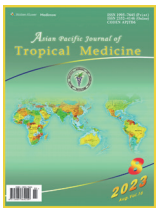

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Clinical characteristics and outcomes of nosocomial COVID−19 in Turkey: A retrospective multicenter study

Süleyman Yıldırım[1]✉, Celalettin Yılmaz[2], Gülru Polat[2], Serap Argun Baris[3], İlknur Başyiğit[3], İlknur Kaya[4], Ceyda Anar[5], Mihriban Bozkurt[5], Hüsnü Baykal[6], Hulya Dirol[7], Gamzenur Ozbey[7], Emine Ozsari[8], Emel Cireli[2], Ali Kadri Çırak[2], Dursun Tatar[2], Mine Gayaf[2], Selen Karaoglanoglu[9], Yener Aydin[10], Atilla Eroglu[10], Yıldız Olçar[11], Berna Botan Yıldırım[12], Bengül Gürsoy[13], Deniz Demir Yılmaz[13], Elif Yelda Ozgun Niksarlioglu[14], Ramazan Eren[14], Ayşegül Tomruk Erdem[15], Müge Meltem Tor[15], Fusun Fakili[16], Mustafa Çolak[17], Merve Erçelik[18], Ali Tabaru[19], Özlem Ediboglu[1]

[1]*Intensive Care Unit, Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital, University of Health Sciences Turkey, İzmir, Turkey*

[2]*Department of Pulmonology, Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital, University of Health Sciences Turkey, İzmir, Turkey*

[3]*Department of Pulmonary Medicine, School of Medicine, Kocaeli University, Kocaeli, Turkey*

[4]*Department of Pulmonology, Kütahya Health Sciences University, Kütahya, Turkey*

[5]*Department of Pulmonology, Atatürk Training and Research Hospital, İzmir Katip Çelebi University, İzmir, Turkey*

[6]*Department of Pulmonology, Ankara Atatürk Sanatory Training and Research Hospital, University of Health Sciences, Ankara, Turkey*

[7]*Department of Pulmonology, Faculty of Medicine, Akdeniz University, Antalya, Turkey*

[8]*Department of Pulmonology, Bolu Abant İzzet Baysal University Training and Research Hospital, Bolu, Turkey*

[9]*Department of Pulmonology, Ordu University Training and Research Hospital, Ordu, Turkey*

[10]*Department of Thoracic Surgery, Medical Faculty, Erzurum, Ataturk University, Turkey*

[11]*Department of Infectious Disease and Clinical Microbiology, Kastamonu Training and Research Hospital, Kastamonu, Turkey*

[12]*Department of Pulmonology, Başkent University Hospital Konya, Konya, Turkey*

[13]*Department of Pulmonology, İstanbul Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, İstanbul, Turkey*

[14]*Department of Chest Diseases, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Health Science University, İstanbul, Turkey*

[15]*Department of Pulmonology, Faculty of Medicine, Zonguldak Bülent Ecevit University, Zonguldak, Turkey*

[16]*Department of Pulmonary Medicine, Gaziantep, Faculty of Medicine, Şahinbey Research Hospital, Gaziantep University, Turkey*

[17]*Department of Pulmonology, Balıkesir, Health Practice and Research Hospital, Balıkesir University, Turkey*

[18]*Department of Pulmonology, Afyonkarahisar Dinar State Hospital, Afyon, Turkey*

[19]*Department of Pulmonology, Söke Fehime Faik Kocagöz State Hospital, Aydın, Turkey*

ABSTRACT

Objective: To identify the clinical characteristics and outcomes of hospital-acquired SARS-CoV-2 infection during the vaccination period nationwide in Turkey.

Methods: COVID-19 patients followed in the pandemic services across Turkey between January 1, 2021, and March 31, 2022 were investigated retrospectively. Nosocomial COVID-19 was defined as a patient neither diagnosed with COVID-19 nor suspected COVID-19 at the hospital admission and was confirmed COVID-19 ⩾5 days after hospital admission. The primary outcome of this study was in-hospital mortality; demographic features and vaccination status was compared between survivors and non-survivors.

