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RESEARCH ARTICLE

Ventilator-associated pneumonia in an intensive care unit: A comparative analysis of clinical and microbiological characteristics of COVID-19 and non-COVID-19 patients

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ABSTRACT

Ventilator-associated pneumonia in an intensive care unit: A comparative analysis of clinical and microbiological characteristics of COVID-19 and non-COVID-19 patients

Introduction: *The incidence and microbiological characteristics of coronavirus disease-2019 (COVID-19) associated ventilator-associated pneumonia (VAP) remain a clinical concern. The present study investigates the risk factors associated with VAP and compares the clinical and microbiological characteristics between the patients with and without COVID-19.*

Materials and Methods: *This retrospective case-control study was conducted in a tertiary intensive care unit (ICU) between March 2020 and February 2023. Patients with COVID-19 were identified through positive SARS-CoV-2 polymerase chain reactionresults, while non-COVID-19 patients served as controls. Demographic characteristics, comorbidities, clinical parameters, and microbiological data were analyzed. Risk factors for VAP were determined using multivariate logistic regression analysis. The Kaplan-Meier method was used to estimate the cumulative probability of VAP.*

Results: *A total of 327 mechanically ventilated patients were enrolled, of whom 154 developed VAP. COVID-19 emerged as an independent predictor of VAP, conferring a 2.47-fold increased risk (p= 0.008). COVID-19 VAP patients had a higher prevalence of acute respiratory distress syndrome (ARDS) (p< 0.001), increased corticosteroid use (p= 0.004) and lower APACHE scores (p< 0.001). Both ICU and hospital case fatality rates were significantly increased in COVID-19 VAP patients. Klebsiella pneumoniae was the predominant pathogen in COVID-19 VAP patients, followed by Acinetobacter baumannii as the second most common pathogen.*

Conclusion: *COVID-19 is a significant risk factor for VAP, with distinct clinical and microbiological characteristics compared to non-COVID-19 VAP. The*

greater occurrence of ARDS, corticosteroid use, and multidrug-resistant organisms in COVID-19–associated VAP highlights the urgent need for individualized antimicrobial strategies aimed at reducing infection-related morbidity and mortality.

Key words: *Intensive care unit; ventilator-associated pneumonia; COVID-19; Klebsiella pneumonia; Acinetobacter baumannii*

ÖZ

Yoğun bakım ünitesinde ventilatörle ilişkili pnömoni: COVID-19 ve COVID-19 olmayan hastaların klinik ve mikrobiyolojik özelliklerinin karşılaştırmalı analizi

Giriş: *Koronavirüs hastalığı-2019 (COVID-19) ile ilişkili ventilatör ilişkili pnömoninin (VİP) insidansı ve mikrobiyolojik özellikleri klinik açıdan önemli bir sorun olmaya devam etmektedir. Bu çalışma, VİP gelişimiyle ilişkili risk faktörlerini araştırmakta ve COVID-19 olan ve olmayan hastalar arasındaki klinik ve mikrobiyolojik özellikleri karşılaştırmaktadır.*

Materyal ve Metod: *Bu retrospektif olgu-kontrol çalışması, Mart 2020-Şubat 2023 tarihleri arasında üçüncü basamak bir yoğun bakım ünitesinde yürütülmüştür. Koronavirüs hastalığı-2019 tanısı, pozitif SARS-CoV-2 polimeraz zincir reaksiyonu testi ile doğrulanan hastalarda konulmuş, COVID-19 dışı hastalar ise kontrol grubunu oluşturmuştur. Demografik özellikler, komorbiditeler, klinik parametreler ve mikrobiyolojik veriler analiz edilmiştir. Ventilatör ilişkili pnömoni ile ilişkili risk faktörleri, çok değişkenli lojistik regresyon analizi ile belirlenmiştir. Ventilatör ilişkili pnömoninin kümülatif olasılığı Kaplan-Meier yöntemi kullanılarak hesaplanmıştır.*

Bulgular: *Toplam 327 mekanik ventilasyon uygulanan hasta çalışmaya dahil edilmiştir ve bu hastaların 154'ünde VİP gelişmiştir. Koronavirüs hastalığı-2019, bağımsız bir VİP belirleyicisi olarak saptanmış ve 2,47 kat artmış riskle ilişkili bulunmuştur (p= 0,008). Koronavirüs hastalığı-2019, VİP hastalarında akut solunum sıkıntısı sendromu (ARDS) prevalansı anlamlı olarak daha yüksek (p< 0,001), kortikosteroid kullanımı daha fazla (p= 0,004) ve APACHE skoru daha düşük bulunmuştur (p< 0,001). Yoğun bakım ve hastane mortalite oranları da COVID-19 VİP hastalarında anlamlı derecede artmış saptanmıştır. Koronavirüs hastalığı-2019 ilişkili VİP olgularında en sık izole edilen etken Klebsiella pneumoniae olup bunu ikinci sıklıkta Acinetobacter baumannii izlemiştir.*

