

From Initiation to Recovery: A Longitudinal Analysis of Polymyxin B-Induced Kidney Injury in Clinical Practice

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Background: Polymyxin B (PMB) is an antibiotic used to treat severe infections, but its use is associated with nephrotoxicity. Identifying risk factors for PMB-associated nephrotoxicity is essential for improving patient outcomes.

Objective: This study aimed to identify risk factors for PMB-associated nephrotoxicity and evaluate their impact on renal function recovery.

Patients and methods: A retrospective analysis was conducted on patients who received PMB therapy at the Second Xiangya Hospital, Central South University, from August 2022 to August 2023. Univariable and multivariable logistic regression analyses were performed to assess risk factors for acute kidney injury (AKI) and factors influencing renal recovery. AKI was defined and staged according to the KDIGO criteria based on serum creatinine changes.

Results: Of the 325 patients treated with intravenous PMB, 112 (34.5%) developed AKI. Independent risk factors for PMB-associated AKI included use of vancomycin (RR=1.398, P=0.027), use of aminoglycosides (RR=2.047, P=0.018), use of amphotericin B (RR=1.834, P=0.006), use of furosemide (>20 mg/day) (RR=1.495, P=0.004), and a higher loading dose of PMB (RR=1.004, P=0.004). The median time to AKI onset was 7 days (IQR: 3–12). Renal recovery occurred in 41.1% of AKI patients, and the use of vasoactive agents was negatively associated with recovery, likely reflecting underlying hemodynamic instability rather than a direct nephrotoxic effect (OR=0.298, P=0.013).

Conclusion: Key risk factors for PMB-associated AKI included the use of vancomycin, aminoglycosides, amphotericin B, high-dose furosemide (>20 mg/day), and the loading dose of PMB. Close monitoring of serum creatinine within the first week of PMB therapy is crucial for improving outcomes. Clinicians should minimize concurrent nephrotoxic agents where feasible and prioritizing rapid hemodynamic stabilization in patients with shock to optimize renal recovery.

Keywords: polymyxin B, acute kidney injury, nephrotoxicity, renal function recovery, risk factors

Introduction

Polymyxins, a class of cyclic peptide antibiotics isolated from *Bacillus polymyxa*, were discovered in the 1950s and include variants A, B, C, D, and E. Among these, polymyxin B (PMB) and polymyxin E (colistin) exhibit potent antibacterial activity against Gram-negative bacteria while demonstrating relatively lower nephrotoxicity, which facilitated their clinical use. However, due to their significant nephrotoxic and neurotoxic effects, their use declined in the 1980s as newer antibiotics emerged.¹ Recently, the rising prevalence of carbapenem-resistant Gram-negative bacilli (CR-GNB) has led to the reintroduction of polymyxins as a last-resort treatment option for CR-GNB infections.²

Nephrotoxicity is a critical safety metric for the safety profile of polymyxins. Despite their strong antibacterial properties against Gram-negative bacilli, the adverse effects associated with polymyxins severely restrict their

clinical application.³ Polymyxins increase the permeability of renal tubular epithelial cell membranes, inducing acute tubular necrosis and resulting in acute kidney injury (AKI).⁴ Clinical manifestations of AKI typically include elevated serum creatinine levels, reduced creatinine clearance, and diminished urine output. Polymyxin-associated nephrotoxicity is a dose-limiting and generally reversible adverse effect, with incidence rates ranging from 11.8% to 60.0%.^{5–8} A recent comparative study indicated that colistin has a higher incidence of AKI than PMB.⁹ Numerous studies have investigated the risk factors and predictors of PMB-associated nephrotoxicity.^{3,8,10–12} Key findings suggest that the loading dose of PMB, high daily doses (~30,000 IU/kg/day), and prolonged treatment duration are independent risk factors for nephrotoxicity.^{3,13,14} Additional potential risk factors include age, obesity, diabetes mellitus, and coadministration of nephrotoxic agents like vancomycin and aminoglycosides.^{10,15} Prior research has shown that $C_{\max}$ (5.23 mcg/mL) and $AUC_{ss,24h} > 100$ (mg·h)/L are reliable predictors of PMB-associated nephrotoxicity.^{8,16} According to international guidelines, the recommended $AUC_{ss,24h}$ range for PMB is 50–100 (mg·h)/L. For critically ill patients, maintaining an $AUC_{ss,24h}$ within this range is associated with reduced nephrotoxicity while ensuring clinical efficacy.⁸

While existing studies have addressed the incidence, risk factors, and predictors of PMB-associated nephrotoxicity, there remains a paucity of research on the time to onset of nephrotoxicity and renal recovery in patients who develop AKI. Patients with PMB-associated AKI often present with severe hemodynamic instability, which may influence renal recovery. Failure to recover from AKI can lead to major adverse renal events, including the onset or progression of chronic kidney disease and the initiation of long-term dialysis. Therefore, this study aims to assess the risk factors for PMB-associated nephrotoxicity in Chinese patients and their impact on renal function recovery, providing valuable insights for the clinical use of PMB.

Methods

Population

This investigation was designed as a retrospective cohort study conducted at The Second Xiangya Hospital of Central South University. We gathered clinical data from patients aged >18 years who received intravenous polymyxin B (PMB) treatment for >72 hours from August 2022 to August 2023. The exclusion criteria comprised: 1) individuals under 18 years of age or those who were pregnant, 2) patients with incomplete clinical records, and 3) patients with more than a 30% fluctuation in serum creatinine within the 48 hours prior to PMB initiation.

