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RESEARCH ARTICLE

Silent pandemic in intensive care units: Post-pandemic rise of extensively drug-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* in ventilator-associated pneumonia

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

ABSTRACT

Silent pandemic in intensive care units: Post-pandemic rise of extensively drug-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* in ventilator-associated pneumonia

Introduction: In the post coronavirus disease-2019 era, as the pandemic's impact diminishes, the state of our intensive care units (ICUs) remains as crucial as the well-being of individuals. While numerous studies have explored the pandemic's effects on patients, our focus is to examine its impact on ICUs.

Materials and Methods: A total of 72 patients who were admitted to the chest diseases ICU due to hypercapnic or hypoxic respiratory failure between October 2018-April 2020 and December 2022-December 2024 and who developed ventilator-associated pneumonia during their follow-up were included in our study.

Results: While *Klebsiella pneumoniae* and *Acinetobacter baumannii* co-growth was observed in 4 of 30 patients (13.3%) pre-pandemic, it increased to 16 of 42 patients (38.1%) post-pandemic. Extensively drug-resistant (XDR) cases rose from 6 (20%) pre-pandemic to 34 (81%) post-pandemic ($p < 0.001$). A significant post-pandemic decline in carbapenem and beta-lactam susceptibility was noted ($p < 0.001$ for all). Although susceptibility to ceftazidime-avibactam, the most effective antibiotic for *K. pneumoniae*, decreased, the change was not statistically significant ($p = 0.09$). Multivariate regression analysis identified advanced age, coronary artery disease, low ejection fraction, and XDR resistance as factors increasing mortality ($p = 0.03, 0.04, 0.04, 0.001$, respectively).

Conclusion: During the pandemic, our ICU, where patients were treated with broad-spectrum antibiotics for a long time, has cured many patients but could

not prevent the development of multi-drug resistance and XDR *Acinetobacter* and *Klebsiella*. Failure to take the necessary precautions will cause significant effects of the silent pandemic.

Key words: COVID-19; multi-drug resistance; extensively-drug resistant; gram negative bacteria

ÖZ

Yoğun bakım ünitelerinde sessiz pandemi: Ventilatörle ilişkili pnömonide yaygın ilaç dirençli *Acinetobacter baumannii* ve *Klebsiella pneumoniae*'nin pandemi sonrası yükselişi

Giriş: Koronavirüs hastalığı-2019 pandemisinin etkilerinin geride bırakıldığı günümüzde, insanlar kadar bu pandemiden etkilenen yoğun bakımların durumu da önemli bir konudur. Pandeminin hastalar üzerindeki etkileri binlerce çalışmayla incelenmişken, biz de yoğun bakım ünitemize olan etkisini değerlendirmeyi hedefledik.

Materyal ve Metod: Çalışmamıza, Ekim 2018-Nisan 2020 ve Aralık 2022-Aralık 2024 tarihleri arasında, hiperkapnik veya hipoksik solunum yetmezliği nedeniyle göğüs hastalıkları yoğun bakımına yatırılan ve takiplerinde ventilatör ilişkili pnömoni gelişen 72 hasta dahil edildi.

Bulgular: Pandemi öncesinde, *Klebsiella pneumoniae* ve *Acinetobacter baumannii* birlikte üremesi 30 hastanın 4 (%13.3)'ünde gözlenirken, pandemi sonrasında 42 hastanın 16 (%38.1)'sında gözlemlendi. Yaygın ilaç direnci (YİD) vakaları pandemi öncesinde 6 (%20) iken, pandemi sonrasında 34 (%81)'e yükseldi ($p < 0.001$). Pandemi sonrasında karbapenem ve beta-laktam duyarlılığında anlamlı bir düşüş kaydedildi (tümü için $p < 0.001$). *K. pneumoniae* için en etkili antibiyotik olan seftazidim-avibaktam karşı duyarlılık azalsa da bu değişim istatistiksel olarak anlamlı değildi ($p = 0.09$). Çok değişkenli regresyon analizine göre, ileri yaş, koroner arter hastalığı, düşük ejeksiyon fraksiyonu ve YİD direnci, mortaliteyi artıran faktörler olarak belirlendi (sırasıyla $p = 0.03, 0.04, 0.04, 0.001$).

