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Healthcare-associated infections in patients with COVID-19: is it different from the pre-pandemic period?

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Abstract

Introduction: Healthcare-associated infections (HAIs) are common in intensive care unit (ICU) patients and may cause devastating consequences. However, the prevalence of HAI and its effects on in-hospital mortality among critically ill COVID-19 patients is ambiguous. We determined the prevalence of HAI and the rate of mortality in critically ill COVID-19 patients and compared it with pre-pandemic ICU patients.

Methodology: This retrospective study was conducted with adult ICU patients admitted to Gazi Yaşargil Training and Research Hospital (Diyarbakir,Turkey) in April-November 2019 (defined as the pre-pandemic period) and in April-November 2020 (defined as the pandemic period). All patients in the pandemic period had COVID-19, while none in the pre-pandemic period did. Patients diagnosed with HAIs during the in-hospital follow-up period were recorded.

Results: Of 4596 enrollees, 3386 (73.7%) were pandemic-period patients and 1210 (26.3%) were pre-pandemic-period patients. HAI prevalence was significantly higher at 5.9% (n = 71) in the pandemic-period patients and 2.7% (n = 91) in the pre-pandemic-period patients ($p < 0.001$). Comorbidities including hypertension (63.4% vs 14.2%, $p < 0.001$), diabetes mellitus (39.4% vs 8.8%, $p < 0.001$), and coronary artery disease (30.9% vs 10.9%, $p = 0.002$) were significantly more frequent in pandemic-period HAI-positive patients. The most common HAI was catheter-related bloodstream infection in both groups, with similar frequency ($p = 0.652$). In-hospital mortality rate was 85.9% versus 65.9% in pandemic- versus pre-pandemic-period HAI-positive patients ($p < 0,05$).

Conclusions: The prevalence of HAI and the in-hospital mortality rate was significantly higher among pandemic-period patients.

Key words: Healthcare-associated infections; intensive care units; COVID-19.

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Introduction

Healthcare-associated infections (HAIs) are one of the most common complications observed among intensive care unit (ICU) patients and are associated with higher morbidity and mortality rates [1]. Although difficult to eradicate, the frequency of HAI can be reduced with effective prevention and control measures. As with the rest of the world, COVID-19 infection was widely diagnosed in Turkey since March 2020 and increased the burden of ICUs [2, 3]. In addition to the high mortality rates observed in severely ill COVID-19 patients admitted to the ICU, the coexistence of HAI also causes higher mortality rates in these patients [4]. In current literature, the prevalence of HAI and the effects on in-hospital mortality among critically ill COVID-19 patients has not been determined. Results of some recent studies showed that the prevalence might vary between 3.6% and 43% [4-6].

It is important to consider the prevalence of HAI, causative microorganisms, and developing foci of

infection in severe COVID-19 ICU patients to implement infection control measures and to ensure the appropriate use of antibiotics. Antibiotic-resistant pathogens found to cause HAI in COVID-19 patients include methicillin-resistant *Staphylococcus aureus*, metallo-β-lactamase-producing carbapenem-resistant *Enterobacterales*, carbapenem-resistant *Acinetobacter baumannii*, extended-spectrum β-lactamase *Klebsiella pneumoniae* and vancomycin-resistant enterococci [6,7]. Well-defined risk factors for HAI are comorbidities, length of ICU stay, advanced age, and malnutrition [8].

In this study, we aimed to determine the prevalence of HAI and the rate of mortality in critically ill COVID-19 patients and to compare it with pre-pandemic ICU patients.

Methodology

This retrospective study was conducted in Gazi Yaşargil Training and Research Hospital (Diyarbakir,Turkey), the regional reference treatment center for severe COVID-19 patients.

The first COVID-19-positive patient in Turkey was identified on March 11, 2020 [9]. Patients admitted to ICU between April and November 2019 were enrolled and defined as pre-pandemic-period patients. Also, patients who were admitted to ICU between April and November 2020 with positive SARS-CoV-2 polymerase chain reaction (PCR) in nasal or respiratory tract samples were enrolled and defined as the pandemic-period patients.