Sonuç: *Koronavirüs hastalığı-2019, VİP gelişimi için önemli bir risk faktörüdür ve COVID-19 ilişkili VİP, COVID-19 dışı VİP'e göre farklı klinik ve mikrobiyolojik özellikler göstermektedir. Koronavirüs hastalığı-2019 ilişkili VİP olgularında ARDS, kortikosteroid kullanımı ve çok ilaca dirençli bakterilerin daha sık görülmesi, enfeksiyona bağlı morbidite ve mortalitenin azaltılabilmesi için bireyselleştirilmiş antimikrobiyal tedavi stratejilerine duyulan gereksinimi vurgulamaktadır.*

Anahtar kelimeler: *Yoğun bakım ünitesi; ventilatör ilişkili pnömoni; COVID-19; Klebsiella pneumoniae; Acinetobacter baumannii*

INTRODUCTION

Coronavirus disease-2019 (COVID-19) pandemic has led to a marked increase in viral pneumonia cases requiring hospitalization, with a considerable proportion of patients progressing to intensive care and more than half necessitating invasive mechanical ventilation (1). Ventilator-associated pneumonia (VAP) represents one of the most frequent complications in individuals undergoing prolonged ventilation and extended intensive care unit (ICU) stays for viral respiratory infections; however, its exact impact on mortality remains controversial (1). Multiple mechanisms have been implicated in VAP pathogenesis, including the presence of acute respiratory distress syndrome (ARDS), impaired host immunity, and bacterial colonization of the lower airways. Moreover, although therapeutic interventions such as corticosteroids have demonstrated mortality benefits in severe COVID-19, their use may concurrently predispose patients to secondary bacterial infections, including VAP (2-4).

Recent evidence suggests that VAP occurs more frequently in patients with COVID-19 than in those without COVID-19, likely reflecting the combined effects of profound immune dysregulation, sustained mechanical ventilation, and systemic inflammation (1,5,6). Compared with non-COVID-19 VAP, COVID-19-associated VAP is often linked to greater clinical severity, a higher incidence of ARDS, and prolonged intensive care stays. Furthermore, multidrug-resistant organisms—particularly *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*—are more commonly isolated in COVID-19 VAP patients, whereas *Staphylococcus aureus* and other gram-negative bacilli remain predominant in non-COVID-19 VAP cases (7–9). These microbiological and clinical distinctions underscore the importance of tailored antimicrobial stewardship and optimized management strategies in COVID-19 VAP patients.

The objective of this study is to pinpoint the risk factors associated with VAP development in ICU patients with and without COVID-19 and to compare the clinical and microbiological characteristics of these two groups.

MATERIALS and METHODS

Study design

This single center, retrospective case-control study was conducted in a medical ICU at a university hospital between March 2020 and February 2023. From

March 2020 to May 2021, the ICU operated as a dedicated COVID-19 facility, subsequently transitioning to a non-COVID-19 ICU in June 2021. The ICU, where the study was carried out, implemented standardized management and infection control policies. The same institutional standards for nurse-to-patient ratios (1:2), hand hygiene, and VAP prevention bundles were maintained throughout the study period.

All patients who underwent mechanical ventilation for at least two consecutive days during their ICU stay were eligible for inclusion. Mechanical ventilation was routinely managed using a standardized volume assist–control ventilation mode as the default strategy in the ICU. Ventilator mode adjustments were performed only in the presence of patient–ventilator asynchrony or in some specific clinical indications. No systematic differences in ventilation strategy were applied between the patient groups. ICU patients diagnosed with VAP and confirmed to have SARS-CoV-2 infection by a positive polymerase chain reaction (PCR) test were categorized as COVID-19 VAP patients. The control cohort comprised of VAP patients who exhibited no clinical suspicion of COVID-19 and had two consecutive negative SARS-CoV-2 PCR results, thereby classified as non-COVID-19 VAP cases. To ensure group comparability, a 1:2 case–control matching was performed according to age, sex, and comorbidity profile. Patients were excluded if they had incomplete clinical data, an ICU stay of <48 hours, or required mechanical ventilation for <48 hours.

Definitions

All ICU admissions were retrospectively reviewed using the U.S. Centers for Disease Control and Prevention diagnostic criteria for VAP. These criteria included respiratory signs and symptoms consistent with pneumonia, worsening oxygenation, mechanical ventilation for at least 48 hours, new or progressive lung infiltrates on chest imaging, and relevant laboratory findings (10). The time to VAP onset was determined by calculating the interval between the initiation of mechanical ventilation and the first recorded VAP occurrence. The diagnosis was further supported by microbiological evidence obtained from respiratory specimens, including tracheal aspirates and bronchoalveolar lavage.

