



Original Article



Relationship of Hypoalbuminemia in Colistin-Induced Acute Kidney Injury (AKI) among Adult Intensive Care Patients

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ABSTRACT

Acute kidney injury incidence ranges from 30-60% among critically ill patients and stands as the primary death cause within this population. A serious concern is a global rise in major drug-resistant-gram-negative organisms among hospital-acquired infections. **Objectives:** To determine the incidence of colistin-induced acute kidney injury in intensive care patients receiving colistin therapy and to investigate its relationship with albumin levels. **Methods:** It was a follow-up prospective cohort study executed at Shaheed Mohtarma Benazir Bhutto Institute of Trauma Pakistan in an adult intensive care unit over 6 months. The study end-point was an injury in intensive care injury at the end of colistin therapy. A total of 250 patients were studied. **Results:** The median age of patients was 40 (IQR=22-48) years with an age range of 18-70 years. The majority of patients were male (75.2%). Median colistin dosage was 4 (IQR=3.5-4.5) MIU. In univariate analysis, the risk of developing injury in intensive care was significantly increased with increased age, use of nephrotoxic drugs, and increasing colistin dosage whereas injury in intensive care risk was decreased with increasing albumin levels. In a multivariable model, only colistin dosage was found to be significantly associated with increasing injury in intensive care risk with increasing colistin dosage. **Conclusions:** It was concluded that the present study analyzed a higher burden of acute kidney injury incidence following colistin therapy. Albumin levels were not found to be linked to acute kidney injury incidence in the multivariable model. Acute kidney injury incidence was significantly related to increasing colistin dosage.

INTRODUCTION

Acute kidney injury (AKI) is a frequent issue in patients with deteriorating health, leading to higher morbidity and mortality rates. It also results in longer hospital stays and increased healthcare expenses [1]. In critically ill patients, AKI occurs in about 30% to 60% of cases, making it a major cause of death in this group. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines define AKI as a rapid loss of kidney function, indicated by a rise in serum creatinine (SCr) of 0.3 mg/dL or more within 48 hours, or an increase to at least 1.5 times the baseline level within the past seven days [2]. The worldwide increase in antibiotic resistance presents a significant public health issue [3]. A significant concern in healthcare is the rising prevalence of multidrug resistance and the proliferation of extensively

drug-resistant Gram-negative bacteria, particularly in hospital-acquired infections [4]. Colistin, a polymyxin-class antibiotic originally developed in the late 1940s and approved by the Food and Drug Administration (FDA) in 1962, has demonstrated in vitro efficacy against the majority of aerobic Gram-negative bacilli. Colistin efficacy has also been demonstrated against a broad spectrum of Gram-negative pathogens including extensively diverse and multiple-drug organisms [7, 8]. Though initially it was effective its utilization was not encouraged owing to the high risk of AKI. Subsequently, colistin was revived into medical practice in the early 2000s as a fundamental rescue therapy for countering the harmful impacts of these infections [8, 9]. In multiple studies, colistin-induced AKI



ranges from 20% to 76% [10, 11]. In these studies, the nephrotoxicity rate was varying with different dosing regimens. Numerous determinants were reported to contribute to colistin-induced AKI such as diabetes, CKD, anemia and exposure to events which are harmful to the kidney (trauma, sepsis, use of nephrotoxic agents in critical illness) [11, 12]. Colistin-induced AKI is generally reversible and rarely results in lasting kidney damage. It is crucial to balance the potential for nephrotoxicity with the risks associated with not adequately treating a severe infection [13]. Hypoalbuminemia, commonly characterized by albumin levels below 3.5–4.0 g/dL or ≤ 3.5 mmol/L, is a notable risk factor for higher rates of morbidity and mortality. Moreover, it has been linked to an increased likelihood of developing AKI [14]. Further in the literature of the study enrolled participants in both intensive care unit (ICU) and surgical patients demonstrated that hypoalbuminemia could serve as a useful indicator to predict death in AKI patients [15–17]. However, despite these findings, the overall effect of hypoalbuminemia remains questionable due to conflicting outcomes from various studies, partly owing to diverse heterogeneity and the occurrence of different types of infection [5, 8]. Data on the prevalence of colistin-associated AKI in our local context is limited.

