ORIGINAL RESEARCH

DOI: 10.4274/globecc.galenos.2023.44153
Glob Emerg Crit Care 2023;2(2):47-55

Impact of the Presence of Chronic Respiratory Diseases on the Mortality of Hospitalized Patients with COVID-19 Pneumonia: A Single Center Experience

Işıl Kibar Akıllı[1], Müge Bilge[2]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pulmonology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Turkey

Abstract

Objective: The influence of coexisting chronic respiratory diseases (CRDs) on the prognosis of patients with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection is debatable. This study aimed to investigate the consequences of CRDs on the mortality of coronavirus disease-2019 (COVID-19) pneumonia inpatients.

Materials and Methods: Hospitalized patients with confirmed SARS-CoV-2 infection were included. The data were derived from electronic medical records retrospectively and patients with and without CRD past history were analyzed concerning in-hospital mortality.

Results: In 1.529 patients with COVID-19 pneumonia, 54 (58.1%) were male and the mean age was 61.18±15.03 years. A total of 245 individuals were diagnosed with CRD. The CRD group consisted of asthma (128 cases, 52.24%), chronic obstructive pulmonary disease [(COPD), 79 cases, 32.37%], lung cancer (15 cases, 6.14%), obstructive sleep apnea syndrome (12 cases, 4.91%), and interstitial lung disease [(ILD), 11 cases, 4.5%]. Mean age, female gender, respiratory rate, and supplemental oxygen requirement were significantly higher in the CRD group ($p=0.001$; $p<0.01$ for all). In-hospital mortality was 11.8% (29 cases) in the CRD group and 8.4% (108 cases) in the group without CRD. In univariate analysis, there was no significant difference in-hospital mortality between the two groups ($p>0.05$). Although CRD patients had a similar mortality ratio compared with non-CRD patients on multivariate logistic analysis [odds ratio (OR): 0.262, 95% confidence interval (CI): 0.071-0.968; $p=0.045$]; COPD and ILD subgroups exhibited 2.1 fold (OR: 2.1, 95% CI: 1.13-3.92; $p=0.017$) and 3.87 fold (OR: 3.87, 95% CI: 1.015-14.772; $p=0.033$) increased risk of in-hospital mortality respectively.

Conclusion: Even though patients with COVID-19 pneumonia and CRDs do not have a higher mortality rate, it is crucial to closely monitor these patients because of the elevated mortality risk associated with COPD and ILD.

Keywords: COPD, asthma, OSAS, interstitial lung disease, COVID-19 pneumonia, mortality

Introduction

Specifying characteristics linked to poor prognosis and identifying vulnerable individuals with higher susceptibility are crucial in the struggle against coronavirus disease-2019 (COVID-19). Age, male gender, comorbidities, and metabolic abnormalities are risk factors associated with poor prognosis in COVID-19 [1]. Following cardiovascular disease and diabetes mellitus (DM) as the leading causes of mortality among the comorbidities, chronic respiratory diseases (CRDs) have been witnessed. It has been demonstrated that prognosis varies among CRDs as well [2,3]. There are still conflicting data about the prevalence of CRDs among COVID-19 patients [4,5].

According to a study comparing hospitalized COVID-19 and influenza cases in France, despite CRDs being reported less frequently in COVID-19 than influenza cases, patients with CRDs had more severe COVID-19 development risk and a higher mortality rate [6]. Previous studies were reporting that

Address for Correspondence: Işıl Kibar Akıllı, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pulmonology, İstanbul, Turkey
Phone: +90 212 414 71 71 **E-mail:** isilkibar@yahoo.com **ORCID-ID:** orcid.org/0000-0002-4969-4512
Received: 20.06.2023 **Accepted:** 13.07.2023

the prevalence of CRD was higher in Middle East respiratory syndrome (MERS) than in severe acute respiratory syndrome (SARS); the prevalence of CRD in influenza was higher than COVID-19, and there was increased susceptibility for MERS coronavirus (CoV) infection in smokers and chronic obstructive pulmonary disease (COPD) cases [6,7]. COPD is defined as a risk factor for severe disease and high mortality in COVID-19 cases [8], whereas asthma is not defined as a risk factor for severe disease and mortality [9].

The issue remains unclear today although numerous researches have been published on the impact of CRD on COVID-19 prognosis. Therefore, the purpose of our study was to determine the association between COVID-19 and CRD and how CRD affects the prognosis of patients with SARS-CoV-2 pneumonia.

Materials and Methods

This retrospective single-center cohort study was carried out at Prof. Dr. Murat Dilmener Emergency Hospital in İstanbul on 1.938 confirmed COVID-19 patients who were recruited from September 1st, 2020 to December 31st, 2020. Based on the instructions from the World Health Organization (WHO), SARS-CoV-2 infection was determined [10]. They were administered in accordance with the Republic of Turkey Ministry of Health's COVID-19 treatment plan [11]. This research was approved by the Local Ethics Committee, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (2021/164/2021-06-40/15.03.2021).

Data of patients were extracted retrospectively from the inpatient electronic medical records. Demographic characteristics, clinical variables, coexisting medical conditions, laboratory parameters, chest computed tomography (CT) scan results, and clinical outcomes were recorded. Patients were classified as having moderate and severe illness [12]. On the chest CT scan, the pulmonary involvement was categorized as low, moderate, and severe [13]. The research consisted of 1.529 inpatients (>18 years) with COVID-19 pneumonia.