Diagnostic criteria for HAI were based on U.S.A. Centers for Disease Control and Prevention diagnostic criteria [10]. We obtained blood, wound, tracheal aspirate, and/or urine samples for culture from patients who were suspected of infection according to clinical, radiological, and laboratory findings. Only culture-positive patients were included as HAI-positive patients. While the pandemic-period HAI-positive patients were named as group 1 patients, the pre-pandemic-period HAI-positive patients were named as group 2 patients.

Patients who were transferred from other centers and whose diagnosis of HAI was confirmed at the time of transfer, patients under the age of 18 years, and patients whose culture positivity did not reflect the infection in either clinical, radiological, or laboratory findings and were accepted as colonization/contamination were excluded from the study.

Age, gender, underlying diseases, length of stay in ICU, time from hospitalization to the development of infection, laboratory values such as leukocytes, neutrophils, lymphocytes, C-reactive protein (CRP), procalcitonin and lactate dehydrogenase (LDH), HAI diagnoses, causative microorganisms, information such as end-of-treatment outcome were obtained from patient files, hospital database, and infection control committee records. The data of patients with non-COVID-19-HAI followed up before the pandemic and those with COVID-19-HAI who were followed up during the pandemic period were compared.

The institutional Clinical Research Ethics Committee approved the study protocol. All procedures were performed following the Turkish Medicine and Medical Devices Agency Good Clinical Practices Guidelines and the Declaration of Helsinki.

Statistical analysis was performed using SPSS 24 for Windows (IBM SPSS, Armonk, NY, USA). Numerical data were expressed as mean ± standard deviation, categorical data were expressed as percentage and frequency values. In the comparison of the two groups, the normal distribution of the data was evaluated using the Kolmogorov–Smirnov test. Among the numerical variables, the student's t-test was used for those with normal distribution, the Mann-Whitney U Test for those without normal distribution, and the chi-square test for comparison of categorical data. In statistical analysis, $p < 0.05$ was considered significant.

Table 1. General characteristics and comorbid conditions of HAI-positive pandemic-period-(Group 1) and pre-pandemic-period (Group 2) patients.

Characteristics	Group 1 (n = 71)	Group 2 (n = 91)	*p*
Age (years), mean (SD)	68.7 (13.7)	59.5 (21.9)	0.020
Female gender, n (%)	20 (28.2)	37 (40.7)	0.100
Comorbidity			
Hypertension, n (%)	45 (63.4)	13 (14.2)	< 0.001
Diabetes mellitus, n (%)	28 (39.4)	8 (8.8)	< 0.001
Coronary artery disease, n (%)	22 (30.9)	10 (10.9)	0.002
Cerebrovascular disease, n (%)	12 (16.9)	39 (42.9)	< 0.001
COPD, n (%)	2 (2.8)	22 (24.2)	< 0.001
Chronic kidney disease, n (%)	9 (12.7)	17 (18.7)	0.303

HAI: Healthcare-associated infection; SD: standard deviation; COPD: chronic obstructive pulmonary disease; *p* values < 0.05 are significant.

Table 2. Comparison of laboratory findings between HAI-positive pandemic-period (Group 1) patients and pre-pandemic-period (Group 2) patients.