Sonuç: Pandemi sürecinde, hastaların uzun süre geniş spektrumlu antibiyotiklerle tedavi edildiği yoğun bakım ünitemiz birçok hastayı iyileştirdi, ancak çoklu ilaç direnci ve YİD *Acinetobacter* ile *Klebsiella*'nin gelişimini önleyemedi. Gerekli önlemlerin alınmaması, bu sessiz pandeminin önemli sonuçlar doğurmasına neden olacaktır.

Anahtar kelimeler: COVID-19; çoklu ilaç direnci; yaygın ilaç direnci; gram negatif bakteriler

INTRODUCTION

Hospital-acquired pneumonia (HAP) continues to be a significant cause of morbidity and mortality despite advances in antimicrobial therapy and supportive care. Pneumonia that develops 48 hours after hospital admission or within 48 hours after extubation in intubated patients without a prior diagnosis of pneumonia is defined as ventilator-associated pneumonia (VAP) (1). Early and appropriate microbiological sampling is crucial for accurate treatment planning in patients with VAP (2).

It has been observed that the number of patients developing HAP has increased since the coronavirus disease-2019 (COVID-19) pandemic (3). Studies suggest that one of the main reasons for this rise is the redeployment of healthcare personnel without prior intensive care experience to manage the overwhelming number of cases. Additionally, the frequent and often inappropriate use of antibiotics in intensive care units (ICUs) during the pandemic has significantly contributed to the development of antimicrobial resistance and multidrug-resistant infections (4). Among Gram-negative bacteria, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* have exhibited a concerning tendency toward antimicrobial resistance, with reported resistance rates reaching up to 53% in some studies (5).

A. baumannii remains one of the most frequently isolated Gram-negative pathogens in VAP cases. However, in recent years, a notable increase in multidrug-resistant *K. pneumoniae* co-infections has been observed, particularly with the emergence of carbapenem-resistant strains (6). Polymyxins have been among the few remaining treatment options for carbapenem-resistant *K. pneumoniae* and *Acinetobacter* infections. However, the widespread use of polymyxins in treating both pathogens has led to the alarming emergence of polymyxin-resistant strains, further complicating treatment strategies (2). Given the limited availability of new antimicrobial agents, utilizing the synergistic effects of combination antibiotic therapy remains one of the few viable options for clinicians (7).

The rising trend of antimicrobial resistance, prolonged hospital stays, and associated morbidity and mortality has posed serious challenges for both patient outcomes and the future of antimicrobial stewardship. Studies indicate that this worsening trend has accelerated following the pandemic, largely due to the increased and often indiscriminate use of antimicrobial agents.

Our study aims to compare the factors influencing antimicrobial resistance and mortality in VAP patients infected with *Acinetobacter* and/or *Klebsiella* before and after the COVID-19 pandemic. By identifying



key differences and trends, we hope to contribute to a better understanding of how the pandemic has impacted the epidemiology and clinical outcomes of these infections.

MATERIALS and METHODS

Study Design

Patients who were admitted to the chest diseases ICU due to hypercapnic or hypoxic respiratory failure between October 2018-April 2020 and December 2022-December 2024 were included in our study. Data on past hospitalizations and antibiotic treatment duration were obtained from our hospital automation system and the Ministry of Health e-Nabız system. Ethics approval was obtained from the local ethics committee before initiating the study.

Study Population

A total of 1.187 patients were monitored in our ICU during the study period. The following patients were excluded from the study:

- Patients with pneumonia at the time of ICU admission,
- Patients who acquired pneumonia while on invasive mechanical ventilation,
- Patients with resistant microorganism growth in respiratory tract isolates within the last six months,
- Patients who developed pneumonia within 48 hours of being connected to or disconnected from the ventilator,
- Patients with previous healthcare-associated pneumonia,
- Patients with concurrent infections (e.g., central catheter infections, urinary tract infections, or gastrointestinal system infections) alongside VAP,
- Patients who died due to causes other than pneumonia after being diagnosed with VAP.

VAP-related mortality was defined as death occurring within 14 days after initiating specific antibiotic therapy in patients with radiologically confirmed VAP. Patients who survived beyond 14 days after targeted antibiotic therapy were not considered to have VAP-related mortality. Patients who completed their treatment in the hospital after VAP were included in our surveillance group.

