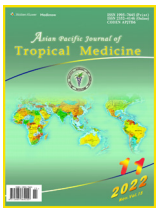

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Post-discharge mortality in the first wave of COVID-19 in Turkey

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ABSTRACT

Objective: To determine post-discharge mortality and associated factors of the first-wave multicenter Turkish Thoracic Society (TTD)-TURCOVID study.

Methods: In this retrospective cohort study, we analyzed the data of 18 of 26 centers included in the first TTD-TURCOVID study, and 1 112 cases diagnosed with COVID-19 between 11 March and 31 July 2020 participated in the study. All causes of death after COVID-19 discharge were recorded.

Results: The mean age of the patients was (51.07±16.93) years, with 57.6% male patients. In the cohort group, 89.1% of COVID-19 treatment locations were hospital wards, 3.6% were intensive care units (ICUs), and 7.2% were community outpatients. In the long-term follow-up, the in-hospital mortality rate was 3.6% (95% *CI* 2.6-4.8), the post-discharge mortality rate was 2.8% (95% *CI* 1.9-3.9), and the total mortality was 6.3% (95% *CI* 5.0-7.8). After discharge, 63.3% of mortality overall occurred during the first six months. Mortality rates in post-discharge follow-ups were 12.7% (95% *CI* 8.0-30.6) in cancer patients, 10.8% (95% *CI* 6.3-22.9) in chronic obstructive pulmonary disease patients, 11.1% (95% *CI* 4.4-22.7) in heart failure patients, 7.8 (95% *CI* 3.8-14.3) in atherosclerotic heart disease patients, and 2.3% (95% *CI* 0.8-5.6) in diabetes mellitus patients. In smokers/ex-smokers, the all-mortality rates were higher than in non-smokers.

Conclusions: This multicenter study showed that patients over 65 years of age, males, former/active smoker, ICU stay, lung, heart disease, and malignancy should be followed up for at least the first six months after discharge due to COVID-19.

KEYWORDS: COVID-19; Post-discharge; Mortality; Comorbidity

Significance

Respiratory, cardiac, and neurological symptoms may persist in some patients after COVID-19 infection. In elderly patients with comorbidities, COVID-19 has higher mortality in the hospital. In this study, mortality rates were higher in men, over 65 years of age, chronic obstructive pulmonary disease, hypertension, and malignancy in the long term after discharge from COVID-19. In addition, in-hospital and post-discharge mortality was higher in COVID-19 patients who were smokers/ex-smokers.

1. Introduction

According to figures by the World Health Organization (WHO) on October 14, 2022, 6 543 138 deaths occurred worldwide and 101 203 people died in Turkey due to COVID-19[1]. In the multicenter Turkish Thoracic Society (TTD)-TURCOVID study conducted in Turkey, the mortality rate due to COVID-19 was 4.5%[2]. Hospital ward and intensive care unit (ICU) mortality rates in the Lombardy region of Italy were respectively 12 and 27 per 1 000 patient days[3]. According to the data from the Centers for Disease Control and Prevention (CDC), 768 204 deaths have been reported in the US so far, 68% of them in hospitals or care centers[4].

Publicly reported COVID-19 death rates often consist of deaths occurring during hospital admission and/or hospitalization. However, there are few limited studies and notifications of COVID-19 post-discharge deaths. According to CDC data, there were 902 097 excess deaths not directly attributable to COVID-19 between the pandemic period on February 1, 2020, and November 27, 2021 in the US[4]. In a 6-year comparison of the January-April 2020 weekly death rates in the US, 87 001 extra deaths were reported between March and April 2020, 56 246 of which were due to COVID-19[5]. An additional 25 030 excess all-cause of deaths were reported in the COVID-19 outbreak between March and May 2020 in France in continental Europe[6]. When the death data between January and May 2020 are analyzed with the last 4 years, 4 084 extra deaths were detected with a 10% weekly increase between the 10th and 15th weeks in Istanbul, Turkey[7]. It has been observed that excess causes of death have increased with the COVID-19 pandemic all over the world.