Acute kidney injury (AKI) remains a critical complication in ICU settings, affecting 30–60% of critically ill patients and significantly contributing to morbidity and mortality. While colistin has re-emerged as a last-resort antibiotic against multidrug-resistant gram-negative organisms, its nephrotoxic potential poses a serious clinical challenge, with AKI incidence ranging from 20–76% across studies. Despite growing evidence linking hypoalbuminemia to AKI risk, its specific role in colistin-induced AKI remains poorly understood due to conflicting findings and limited data from low-to-middle-income settings like Pakistan. This study aims to assess the incidence of colistin-induced AKI among intensive care unit (ICU) patients and investigate the relationship between serum albumin levels and the development of AKI in ICU patients receiving colistin therapy.

METHODS

This prospective cohort (follow-up) study was conducted in the adult intensive care unit at the “Shaheed Mohtarma Benazir Bhutto Institute of Trauma, Pakistan”, from August 2023 to December 2023. The study commenced following the approval of “Ethics Review Committee (ERC-000113/SMBBIT)”. After obtaining dual linguistic consent, all patients aged 18 years who were admitted to the ICU and receiving intravenous colistin therapy for 72 hours as part of their infection treatment were included in the study. Patients with AKI injury before receiving colistin therapy,

requiring renal replacement therapy before colistin initiation and those patients receiving only inhaled colistin were excluded. An informed consent was taken. WHO sample size calculator was used for a Sample size of 229 patients, estimated by taking 68.8% AKI injury among patients on colistin therapy [14] at a 95% confidence interval and 6% margin of error. Patients were enlisted into the study using non-probability consecutive sampling. In this study, the duration of colistin therapy was set at either 7 or 14 days. This study used KDIGO guidelines [2], while the primary outcomes of the study were the incidence of AKI at 48 hours and after colistin therapy (Table 1).

Table 1: KDIGO Guidelines

Stages	Serum Creatinine
Stage 1	1.5 to 1.9 Baseline OR ≥ 0.3 mg/dL (≥ 26.5 μ mol/L)
Stage 2	2.0 to 2.9 Times Baseline
Stage 3	3.0 Times Baseline OR Increase in Serum Creatinine to ≥ 4.0 mg/dL (≥ 353.6 μ mol/L) OR Initiation of Renal Replacement Therapy, OR inpatient < 18 Years, Decrease in eGFR to < 35 mL/min/1.73m ²

The statistical analysis was performed using SPSS version 26. Categorical data were shown as counts and percentages, whereas continuous data, due to their non-normal distribution, were displayed as medians with “interquartile ranges (IQR)”. The “Shapiro-Wilk test” evaluated the normality of numerical data. “Pearson’s Chi-square” or “Fisher’s exact test” for categorical variables, and the “Mann-Whitney U” test for continuous data, were employed to compare patients with and without AKI. The independent sample t-test was used for inferential analysis of continuous data. A “Kaplan-Meier survival curve” assessed the likelihood of AKI recovery after therapy. A “Cox proportional hazards regression model” was used to obtain “hazard ratios (HRs)” with 95% confidence intervals. Variables with significant unadjusted hazard ratios were included in the model to compute adjusted hazard ratios. Statistical significance was set at a two-sided p-value of 0.05.

RESULTS

A total of 250 patients were studied. On Shapiro-Wilk the normality of the residual was > 0.05 . The median age of patients was 40 (IQR=22–48) years with an age range of 18–70 years. The majority of patients were male 200 (80%). More than three-fourths of patients were receiving concomitant antibiotics 195 (78%). Of 195 (78%) patients who were receiving concomitant antibiotics, 93 (47.7%) were on vancomycin and 72 (37%) were on meropenem. Around a quarter of them were administered with nephrotoxic drugs 204 (81.6%). Median colistin dosage was 4 (IQR=3.5–4.5) MIU (Table 2).

Table 2: Comorbidities and Diagnosis of the Patients Presented at ICU

Variables	Frequency (%)
Gender	
Male	200 (80%)
Female	50 (20%)
Hypertension	
Present	175 (70%)
Absent	75 (30%)
Diabetes	
Present	150 (60%)
Absent	100 (40%)
Heart Disease	
Present	137 (55%)
Absent	112 (45%)
Chronic Kidney Disease	
Present	50 (20%)
Absent	200 (80%)
Respiratory Tract Infection	
Present	100 (40%)
Absent	150 (60%)
Infection in Blood	
Present	125 (50%)
Absent	125 (50%)
Infection in Urine	
Present	75 (30%)
Absent	175 (70%)
Infection in Sputum	
Present	25 (10%)
Absent	225 (90%)
Infection in CNS	
Present	12.5 (5%)
Absent	237.5 (95%)
Hypoalbuminemia	
Present	175 (70%)
Absent	75 (30%)
Concomitant Antibiotics	
Patients Receiving Concomitant Antibiotics	195 (78%)
Receiving Vancomycin	93 (47.7% of 78%)
Receiving Meropenem	72 (37% of 78%)
Patients Administered Nephrotoxic Drugs	204 (81.6%)
Median Colistin Dosage	4 MIU (IQR: 3.5-4.5)