Comorbidities were classified as hypertension, DM, coronary artery disease (CAD), valvular heart disease, congestive heart failure (CHF), atrial fibrillation, peripheral artery disease, cerebrovascular disease, neurodegenerative disease, dyslipidemia, chronic kidney disease, rheumatic disease, malignancy, and CRD. The following diseases were considered CRDs: asthma, COPD, lung cancer, obstructive sleep apnea syndrome (OSAS), and interstitial lung disease (ILD). Patients were divided into groups based on whether they had a CRD or not. The primary endpoint of this trial was defined as in-hospital mortality.

Statistical Analysis

Analyses were performed using the Number Cruncher Statistical System program. Continuous variables were presented by mean ± standard deviation or median (min-max). Categorical variables are expressed as numbers (%). Comparison of characteristics between the two groups was performed using the student t-test and Mann-Whitney U test for continuous variables. Categorical variables were compared using the Pearson chi-square test and Fisher's exact test. Multivariable logistic regression analysis was performed to investigate risk factors for mortality. Receiver operating characteristic (ROC) analysis and Binomial exact test were used to evaluate the mortality. A p value <0.05 was considered significant.

Results

One thousand five hundred and twenty nine adults, 889 male (58.1%) and 640 female (41.96%) with a mean age of 61.18±15.03 were included in the cohort (age >18 years) between September 1, 2020 and December 31, 2020. One thousand five hundred and twenty nine patients, had comorbidities mainly including hypertension (737, 48.2%), DM (512, 33.5%), and CAD (221, 14.5%). 245 people (16%) had underlying CRDs. In CRDs, the most common respiratory diseases were asthma (128 cases - 52.24%), COPD (79 cases - 32.37%), and lung cancer (15 cases - 6.14%). In overall patients, asthma 8.37% (128/1529), COPD 5.2% (79/1529), lung cancer 1% (15/1.529), OSAS 0.8% (12/1.529), and ILD 0.7% (11/1.529) were found. (Tables 1, 2). Table 1 summarizes general information and baseline patient characteristics, Table 2 presents the distribution of CRDs.

The mean respiratory rate (breaths per minute) was 21.06±5.23, the oxygen saturation (SpO_2) while receiving oxygen was 94.33±1.95, and oxygen support was 4.95±7.14 L/per min.

Based on established categories 830 (54.3%) patients were classified as moderate and 699 (45.7%) patients as severe. Pulmonary involvement in chest CT scans was low in 329 (21.5%), moderate in 738 (48.3%), and severe in 462 (30.2%) patients. In-hospital death was found to be 9% (137/1.529 cases) and overall intensive care unit (ICU) admission was 11% (168/1.529) in this study. The duration of the length of stay was 11.52±6.81 days (range, 1-64 days).

The clinical characteristics of patients with and without CRD were compared. The mean age was 64.69±13.78 in patients with CRD vs. 60.51±15.16 in patients without CRD (p=0.001; p<0.01). The gender difference was statistically significant in two groups; female gender was higher in patients with CRD (p=0.001; p<0.001). Hypertension, CHF, and malignancy were more common in patients with CRD (p=0.008; p=0.001; p=0.001; p<0.01; respectively). No significant difference was observed between the two groups concerning other comorbidities (p>0.05). Respiratory rate and supplemental

oxygen requirement was significantly higher in the CRD group (p=0.001; p<0.01 for both). There were no significant differences in body temperature, SpO_2 while receiving oxygen support, pulse rate, or diastolic/systolic blood pressure between patients with and without CRD (p>0.05) (Table 1).

Total cholesterol, high-density lipoprotein, cholesterol and D-dimer concentrations were significantly higher in the CRD group (p values, respectively 0.031; 0.008, and, 0.008). On the other hand, calcium, aspartate aminotransferase, alanine aminotransferase, albumin, lactate dehydrogenase (LDH), and ferritin levels were observed to be significantly lower in those with CRD than in another group (p values, respectively 0.003; 0.002; 0.019; 0.012; 0.041; 0.002). Other laboratory test results revealed no differences between patients with and without CRD (p>0.05). Although cases with CRDs had a significantly higher disease severity status than the other group (p=0.003;