Ethics

Our study was approved by the Ethics Committee of The Second Xiangya Hospital of Central South University (approval number: LYF20230216). Due to the retrospective and observational nature of the study, the requirement for written informed consent was waived by the Committee. The study adhered to the ethical standards of the 1964 Declaration of Helsinki. All patient data were anonymized prior to analysis, and strict confidentiality was maintained throughout the study. Patient records were accessed only by authorized research personnel, and no identifiable personal information was disclosed.

Clinical Data Collection

Clinical data extracted from patients' electronic records included age, sex, weight, comorbidities, type of infection, site of infection, details of PMB use (loading dose, maintenance dose, duration of treatment, and cumulative dose), concomitant nephrotoxic agents, pre-medication kidney disease, and changes in serum creatinine values during the patients using PMB. The loading dose of polymyxin B was entered as a continuous variable, and the maintenance dose was entered as a continuous variable using the actual administered dose in mg/kg or mg per 12 hours. The use of continuous renal replacement therapy (CRRT) and hemodialysis was recorded as a binary variable indicating whether patients received renal replacement therapy during PMB administration. These variables were included in the analysis as markers of clinical severity.

Outcome Definitions

AKI was defined and staged according to the KDIGO criteria based on serum creatinine changes: Stage 1 (1.5–1.9 times baseline), Stage 2 (2.0–2.9 times baseline), and Stage 3 (≥ 3.0 times baseline or initiation of renal replacement therapy).¹⁷ We diagnosed AKI based on changes in serum creatinine alone; urine output was not assessed. Acute kidney disease (AKD) was defined as $\text{GFR} < 60 \text{ mL/min per } 1.73 \text{ m}^2$ for < 3 months, and chronic kidney disease was defined as $\text{GFR} < 60 \text{ mL/min per } 1.73 \text{ m}^2$ for ≥ 3 months.¹⁸ Normal kidney function was considered $\text{GFR} \geq 60 \text{ mL/min per } 1.73 \text{ m}^2$. Baseline creatinine was the last creatinine obtained before PMB initiation. Follow-up was continued until 48h after the last dose, and serum creatinine for patients with AKI were followed until discharge from hospital. Renal function recovery was defined as cessation of renal replacement therapy and a return of serum creatinine to baseline or a decrease in AKI classification level in the absence of ongoing renal replacement therapy.¹⁹ In this study, renal function recovery was defined as the return of serum creatinine to baseline.

All data were analyzed using SPSS 27.0, R 4.5.0, and GraphPad Prism 10.0 was applied for graphing. Continuous data were represented by median and interquartile ranges (IQRs), and comparisons between groups were made using the Mann–Whitney test. Count data were presented as absolute numbers and percentages, and comparisons between groups were made using the Pearson chi-square test. To determine factors associated with the occurrence of AKI in this cohort study, univariate analysis was first performed to identify potential risk factors PMB-associated AKI. Factors with $P < 0.05$ in univariate analysis were considered candidates for the multivariable model. Before entering these variables into the multivariable analysis, collinearity diagnostics were performed using variance inflation factor (VIF) to assess potential multicollinearity among the covariates. Variables with $\text{VIF} > 5$ were excluded from the multivariable analysis to maintain model stability. A modified poisson regression approach with robust error variance was then constructed to estimate the relative risks (RRs) and 95% confidence intervals (CIs) for factors associated with AKI occurrence. The Kaplan–Meier curves were used to compare the duration of AKI in patients with AKI of different severities. Nonparametric tests of K-independent samples were used to determine differences in clinical outcomes among patients with AKI. Multivariate logistic analysis was used to investigate the factors associated with renal function recovery in patients with AKI. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

According to the established inclusion and exclusion criteria, a total of 325 patients treated with PMB were ultimately enrolled in this study. The study cohort and clinical outcomes for patients who developed AKI are illustrated in [Figures 1 and 2](#), while the baseline demographic and clinical characteristics of the patients are detailed in [Table 1](#). The median age of the patients was 61 years (IQR, 48–73 years), with a predominance of males (75.7%). During hospitalization, 87.7% of the patients were admitted to the intensive care unit, 197 (60.6%) required mechanical ventilation, and vasoactive drugs were administered to 144 (44.3%) patients. The underlying conditions primarily included cardiovascular and cerebrovascular diseases (45.5%), hypertension (51.4%), diabetes mellitus (30.8%), and COVID-19 (29.2%). Prior to PMB administration, 162 patients (49.8%) had AKD or CKD, while 163 patients (50.2%) exhibited normal renal function. Concomitant nephrotoxic agents included vancomycin (15.4%), furosemide (doses > 20 mg/day) (27.1%), torasemide (doses > 10 mg/day) (13.8%), amphotericin B (6.2%), trimethoprim/sulfamethoxazole (TMP-SMZ) (11.4%), non-steroidal anti-inflammatory drugs (NSAIDs) (4.0%), and aminoglycosides (3.4%). The median maintenance dose of PMB administered was 75 mg (interquartile range [IQR], 50–75 mg) or 1.153 mg/kg (IQR, 0.833–1.250 mg/kg) every 12 hours, with a cumulative PMB dose of 1350 mg (IQR, 750–2100 mg). The treatment duration averaged 10 days (IQR, 6–15 days). The mean creatinine level prior to administration was $106.8 \mu\text{mol/L}$ (IQR, 63.7 – $191.7 \mu\text{mol/L}$). Notably, 64 patients (19.7%) underwent continuous renal replacement therapy (CRRT), and 17 patients (5.2%) received hemodialysis.