The incidence rate of AKI at the end of therapy was 5.1 per 100 patients. The survival probability from AKI at the end of therapy was 2.1%. Median survival days were 14 days (95% CI: 13.3-14.7). The Kaplan-Meier survival analysis demonstrates a progressive decline in cumulative survival throughout the study, with significant drops indicating clustered event occurrences and censored data points reflecting incomplete follow-up for certain subjects. The survival analysis on the 5th, 10th, 15th and 20th days were 0.85, 0.75, 0.55, and 0.35 respectively where the curve has a visible decrease indicating more events occurring (Figure 1).

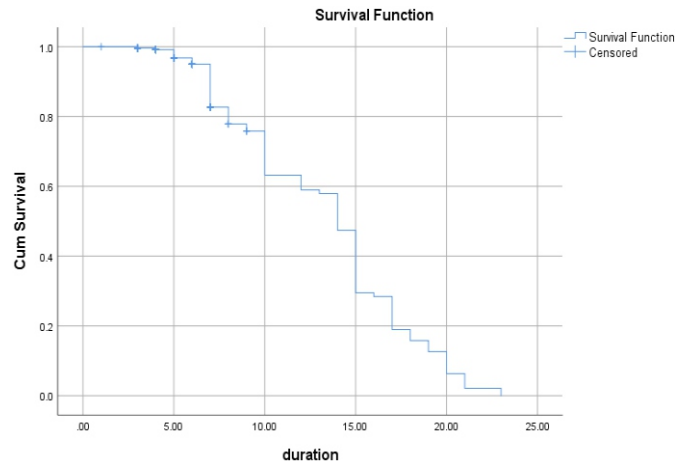


Figure 1: Kaplan-Meier Curve for the Probability of Survival from AKI During Colistin Therapy During the Study Period

At baseline and 48 hours, the median serum creatinine level was 0.5 (IQR=0.2-0.6) and 0.5 (IQR=0.5-0.3-0.9) and at the end of therapy it was 0.6 (IQR=0.3-1.4). At 48 hours, AKI was developed in 32% of patients whereas at the end of therapy, AKI incidence was seen in 42.8% which is the highest among all the stages of AKI. The serum levels at baseline and after colistin therapy and AKI incidence are displayed (Table 3).

Table 3: Serum Creatinine and AKI Incidence Following Colistin Therapy

Variables	Frequency (%)
Serum Creatinine at Baseline	0.5 (IQR=0.2-0.6)
Serum Creatinine at 48 Hours	0.5 (IQR=0.5-0.3-0.9)
Serum Creatinine at End of Therapy	0.6 (IQR=0.3-1.4)
AKI Incidence at 48 Hours	80 (32%)
AKI Staging at 48 Hours	
Stage 1	28 (35%)
Stage 2	23 (28.8%)
Stage 3	29 (36.3%)
AKI Incidence at End of Therapy	107 (42.8%)
AKI Staging at the End of Therapy	
Stage 1	37 (34.6%)
Stage 2	20 (18.7%)
Stage 3	50 (46.7%)

Patients developing AKI at the end of therapy were elderly ($p < 0.001$). All co-existing diseases were significantly higher among patients developing AKI. The use of nephrotoxic drugs was significantly higher among AKI patients ($p < 0.001$). Albumin levels were significantly lower in patients having AKI than those who did not have AKI at the end of therapy ($p < 0.001$) (Table 4).