Respiratory, cardiac, and neurological symptoms may continue after COVID-19[8]. Respiratory failure and long-term oxygen demand may develop after COVID-19 discharge. Deteriorations in lung diffusion capacity, total lung capacity, forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC have been demonstrated in post-discharge COVID-19 cases[9]. It is not clear how long these complications persist, terminate, or relapse. Although deaths in the hospitalization period due to COVID-19 have been reported all over the world, the death reports of COVID-19 patients after discharge from the hospital are not clear[1]. Information on post-discharge mortality rates in COVID-19 has begun to be reported with studies[10–13]. Information on the follow-up and long-term mortality rates of patients discharged with the diagnosis of COVID-19 is insufficient.

In the first wave of the COVID-19 pandemic, long-term follow-ups of patients who were diagnosed and received treatment are curious. This study was planned to determine the post-discharge mortality and associated risk factors of the first-wave multicenter TTD-TURCOVID cohort study.

2. Subjects and methods

2.1. Study design and participants

This study was conducted to determine the post-discharge mortality rates and related risk factors of a multicenter cohort study conducted with 1 500 adult patients diagnosed with COVID-19 from 26 centers hospitalized between 11 March and 31 July 2020, in Turkey.

2.2. Data collection

In-hospital mortality and mortality-related risk factors were calculated with the data obtained from the TTD-TURCOVID study[2]. In this study, it was planned to collect post-discharge mortality data by evaluating the same patient cohort. For this cohort study, 18 of the 26 centers in the initial study participated with 1 112 cases. Demographic information, smoking history, first treatment place, and comorbidities of the cases in the participating centers were recorded. Researchers at participating centers recorded deaths retrospectively by checking the cases recorded in the first study from the hospital systems where they were treated and/or from the Turkish national death reporting systems. All-cause of deaths and dates after COVID-19 discharge were recorded. Case definitions were taken in the same way as in the TTD-TURCOVID study[2]. The WHO COVID-19 case definition sheet was used to create the case definition. As a result, a confirmed case was defined as the presence of a positive nucleic acid amplification test or a positive rapid antigen detection test, as well as clinical and radiographic findings strongly suggestive of COVID-19.

2.3. Ethical approval

This multicenter registry study was approved by the Gazi University Faculty of Medicine ethics review board (356/22.05.2020).

2.4. Statistical analysis

As descriptive statistics, frequencies and percentages (%) for categorical variables and mean ± SD for numerical variables were given. Mortality rates and 95% confidence intervals (*CI*) were estimated. Statistical analysis was performed using SPSS for Windows version 24.0.

3. Results

3.1. Study population

In the study, 57.6% of the participants were male and the mean age was (51.07±16.93) years. Of the study population, 65.7% never smoked, and 34.3% were smokers or ex-smokers. Body mass index (BMI) was below 30 in 78.4% of the cases. First treatment hospital locations for COVID-19 in the cohort group: 89.1% were in hospital wards, 3.6% were in the ICUs, and 7.2% were outpatients in the community. During follow-up, 78 (8.8%) of the patients in the hospital ward were taken to the ICU. At admission, 77.2% of the cases had pneumonia and 14.5% had severe pneumonia. Acute respiratory distress syndrome (ARDS), multi-organ failure, macrophage activation syndrome (MAS), sepsis, and septic shock developed in fewer patients. The most common comorbidity in the study population was hypertension (26.0%) (Table 1).

Table 1. Descriptive statistics for demographic and clinical characteristics at admission.

Variable	*n*	%
Age, years, median (min-max)	51 (17-92)	
<65	843	76.1
⩾65	265	23.9
Sex		
Male	637	57.6
Female	469	42.4
BMI, kg/m^2		
<30	534	78.4
⩾30	147	21.6
Smoking		
Smoker/ex-smokers	349	34.3
Non-smokers	669	65.7
Treatment area		
Community	72	7.2
Non-ICU in hospital	887	89.1
ICUs	36	3.6
Syndromes at admission		
Pneumonia	859	77.2
Severe pneumonia	161	14.5
ARDS	24	2.2
Multi-organ failure	8	0.7
Sepsis	28	2.5
Septic shock	3	0.3
MAS	19	1.7
Comorbidity		
Hypertension	289	26.0
Malignancy	55	4.9
COPD	74	6.7
Diabetes mellitus	177	15.9

BMI, body mass index; ICUs, intensive care units; ARDS, acute respiratory distress syndrome; MAS, macrophage activation syndrome; COPD, chronic obstructive pulmonary disease. Unclear data in the retrospective patient cohort were not included in the statistics. Therefore, the total number of cases is not 1 112 occasionally. However, the total number of cases in syndrome at admission and comorbidity data was made over 1 112 patients. Active daily smokers were defined as smokers, patients who had not smoked for at least one month but had previously smoked regularly were defined as ex-smokers, and those who had never smoked regularly were defined as non-smokers.