Table 1. Baseline characteristics of the patients

		All patients (n=1529)	CRD (n=245)	No CRD (n=1284)	p
Age, years	Mean ± SD	61.18±15.03	64.69±13.78	60.51±15.16	[a]0.001**
	Median (min-max)	61 (20-103)	65 (32-97)	60 (20-103)	
Sex, n (%)	Female	640 (41.9)	128 (20.0)	512 (80.0)	[b]0.001**
	Male	889 (58.1)	117 (13.2)	772 (86.8)	
Physical findings					
Body temperature, °C	Mean ± SD	36.92±0.67	36.86±0.63	36.93±0.68	[c]0.316
	Median (min-max)	36.7 (35.9-40)	36.7 (35.9-40)	36.7 (36-39.4)	
Systolic blood pressure, mmHg	Mean ± SD	126.80±18.60	126.57±18.16	126.85±18.69	[a]0.830
	Median (min-max)	126 (70-208)	127 (81-182)	126 (70-208)	
Diastolic blood pressure, mmHg	Mean ± SD	70.65±10.46	70.42±9.95	70.7±10.55	[a]0.699
	Median (min-max)	70 (37-123)	70 (44-99)	70 (37-123)	
Heart rate, per minute	Mean ± SD	83.14±15.20	82.65±13.68	83.23±15.48	[a]0.580
	Median (min-max)	82 (45-206)	82 (48-130)	82 (45-206)	
Respiratory rate, breaths per minute	Mean ± SD	21.06±5.23	22.01±5.13	20.87±5.23	[c]0.001**
	Median (min-max)	20 (12-40)	22 (12-40)	20 (12-40)	
SpO_2, under oxygen support, mean	Mean ± SD	94.33±1.95	94.37±1.85	94.32±1.97	[a]0.718
	Median (min-max)	94 (86-99)	94 (89-99)	94 (86-99)	
Oxygen support, L/per min	Mean ± SD	4.95±7.14	6.11±7.56	4.73±7.04	[c]0.001**
	Median (min-max)	3 (0-30)	4 (0-30)	2 (0-30)	
Comorbidities, n (%)		1151 (75.3)	-	-	-
Hypertension		737 (48.2)	137 (56)	600 (46.7)	0.008**
Diabetes mellitus		512 (33.5)	88 (36)	424 (33)	[b]0.379
Coronary artery disease		221 (14.5)	37 (15)	184 (14.3)	[b]0.753
Atrial fibrillation		87 (5.7)	17 (6.9)	70 (5.5)	[b]0.357
Congestive heart failure		94 (6.1)	28 (11.4)	66 (5.1)	[b]0.001**
Valvular heart disease		11 (0.7)	1 (0.4)	10 (0.8)	[d]1.000
Peripheral artery disease		10 (0.7)	3 (1.2)	7 (0.5)	[d]0.207
Cerebrovascular disease		54 (3.5)	5 (2)	49 (3.8)	[b]0.168
Neurodegenerative disease		62 (4)	13 (5.32)	49 (3.82)	[b]0.460
Dyslipidemia		73 (4.8)	9 (3.7)	64 (5)	[b]0.378
Cerebrovascular disease		54 (3.5)	5 (2)	49 (3.8)	[b]0.168
Neurodegenerative disease		62 (4)	13 (5.32)	49 (3.82)	[b]0.460
Chronic kidney disease		71 (4.6)	11 (4.50)	60 (4.68)	[b]0.901
Rheumatic disease		27 (1.8)	8 (3.3)	19 (1.5)	[d]0.063
Malignancy		76 (5.0)	25 (10.2)	51 (4)	[b]0.001**

[a]Student's t-test, [b]Pearson chi-square test, [c]Mann-Whitney U test, [d]Fisher's exact test, *p<0.05, **p<0.01, SpO_2: Oxygen saturation, SD: Standard deviation, CRD: Chronic respiratory disease, min-max: Minimum-maximum range

p<0.01), regarding chest CT score, there was no difference between CRD cases and those without CRD (p=0.707; p>0.05) (Table 3). Table 3 displays laboratory results, chest CT results, disease severity status, and patient outcomes.

Among 1.529 patients with COVID-19 of, 137 (9%) died during hospitalization. In-hospital mortality was found to be 11.8% (29/245) in patients with CRD, 8.4% (108/1.284) in patients without CRD; ICU admission was 14.3% (35/245) in patients with CRD, 10.4% (133/1.284) in cases with no CRD. In-hospital mortality and ICU admission did not significantly differ between CRD and non-CRD patients (p>0.05). It was discovered that patients with CRD had greater hospital length of stay (13.69±9.17 vs. 11.11±6.17 days, p= 0.001; p<0.01) (Table 3).

When the variables considered to have an effect on mortality in the univariate analysis were assessed with backward stepwise logistic regression analysis, the model was determined to be significant (p=0.001; p<0.01). According to the results of multivariate analysis, age, respiratory rate, fibrinogen, C-reactive protein (CRP), LDH, and the presence of malignancy significantly affect mortality (p values, respectively 0.001; 0.001; 0.049; 0.021; 0.002; 0.013; p<0.05). The coefficient of determination of the model was 96.5%, the sensitivity was 58.5% and the specificity was 99.1%. CRDs were not associated with the risk of in-hospital death. The presence of malignancy multiplied the risk of death by more than 6.43 [%95 confidence interval (CI): 1.483-27.940] (Table 4). Table 4 provides univariate ve multivariate regression analysis for in-hospital mortality in the study population.

In ROC analysis, respiratory rate presented the highest AUROC (0.916; 95% CI: 0.893-0.935), followed by age (0.731; 95% CI: 0.698-0.763) and CRP (0.669; 95% CI: 0.633-0.703) in predicting mortality (Table 5, Figure 1). The binomial exact test figured out the respiratory rate in predicting mortality as a superior reference, compared with age, fibrinogen, and CRP (p=0.001). Similarly taking age as a reference, age was superior compared with fibrinogen in predicting mortality (p=0.045).

