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Effects of comorbidities associated with COVID-19 cases in Intensive Care Unit on mortality and disease progression

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Abstract. – OBJECTIVE: The patient's age, gender and the presence of certain concomitant diseases have been reported to play a part in the course and progression of COVID-19 in the literature. In this study, we aimed to compare the comorbidities causing mortality in critically ill Intensive Care Unit (ICU)-patients diagnosed with COVID-19.

PATIENTS AND METHODS: The data as regards the COVID-19 cases followed up in the ICU were retrospectively reviewed. 408 COVID-19 patients with positive PCR test were included in the study. In addition, a subgroup analysis was performed in patients treated with invasive mechanical ventilation. While the primary aim of this study was to evaluate the difference in survival rates due to comorbidities in critical COVID-19 patients, we also aimed to assess the comorbidities in severely intubated COVID-19 patients in terms of mortality.

RESULTS: A statistically significant increase in mortality was observed in patients with underlying hematologic malignancy and chronic renal failure (p=0.027, 0.047). Body mass index value in the mortal group was significantly higher in both the general study group and subgroup analysis (p=0.004, 0.001).

CONCLUSIONS: Advanced age and comorbidities such as chronic renal failure and hematologic malignancy in COVID-19 patients are associated with poor survival prognosis in critically ill COVID-19 patients.

Key Words:
Acute respiratory distress syndrome, COVID-19, Comorbidity, Mechanical ventilation, Obesity.

Abbreviations

ARDS: Acute respiratory distress syndrome; HFNO: High flow nasal oxygen; IMV: Invasive mechani-cal ventilation; ICU: Intensive Care Unit; PCR: Polymerase Chain Reaction; HT: Hypertension; DM: Di-abetes mellitus; COPD: Chronic obstructive pulmonary disease; CRF: Chronic renal failure; HFNC: High flow nasal cannula; CT: Computed tomography; SOFA: Sequential organ failure assesment; BMI: Body mass index; MODS: Multiple organ dysfunction sydrome; NIMV: Non-invasive mechanical ventilation.

Introduction

SARS-CoV-2 virus, which emerged in 2019 in Wuhan China, causes severe acute respiratory failure[1]. Since its outbreak, the COVID-19 pandemic has had impacts on the whole world together with its high mortality rate, causing more than a death toll of 3.4 million worldwide so far. The number of confirmed COVID-19 cases and deaths worldwide has been continuing to rise rapidly[2].

During the course of the disease, such conditions as acute respiratory distress syndrome (ARDS)-related respiratory failure developing 7-12 days after the onset of the symptoms, septic shock, multi-organ failure, myocarditis, arrhythmias, cardiogenic shock, coagulation disorders, endocrinopathies, liver and kidney damage, metabolic acidosis and also neurological complications may be encountered[3,4].

For these patients, non-invasive mechanical ventilation (NIMV), high flow nasal oxygen (HFNO) therapy and invasive mechanical ventilation (IMV) methods are applied. Life support treatments such as vasopressors, inotropes and hemodialysis are also provided for the patients with renal failure, multiorgan failure and shock. Such factors as obesity, diabetes mellitus, hypertension, advanced age, smoking, immunosuppressive disease, chronic lung disease, being male gender and chronic renal failure (CRF) give rise to higher mortality and morbidity rate in COVID-19 patients. Though in varying rates depending on the country, the overall mortality rate is 5.2%, yet this rate varies between 30% and 100% in critically ill patients in need of mechanical ventilation[5-9].

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Therefore, successful treatment of severe and critical cases is of big importance to reduce complications and mortality. Various treatment modalities are still examined in order to increase the survival rate in ARDS caused by highly mortal COVID-19 disease. In addition, while various evaluations towards prognosis are carried out on patient groups, predictive evaluations regarding in which conditions the course of the disease may prove more severe are also carried out. In the current literature, prognostic evaluation is mainly on several comorbid factors such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, being male gender, hematological malignancies, and the relationship between these and disease severity has been attempted to be determined[10-13]. However, these studies[10-13] have been mostly conducted on the general patient population to predict their need for Intensive Care Unit (ICU) and mortality risks, therefore the results from these studies remain insufficient to evaluate the possible relationship with mortality when the patients with a non-severe course are investigated. Although the course of the disease and the need for intensive care hospitalization can be evaluated in COVID-19, the risk factors for mortality are yet to be clearly revealed.

The primary aim of this study was to reveal the difference caused by comorbidities in terms of survival rate in the disease by just evaluating the intensive care patient population with a severe course of the disease and also to determine which comorbidities may lead to more risk in terms of mortality in COVID-19 patients. The secondary aim of the study, on the other hand, was to evaluate the differences in survival rate by evaluating the laboratory data obtained in the clinical follow-ups of intensive care patients and also to observe whether some parameters evaluated in the study together with subgroup analysis make a difference in terms of this subgroup in the patient group treated with invasive mechanical ventilation, developing severe ARDS.

