ORIGINAL ARTICLE

Comparison of clinical characteristics and outcome of carbapenem sensitive and carbapenem resistant *Klebsiella Species* infection from a Tertiary-Care-Hospital, Karachi, Pakistan

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ABSTRACT

Background: The prevalence of carbapenem-resistant (CR) *Klebsiella* species (KS*)* exceeds 60% in South Asia, leading to high morbidity and mortality. Data on KS clinical aspects from Pakistan is limited. This study aimed to examine the clinical characteristics, outcomes, and mortality risk factors associated with KS-infections.

Material and Methods: A prospective study conducted between September 2022 and March 2023 compared patients with carbapenem-resistant KS (CR-KS) and carbapenem-susceptible KS (CS-KS*)* in terms of demographics, clinical features, Charlson comorbidity index, source of infection, previous hospitalization, source control, and receipt of appropriate empirical antibiotics. Outcomes were recorded as admission status, discharge, or death at day 14.

Results: A study of 217 patients with a median age of 48 years found that 52% had a history of prior hospitalization, and 47.5% presented with bacteremia. Carbapenem-resistant KS (CRKS) was present in 58.9% of patients. CR-KS infection was significantly linked to recent hospitalization (p=0.01), fever (p=0.01), altered mental status (p=0.002), ICU admission (p=0.003), mechanical ventilation (p= 0.02), and pneumonia (*p*=0.004). CR-KS had poor bacterial clearance and a low rate of appropriate empirical antibiotic use (3.2%). At day 14, the all-cause mortality rate was 29%, with significantly higher mortality in CRKS patients, as shown by the survival curve. Multivariate analysis indicated that CR-KS patients did not receive appropriate empirical antibiotics.

Conclusion: The study revealed a high prevalence of CR-KS infections associated with significant morbidity and mortality. Patients with CRKS infection did not receive appropriate empirical antibiotics. Timely availability of antibiogram with good infection control practices are critical in preventing mortality and spread this highly pathogenic organism.

Keywords: Carbapenem resistant, *Klebsiella*, Antimicrobial resistance

BACKGROUND

The major causative agents of health care associated infections (HAIs) are bacterial pathogens. K. Pneumoniae (KP) is one of the leading causes of HAI in hospitals globally including urinary tract infection, pneumonia, wound infections. Carbapenemase producing KP combined with Extended spectrum beta lactamase KP make up fastest growing cause of drug resistant infections in Europeans hospitals. Asymptomatic colonization of KP is found to be a source of HAI with estimated attack rates between 4-35% in colonized hospital patients.[1] .Species other than *Klebsiella pneumoniae* like *Klebsiella Oxytoca* and *Klebsiella variicola* also cause human infections but are overall less frequent.[2] *Klebsiella pneumoniae* is highly prevalent and most pathogenic of all species with a prevalence of around 85% among clinical isolates.[3] Since majority of clinical isolates are KP, a large number of studies were on this species and it is divided into classical KP and hyper-virulent KP.[4] KS is found to be notorious in readily acquiring genetic mutations and plasmids leading to development of highly resistant clones.[5] Carbapenem resistance (CR-KS) has become a major public health threat worldwide. The prevalence of CR-KS among all KS infections worldwide is around 28.69% with more than 60 % in our part of the world i.e., South Asia.[6] The morbidity and mortality is extremely high among these patients with very limited treatment options especially in low-middle income countries like Pakistan.[7-9]

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The risk factors for carbapenem resistance (CR) in KP infections have been investigated in various studies. Prolonged hospital stay, ICU admission, antibiotics exposure and use of indwelling urinary catheters were some of the risk factors identified.[10] A retrospective single center study in China compared carbapenem sensitive KP (CSKP) and CRKP infections and found significant high mortality among CRKP group.[11] Yuanyuan Li et al looked into KP blood stream infection and reported very high death ratio in resistant as compared to sensitive arm.[8] Studies have demonstrated that prior hospitalization, β-lactam or aminoglycoside antibiotics use, older age and high median Charlson comorbidity index were the risk factors for mortality.[12-13] Data on clinical aspects of *Klebsiella* infection from Pakistan is scarce. Majority of studies were based on clinical isolates. Fatima et al studied 175 patients and reported *Klebsiella* species as the most common cause of carbapenem resistant gram-negative bacteremia and significantly associated with mortality.[14] We aimed to study clinical characteristics and outcome of *Klebsiella* Species infection and compare risk factors for mortality between Carbapenem sensitive *Klebsiella* species and Carbapenem resistant *Klebsiella* Species infection.

