scientific reports

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To prescribe or not: a two-center retrospective observational study of antibiotics usage and outcomes of COVID-19 in Turkey

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This retrospective cohort study conducted in Turkey between December 2020 and June 2022 aimed to assess antibiotic use, bacterial co-infections, and the associated factors on mortality in hospitalized patients with mild-to-severe COVID-19. Among the 445 patients, 80% received antibiotics, with fluoroquinolones being the most common choice, followed by beta-lactams and combinations. Various clinical and laboratory parameters, including symptoms, comorbidities, CCI, oxygen requirements, and CRP levels were observed to be elevated in the antibiotic group. Non-survivors had more ICU admissions and longer hospital stays compared to survivors. We conducted a multivariate Cox regression analysis to evaluate factors related to mortality. However, we did not find an association between antibiotic use and mortality [HR 2.7 (95% CI 0.4–20)]. The study identified significant factors associated with an antibiotic prescription, such as CCI (OR 1.6), CRP (OR 2.3), and ICU admission (OR 8.8), ($p < 0.05$). The findings suggest re-evaluating the necessity of antibiotics in COVID-19 cases based on clinical assessments, focusing on the presence of bacterial infections rather than empirical treatment. Further research is necessary to more accurately identify patients with bacterial co-infections who would benefit from antibiotic treatment.

Keywords Antibiotic usage, Bacterial co-infections, Mortality, COVID-19, SARS-CoV-2

The COVID-19 pandemic has raised numerous challenges in managing hospitalized patients[1]. Given the paucity of specific antiviral therapy for COVID-19, supportive care has been a cornerstone of clinical management, with supplemental oxygen and mechanical ventilation being critical interventions for severe cases[2,3]. Even though COVID-19 is a viral disease, the empirical use of antibacterial agents is very common[4,5]. Bacterial co-infections are known to complicate viral respiratory illnesses, contribute to increased morbidity and mortality, and require prompt antibacterial therapy[6,7]. While bacterial co-infection rates in severe influenza can reach 20–30%, the prevalence and characteristics of such infections in COVID-19 patients are less well characterized[7–9]. Differentiating between COVID-19 and bacterial infections can be challenging due to overlapping symptoms and imaging findings, especially with limited resources[10,11].

Current guidelines for community-acquired pneumonia recommend initial empirical antibiotic treatment due to the frequent coexistence of bacterial infections despite the lack of definitive diagnostic tests at the onset of pneumonia[12,13]. Preliminary studies suggest that antibiotics were prescribed in over 70% of COVID-19 cases, primarily based on suspicion of bacterial co-infection. However, emerging evidence suggests that actual rates of bacterial co-infection among hospitalized individuals with COVID-19 may be below 15%, with some studies reporting even lower figures[13–15]. The exact role of antibiotics in this respect is still unclear.

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Furthermore, overuse of antibiotics in COVID-19 pneumonia can increase anti-microbial resistance and lead to complications such as *Clostridium difficile* infections and renal failure. Therefore, antibiotic decisions should be based on the risk of multi-drug-resistant bacteria and potential complications[14,16,17].

The importance of rational antibiotic use cannot be overstated, as the irresponsible or incorrect use of these antimicrobials can lead to serious consequences. Overprescribing or inappropriate use of antibiotics can increase healthcare costs and contribute to the rise in the risk of drug toxicities and adverse drug interactions, thereby compromising patient safety[18].

Understanding antibiotic prescribing patterns in COVID-19 may help improve the quality and safety of antibiotic use. This study aims to address the current knowledge gap by evaluating antibiotic use, identifying factors influencing antibiotic use, and assessing factors related to mortality in patients hospitalized with mild-to-severe COVID-19.

Materials and methods

Study design and setting

This retrospective cohort study enrolled patients who were hospitalized with a COVID-19 diagnosis at Bitlis Tatvan State and Kastamonu Training and Research Hospital between December 1, 2020, and June 1, 2022. A total of 445 patients met the inclusion criteria, which comprised those with SARS-CoV-2 detected by PCR (n = 431, 97%) or those with clinically compatible signs and symptoms (n = 14, 3%), bilateral pulmonary infiltrates, or high clinical suspicion lymphopenia. The bed occupancy rate was 93%. The Clinical Research Ethics Committee of KTO Karatay University approved this study (2022/019; 23.05.2022). Due to the retrospective nature of the study informed consent was waived by the KTO Karatay Ethics Committee and anonymous clinical data were utilized in the analysis. The research has been performed in accordance with the Declaration of Helsinki.