After applying the exclusion criteria, 72 VAP patients with *A. baumannii* and/or *K. pneumoniae* growth in tracheal aspirate cultures were included in the study. To assess the impact of the COVID-19 pandemic, VAP cases were categorized into two periods: Pre-pandemic and post-pandemic. Thirty patients were identified in the pre-pandemic period, while 42 patients were identified in the post-pandemic period, following the exclusion criteria.

During the period when VAP was diagnosed, empirical antibiotic therapy was initiated until culture results were obtained. Once the culture and antibiogram results were available, treatment regimens were adjusted accordingly. Hematological and biochemical parameters were recorded on the day of culture positivity and on the third day after initiating targeted treatment. Patients were monitored until ICU discharge or completion of hospital treatment.

Taking a Sputum Sample

Empirical antibiotic therapy for sputum analysis was initiated only after obtaining the sample. For tracheal aspirate sampling, aspiration was performed using:

- A 50-cc sterile disposable irrigation syringe connected to the outer end of the intubation tube, or
- A disposable lavage tube attached to the endotracheal tube.

The aspirate sample was immediately sealed with its original cap and transported to the microbiology laboratory. Samples not processed within 48 hours were stored at 4°C and transported on wet ice.

A high-quality sputum sample was defined as one with <10 squamous epithelial cells per field at 10x magnification and a polymorphonuclear leukocyte count >25. Suitable sputum samples were cultured on blood, EMB, and chocolate agar media. Cultures were incubated at 37°C for 24-48 hours for bacterial growth evaluation.

Bacterial identification and antibiotic susceptibility testing were performed using the BD PHOENIX 100 automated system (Becton-Dickinson, USA), with antibiotic resistance patterns evaluated according to EUCAST criteria.

- Multi-drug resistance (MDR) was defined as resistance to at least one antibiotic in three or more antibiotic groups.

- Extensively drug-resistant (XDR) strains were defined as resistant to all antibiotics except for two or fewer antibiotic groups.

Echocardiographic Evaluation

Echocardiographic (ECHO) examinations were conducted by three cardiologists using a Toshiba S270-A device equipped with a 2.5 MHz probe. The procedure was performed in a quiet environment while the patient was calm, positioned in the left lateral decubitus position, and breathing comfortably. Before ECHO examination, cardiac auscultation, electrocardiography, and chest radiography were performed for all patients to ensure comprehensive cardiac assessment.

During ECHO examination, multiple imaging planes were utilized, including the parasternal long-axis view, the aorto-mitral-papillary muscle view, and the parasternal short-axis view at the apical level. Additionally, apical four-chamber and two-chamber images were obtained using two-dimensional, M-mode, color Doppler, pulse Doppler, and continuous Doppler modalities. When necessary, the interatrial septum was evaluated using subcostal ECHO images, while the aortic arch was assessed with suprasternal ECHO imaging.

Transthoracic echocardiography was used to evaluate right heart hemodynamics, particularly systolic pulmonary artery pressure (SPAP). SPAP was estimated based on the measurement of maximum tricuspid regurgitation velocity, the peak pressure gradient of tricuspid regurgitation, and an assumed fixed value of 10 mmHg for right atrial pressure. ECHO findings were integrated into the study to explore potential correlations between cardiovascular function and mortality in patients diagnosed with VAP.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows version 27.0 (IBM Corp., Armonk, NY). Between-group comparisons were performed using Pearson's chi-square test for parametric data and Mann-Whitney U test for non-normally distributed numerical data. The groups' demographic data and laboratory parameters were compared using Kruskal Wallis test. Independent sample t-test was used to compare the parameters for which significant results were detected with the Kruskal Wallis test between groups. Multivariate logistic

regression analysis was applied to calculate the factors affecting mortality. A $p < 0.05$ was considered statistically significant.

RESULTS

Mean age of the patients included in our study was 69.3 ± 12.9 years. While the mean age of the patients included in the study during the pre-pandemic period was 71.5 ± 13.3 years, it was 67.7 ± 12.6 years in the post-pandemic period. No statistically significant difference was observed between the mean ages of the groups ($p = 0.23$). Forty-two (58.3%) of the patients included in our study were male. No statistically significant difference was observed in the analysis of the groups according to sex ($p = 0.09$).