Lab. results	Group 1 (n = 71)	Group 2 (n = 91)	*p*
At time of hospitalization			
Leukocyte (cells × 10^3/μL), mean (min-max)	11 (1.6-28.7)	13.5 (2.5-32.1)	0.004
Neutrophil (cells × 10^3/μL), mean (min-max)	9.7 (1.4-26.2)	11.2 (1.8-30.9)	0.060
Lymphocyte (cells × 10^3/μL), mean (min-max)	0.9 (0.2-3.0)	1.6 (0.2-4.8)	< 0.001
CRP (mg/L), mean (min-max)	68.7 (25-88)	53 (2-361.7)	< 0.001
Procalcitonin, (ng/ml), mean (min-max)	1.9 (0.02-35.5)	0.2 (0.02-2.2)	< 0.001
LDH (U/L), mean (min-max)	472 (173-908)	336 (144-940)	< 0.001
At time of HAI diagnosis			
Leukocyte (cells × 10^3/μL), mean (min-max)	13.7 (2.7-34.2)	13.5 (3.1-43.8)	0.483
Neutrophil (cells × 10^3/μL), mean (min-max)	12.1 (2.3-33.2)	10.9 (2.3-40.7)	0.106
Lymphocyte (cells × 10^3/μL), mean (min-max)	0.96 (0.04-3.39)	1.5 (0.2-4.2)	< 0.001
CRP (mg/L), mean (min-max)	136.2 (2-230)	146.3 (13-350)	0.540
Procalcitonin, (ng/ml), mean (min-max)	6.3 (0.08-132)	9.2 (0.05-100)	< 0.001
LDH (U/L), mean (min-max)	562.5 (159-2105)	342.6 (104-1086)	< 0.001

HAI: Healthcare-associated infection; CRP: C-reactive protein; LDH: lactate dehydrogenase; *p* values < 0.05 are significant.

Results

A total of 4596 ICU patients were included in the study. While 73.7% (n = 3386) of them were pandemic-period patients diagnosed with COVID-19, 26.3% (n = 1210) were pre-pandemic-period patients.

The prevalence of HAI was significantly higher at 5.9% (n = 71) in the pandemic-period patients and 2.7% (n = 91) in the pre-pandemic-period patients ($p < 0.001$). The in-hospital mortality rate was significantly higher among the pandemic-period HAI-positive patients (85.9%) than the pre-pandemic-period HAI-positive patients (65.9%) ($p < 0,05$).

The mean age of participants in the pandemic-period HAI-positive patients (Group 1) was 68.7 ± 13.7 (min, 22; max, 88) years, significantly higher than the pre-pandemic-period HAI-positive patients (Group 2), whose mean age was 59.5 ± 21.9 (min, 18; max, 92) years ($p < 0.05$). With respect to gender, 28.2% (n = 20) of Group 1, and 40.7% (n = 37) of Group 2 patients were female, and statistically similar ($p > 0.05$) (Table 1).

While comorbidities such as hypertension (63.4% vs. 14.2%, $p < 0.001$), diabetes mellitus (39.4% vs. 8.8%, $p < 0.001$), and coronary artery disease (30.9% vs. 10.9%, $p = 0.002$) were significantly more prevalent among the pandemic-period HAI-positive (Group 1) patients, cerebrovascular diseases (16.9% vs. 42.9%, $p < 0.001$), and chronic obstructive pulmonary diseases (2.8% vs. 24.2%, $p < 0.001$) were observed more frequently in the pre-pandemic-period HAI positive

Table 3. Comparison of HAI-associated data and outcomes between HAI-positive pandemic-period (Group 1) patients and pre-pandemic-period (Group 2) patients.

Data and outocomes	Group 1 (n = 71)	Group 2 (n = 91)	*p*
Time from hospitalization to diagnosis of HAI, days, mean (SD)	17.7 (14.9)	60.6 (38.8)	< 0.001
Length of hospital stay, days, mean (SD)	32.6 (24.6)	112.2±109.7	< 0.001
Mortality, n (%)	61 (85.9)	60 (65.9)	0.040
Type of infection			
CRBSI, n (%)	42 (59.2)	57 (62.6)	0.652
VAP, n (%)	22 (30.9)	22 (24.2)	0.430
CAUTI, n (%)	5 (7.04)	10 (10.9)	0.557
SSTI, n (%)	2 (2.8)	2 (2.2)	0.982
Causative microorganism			
Acinetobacter baumannii, n (%)	34 (47.9)	19 (20.9)	< 0.001
Klebsiella pneumoniae, n (%)	15 (21.1)	27 (29.7)	0.293
Escherichia coli, n (%)	3 (4.2)	4 (4.4)	1
Pseudomonas aeruginosa, n (%)	4 (5.6)	6 (6.6)	1
Proteus mirabilis, n (%)	1 (1.4)	1(1.1)	1
Enterococcus faecium, n (%)	1 (1.4)	2 (2.2)	1
Staphylococcus aureus, n (%)	1 (1.4)	6 (6.6)	0.137
Coagulase-negative staphylococci, n (%)	6 (8.5)	6 (6.6)	0.884
Candida spp., n (%)	8 (11.3)	17 (18.7)	0.282
Morganella morganii, n (%)	-	1 (1.1)	N/A
Providencia rettgeri, n (%)	-	2 (2.2)	N/A

