Araştırma Makalesi
Research Article

Risk factors and mortality associatied with Carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections; a tertiary hospital experience from Türkiye

KARBAPENEM DİRENÇLİ *KLEBSİELLA PNEUMONIAE* KAN DOLAŞIM YOLU ENFEKSİYONLARINDA RİSK FAKTÖRÜ VE MORTALİTE; TÜRKİYEDEN BİR ÜÇÜNCÜ BASAMAK HASTANE DENEYİMİ

Tuba TATLI KIŞ[1], Yıldız TEZEL[2], Feride TAMAY TATLI[3], Süleyman YILDIRIM[4], Can BİÇMEN[5], Cenk KIRAKLI[4]

[1]Health Sciences University Izmir Suat Seren Chest Diseases and Surgery Training and Research Hospital, Department of Clinical Microbiology and Infectious Diseases, İzmir, Türkiye
[2] İzmir City Hospital, Department of Intensive Care Unit, İzmir , Türkiye,
[3] Health Sciences University Izmir Suat Seren Chest Diseases and Surgery Training and Research Hospital, Department of Chest Diseases, İzmir, Türkiye
[4] Health Sciences University Izmir Suat Seren Chest Diseases and Surgery Training and Research Hospital, Department of Intensive Care Unit, İzmir, Türkiye
[5] Health Sciences University Izmir Suat Seren Chest Diseases and Surgery Training and Research Hospital, Department of Microbiology, İzmir, Türkiye

ABSTRACT

Objectives: *Klebsiella pneumoniae* is one of the most important multidrug-resistant microorganisms. Among the infections caused by Carbapenem-resistant *Klebsiella pneumoniae* (CRKP), bloodstream infections (BSI) have the highest mortality rate. The aim of this study was to evaluate the risk factors associated with healthcare-associated CRKP BSI, mortality rates of *K. pneumoniae* BSI and the factors affecting mortality in patients followed in the intensive care unit (ICU).

Material and Methods: This study was designed as a retrospective case-control study. Patients were divided into two groups according to their carbapenem resistance; Group 1: Patients with CRKP growth in blood cultures and Group 2: Patients with carbapenem sensitive *K. Pneumoniae* (CSKP) growth in blood cultures. Clinical and demographic characteristics, 14-day and all-cause mortality rates and factors affecting mortality were compared between the groups.

Results: Rates of having higher body mass index, having DM, ICU admission due to COVID-19, prior use of carbapenems, a longer ICU stay before the infection were significantly higher in the CRKP group compared to CSKP group. In multivariate regression analysis having DM, ICU admission due to COVID-19, prior use of carbapenems, CRRT in the ICU were risk factors for CRKP BSI. When ICU deaths due to all causes are evaluated, only infection with CRKP was found to be a risk factor for ICU mortality.

Conclusions: Detection of CRKP BSI risk factors is important. In our study, the presence of CRKP BSI was found to be an independent risk factor for mortality in ICUs.

Keywords: Bloodstream infections, Carbapenem-resistant *Klebsiella pneumonia*, Intensive care unit.

Tuba TATLI KIŞ
Health Sciences University Izmir Suat Seren Chest Diseases and Surgery Training and Research Hospital, Department of Clinical Microbiology and Infectious Diseases, İzmir, Türkiye
E-posta: tubatatlii@hotmail.com
https://orcid.org/0000-0001-6952-3748

DEU Tıp Derg 2024;38(3): 273-280
J DEU Med 2024;38(3):273-280
doi: 10.18614/deutip.1591209

Gönderim tarihi / Submitted:25.11.2024
Kabul tarihi / Accepted: 29.11.2024

ÖZ

Amaç: *Klebsiella pneumoniae*, en önemli çoklu ilaca dirençli mikroorganizmalardan biridir. Karbapenem dirençli *Klebsiella pneumoniae*'nın (CRKP) neden olduğu enfeksiyonlar arasında, kan dolaşım yolu enfeksiyonları (KDYE) en yüksek ölüm oranına sahiptir. Bu çalışmanın amacı, sağlık bakımıyla ilişkili CRKP KDYE ile ilişkili risk faktörlerini, *K. pneumoniae* KDYE ölüm oranlarını ve yoğun bakım ünitesinde takip edilen hastalarda mortaliteyi etkileyen faktörleri değerlendirmektir.