Significance

Nosocomial COVID-19 patients had a higher rate of mortality than community-acquired cases. Vaccination against SARS-CoV-2 decreases the need for intensive care unit admission and in-hospital mortality in patients with nosocomial COVID-19.

✉To whom correspondence may be addressed. E-mail: deu.syldrm@gmail.com

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Results: During the study period, 15 573 COVID-19 patients were followed in 18 centers and 543 (3.5%) patients were nosocomial COVID-19. Most patients with nosocomial COVID-19 (80.4%) were transferred from medical wards. 162 (29.8%) of the patients with nosocomial COVID-19 admitted to the intensive care unit due to disease severity and 138 (25.4%) of the patients died during hospital stay. Advanced age (≥65 years) and number of comorbid diseases (≥2) was found to be associated with mortality in nosocomial COVID-19 (*OR* 1.74, 95% *CI* 1.11-2.74 and *OR* 1.60, 95% *CI* 1.02-2.56, respectively). Vaccination was associated with survival in nosocomial COVID-19 (*OR* 0.25, 95% *CI* 0.16-0.38).

Conclusions: Patients with nosocomial COVID-19 had increased admission to intensive care units and higher mortality rate. Vaccination can decrease the in-hospital mortality rate.

KEYWORDS: COVID-19; Nosocomial infection; Vaccination; Intensive care unit

1. Introduction

The coronavirus disease-19 (COVID-19) spread rapidly and turned into an outbreak over the last two years. The virus can be transmitted from a person to others *via* respiratory droplets and close contact increases the risk of transmission[1].

Closed, crowded, and poorly ventilated places are especially risky for transmission. Unfortunately, hospitals are one of the most high-risk places for spreading COVID-19. In multicenter studies, 12.5% to 17.3% of patients with COVID-19 who followed up in hospital were defined as having nosocomial COVID-19[2,3]. The incidence of nosocomial COVID-19 varies from 0% to 65%[4,5]. Dialysis centers and long-term care facilities had higher nosocomial COVID-19 rates while surgical wards had lower nosocomial COVID-19 rates[6].

Nosocomial COVID-19 patients had a higher rate of mortality than community-acquired cases. Advanced age and comorbid conditions such as cancer were associated with mortality in nosocomial COVID-19, and the mortality rate was 1.3 times greater in nosocomial COVID-19 than in community-acquired cases[2,7,8].

This study aimed to determine the clinical characteristics and outcomes of hospital-acquired SARS-CoV-2 infection during the vaccination period nationwide in Turkey.

2. Subjects and methods

2.1. Study population

This is a retrospective study carried out in eighteen hospitals in Turkey between January 1, 2021, and March 31, 2022. Patients (18 years and older) diagnosed with nosocomial COVID-19 and transferred to pandemic services were included in the study. Nosocomial COVID-19 was defined as a patient neither diagnosed with COVID-19 nor suspected COVID-19 at the hospital admission and a confirmed COVID-19 by reverse-transcription polymerase chain reaction (RT-PCR) after ≥5 days after hospital admission[9] (Figure 1).