Patients and Methods

The study was planned as a retrospective cohort including the patients in the tertiary Intensive Care Unit. All SARS-CoV-2 PCR positive patients hospitalized in the Intensive Care Unit between 18 March 2020 and 15 January 2021 were included in the study. Inclusion criteria for the study was all patients over the age of 18 followed-up in the Intensive Care Unit with a diagnosis of COVID-19 confirmed by rt-PCR, while the patients with a non-confirmed COVID-19 diagnosis were exluded.

Sample Size

A total of 632 patient records were investigated and those with negative SARS-CoV-2 PCR results (n=205), those hospitalized in the Intensive Care Unit more than once (n=22), and those whose full data could not be accessed (n=35) were excluded from the study. A total of 224 patients were excluded, while 408 patients were included (Figure 1). The clinical and laboratory data of the patients were retrospectively obtained from the hospital information system and clinical follow-up files. Patients were divided in 2 groups as survival group (n=176) and mortality group (n=232). Age, gender, comorbidities, SOFA scores, mechanical ventilation parameters, laboratory values on intensive care admission were evaluated in terms of predictive values for mortality. In addition to this, subgroup analysis was performed in patients treated with an invasive mechanical ventilator, and these same parameters were evaluated in terms of predicting mortality in ARDS patients with a more severe course.

Statistical Analysis

Data analysis was done with the SPSS 22.0 program (IBM Corp., Armonk, NY, USA). The normality of the distribution of the data was determined using the Shapiro-Wilk test. Categorical variables were given as frequency (n) and percentage (%), and numerical variables as mean ± standard deviation. The differences between the two groups were analyzed using the Mann-Whitney U test for non-normally distributed continuous data and non-continuous data. Categorical data were analyzed using the Fisher's test. p-value <0.05 was considered statistically significant for between-group comparison. The permission from the Ministry of Health and the approval of the Hospital Ethics Committee were obtained for the study (Decision number: 0159, date: 10.03.2021).

Results

The data of 408 patients hospitalized in intensive care due to COVID-19 between 18 March 2020 and 15 January 2021 were included in the study. These 408 patients screened retrospectively were divided into two groups as survival group (n=176;

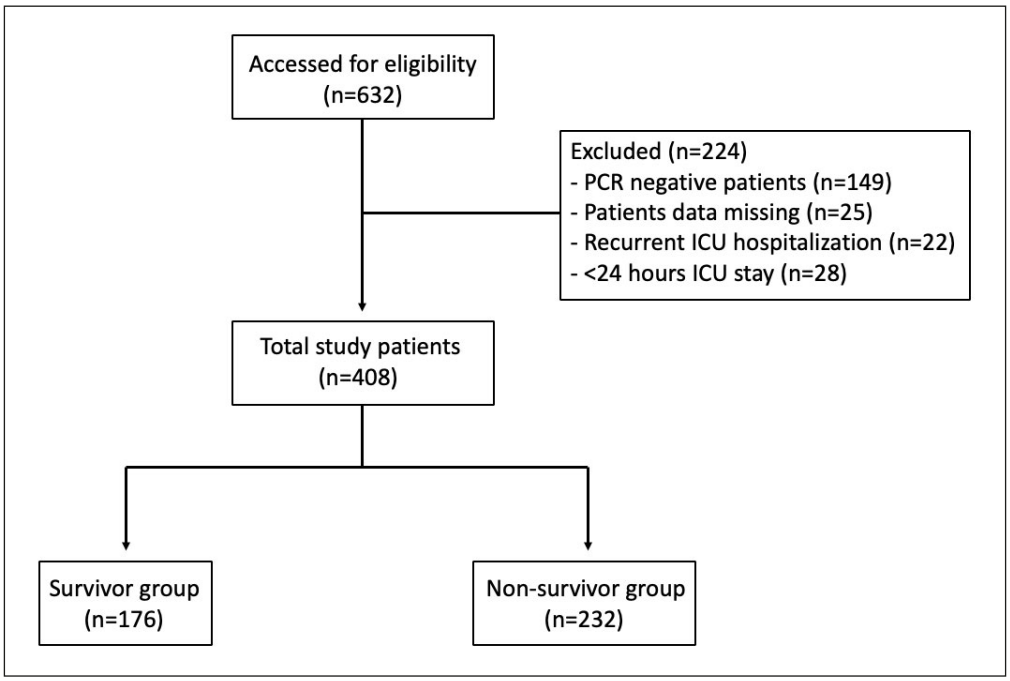

Figure 1. Flow diagram of the study.

43.2%) and mortality group (n=232; 56.8%). The results of the 90-day survival analysis are shown in Figure 2. Demographic characteristics and comorbidities of the patients are given in Table I.