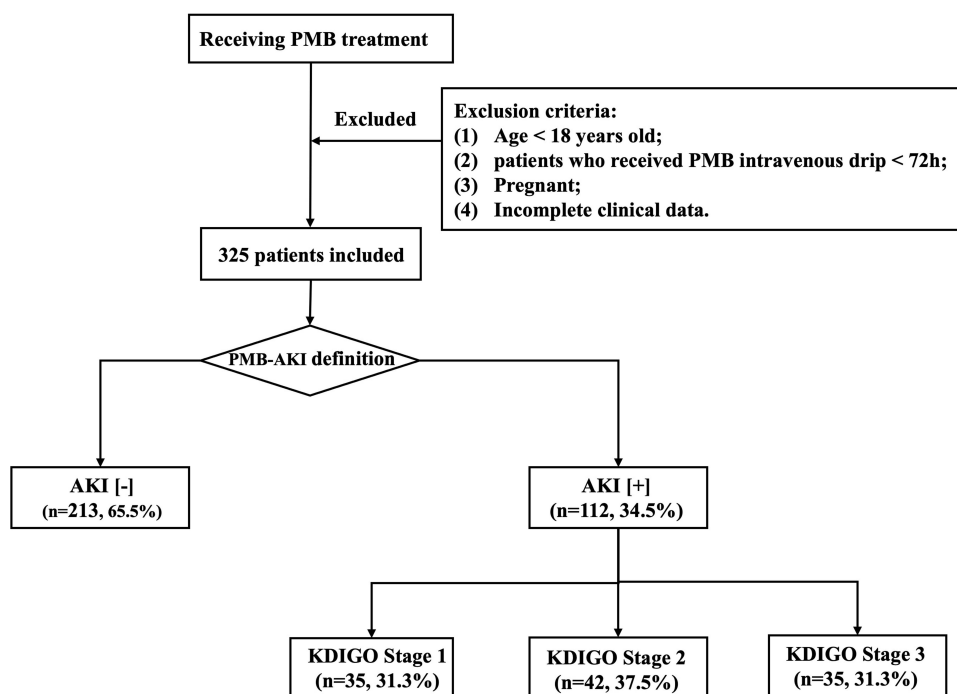


Figure 1 Study cohort flowchart. Flow diagram showing patient enrollment, exclusion criteria applied, and the number of patients who developed AKI during PMB therapy.

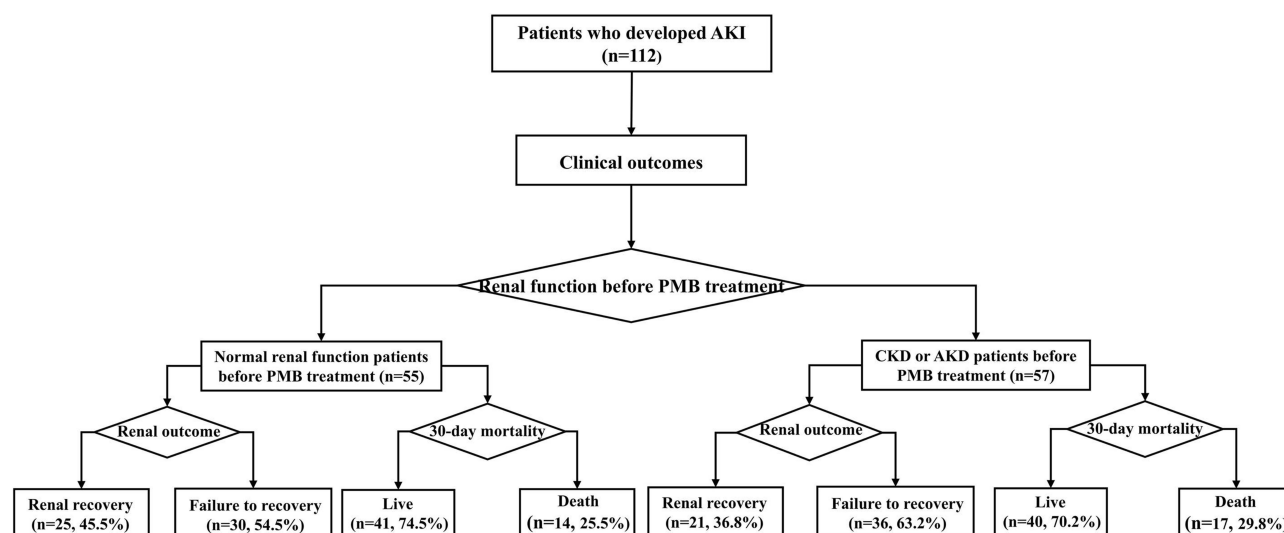


Figure 2 Clinical outcomes of patients who developed AKI. Bar chart showing 30-day mortality and renal recovery rates according to KDIGO stage.

Incidence and Occurrence Time of AKI

Among the 325 patients treated with PMB, 112 (34.5%) developed AKI. The median time to AKI occurrence was 7 days (IQR, 3–12 days), with 50.9% of patients experiencing AKI after seven days of PMB treatment (Figure 3). When comparing the cumulative incidence of AKI between patients with AKD or CKD before PMB treatment and those with normal renal function, no significant differences were found (Figure 4).