MATERIAL AND METHODS

This prospective cohort study was conducted at Sindh Institute of Urology and Transplantation (SIUT) Karachi, from September 2022 to March 2023. The study was approved from institutional Ethical Review Committee (SIUT-ERC-2023/A-409).

All admitted patients ≥18 years with KS infection (confirmed by culture) for the first-time during hospitalization during were included. Transplant recipients, poly-microbial infections (patients with positive cultures for any microorganisms other than KS and Patients who were labelled as colonization by primary or infectious disease physician (excluding KS positive blood cultures) were excluded from the study.

Reports of positive culture and susceptibility of *Klebsiella* spp. were taken from electronic medical record of microbiology laboratory. All patients with active *Klebsiella* spp. infection defined below were identified in wards or intensive care units. After taking informed consent, a Performa was filled. Age, gender, clinical features, laboratory parameters, underlying disease, Charlson co-morbidity index, source of infection and bacteremia (in case of blood stream infection), previous antibiotics received in the last 3 months, empirical antibiotic (therapy given within 24 h of the culture being taken) and definitive antibiotic therapy or any change in empirical therapy according to culture and sensitivity were noted. Blood culture was repeated after 72 hours of appropriate antibiotics to document blood culture clearance. Based on C/S reports two groups were identified carbapenem resistant CR and carbapenem sensitive CS. Patients were followed till day 14 during hospitalization or till discharge whichever comes first. Medical record was obtained from hospital electronic system and patient files.

The following definitions were followed during the course of the study.

KS Blood Stream Infection (BSI): is defined as positive blood culture for *Klebsiella species* along with clinical signs of systemic inflammatory response. BSI sources were defined as per Center for Disease Control and Prevention (CDC) criteria and primary BSI labelled when no source is identified.[16]

Pneumonia: is defined based on CDC criteria by clinical features (fever, cough and purulent sputum), lung infiltrates and sputum culture growth of *Klebsiella species*.[17]

Surgical Site Infection (SSI): an infection that occurs within 30-days after surgical procedure and at least one of the following: pus discharge, wound culture growing organism, and one of the following signs: redness, warm, tender, and swelling of surgical incision; or diagnosis by the surgeon as SSI.[18]

Urinary Tract Infection: it is defined as presence of ≥1 symptoms (fever, flank pain, dysuria, burning or increased frequency of micturition) along with positive urine culture $>10^5$ CFU/ml of *Klebsiella species*.[19]

Appropriate empiric antibiotic: Initiation of antibiotics in patients presenting with sepsis after sending cultures to which pathogen isolated from culture was sensitive.

Antimicrobial susceptibility testing: Identification and drug susceptibility testing was performed as per Clinical Laboratory Standards Institute (CLSI) guidelines.[15] Antimicrobial susceptibilities were determined on Mueller Hinton agar medium using modified Kirby Bauer's disc diffusion method. Carbapenem resistance was detected by using meropenem disc, isolates showing meropenem zone

size ≤19mm were considered as resistant while a zone size of ≥23 as sensitive. Colistin MICs were done through broth micro dilution method (MICs ≤2 as intermediate and ≥4 as resistant).

The data were collected and analyzed using Statistical Package for the Social Sciences (IBM-SPSS; version 22.0). Normally distributed continuous variables are expressed as mean ± standard deviation (SD) and non-normally distributed as median (IQR). Group comparisons are conducted using the chi-square test for categorical variables, and t-tests or Mann-Whitney U test for continuous variables (mean or median differences) numerical variables, with a significance level set at $p < 0.05$. All variables found significant at univariate level are entered in a multivariate model using multivariate logistic regression. Crude and adjusted odd ratios with 95% CI are reported.

RESULTS

A cohort of 217 patients with KS infection was identified, comprising 128 (58.98%) CR and 89 (41.01%) CS cases. Table-I presents the baseline characteristics and a comparison between CS and CR infections. The median age was 48 years (IQR 18-45), and 39.6% were female. The median Charlson comorbidity index was 5 (IQR 4-6). A total of 114 patients (52%) had a history of prior hospitalization. Eighty-five patients (39.4%) received antibiotics within 3 months prior to admission, and 22 patients (10%) had prior carbapenem exposure. The most common presentations were bacteremia (103 patients, 47.5%) and pneumonia (20%). Source control was achieved in 78 out of 102 patients (70.5%). Appropriate empirical antibiotics were administered to 61 patients (28.8%). By day 14, 47 patients (27.7%) remained hospitalized, while 107 (49.3%) were discharged. The mortality rate at day 14 was 29%.