The microbiological profiles of COVID-19 and non-COVID-19 VAP patients were analyzed based on the isolated pathogens and antimicrobial resistance patterns. Multi drug resistance (MDR) organisms were defined as isolates showing non-susceptibility to at least one antimicrobial agent in three or more distinct antimicrobial classes. Extensively drug-resistant organisms were defined as isolates exhibiting non-susceptibility to at least one agent in all but two or fewer antimicrobial classes. Pan-drug resistant (PDR) organisms were defined as isolates showing non-susceptibility to all available antimicrobial classes.

Immunosuppression was categorized based on the presence of predefined clinical criteria upon ICU admission or during the hospital stay. These included: prolonged systemic corticosteroid therapy (prednisolone equivalent of ≥20 mg/day for at least 14 days), administration of immunomodulatory or immunosuppressive drugs (including chemotherapeutic and biological agents), history of solid organ or hematopoietic stem cell transplantation, active solid organ or hematological malignancy, primary immunodeficiencies, or acquired immune deficiency syndrome.

Variables

Patient-level information was retrospectively obtained from the institutional electronic medical records and hospital databases. The extracted variables included demographic data (age and sex), comorbid conditions (hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney or liver disease, rheumatologic disorders, cerebrovascular disease, malignancy, and immunosuppression), Acute Physiology and Chronic Health Evaluation (APACHE) score, tracheostomy status, and presence of ARDS.

Corticosteroid exposure was recorded as part of baseline clinical characteristics. In the pre–COVID-19 period, corticosteroids were administered primarily for acute exacerbations of chronic obstructive pulmonary disease or other respiratory indications, typically at moderate doses equivalent to 40–80 mg/day of prednisolone, and for short treatment durations. During COVID-19 period, corticosteroid use was restricted to low-dose dexamethasone (6–8 mg/day) or equivalent corticosteroid dosing, in accordance with contemporaneous treatment guidelines. High-dose or prolonged corticosteroid regimens were not employed in either period.

For patients who developed VAP, additional parameters were evaluated, such as the duration of

mechanical ventilation before VAP onset and ICU length of stay prior to infection. Episodes in which more than one clinically relevant pathogen was isolated and pathogen-directed therapy was initiated were defined as polymicrobial infections. Clinical outcomes were assessed using key indicators, including ICU stay, total hospital stay, ICU mortality, and overall in-hospital mortality.

Study Outcomes

The primary aim of this study was to identify factors associated with VAP development and to determine its cumulative probability in COVID-19 and non-COVID-19 patients according to the duration of mechanical ventilation. Secondary objectives included a comparative analysis of the epidemiological, clinical, and microbiological characteristics of VAP between the two groups.

Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation (SD) for normally distributed quantitative variables and as median (minimum–maximum) for non-normally distributed variables. Categorical variables were presented as frequencies and corresponding percentages. Differences between the groups were assessed using the student's t-test or the Mann–Whitney U test for continuous variables, depending on data distribution. The chi-square or Fisher's exact test, where appropriate, was applied to compare categorical variables. Multivariate logistic regression analysis was performed to identify independent factors associated with VAP development among the ICU patients, with variables showing a $p \leq 0.05$ in univariate analysis included in the multivariate model. Kaplan–Meier survival analysis was used to estimate the cumulative probability of VAP in COVID-19 and non-COVID-19 groups according to the duration of mechanical ventilation, and comparisons were made using the log-rank test. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Risk factors and cumulative probability of VAP based on mechanical ventilation duration

Among 327 mechanically ventilated ICU patients (121 COVID-19 and 206 non-COVID-19), VAP developed in 154 individuals, accounting for 48% of the study population. A comparison between patients with and without VAP identified that corticosteroid use, malignancy, tracheostomy and COVID-19 were independent risk factors for VAP development. Notably, the risk of developing VAP was 2.47 times higher in COVID-19 patients (Table 1). VAP developed in 64.5% of COVID-19 patients, whereas it occurred in 36.9% of non-COVID-19 patients, demonstrating a statistically significant difference ($p < 0.001$).