Multivariable logistic regression model analysis revealed no increase in death in patients with both SARS-CoV-2 pneumonia and CRD (OR: 0.26; 95% CI: 0.071-0.968; p=0.045). When CRDs were divided into five distinct disorders, several CRDs had a considerable risk of in-hospital mortality. Patients with COPD and ILD showed 2.1-fold [odds ratio (OR): 2.1, 95% CI: 1.13-3.92; p=0.017] and 3.87-fold (OR: 3.87, 95% CI: 1.015-14.772; p=0.033) higher risk of in-hospital mortality of COVID-19 pneumonia compared with those without. Although OSAS had a remarkable OR of 2.047, it was not statistically significant (p=0.293). Asthma and lung cancer were not associated with in-hospital mortality in COVID-19 patients (p>0.05) (Table 6). Table 6 shows the risk of mortality for inpatients with COVID-19 according to CRD.

Table 2. Distribution of CRDs

	CRD n=245 (%)	All patients n=1529 (%)
Any CRDs	245	245 (16.0)
Asthma	128 (52.24)	128 (8.37)
Chronic obstructive pulmonary disease	79 (32.37)	79 (5.2)
Lung cancer	15 (6.14)	15 (1.0)
Obstructive sleep apnea syndrome	12 (4.91)	12 (0.8)
Interstitial lung disease	11 (4.50)	11 (0.7)

CRD: Chronic respiratory disease

Discussion

Investigating the effect of CRDs on COVID-19 pneumonia-related hospital mortality was the goal of this study. In our cohort, the prevalence of CRD was 16% (245/1.529). The distribution of CRDs was as follows: asthma 8.37% (128/1.529), COPD 5.2% (79/1.529), lung cancer 1% (15/1.529), OSAS 0.8% (12/1.529), and ILD 0.7% (11/1.529).

Our cohort demonstrated a prevalence of 5.2% for COPD, which was markedly lower than the general population in Turkey (19%), although the prevalence of asthma was concordant in the general population (8.37% and 2-17%, respectively) [14,15]. The prevalence of COPD varies from 3-21%, while the prevalence of asthma is 1-18% globally [16].

While Guan et al. [4] demonstrated a prevalence of 2.8% for any CRD, 1.6% for COPD, and 0.6% for asthma, a greater number of patients with both asthma (10.4%) and CRDs (26.8%)

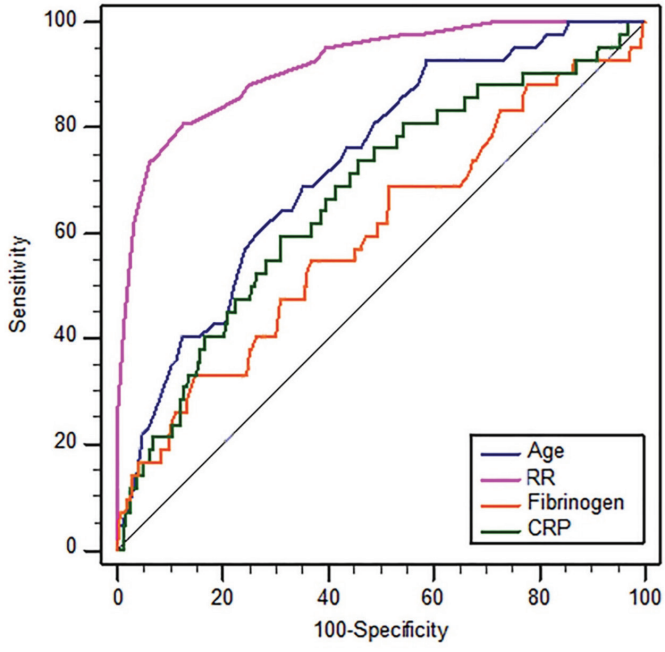

Figure 1. Receiver operating characteristic curves for age, respiratory rates, fibrinogen and CRP for mortality

CRP: C-reactive protein, RR: Respiratory rate

Table 3. Laboratory findings, chest CT scan results, disease severity status and outcomes of the patients