Table 4: Comparison of Patient's Characteristics with AKI (with and without) at the End of Colistin Therapy

Variables	Groups	AKI at the End of Therapy		p-Value
		Yes n (%)	No n (%)	
Age (in years)	-	Mean 58 (Range: 50-63)	Mean 35 (Range: 22-25)	*<0.001
Gender	Male	78 (41.5%)	110 (58.5%)	0.466
	Female	29 (46.8%)	33 (53.2%)	
Comorbid	Hypertension	36 (80%)	9 (20%)	*<0.001
	Diabetes	36 (75%)	12 (25%)	*<0.001
	CKD	12 (75%)	4 (25%)	*0.007
	Heart Diseases	16 (66.7%)	8 (33.3%)	*0.013
Concomitant Use of Antibiotics	Yes	83 (42.6%)	112 (57.4%)	0.887
	No	24 (43.6%)	31 (56.4%)	
Nephrotoxic Drugs	Yes	44 (95.7%)	2 (4.3%)	*<0.001
	No	66 (36.5%)	115 (63.5%)	
Site of Infection	Blood	83 (50.3%)	82 (49.7%)	*0.001
	Urine	14 (40%)	21 (60%)	0.718
	Sputum	9 (42.9%)	12 (57.1%)	0.996
	CNS	7 (50%)	7 (50%)	0.575
	Respiratory tract	63 (43.2%)	83 (56.8%)	0.894
Albumin Level (Mean ± SD)		Mean 1.7 (Range: 1.3-2.3)	Mean 3.6 (Range: 3.4-4.0)	*<0.001

AKI: Acute kidney injury, CKD: Chronic kidney disease, CNS: Central nervous system, **=0.05, alndependent Sample t-test applied, bChi Square test applied

In univariate analysis, the risk of developing AKI was significantly increasing with increased age, use of nephrotoxic drugs, and increasing colistin dosage whereas AKI risk was decreasing with increasing albumin levels. In a multivariable model, only colistin dosage was found to be significantly associated with increasing AKI risk with increasing colistin dosage (Table 5).

Table 5: Patients' Characteristics with AKI at the End of Colistin Therapy in Univariate and Multivariable Regression

Variables	HR (95% CI)	p-Value	A HR (95% CI)	p-Value
Age	1.04 (1.02-1.05)	0.176	1.01 (0.98-1.02)	0.693
Gender, Male	1.16 (0.75-1.80)	0.485	1.10 (0.90-1.35)	0.560
Hypertension	0.94 (0.63-1.40)	0.748	0.97 (0.70-1.20)	0.720
Diabetes	1.30 (0.86-1.96)	0.209	1.15 (0.85-1.45)	0.450
CKD	0.98 (0.53-1.78)	0.943	0.99 (0.65-1.52)	0.930
Heart Diseases	1.41 (0.82-2.41)	0.210	1.20 (0.95-1.60)	0.250
Concomitant Antibiotics Use	1.20 (0.76-1.89)	0.432	1.05 (0.80-1.40)	0.650
Nephrotoxic Drugs	1.48 (1-2.19)	*0.050	1.28 (0.85-1.93)	0.228
Colistin Dosage	1.08 (1.03-1.15)	*0.006	1.06 (1.01-1.14)	*0.049
Albumin	0.72 (0.53-0.98)	*0.038	0.82 (0.58-1.14)	0.232

CI: Confidence Interval at 95%, HR: Hazard ratio, *=0.05

DISCUSSION

This study of 250 patients (75.2% male, median age 40) found high exposure to nephrotoxic drugs and antibiotics, with a median colistin dose of 4 MIU. The AKI incidence rate