Table 1. Risk factors for the development of VAP among mechanically ventilated patients in ICU (n= 327)

	Total Patients (327)	Non-VAP Patients (173)	VAP Patients (154)	Univariate p value	Multivariate [p value (Odds ratio (CI 95%)]
Age median (min-max)	71 (20-100)	70 (20-100)	72 (22-98)	0.226	
Male sex n (%)	183 (56)	93 (53.8)	90 (58.4)	0.394	
ARDS	102 (31.2)	41 (23.7)	61 (39.6)	**0.002**	[0.726, (OR 0.98 (0.95-1.01)]
APACHE score mean (+/-SD)	50 (15.3)	27 (8.9)	23 (8.6)	**<0.001**	[0.253, (OR 0.88 (0.43-1.78)]
DM	130 (39.8)	61 (35.3)	69 (44.8)	0.078	
HT	174 (53.2)	92 (53.2)	82 (59.7)	0.233	
CAD	118 (36.1)	57 (32.9)	61 (39.6)	0.210	
CHF	85 (26)	45 (26)	40 (25.9)	0.988	
COPD	68 (20.8)	38 (22)	30 (19.5)	0.581	
Chronic renal failure	33 (10.1)	15 (8.7)	18 (9.7)	0.738	
Chronic liver disease	17 (5.2)	12 (6.9)	5 (3.2)	0.134	
Rheumatologic disease	13 (4)	5 (2.9)	8 (5.2)	0.287	
Cerebrovascular event	32 (9.8)	18 (10.4)	14 (9.1)	0.690	
Malignancy	116 (35.5)	37 (21.4)	79 (51.3)	**<0.001**	[**0.005**, (OR, 2.15 (1.27-3.67)]

Table 1. Risk factors for the development of VAP among mechanically ventilated patients in ICU (n= 327) (continue)

	Total Patients (327)	Non-VAP Patients (173)	VAP Patients (154)	Univariate p value	Multivariate [p value (Odds ratio (CI 95%)]
Immunosuppression	56 (17.1)	33 (19)	23 (14.9)	0.456	
Corticosteroid use	162 (49.5)	65 (37.6)	97 (63)	**<0.001**	[**0.001**, (OR, 2.36 (1.39-4.01)]
Tracheostomy status	20 (6.1)	2 (1.2)	18 (11.7)	**<0.001**	[**0.001**, (OR 6.91 (2.82-13.32)]
COVID-19	121 (37)	43 (24.9)	78 (50.6)	**<0.001**	[**0.008**, (OR, 2.47 (1.26-4.85)]

VAP: Ventilator associated pneumonia, ICU: Intensive care unit, ARDS: Acute respiratory distress syndrome, APACHE: Acute physiology and chronic health evaluation, DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, COVID-19: Coronavirus disease-2019.

Table 2. Cumulative probability of VAP in non-COVID-19 and COVID-19 patients over time based on mechanical ventilation duration

Duration (days)	non-COVID-19 Patients	COVID-19 Patients
7	17.5%	41.7%
14	41.8%	68.6%
21	59.1%	85.4%
28	66.0%	85.4%

VAP: Ventilator associated pneumonia, COVID-19: Coronavirus disease-2019.

The log-rank test results indicated that the risk of developing VAP was significantly higher in COVID-19 patients compared to non-COVID-19 patients ($p< 0.001$). Table 2 showed the cumulative probability of VAP in COVID-19 and non-COVID-19 patients over time. The probability of developing VAP was consistently higher in COVID-19 patients at all time points, with a significant difference observed by day 7 (41.7% vs. 17.5%) and increasing further by day 28 (85.4% vs. 66.0%). Figure 1 illustrates the