There was no difference between the groups in terms of gender. The male gender ratio was higher in both groups. The patients in the survival group were younger than those in the mortality group (p=0.004). Mean age for the survival group was 64, while it was 67 for the mortality group. Hypertension (HT) and diabetes mellitus (DM) were found to be the most common comorbidities in both groups, but no significant difference was found between the groups in terms of

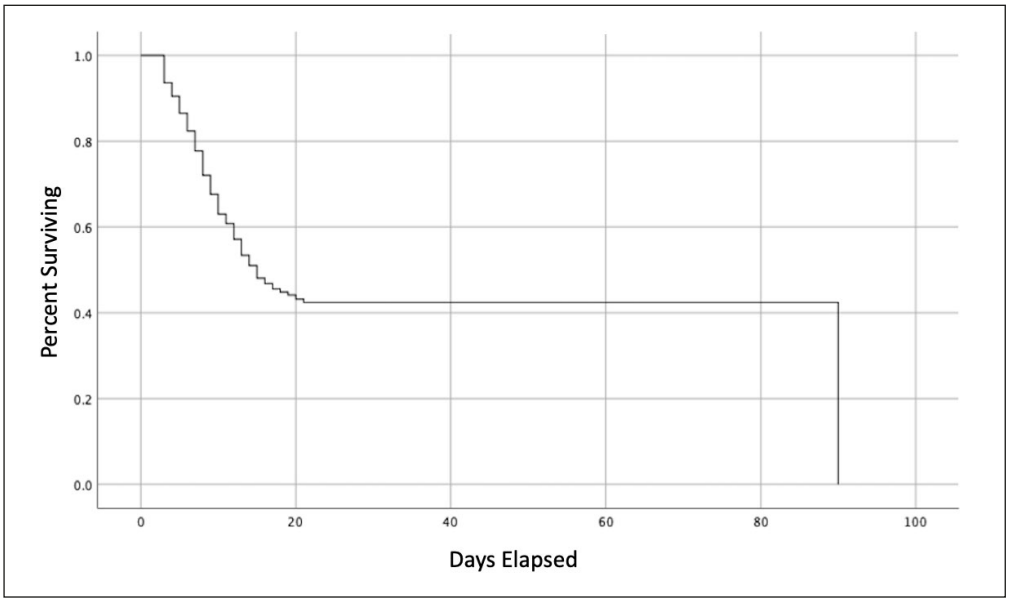

Figure 2. Survival analysis.

Table I. Demographic data-comorbidity.

Demographic data-comorbidity	Survival Group (n=176)	Mortality Group (n=232)	*p*-value
Age	64 [19-99]	67 [24-91]	0.004*
Sex (Male)	111 (63)	146 (62)	1
Comorbity			
Diabetes mellitus	65 (56)	99 (42)	0.263
Hypertension	88 (50)	118 (50)	0.920
Chronic obstructive pulmonary disease	28 (15)	33 (14)	0.675
Cardiovascular disease	44 (25)	65 (28)	0.572
Solid tumor	10 (5)	20 (8)	0.339
Hematologic malignancy	1 (1)	10 (4)	0.027*
Immunosuppressive	6 (3)	9 (3)	1
Obesity	11(6)	28 (12)	0.061
Chronic renal failure	9 (5)	25 (10)	0.047*
Chronic liver disease	2 (1)	6 (2)	0.475
Thyroid dysfunction	8 (4)	6 (2)	0.289
Dementia	16 (9)	25 (10)	0.621
Postoperative hospitalization	6 (3)	12 (5)	0.470

*: $p<0.05$ was considered statistically significant. Values are expressed as frequency (%) and mean [min-max].

the frequency of HT and DM. There was also no significant difference between the two groups in terms of chronic obstructive pulmonary disease (COPD), coronary artery disease, solid tumor, immuno-suppressive status, obesity, chronic liver disease, thyroid dysfunction, dementia, and postoperative hospitalization. On the other hand, a statistically significant difference was found between the two groups in terms of mortality in patients with hematological malignancies and chronic renal failure (p=0.027, p=0.047). Clinical data-preliminary laboratory parameters of the patients are given in Table II.

Considering their ventilation status, the rate of patients followed-up with high flow nasal cannula (HFNC), O_2 mask and nasal cannula was higher in the survival group than in the mortality group (p=0.008, p=0.001, p=0.001), however, it was determined that the mortality rates in patients who received invasive mechanical ventilation treatment were higher than those of the survival group (p=0.001). In the two groups, the presence of ARDS and severe computed tomography (CT) involvement on admission to the Intensive Care Unit was higher in the mortality group (p=0.001, p=0.001). It was also observed that the survival group had longer hospitalization duration compared to the mortality group in terms of hospital stay, which was a significant difference between the two groups, and there was no significant difference between the groups in terms of the number of days of hospitalization in the Intensive Care Unit (p=0.001, p>0.05). On admission to the ICU, a significant difference was found in terms of high APACHE-2 score, low lymphocyte count, high Neutrophil/Lymphocyte ratio, low platelet count, high procalcitonin, high C-reactive protein (CRP), blood urea nitrogen (BUN), high creatinine level, high aspartate transaminase (AST) level, lactate dehydrogenase (LDH), D-dimer, ferritin, troponin and lactate elevation in mortality group (p=0.001, p=0.001, p=0.016, p=0.000, p=0.025, p=0.000, p=0.000, p=0.003, p=0.000, p=0.009, p=0.000, p=0.004, p=0.032). Also, a significant difference was found in the mortality group in terms of low PaO_2/FiO_2 ratio and high sequential organ failure assesment (SOFA) scores on day 1 and day 3 (p=0.001, p=0.001, p=0.001). Invasive mechanical ventilation therapy subgroup analysis are given in Table III.