Participants

The preliminary and confirmed diagnoses of COVID-19 pneumonia, along with all treatment approaches, were determined following the guidelines established by the Ministry of Health Scientific Committee[19]. During the study period, all patients who were hospitalized with COVID-19 pneumonia were evaluated for eligibility. The inclusion criteria were as follows: the patient was 18 years or older, had positive nasal or nasopharyngeal RT-PCR test results or strong CT findings suggestive of COVID-19 pneumonia, and had not received antibiotics or had received antibiotic therapy within 24 h of admission. Eligible patients were included in the study if they were hospitalized. The study excluded subjects aged < 18 years or > 89 years, pregnant or lactating women, active malignancy, immunosuppressed subjects, and patients receiving additional antibiotic therapy for at least 24 h after hospital admission.

Data collection

A standard data collection form was used to collect demographic, clinical, laboratory, and radiological data from the electronic medical records (Sisohbys, Hospital Information Management System, Turkey). Only one result such as on antibiotic usage and biochemical parameters per patient was included in the study.

The presence of hypertension, history of smoking, chronic obstructive pulmonary disease (COPD), chronic cardiac conditions, diabetes mellitus, oral corticosteroid therapy during hospitalization, tumor presence, and immunosuppression was recorded.

During their hospitalization, from admission to discharge or death, patients' clinical symptoms and laboratory results were typically monitored as follows: Laboratory tests included routine blood tests such as complete blood count and serum biochemistry (including lactate dehydrogenase [LDH], creatinine, C-reactive protein [CRP], procalcitonin, ferritin, and D-dimer). CT scans were performed on all hospitalized patients. The criteria for determining disease severity on admission were based on the COVID-19 diagnosis and treatment protocols issued by the Turkish Ministry of Health[19]. The severity of infection was classified according to the NIH COVID-19 Treatment Guidelines at the time of hospital admission[20]. In addition, patient comorbidities and the Charlson Comorbidity Index (CCI), which estimates the risk of mortality, were documented[21–23].

Antibiotic usage and other drugs

All medications taken during their hospital stay and COVID-19 vaccine information were also recorded. Medications prescribed for COVID-19 included favipiravir, lopinavir/ritonavir, corticosteroids, hydroxychloroquine, monoclonal antibodies (tocilizumab, anakinra), Intravenous immunoglobulin therapy (IVIG), COPD medications, antihypertensives, antidiabetics, antiarrhythmics, and antidepressant/antipsychotic drugs. The use of antibiotics in all patients who met the inclusion criteria was compared between survivors and non-survivors according to the severity of COVID-19. Classes of antibiotics prescribed (β-lactams, second- and third-generation cephalosporins, fluoroquinolones, glycopeptides, linezolid, colistin), time of antibiotic initiation (on admission or empiric vs post-admission), duration of treatment, antibiotic administration, the prevalence of bacterial co-infections (blood, respiratory and urinary tract) and antibiotic use rates were recorded. At the beginning of the first wave, studies reporting the efficacy of azithromycin in combination with hydroxychloroquine as a potential treatment for COVID-19 led to its widespread use, and azithromycin was prescribed both for this purpose and its antibacterial properties.

To determine the rate of bacterial co-infections among these patients, all positive microbiology results and suspected or culture-confirmed bacterial co-infections documented by the physician in clinical records after COVID-19 diagnosis were collected.

Statistical analysis

All statistical analyses were conducted using the IBM SPSS software, version 23 (IBM Corp., Armonk, N.Y., USA). Categorical variables are presented as frequencies (n) and percentages (%), while continuous variables are displayed as medians with interquartile ranges or means ± standard deviations (SD). Categorical variables were analyzed using the chi-square test or Fisher's exact test. The Kolmogorov–Smirnov test was used to confirm the normality assumption for continuous variables. For the comparison of independent continuous variables between survivors and non-survivors, the student's t-test or the Mann–Whitney U-test was utilized, depending on whether or not the statistical hypotheses were met. Repeated measures analysis of variance was conducted to compare differences between and within groups for time-dependent variables. A univariate and multivariate logistic regression model was employed to evaluate the association between antibacterial therapy and clinical mortality. For survival analysis, the multivariable Cox model was used to analyze the variables that were significant in comparing survival and non-survival variables. Odds ratios (ORs), Hazard ratios (HR), and 95% confidence intervals (CIs) were calculated and reported. The level of statistical significance for all tests was set at < 0.05.