Table 2. Mortality rates and 95% confidence intervals for overall data and sex.

Variable	Overall (n=1 112)		Male (n=637)		Female (n=469)	
	Mortality count	Mortality rate (95% *CI*)	Mortality count	Mortality rate (95% *CI*)	Mortality count	Mortality rate (95% *CI*)
In-hospital mortality	40	3.6 (2.6-4.8)	31	4.9 (3.4-6.7)	9	1.9 (1.0-3.5)
Post-discharge mortality	30	2.7 (1.9-3.9)	21	3.3 (2.2-5.1)	9	1.9 (1.0-3.5)
Total mortality	70	6.3 (5.0-7.8)	52	8.2 (6.2-10.5)	18	3.8 (2.4-5.9)

CI, confidence interval.

3.2. Mortality analysis

Out of 1 112 cases included in the study, in-hospital mortality rate was 3.6% (95% *CI* 2.6-4.8), post-discharge mortality rate was 2.7% (95% *CI* 1.9-3.9), total mortality was 6.3% (95% *CI* 5.0-7.8) at 18-months follow-up. None of the patients treated in the community died during the acute or long-term follow-ups. In-hospital [4.9% (95% *CI* 3.4-6.7)], post-discharge [3.3% (95% *CI* 2.2-5.1)], and total mortality rate [8.2% (95% *CI* 6.2-10.5)] were higher in men (Table 2).

In the patient population over 65 years of age, the in-hospital mortality rate was 9.1% (95% *CI* 6.0-13.0), the post-discharge mortality was 7.5% (95% *CI* 5.3-12.3), and the total mortality was 16.6% (95% *CI* 12.5-21.4) (Table 3).

Table 3. Mortality rates and 95% confidence intervals for age groups.

Variable	Age ≥65 years (n=265)		Age <65 years (n=843)	
	Mortality count	Mortality rate (95% *CI*)	Mortality count	Mortality rate (95% *CI*)
In-hospital mortality	24	9.1 (6.0-13.0)	16	1.9 (1.1-3.0)
Post-discharge mortality	20	7.5 (5.3-12.3)	10	1.2 (0.6-2.1)
Total mortality	44	16.6 (12.5-21.4)	26	3.1 (2.1-4.4)

CI, confidence interval.

For patients followed up in the ICUs, in-hospital mortality was 19.4% (95% *CI* 9.1-34.4), post-discharge mortality was 8.3% (95% *CI* 3.0-25.1), and total mortality was 27.8% (95% *CI* 15.3-43.7) (Table 4).

Table 4. Mortality rates and 95% confidence intervals for the first treatment setting.

Variable	Non-ICU hospitalization (n=887)		ICU hospitalization (n=36)	
	Mortality count	Mortality rate (95% *CI*)	Mortality count	Mortality rate (95% *CI*)
In-hospital mortality	28	3.2 (2.2-4.5)	7	19.4 (9.1-34.4)
Post-discharge mortality	25	2.8 (1.9-4.2)	3	8.3 (3.0-25.1)
Total mortality	53	6.0 (4.6-7.7)	10	27.8 (15.3-43.7)

CI, confidence interval; ICUs, intensive care units.

Considering the smoking status of the cohort group, in smokers or ex-smokers, the in-hospital mortality rate was 5.7% (95% *CI* 3.6-8.5), post-discharge 5.2% (95% *CI* 3.4-8.3), and a total of 10.9% (95% *CI* 7.9-14.5) were found higher than non-smokers (Table 5).

Table 5. Mortality rates and 95% confidence intervals for smoking status.

Variable	Non-smokers (n=669)		Smokers/ex-smoker (n=349)	
	Mortality count	Mortality rate (95% *CI*)	Mortality count	Mortality rate (95% *CI*)
In-hospital mortality	9	1.3 (0.7-2.4)	20	5.7 (3.6-8.5)
Post-discharge mortality	10	1.5 (0.8-2.7)	18	5.2 (3.4-8.3)
Total mortality	19	2.8 (1.8-4.3)	38	10.9 (7.9-14.5)

CI, confidence interval.