In the subgroup analysis performed for patients with severe ARDS under invasive mechanical ventilation support, no significant difference was found between the two groups in terms of age and gender (p>0.05, p>0.05). Also, no significant difference was observed between the groups in terms of any comorbidity for the patients evaluated for their existing comorbidities. Length of hospital stay and length of stay in the Intensive Care

Table II. Clinical data-preliminary laboratory parameters.

Clinical data-preliminary laboratory parameters	Survival Group (n=176)	Mortality Group (n=232)	*p*-value
Ventilation therapy			
Invasive mechanical ventilation	91 (51)	225 (96)	0.001*
Non-invasive mechanical ventilation	27 (15)	26 (11)	0.236
High flow nasal cannula	33 (18)	22 (9)	0.008*
O2 mask with reservoir	82 (46)	53 (22)	0.001*
Simple O2 Mask	68 (38)	43 (18)	0.001*
Nasal cannula	14 (7)	2 (0)	0.001*
ARDS in admission	136 (77)	212 (91)	0.001*
Number of days of hospital stay	21 [5-134]	12 [3-54]	0.001*
Number of days of ICU stay	8 [3-52]	9 [3-30]	0.904
Computed tomography			
None	11 (6)	2 (0)	0.001*
<50% Infiltration	36 (20)	10 (4)	0.001*
>50% Infiltration	95 (53)	108 (46)	0.001*
Totally Infiltration	33 (18)	112 (48)	0.001*
APACHE-2 Score	16 [2-53]	22 [7-43]	0.001*
SOFA score day 1	5 [1-13]	7 [1-18]	0.001*
SOFA score day 3	6 [2-16]	8 [1-17]	0.001*
Body mass index	27 [19-38]	28 [19-38]	0.004*
White blood cell count	14.9 [1.6-33.4]	13.3 [1.5-522]	0.210
Lymphocyte count	0.8 [0.1-4.2]	0.6 [0.05-26.3]	0.001*
Neutrophil/lymphocyte ratio	13.5 [2.1-220]	18.6 [0.2-257]	0.016*
Polymorphonuclear leukocytes count	13.1 [1.4-30]	11.6 [0.9-69]	0.389
Platelet count	307 [77-656]	228 [15-506]	0.000*
Procalcitonin	0.3 [0.01-75]	0.82 [0.06-75]	0.000*
C-Reactive protein	121 [0.2-334]	144 [3.2-425]	0.025*
BUN	26 [5-133]	39 [10-145]	0.000*
Creatinine	0.8 [0.4-6.7]	1.2 [0.3-11]	0.000*
AST	37 [6-913]	55 [13-913]	0.003*
ALT	34 [7-4110]	36 [6-1227]	0.457
LDH	324 [125-1355]	476 [138-2235]	0.000*
D-Dimer	886 [134-5572]	1200 [148-30309]	0.009*
Ferritin	719 [11-2283]	1210 [116-5255]	0.000*
Troponin	0.03 [0.01-17]	0.06 [0.01-6.7]	0.004*
Lactate	1.3 [0.4-6.9]	1.7 [0.6-22]	0.032*
PaO_2/FiO_2 Ratio	137 [43-390]	116 [42-500]	0.001*

*: $p<0.05$ was considered statistically significant. Values are expressed as frequency (%) and mean [min-max]. Blood urea nitrogen (BUN), aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH).

Unit were significantly lower in the mortality group (p=0.000, p=0.000). No significant difference was found between the two groups in terms of day 1 and day 3 SOFA scores, high lactate levels on admission to the Intensive Care Unit, and high APACHE-2 scores (p>0.05, p>0.05, p>0.05).

There was also no significant difference between the two groups in terms of obesity [body mass index (BMI) >30]. However, BMI elevation was found to be significantly different in the mortality group compared to the survival group both in the general group and in the subgroup analysis (p=0.004, p=0.001). Respiratory failure was seen in 70 patients, septic shock development in 71 patients, multiple organ dysfunction sydrome (MODS) in 79 patients and sudden cardiac arrest in 12 patients, which were the cause of mortality in these patients.

Table III. Invasive mechanical ventilation therapy subgroup analysis.