Gereç ve Yöntem: Bu çalışma retrospektif bir vaka-kontrol çalışması olarak tasarlanmıştır. Hastalar karbapenem dirençlerine göre iki gruba ayrıldı; Grup 1: Kan kültürlerinde CRKP üremesi olan hastalar ve Grup 2: Kan kültürlerinde karbapenem duyarlı *K. Pneumoniae* (CSKP) üremesi olan hastalar. Gruplar arasında klinik ve demografik özellikler, 14 günlük ve tüm nedenlere bağlı mortalite oranları ve mortaliteyi etkileyen faktörler karşılaştırıldı.

Bulgular: CRKP grubunda daha yüksek vücut kitle indeksi, DM, COVID-19 nedeniyle yoğun bakıma yatış, daha önce karbapenem kullanımı, enfeksiyondan önce daha uzun süre yoğun bakımda kalma oranları CSKP grubuna kıyasla anlamlı derecede daha yüksekti. Çok değişkenli regresyon analizinde DM, COVID-19 nedeniyle yoğun bakıma yatış, daha önce karbapenem kullanımı, yoğun bakımda devamlı renal replasman tedavisi CRKP KDYE için risk faktörleriydi. Tüm nedenlere bağlı yoğun bakım ölümleri değerlendirildiğinde, yalnızca CRKP enfeksiyonunun yoğun bakım mortalitesi için bir risk faktörü olduğu bulundu.

Sonuç: CRKP KDYE risk faktörlerinin tespiti önemlidir. Çalışmamızda CRKP KDYE varlığının yoğun bakımlarda mortalite için bağımsız bir risk faktörü olduğu bulundu.

Anahtar Kelimeler: Kan dolaşım yolu enfeksiyonu, karbapenem dirençli *Klebsiella pneumoniae*, yoğun bakım ünitesi

Klebsiella pneumoniae is a member of the *Enterobacteriaceae* family and one of the most important multidrug-resistant microorganisms. Carbapenem-resistant *K. Pneumoniae* (CRKP) is one of the microorganisms listed as Priority 1 (critical) in the World Health Organization's (WHO) priority list for the research and development of new antibiotics for antibiotic-resistant bacteria (1). Among the infections caused by CRKP, bloodstream infections (BSI) have the highest mortality rate. (2-3). Therefore, determination of the risk factors causing CRKP BSIs and the factors affecting mortality is important in terms of improving the results and preventing modifiable factors. Antibiotic resistance is one of the biggest growing public health threats and a worldwide priority. According to recent assessments by the European Center for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), antimicrobial resistance was responsible for 670,000 drug-resistant bacterial infections in the European region in 2020 and 2.8 million antibiotic-resistant infections in the United States (US) in 2017 (4-5). According to WHO's Antimicrobial resistance surveillance data, the rate of carbapenem resistance in *K. pneumoniae* strains in Turkey increased from 32% in 2017 to 49% in 2021 (6). There are studies in the literature investigating the risk factors of CRKP infections (3). This study is important because it evaluated the risk factors associated with healthcare-associated CRKP BSI, mortality rates of *K. pneumoniae* BSI and factors affecting mortality in patients followed up in the intensive care unit (ICU).

METHODS

This retrospective case-control study was performed in İzmir Suat Seren Hospital in Turkey.

Study population and design

Patients older than 18 years with positive blood cultures for K. *pneumoniae* between January 2017 and December 2022 were included. A healthcare-associated BSI was defined as a positive blood culture from a peripheral vein or a central catheter obtained at least 48 hours after hospitalization. Clinical signs of bacteremia were considered to be the presence of at least one of fever, chills or hypotension.