Laboratory findings		All patients (n=1529)	CRD (n=245)	No CRD (n=1284)	p
Neutrophil count, cells/mL	Mean ± SD	5.58±3.04	5.89±3.5	5.52±2.84	[c]0.415
Median (min-max)	Median (min-max)	5 (0.87-23.67)	5.2 (0.9-18.8)	4.9 (1.1-23.7)	
Lymphocytes count, cells/mL	Mean ± SD	1.19±0.62	1.17±0.66	1.20±0.61	[c]0.175
Median (min-max)	Median (min-max)	1.06 (0.15-6.9)	0.99 (0.3-4.7)	1.1 (0.2-6.9)	
Neutrophil/lymphocytes ratio	Mean ± SD	6.31±5.88	6.95±6.85	6.18±5.67	[c]0.280
Median (min-max)	Median (min-max)	4.46 (0.35-47.95)	4.9 (0.6-47.95)	4.4 (0.35-46.33)	
Platelet count, $10^3/mm^3$	Mean ± SD	248.76±112.83	246.5±103.83	249.2±114.51	[c]0.972
Median (min-max)	Median (min-max)	229 (0.7-1207)	237 (0.9-571)	228 (0.7-1207)	
Hematocrit, %	Mean ± SD	37.43±4.99	36.94±5.05	37.5±5.08	[a]0.113
Median (min-max)	Median (min-max)	37.7 (0.38-58.9)	36.9 (23.5-58.9)	37.8 (0.4-52)	
Glucose, mg/dL	Mean ± SD	153.04±71.97	149.99±70.56	153.62±72.25	[c]0.233
Median (min-max)	Median (min-max)	127.2 (11.3-791)	123 (62.9-526.7)	128.1 (11.3-791)	
Urea, mg/dL	Mean ± SD	42.86±29.73	43.91±28.32	42.66±30	[c]0.438
Median (min-max)	Median (min-max)	35 (10-328)	36 (10.8-204)	35 (10-328)	
Creatinine, mg/dL	Mean ± SD	0.99±0.86	0.94±0.76	0.99±0.88	[c]0.271
Median (min-max)	Median (min-max)	0.8 (0.07-11.98)	0.8 (0.4-11.2)	0.8 (0.1-12)	
Alanine transaminase, ALT, U/L	Mean ± SD	42.65±39.07	37.66±32.02	43.61±40.22	[c]0.019*
Median (min-max)	Median (min-max)	29 (4-321)	26 (4.8-271)	30 (4-321)	
Aspartate aminotransferase, AST, U/L	Mean ± SD	43.19±31.2	38.46±24.41	44.1±32.26	[c]0.002**
Median (min-max)	Median (min-max)	34 (4.8-356)	31 (4.8-170)	35 (9-356)	
Lactate dehydrogenase, LDH, U/L	Mean ± SD	353.71±155.48	345.72±165.58	355.23±153.51	[c]0.041*
Median (min-max)	Median (min-max)	318 (2.3-1386)	297 (125-1103)	323 (2.3-1386)	
Potassium, mEq/L	Mean ± SD	4.22±0.53	4.23±0.5	4.22±0.54	[a]0.798
Median (min-max)	Median (min-max)	4.2 (1.1-6)	4.2 (2.6-5.8)	4.2 (1.1-6)	
Sodium, mEq/L	Mean ± SD	137.14±5.38	137.37±3.96	137.09±5.61	[c]0.168
Median (min-max)	Median (min-max)	137 (38-237)	138 (121-147)	137 (38-237)	
Calcium	Mean ± SD	8.71±0.63	8.62±0.66	8.72±0.63	[c]0.003**
Median (min-max)	Median (min-max)	8.7 (3.4-12.2)	8.6 (4.3-11)	8.7 (3.4-12.2)	
C-reactive protein, CRP, mg/L	Mean ± SD	105.16±78.08	100.77±79.63	106±77.78	[c]0.288
Median (min-max)	Median (min-max)	95.8 (0.3-620.2)	83.8 (0.3-620.2)	97 (0.6-476)	
Procalcitonin, ng/mL	Mean ± SD	0.45±2.87	0.24±0.7	0.51±3.11	[c]0.786
Median (min-max)	Median (min-max)	0.1 (0-68)	0.1 (0.01-10.2)	0.1 (0.01-68)	
Ferritin, µg/L	Mean ± SD	525.93±582.41	455.39±559.92	539.39±585.85	[c]0.002**
Median (min-max)	Median (min-max)	350 (0.8-5357)	276.6 (5.7-4075)	363.6 (0.8-5357)	
D-dimer, µg FEU/mL	Mean ± SD	0.87±1.10	1.01±1.22	0.84±1.07	[c]0.008**
Median (min-max)	Median (min-max)	0.4 (0-8.82)	0.5 (0-8.82)	0.4 (0-7.99)	
Fibrinogen, mg/dL	Mean ± SD	514.81±135.23	515.51±129.23	514.68±136.4	[a]0.929
Median (min-max)	Median (min-max)	507 (187-1195)	504 (212-1104)	507 (187-1195)	
International normalized ratio, INR	Mean ± SD	1.07±0.21	1.08±0.22	1.07±0.21	[c]0.593
Median (min-max)	Median (min-max)	1 (0.2-3.7)	1 (0.5-2.9)	1 (0.2-3.7)	
Troponin I, ng/mL	Mean ± SD	28.04±177.22	38.19±267.54	26.25±156.05	[c]0.616
Median (min-max)	Median (min-max)	6 (0-3896)	7 (1-3896)	6 (0-3816)	
Albumin, g/L	Mean ± SD	35.61±5.54	34.8±5.57	35.77±5.52	[a]0.012*
Median (min-max)	Median (min-max)	35.5 (1.5-59.3)	34.7 (3.8-49.1)	35.5 (1.5-59.3)	

Table 3. Continued

Laboratory findings		All patients (n=1529)	CRD (n=245)	No CRD (n=1284)	p
Total cholesterol, mg/dL	Mean ± SD	158.73±42.50	163.68±41.17	157.80±42.69	[c]0.031*
	Median (min-max)	155 (64-477)	158.5 (72-310)	154 (64-477)	
HDL, HDL cholesterol, mg/dL	Mean ± SD	34.05±10.04	35.63±9.95	33.75±10.03	[a]0.008**
	Median (min-max)	33 (9-95)	35 (13-82)	33 (9-95)	
Disease severity status, n (%)					
Moderate		830 (54.3)	112 (45.7)	718 (55.9)	[b]0.003**
Severe		699 (45.7)	133 (54.3)	566 (44.1)	
CT involvement, n (%)					
Low		329 (21.5)	52 (21.2)	277 (21.5)	
Moderate		738 (48.2)	114 (46.5)	624 (48.6)	[b]0.707
Severe		462 (30.2)	79 (32.2)	383 (29.8)	
Clinical outcomes, n (%)					
Hospital length of stay, dL	Mean ± SD	11.52±6.81	13.69±9.17	11.11±6.17	[c]0.001**
	Median (min-max)	10 (1-64)	11 (1-64)	10 (1-42)	
ICU admission		168 (11.0)	35 (14.3)	133 (10.4)	[b]0.072
ICU ex		118 (7.7)	25 (10.2)	93 (7.2)	[b]0.111
Discharge from hospital		1392 (91.0)	216 (88.2)	1176 (91.6)	[b]0.088
Death		137 (9.0)	29 (11.8)	108 (8.4)	[b]0.088