Results

Patients and clinical characteristics with antibiotic usage

A total of 445 patients hospitalized with COVID-19 disease were included in the study. The mean age of the patients was 57 ± 18 years (range, 18–89 years). The mean age of patients receiving antibiotics was 60 ± 16 years, which was higher than that of those not receiving antibiotics, at 45 ± 18 years ($p < 0.001$). Of the patients, 274 (62%) were male and 171 (38%) were female. Nasal or nasopharyngeal RT-PCR tests for SARS-CoV-2 were confirmed positive in 431 (97%) of patients. The remaining 14 patients had bilateral lung infiltrates on their CT scans and a high clinical suspicion for COVID-19. The demographic and clinical profiles of the patients are detailed in Table 1.

Patients were categorized into two groups based on whether or not they received antibiotic therapy. Antibiotics were administered in 354 cases (80%), while antibiotics were not used in 91 cases (20%).

Of all the patients, the most common symptom was sore throat (65%), followed by cough (57%) and fatigue (54%). In addition to these symptoms, myalgia, headache, arthralgia, nausea, and flutter were higher in antibiotic-treated patients ($p < 0.05$). Comorbidities were present in 279 (63%) patients. Compared to the without antibiotics group, comorbidities and the associated medications were higher in the antibiotic-treated group ($p < 0.05$, Table 1).

Clinical evaluation, medications, and laboratory results with antibiotic usage

During the follow-up period, 93 patients (21%) were admitted to the intensive care unit. Of these, 47 patients (11%) required invasive mechanical ventilation and 46 patients (10%) required non-invasive mechanical ventilation. Although the necessity for ICU admission varied among groups, the duration of ICU stays showed no differences. The mean hospital stay was 14 ± 10 days. The duration of hospital stays in the group receiving antibiotics was longer than the group not receiving antibiotics ($p < 0.001$).

Clinical evaluation scores for patients receiving and not receiving antibiotics were evaluated. The CCI was 3 (IQR, 1–5) in the antibiotic group and 1 (IQR, 0–3) in the non-antibiotic group ($p < 0.001$). Oxygen saturation (SO_2) levels of the patients were evaluated during their hospital stay, on the day of admission for antibiotic treatment, and at the time of discharge. The groups receiving antibiotics had lower SO2 values upon admission ($p < 0.001$).

During the follow-up period, low- and high-dose corticosteroids were more commonly used in those receiving antibiotics, while hydroxychloroquine was more commonly used in those not receiving antibiotics. Furthermore, lopinavir/ritonavir (4%), tocilizumab/anakinra (3%), and IVIG (3%) were used only by the antibiotic group.

CT findings of 428 patients were evaluated during hospitalization. Pulmonary infiltration was detected in 192 (45%) of 428 patients; 151 patients received antibiotic treatment. Regarding in-hospital mortality, 55 out of 56 patients were in the antibiotic group, and one was in the non-antibiotic group ($p < 0.001$; Table 2).

Cultures were taken from 298 patients and 61 samples from 38 patients were positive (%13). 59 of the 61 positive cultures were seen in patients receiving antibiotics. The positive cultures were found in 26 blood, 15 sputum, and 20 urine samples. These cultures were accepted as microbiologically confirmed bacterial co-infection.

Table 3 presents the laboratory parameters with antibiotic usage. When laboratory parameters were compared between the antibiotic and without antibiotic groups, neutrophil, CRP (C-reactive protein), and ferritin levels were higher in the antibiotic group (Table 3).

Clinical characteristics and antibiotic usage of survivors and non-survivors

Table 4 present the survivors and non-survivors clinical characteristics and antibiotic usage. The survival rate among all patients was 87%. Non-survivors (69 ± 12) were older than survivors (55 ± 18; $p < 0.001$). In addition, the proportion of non-survivors was substantially higher in males (%80).

As defined by NIH guidelines[20], 445 COVID-19 patients were categorized into three groups according to the severity of their disease: mild (42% (n = 186), moderate (19% (n = 85), and severe (39% (n = 174). All mild COVID-19 patients were included in the survivors.

The mean length of hospital stay was 14 ± 10 days. The length of hospital stay was longer in non-survivors (21 ± 13) than in survivors (13 ± 8). In terms of ICU admission was higher among non-survivors (62%). The mean length of ICU stay was also higher among non-survivors (18 ± 13) than survivors (8 ± 10; $p = 0.001$).

During follow-up, 354 patients were treated with antibiotics for 12 ± 7 days. The duration of antibiotic treatment was 18 ± 9 days in the non-survivors, while it was 10 ± 5 days in the survivors ($p < 0.001$).