Risk Factors for AKI

The total incidence of AKI among all patients treated with PMB was 112 (34.5%). Univariable analysis identified multiple factors significantly associated with AKI, including sex, age, weight, mechanical ventilation, use of vasoactive

Table 1 Demographics and Clinical Characteristics of the Study Cohort

Clinical Characteristic	Normal Renal Function Patients Before PMB Treatment (N=163)	AKD or CKD Patients Before PMB Treatment (N=162)	Total Patients Treated with PMB (N=325)
Male gender	122 (74.8)	124 (76.5)	246 (75.7)
Age (years)	63 (51–75)	59 (47–71)	61 (48–73)
Weight (kg)	61.0 (55.0–65.0)	61.9 (55.0–65.0)	61.9 (55.0–65.0)
Mechanical ventilation	103 (63.2)	94 (58.0)	197 (60.6)
Vasoactive agents	67 (41.1)	77 (47.5)	144 (44.3)
Admission to ICU	143 (87.7)	142 (87.7)	285 (87.7)
ECMO	8 (4.9)	10 (6.2)	18 (5.5)
Multi-site infection	60 (36.8)	56 (34.6)	116 (35.7)
Site of infection			
Respiratory tract	144 (88.3)	118 (72.8)	262 (80.6)
Urinary system	23 (14.1)	22 (13.6)	45 (13.8)
Bloodstream	41 (25.2)	36 (22.2)	77 (23.7)
Abdomen	8 (4.9)	2 (1.2)	10 (3.1)
Underlying disease			
Cardiovascular and cerebrovascular diseases	74 (45.4)	74 (45.7)	148 (45.5)
Respiratory disease	32 (19.6)	43 (26.5)	75 (23.1)
Liver disease	32 (19.6)	22 (13.6)	54 (16.6)
Diseases of digestive system	10 (6.1)	9 (5.6)	19 (5.8)
Nutritional diseases	20 (12.3)	15 (9.3)	35 (10.8)
Hypertension	78 (47.9)	89 (54.9)	167 (51.4)
Diabetes mellitus	39 (23.9)	61 (37.7)	100 (30.8)
COVID-19	40 (24.5)	55 (34.0)	95 (29.2)
Pathogenic bacteria			
<i>Acinetobacter baumannii</i>	112 (68.7)	78 (48.1)	190 (58.5)
<i>Pseudomonas aeruginosa</i>	14 (8.6)	15 (9.3)	29 (8.9)
<i>Klebsiella pneumoniae</i>	41 (25.2)	35 (21.6)	76 (23.4)
Concomitant nephrotoxic agents			
Vancomycin	33 (20.2)	17 (10.5)	50 (15.4)
Aminoglycosides	8 (4.9)	3 (1.9)	11 (3.4)
Amphotericin B	11 (6.7)	9 (5.6)	20 (6.2)
Furosemide (>20 mg/day)	35 (21.5)	53 (32.7)	88 (27.1)
Torsemide (>10mg/day)	23 (14.1)	22 (13.6)	45 (13.8)
Diuretic	5 (3.1)	10 (6.2)	15 (4.6)
NSAIDs	10 (6.1)	3 (1.9)	13 (4.0)
TMP-SMZ	16 (9.8)	21 (13.0)	37 (11.4)
PMB use			
Loading dose (mg)	100 (100–150)	100 (0–125)	100 (0–125)
Maintenance dose q12h (mg)	75 (50–75)	62.5 (40–75)	75 (50–75)
Maintenance dose q12h (mg/kg)	1.153 (1.000–1.333)	0.980 (0.749–1.153)	1.153 (0.833–1.250)
Cumulative dose (mg)	1500 (850–2275)	1200 (650–1725)	1350 (750–2100)
Treatment duration time (days)	11 (6–15)	9 (7–14)	10 (6–15)

(Continued)

Table 1 (Continued).

Clinical Characteristic	Normal Renal Function Patients Before PMB Treatment (N=163)	AKD or CKD Patients Before PMB Treatment (N=162)	Total Patients Treated with PMB (N=325)
Kidney disease-related clinical characteristics			
Creatinine before administration (umol/L)	69.0 (51.0–91.2)	180.5 (130.5–336.4)	106.8 (63.7–191.7)
CRRT	19 (11.7)	45 (27.8)	64 (19.7)
Hemodialysis	4 (2.5)	13 (8.0)	17 (5.2)

Notes: Vasoactive agents mainly contain epinephrine, norepinephrine, isopropyl epinephrine, and dopamine during hospitalization; admission to ICU means that the patients were already admitted to the ICU at the time of receiving PMB. Bold font indicates data with significant differences.

Abbreviations: ICU, intensive unit care; NSAIDs, nonsteroidal anti-inflammatory drugs; TMP-SMZ, trimethoprim/sulfamethoxazole; PMB, polymyxin B; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

agents, ICU admission, extracorporeal membrane oxygenation (ECMO), multi-site infections, pulmonary infections, bloodstream infections, *Acinetobacter baumannii* infections, *Pseudomonas aeruginosa* infections, diabetes mellitus, COVID-19, loading dose of PMB, maintenance dose (mg), cumulative dose (mg), treatment duration, use of vancomycin, use of amphotericin B, use of aminoglycosides, use of furosemide (>20 mg/day), use of torasemide (>10 mg/day), and CRRT (all $P < 0.05$) (Table 2).