Study protocol

Patients were divided into two groups according to their carbapenem resistance; **Group 1:** Patients with CRKP growth in blood cultures and **Group 2:** Patients with carbapenem sensitive *K. pneumoniae* (CSKP) growth in blood cultures. Information on clinical and demographic characteristics, 14-day and all-cause mortality rates were evaluated in Group 1 and Group 2. Patients were divided into survival and death groups according to the prognosis until hospital discharge and differences in clinical data between the two groups were compared.

Microbiological Analysis

Blood culture samples were properly collected and delivered to the laboratory and loaded into the automated blood culture device (BacTAlert, bioMérieux, Marcy l'Etoile, France) for incubation, shaking and monitoring processes. When a positive signal for growth was received, gram staining was performed for microscopic examination. At the same time, subcultures from positive bottles were done into enriched chocolate, eosin methylene blue and 5% sheep blood agar media and incubated at 37°C for 18-24 hours. Pure colonies were selected from the plates where growth was detected, and conventional biochemical methods and automated BD Phoenix system (Becton Dickinson Instrument Systems, Sparks, USA) were used for bacterial identification at species level. Drug susceptibility testing was performed by using both disc diffusion method and automated BD Phoenix system. The susceptibility results were evaluated according to the recommendations of European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Statistical Analysis

Continuous data were represented by the median and interquartile range since they were not normally disturbed. Categorical data were represented by n (%). Continuous data were compared with Mann-Whithey U test, and categorical data were compared with Chi-Square test or Fisher exact test. Multivariate regression analysis was performed for risk factors associated with the isolation of CRKP and ICU mortality. The variables that were found to be associated with isolating CRKP or ICU mortality in univariate analysis were included in multivariate regression analysis. A P value ≤0.05 was considered statistically significant.

RESULTS

A total of 77 patients were included in the final analysis; 53 (69%) of them were male, and the median age was 69 years. Forty-two isolates were CRKP, and 35 isolates were CSKP. The frequency of DM was significantly higher in the CRKP group [18/42 (42.9%)] compared to the CSKP group [3/35 (8.6%)] (p=0.001). Similarly, COVID-19 was significantly higher in the CRKP group [21/42 (50.0%)] compared to the CSCP group [4/35 (11.4%)] (p<0.001). Other comorbid diseases were similar in both groups (Table-1).

Table 1. Demographic features and clinical characteristics of patients

	All patients (n=77)	**CRKP (n=42)**	**CSKP (n=35)**	***P value***
Age, median (IQR), years	69 (56 – 73)	69 (58 – 73)	67 (44 – 75)	0. 376
Gender, male, n (%)	53 (68.8)	28 (66.7)	25 (71.4)	0.653
Body Mass Index, median (IQR), kg/m^2	24.2 (22.1– 27.7)	25.1 (22.9 – 29.3)	23.4 (21.2 – 25.2)	**0.025**
Coronary artery disease, n (%)	4 (5.2)	3 (7.1)	1 (2.9)	0.399
Myocardial infarction, n (%)	9 (11.7)	7 (16.7)	2 (5.7)	0.136
COPD, n (%)	25 (32.5)	13 (31.0)	12 (34.3)	0.100
Diabetes mellitus, n (%)	21 (27.3)	18 (42.9)	3 (8.6)	**0.001**
Solid organ malignancy, n (%)	19 (24.7)	9 (21.4)	10 (28.6)	0.467
COVID-19, n (%)	25 (32.5)	21 (50.0)	4 (11.4)	**<0.001**
APACHE-2, median (IQR)	18 (13 – 24)	21 (15 – 24)	16 (12 – 23)	0.118
Invasive mechanical ventilation, n (%)	58 (75.3)	35 (83.3)	23 (65.7)	0.074
Presence of central venous catheter, n (%)	28 (36.4)	12 (28.6)	16 (45.7)	0.119
Use of vasopressor, n (%)	20 (26.0)	14 (33.3)	6 (17.1)	0.107
Continue renal replacement therapy, n (%)	19 (24.7)	14 (33.3)	5 (14.3)	0.054
Prior antibiotic use, n (%)				
Carbapenems	35 (45.5)	26 (61.9)	9 (25.7)	**0.001**
Broad-spectrum cephalosporins	18 (23.4)	11 (26.2)	7 (20.0)	0.523
Fluroquinolones	13 (16.9)	6 (14.3)	7 (20.0)	0.505
Piperacillin-tazobactam	19 (24.7)	8 (19.0)	11 (31.4)	0.210
Glycopeptides	8 (10.4)	4 (9.5)	4 (11.4)	0.758
Antifungals	9 (11.7)	5 (11.9)	4 (11.4)	0.948
Prior chemotherapy use, n (%)	9 (11.7)	3 (7.1)	6 (17.1)	0.174
Length of stay in Intensive Care Unit before infection, median (IQR), days	11 (3 – 23)	14 (5 – 28)	7 (2 – 20)	**0.033**
Total length of stay in hospital, median (IQR), days	24 (13 – 48)	29 (18 – 51)	21 (9 – 45)	0.076
Mortality on day 14, n (%)	23 (29.9)	17 (40.5)	6 (17.1)	**0.025**
Intensive care unit mortality, n %)	52 (67.5)	33 (78.6)	19 (54.3)	**0.023**