Characteristics	Total (n = 445)	with antibiotic (n = 354)	without antibiotic (n = 91)	*p-value*
Age mean (SD), years	56.6 ± 17.6	59.7 ± 16.4	44.7 ± 17.5	**< 0.001**
Sex				
Women	171 (38.4%)	127 (35.9%)	44 (48.4%)	**0.029**
Man	274 (61.6%)	227 (64.1%)	47 (51.6%)	
Symptoms				
Fever	138 (34.7%)	123 (36.9%)	15 (23.1%)	**0.033**
Dyspnoea	77 (17.3%)	70 (19.8%)	7 (7.7%)	**0.007**
Cough	254 (57.1%)	227 (64.1%)	27 (29.7%)	**< 0.001**
Sore throat	287 (64.5%)	258 (72.9%)	29 (31.9%)	**< 0.001**
Myalgia	119 (26.8%)	109 (30.8%)	10 (11.1%)	**< 0.001**
Arthralgia	82 (18.4%)	70 (19.8%)	12 (13.2%)	0.173
Fatigue	242 (54.4%)	222 (62.7%)	20 (22.0%)	**< 0.001**
Headache	110 (24.7%)	99 (28.0%)	11 (12.1%)	**0.002**
Diarrhea	12 (2.7%)	8 (2.3%)	4 (4.4%)	0.272
Nausea	74 (16.6%)	65 (18.4%)	9 (9.9%)	0.058
Chest pain	29 (6.5%)	25 (7.1%)	4 (4.4%)	0.478
Flutter	27 (6.1%)	27 (7.6%)	0 (0%)	**0.002**
Smoking				
Non-smoker	181 (65.3%)	129 (63.2%)	52 (71.2%)	0.352
Smoker	80 (28.9%)	61 (29.9%)	19 (26.0%)	
Ex-smoker	16 (5.8%)	14 (6.9%)	2 (2.7%)	
Comorbid conditions	279 (62.7%)	244 (68.9%)	35 (38.5%)	**< 0.001**
Hypertension	170 (38.2%)	148 (41.8%)	22 (24.2%)	**0.002**
Diabetes	74 (16.6%)	65 (18.4%)	9 (9.9%)	0.058
Coronary artery disease	88 (19.8%)	80 (22.6%)	8 (8.8%)	**0.003**
COPD	69 (15.5%)	62 (17.5%)	7 (7.7%)	**0.021**
Related medications				
Antihypertensives	175 (39.3)	152 (42.9)	23 (25.3)	**0.002**
Antidiabetic	66 (14.8%)	58 (16.4%)	8 (8.8%)	0.071
Immunosuppressive	10 (2.5%)	10 (2.8%)	0 (0%)	0.225
Inhaled corticosteroids β2 adrenergic agonists	57 (12.8%)	51 (14.4%)	6 (6.6%)	0.053

Table 1. Patient demographics and clinical characteristics between with antibiotic treatment (n = 354) and without antibiotic treatment (n = 91). Results were presented as mean ± standard deviation (SD) or count (n) and percentages (%). According to distribution Student t-test or Mann–Whitney U test was performed. $p < 0.05$, results were statistically significant. Chi-square test (or Fisher's exact) was applied for categorical variables. COPD: Chronic obstructive pulmonary disease. Significant values are in bold.

While 299 (77%) of the 389 survivors were treated with antibiotics, 55 of the 56 non-survivors were treated with antibiotics. The most frequently used antibiotics were the fluoroquinolones, followed by the beta-lactam antibiotics. In addition, a combination of glycopeptide, linezolid, and colistin was also given. Within the fluoroquinolones, moxifloxacin (n = 117), levofloxacin (n = 88), and ciprofloxacin (n = 6) were used. Of the remaining patients, 17 used glycopeptides or linezolid, and 16 used colistin. The distribution of antibiotics prescribed is given in Table 4.

Univariable and multivariable logistic regression analysis influencing antibiotic use in patients with COVID-19

Table 5 presents the univariable and multivariable logistic regression analysis influencing antibiotic use in patients with COVID-19. Logistic regression analysis was used to determine factors associated with antibiotic use. Variables significant ($p < 0.05$) or borderline significant in other analyses were included in univariate logistic regression analysis ($p < 0.10$).

Univariate regression analysis was performed on eight variables: age, sex, pneumonic infiltration, SO_2 on admission, ICU admission, CCI, corticosteroid use, CRP, and neutrophil count on admission. The multivariate regression analysis included the variables found to be statistically significant in the univariate regression analysis and we found that CCI (OR 1.6 [95% CI 1.1–2.3]), CRP levels (OR 2.3 [95% CI 1–5.1]), and ICU admissions (OR 8.8 [95% CI 1.1–71.3]) influence antibiotic prescriptions (Table 5).

We also examined the Cox regression analysis to assess the factors related to in-hospital mortality in mild to severe COVID-19 disease. However, we did not find an association between antibiotic use and mortality (HR 2.7 [95% CI 0.4–20] (Table 6), but there was just one death in the non-antibiotics group.