Of the patients included in our study, 65 (90.3%) had chronic obstructive pulmonary disease, 38 (52.7%) had hypertension, 16 (22.2%) had diabetes mellitus, 12 (16.7%) had coronary artery disease, 16 (22.2%) had Alzheimer's dementia, and 10 (13.9%) were receiving immunosuppressive treatment due to malignancy or rheumatologic diseases.

While *K. pneumoniae* growth was observed alongside *A. baumannii* in 4 out of 30 patients (13.3%) in the pre-pandemic period, it was noted in 16 out of 42 patients (38.1%) in the post-pandemic period. In the comparison made before and after the pandemic, an increase in the percentage of *Klebsiella* growth was observed after the pandemic. It was also determined that the XDR rate increased in the post-pandemic period ($p = 0.009$, <0.001 respectively) (Table 1).

A comparison of age, laboratory parameters, and ECHO findings on the day growth was observed (first day of specific treatment) and on the third day of specific treatment among all patients with and without mortality in the study is shown in Tables 2 and 3. Accordingly, it was observed that age, white blood cell count, and neutrophil-to-lymphocyte ratio (NLR) were higher in the group that experienced mortality on the day specific treatment was started ($p = 0.04$, <0.001 , 0.03 , respectively). However, ejection fraction was lower in patients who experienced mortality ($p = 0.03$). It was observed that blood urea nitrogen (BUN), C-reactive protein (CRP), procalcitonin, CRP/albumin ratio, and BUN levels were statistically significantly higher in cases that experienced mortality on the third day of treatment ($p = <0.001$ for all).

Table 1. Demographic characteristics of the patients included in the study during the pre- and post-pandemic periods, bacteria grown in tracheal aspirate, and resistance levels

	Before the Pandemic (n= 30)	After the Pandemic (n= 42)	p
Age (year)	71.5 ± 13.4	67.6 ± 12.6	0.23
Sex (n/%)			
Male	14 (33.3%)	28 (66.7%)	0.09
Female	16 (53.3%)	14 (46.7%)	
Comorbidities (n)			
Hypertension	20	18	0.76
Diabetes mellitus	9	7	0.8
COPD	27	38	0.65
CAD	6	6	N/A
Alzheimer-dementia	10	6	0.6
Immunosuppression	6	4	0.82
<i>A. baumannii</i> (n/%)	30 (100%)	40 (95.2%)	0.009
<i>K. pneumoniae</i> (n/%)	4 (13.3%)	18 (42.9%)	
Drug Resistance (n/%)			
MDR	24 (80%)	8 (19%)	<0.001
XDR	6 (20%)	34 (81%)	

COPD: Chronic obstructive pulmonary diseases, CAD: Coronary arterial diseases, *A. baumannii*: *Acinetobacter baumannii*, *K. pneumoniae*: *Klebsiella pneumoniae*, MDR: Multi-drug resistance, XDR: Extensively-drug resistant.

Table 2. Comparison of laboratory parameters and echocardiography findings between the groups with and without mortality on the specific day treatment was started according to culture growth

	Mean ± SD Survey n= 24	Mean ± SD Mortality n= 48	p
Age	64.7 ± 13.6	71.5 ± 12.1	0.04
WBC (/μL)	9879.2 ± 4506.9	12525.4 ± 6496.1	<0.001
Neutrophil (/μL)	8643.3 ± 4270.1	12884.2 ± 6516.3	0.005
Lymphocyte (/μL)	780.8 ± 460.7	797.9 ± 444.6	0.8
Eosinophil (/μL)	52.5 ± 86.9	67.1 ± 138.5	0.63
Basophil (/μL)	14.2 ± 20.2	20.8 ± 21.4	0.2
Platelet (/μL)	260750 ± 72584.7	247041.7 ± 140250.7	0.65
NLR	14.3 ± 8.4	24.4 ± 21.5	0.03
PLR	521.5 ± 555.8	404.2 ± 304.2	0.34
AST (U/L)	42.4 ± 37.1	58.8 ± 150.3	0.48
ALT (U/L)	41.1 ± 37.3	35.1 ± 30.2	0.53
GGT (U/L)	69.7 ± 56.1	78.9 ± 93.1	0.6
ALP (U/L)	101.6 ± 46.3	93.1 ± 46.9	0.47
BUN (mg/dL)	33.8 ± 24.7	41.8 ± 24.2	0.2
Creatinine (mg/dL)	0.7 ± 0.5	0.9 ± 0.8	0.14
Total protein (g/dL)	5.5 ± 0.6	5.3 ± 0.6	0.41
Albumine (g/dL)	2.5 ± 0.4	2.4 ± 0.3	0.28
CRP (mg/L)	125.4 ± 106.8	143.4 ± 102.7	0.49
Procalcitonin (ng/mL)	0.9 ± 1.4	1.9 ± 1.9	0.45