APACHE, Acute Physiology and Chronic Health Evaluation; **COVID-19**, Coronavirus Disease-19; **COPD,** Chronic obstructive pulmonary disease; **CRKP,** Karbapenem Resistant *K. Pneumoniae*; **CSKP**, Carbapenem Sensitive K. *Pneumoniae;* **IQR,** Interquartile Range.

Higher body mass index [in the CRKPgroup, median 25.1(IQR 22.9 – 29.3), in the CSKPgroup, median 23.4 (IQR 21.2 – 25.2) p=0.025)], having DM [in the CRKP group, median 18/42 (%42.9) in the CSKP group, 3/35 (%8.6) p= 0.01)], ICU admission due to COVID-19 [in the CRKP group, 21/42 (%50.0) in the CSKP group, 4/35 (%11.4) p< 0.001)], prior use of carbapenems [in the CRKP group, median 26/42 (%61.9) in the CSKP group, 9/35 (%25.7) p= 0.001)] and a longer ICU stay before the infection [in the CRKP group, median 24 (IQR 13 – 39), in the CSKP group, median 10 (IQR 4 – 30) p=0.002)] were found to be associated with isolating CRKP (Table-1).

Having DM was found to be the most important risk factor for CRKP in multivariate regression analysis (OR 6.98; 95% CI 1.54–31.87, p=0.012) (Table 2). Other risk factors for isolating CRKP were, admitted to ICU due to COVID-19 (OR 4.58; 95% CI1.18 – 17.29, p=0.028), prior use of carbapenems (OR 3.46; 95% CI 1.08 – 11.10, p=0.036), and continuous renal replacement therapy (CRRT) during ICU stay (OR 3.97; 95% CI 1.05 – 15.00, p=0.042) (Table 2).

Table 2. Results of multivariate analysis for Karbapenem Resistant K. *Pneumoniae*

	OR	**95% CI**	**P Value**
Diabetes mellitus	6.98	1.54 – 31.87	**0.012**
COVID-19	4.58	1.18 – 17.29	**0.028**
Prior use of Carbapenems	3.46	1.08 – 11.10	**0.036**
Length of stay in ICU before infection	1.01	0.96 – 1.04	0.921
CRRT	3.97	1.05 – 15.00	**0.042**
Invasive mechanical ventilation	3.43	0.70 – 16.68	0.127

CI, Confidence Interval; **CRRT**, Continuous Renal Replacement Therapy; **COVID-19**, Coronavirus Disease-19; **CRKP,** Karbapenem Resistant K. *Pneumoniae*; **ICU,** Intensive Care Unit; **OR,** Odds Ratio.