Parameters	Total (n = 445)	with antibiotic (n = 354)	without antibiotic (n = 91)	*p*-value
ICU admission				
No	352 (79.1%)	265 (74.9%)	87 (95.6%)	**< 0.001**
Yes	93 (20.9%)	89 (25.1%)	4 (4.4%)	
Intubation requirement				
No-intubation	46 (10.3%)	43(12.1%)	3 (3.3%)	
Intubation	47(10.6%)	46(13.0%)	1 (1.1%)	
ICU duration median (IQR) (days)	10 (5–17)	10 (5–17)	3 (1–11)	0.163
Length of hospital stay median (IQR) (days)	11.5 (7–17)	12 (8–20)	7.5 (5–10)	**< 0.001**
Clinical evaluation scores				
CCI median (IQR)	2(1–4)	3 (1–5)	1 (0–2.5)	**< 0.001**
SO_2 (admission) median (IQR)	88 (81–92)	87 (80–91)	92 (88–96)	**< 0.001**
COVID-19 medications				
Low-dose systemic corticosteroids	290 (65.2%)	246 (69.5%)	44 (48.4%)	**< 0.001**
High-dose systemic corticosteroids	164 (36.9%)	148 (41.8%)	16 (17.6%)	**< 0.001**
Hydroxychloroquine	123 (26.6%)	86 (24.3%)	37 (40.7%)	**0.002**
Pulmonary infiltration in the CT scan	192 (43.0%)	151 (44.8%)	41 (45.1%)	0.966
Lopinavir/Ritonavir	17 (3.8%)	17 (4.8%)	0 (0%)	**0.030**
Monoclonal antibodies (Tocilizumab/Anakinra)	13 (2.9%)	13 (3.7%)	0 (0%)	0.064
IVIG	13 (2.9%)	13 (3.7%)	0 (0%)	0.080
In-hospital mortality	56 (12.6%)	55 (15.5%)	1 (1.1%)	**< 0.001**

Table 2. The comparison of clinical evaluation and medications between with antibiotic treatment (n = 354) and without antibiotic treatment (n = 91). Results were presented as median (IQR) or count (n) and percentages (%). According to distribution Student t-test or Mann–Whitney U test was performed. Chi-square test (or Fisher's exact) was applied for categorical variables. $p < 0.05$, results were statistically significant. ICU: Intensive Care Unit, CCl: Charlson Comorbidity Index, IQR: Interquartile Range, SO2: Oxygen Saturation, IVIG: Intravenous Immunoglobulin, CT: Computed Tomography. Significant values are in bold.

Laboratory Parameters	With antibiotic (n = 354)	Without antibiotic (n = 91)	*p*-value
WBC ($\times 10^9$/L, nr: 4 –10)	6400 (4680–9790)	5085 (3950–6300)	**< 0.001**
Neutrophil ($\times 10^9$/L, nr: 1.3–7.4)	5215 (3625–8320)	3655 (2610–5180)	**0.001**
Lymphocytes ($\times 10^9$/L, nr: 0.9–5.3)	930 (670–1290)	1150 (780–1650)	**0.014**
Platelets (1000 u/L), nr: 150–450)	188 (145–236)	190 (166–219)	0.596
C-reactive protein (mg/L, nr: 0–5)	93 (47–157.2)	36.5 (5.7–74)	**< 0.001**
Ferritin (µmol/L, nr: 30–220)	225 (114.5–515.5)	166 (59–268)	**0.001**
LDH (U/L, nr: 0–248)	356 (281–470)	311 (282–361)	0.099
AST (U/L, nr: 0–35)	36 (26–50)	31.5 (23–39)	0.988
ALT (U/L, nr: 0–45)	27 (16–41)	25.5 (19–38)	0.036
Creatinine (mg/dL, nr: 0.8–1.5)	1 (0.8–1.2)	0.9 (0.8–1.1)	0.242

Table 3. The comparison of laboratory parameters between with antibiotic treatment (n = 354) and without antibiotic treatment (n = 91) at admission. Results were presented as mean ± standard deviation (SD) or median (IQR). Independent sample T-test was used for these comparisons. $p < 0.05$, results were statistically significant. WBC: White blood cell counts, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, Nr: normal range, IQR: Interquartile Range. Significant values are in bold.

Discussion

A key challenge during the COVID-19 pandemic has been the lack of substantial evidence of reliable treatment options[24,25]. Due to the virus's ability to change rapidly and the newness of the disease, the uncertainty of proven and effective treatments has led to challenges in clinical management[26]. Although COVID-19 is a viral disease, antibiotics may have to be prescribed in several situations, such as a concurrent clinical suspicion of bacterial pneumonia, patients with multiple comorbidities, or elevated markers of inflammation[27]. These factors raise concerns about bacterial co-infections and may influence decisions to prescribe antibiotics as a precautionary measure to prevent potential bacterial complications.