Clinical data-preliminary laboratory parameters	Survival Group (n=90)	Mortality Group (n=226)	*p*-value
Age	66 [35-99]	68.5 [24-93]	0.588
Sex (Male)	32 (35)	86 (38)	0.701
Comorbidity			
Diabetes mellitus	36 (40)	102 (45)	0.452
Hypertension	47 (52)	122 (53)	0.804
Chronic obstructive pulmonary disease	8 (8)	39 (17)	0.079
Cardiovascular disease	25 (27)	62 (26)	1.000
Solid tumor	8 (8)	17 (7)	0.651
Hematologic malignancy	4 (4)	6 (2)	0.479
Immunosuppressive	4 (4)	6 (2)	0.479
Obesity	7 (7)	26 (11)	0.417
Chronic renal failure	9 (10)	20 (8)	0.826
Chronic liver disease	4 (4)	2 (0)	0.057
Thyroid dysfunction	3 (3)	7 (3)	1.000
Dementia	10 (11)	23 (9)	0.839
Postoperative hospitalization	3 (3)	11 (4)	0.764
SOFA score day 1	7 [2-18]	7 [1-17]	0.441
SOFA score day 3	8 [3-17]	8 [1-17]	0.433
Body mass index	27 [21-38]	28 [19-38]	0.001*
Number of days of ICU stay	15 [3-52]	9 [3-30]	0.000*
number of days of hospital stay	27 [3-52]	10 [3-30]	0.000*
Lactate	1.7 [0.6-22]	1.6 [0.5-30]	0.786
PaO_2/FiO_2 Ratio	131 [43-360]	115.5 [42-500]	0.197
APACHE-2 Score	20 [4-38]	22 [3-43]	0.134

*: $p<0.05$ was considered statistically significant. Values are expressed as frequency (%) and mean [min-max].

Discussion

During the COVID-19 pandemic, 5-20% of the hospitalized patients were determined to develop a serious clinical picture requiring intensive care admission[14]. In this study, critical COVID-19 cases followed in the Intensive Care Unit were evaluated retrospectively in terms of age, gender, biochemical markers, and survival outcomes associated with the comorbid diseases. Two groups were formed between the patients in terms of survival outcomes and comorbidities with significant differences, and also their associated entry laboratory parameters were also evaluated. Our overall mortality rate for the COVID-19 patient group in the Intensive Care Unit was 56%, which was found to be higher than the literature. Armstrong et al[15] reported some results associated with a high mortality as high as 41.6% in the COVID-19 Intensive Care Unit. Our mortality rates were similar to studies reported from, Italy[8] (61%), America[16] (57%), and China[17] (42%).

The mean PaO_2/FiO_2 ratios of the patients enrolled in the study was found to be as low as 137 in the survival group and 116 in the mortality group, and this led us to assume that these patients were admitted to the Intensive Care Unit at a late period with a severe ARDS clinic compared to other study populations in the literature, which can be attributed to the long time spent waiting for a bed in the Intensive Care Unit due to the pandemic conditions until the condition worsened to an advanced stage. Late follow-up and treatment could be provided to the critically ill group, as these patients were admitted to the Intensive Care Unit in a late period. Accordingly, there was a high need for invasive mechanical ventilation (77%) in the patients included in the study. Our rates of invasive mechanical ventilation were found to be higher than those reported in China[7] (30-42%), and similar to those reported in the United States[16] (71%), while lower than those in Italy[8] (88%). Our rates of non-invasive mechanical ventilation (NIMV) or high flow nasal cannula (HFNC) use (24%) were similar to other studies[17].

As expected, survival rates were significantly higher in the patient group requiring lower oxygen support, for whom non-invasive strategies were pursued using nasal O_2, simple O_2 mask, O_2 mask with reservoir, and HFNC. There were approaches forcing the professionals to avoid non-invasive strategies in an attempt to prevent transmission of the condition and protect healthcare workers, especially in the early stages of the pandemic. When the results of our study are evaluated, the importance of algorithms that avoid early intubation is increasing, particularly for the intensive care patient groups not requiring a high oxygen demand[18,19].

Although there are many studies reporting high mortality results in intensive care, the studies that can define clinical risk factors in intensive care have not yet yielded quite clear results. Defining and evaluating risk factors and their management appropriately will contribute to our understanding of mortality-related factors and to the selection of patient groups to be prioritized in the course of the treatment[20]. Various underlying comorbidities have been defined in the literature[17-21] as risk factors for the development of critical illness, intensive care hospitalization and increased mortality rates in COVID-19 patients, which are mainly HT, DM, cardiovascular diseases, obesity, COPD, chronic renal failure and cancer.

In our study, critically ill patients followed in the Intensive Care Unit were mostly made up of elderly patients, and age was found to be significantly older in the mortality group (p=0.004). In many descriptive studies available in the literature, advanced age has been reported as a risk factor for intensive care admission and mortality. Mortality rates in the Intensive Care Unit were also found[17-22] to be higher in the elderly patient group. However, Levin et al[23] reported that age-related risk factors cannot be differentiated by studies due to the fact that chronic diseases are presented as risk factors for COVID-19 severity along with advanced age, and that the isolated effect of age on the severity of COVID-19 disease should be determined in accordance with the risk score based on existing evidence.