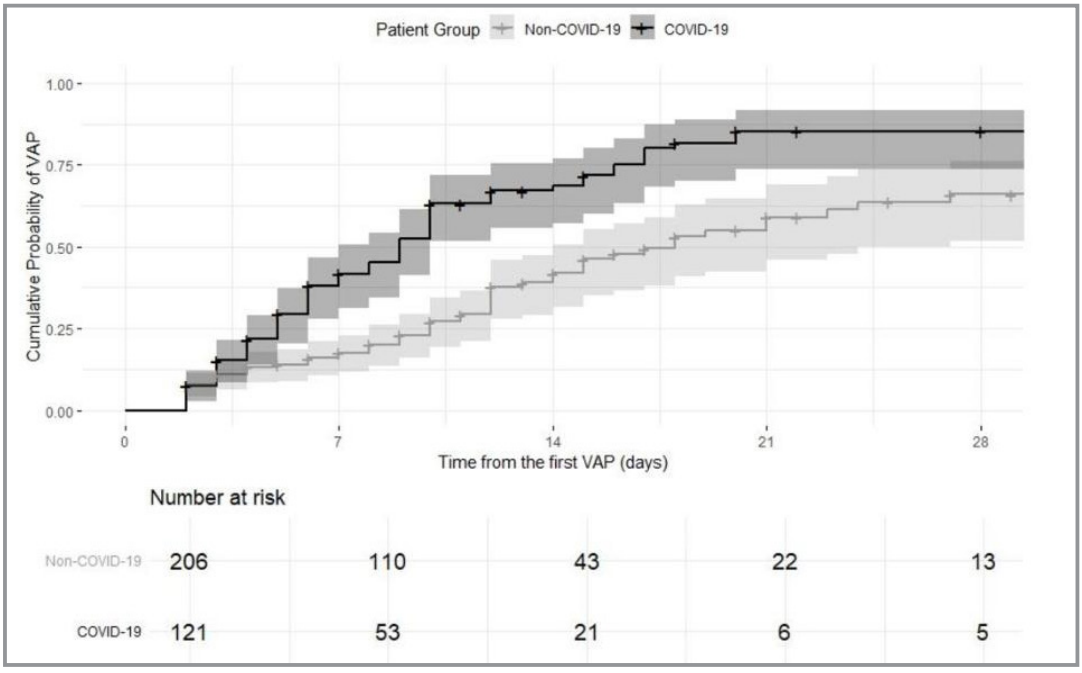


Figure 1. Kaplan-Meier curves for the cumulative probability of ventilator-associated pneumonia in COVID-19 and non-COVID-19 patients over time.

Kaplan-Meier curves for the cumulative probability of VAP in COVID-19 and non-COVID-19 patients over time based on mechanical ventilation duration. The probability of developing VAP was consistently higher in COVID-19 patients, with a steeper increase observed in the early days. Shaded areas represent 95% confidence intervals.

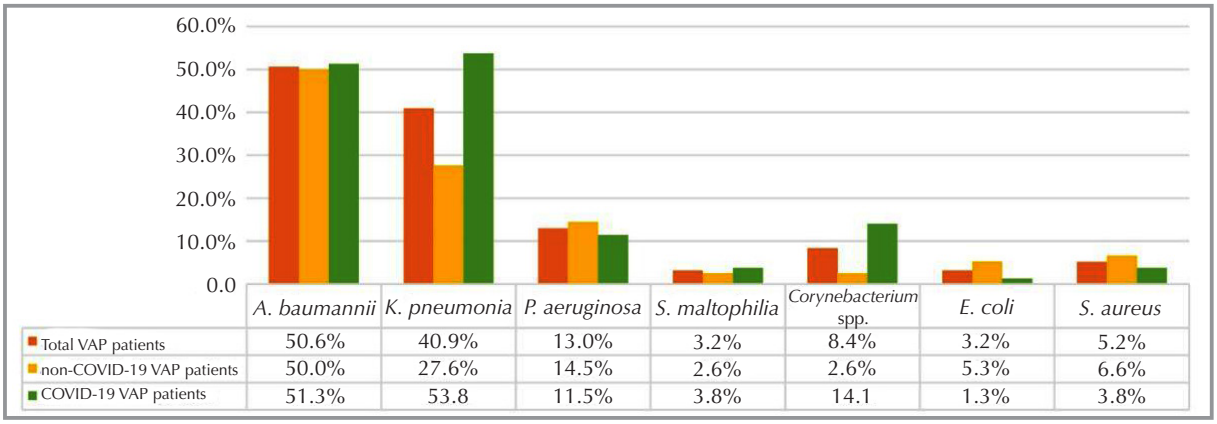
Demographic characteristics and clinical differences between COVID-19 VAP and non-COVID-19 VAP

Most patients diagnosed with VAP were male (58.4%), and median age of the cohort was 71 years. Compared to non-COVID-19 VAP, COVID-19 VAP demonstrated a significantly higher prevalence of ARDS (p< 0.001) and increased corticosteroid use (p= 0.004). Conversely, this group exhibited lower APACHE II scores (p< 0.001) and a lower rate of tracheostomy (p= 0.005). The two groups were comparable with respect to age, sex, comorbidity profile, duration of mechanical ventilation and ICU stay preceding VAP development (Table 3). Among the patients with COVID-19, the use of immunomodulatory therapies was further analyzed according to VAP development. Anakinra use was numerically higher

Table 3. Comparison of demographic characteristics and clinical features between non-COVID-19 VAP and COVID-19 VAP patients (n= 154)