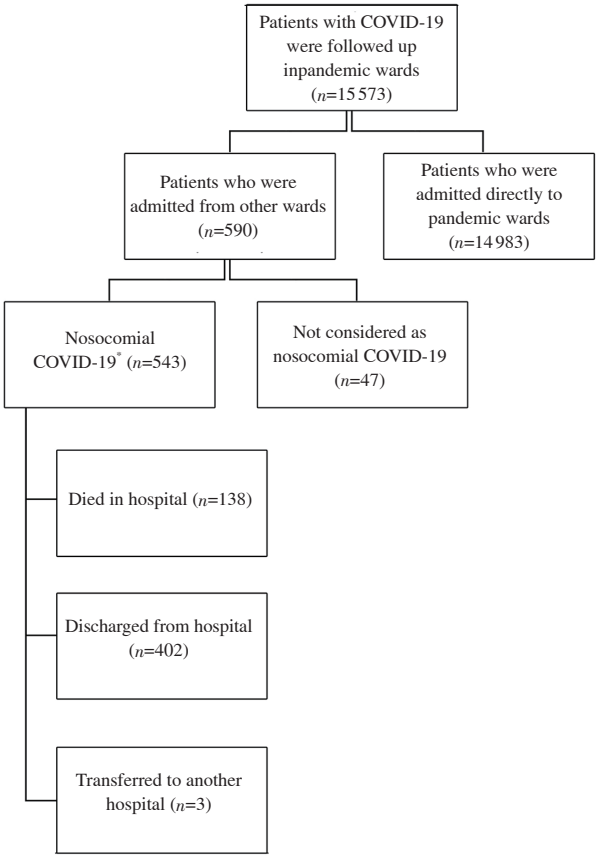

Figure 1. Flow chart of patient selection process. *Nosocomial COVID-19 was defined as a patient neither diagnosed with COVID-19 nor suspected COVID-19 at the hospital admission and a confirmed COVID-19 by reverse-transcription polymerase chain reaction (RT-PCR) after ≥5 days after hospital admission.

2.2. Data collection

Patients' demographic features, comorbidities, smoking status, vaccination status and ward which patient was followed before transferred pandemic ward were obtained from medical records of each center.

2.3. Statistical analysis

Continuous variables were shown as mean±standard deviation

(SD) if they were normally disturbed, and they were presented as median and interquartile range (IQR) if they were not normally disturbed. Nomimal variables were shown as *n* (%). Continuous variables were compared with the *t*-test or Mann-Whitney *U* test and nominal variables were compared with *Chi*-square test. Among 543 patients with nosocomial COVID-19, 3 of them were transferred to other health care centers so their survivor status was unknown. The remaining 540 patients were compared for mortality. A multivariate regression analysis was performed to detect risk factors for mortality. *P* value <0.05 was considered as statistically significant.

2.4. Ethical statement

The study was conducted after the approval of the local ethic committee (IRB number: 2022/21-23). The study was carried out in accordance with Declaration of Helsinki 2013.

3. Results

A total of 543 patients were included in the final analysis with the mean age of (65.1±15.7) years, and 333 (61.3%) patients were male. The most common comorbidities were hypertension (*n*=259, 47.7%), diabetes mellitus (*n*=158, 29.1%), and 64.1% of patients had at least two comorbidities. We summarized the demographic features of patients in Table 1.

Among the 543 nosocomial COVID-19 patients who followed pandemic services, 106 (19.5%) patients transferred from surgical wards and 437 (80.5%) patients were transferred from medical wards. Most patients transferred to pandemic services were from pulmonology wards (*n*=183, 33.7%) and internal medicine wards (*n*=176, 32.94%). Nosocomial COVID-19 patients from medical wards were older and had more comorbid diseases than surgical patients (mean ages were 66 *vs*. 60 years, *P*=0.001). The time from admission to PCR positivity was longer in medical ward patients than in surgical patients (median 14 *vs*. 10 days, *P*=0.023) (Table 2).

A total of 342 (63.0%) patients were vaccinated, 181 (33.3%) patients were non-vaccinated, and the vaccination status of 18 (3.3%) patients was unknown. The demographic and clinical characteristics of vaccinated and non-vaccinated patients were similar, except that the vaccinated patients were older. Intensive care unit (ICU) admission and mortality rates were lower in vaccinated patients (24.9% *vs*. 42.5%, *P*<0.001 and 17% *vs*. 43.1%, *P*<0.001, respectively), despite the fact that vaccinated patients were older than non-vaccinated patients [mean age (65±14) years *vs*. (60±18) years, respectively, *P*=0.008] (Table 3).

The mean length of hospital stay was (24.8±21.5) days, and the mean length of pandemic service was (12.2±13.9) days. 162 (29.8%) nosocomial COVID-19 patients admitted to ICU due to disease severity and 138 (25.4%) dead during hospital stay.

Table 1. Demographic characteristics of patients with nosocomial COVID-19.