[a]Student's t-test, [b]Pearson chi-square test, [c]Mann-Whitney U test, [d]Fisher's exact test, *p<0.05, **p<0.01, CT: Computed tomography, SD: Standard deviation, CRD: Chronic respiratory disease, min-max: Minimum-maximum range, AST: Aspartate aminotransferase, ICU: Intensive care unit

was reported by the ISARIC WHO study [5]. In a previous study in Italy, diabetes was reported in 20.3% of COVID-19 patients who died, however, COPD was not listed as a comorbidity for any patient [17]. Reporting of COPD at a lower prevalence might have been caused by missed diagnosis, poor recognition due to failure to perform a proper lung function test, and lack of documentation. Asthma and COPD are heterogeneous diseases with many overlapping clinical and pathophysiologic diagnostic features. Another likely explanation for the low presentation of CRDs in COVID-19 could be that this vulnerable group of patients might have behaved more cautiously to prevent COVID-19 and that ICSs, often used to treat COPD and asthma, could protect them [5]. Under these circumstances, it seems hard to compare the prevalence of separate CRDs in patients with COVID-19 pneumonia.

According to our results, there was no increase in the mortality of COVID-19 pneumonia in hospitalized patients due to CRDs. However, patients with COPD and ILD had a higher risk of hospital death compared with those without. Even though CRD was not associated with in-hospital mortality in COVID-19, Oh and Song [3] suggested that COPD and lung disease due to external agents had a greater risk of hospital death in patients with COVID-19, and also patients with ILD and OSAS may have an increased risk of COVID-19. The fact that lung disease due to external agents was not classified separately and this group of patients was included in ILD in our study may be the reason why we have reached similar results to the study mentioned above.

Another study also published that CRD was associated with the risk of reaching the combined endpoint (invasive ventilation, ICU, or death within 30 days after hospitalization) but not particularly of death from COVID-19 [4]. In contrast, Aveyard et al. [2] identified an association between preexisting CRDs (including COPD, lung cancer, asthma, bronchiectasis, and idiopathic pulmonary fibrosis) and a higher risk of hospitalization and death. The same study noted that COPD and ILD were associated with a 50% greater risk of developing severe COVID-19, although asthma did not appear significantly associated with a higher risk of COVID-19 severity.

Many studies have classified COPD as pathology associated with severe disease and poor outcomes, such as ICU treatment and death, based on our findings [2,3,5,8,18,19]. The exact pathophysiology of how COPD increases the severity of COVID-19 pneumonia is not clear; underlying lung malfunction, the presence of increased expression of angiotensinconverting enzyme 2 (ACE-2) receptors, endothelial cell dysfunction, and increased coagulation have all been implicated [20].

Table 4. Univariate and multivariate logistic regression analysis for risk factors on mortality

	Univariate analysis				Multivariate analysis			
	OR	%95 CI		p	OR	%95 CI		p
		Lower	Upper			Lower	Upper	
Age	1.073	1.057	1.089	0.001**	1.095	1.046	1.147	0.001**
Respiratory rate	1.520	1.435	1.610	0.001**	1.508	1.323	1.717	0.001**
Fibrinogen	1.002	1.000	1.003	0.007**	1.004	1.000	1.009	0.049*
CRP	1.006	1.004	1.008	0.001**	0.990	0.981	0.998	0.021*
LDH	1.004	1.003	1.005	0.001**	1.004	1.001	1.007	0.002**
CRD	1.462	0.946	2.258	0.087	0.262	0.071	0.968	0.045*
Malignancy	2.121	1.184	4.131	0.013*	6.437	1.483	27.940	0.013*
Heart rate	1.014	1.003	1.025	0.011*				
Oxygen support	1.152	1.130	1.176	0.001**				
PLT	0.997	0.995	0.999	0.003**				
NLR	1.110	1.085	1.136	0.001**				
Troponin I	1.002	1.001	1.003	0.003**				
D-dimer	1.347	1.191	1.523	0.001**				
INR	4.229	2.293	7.800	0.001**				
Ferritin	1.001	1.000	1.001	0.001**				
Urea	1.022	1.017	1.027	0.001**				
Creatinine	1.413	1.234	1.619	0.001**				
Calcium	0.525	0.405	0.682	0.001**				
Albumin	0.912	0.883	0.941	0.001**				
Hypertension	2.743	1.875	4.014	0.001**				
CAD	3.120	2.105	4.625	0.001**				
AF	5.111	3.105	8.411	0.001**				
CHF	3.754	2.259	6.237	0.001**				
CVD	4.265	2.286	7.958	0.001**				
CKD	2.666	1.444	4.921	0.002**				
Chest CT score								
Low	2.768	1.541	4.970	0.001**				
Moderate	2.008	1.383	2.914	0.001**				
Severe	3.537	2.468	5.068	0.001**				
Severe illness	48.524	17.845	131.947	0.001**				