Considering the analysis of antibiotic regimens, previous carbapenem use was statistically significantly higher in the CRKP group compared to the CSKP group (p = 0.001). (Table-1). ICU length of stay before infection was; median 14 (IQR 25-75: 5 - 28) days in the CRKP group and median 7 (IQR 25-75: 2 - 20) days in the CSKP group (p = 0.033). Total length of stay in hospital did not differ between the two groups; median 29 (IQR 25-75: 18 - 51) days in the CRKP group and 21 (IQR 25-75: 9 - 45) days in the CSKP group (p=0.076). In terms of mortality, 14-day mortality (p= 0.025) was significantly higher in the CRKP group compared to the CSKP group. All-cause ICU mortality was similarly higher in the CRKP group (p=0.023).

Fifty-two patients (67%) died during their ICU stay. Survivors and non-survivors had comparable clinical characteristics except that non-survivors had higher APACHE-2 scores (median APACHE-2 score 15 vs. 21, p=0.023) and a higher number of CRKP isolated in non-survivors (63% vs. 36%, p=0.023). In multivariate regression analysis, only infection with CRKP was found to be a risk factor for ICU mortality (OR 3.46; 95% CI 1.16–10.33, p=0.026) (Table 3).

Table 3. Results of multivariate analysis for Intensive Care Unit mortality

	OR	95% CI	P Value
CRKP	3.46	1.16 – 10.33	**0.026**
Age	1.00	0.96 – 1.03	0.969
APACHE-2	1.06	0.99 – 1.15	0.081
COVID-19	1.04	0.27 – 3.97	0.948
CRRT	1.09	0.28 – 4.28	0.891
Use of vasopressor	0.95	0.26 – 3.48	0.944

APACHE, Acute Physiology and Chronic Health Evaluation**; CI,** Confidence Interval; **COVID-19,** Coronavirus Disease-19; **CRRT,** Continuous Renal Replacement Therapy; **CRKP**, Karbapenem Resistant *K. Pneumoniae***; ICU,** Intensive Care Unit**; OR**, Odds Ratio.

DISCUSSION

Rates of having higher body mass index, having DM, ICU admission due to COVID-19, prior use of carbapenems, a longer ICU stay before the infection were significantly higher in the CRKP group compared to CSKP group. In multivariate regression analysis having DM, ICU admission due to COVID-19, prior use of carbapenems, CRRT in the ICU were risk factors for CRKP BSI. When ICU deaths due to all causes are evaluated, only infection with CRKP was found to be a risk factor for ICU mortality.

In our study, DM was found to be the most important risk factor. There are studies suggesting that DM is one of the most important risk factors for CRKP infections in older adults (7-8). On the contrary, there is also a study reporting that DM is not a significant risk factor. (9). Prior use of carbapenems, ICU admission due to COVID-19, CRRT in the ICU were the other risk factors for CRKP BSI. In meta-analyses conducted in the literature, previous exposure to carbapenems and aminoglycosides was defined as a risk factor for CRKP infections (3,10). In another meta-analysis, exposure to carbapenems, quinolones and glycopeptides was defined as a risk factor for CRKP infections (11).

In our study, CRRT in the ICU was found to be a risk factor for CRKP BSI. In the literature, there are publications stating that especially the presence of a central venous catheter is a defined risk factor for CRKP BSIs (3-11). In a study including 156 patients with BSI and evaluating prognostic factors in BSI, it was reported that CRRT after bacteremia positively affected survival (12). However, in a retrospective study including 296 patients with candida/bacterial BSI, CRRT was found to be an independent risk factor for BSI (13).

In our study, a longer ICU stay before the infection were significantly more common in the CRKP group than in the CSKP group. In a retrospective case control study, the time from ICU hospitalization to the development of infection was found to be associated with the development of carbapenem-resistant gram negative bacterial infection (14).