	Total VAP Patients (154)	non-COVID-19 VAP Patients (76)	COVID-19 VAP Patients (78)	p
Demographics characteristics				
Age median (min-max)	71 (22-98)	73 (22-98)	70 (26-93)	0.175
Male sex n (%)	90 (58.4)	42 (55.3)	48 (61.5)	0.430
APACHE score mean (+/-SD)	25 (8.5)	27 (9)	20 (7)	**<0.001**
ARDS n (%)	61 (39.6)	5 (6.6)	56 (71.8)	**<0.001**
Comorbidities n (%)				
DM	69 (44.8)	33 (43.4)	36 (46.2)	0.733
HT	92 (59.7)	46 (60.5)	46 (59)	0.844
CAD	61 (39.6)	30 (39.5)	31 (39.7)	0.973
CHF	40 (25.9)	21 (27.6)	19 (24.4)	0.689
COPD	30 (19.5)	16 (21.1)	14 (17.9)	0.627
Chronic renal failure	15 (9.7)	7 (9.2)	8 (10.3)	0.827
Chronic liver disease	5 (3.2)	2 (2.6)	3 (3.8)	0.671
Rheumatologic disease	8 (5.2)	4 (5.3)	4 (5.1)	0.970
Cerebrovascular event	14 (9.1)	7 (9.2)	7 (9)	0.959
Malignancy	37 (24)	21 (27.6)	16 (20.5)	0.301
Immunosuppression	23 (14)	13 (17.1)	10 (12.8)	0.825
Tracheostomy status	18 (11.7)	15 (19.7)	3 (3.8)	**0.005**
Corticosteroid use	97 (63)	39 (51.3)	58 (74.4)	**0.004**
Duration of ventilation prior to VAP (days) median(min-max)	8 (2-93)	9 (3-93)	6 (2-58)	0.158
Duration of ICU stay prior to VAP (days) median(min-max)	8 (2-93)	9 (3-93)	7 (2-59)	0.966
Clinical outcomes n (%)				
ICU length of stay	28 (3-231)	29 (3-231)	26.5 (3-112)	0.773
Hospital length of stay	27 (3-231)	35 (3-231)	24.5 (3-143)	**0.006**
ICU case-fatality	96 (62.3)	41 (53.9)	55 (70.5)	**0.034**
Hospital case-fatality	113 (73.4)	50 (65.8)	63 (80.8)	**0.035**

COVID-19: Coronavirus disease-2019, VAP: Ventilator associated pneumonia, SD: Standard deviation, APACHE: Acute physiology and chronic health evaluation, ARDS: Acute respiratory distress syndrome, DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit.



	A. baumannii	*K. pneumonia*	*P. aeruginosa*	*S. maltophilia*	*Corynebacterium* spp.	*E. coli*	*S. aureus*
Total VAP patients	50.6%	40.9%	13.0%	3.2%	8.4%	3.2%	5.2%
non-COVID-19 VAP patients	50.0%	27.6%	14.5%	2.6%	2.6%	5.3%	6.6%
COVID-19 VAP patients	51.3%	53.8	11.5%	3.8%	14.1	1.3%	3.8%

Figure 2. Comparison of bacterial profiles in COVID-19 ventilator-associated pneumonia vs. non-COVID-19 ventilator-associated pneumonia.

in patients who developed VAP compared with those without VAP (16.7% vs. 7.0%); however, this difference did not reach statistical significance (p= 0.213). Tocilizumab use was low and comparable between the two groups (3.8% vs. 2.3%, p= 0.890). Mortality rates, both in the ICU and during overall hospitalization, were significantly higher in COVID-19 VAP patients compared to non-COVID-19 VAP (p= 0.034 and p= 0.035, respectively).

Microbiological profiles of COVID-19- VAP vs. non-COVID-19 VAP

Figure 2 represents a comparative analysis of bacterial profiles between COVID-19 VAP and non-COVID-19 VAP patients. In COVID-19 VAP patients, *K. pneumoniae* was the most frequently identified pathogen, whereas *A. baumannii* was the predominant causative agent in non-COVID-19 VAP patients and the second most common agent in COVID-19 VAP patients. Key findings included a significant increase in *K. pneumoniae* as gram negative bacteria (53.8% vs. 27.6%, p< 0.001) and a notably higher prevalence of *Corynebacterium* spp. as gram positive bacteria (14.1% vs. 2.6%, p= 0.010) among the COVID-19 VAP patients. The occurrence of polymicrobial infections was markedly higher in COVID-19–associated VAP compared to non-COVID-19 VAP cases (34.6% vs. 13.1%, p= 0.038). However, analysis of antimicrobial resistance patterns revealed no significant differences between the two groups (Supplement 1).