In long-term follow-up, 63.3% of the deaths occurred after discharge within the first six months. Of those with hypertension, 7.6% (95% *CI* 5.0-11.1) died in the hospital, 4.8% (95% *CI* 3-8.4) in the post-discharge, and a total of 12.5% (95% *CI* 9.0-16.6) died. Mortality rates in post-discharge follow-ups were 12.7% (95% *CI* 8.0-30.6) in cancer patients, 10.8% (95% *CI* 6.3-22.9) in chronic obstructive pulmonary disease (COPD) patients,11.1% (95% *CI* 4.4-22.7) in heart failure patients, 7.8 (95% *CI* 3.8-14.3) in atherosclerotic heart disease patients, and 2.3% (95% *CI* 0.8-5.6) in diabetes mellitus patients. The highest comorbidity for total mortality was malignancy, with a rate of 38.2 (95% *CI* 26.2-51.4) (Table 6).

The most common causes of post-discharge deaths were sepsis (13.3%, 4/30) and malignancies other than lung cancer (13.3%, 4/30). There were 23.3% (7/30) deaths of unknown cause after COVID-19 discharge.

4. Discussion

In the follow-up of COVID-19 patients treated at the hospital, the all-cause total mortality rate was 6.3%. Those over 65 years of age, male sex, those with comorbidities and those followed in the intensive care unit were among the risky groups.

Annual expected deaths in the United States for 2019 showed a 20% increase over annual estimates. In the United States, there was a 35% increase in expected deaths during March-April 2019, not attributed to COVID-19[5]. It has been shown that deaths from all causes in the elderly population increased during the pandemic period in France[6]. Mortality in the first 30 days after COVID-19 was found to be 39.9% in long-term care centers in Sweden[11]. In a study conducted in Norway, six-month mortality increased with age and the mortality rate was 21% in individuals over the

Table 6. Mortality rates and 95% confidence intervals for comorbidities.

Variable	In-hospital mortality		Post-discharge mortality		Total mortality	
	Mortality count	Mortality rate (95% *CI*)	Mortality count	Mortality rate (95% *CI*)	Mortality count	Mortality rate (95% *CI*)
Hypertension (*n*=289)	22	7.6 (5.0-11.1)	14	4.8 (3.0-8.4)	36	12.5 (9.0-16.6)
COPD (*n*=74)	12	16.2 (9.2-25.8)	8	10.8 (6.3-22.9)	20	27.0 (17.9-37.9)
Heart failure (*n*=45)	5	11.1 (4.4-22.7)	5	11.1 (4.4-22.7)	10	22.2 (12.0-35.8)
Diabetes mellitus (*n*=177)	10	5.6 (2.9-9.8)	4	2.3 (0.8-5.6)	14	7.9 (4.6-12.6)
Atherosclerotic Heart disease (*n*=102)	8	7.8 (3.8-14.3)	8	7.8 (3.8-14.3)	16	15.7 (9.6-23.7)
Malignancy (*n*=55)	14	25.5 (15.4-38.0)	7	12.7 (8.0-30.6)	21	38.2 (26.2-51.4)

CI, confidence interval. COPD, chronic obstructive pulmonary disease.

age of 60 who were discharged after COVID-19[14]. Similarly, in our study, the first six months were the period with the highest number of deaths in cases discharged after COVID-19, and post-discharge mortality rates were found higher in cases over the age of 65. It is not clear how many of the world's excess deaths are due to COVID-19. In March-June 2020, post-discharge (mean 80 days) mortality from COVID-19 was reported as 6.4% in the Netherlands. In the same study, the most common causes of rehospitalization were respiratory, vascular, or existing co-morbidities[10].

In our study, all mortality rates of the male sex were higher than the females. In the registry study involving the same cases, the male sex was determined as a risk factor for COVID-19 mortality in the hospital period[2]. COVID-19 cases in the male sex may have a more severe course[15]. In the first wave of the COVID-19 pandemic in France, all-cause of mortality was higher in men[6]. In Sweden, the male sex (*OR* 2.60; 95% *CI* 2.22-3.05) was found a risk factor for mortality in the first 30 days after COVID-19[11].