The relationship between gender and mortality has also been investigated in various studies[24], and higher mortality rates have been reported in men than in women. Meijs et al[25] found that women had a 40% higher chance of survival in the Intensive Care Unit than men in their study, which was determined independent of age, disease severity, obesity, smoking status, presence of any major comorbidity, and all treatments. These results were also found at a similar rate in the invasive ventilating patient group. However, contrary to the literature, no difference was found in gender-related survival outcomes in our study (p>0.05), which might be due to the fact that many studies in the literature have been conducted with a general COVID-19 patient population and that although men are reported[24] to be predisposed to develop critical illness, this relationship has not been reported in such a more limited patient group as intensive care patients. We also believe that this might be due to the fact that the accompanying factors such as BMI scores were higher in female patients in the patient group in their study, thus making it hard to investigate the the isolated effect of gender.

In addition to studies[26,27] showing an increased risk of developing critical illness in patients with various comorbidities such as DM, HT, cardiovascular disease and COPD, there are also several studies[17-21] reporting increased risk of mortality in COVID-19 as a result of these comorbidities. All patients with fatal outcomes examined in the first studies[20,21] were reported to have at least one comorbidity, the most common of which were HT, cardiovascular diseases and DM in line with several other studies[28,29]. In our study, DM and HT were the most common comorbidities similar to the literature. However, there was a difference compared with several studies in the literature which reveal no difference in survival outcomes. This can be explained by the fact that the patient group included in these studies[26-29] generally consisted of the general patient population in terms of critical and non-critical patients, while our study was conducted with intensive care patient population including only the critical patient group, and also that our mortality rate was found to be high due to late admission of these patients to the Intensive Care Unit.

In a meta-analysis[30], HT was found to increase the risk of mortality in COVID-19 (OR: 2.42). It was reported[31] in Italy that approximately 75% of the patients who died in the pandemic in this country were present with hypertension. However, there is also a study[24] in which HT was not associated with the increased risk of mortality in the process, contradicting with the available findings in the literature, but consistent with our study not reporting HT as a risk factor in terms of mortality (p>0.05).

In the study[32] conducted in patients with DM in China, it was observed that the need for inten-

sive care referral and invasive mechanical ventilation was high at similar rates, correlating with the results obtained in our study. However, it was observed in our study that the presence of DM did not affect the survival outcomes (p>0.05). In the longitudinal analysis performed on 7,300 patients in China[33], it was shown that the risk of death from COVID-19 in the patient group with diabetes was 3 times higher than the non-diabetic patients. It was also revealed[34] that the risk of severe COVID-19 development was 5 times higher in cases with COPD in the USA. COPD was identified as an independent risk factor for mortality in COVID-19 patients in the meta-analysis by Wang et al[35]. Survival outcomes in terms of COPD were not different in our study population (p>0.05). However, weaning results, number of days on mechanical ventilator and associated infection rates could not be evaluated with long-term follow-ups in our patient population who were provided a short-term intensive care follow-up. In this respect, this posed a serious limitation in our study in terms of not being able to evaluate the above mentioned effects on the long-term outcomes.

In a study conducted by Wu and McGoogan[36] on 44,000 patients, it was shown that mortality was 5 times higher in patients with cardiovascular disease (10.5% and 2.3%, respectively). On the other hand, we found that the presence of cardiovascular disease did not lead to a difference in survival outcomes (p>0.05), which might be attributed to the lower incidence of coronary artery disease in our country compared to developed countries and, accordingly, the low incidence of the condition in our study population[37]. Contrary to the large number of studies[31,35,36] reported in the literature, the effect of underlying DM, COPD and cardiovascular disease on increased risk of mortality was not found to be significant in both groups of our study in which it was seen that HR for DM=1.25, 95% CI (0.94-1.88), SE=0.2, while it was seen that HR for COPD=0.87, 95% CI (0.50-1.50), SE=0.2 and HR for cardiovascular disease=1.16, 95% CI (0.74-1.82), SE=0.2. This difference obtained in our results can be attributed to the high need for invasive mechanical ventilation in patients (77%) and the high mortality rate (56%) and among other factors contributing to this condition can be identified as: the patients were admitted to the Intensive Care Unit in the late onset, and the mean PaO_2/FiO_2 rates were seen to be 137 in the survival group and 116 in the mortality group at the time of admission, and the patients with severe ARDS could access follow-up-treatment quite late, which can be defined as the reason why a key difference-making result could not be achieved in terms of these underlying comorbid conditions in our study.

Underlying chronic renal failure has been identified[38] as a risk factor for both mortality and acute renal failure development in critical COVID-19 patients. Similar results were found in our study in parallel with the existing literature in our study, and also a highly significant difference was found between the two groups in terms of rates of concomitant chronic renal failure. It was found that the underlying chronic renal failure increased the risk of a fatal course of critical COVID-19 as a result of HR=2.24, 95% CI (1.01-4.93), SE=0.4. This situation, compatible with the literature, might account for the elevated incidence of acute renal failure in the patients with chronic renal failure who already had limited renal reserve due to deteriorated general condition, loss of consciousness, and decreased oral intake in the early stages of the disease[38].

