers’ reports (25,26). These percentages were the initial PCR results at admission to hospital. However, it was important for the first distinguishing
diagnosis from the exacerbation of asthma and COPD. Negative initial RT-PCR test in asthma and COPD patients might be attributed easily to the exacerbation of these diseases.

Our findings of CT were similar to other researchers’ findings [6,25,27]. Most common imaging findings in chest CT were ground glass opacities (GGOs), whether isolated or coexisting with consolidations, in bilateral and sub-pleural distribution in a systematic review comprising 4410 cases [27]. Many radiological findings didn’t differ significantly in CoV-alone, CoV-asthma and CoV-COPD groups in our study. The prevalence of emphysema was, unsurprisingly, higher in CoV-COPD patients (17.4%) than the other groups. Zhang et al. [28] also found that severe COVID-19 patients with COPD had different patterns on the CT when compared to patients without comorbidity.

Treatments and clinical outcome

Medical treatments were used in accordance with the Ministry of Health guidelines in that time period. CoV-COPD patients more frequently used favipiravir and enoxaparin, they were admitted to ICU and intubated more frequently than the other groups. Death rate was also higher than the other groups. Poor outcome of COPD patients has already been demonstrated in other studies [1,18].

In regard to the underlying treatments of patients; Wang L et al found that using SABA was associated with hospitalization in asthma and COVID patients after multivariate analysis [29]. One quarter of CoV-asthma patients used SABA as needed only without ICS, 75% had treatments with ICS or ICS/LABA. Using SABA without ICS was not yet recommended in GINA as it increases the risk of exacerbation (www.ginasthma.org). But these patients didn’t use oral steroid during their hospitalization as they didn’t have asthma exacerbation at the same time. None of them used regular oral corticosteroids that can alter immune response to viral infections. There was one CoV-asthma patient from a phase 3 study using a biologic or placebo.

Treatment of COPD patients showed that they were from different groups of the GOLD Guideline (www.goldcopd.org). They were also very severe COPD patients on triple therapies.

The worst outcome was in CoV-COPD group as 28.9% of CoV-COPD patients admitted to ICU and 17.8% died. The Global Alliance Against Chronic Respiratory Diseases (GARD) editorial described chronic respiratory diseases as important causes of death and advised special collaboration and partnership, sharing resources and experiences, which are essential to control the pandemic [30].

Limitations of this Study

First, the study population included only hospitalized patients within a certain time period of one center, while the study population of asthma and COPD groups was small. Second, asthma and COPD patients did not have spirometry results as we did not recommend doing routine pulmonary function tests during the COVID-19 pandemic, especially for COVID-19 patients [16]. However, their diagnoses were checked by the national health system data written by the physicians. Also, we didn’t have a control group of asthma and COPD patients with exacerbation without COVID-19 to compare with the study groups; CoV-asthma and CoV-COPD.

Conclusions

Cough, shortness of breath, fever and weakness were most common four symptoms seen in all COVID-19 patients. Shortness of breath, myalgia, and headache symptoms were more common in CoV-asthma than the other groups. Sputum was more common in CoV-COPD than other groups.

For COPD patients suspected of having COVID-19, physicians must ask for a PCR test and also requesting CRP, D-dimer, troponin, INR, CK-MB and PT levels might guide them for the differential diagnosis between COVID-19 and exacerbation of their diseases.

NT-proBNP was found to have the highest AUC value and the best differentiating parameter for CoV-asthma from COV-alone.

The outcome of CoV-COPD was remarkably worse than the other groups.

Authors’ Contribution

Designed the study: BG, HU, SB, RK, SK, SS, SD, PA, AD, MAK, FT. Performed the study: BG, HU, SB, RK, SK, SS, SD, PA, AD, MAK, FT. Contributed important reagents / collected data: BG, HU, SB, RK, SK, SS, SD, PA, AD, MAK, FT. Analyzed data: AD, SD, BG, HU. Concept, supervision, literature search: BG, HU. Drafted, wrote, reviewed and approved the submission of the manuscript: BG, HU, SB, RK, SK, SS, SD, PA, AD, MAK, FT.

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Conflict of interests: No conflict of interests is declared.