Patients who were followed up in the ICU due to COVID-19 had higher in-hospital and post-discharge mortality rates than those who were not in the ICUs. The total mortality rate in COVID-19 patients followed in the ICU is 27.8%. Patients discharged from ICUs may need to be checked earlier and more frequently.

Post-discharge pulmonary, cardiac, and neurological complications due to COVID-19 may negatively affect mortality compared to the general population. In our study, the most common causes of mortality were malignancies. However, there were causes of death whose cause could not be well documented after COVID-19 discharge. Some of these deaths were officially recorded as cardiac arrests. In other studies, cardiovascular diseases were the most common cause of death in the first six months in cases discharged after COVID-19, and myocardial involvement may accompany COVID-19 infection. SARS-CoV-2 binds to ACE2, which is commonly found in alveolar tissue and myocardial tissue[12,16]. Cardiovascular medicine societies have recommendations for thrombo-prophylaxis, and low molecular weight heparin for cases discharged after COVID-19[17]. For adults hospitalized with COVID-19 pneumonia and confirmed venous thromboembolism, recommendation of three months of therapeutic dose anticoagulant therapy is to reduce the risk of recurrent venous thromboembolism[18]. In our study, patients do not have data on cardiac involvement in acute COVID-19 infection. The follow-up of cardiovascular and pulmonary symptoms that continue for six months or newly emerged after COVID-19 discharge has gained importance. Pulmonary, cardiac, and neurological evaluations are required for the first six months. In a cohort study, a high in-hospital mortality rate and an increase in one-year all-cause mortality were seen in COVID-19 patients with cancer[19]. In our study, 7 of 55 patients diagnosed with malignancy at the time of COVID-19 diagnosis died after discharge.

The most common comorbidity of COVID-19 cases in the study was hypertension, and in-hospital, post-discharge, and total mortality rates were found higher. Among other comorbidities, patients with malignancy had the highest mortality rate. In the study conducted in the acute period of COVID-19 in the same cohort group, COPD and malignancy were risk factors for mortality[2]. In addition, in-hospital, post-discharge, and total mortality rates of ex/active smokers were higher than those of non-smokers. The follow-up of patients with malignancy, COPD, and cardiovascular disease after discharge from COVID-19 has gained importance. In COVID-19 cases, evaluation should be made for long-term oxygen needs after discharge. It has been shown that the regulation of hypertension and type 2 diabetes can be impaired in the post-COVID-19 period[20].

Due to the retrospective registry study, the causes of death in the health systems of the cases were recorded. There are seven unknown causes of death in this system. In the first wave of the pandemic, COVID-19 cases were mostly isolated in the hospital, albeit with mild symptoms. However, in the latter stages of the pandemic, with the increasing number of cases, cases with pneumonia and respiratory failure were followed in the hospital, while asymptomatic or less symptomatic cases were followed up in outpatient. Therefore, the cases in the registry reflect the first wave in Turkey and the mild symptomatic cases of the population. Our data in the study cannot be generalized as it reflects the first wave in Turkey. There is a need for larger studies investigating the causes of death after COVID-19 discharge.

In conclusion, all causes of death and accompanying factors after discharge of patients infected in the first wave of COVID-19 were determined in this multicenter study. According to these findings, cases over the age of 65, male sex, ex/active smokers, followed in ICUs, and suffering from pulmonary disease, cardiac disease, and malignancy should be followed for at least 6 months after discharge due to COVID-19.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Authors' contributions

FF, NK, PDC, SAB and OB designed the study; FF, NK, PDC, SAB, OB, OK, PAY, II, YS, EA, SM, CC, BK, BBK, HSO, GO, ZT, ME, TUC, OA, ENT, OA, NK, MMT, GG, SA, OO, PYG, IB, HB, IKO, SB, BG, IH, HKO, GS, MA, AFK, OI and HB collected the data; SK and FF analyzed the data; FF and NK searched the literature and wrote the manuscript; FF, OB, PDC, SAB and NK edited and revised manuscript according to journal's instructions; FF, PDC and OB edited and controlled the final version of the manuscript. All the authors approved the final version of the manuscript.

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