Variables	All patients (*n*=543)
Age, mean±SD, years	65.1±15.7
Sex, male/female	333/210
Residency, nursing home/home	15/528
Smoking status^, *n* (%)	
Non-smoker	190 (35.0)
Active smoker	87 (16.0)
Ex-smoker	171 (31.5)
Unknown	95 (17.5)
Comorbidities, *n* (%)	
Hypertension	259 (47.7)
Diabetes mellitus	158 (29.1)
Chronic obstructive pulmonary disease	110 (20.3)
Asthma	26 (4.8)
Coronary artery disease	138 (25.4)
Congestive heart failure	78 (14.4)
Malignity of solid organ	141 (26.0)
Hematologic malignity	42 (7.7)
Cerebrovascular disease	43 (7.9)
Neurodegenerative disease	38 (7.0)
Chronic kidney failure	84 (15.5)
Liver cirrhosis	15 (2.8)
COVID-19 vaccination status, *n* (%)	
Non-vaccinated	181 (33.3)
Vaccinated	342 (63.0)
Unknown	20 (3.7)
The day COVID-19 diagnose, mean±SD, days	13.7±12.7
Intensive care unit admission, *n* (%)	162 (29.8)
Non-survivors, *n* (%)	138 (25.4)
Length of stay in hospital, mean±SD, days	24.8±21.5
Length of stay in hospital after COVID-19, mean±SD, days	12.1±13.9

^Non-smoker: someone who has not smoked more than 100 cigarettes in their lifetime and does not currently smoke; Active smoker: somenoe who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes; Ex-smoker: someone who has smoked more than 100 cigarettes in their lifetime but has not smoked in the last 28 days.

Table 2. Comparison of surgical and medical patients with nosocomial COVID-19.

Variables	Medical ward (*n*=437)	Surgical ward (*n*=106)	*P* value
Age, mean±SD, years	66±15	60±18	0.001#
Number of comorbid diseases, median (IQR)	2 (0-3)	2 (1-3)	0.005*
Day of PCR positivity, median (IQR), days	10 (8-12)	14 (7-15)	0.023*
Length of hospital stay, median (IQR), days	14 (8-27)	19 (13-30)	0.002*

IQR, Interquartile range; PCR, Polymerase chain reaction; SD, Standard deviation.#*P*<0.05, *t* test; *P<0.05, Mann-Whitney *U* test was used for analysis.

Table 3. Comparison of vaccinated and unvaccinated nosocomial COVID-19 patients.

Variables	Vaccinated (n=342)	Unvaccinated (n=181)	P value
Age, mean±SD, years	65±14	60±18	0.008*
Sex, male, n (%)	215 (62.9)	106 (58.6)	0.336
Comorbidities, n (%)			
Hypertension	169 (49.4)	84 (46.4)	0.513
Diabetes mellitus	107 (31.3)	48 (26.5)	0.256
Chronic obstructive pulmonary disease	73 (21.3)	34 (18.8)	0.490
Asthma	17 (4.9)	8 (4.4)	0.779
Coronary artery disease	91 (26.6)	40 (22.1)	0.258
Congestive heart failure	47 (13.7)	25 (13.8)	0.983
Malignity of any solid organ	82 (24.0)	52 (28.7)	0.236
Hematologic malignity	21 (6.1)	19 (10.5)	0.075
Cerebrovascular disease	19 (5.5)	22 (12.2)	0.008*
Neurodegenerative disease	25 (7.3)	13 (7.2)	0.957
Chronic kidney failure	57 (16.6)	23 (12.7)	0.231
Number of comorbidities, median (IQR)	2 (1-3)	2 (1-3)	0.935
Medical wards, n (%)	272 (79.5)	149 (82.3)	0.444
The day COVID-19 diagnose, median (IQR), days	10 (6-15)	10 (7-15)	0.518
Intensive care unit admission, n (%)	85 (24.9)	77 (42.5)	<0.001*
Non-survivors, n (%)	58 (17.0)	78 (43.1)	<0.001*
Length of hospital stay, median (IQR), days	18 (12-29)	19 (12-31)	0.831

*P<0.05. IQR, Interquartile range; t test, *Chi* square test, and Mann-Whitney U and were used for analysis.

Table 4. Comparison of survivors and non-survivors with nosocomial COVID-19.