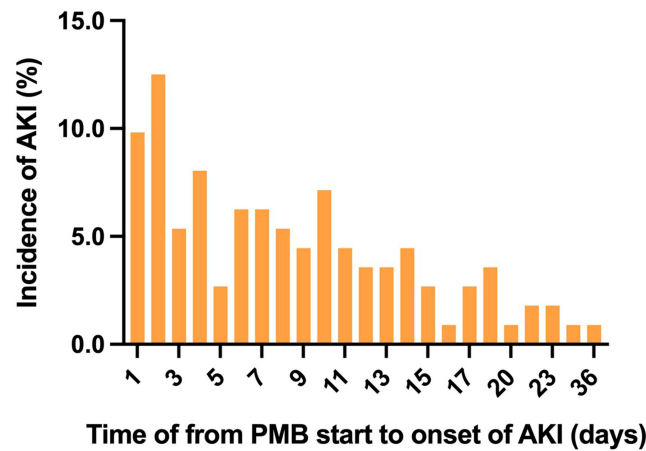


Figure 3 Time to AKI onset. Histogram (or Kaplan-Meier curve) showing the distribution of time (days) from PMB initiation to AKI diagnosis.

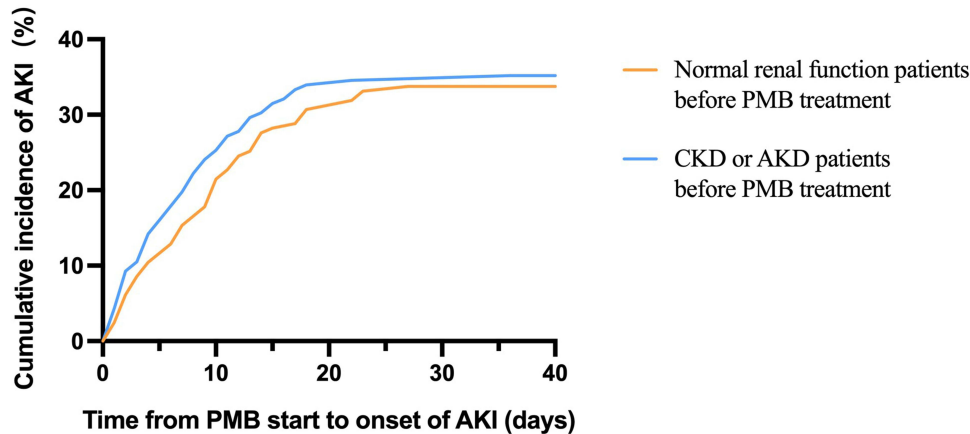


Figure 4 Cumulative incidence of AKI over time. Comparison between patients with normal baseline renal function and those with pre-existing AKD or CKD.

Table 2 Univariate and Multivariable Analysis of the Factors Potentially Associated with Acute Kidney Injury in Patients Treated with PMB

Variable	Univariate Analysis			Poisson Regression	
	AKI [+] (N=112)	AKI [-] (N=213)	p-value	RR (95% CI)	p-value
Male gender	94 (83.9)	152 (71.4)	0.012	0.690 (0.398–1.132)	0.060
Age (years)	67.50 (58.00–77.75)	59.00 (46.00–70.00)	<0.001	1.009 (0.994–1.024)	0.116
Weight (kg)	65.00 (60.00–67.12)	60.00 (54.37–65.00)	<0.001		
Mechanical ventilation	93 (83.0)	104 (48.8)	<0.001	1.765 (0.903–3.549)	0.059
Vasoactive agents	75 (67.0)	69 (32.4)	<0.001	1.403 (0.850–2.369)	0.089
Admission to ICU	105 (93.8)	180 (84.5)	0.016	1.019 (0.448–2.635)	0.954
ECMO	11 (9.8)	7 (3.3)	0.014	1.106 (0.525–2.153)	0.645
Multi-site infection	52 (46.4)	64 (30.0)	0.003	0.979 (0.536–1.712)	0.928
Site of infection					
Respiratory tract	100 (89.3)	162 (76.1)	0.004	0.691 (0.298–1.639)	0.292
Urinary system	20 (17.9)	25 (11.7)	0.129		
Bloodstream	38 (33.9)	39 (18.3)	0.002	1.006 (0.551–1.878)	0.980
Abdomen	4 (3.6)	6 (2.8)	0.708		
Underlying disease					
Cardiovascular and cerebrovascular diseases	53 (47.3)	95 (44.6)	0.640		
Respiratory disease	28 (25.0)	47 (22.1)	0.551		
Kidney disease	34 (30.4)	71 (33.3)	0.586		
Liver disease	18 (16.1)	36 (16.9)	0.848		
Diseases of digestive system	7 (6.3)	12 (5.6)	0.822		
Nutritional diseases	14 (12.5)	21 (9.9)	0.465		
Hypertension	61 (54.5)	106 (49.8)	0.421		
Diabetes mellitus	45 (40.2)	55 (25.8)	0.008	1.129 (0.745–1.696)	0.451
COVID-19	43 (38.4)	52 (24.4)	0.008	0.935 (0.592–1.464)	0.689
Pathogenic bacteria					
<i>Acinetobacter baumannii</i>	77 (68.8)	113 (53.1)	0.006	1.001 (0.593–1.736)	0.993
<i>Pseudomonas aeruginosa</i>	15 (13.4)	14 (6.6)	0.040	1.429 (0.720–2.688)	0.125
<i>Klebsiella pneumoniae</i>	27 (24.1)	49 (23.0)	0.823		
Concomitant nephrotoxic agents					
Vancomycin	28 (25.0)	22 (10.3)	<0.001	1.398 (0.870–2.191)	0.027
Aminoglycosides	7 (6.3)	4 (1.9)	0.038	2.047 (0.816–4.445)	0.018
Amphotericin B	12 (10.7)	8 (3.8)	0.013	1.834 (0.908–3.410)	0.006
Furosemide (>20 mg/day)	46 (41.1)	42 (19.7)	<0.001	1.495 (0.998–2.222)	0.004
Torsemide (>10mg/day)	28 (24.1)	19 (8.5)	<0.001	1.378 (0.836–2.212)	0.053
Diuretic	7 (6.3)	8 (3.8)	0.308		
NSAIDs	3 (2.7)	10 (4.7)	0.378		
TMP-SMZ	16 (14.3)	21 (9.9)	0.232		
PMB use					
Loading dose (mg)	125 (100–150)	100 (0–100)	<0.001	1.004 (1.000–1.008)	0.004
Maintenance dose q12h (mg)	75 (50–75)	75 (50–75)	<0.001		
Maintenance dose q12h (mg/kg)	1.153 (0.909–1.265)	1.071 (0.778–1.239)	0.025		
Cumulative dose (mg)	1687 (1047–2831)	1100 (650–1737)	<0.001		
Treatment duration time (days)	12.00 (8.00–19.00)	9.00 (6.00–14.00)	<0.001		
Kidney disease-related clinical characteristics					
Creatinine before administration (umol/L)	107.00 (76.17–144.80)	105.20 (57.10–235.00)	0.906		
CRRT	35 (31.3)	29 (13.6)	<0.001	1.085 (0.683–1.700)	0.628
Hemodialysis	8 (7.1)	9 (4.2)	0.262		