was 5.1 per 100 patient days, and survival at therapy's end was only 2.1%, with a median survival of 14 days. Kaplan-Meier analysis showed a steady decline in survival over the treatment period, underscoring significant risks associated with colistin use. At the 48-hour mark, 32% of patients had developed AKI, which increased to 42.8% by the end of therapy, marking the highest incidence among AKI stages. Elderly patients and those with pre-existing conditions were more likely to develop AKI ($p < 0.001$), and AKI was significantly associated with the use of nephrotoxic drugs. Lower albumin levels were noted in patients with AKI ($p < 0.001$). Univariate analysis indicated that AKI risk increased with age, nephrotoxic drug use, and higher colistin doses, while higher albumin levels were protective. Multivariable analysis confirmed that increased colistin dosage was the only significant independent risk factor for AKI. Our study identified a rise in AKI after colistin therapy. The incidence was 11.1% at 48 hours and 25% by treatment completion, mirroring the findings of a retrospective study conducted by Deniz (12% at 48 hours, 29% by day 7) [18]. However, discrepancies exist with prior literature reporting a wider range of AKI risk (44.3%-76.1%) [19-21]. These variations likely stem from differing AKI criteria, therapy duration, infection severity, underlying conditions, and concomitant nephrotoxic medications. We observed a high prevalence of AKI stages following colistin use. At 48 hours, 35.0%, 28.8%, and 36.3% of patients had Stage I, II, and III AKI, respectively. Notably, Stage III AKI prevalence rose to 46.7% by treatment conclusion, accompanied by a decrease in Stages I (34.6%) and II (18.7%). These findings align with previous research demonstrating a link between colistin and AKI development [19]. Similar studies support this, with Alotaibi et al., reporting a distribution of AKI stages at treatment completion as 24.5% Stage I, 37.32% Stage II, and 14.5% Stage III [20]. Likewise, Moghnieh et al., documented an incidence of AKI at Stages I, II, and III of 21.2%, 28.8%, and 50.0%, respectively [21]. Univariate analysis revealed a significant correlation between increasing age and AKI occurrence, but not on multivariable analysis. This discrepancy might be due to our limited sample size. Nevertheless, our findings are consistent with prior research highlighting increasing age as a key factor in colistin-induced AKI [18, 20]. Hypoalbuminemia, frequently observed in critically ill patients, serves as an indicator of malnutrition and inflammation and is also predictive of AKI and mortality [22]. In our study, univariate analysis showed a significant association between higher albumin levels and a reduced risk of AKI, aligning with previous research that identifies hypoalbuminemia as a risk factor for colistin-induced AKI [14-15]. However, Alotaibi et al., reported no such association [20]. The link between hypoalbuminemia and

colistin-induced AKI is likely multifaceted, with albumin's various physiological functions playing a significant role [14]. Shah *et al.*, in their retrospective study, reported Kaplan-Meier survival analysis as significantly lower survival for patients with AKI-related kidney failure compared to other etiologies (log-rank test, $p < 0.001$). Sensitivity analysis, excluding AKI patients who started dialysis with arteriovenous access and non-AKI patients who recovered renal function, yielded hazard ratios consistent with the primary model, with a marginal attenuation of roughly 10% [23]. In a study conducted by Nagata *et al.*, Kaplan-Meier survival analysis revealed that transient AKI, persistent AKI, and AKD were all significantly linked to an increased incidence of events characterized by a reduction in estimated glomerular filtration rate ($\text{ReGFR} < 0.7$) compared to individuals without AKI, especially within the first year. Among these groups, the rates of adverse outcomes were substantially higher in those with persistent AKI and AKD than in those with transient AKI [24]. The findings of this study carry important implications for clinical practice and patient management. The high incidence of AKI, particularly among elderly patients and those exposed to nephrotoxic drugs, emphasizes the need for vigilant monitoring of renal function during colistin treatment. The frequent use of concomitant antibiotics, such as vancomycin and meropenem, points to the importance of optimizing antibiotic regimens to minimize cumulative nephrotoxic effects. Additionally, the significant relationship between higher colistin dosages and increased AKI risk suggests that dose adjustments may be necessary to achieve a balance between efficacy and safety. Identifying high-risk patients, such as those with comorbidities or lower albumin levels, could inform more personalized treatment strategies to mitigate AKI risk. Overall, these results provide valuable insights for guiding future research aimed at developing safer treatment protocols and protective measures for patients undergoing colistin therapy.

This study was limited by its single-center design, a relatively small sample size of 250 patients, and a short follow-up period of six months, which may restrict the generalizability of the findings to broader ICU populations. The non-probability consecutive sampling method and the absence of long-term renal outcome data further constrain the robustness of the conclusions. Future research should employ multicenter, larger-scale prospective designs with extended follow-up periods to better capture the long-term renal consequences of colistin therapy. Additionally, investigating protective strategies such as albumin supplementation, dose optimization protocols, and pharmacokinetic monitoring may help develop safer therapeutic guidelines for high-risk ICU patients receiving colistin.

CONCLUSIONS

It was concluded that this analysis identified a higher incidence of AKI following colistin therapy. However, albumin levels did not show a significant association with AKI risk in the multivariable model. Conversely, a significant correlation was observed between increasing colistin dosage and AKI incidence.

Authors' Contribution

Conceptualization: SUM

Methodology: SUM, SS, NM, SK

Formal analysis: SM, SK

Writing and Drafting: SI, SUM, SS, NM, SK

Review and Editing: SI, SUM, SS, NM, SK

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

The authors declare no conflict of interest.

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