Table 2. Comparison of laboratory parameters and echocardiography findings between the groups with and without mortality on the specific day treatment was started according to culture growth (continue)

	Mean ± SD Survey n= 24	Mean ± SD Mortality n= 48	p
CRP/Albumine ratio	52.5 ± 52.7	62.2 ± 48.6	0.45
EF (%)	55.5 ± 1.7	52.9 ± 5.8	0.03
sPAP (mm_Hg)	41.4 ± 13.1	40.6 ± 11.4	0.8

SD: Standard deviation, WBC: White blood cells, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, AST: Aspartat aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, BUN: Blood urea nitrogen, CRP: C-reactive protein, EF: Ejection fraction, sPAP: Systolic pulmonary arterial pressure.

Table 3. Comparison of laboratory parameters on the third day of treatment between the groups with and without mortality

	Mean ± SD Survey n= 24	Mean ± SD Mortality n= 48	p
WBC (/μL)	10651.6 ± 4239.5	14225.3 ± 7674.3	0.04
Neutrophil (/μL)	87890 ± 3735.6	12530 ± 7775.6	0.03
Lymphocyte (/μL)	1216.6 ± 574.4	1057.4 ± 698.8	0.35
Eosinophil (/μL)	109.2 ± 140.5	77.4 ± 123.5	0.35
Basophil (/μL)	10.8 ± 11.4	16.3 ± 14.8	0.1
Platelet (/μL)	231333.3 ± 124082.3	212842.1 ± 124443.1	0.57
NLR	8.9 ± 5.2	18.2 ± 16.9	0.01
PLR	257.9 ± 269.4	253.3 ± 140.4	0.93
AST (U/L)	38.3 ± 33.4	67.4 ± 146.1	0.34
ALT (U/L)	50.8 ± 70.9	53.1 ± 124.5	0.9
GGT (U/L)	73.8 ± 65.1	53.4 ± 41.1	0.14
ALP (U/L)	103.4 ± 42.9	95.5 ± 53.9	0.52
BUN (mg/dL)	28.1 ± 11.1	48.2 ± 32.5	<0.001
Creatinine (mg/dL)	0.6 ± 0.2	0.9 ± 0.9	0.02
Total protein (g/dL)	5.6 ± 0.6	5.2 ± 0.8	0.02
Albumine (g/dL)	2.6 ± 0.3	2.3 ± 0.3	<0.001
CRP (mg/L)	79.4 ± 69.2	163.5 ± 78.4	<0.001
Procalcitonin (ng/mL)	0.3 ± 0.5	8.4 ± 2.3	<0.001
CRP/Albumine ratio	33.2 ± 30.2	72.8 ± 37.3	<0.001

SD: Standard deviation, WBC: White blood cells, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, AST: Aspartat aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, BUN: Blood urea nitrogen, CRP: C-reactive protein.

The comparison of antibiotic susceptibility rates is given in Table 4. Accordingly, a statistically significant decrease in susceptibility to carbapenems was observed along with beta-lactam antibiotics ($p < 0.001$). Although there was a decrease in susceptibility to ceftazidime-avibactam, the most sensitive antibiotic for *K. pneumoniae*, it was noted that there was no statistically significant difference ($p = 0.09$). While the number of patients with XDR in the pre-pandemic period was 6 (20%), this number increased to 34 (81%) after the pandemic. A statistically significant

difference was observed in the comparison ($p < 0.001$).