Variables	Survivors (n=402)	Non-survivors (n=138)	P value
Age, mean±SD, years	64±16	70±13	0.001*
Sex, male, n (%)	249 (61.9)	83 (60.1)	0.567
Smoking status^, n (%)			
Non-smoker	157 (39.1)	35 (25.4)	0.245
Active smoker	72 (17.9)	13 (9.4)	
Ex-smoker	125 (31.1)	38 (27.5)	
Unknown	48 (11.9)	52 (37.7)	
Comorbidities, n (%)			
Hypertension	190 (47.2)	68 (49.2)	0.193
Diabetes mellitus	115 (28.6)	42 (30.4)	0.908
Chronic obstructive pulmonary disease	88 (21.8)	22 (15.9)	0.221
Asthma	20 (4.9)	6 (4.3)	0.887
Coronary artery disease	93 (23.1)	45 (32.6)	0.053
Congestive heart failure	51 (12.7)	27 (19.5)	0.108
Malignity of any solid organ	96 (23.9)	44 (31.9)	0.173
Hematologic malignity	28 (6.9)	13 (9.4)	0.162
Cerebrovascular disease	25 (6.2)	18 (13.1)	0.033*
Neurodegenerative disease	22 (5.5)	16 (11.5)	0.046*
Chronic kidney failure	52 (12.9)	32 (23.2)	0.012*
COVID-19 vaccination status, n (%)			
Non-vaccinated	103 (25.6)	78 (56.5)	<0.001*
Vaccinated	284 (70.6)	58 (42.1)	
Unknown	15 (3.8)	2 (1.4)	
Medical wards, n (%)	316 (78.6)	119 (86.2)	0.124

*P<0.05. Mann-Whitney U and *Chi* square test were used for analysis.

Table 5. Multivariate regression analysis for mortality.

Variables	*OR* (95% *CI*)	P value
Age (⩾65 years *vs*. <65 years)	1.74 (1.11-2.74)	0.015
Number of comorbidities (patients had 2 comorbid diseases *vs*. <2 comorbid diseases)	1.60 (1.02-2.56)	0.050
Vaccination status (vaccinated *vs*. non-vaccinated)	0.25 (0.16-0.38)	<0.001

Advanced age (≥65 years), vaccination status, and comorbid conditions such as cerebrovascular disease, neurodegenerative disease, and chronic kidney failure were associated with higher mortality (Table 4).

Advanced age (≥65 years) and the number of comorbid diseases (≥2) were found to be independent risk factors for mortality in multivariate regression analysis (*OR* 1.74, 95% *CI* 1.11-2.74 and *OR* 1.60, 95% *CI* 1.02-2.56, respectively). Vaccination decreased the risk of mortality in nosocomial COVID-19 patients (*OR* 0.25, 95% *CI* 0.16-0.38, *P*<0.001) (Table 5).

4. Discussion

COVID-19 is a contagious disease that can be transmitted quickly from one person to another. Hospitals are one of the most susceptible places to infection, despite all preventive measures to limit disease spread. During the study period, 15 573 COVID-19 patients were followed in 18 centers, and 543 (3.5%) were nosocomial COVID-19 patients. The majority of nosocomial COVID-19 patients (80.4%) were from medical wards. One-third of nosocomial COVID-19 patients required ICU admission, and 138 (25.4%) of them died during their hospital stay. Vaccination against COVID-19 was associated with fewer intensive care requirements and decreased mortality.

The incidence of hospital-acquired SARS-CoV-2 infection varies widely from 0% to 65%[5,10]. Read *et al.* reported that 11.6% of COVID-19 patients became infected after hospital admission in the United Kingdom[11]. In a study conducted in the UK and Italy, 12.5% of hospitalized COVID-19 patients were hospital-acquired SARS-CoV-2 infection[3]. In a meta-analysis that included 8251 COVID-19 patients, 1 513 (18.3%) of them were defined as probable or definite nosocomial COVID-19. The rate of nosocomial COVID-19 was lower in our study than in previous studies conducted in the pre-vaccination era; while our study was performed during the mass vaccination era in Turkey. Vaccination may have caused a lower rate of nosocomial COVID-19 in our study. Another reason is that the increased awareness of nosocomial COVID-19 over time and the implementation of prevention measures may have caused the nosocomial COVID-19 rate to be lower.