Supplement 1. Comparison of bacterial profiles and antibiotic resistance patterns in COVID-19-associated VAP vs. non-COVID-19 VAP patients

	Total VAP Patients (154)	**non-COVID-19 VAP Patients (76)**	**COVID-19 VAP Patients (78)**	**p**
Polymicrobial	37 (24)	10 (13.1)	27 (34.6)	**0.038**
Gram negative microorganisms				
Non fermentative				
Acinetobacter baumanii	78 (50.6)	38 (50)	40 (51.3)	0.874
MDR	61 (78.2)	26 (68.4)	35 (87.5)	0.302
PDR	16 (20.5)	11 (28.9)	5 (12.5)	0.072
Pseudomonas aeruginosa	20 (13)	11 (14.5)	9 (11.5)	0.588
MDR	13 (65)	7 (63.6)	6 (66.7)	0.888
PDR	2 (10)	1 (9.1)	1 (11.1)	0.881
Stenotrophomonas maltophilia	5 (3.2)	2 (2.6)	3 (3.8)	0.649

Supplement 1. Comparison of bacterial profiles and antibiotic resistance patterns in COVID-19-associated VAP vs. non-COVID-19 VAP patients (continue)

	Total VAP Patients (154)	non-COVID-19 VAP Patients (76)	COVID-19 VAP Patients (78)	p
Enterobacterales				
Klebsiella pneumonia	63 (40.9)	21 (27.6)	42 (53.8)	**<0.001**
MDR	41 (65.1)	13 (61.9)	30 (71.4)	0.080
PDR	14 (22.2)	6 (28.6)	8 (19)	0.388
Escherichia coli	5 (3.2)	4 (5.3)	1 (1.3)	0.150
MDR	3 (60)	2 (50)	1 (100)	1.000
Gram positive microorganisms				
Staphylococcus aureus	8 (5.2)	5 (6.6)	3 (3.8)	0.443
MRSA	3 (37.5)	1 (20)	2 (66.7)	0.464
Corynebacterium spp.	13 (8.4)	2 (2.6)	11 (14.1)	**0.010**

VAP: Ventilator-associated pneumonia, COVID-19: Coronavirus disease-2019, MDR: Multi drug resistance, PDR: Pan drug resistance, MRSA: Methicillin-resistant *Staphylococcus aureus*.

DISCUSSION

COVID-19 pandemic has resulted in a substantial global increase in healthcare-associated infections, reversing the previously declining trend due to effective infection prevention and control interventions. National Healthcare Safety Network surveillance data demonstrated a marked increase in the incidence of central line–associated bloodstream infections, catheter-associated urinary tract infections, ventilator-associated events, and methicillin-resistant *S. aureus* bacteremia in 2021 relative to 2019 (11). The incidence of VAP has also increased at an alarming rate (12,13). Multiple factors may contribute to the higher incidence of VAP in COVID-19 patients. This increased risk can be attributed to the frequent association with ARDS, diffuse alveolar damage, impaired lung perfusion, and virus-induced immunoparalysis. Furthermore, corticosteroid use and other immunosuppressive therapies, such as tocilizumab and anakinra, may further predispose patients to VAP. Additionally, staffing shortages, inadequate personal protective equipment, and the involvement of non-ICU healthcare workers unfamiliar with infection prevention protocols may have led to higher cross-contamination rates, further exacerbating VAP incidence in critically ill COVID-19 patients (1,14-17).

The incidence of VAP in COVID-19 patients varies widely in the literature, ranging from 48% to 79% (5,16,18-22). A previous study reported that VAP development was significantly higher in COVID-19 patients compared to non-COVID-19 patients (51.9% vs. 31.2%, p< 0.001) (23). Consistent with earlier reports, our study results showed that COVID-19 patients exhibited a significantly greater rate of VAP than non-COVID-19 patients (64.5% vs. 36.9%, p< 0.001). Furthermore, a multicenter study demonstrated that the cumulative incidence of the first VAP episode at 7, 14, and 28 days was markedly higher in patients with COVID-19 than in those without the infection (1). Consistent with these findings, our study showed that the probability of developing VAP remained consistently high in COVID-19 patients compared to non-COVID-19 patients throughout the entire study period. The presence of COVID-19 was found to increase the risk of developing VAP by a factor of 2.47.

Corticosteroids, while life-saving in SARS-CoV-2-associated respiratory failure, may also increase the risk of VAP (24). Several studies have demonstrated a significant association between corticosteroid use and increased VAP risk in COVID-19 patients. Scaravilli et al. reported in a multicenter cohort study that early corticosteroid treatment nearly doubled the incidence of VAP (25). Similarly, Lamouche-Wilquin et al. found that corticosteroid use for SARS-CoV-2 infection was associated with a 30% increased risk of VAP in ICU patients (26). However, some studies contradicted these findings, suggesting that corticosteroid treatment did not universally increase VAP rates. Unlike prior research, Saura et al. observed that

the impact of corticosteroids on VAP risk varied depending on the duration of mechanical ventilation, suggesting that VAP risk was not constant over time. Their findings proposed that survival bias may influence VAP development, as patients who survived longer may possess intrinsic resilience, altering their susceptibility to infection (27). In this study, both COVID-19 and non-COVID-19 VAP patients had similar durations of mechanical ventilation. Corticosteroid therapy was associated with an increased risk of VAP in the overall population, being considerably more common among COVID-19 VAP cases. Despite accumulating evidence, the association between corticosteroid therapy and VAP risk remained a subject of ongoing debate. Our study results showed that corticosteroid use, malignancy, and COVID-19 were independent risk factors for the development of VAP in mechanically ventilated patients in ICU.