HAI: Healthcare-associated infection; SD: standard deviation; CRBSI: catheter-related bloodstream infection; VAP: ventilator-associated pneumonia; CAUTI: catheter-associated urinary tract infection; SSTI: skin and soft tissue infection; N/A: not applicable; *p* values < 0.05 are significant.

(Group 2) patients (Table 1). Laboratory findings of participants on the day of hospitalization and on the day of diagnosis with HAI were given in Table 2.

The mean of the elapsed time from hospitalization to the diagnosis of HAI (Group 1: 17.7 ± 14.9 days vs. Group 2:60.6 ± 38.8 days, $p < 0.001$) and the length of stay in hospital (Group 1: 32.6 ± 24.6 days vs. Group 2: 112.2 ± 109.7, $p < 0.001$) were both significantly shorter in group 1 patients (Table 3).

Considering the types of infections, the most common type of HAI was catheter-related bloodstream infection in both groups with similar frequency ($p = 0.652$) followed by ventilator-associated pneumonia and catheter-associated urinary tract infection. The site of infection rates is given in Table 3. In group 1, the most common agent was *Acinetobacter baumannii* at 47.9%, followed by *Klebsiella pneumoniae* at 21.1% and *Candida* spp. at 11.3%, respectively. In group 2, *K. pneumoniae* was in first place at 29.7%, *A. baumannii* was in second place at 20.9%, and *Candida* spp. was in third place at 18.7%. Other agents isolated from cultures are given in Table 3.

Discussion

ICU patients frequently suffer from HAIs which cause higher morbidity and mortality rates [1]. Severely ill COVID-19 patients are almost always treated in ICUs, and the coexistence of HAI and COVID-19 infection also causes higher mortality rates in such patients [11]. Immunosuppressive agents such as steroids and tocilizumab are frequently administered in the treatment of severe COVID-19 infection, and this treatment may cause a higher prevalence of HAIs [12]. However, in current literature, the prevalence of HAI and its effects on in-hospital mortality among critically ill COVID-19 patients has not been revealed yet. In this study, we examined the prevalence of HAI and the rate of mortality in critically ill COVID-19 patients and compared it with pre-pandemic ICU patients. The results of the study revealed that the prevalence of HAI and the in-hospital mortality rate was significantly higher among pandemic-period patients.

In our study, the prevalence of HAI in patients followed in the ICU with the diagnosis of COVID-19 was 5.9%, and it was more than twice the prevalence of HAI in the pre-pandemic period, and the difference was statistically significant. In the study by Su *et al*., the prevalence of HAI was 2.6% in 2019, but was reported to be 1.39% in 2020 during the pandemic period [12]. This was attributed to the increase in the number of protective equipment such as hand hygiene, gloves, and gowns per person during the COVID-19 period, and the increase in the number of healthcare personnel per patient. However, this study was carried out not only in ICUs but also in all clinics. In the same study, it was determined that while the rate of HAI in ICU was 5.03% before the pandemic, it was 6.20% during the pandemic, which was similar to our study. During the pandemic period, HAI rates increased in the ICU. This may be related to the immunosuppressive therapy received by COVID-19 patients in the ICU. In our study, the increase in ICU patient density and high workload may be among the reasons for the increase in HAI during the pandemic period.

The mean age of the COVID-19-HAI-positive group was higher than the non-COVID-19 group, and it was significant. This is because elderly patients are more affected by COVID-19 and need more intensive care compared to the younger patients. The literature shows that older adults are at higher risk of being infected with COVID-19 and dying if they become ill [13,14].