Lower estimated rates of hospital-acquired SARS-CoV-2 infection were observed in surgical wards, and higher estimated rates of hospital-acquired SARS-CoV-2 infection were observed in long-term care facilities, hemodialysis centers, and general wards[6]. Advanced age, number of comorbidities, and length of hospital stay were associated with nosocomial COVID-19[3,12–14]. The vast majority of nosocomial COVID-19 patients (80.4%) were from medical wards in the current study. In our study, patients who followed up in the medical wards were older and had more comorbid conditions than patients who followed up in the surgical wards, which was considered the main reason for this situation.

The association between worse outcomes, such as admission to the ICU or mortality, and nosocomial COVID-19 is controversial. Khan *et al.* reported that there was no significant difference in 30-day mortality between nosocomial COVID-19 and community-acquired COVID-19[15]. In a multi-center study conducted in the United Kingdom and Italy, the mortality rate for nosocomial COVID-19 was found to be lower than that of community-acquired COVID-19[3]. These two studies were published early-term in the outbreak. In contrast with these studies, the mortality rate was found to be higher in nosocomial cases than in community-acquired cases in studies in the late stages of outbreak[2,8]. The risk of mortality was found 1.3 times greater in nosocomial COVID-19 patients than in community-acquired COVID-19 patients in a meta-analysis[7]. The mortality rates of hospitalized COVID-19 patients varied from 2.3% to 7.3%, and ICU admission rates varied from 6.3% to 11.5% in Turkey[16–18]. In our study, 162 (29.8%) patients with nosocomial COVID-19 were admitted to the ICU, and in-hospital mortality rate was 25.4%. Advanced age (≥65 years) and the number of comorbid diseases (≥2) increased the risk of in-hospital mortality in nosocomial COVID-19 patients. Advance age and the number of comorbidities were well-defined risk factors for mortality in COVID-19 patients[19,20]. These factors are also risk factors for nosocomial COVID-19 patients. Therefore, a higher mortality rate in nosocomial COVID-19 patients is expected.

Vaccination was found effective against the development of severe disease in randomized controlled trials and nationwide studies[21–24]. Whittaker *et al*. reported that vaccinated patients also had a lower risk of ICU admission when compared to unvaccinated patients, but there was no difference in in-hospital mortality[25]. We found that vaccination against SARS-CoV-2 decreased the risk of mortality in nosocomial COVID-19 patients. The results of our study were consistent with the results of previous studies. In previous studies, vaccination has been shown to reduce mortality in COVID-19 patients requiring hospitalization[26–28].

Our study has several limitations. Firstly, this was a retrospective study, and patients in our cohort were transferred to pandemic services due to nosocomial COVID-19, so we could not determine the true incidence of nosocomial COVID-19 and could not evaluate risk factors for nosocomial COVID-19. Secondly, since we did not compare patients with nosocomial COVID-19 and community-acquired COVID-19 for in-hospital mortality, it is difficult to associate nosocomial COVID-19 with higher mortality. Thirdly, we could not determine whether the source of transmission is from relatives of patients or health workers due to the higher prevalence of COVID-19 during study periods.

Despite the limitations, our study included several centers in the study, so our results can be generalized to Turkey. Our results show that vaccination against SARS-CoV-2 is protective against admission to the ICU and mortality in nosocomial COVID-19. Hospitalized patients are at risk of COVID-19 transmission, especially patients who followed up in medical wards. Vaccination against SARS-CoV-2 decreases the need for ICU admission and in-hospital mortality in patients with nosocomial COVID-19.

Conflict of interest statement

The authors declare that they have no conflict of interst.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Authors' contributions

SY, CY, and ÖE designed the study; CY, GP, SAB, İB, İK, CA, MB, HB, GO, EO, EC, AKÇ, DT, MG, SK, YA, AE, YO, BBY, BG, DDY, EYON, RE, ATE, MMT, FF, MÇ, ME, and AT collected the data; SY, GP and ÖE analyzed the data; SY, and CA, searched the literature and wrote the manuscript; ÖE edited and controlled the final version of the manuscript. All the authors approved the final version of the manuscript.

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