Previous studies have consistently identified tracheostomy as a significant risk factor for VAP, particularly in the setting of invasive airway interventions and late-onset VAP (28). In a recent updated systematic review and meta-analysis, tracheostomy was strongly associated with VAP development (OR 3.44; 95% CI 2.0–5.92), underscoring its clinical relevance. In line with this literature, our findings demonstrated that tracheostomy was independently associated with VAP development, even after adjustment for major clinical confounders. While non-modifiable factors such as malignancy may aid risk stratification, treatment-related and potentially modifiable factors—including tracheostomy—represent important targets for preventive strategies aimed at reducing VAP incidence and improving outcomes in critically ill patients (29).

The increased incidence of VAP in COVID-19 patients has led to broader antibiotic use, further accelerating the spread of MDR bacterial pathogens (24). A study reported that *K. pneumoniae* was the most common bacterial pathogen in Latin America, whereas *P. aeruginosa* was the most frequent in Europe. Additionally, *A. baumannii* was more prevalent in Latin America than in Europe (30). Both *K. pneumoniae* and *A. baumannii* pose significant concerns due to their high resistance rates, particularly in resource-limited settings, where they have a substantial impact on COVID-19 patients (27). Similarly, in this study, *A. baumannii* and *K. pneumoniae* were the two most frequently identified pathogens across all patients, with *K. pneumoniae* being the most prevalent pathogen in COVID-19 VAP patients. Polymicrobial infection tendency was also predominant in the COVID-19 VAP group. The microbial profile of COVID-19 VAP patients were influenced by multiple factors, including hospital and ICU length of stay, duration of mechanical ventilation, local bacterial epidemiology, antimicrobial exposure, and geographic variations (17,30).

A systematic review and meta-analysis reported that COVID-19 VAP patients had a pooled mortality estimate of 42.7% (13). Additionally, a study comparing COVID-19 and non-COVID-19 VAP patients found that ICU and hospital case fatality rates were significantly higher in COVID-19 patients (71% vs. 33%, $p< 0.001$ and 74% vs. 43%, $p< 0.001$, respectively) (23). Consistent with these findings, we also observed that COVID-19 VAP patients experienced more severe clinical manifestations, including increased frequency of ARDS, and exhibited higher ICU and hospital case fatality rates when compared to non-COVID-19 VAP patients.

The retrospective, single-center design and the limited sample size were among the main limitations of this study. Another limitation was that the study did not account for factors that could influence the results, such as immunity acquisition following successive epidemic waves, COVID-19 vaccination, or the emergence of SARS-CoV-2 variants. Additionally, the use of corticosteroids as a standard treatment for COVID-19, while also being a recognized risk factor for increased VAP incidence, may have introduced potential bias in the analysis. Due to the retrospective nature of the study, detailed information required to accurately calculate cumulative corticosteroid dose—such as exact treatment duration and tapering schedules—was not consistently available. Therefore, corticosteroid exposure was analyzed as a binary variable. However, standardized low-to-moderate dosing throughout the entire study period minimizes the risk of meaningful confounding. Finally, despite maintaining institutional standards for infection control practices, transient pandemic-related operational strain and increased workload may have affected adherence to preventive measures at unit level.

CONCLUSION

This study demonstrated that COVID-19 patients have a significantly higher incidence of VAP compared to non-COVID-19 patients. COVID-19-associated VAP was characterized by a higher prevalence

of ARDS, increased case fatality rates, and distinct microbiological profiles. Notably, MDR bacterial pathogens such as *K. pneumoniae* and *A. baumannii* were predominated in COVID-19 VAP patients. These findings highlighted the need for optimized antimicrobial stewardship strategies in critically ill COVID-19 patients to mitigate VAP-associated morbidity and mortality. These findings are particularly important to consider in empirical treatment planning for VAP cases occurring in the post-COVID-19 setting.

Ethical Committee Approval: This study was approved by the Ethics Commission of Ankara University (Decision no: İ02-100-23, Date: 06.03.2023).

Peer-review: Externally peer-reviewed.

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: EMS, LF, FY, NDA

Analysis/Interpretation: All of authors

Data acquisition: EMS, LF, EG, GC, İA, MİH, İK

Writing: All of authors

Clinical Revision: EMS, LF, EG, GC, İA, NDA, FY

Final Approval: EMS, FY

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