In our study, the most common comorbidities in patients followed up for COVID-19 were hypertension, diabetes mellitus, and coronary artery disease. In non-COVID-19 patients, the most common comorbidities were cerebrovascular disease, chronic lung disease, and chronic renal failure. It has been reported previously that the most common comorbid diseases in COVID-19 patients are hypertension, diabetes, and coronary artery disease [15,16]. In the study by He *et al*., 65 of 918 COVID-19 patients developed HAI, and the most common comorbid diseases in these patients were hypertension, diabetes, and cardiovascular diseases, respectively [11]. Our findings also support these studies.

In our study, the mean time from ICU admission to the development of HAI was 17.7 days in patients diagnosed with COVID-19 and was shorter than in non-COVID-19 patients, and the difference was significant. In the study by Garcia-Vidal *et al*. in which HAI was examined, the time from hospitalization to the development of HAI was 10.6 days [17]. In the study by Bardi *et al*. [5], the median time from admission to the ICU to the onset of HAI was 9 days. The development time of HAI was short in patients followed up for COVID-19. The hospital stay was also shorter for COVID-19 patients than non-COVID-19 patients. Considering the types of infections in COVID-19 and non-COVID-19 patients, the most common HAI was catheter-related bloodstream infection, followed by VAP and catheter-associated urinary tract infection, respectively. In the study by He *et al*., the most common infection among COVID-19 patients was pneumonia

(32.3%) [11] followed by bacteremia (24.6%) and urinary tract infection (21.5%), respectively. In the study by Bardi *et al*., 57 (40.7%) of 140 patients followed up in the ICU developed HAI [5], with bloodstream infection being the most common, followed by ventilator-associated pneumonia.

Considering the causative microorganisms, in our study, *A. baumannii* was the first in pandemic COVID-19 patients, while *K. pneumoniae* was more common in pre-pandemic non-COVID patients. In both patient groups, *Candida* spp. was the third most common HAI. In the study by He *et al*., the most common causative agents detected among COVID-19 patients were coagulase-negative staphylococci, *A. baumannii* was second and *P. aeruginosa* was third [11]. In the study by Garcia-Vidal *et al*., the most frequently isolated microorganisms were *P. aeruginosa*, *E. coli*, *Klebsiella* spp., and *S. aureus* [17].

Death was the outcome for 85.9% of patients with COVID-19-HAI followed in the ICU and 65.9% for patients with non-COVID-19-HAI, and the difference was significant. He *et al*. reported a 15.4% mortality rate in patients with COVID-19-HAI [11].

Considering the laboratory values on the day of hospitalization, in COVID-19 patients mean leukocyte and lymphocyte values were lower, and CRP, procalcitonin, and LDH values were higher. It is known that lymphopenia, CRP, procalcitonin, and LDH elevation are poor prognostic factors in COVID-19 patients [18-20]. The fact that the patients in our study group were severely ill explains this.

Our study has some limitations. First, our study is a single-center retrospective study and cannot reflect the totality of ICU patients from the general population. Second, although the same periods of consecutive years were selected for inclusion of pandemic- and pre-pandemic-period patients, due to the retrospective design of our study and different properties of COVID-19 and other ICU patients, demographic characteristics of participants including age, comorbidities, and baseline laboratory findings were found to be statistically different between groups, diminishing the certainty of our results. Third, the design of the study and the characteristics of participants did not enable multivariate analysis to identify causation and determine independent risk factors for the risk of HAI and mortality.

Conclusions

In this study, we compared the prevalence of HAI in pre-pandemic and pandemic-period ICU patients and the in-hospital mortality rate in HAI-positive pre-pandemic and pandemic-period ICU patients. The results of the study demonstrated that the prevalence of HAI and the in-hospital mortality rate was significantly higher among pandemic-period patients. However, although significant findings were obtained, we believe further studies with prospective enrollment would be beneficial for more accurate conclusions.

Statement

This study was conducted in University of Health Sciences, Gazi Yasargil Training and Research Hospital.

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