This retrospective cohort study demonstrated a high rate of antibiotic prescriptions in hospitalized COVID-19 patients from two health centers in Turkey. Approximately 80% of the patients included in the study received antibiotics during their hospitalization. Despite the high rate of antibiotic prescriptions, microbiologically confirmed

Parameters	Total (%100)	Non-Survivors (12.6%)	Survivors (87.4%)	*p*-value
Age mean (SD), years	56.6 ± 17.6	68.9 ± 12.4	54.9 ± 17.6	**< 0.001**
Sex		56 (12.6)	389 (87.4)	**0.002**
Female	171 (38.4)	11 (19.6)	160 (41.1)	
Male	274 (61.6)	45 (80.4)	229 (58.9)	
Severity of COVID Disease (NIH)				**< 0.001**
Mild	186 (41.8)	0(0)	186 (47.8)	
Moderate	85 (19.1)	13 (23.2)	72 (18.5)	
Severe	174 (39.1)	43 (76.8)	131 (33.7)	
Length of hospital stay mean (SD) (days)	14.2 ± 9.8	21.1 ± 13.4	12.8 ± 8.3	**< 0.001**
ICU admission	93 (20.9)	56 (62.1)	37 (37.9)	**< 0.001**
Intensive care duration mean (SD) (days)	13.3 ± 12.5	17.1 ± 12.8	8 ± 10	**0.001**
Antibiotics				
Duration of Antibiotic Therapy	11.5 ± 6.8	18.1 ± 8.8	10 ± 5.1	**< 0.001**
Any antibiotic	354 (77.8)	55 (98.2)	299 (76.9)	**< 0.001**
Beta-lactams	77 (17.3)	8 (14.29)	69 (17.74)	0.523
Fluoroquinolones	108 (24.27)	4 (7.14)	104 (26.74)	**0.001**
Beta-lactams + Fluoroquinolones	70 (15.73)	12 (21.43)	58 (14.91)	0.210
Beta-Lactams + Fluoroquinolones + Glycopeptide or linezolid	17 (3.82)	13 (23.21)	4 (1.03)	**< 0.001**
Beta-Lactams + Fluoroquinolones + Glycopeptide or linezolid + Colistin	16 (3.60)	16 (28.57)	0 (0)	**< 0.001**
Others	8 (1.80)	2 (3.57)	6 (1.54)	0.266
Macrolides (Azithromycin)	87 (19.6)	3 (5.4)	84 (21.6)	

Table 4. The comparison of patient demographics and clinical characteristics between the survivors (n = 389) and the non-survivors (n = 56). Results were presented as mean ± standard deviation (SD; median Q1-Q3) or count (n) and percentages (%). According to distribution Student t-test or Mann–Whitney U test was performed. Chi-square test (or Fisher's exact) was applied for categorical variables. $p < 0.05$, results were statistically significant. ICU: Intensive Care Unit. Significant values are in bold.

Parameters	Univariate logistic regressions OR (95% CI)	*p-value*	Multivariate logistic regressions OR (95% CI)	*p*-value
Age	1.053 (1.037–1.069)	**< 0.001**	0.988 (0.946–1.032)	0.595
Gender (male)	1.673 (1.051–2.664)	**0.030**	0.793 (0.349–1.799)	0.578
CCI	1.434 (1.198–1.716)	**< 0.001**	1.565 (1.052–2.327)	**0.027**
Steroid used	2.499 (1.562–3.988)	**< 0.001**	1.168 (0.274–4.976)	0.834
ICU admission	7.305 (2.606–20.474)	**< 0.001**	8.797 (1.086–71.240)	**0.042**
Pneumonic infiltration	0.990 (0.622–1.577)	0.966		
Oxygen saturation (SO2/room air)	0.889 (0.852–0.927)	**< 0.001**	0.988 (0.938–1.041)	0.650
C-reactive protein (> 50)	4.533 (2.456–8.366)	**< 0.001**	2.273 (1.008–5.125)	**0.048**
Neutrophil ($> 7.1*10^3$)	2.284 (0.911–5.723)	0.078		

Table 5. Presents the results of the univariate and multivariate logistic regression models, analyzing the factors influencing antibiotic use in patients with COVID-19. OR: Odds Ratio, CI: Confidence Interval, CCI: Charlson Comorbidity Index, SO2: Oxygen Saturation. $p < 0.05$, results were statistically significant. *Wald test. Significant values are in bold.

bacterial co-infections were relatively low in our study, with only 14% of patients being affected. The bacterial co-infection rates vary from one country to another and even in different communities within the same country, ranging from 3 to 53% in COVID-19 patients[25,28–34].