*p<0.05, **p<0.01, OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein, LDH: Lactate dehydrogenase, CRD: Chronic respiratory disease, PLT: Platelet count, NLR: Neutrophil/lymphocytes ratio, INR: International normalized ratio, CAD: Coronary artery disease, AF: Atrial fibrillation, CHF: Congestive heart failure, CVD: Cerebrovascular disease, CKD: Chronic kidney disease, CT: Computed tomography

Our study revealed that the presence of ILD was associated with a 3.8-fold higher risk of in-hospital mortality. Similarly, previous studies have revealed that the presence of ILD was associated with older age, obesity, and male gender with higher mortality, severe disease, and ARDS [2,3,21]. Contrary to these findings, Guiot et al. [22] found that only 1% of patients with ILD were hospitalized for COVID-19, with no increase in the incidence of severe illness. Patients with ILD are susceptible to respiratory viral infections, and SARS-CoV-2 could exacerbate underlying ILDs and lead to poor outcomes. On the other hand, it is thought that viral infections may contribute to the pathogenesis of ILD by causing inflammation in the lung tissue [23].

Similar to our findings, numerous studies have reported that asthma was not associated with elevated risks of serious pneumonia and death in patients with COVID-19 [2,9]. Since our cohort group consists of half of CRD patients with asthma, this may be the reason for similar mortality in the CRD group. Conversely, it was reported that the risk of COVID-19 mortality

Table 5. ROC analysis for mortality

	AUROC (95% CI)	Standard error	p
Age	0.731 (0.698-0.763)	0.0373	0.001**
Respiratory rate	0.916 (0.893-0.935)	0.0227	0.001**
Fibrinogen	0.596 (0.560-0.632)	0.0492	0.036*
CRP	0.669 (0.633-0.703)	0.0444	0.001**

*p<0.05; **p<0.01, AUROC: Area under the receiver operating characteristic, CI: Confidence interval, CRP: C-reactive protein

Table 6. Risk of mortality for patients hospitalized COVID-19 according to CRD

			95% CI	
	p	OR	Lower	Upper
Asthma	[b]0.560	0.820	0.419	1.602
COPD	[b]**0.017***	**2.106**	1.130	3.925
Lung cancer	[d]0.638	1.572	0.351	7.037
OSAS	[d]0.293	2.047	0.444	9.440
ILD	[b]**0.033***	**3.873**	1.015	14.772

[b]Pearson chi-square test, [d]Fisher's exact test,*p<0.05: significantly increased prevalence, COVID-19: Coronavirus disease-2019, CRD: Chronic respiratory disease, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, OSAS: Obstructive sleep apnea syndrome, ILD: Interstitial lung disease, OR: Odds ratio

was increased in patients who had recently required oral corticosteroid treatment or were hospitalized with severe asthma [5]. Untreated asthma patients may have reduced airway ACE-2 expression and transmembrance protease serine 2 mRNA expression due to type 2 inflammation. A previous study reported that the differences in disease severity and mortality between asthma and COPD may be related to different ACE-2 expression pathways [24].

Although our cohort did not show any relationship between OSAS and mortality in COVID-19 pneumonia, previous studies stated that patients with OSAS had an increased rate of COVID-19, hospitalization, critical illness and mortality related to COVID-19 [3,25]. Hypertension, heart failure, coronary heart disease, cerebrovascular disease, obesity, DM, age, and male gender are all cluster risk factors for OSAS and all these comorbidities have been associated with poor outcomes in COVID-19 [18,26]. OSAS leads to a reduction of respiratory functions, an increase of inflammatory lung disease and a higher incidence of thromboembolic disease [27]. Hypoxia leads to higher ACE-2 expression due to damage in the renin-angiotensin system in patients with OSAS. This mechanism may lead to a rise in death and disease severity in patients with both COVID-19 and OSAS [28].

Oncology patients are vulnerable to SARS-CoV-2 infections due to an immunocompromised state from cancer or its therapies including corticosteroids, older age, and comorbidities. The severity of disease, prolonged hospitalisation, pulmonary complications, and need for ICU and mechanical ventilation have been higher in patients with lung cancer compared with the general population and other malignancies reported with a death rate of 17.7-55% [29]. Death rates were reported to be 33% and 25%, respectively, in Europe and the US. Similar to lung cancer, patients with hematological malignancies have an increased risk of mortality compared with other cancer types [30].

In line with earlier research, age, respiratory rate, fibrinogen, CRP, LDH, and malignancy emerged as independent risk factors for in-hospital mortality in this cohort [2-6,8,18,19,21,24,26,30].

Study Limitations

There are some potential limitations to our analysis. It is a single-center study with a retrospective design that only involves hospitalized patients with moderate to severe illness. There was no available information about previous medication or lung function test results, the severity of CRD, or smoking status. It was not possible to perform lung function tests due to pandemic measures.

Conclusion

Our study shows that only COPD and ILD types of CRD lead to an increase in the mortality of COVID-19 infection. Therefore, these patients group should be closely monitored during COVID-19 infection to decrease the poor outcomes. Most importantly, they should be given priority in immunization programs for such infectious diseases. Still, further detailed studies are needed in this field.