Regression analysis of age, comorbidities, ECHO findings, drug resistance status (MDR or XDR), the number of hospitalizations in the last year, and the number of days of antibiotic use in patients who developed mortality during follow-up are shown in Table 5. Accordingly, it was observed that advanced age, the presence of coronary artery disease, a low ejection fraction, and XDR drug resistance increased mortality ($p = 0.03, 0.04, 0.04, 0.001$, respectively).

Table 4. Drug susceptibility rates of *A. baumannii* and *K. pneumoniae* in the pre-pandemic and post-pandemic periods

	pre-Pandemic Sensitivity (%)		post-Pandemic Sensitivity (%)		p
	<i>A. baumannii</i> (n= 30)	<i>K. pneumoniae</i> (n= 4)	<i>A. baumannii</i> (n= 40)	<i>K. pneumoniae</i> (n= 18)	
Imipenem	80	25	12.5	27.7	<0.001
Colistin	100	-	100	-	N/A
Levofloxacin	13.3	25	12.5	16.6	0.87
Cefazolin	-	0	-	0	N/A
Cefepime	-	25	-	11.1	0.03
Cefoxitin	-	50	-	22.2	<0.001
Ceftazidime	16.6	25	15	5.5	0.02
Ticarcillin-clavulanic acid	-	0	-	0	N/A
Ceftazidime-avibactam	-	100	-	83.3	0.09
TMP/SMX	80	50	20	11.1	<0.001
Piperacillin	-	50	-	50	N/A
Ceftriaxone	-	25	-	0	<0.001
Amoxicillin-clavulanate	-	25	-	0	<0.001
Amikacin	-	50	-	5.5	<0.001
Ampicillin-sulbactam	-	25	-	0	<0.001
Piperacillin-tazobactam	0	25	0	5.5	<0.001
Cefoperazone	0	50	0	50	N/A
Cefotaxime	0	25	0	5.5	<0.001
Gentamicin	-	25	-	11.1	0.01
Meropenem	80	50	15	11.1	<0.001
Cefuroxime	-	0	0	0	N/A
Ciprofloxacin	0	0	0	0	N/A

A. baumannii: *Acinetobacter baumannii*, *K. pneumoniae*: *Klebsiella pneumoniae*, TMP/SMX: Trimethoprim/sulfamethoxazole.

p: Comparison of total antibiotic susceptibility rates before and after the pandemic.

Table 5. Multivariate regression analysis of the effects of age, comorbidities, echocardiographic findings, drug resistance, the number of hospitalizations in the last year, and the duration of antibiotic use on mortality

	B	S.E.	Wald	df	p	EXP(B)	95% CI for EXP(B)	
							Lower	Upper
Age (year)	0.10	0.05	4.49	1	0.03	1.11	1.01	1.22
COPD	0.52	1.15	0.21	1	0.65	1.68	0.17	16.07
Diabetes mellitus	0.19	1.33	0.02	1	0.89	1.2	0.09	16.34
CAD	3.28	1.57	4.37	1	0.04	26.56	1.23	575.16
Hypertension	1.33	0.93	2.04	1	0.15	0.26	0.04	1.64
Immunosuppression	-2.07	1.2	2.97	1	0.09	0.13	0.01	1.33
EF (%)	-0.29	0.15	4.03	1	0.04	0.75	0.56	0.99
sPAB (mm_Hg)	-0.03	0.04	0.55	1	0.46	0.97	0.91	1.04
Drug resistance	-4.31	1.34	10.35	1	0.001	0.01	0.001	0.19
Number of hospitalizations in the last year	0.79	0.87	0.84	1	0.36	2.21	0.41	12.03
Duration of antibiotic use in the past year	-0.16	0.12	1.68	1	0.19	0.85	0.67	1.08

CI: Confidence interval, COPD: Chronic obstructive pulmonary diseases, CAD: Coronary arterial diseases, EF: Ejection fraction, sPAP: Systolic pulmonary arterial pressure.

DISCUSSION

In our study evaluating the ICU dynamics before and after the COVID-19 pandemic, we observed a significant increase in XDR *K. pneumoniae* cases. Among patients with *A. baumannii* and/or *K. pneumoniae* detected in tracheal aspirates, the primary cause of mortality was antibiotic resistance, followed by advanced age, low ejection fraction, and immunosuppression. Additionally, we found that elevated CRP/albumin and NLR levels on the third day of targeted antibiotic therapy could serve as potential indicators of mortality risk.