A study conducted in the United States showed a high antibiotic prescribing rate, reaching 83% of patients who received at least one course of antibiotics despite a low rate of microbiologically confirmed infection (12%)[30]. In a retrospective study of 1269 COVID-19 patients in 2020–2022 in two Italian hospitals, 84% of patients (n = 1062) received antibiotic treatment, with only 15% having an obvious source of bacterial infection[31]. A multicentre point-prevalence study conducted in Turkey with a large participant population showed that the antibiotic prescription rate was 75%. However, the rate of clinically or microbiologically confirmed bacterial infections was 29%, and culture positivity was 7%[25]. In our study, the relationship between antibiotic prescription rate and microbiologically confirmed bacterial co-infection was consistent with previous studies.

Parameters	Univariate cox regressions HR (95% CI)	*p*-value	Multivariate cox regressions HR (95% CI)	*p*-value
Age	1.032 (1.009–1.055)	**0.006**	1.035 (0.998–1.074)	0.067
Gender (male)	1.582 (0.762–2.272)	0.216	1.489 (0.712–3.113)	0.290
Antibiotic treatment	3.491 (0.479–25.450)	0.217	2.703 (0.365–20.045)	0.331
Severity of COVID-19 Disease	1.154 (0.678–1.964)	0.598	1.153 (0.649–2.048)	0.627
CCI	1.134 (1.005–1.279)	**0.042**	0.971 (0.782–1.206)	0.792

Table 6. Multivariate Cox regression model for mortality in patients with COVID-19. HR: Hazard Ratio, CI: Confidence Interval, CCI: Charlson Comorbidity Index. $p < 0.05$, results were statistically significant. *Among the study participants, 299 (77%) of the 389 survivors received antibiotic treatment. In terms of in-hospital mortality, 55 of the 56 non-survivors (98%) were in the antibiotic group, and one was in the non-antibiotic group. Significant values are in bold.

Two systematic reviews and meta-analyses by Langford et al. reported the prevalence of antibiotic prescription to be 72% (95% CI 56 to 88%) and 75% (95% CI 68–80%), and the prevalence of bacterial co-infection to be 7% (95% CI 4–10%) and 9% (95% CI 5–15%), respectively[32,33]. The high antibiotic prescribing rate compared to the low bacterial co-infection rate in our study and other studies may be related to empirical antibiotic use and the severe clinical conditions of the patients.

In early studies, clinicians followed the initiation of treatment for COVID-19 patients based on local guidelines for community-acquired pneumonia[12]. In addition, some medical centers have recommended empiric antibiotics for the majority of COVID-19 patients based on institutional guidelines[30]. The most commonly used antibiotics in the treatment of COVID-19 patients are fluoroquinolones, macrolides, and beta-lactams[25,30,33]. In our study, respiratory fluoroquinolones such as levofloxacin, moxifloxacin, and ciprofloxacin were the most prescribed antibiotics, followed by beta-lactams, especially second/third-generation cephalosporins. These results suggest that healthcare providers prefer these antibiotics to treat respiratory tract infections, especially in COVID-19 patients. In addition, beta-lactams, fluoroquinolones, and their combinations were more commonly used in survivors. In contrast, high-end antibiotics such as glycopeptide/linezolid and colistin were more commonly used in non-survivors ($p < 0.001$). This highlights the importance of disease severity and specific medical interventions to guide antibiotic prescribing decisions in critically ill patients.

Understanding the predictive factors for the need for antibiotic treatment not only ensures proper management of antibiotic therapy but also improves the patient's overall prognosis and enhances the management of antimicrobial resistance (AMR)[33].

The patient's comorbidities, clinical symptoms, and laboratory findings were evaluated to determine whether or not they had received antibiotic treatment. The lack of precise data on the relationship between comorbidity and antibiotic use in COVID-19 may have led to a perception that antibiotics were prescribed at a higher rate in patients without comorbidities. Al-Hadidi et al. reported no difference in antibiotic use between patients with and without comorbidities[34]. In contrast to this study, we observed that comorbidities and the use of medications associated with comorbidities were higher in the group receiving antibiotics. Calderón-Parra et al. concluded that fewer comorbidities, dry cough, and flu-like symptoms may be associated with inappropriate antibiotic use[14]. In our study, flu-like symptoms such as sore throat, cough, fatigue, myalgia, arthralgia, headache, and nausea were more common in patients treated with antibiotics.