The COVID-19 pandemic has hampered several infection prevention and control measures, including hand hygiene, equipment cleaning, patient isolation, and the use of personal protective equipment (PPE) (15). A study based on 2534 patients from a tertiary university hospital found that patients admitted to COVID-19 settings were at higher risk of developing BSI compared to other hospital settings, with the highest risk found in COVID-19 ICUs (16).

A large multicenter study on Health Care-Associated Infections (HAI) among ICU inpatients in 2020 showed that the overall rate of HAI in the SARS-CoV-2-infected group in 2020 compared to 2019 was higher than both the 2019 group and patients not infected with SARS-CoV-2 in 2020 (17). On the other hand, in a study which included 1895 patients with positive blood cultures, the authors found that the frequency of CRKP and *E. coli* did not increase (18).

When all-cause ICU mortality was evaluated in our study, only infection with CRKP was found to be a risk factor for ICU mortality. In a retrospective study including 87 patients with CRKP BSI and 321 patients with CSKP BSI, 30-day crude mortality rates were 43.7% in patients with CRKP BSI and 17.8% in patients with CSKP BSI (p<.001) (24). CRKP was independently associated with mortality in BSI (19). In a review study, carbapenem resistance in K. *pneumoniae* was among the most common risk factors for mortality in patients with BSI (20). In a retrospective cohort study of 252 patients with K. pneumoniae BSI, multivariate analysis showed that CRKP isolation (OR 2.881, 95% CI 1.228-6.756, p=0.015) were independent risk factors for 28-day mortality of KP BSI (21).

Conclusion

Higher body mass index, having DM, ICU admission due to COVID-19, prior use of carbapenems, a longer ICU stay before the infection were significantly more common in CRKP group than in the CSKP group. In our study, having DM was detected as the most important risk factor. When all-cause ICU mortality was evaluated, only infection with CRKP was found to be a risk factor for ICU mortality.

Limitations

The small number of patients included in the study is one of the main limitations. Other limitations of our study include the retrospective nature of the study, lack of information on carbapenemase type and presence since resistance genes could not be examined, and lack of data on colonization of patients.

REFERENCES

1. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 2018;18(3):318–327.
2. Gomez-Simmonds, A. B. Nelson, D. Eiras, A. Loo, S. Jenkins, S. Whittier, et al. Combination regimens for treatment of carbapenem-resistant Klebsiella pneumoniae bloodstream infections. Antimicrob. Agents Chemother 2016;60:3601–3607.
3. Zhu WM, Yuan Z, Zhou HY. Risk factors for carbapenem-resistant Klebsiella pneumoniae infection relative to two types of control patients: a systematic review and meta-analysis. Antimicrob Resist Infect Control. 2020;9(1):1–13.
4. WHO Regional Office for Europe; European Centre for Disease Prevention and Control. Antimicrobial Resistance Surveillance in Europe 2022–2020 Data; WHO Regional Office for Europe: Copenhagen, Denmark, 2022.
5. Centers for Disease Control and Prevention (U.S.). Antibiotic Resistance Threats in the United States, 2019; Centers for Disease Control and Prevention (U.S.): Atlanta, GA, USA, 2019.
6. WHO, Antimicrobial resistance surveillance in Europe 2023–2021 data. Available from https://www.who.int/europe/publications/i/item/9789289058537 date 28.07.2024.
7. Çölkesen F, Tarakçı A, Eroğlu E, Kacar F, Özdemir Armağan Ş, Can S, et al. Carbapenem-Resistant Klebsiella pneumoniae Infection and Its Risk Factors in Older Adult Patients. Clin Interv Aging. 2023 Jul 6;18:1037-1045.
8. Brennan BM, Coyle JR, Marchaim D, Pogue JM, Boehme M, Finks J, et al. Statewide surveillance of carbapenem-resistant enterobacteriaceae in Michigan. Infect Control Hosp Epidemiol. 2014;35:342–9.
9. Chen YC, Tsai IT, Lai CH, Lin KH, Hsu YC. Risk Factors and Outcomes of Community-Acquired Carbapenem-Resistant Klebsiella pneumoniae Infection in Elderly Patients. Antibiotics (Basel). 2024 Mar 20;13(3):282.
10. Zhu L, Liang L, Hui J, Lu J, Yang R, He Q, et al. Relationship between antibiotic exposure and carbapenem-resistant Klebsiella pneumoniae infection within four types of control patients: A systematic review and meta-analysis. J Glob Antimicrob Resist. 2023 Jun;33:137-151. doi: 10.1016/j.jgar.2023.02.020. Epub 2023 Mar 10.
11. Li J, Li Y, Song N, Chen Y. Risk factors for carbapenem-resistant Klebsiella pneumoniae