Comparison of CS-KS and CR-KS infections revealed no significant differences in age, gender, or comorbidities. However, recent hospitalization was more frequently associated with CR-KS patients (59.4% vs. 42.1%, p=0.016). CR-KS patients exhibited significantly higher rates of fever, altered mental status, ICU care, and mechanical ventilation requirements. Pneumonia was significantly more prevalent in CR-KS patients compared to CS-KS patients (p=0.004). Among the 103 patients with bacteremia, repeat blood cultures at 72 hours were available for 84 patients. Bacterial clearance was significantly lower in CR-KS patients compared to CSKS patients (83.7% vs. 97.1%, p=0.048). There was no difference in source control between the two groups. Only 4 patients (3.2%) in the CR-KS group received appropriate empirical antibiotics (p<0.001). Regarding outcomes, a significantly higher proportion of CR-KS patients either died or remained hospitalized within 14 days compared to CS-KS patients (37.5% vs. 16.9%, and 25.8% vs. 15.7%, respectively; p<0.001). A survival curve indicated a statistically significant difference in mortality between CRKS and CSKS over the 14-day follow-up period (Figure-I). Risk factors for mortality between CR-KS and CS-KS are detailed in Table-II. A significantly higher mortality rate was observed in CR-KS patients aged 41-70 years (p=0.014). Comorbidities significantly associated with 14-day mortality in the CR-KS group included diabetes mellitus (p=0.019), hypertension (p=0.001), ESRD (p=0.014), and dialysis requirement (p=0.006). There were no differences in bacterial clearance and source control between the groups. Inappropriate empirical antibiotics were administered significantly more frequently in the CR-KS group (97.87% vs. 64.28%, p=0.002). The type of infections among deceased patients with CR-KS and CS-KS is depicted in Figure-II, with bacteremia significantly more common in deceased CR-KS patients (p=0.008). Multivariate analysis indicated that CR-KS infected patients were significantly less likely to receive appropriate empirical antibiotics (Table-III)

Table-I: Demographics, Risk factors & Outcomes of Carbapenem Resistant vs Sensitive KS.

	Total n=217	**Carbapenem Resistant KS (n=128)**	**Carbapenem sensitive KS (n=89)**	**P value** **Categorical:** x^2 test /fisher exact **Numerical:** t-test or Mann-Whitney U test
Demographics				
Age (years)	47.37 ±15 SD	47.55 ± 16.03 SD	47.11 ± 14.74 SD	0.837
Female	86(39.6%)	48(37.5%)	38(42.7%)	0.444
Comorbidities n (%)				
Charlson comorbidity Index (CCI) (median; IQR)	5 (4-6)	5 (4-6)	5 (4-6)	0.724