Notes: Vasoactive agents mainly contain epinephrine, norepinephrine, isopropyl epinephrine, and dopamine during hospitalization; admission to ICU means that the patients were already admitted to the ICU at the time of receiving PMB. Bold font indicates data with significant differences.

Abbreviations: ICU, intensive unit care; NSAIDs, nonsteroidal anti-inflammatory drugs; TMP-SMZ, trimethoprim/sulfamethoxazole; PMB, polymyxin B; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

Variables with $P < 0.05$ in univariable analysis were considered candidates for the multivariable model. Collinearity diagnostics using VIF excluded weight (kg), maintenance dose q12h (mg), maintenance dose q12h (mg/kg), cumulative dose (mg), and treatment duration (days) due to $VIF > 5$.

Following modified Poisson regression, the use of amphotericin B (RR=1.834; 95% CI: 0.908–3.410; $P=0.006$) and a higher loading dose of PMB (RR=1.004; 95% CI: 1.000–1.008; $P=0.004$) were significantly associated with an increased risk of PMB-associated AKI. The use of vancomycin (RR=1.398; $P=0.027$), aminoglycosides (RR=2.047; $P=0.018$), and high-dose furosemide (RR=1.495; $P=0.004$) also showed statistically significant associations, although their 95% confidence intervals narrowly crossed or approximated 1.0, suggesting these estimates should be interpreted with consideration of the limited sample size in certain exposure groups (Table 2).

Clinical Outcome of Patients Who Developed AKI

Of the 112 patients with AKI, 35 had KDIGO stage 1 AKI, 42 (37.5%) had stage 2 AKI, and 35 (31.3%) had stage 3 AKI (Figure 1). The overall 30-day mortality rate was 27.6%, with 8 cases (7.1%) in stage 1, 14 cases (12.5%) in stage 2, and 9 cases (8.0%) in stage 3 (Table 3). Among all AKI patients, 41.1% (46/112) experienced renal recovery, with 13 cases in stage 1, 18 cases in stage 2, and 15 cases in stage 3 (Table 3). No significant differences in 30-day mortality or renal recovery were observed across KDIGO stages (Table 3). Multivariable analysis identified use of vasoactive agents as the sole factor associated with renal recovery (OR=0.298; 95% CI: 0.114–0.778; $P=0.013$) (Table 4).

The median time to renal recovery was 8 days (IQR, 5–13 days) following the onset of AKI. When comparing patients with KDIGO stage 1, stage 2, and stage 3 AKI, the time to renal recovery did not differ significantly among the three groups ($P > 0.05$) (Figure 5).

Table 3 Outcomes of All AKI Patients

Severity	N (%)	30-day Mortality, n (%)	Renal Recovery, n (%)
KDIGO Stage 1	35 (31.3%)	8 (7.1%)	13 (11.6%)
KDIGO Stage 2	42 (37.5%)	14 (12.5%)	18 (16.1%)
KDIGO Stage 3	35 (31.3%)	9 (8.0%)	15 (13.4%)

Notes: Bold font indicates data with significant differences. p-value, the comparison of three groups.

Abbreviation: AKI, acute kidney injury.