Ethics

Ethics Committee Approval: This research was approved by the Local Ethics Committee, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (2021/164/2021-06-40/15.03.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: I.K.A., M.B., Concept: I.K.A., M.B., Design: I.K.A., M.B., Data Collection or Processing: I.K.A., M.B., Analysis or Interpretation: I.K.A., M.B., Literature Search: I.K.A., M.B., Writing: I.K.A., M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20.

2. Aveyard P, Gao M, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, et al. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. Lancet Respir Med. 2021;9:909-23.

3. Oh TK, Song IA. Impact of coronavirus disease-2019 on chronic respiratory disease in South Korea: an NHIS COVID-19 database cohort study. BMC Pulm Med. 2021;21:12.

4. Guan WJ, Liang WH, Shi Y, Gan LX, Wang HB, He JX, et al. Chronic respiratory diseases and the outcomes of COVID-19: a nationwide retrospective cohort study of 39,420 cases. J Allergy Clin Immunol Pract. 2021;9:2645-55.

5. Bloom CI, Drake TM, Docherty AB, Lipworth BJ, Johnston SL, Nguyen-Van-Tam JS, et al. Risk of adverse outcomes in patients with underlying respiratory conditions admitted to hospital with COVID-19: a national, multicentre prospective cohort study using the ISARIC WHO Clinical Characterisation Protocol UK. Lancet Respir Med. 2021;9:699-711.

6. Beltramo G, Cottenet J, Mariet AS, Georges M, Piroth L, Tubert-Bitter P, et al. Chronic respiratory diseases are predictors of severe outcome in COVID-19 hospitalised patients: a nationwide study. Eur Respir J. 2021;58:2004474.

7. Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. Respirology. 2018;23:130-7.

8. Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, et al. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: a rapid systematic review and meta-analysis. PLoS One. 2020;15:e0233147.

9. Liu S, Cao Y, Du T, Zhi Y. Prevalence of comorbid asthma and related outcomes in COVID-19: a systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2021;9:693-701.

10. World Health Organization. WHO Coronavirus Disease (COVID-19)/ Technical Guidance. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications

11. Republic of Turkey Ministry of Health. COVID-19 (SARS-CoV-2 Infection) Guide. https://covid19.saglik.gov.tr/TR-66926/eriskin-hasta-tedavisi.html

12. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. http://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum

13. Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, et al. Chest CT Severity score: an imaging tool for assessing severe COVID-19. Radiol Cardiothorac Imaging. 2020;2:e200047.

14. Kocabas A, Hancioglu A, Turkyilmaz S, et al. Prevalence of COPD in Adana, Turkey (BOLD-Turkey Study). Proceedings of the American Thoracic Society. 2006;3:A543.

15. Turkish Thoracic Journal. Official Journal of the Thoracic Society Supplement 1 October 2016 Volume 17 Türk Toraks Derneği Tanı ve Tedavi Rehberi. 2016. https://www.chiesi.com.tr/img/download/documenti/934_ttd-astim-tani-ve-tedavi-rehberi-2016.pdf

16. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2022 Report. https://goldcopd.org/2022-gold-reports/

17. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020;323:1775-6.

18. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62.

19. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55:2000547.

20. Leung JM, Yang CX, Tam A, Shaipanich T, Hackett TL, Singhera GK, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J. 2020;55:2000688.

21. Drake TM, Docherty AB, Harrison EM, Quint JK, Adamali H, Agnew S, et al. Outcome of Hospitalization for COVID-19 in patients with interstitial lung disease. An international multicenter Study. Am J Respir Crit Care Med. 2020;202:1656-65.

22. Guiot J, Henket M, Frix AN, Delvaux M, Denis A, Giltay L, et al. Single-center experience of patients with interstitial lung diseases during the early days of the COVID-19 pandemic. Respir Investig. 2020;58:437-9.

23. Vassallo R. Viral-induced inflammation in interstitial lung diseases. Semin Respir Infect. 2003;18:55-60.

24. Song J, Zeng M, Wang H, Qin C, Hou HY, Sun ZY, et al. Distinct effects of asthma and COPD comorbidity on disease expression and outcome in patients with COVID-19. Allergy. 2021;76:483-96.

25. Maas MB, Kim M, Malkani RG, Abbott SM, Zee PC. Obstructive sleep apnea and risk of COVID-19 infection, hospitalization and respiratory failure. Sleep Breath. 2021;25:1155-7.

26. Insalaco G, Dal Farra F, Braghiroli A, Sacco, Salvaggio A; on behalf of the Italian Thoracic Society (ITS-AIPO). Sleep Breathing Disorders in the COVID-19 Era: Italian Thoracic Society Organizational Models for a Correct Approach to Diagnosis and Treatment. Respiration. 2020;99:690-4.

27. Bikov A, Losonczy G, Kunos L. Role of lung volume and airway inflammation in obstructive sleep apnea. Respir Investig. 2017;55:326-33.

28. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care. 2020;24:422.

29. Peravali M, Joshi I, Ahn J, Kim C. A systematic review and meta-analysis of clinical characteristics and outcomes in patients with lung cancer with coronavirus disease 2019. JTO Clin Res Rep. 2021;2:100141.

30. Tiotiu A, Chong Neto H, Bikov A, Kowal K, Steiropoulos P, Labor M, et al. Impact of the COVID-19 pandemic on the management of chronic noninfectious respiratory diseases. Expert Rev Respir Med. 2021;15:1035-48.