CCI ≥ 5	56(25.8%)	35(27.3%)	21(23.6%)	0.535
Diabetes Mellitus	61(28.1%)	34(26.6%)	27(30.3%)	0.543
Hypertension	74(34.1%)	40(31.3%)	34(38.2%)	0.288
Acute Renal Failure (ARF)	65(30%)	43(33.6%)	22(24.7%)	0.160
Chronic Renal Failure (CRF)	21(9.7%)	11(8.6%)	10(11.2%)	0.517
End stage renal disease (ESDR)	97(44.9%)	56(44.1%)	41(46.1%)	0.774
Requiring Hemodialysis	134(62.3%)	81(64.3%)	53(59.6%)	0.480
Cancer without metastasis	27(12.4%)	16(12.8%)	11(12.4%)	0.975
Recent Hospitalization (< 3 months)	114(52.2%)	76(59.4%)	38(42.1%)	0.016
Recent Antibiotics (< 3 months)	85(39.4%)	50(39.4%)	35(39.3%)	0.995
Carbapenem Exposure (< 3 months)	23(10.6%)	15(11.7%)	08(9.0%)	0.795
Surgical Procedure (within 30 days)	161(74.0%)	99(77.0%)	62(69.6%)	0.971
Foleys Catheterization	112(51.9%)	72(56.7%)	40(44.9%)	0.089
Clinical characteristics n (%)				
Fever	134(61.8%)	88(68.8%)	46(51.7%)	0.011
Hypotension requiring vasopressors	30(13.9%)	22(17.3%)	08(9.0%)	0.081
Altered Mental status	61(28.1%)	46(35.9%)	15(16.9%)	0.002
ICU admission	84(38.7%)	60(46.9%)	24(27.0%)	0.003
Mechanical Ventilation	43(19.8%)	32(25.0%)	11(12.4%)	0.022
Laboratory parameters				
Total leucocyte count (TLC) 10^9/L (median; IQR)	14.6(8.4-20.1)	15.0(9.5-20.9)	12.0(7.0-19.3)	0.080
Platelets count median 10^9/L (IQR)	208(118-314)	203(121-310)	218(107-316)	0.947
Serum creatinine mg/dl median (IQR)	4.6 (1.9-6.6)	4.5(2.0-6.6)	4.6(1.8-6.9)	0.988
Type of infection n(%)				
Bacteremia	103(47.5%)	56(43.8%)	47(52.8%)	0.189
Source of Bacteremia				
Dialysis line	56(54.3%)	30(53.5%)	26(55.3%)	
Respiratory tract	04(3.8%)	02(3.5%)	02(4.2%)	
Urinary-tract	25(24.2%)	17(30.3%)	08(17.0%)	
Abdomen	11(10.6%)	03(5.3%)	08(17.0%)	
Un-identified	07(6.7%)	-	-	
Surgical Site Infection (SSI)	11(5.1%)	07(5.5%)	04(4.5%)	0.504*
Pneumonia	45(20.7%)	35(27.3%)	10(11.2%)	0.004
Urinary Tract Infection (UTI)	36(16.6%)	24(18.8%)	12(13.5%)	0.305
Skin / Soft Tissue Infection	17 (7.8%)	07 (5.5%)	10 (11.2%)	0.120*
Bacterial Clearance at 72 hours (blood cultures repeated n=81)	72/82(88.88%)	41/49(83.7%)	34/35(97.1%)	0.821
Source Control (n=78)	78/102(76.5%)	38/52(53.84%)	40/50(80.0%)	0.410
Appropriate Empirical Antibiotics	61(28.8%)	04(3.2%)	57(66.3%)	<0.001
Mortality at day 14	63(29.0%)	48(37.5%)	15(16.9%)	
Remained admitted	47(21.7%)	33(25.8%)	14(15.7%)	<0.001
Alive and Discharged	107(49.3%)	47(36.7%)	60(67.4%)	

Table-II: Mortality risk factors in carbapenem resistant patients

Variables	**14 days' mortality n(%)**		**P Value**
	CR-KS	**CS-KS**	Categorical: **x^2 test/fisher exact** Numerical: **t-test or Mann-Whitney U test**
Age & Gender			
Age (years)	51.29±16.29 SD	49.27±12.87 SD	0.68
Age groups n (%)			
18-40 years	12/47 (25.5%)	6/34(17.6%)	0.400
41-70years	30/72(41.7%)	11/43 (20.8%)	0.014
>70 years	6/9(66.6%)	0	0.182
Female Gender	18/48(37.5%)	6/38(15.8%)	0.026
Clinical Characteristics n (%)			
Hypotension requiring ionotropic support	12/22(54.5%)	6/8(75.0%)	0.419

Altered mental status	30/46(65.2%)	10/15(66.7%)	0.918
ICU Stay	33/60(55.0%)	9/24(37.5%)	0.147
Mechanical ventilation	22/32(68.8%)	7/11(63.6%)	0.999
Co-morbidities n (%)			
Diabetes Mellitus	19/34(55.9%)	7/27(25.9%)	0.019
Hypertension	19/40(47.5%)	4/34(11.8%)	0.001
Acute renal failure	18/43(41.9%)	7/22(31.8%)	0.431
Chronic renal failure	5/11(45.45%)	3/19(15.8%)	0.104
End stage renal disease	19/56(33.9%)	5/41(12.2%)	0.014
On hemodialysis	30/81(37.03%)	8/53(15.09%)	0.006
Malignancy	7/16(43.8%)	1/11(9.1%)	0.090
Recent antibiotics exposure	20/50(40.0%)	3/35(8.6%)	0.001
Surgical procedures	14/52(26.9%)	5/35(14.3%)	0.162
Bacterial clearance (Repeat Blood cultures n=81)	9/41(21.9%)	3/34(8.8%)	0.205
Source control (n=78)	8/40(20.0%)	13/38(34.2%)	0.157
Inappropriate empiric antibiotics (n=55)	46/47(97.9%)	9/14(64.28%)	0.002*