Guan et al[39] found a cancer rate of 0.9% in their study carried out with 1,099 patients and reported that 30% of them had critical COVID-19 results. Opposing results are also available in a limited number of studies in the literature. In a study[40] evaluating two groups of COVID-19 patients with and without underlying cancer disease, no significant difference was found in terms of mortality, intubation, and admission to Intensive Care Unit. Also, in a study[41] carried out with a small number of patients, no difference was found in terms of solid tumors and hematological malignancies. However, it has been reported[41] that there is a trend indicating earlier occurrence of serious adverse effects associated with COVID-19 in patients with hematological malignancies. Consistent with the results in the literature on hematological malignancy, the independent risk factor for mortality was found to be HR=7.94, 95% CI (1.005-62.8), SE=1.05 in our study (p=0.02). However, no difference was found in terms of survival outcomes related to solid tumors (p>0.05). In addition, in a meta-analysis by Armstrong et al[15] carried out during the COVID-19 pandemic, it was reported that the mortality rate in critically ill patients with COVID-19 fell from 50% to 40% over the course of the pandemic. The 60% mortality rate in cancer patients with COVID-19 admitted to the Intensive Care Unit indicates that the outcomes in cancer patients are not excessively high when compared to the general population of patients with COVID-19[41].

Rossi et al[42] reported obesity as a risk factor in critically ill patient outcomes. In addition to this, prolonged hospital stay and a 5-fold increase in mortality were also reported. In a retrospective cohort analysis[43] of 124 patients, hospitalization rates of 47.6% and 28.2% were respectivly reported for severely obese (BMI>30 kg/m^2 and BMI>35 kg/m^2) individuals. In these patients, the invasive menchanical ventilation (IMV) requirement rate was 68.6%. The increase in BMI was found to be associated with disease severity. The OR for IMV was 7.36 for the patient group with a BMI>35 and BMI<25. In our study, we defined obesity as a comorbid disease for patients with a BMI>30. Although statistical analysis did not show any difference between groups in terms of survival, the mean BMI was found to be lower in the survival group and there was a statistically significant difference (p=0.004) when BMIs were analyzed numerically. We believe that this situation creates a statistical misconception because the patients followed-up due to the low prevalence of obesity in our country are frequently below BMI>30 and obesity was defined as a comorbid disease in only 39 patients in the study. The current number of obese patients is not sufficient to evaluate obesity as an indicator of a mortality risk factor, but after evaluating the difference between mean BMIs in the entire patient group, we assume that the result is consistent with the literature.

In the quantitative analysis of survival and non-survival patients, it was determined that the risk of central nervous system disease increased 3.3 times, indicating the higher risk of developing critical illness and mortality from COVID-19[44]. Due to the low mean age in both groups (64 and 67 years) in the patients included in our study, the number of patients with dementia or previous cerebrovaskular disease is quite low, therefore, we believe that the inability to detect a significant difference between the groups makes statistical analysis inappropriate due to the small number of patients.

It was not observed that chronic liver disease did not affect the survival outcomes of patients with thyroid dysfunction, immunosuppression and patients with a postoperative hospitalization after emergency surgery. Although there are studies[45,46] reporting an increased risk for these patient groups in the literature, no increased risk was observed between groups in our study (p>0.05). However, we think that this is not statistically suitable for an evaluation in terms of being a risk factor due to the low number of patients included in our study in terms of accompanying comorbidities. This may be explained by the data loss, incomplete detailed access to patient information due to the retrospective collection of the data in the study, and also our study was conducted only in the critical intensive care patient group and therefore differed from all other studies in terms of the study population.

Since comorbid diseases such as obesity and COPD may affect the follow-up of patients in intubated invasive mechanical ventilation, subgroup analysis was performed in intubated patients. The mortality rate in patients treated with IMV was found to be as high as 71%. Although no underlying comorbidity seemed to increase the risk when evaluated in two groups, we think that the high mortality rate observed in intubated patients could statistically mislead us. There was no significant difference in the survival rate of the intubated patient subgroup in terms of any additional comorbidity. However, it was concluded that the disease displayed a higher mortality rate in the patient group with a high BMI (p=0.001). This situation can be explained as the need to keep the driving pressure high in the mechanical ventilation treatment strategies of the COVID-ARDS patient group. Ventilator-induced lung injury can be explained by the inability to manage hypercapnia with low tidal volumes in severely damaged lungs and by the development of high transpulmonary pressure caused by high intra-abdominal pressure in obese patients. Similar results were also evaluated in the same way in the studies[47] conducted with obese patients in literature.

No similar study has been found in the literature performing a risk analysis – except for demographic data –for comorbidities that evaluate only the patients under invasive mechanical ventilation. There are limited number of studies[48] reporting intubation and the need for invasive mechanical ventilation as risk factors in the critical COVID-19 patient group.

Our study results are valuable and significant in terms of this subgroup analysis, particularly in reporting the effect of comorbid diseases such as COPD and obesity on mortality and intubated patient follow-up results. However, in order to reveal comorbid diseases that may increase the risk of mortality in the intubated patient group, there is a need for prospective studies with a larger number of patient groups in which data loss can be prevented and reliable data can be collected, and there is also a need for studies conducted in more than one center with various treatment modalities.