Table 4 Univariate and Multivariable Logistic Regression of Factors for Renal Recovery of AKI Patients

Variable	Univariate Analysis			Multivariable Analysis	
	Renal Recovery [+] (N=46)	Renal Recovery [-] (N=66)	p-value	OR (95% CI)	p-value
Male gender	39 (84.8)	55 (83.3)	0.837	0.298 (0.114–0.778) 0.335 (0.032–3.547)	0.013 0.364
Age (years)	67 (52–75)	68 (58–78)	0.300		
Weight (kg)	65 (60–65)	65 (57–68)	0.838		
Mechanical ventilation	36 (78.3)	57 (86.4)	0.261		
Vasoactive agents	24 (52.2)	51 (77.3)	0.005		
Admission to ICU	40 (87.0)	65 (98.5)	0.013		
ECMO	6 (13.0)	5 (7.6)	0.339		
Multi-site infection	25 (54.3)	27 (40.9)	0.161		
Site of infection					
Respiratory tract	40 (87.0)	60 (90.9)	0.506		
Urinary system	9 (19.6)	11 (16.7)	0.694		
Bloodstream	16 (34.8)	22 (33.3)	0.873		
Abdomen	3 (6.5)	1 (1.5)	0.160		

(Continued)

Table 4 (Continued).

Variable	Univariate Analysis			Multivariable Analysis	
	Renal Recovery [+] (N=46)	Renal Recovery [-] (N=66)	p-value	OR (95% CI)	p-value
Underlying disease					
Cardiovascular and cerebrovascular diseases	23 (50.0)	30 (45.5)	0.636		
Respiratory disease	8 (17.4)	20 (30.3)	0.121		
Liver disease	9 (19.6)	9 (13.6)	0.401		
Diseases of digestive system	3 (6.5)	4 (6.1)	0.921		
Nutritional diseases	6 (13.0)	8 (12.1)	0.885		
Hypertension	26 (56.5)	35 (53.0)	0.715		
Diabetes mellitus	17 (37.0)	28 (42.4)	0.561		
COVID-19	12 (26.1)	31 (47.0)	0.025	0.519 (0.192–1.400)	0.195
Pathogenic bacteria					
<i>Acinetobacter baumannii</i>	31 (67.4)	46 (69.7)	0.796		
<i>Pseudomonas aeruginosa</i>	8 (17.4)	7 (10.6)	0.300		
<i>Klebsiella pneumoniae</i>	13 (28.3)	14 (21.2)	0.391		
Concomitant nephrotoxic agents					
Vancomycin	10 (21.7)	18 (27.3)	0.506		
Aminoglycosides	3 (6.5)	4 (6.1)	0.921		
Amphotericin B	6 (13.0)	6 (9.1)	0.506		
Furosemide (>20 mg/day)	14 (30.4)	32 (48.5)	0.056		
Torsemide (>10mg/day)	10 (21.7)	17 (25.8)	0.625		
Diuretic	2 (4.3)	5 (7.6)	0.488		
NSAIDs	1 (2.2)	2 (3.0)	0.782		
TMP-SMZ	9 (19.6)	7 (10.6)	0.183		
PMB use					
Loading dose (mg)	100 (100–150)	125 (100–150)	0.472		
Maintenance dose q12h (mg)	75 (75–75)	75 (50–75)	0.401		
Maintenance dose q12h (mg/kg)	1.153 (0.978–1.328)	1.153 (0.890–1.250)	0.336		
Cumulative dose (mg)	2287 (1481–3175)	1425 (825–2043)	<0.001	1.000 (1.000–1.001)	0.256
Treatment duration time (days)	19 (10–23)	10 (6–15)	<0.001	1.008 (0.887–1.147)	0.899
Kidney disease-related clinical characteristics					
Creatinine before administration (umol/L)	98.7 (70.5–157.2)	116.5 (78.6–144.4)	0.344		
CRRT	9 (19.6)	26 (39.4)	0.026	0.516 (0.184–1.445)	0.208
Hemodialysis	6 (13.0)	2 (3.0)	0.043	3.320 (0.463–23.795)	0.232

Notes: Vasoactive agents mainly contain epinephrine, norepinephrine, isopropyl epinephrine, and dopamine during hospitalization; admission to ICU means that the patients were already admitted to the ICU at the time of receiving PMB. Bold font indicates data with significant differences.

Abbreviations: ICU, intensive unit care; NSAIDs, nonsteroidal anti-inflammatory drugs; TMP-SMZ, trimethoprim/sulfamethoxazole; PMB, polymyxin B; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

Discussion

We conducted a retrospective cohort study to investigate PMB-associated nephrotoxicity. Our findings indicated that the incidence of AKI among the 325 patients treated with PMB was 34.5%. Factors associated with an increased risk of PMB-related AKI included use of vancomycin, use of aminoglycosides, use of amphotericin B, and use of furosemide (>20 mg/day), and the loading dose (mg) of PMB. Among patients who developed AKI, the rate of renal function recovery was 41.1%, with no significant differences noted across varying severity levels. Use of vasoactive agents was associated with lower renal recovery.