Table-III: Multivariate analysis on risk factors for CRKS and CSKS

Variables		Unit of measurement	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
									Lower	Upper
Step 1[a]	Recent Hospital stay	Categorical variable (1=Yes,2=No)	1.118	.818	1.870	1	.171	3.060	.616	15.199
	Fever within 48h	Categorical variable (1=Yes,2=No)	.223	.756	.087	1	.768	1.250	.284	5.495
	Mechanical ventilation	Categorical variable (1=Yes,2=No)	-.290	.979	.088	1	.767	.748	.110	5.100
	Bacterial clearance	Categorical variable (1=Yes,2=No)	.086	1.297	.004	1	.947	1.090	.086	13.847
	Appropriate empiric antibiotics received	Categorical variable (1=Yes,2=No)	-4.862	1.146	17.994	1	.000	.008	.001	.073
	Death	Categorical variable (1=Yes,2=No)	.355	.998	.126	1	.722	1.426	.202	10.091
	Constant		.902	1.413	.407	1	.523	2.464		

a. Variable(s) entered on step 1: Recent Hospital, Fever within 48h, MV, BCD, App_Abx_rcvd, death.

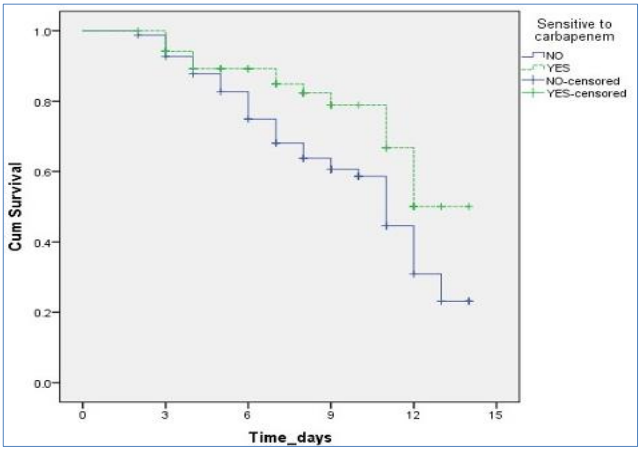

Figure-I: Survival curve of patients with *Klebsiella species* infection stratified by carbapenem resistant (n=128) vs carbapenem sensitive (n=89). (p=0.019).

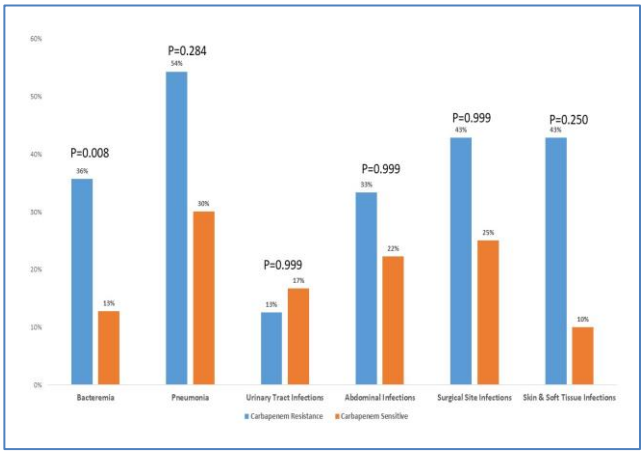

Figure-II: Comparison of Mortality between CR-KS & CS-KS with different types of Infections

DISCUSSION

The proportion of carbapenem resistant KS has increased steeply worldwide.[20] A systematic review and meta- analysis of 61 studies from14 countries found that, South Asia especially Indian hospitals have a much higher global burden of carbapenem resistant *Klebsiella* pneumoniae infection.[6] Studies from Pakistan reported similar prevalence rate between 30-50% in clinical isolates.[21-23] Our study also found that 58.98% of KS were carbapenem resistant endorsing previous studies from South Asia. The reason of this high burden can be due to the fact that carbapenemase genes are mostly carried by plasmids or mobile genetic elements. [24] Plasmid transmission between organisms in low-middle income countries can be very high due to overcrowding and poor infection control practices.[25] More focus should be emphasized on implementing strict infection control practices in our part of the world in order to contain this highly resistant organism.