Laboratory abnormalities have contributed to the use of antibiotics in COVID-19 patients. A recent meta-analysis indicated that procalcitonin (PCT) has limited predictive value for detecting co-infection in patients with COVID-19. However, lower PCT levels appear to be associated with a reduced probability of co-infection[35].

Although studies have shown that elevated CRP levels are associated with an increased frequency of antibiotic prescription, CRP is not a reliable indicator of antibiotic prescription during the COVID-19 pandemic. This may be due to the respiratory distress leading to elevated CRP levels observed in the initial presentation of patients with COVID-19[25,36–38]. In our study, we observed that elevated CRP levels in patients who received antibiotics contributed to increased antibiotic use. However, PCT (procalcitonin) values could not be assessed for all patients due to limited laboratory resources.

In our study, we used univariate logistic regression analysis to determine factors associated with antibiotic use. We identified eight independent factors that were associated with an increased use of antibiotics. These factors are as follows: age, gender, Charson comorbidity index, requirement for supplemental oxygen, steroid usage, presence of moderate/diffuse lung involvement, neutrophil count, and C-reactive protein levels. These factors significantly influenced the higher antibiotic utilization among the individuals included in the study (Table 5).

A study in Turkey identified several risk factors associated with antibiotic use in COVID-19 patients, including age, hospitalization in ICU, need for supplemental oxygen, moderate or diffuse lung involvement, and a lymphocyte count < 800. It was also reported that moderate or extensive lung involvement and CRP levels above the upper limit of normal (ULT) were associated with antibiotic use[25]. In a meta-analysis study conducted on 30,212 patients, it was observed that antibiotic prescribing prevalence was more common in older age groups and in patients with higher severity of illness[33].

In our study, the in-hospital mortality rate was 12.6%, which is in line with the results of other studies in the literature[31]. Mortality was observed in 14.1% of the patients treated with antibiotics. The group of patients receiving antibiotics consisted of clinically more severe cases with high pulmonary infiltration, low SO_2 saturation and high comorbidities. Thus, the severity of illness was also a cause for administering antibiotics, creating a selection

bias between the two groups. We also wanted to examine the effect of antibiotics on mortality; however, due to the presence of selection bias, this analysis could not be effectively evaluated. Although our study did not find an association between antibiotic use and increased mortality, we observed that patients treated with antibiotics had higher rates of comorbidities and severe forms of COVID-19.

Some limitations should be recognized for this study. The retrospective nature of this study, the small number of patients, and the fact that it was a two-center study conducted predominantly in the Turkish population may limit the generalizability of the results. In addition to the fact that similar microbiologic tests were performed in patients and only the results of positive tests were reported, there is also a lack of data on isolated bacteria and their antibiotic susceptibility. Furthermore, bacterial co-infections may have been missed due to antibiotic treatment before hospitalization, and microbiology sampling may have influenced microbiology test results. The presence of an unknown false-negative rate for cultivation. Another limitation is that it was not possible to measure PCT levels in all patients due to laboratory problems, and the duration of MV support is unknown. Although our study has several limitations, its strength is that it covers both the quarantine period and the period when no strict pandemic measures were taken (December 2020 to June 2022).

Conclusion

In summary, our study reveals a concerning trend of considerable antibiotic use in COVID-19 patients, even in the absence of clinical or laboratory diagnosis. This practice may have serious consequences due to the low rate of bacterial co-infection and the potential risks associated with antibiotic use, such as the development of antimicrobial resistance and drug-induced toxicity. Therefore, it is crucial to limit the empirical use of antibiotics in COVID-19 patients and to consider antibiotic treatment only when there is clear microbiologic evidence or strong clinical suspicion of bacterial infection. These precautions minimize the potential harm of unnecessary antimicrobial use while preserving the efficacy of these important drugs for future medical needs. Further research is necessary to more accurately identify patients with bacterial co-infections who would benefit from antibiotic treatment.

Data availability

The datasets generated during the current study are not publicly available due to the hospital's personal data protection policy but are available from the corresponding author on reasonable request.

Received: 1 July 2024; Accepted: 3 September 2024
Published online: 09 September 2024

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Acknowledgements

None.

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H.N.K.: Conceptualization; Methodology; Formal analysis; Investigation; Data curation; Writing-original draft; Supervision; MA: Formal Analysis; Data curation; Writing-original draft; Writing-review & editing; SÖ: Methodology; Investigation; YO: Methodology; Investigation; ES: Data curation; Writing-original draft; Writing-review& editing; EKD: Methodology; Investigation; YKA: Formal Analysis; Data curation; MMS: Writing-original draft; Writing-review & editing; Supervision. All authors reviewed the manuscript.

Competing interests

The authors declare no competing interests.

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