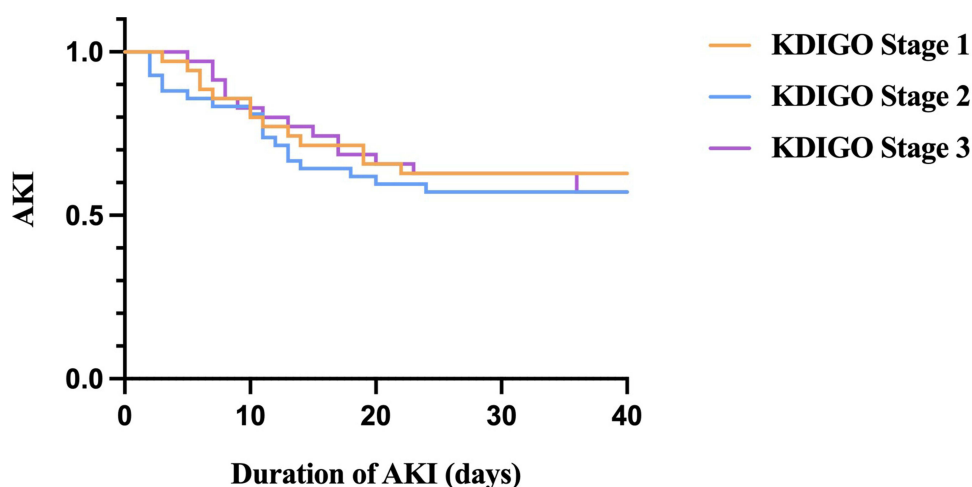


Figure 5 Renal recovery time after AKI onset. Comparison of recovery time among patients with KDIGO stage 1, stage 2, and stage 3 AKI ($P > 0.05$).

The reported incidence of PMB-associated nephrotoxicity in previous studies has varied widely, ranging from 11.8% to 60.0%.^{5–8} Our study's AKI rate of 34.5% is consistent with findings from Chang et al (33.5%) and Xia et al (37.2%).^{3,20} The variability in PMB-associated AKI incidence may reflect differences in AKI definitions, PMB dosing, and treatment duration.

Concomitant nephrotoxic agents have been consistently associated with increased AKI risk. Vancomycin can cause acute tubulointerstitial nephritis, acute tubular necrosis, and intratubular crystal deposition.^{21,22} Studies have shown higher AKI incidence with PMB plus vancomycin than with PMB alone.^{15,23} Aminoglycosides are internalized by proximal tubular cells, leading to lysosomal accumulation and tubular injury.²⁴ Thus, use of vancomycin and use of aminoglycosides may increase the incidence of PMB-associated AKI.

The use of loop diuretics is a well-established risk factor for AKI, as demonstrated in previous studies involving PMB.^{25,26} Our research indicated that the use of furosemide was associated with the onset of nephrotoxicity. While diuretics can improve short-term survival and renal function recovery in patients with mild AKI, they may also exacerbate nephrotoxicity.²⁷ Zhou et al reported that loop diuretics are associated with increased risks of hospital-acquired AKI (HA-AKI) in hospitalized adults.²⁸ It has been suggested that loop diuretics may induce acute interstitial nephritis by binding to renal antigens or acting as antigens deposited in the interstitium, prompting an immune response.²⁹ Furthermore, loop diuretics can lead to hypovolemia and inadequate renal perfusion, further compromising renal function.³⁰ Additional research is warranted to elucidate the mechanisms by which loop diuretics induce and exacerbate AKI.

Our study also confirmed that a higher loading dose of PMB is an independent risk factor for AKI, consistent with Chang et al.³ Prudent PMB dosing is therefore essential for patient safety.

A key contribution of this study is its focus on the timing of AKI onset and subsequent renal recovery—an area with limited existing data.^{20,31} We found that 41.1% of AKI patients achieved renal recovery after a median of 8 days. This rate is comparable to the 35% reported by Xia et al in elderly patients.²⁰

Multivariate analysis revealed that the use of vasoactive agents was associated with an increased risk of recovery failure. Commonly utilized vasoactive agents include norepinephrine, epinephrine, and vasopressin, which can adequate organ perfusion pressure in sepsis-related AKI.³² The association between vasoactive agent use and lower renal recovery is likely explained by confounding by indication. Patients requiring vasoactive agents typically present with profound septic or cardiogenic shock, which itself is a major driver of irreversible kidney injury. Therefore, vasoactive agent use should be interpreted as a marker of disease severity rather than a direct cause of recovery failure. Unresolved AKI significantly increases the risk of major renal adverse events, including the onset or progression of chronic kidney disease and the initiation of long-term dialysis.³³ Major renal adverse events are defined as the onset or progression of chronic kidney disease and initiation of long-term dialysis.^{33,34} Future larger prospective studies are essential to further explore renal function recovery in patients with PMB-associated AKI.

Several limitations should be noted. First, as a single-center retrospective study, we may have introduced selection bias. Second, other relevant factors influencing AKI development may not have been captured. Third, post-discharge renal function data were unavailable for some patients. Fourth, renal recovery was defined strictly as return to baseline creatinine; patients with partial recovery were not counted, which may have underestimated the true recovery rate. Fifth, AKI diagnosis relied solely on serum creatinine changes; urine output data were not consistently available, potentially leading to underestimation of AKI incidence, particularly in early stages. Larger multicenter prospective studies are needed to validate our findings.

Conclusion

In conclusion, independent risk factors for PMB-associated AKI included the use of vancomycin, aminoglycosides, amphotericin B, high-dose furosemide (>20 mg/day), and the loading dose of PMB. The median time to AKI onset was 7 days, highlighting the need for vigilant serum creatinine monitoring during the first week of therapy. Renal recovery occurred in 41.1% of AKI patients. The use of vasoactive agents was associated with lower recovery, likely reflecting underlying hemodynamic instability rather than a direct nephrotoxic effect. To optimize renal recovery, clinicians should minimize concurrent nephrotoxic agents where feasible, closely monitor serum creatinine within the first week of therapy, and prioritize rapid hemodynamic stabilization in patients with shock.

Data Sharing Statement

The datasets supporting the conclusions of this article are included within the article. Deidentified individual participant data will be provided. The data supporting this study are available from the corresponding author (Jian Qu, qujainstanley@1csu.edu.cn) upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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