The recent increase in antibiotic resistance has caused significant increases in hospital stays. In addition, MDR and XDR infections due to gram-negative agents are among the most important causes of mortality in ICUs (8). It has been reported that nearly five million people worldwide lost their lives due to MDR infections in 2019 (9). *A. baumannii* and *K. pneumoniae* were the most frequently isolated gram-negative agents in HAP infections observed in ICUs (10). In the study conducted by Durdu et al., the rate of *Klebsiella* isolates with MDR was 73%, while the rate of XDR was 14% (11). In the study conducted on the resistance rate in *A. baumannii* strains observed in ICUs in our country, the XDR rate was 71.6% (9). In our study, when evaluating both *A. baumannii* and *K. pneumoniae* strains together, we found that the XDR rate before the pandemic was significantly lower than previously reported national data. However, this rate dramatically increased after the pandemic, rising from 20% to 81%. This stark increase highlights the profound impact of the COVID-19 pandemic on antimicrobial resistance patterns in the ICU setting.

During and after the COVID-19 pandemic, no effective antiviral treatment was available for the virus itself. Consequently, high-dose corticosteroid therapy and anti-cytokine treatments were widely administered to manage severe cases. However, these interventions facilitated the development of secondary bacterial infections, particularly among critically ill patients. Despite global warnings against the indiscriminate use of antibiotics, effective antimicrobial stewardship programs remained insufficient (12,13). Our ICU, which we included in the study, was used by the chest diseases clinic before the pandemic. However, during the pandemic, it was transformed into an ICU that only accommodated COVID-19 patients. Although the ICU was transferred back to

our clinic after the pandemic, it became painfully clear that some things were not the same. The most critical situation that caught our attention at first was the resistance to carbapenems, which are widely used in COVID-19 patients. However, it was later determined that the same situation existed in XDR and MDR *Acinetobacter* and *Klebsiella* species.

In our study, we observed an increase in XDR *Acinetobacter* and *Klebsiella* in our ICU and the frequency of these agents in patients who developed VAP. This situation was evaluated as compatible, especially compared to studies conducted during and after the pandemic (14-17). However, the rate of XDR gram-negative pathogens was higher in our ICU. In the laboratory analysis performed on the third day of specific treatment, it was observed that the acute phase reactant and BUN levels were higher in cases with mortality. This situation may have developed due to a lack of response to specific treatment and impaired tissue perfusion in cases with mortality. Carbapenem susceptibility has decreased significantly in resistant *Klebsiella* strains. Ceftazidime-avibactam has been determined to be the most reliable treatment we can currently use. Studies have also reported a significant decrease in *Klebsiella* growth after ceftazidime-avibactam (18). In the multivariate regression analysis of mortality risk factors in VAP patients, increased antimicrobial resistance was identified as a more critical determinant of mortality than coronary artery disease, low ejection fraction, or advanced age. This finding reinforces the urgent need for enhanced antimicrobial stewardship programs to mitigate ICU mortality driven by drug resistance.

Our study focused on evaluating only one ICU before and after the pandemic, and the results need to be strengthened with studies that evaluate data from many ICU together. However, the only ICU in our hospital where the COVID-19 impact was most clearly observed was the chest diseases ICU, and we aimed to show the unnecessary antibiotic effect clearly.

Antibiotic resistance, particularly the rise of MDR and XDR *Acinetobacter* and *Klebsiella* strains, is creating a silent pandemic in ICUs worldwide. If urgent measures are not taken, the increasing prevalence of drug-resistant infections will lead to uncontrollable consequences. Without immediate global and national interventions, the mortality burden of HAP will continue to rise exponentially.

Ethical Committee Approval: This study was approved by Erzurum University Faculty of Medicine Clinical Research Committee (Decision no: BAEK 2024/03-59 Date: 13.03.2024).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: BK, FK

Analys/Interpretation: KÇ, GK

Data acquisition: KÇ, GK

Writing: BK, FK

Clinical Revision: FK

Final Approval: BK, FK

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