In terms of the length of stay in the Intensive Care Unit, the patients in both groups stayed in the Intensive Care Unit for an average of 9 days (p>0.05). However, the survival group stayed in the hospital for an average of 21 days. There was no significant difference between the two groups in terms of the number of days until admission to the Intensive Care Unit. In our study, the results of the number of days until admission to the Intensive Care Unit were not reported, but some findings showing that late admission caused an increased risk of mortality have been reported in the literature[49,50].

There was no significant difference between APACHE-2 scores and day 1 and day 3 SOFA scores in patients receiving invasive mechanical ventilation therapy. This situation can be understood in the early period SOFA scores of patients already intubated with an advanced clinical picture, but during the intensive care follow-ups, the SOFA score elevations could not be measured in terms of the secondary infection risk and septic clinical development brought about by intubation, therefore the main evaluation could not be made. The main deficiency of our study is that it could not report the late-term results in the intubated patient subgroup.

We believe that the reason why we could not find a difference in admission lactate levels in this patient group, mostly transferred to the Intensive Care Unit as intubated, was due to the temporary improvement of hypoxia. It is not surprising that no difference was found in the group of patients who were followed-up with already low PaO_2/FiO_2 ratios in the severe ARDS clinic and who were intubated due to respiratory distress associated with this condition (p>0.05).

In addition, one of the limitations of our study is that we did not specify the mortality risk caused by increased lactate follow-ups. In addition, randomized controlled studies are needed to evaluate the efficacy of treatment with lactate clearance in the future.

Although the results in the literature reveal the severity of the disease by evaluating the entire critical and non-critical patient population, parameters that can be considered as an indicator of mortality in the critically ill group have been investigated in quite a few studies[7-11]. This study is a cross-sectional longitudinal study that was carried out retrospectively, aiming to define which variables the patient group with mortality in the Intensive Care Unit differed from the patient group with survival. With these findings obtained, current clinical treatment guidelines can be reformed for certain patient groups, and COVID-19 follow-up and course of treatment will be shaped based on various prognostic scales.

Limitations

In addition to having such strengths as applying the same treatment protocol to all patients and not experiencing any data loss as the patients included in the study spent the entire process in our hospital, there are also some limitations of the study. The first one is that it is a single-center study with a small sample size. Due to its retrospective design, it lacks dynamic clinical and laboratory data. All of our patients were treated in a single health center from a single geographic region. Therefore, despite the diversity in the patient population, the factors associated with outcomes may differ in other geographic regions. Also, having information about the trends and prognosis obtained by evaluating the recurrent clinical and laboratory parameters *via* short and long-term follow-ups would make an additional contribution to our study.

Conclusions

In the literature, higher rates of mortality have been reported in patients with HT, DM and obesity. Although no significant difference was found for HT, DM and obesity in our study, a significant difference was found between the two groups when BMI elevation was considered. A higher mortality connection was observed in hematological malignancies compared to malignancies caused by solid tumors, which is also consistent with the literature. In the subgroup analysis, however, the relationship between CRF and hematological malignancy as a comorbidity relationship in patients who underwent invasive mechanical ventilation compared to the general group was not found statistically. Advanced age and concomitant comorbidities in COVID-19 patients are associated with poor prognosis in critically ill COVID-19 patients. Also, a greater number of comorbidities are associated with higher disease severity of COVID-19. In addition, it is thought that low lymphocyte count, high CRP, ferritin and procalcitonin levels can guide clinicians in the early identification of patients with high mortality risks. There is also a need for reliable biomarkers that can predict the prognosis of severely ill patients. Some biomarkers have been proposed to determine disease severity.

In this study, the relationship between mortality and comorbidity was investigated in patient

groups followed-up in the admissionlactate due to COVID-19 disease and no relationship was found in terms of HT, DM, COPD, cardiovascular disease and obesity reported in the current literature. Yet, only patient groups with hematological malignancies and chronic renal failure comorbidities were found to be associated with high mortality rate.

In the COVID-19 pandemic, it is important to identify the patient group in the early period in terms of the need for intensive care and early treatment, which can guide the clinicians to predict mortality outcomes.

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Author's Contribution

Senem Girgin and Murat Aksun wrote the first draft of the protocol manuscript. Ahmet Salih Tüzen, Bir-zat Emre Gölboyu, Atilla Şencan and Senem Girgin planned the conception and design of the study and the protocol. Gizem Kırbaş, Ozan Sanlı, Sevinç Güven and Nagihan Karahan contributed to the design and implementation of the protocol. All authors provided critical revisions to the manuscript before app-roving the final version.

Data Availability

All data necessary to support the protocol are available upon reasonable request.

Conflict of Interest

Each of the authors discloses no conflicts of interest related to this work.

Ethics Approval

The permission from the Ministry of Health and the approval of the Hospital Ethics Committee were ob-tained for the study (Decision number: 0159, date: 10.03.2021).

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Informed Consent

Signed informed consent was obtained from all patients' relatives included in the study.

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