Our study is first from Pakistan focusing on clinical features and outcome of *Klebsiella* infections. We found that infection with *Klebsiella* spp. occurs in patients with Charlson comorbidity index of 5 and higher and majority had either surgical interventions, Foley's catheter or dialysis lines. This is an established fact that *Klebsiella* species are mostly nosocomial pathogens.[26] Patients with comorbidities are more prone to get admitted in hospitals and received invasive procedures, hence get colonized with many pathogenic organisms. Rao et al studied 2000 hospital encounters and found a significant number of colonized patients with *Klebsiella* species progressed to infection. They reported high comorbidities, low albumin and depression as significant risk factors for infection.[27] Indeed we found that CRKS infections were observed more in patients who has recent hospitalization.

Bacteremia and pneumonia were found to be the most common type of *Klebsiella* infection in our study. This finding is similar to studies worldwide where urinary tract, blood stream infection and respiratory tract infection are reported to be the most common infections caused by *Klebsiella* species.[26] Furthermore, our center mainly caters to dialysis patients and dialysis line associated bacteremia is the most common type of infection in our patient population.

Regarding clinical characteristic and outcome, *Klebsiella* infection was commonly seen in sick patients with 40% admitted in intensive care unit and one fourth were on mechanical ventilation. This finding endorsed the fact that *Klebsiella* is a highly pathogenic nosocomial organism. It is known to be the most frequently isolated pathogen from ICU and known to cause 5-10% of ICU infections.[28] Moreover, we found a prolonged hospital stay and case fatality rate of 29% in our patients. In the literature mortality rate ranges from 10-69.3% depending on the underlying comorbidities and resistant strains.[28] A large number of patients in our study have high comorbidities and more than half were infected with carbapenem resistant strains which reflects a very high mortality in our study population.

When patients with CRKS and CSKS infection were compared, we found recent hospitalization and being critically ill were significantly associated with CRKS. In a meta-analysis on *Klebsiella pneumoniae*, risk factors for carbapenem resistance were reported as ICU admission, invasive procedures, antimicrobial exposure including carbapenem and presence of comorbidities.[20] Moreover, carbapenem resistant infections had worse outcome as evidenced by longer length of hospital stay and increased mortality. Presence of comorbidities, recent history of antibiotic exposure, blood stream infection and inappropriate empiric antibiotics were observed as significant risk factors for death. These results are consistent with previous reports in which high Charlson comorbidity index and previous exposure to antibiotics were reported as risk factors for mortality in carbapenem resistant *Klebsiella* infections.[12]

Although we could not find any independent risk factor for CRKS in our cohort, however patients with carbapenem resistant infection failed to receive appropriate empirical antibiotics. Early appropriate and effective antibiotic therapy is critical in reducing mortality. A systemic review and meta-analysis have shown proportion of empiric antibiotics is generally low in case of resistant pathogens leading to higher mortality.[29] Babar et al in a prospective observational study from Pakistan reported significantly high mortality in patients who received inappropriate empiric antibiotics for carbapenem resistant gram negative bacteremia.[30] Provision of latest antibiogram in ICUs and emergency units may help physicians in prescribing appropriate empirical antibiotics which may reduce mortality.

There are few limitations of this study. First a single center study and our hospital caters a substantial number of renal failure patients which might led to selection bias and high mortality. Second, the study did not include all patients with KS infection but only those whose cultures were sent in microbiology laboratory, this may cause falsely lower number of infections.

CONCLUSION

In conclusion, *Klebsiella* infections are found in patients with high comorbidities. Our study findings show that carbapenem resistant *Klebsiella* is associated with severe illness leading to prolonged hospital stay and significantly high mortality. Provision of timely microbiology culture findings along with antimicrobial stewardship and infection prevention and control practices play an important role in curtailing the MDR infections.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Muhammad Kashif Farooq: Conceptualization, study design, methodology, data collection, analysis, critical review, manuscript writing, final approval, agreement to be accountable for all aspects of the work

Zaheer Udin Babar: Methodology, manuscript writing, final approval, agreement to be accountable for all aspects of the work

Sunil Kumar Dodani: Research ideology, data collection, writing, final approval, agreement to be accountable for all aspects of the work

Muhammad Hassan: Data collection, data analysis, final approval, agreement to be accountable for all aspects of the work

Asma Nasim: Ideology, critical review for intellectual content, revisions, final approval, agreement to be accountable for all aspects of the work

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