infection: A meta-analysis. J Glob Antimicrob Resist. 2020 Jun;21:306-313.

12. Huang Y, Gong C, Fu J, Liu X, Bi H, Wang H, et al. Analysis of prognostic risk factors of bloodstream infection in intensive care unit patients. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2020 Dec;32(12):1440-1444.

13. Zhong L, Dong Z, Liu F, Li H, Tang K, Zheng C, et al. Incidence, clinical characteristics, risk factors and outcomes of patients with mixed Candida/bacterial bloodstream infections: a retrospective study. Ann Clin Microbiol Antimicrob. 2022 Nov 1;21(1):45.

14. Kuloglu TO, Unuvar GK, Cevahir F, Kilic AU, Alp E. Risk factors and mortality rates of carbapenem-resistant Gram-negative bacterial infections in intensive care units. J Intensive Med. 2024 Jan 9;4(3):347-354.

15. Micheli G, Sangiorgi F, Catania F, Chiuchiarelli M, Frondizi F, Taddei E, et al. The Hidden Cost of COVID-19: Focus on Antimicrobial Resistance in Bloodstream Infections. Microorganisms. 2023 May 16;11(5):1299.

16. Segala F.V, Pafundi P.C, Masciocchi C, Fiori B, Taddei E, Antenucci L, et al. Incidence of Bloodstream Infections Due to Multidrug-Resistant Pathogens in Ordinary Wards and Intensive Care Units before and during the COVID-19 Pandemic: A Real-Life, Retrospective Observational Study. Infection. 2023 Aug;51(4):1061-1069.

17. Lepape A, Machut A, Bretonnière C, Friggeri A, Vacheron C.H, Savey A. Effect of SARS-CoV-2 Infection and Pandemic Period on Healthcare-Associated Infections Acquired in Intensive Care Units. Clin. Clin Microbiol Infect. 2023 Apr;29(4):530-536.

18. Sinto R, Lie K.C, Setiati S, Suwarto S, Nelwan E.J, Djumaryo D.H, et al. Blood Culture Utilization and Epidemiology of Antimicrobial-Resistant Bloodstream Infections before and during the COVID-19 Pandemic in the Indonesian National Referral Hospital. Antimicrob Resist Infect Control. 2022 May 19;11(1):73.

19. Wang L, Zeng C, Li X, Li Y, Liu Z, Hu J. Mortality associated with carbapenem resistance in Klebsiella pneumoniae bloodstream infection: A propensity score-matched study. Infect Control Hosp Epidemiol. 2024 Mar 15:1-8.

20. Viale P, Giannella M, Lewis R, Trecarichi EM, Petrosillo N, Tumbarello M. Predictors of mortality in multidrug-resistant Klebsiella pneumoniae bloodstream infections. Expert Rev Anti Infect Ther. 2013 Oct;11(10):1053-63.

21. Chen Y, Chen Y, Liu P, Guo P, Wu Z, Peng Y, et al. Huang. Risk factors and mortality for elderly patients with bloodstream infection of carbapenem resistance Klebsiella pneumoniae: a 10-year longitudinal study. BMC Geriatr. 2022 Jul 13;22(1):573.