Research Article

Risk Factors for Acute Kidney Injury in Patients Receiving Intravenous Colistin

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Abstract

Background: Colistin use is primarily associated with nephrotoxicity, which has been shown to be reversible with a low incidence of long-term kidney impairment. This study aimed to investigate the risk factors for acute kidney injury (AKI) in patients receiving intravenous colistin.

Methods: A retrospective cohort study was conducted at Nakornping Hospital in northern Thailand from 2015 to 2020. Adult patients who received intravenous colistin were included, while those with chronic kidney disease or prior renal replacement therapy were excluded. The study assessed potential AKI risk factors, including demographics, comorbidities, and concurrent use of medications. Cases of AKI are identified among the cohort, while the control group includes individuals not experiencing AKI during the follow-up but similar to the cases in terms of the exposure. Univariate and multivariable logistic regression analyses were performed to identify risk factors associated with AKI.

Results: Among the 206 patients included in the study, a majority were admitted to the intensive care unit, required mechanical ventilation, and experienced septic shock. Univariate analysis revealed diabetes (odd ratio (OR)=2.82, 95% CI: 1.21–6.59, p=0.016), malignancy (OR=2.06, 95% CI:1.12–3.77, p=0.020), and baseline Scr (OR=0.71, 95% CI: 0.51–0.99, p=0.048) as significant risk factors for AKI. Multivariate analysis confirmed the association of diabetes (adjusted odd ratio(aOR)= 3.09, 95% CI: 1.20–7.96, p=0.019), malignancy (aOR= 2.31, 95% CI: 1.18–4.52, p=0.015), septic shock (aOR = 2.80, 95% CI: 1.02–7.69, p=0.045), and vasopressor use (aOR = 2.85, 95% CI: 1.12–7.23, p=0.028) with an increased risk of AKI. Conversely, baseline Scr (aOR = 0.54, 95% CI: 0.36–0.82, p=0.004) were associated with a decreased risk of AKI. Other factors, including concomitant use of aminoglycosides, vancomycin, rifampin, combination therapy, nephrotoxins, hypertension, and intensive care unit admission, did not show significant associations.

Conclusion: This study identified diabetes, malignancy, septic shock, and vasopressor use as significant risk factors for AKI in patients receiving colistin. Baseline Scr levels were found to be inversely associated with the risk of AKI. These findings contribute to a better understanding of colistin-related nephrotoxicity and can guide clinical management to mitigate the risk of AKI in this patient population.

Introduction

The use of colistin has witnessed a significant increase in the twenty-first century, primarily driven by the emergence of gram-negative multidrug-resistant pathogens such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*.[1] Colistin, which has been reintroduced due to its efficacy and lower toxicity compared to earlier studies, has gained prominence in combating these drug-resistant pathogens.

The reduced toxicity observed in recent studies can be attributed to an improved understanding of colistin's pharmacokinetics and pharmacodynamics, as well as the implementation of dosage regimens that optimize effectiveness while minimizing harm. The average incidence of colistin-induced AKI has been observed to range between 20 and 60%.[2,3] This variation between studies could be related to the use of diverse definitions of AKI, the inclusion of different patient demographics,

and the use of a wide variety of colistin dose regimens.[2,3] Notably, the nephrotoxicity associated with colistin is reversible and rarely leads to long-term damage, with a small proportion of cases requiring renal replacement therapy or dialysis.[4] Despite this relatively moderate incidence of severe renal complications, there is a paucity of detailed studies investigating the specific risk factors associated with colistin-induced nephrotoxicity. Several colistin-related AKI risk factors have been identified, including underlying disease severity,[2] baseline renal function,[5,6] coadministration of nephrotoxic agents,[2,3,7] advanced age,[2,6] higher weight independent of dose,[3] chronic comorbidities such as hypertension, diabetes mellitus, chronic liver disease, and chronic obstructive pulmonary disease,[3,5,7] and a high Charlson Comorbidity index score (CCI score).[2]

Understanding these risk factors is crucial for identifying high-risk patients, optimizing treatment strategies, and minimizing potential harm. Therefore, the objective of this study is to contribute to the existing knowledge on colistin nephrotoxicity by exploring and identifying the risk factors associated with its occurrence. By shedding light on these risk factors, this study aims to enhance our understanding of colistin-induced nephrotoxicity and provide valuable insights for clinical decision-making.

Methods
Study population
A retrospective cohort study was performed on adult (≥18-year-old) patients who received intravenous colistin at Nakornping Hospital between January 2015 and December 2020. The Nakornping Hospital is a tertiary teaching hospital in northern Thailand. Patients were discovered through a search of medical charts and pharmacy databases. Patients were excluded if they were <18 years old, had received < 48 hours of colistin, had chronic kidney disease, or were receiving renal replacement therapy prior to receiving colistin. If a patient had repeated rounds of colistin, only the first one was studied. The current study was approved by the Nakornping Hospital's ethical committee for human research (093/65).

Sample size and selection of patients
A sample of 196 patients was calculated to determine 95% confidence intervals with a margin of ±7% around the assumed 50% incidence of AKI.[8-11] We excluded a total of 90 patients who had received colistin treatment, obtaining in a final sample size of 206 (Figure 1). These patients were divided into two groups based on their experience with AKI during colistin therapy, with the inclusion and exclusion criteria carefully defined to ensure the study's focus on the relevant patient population. The treatment group consists of patients who developed AKI, while the control group comprises those who did not experience AKI. The data collection methods were used to compare various patient characteristics between the two groups.

Data collection
The study collected comprehensive demographic and hospitalization-related data from all patients included in the analysis. This information encompassed patients' age, gender, and weight, providing a comprehensive overview of the study population. Additionally, comorbidities such as hypertension, diabetes, cardiovascular disease, cancer, chronic pulmonary disease, and chronic liver disease were recorded to assess their potential influence on the outcomes. The concurrent use of medications, specifically nephrotoxic medications, was also documented. This included aminoglycosides, furosemide, amphotericin B, and vancomycin, which are known to have nephrotoxic effects. The use of these medications was evaluated to determine any potential associations with the development of acute kidney injury. Data pertaining to sepsis were also collected, including the presence of septic shock or other types of shock, the requirement for invasive ventilation, the source of infection, and the administration of vasopressor drugs. These factors were taken into consideration as they are known to influence the risk of acute kidney injury in critically ill patients. Furthermore, detailed information regarding colistin usage was recorded, including the dosage, frequency of use per day, duration of use, and cumulative dose. These parameters were essential in evaluating the potential relationship between colistin administration and the development of acute kidney injury.

Outcome assessment
The primary outcome was to determine the occurrence of acute kidney injury (AKI) after the initiation of colistin treatment. AKI was defined and classified using the RIFLE criteria.[12] This consensus definition is termed the Risk/Injury/Failure/Loss/End-stage (RIFLE) criteria and the following categories were used: 'Risk' is the least severe category of AKI, followed by 'Injury', 'Failure', 'Loss' and 'End-stage renal disease'. Nephrotoxicity was counted if patients progressed through the stages of 'Injury', 'Failure,' 'Loss,' and 'End-stage renal disease' according to the RIFLE criteria.[12]
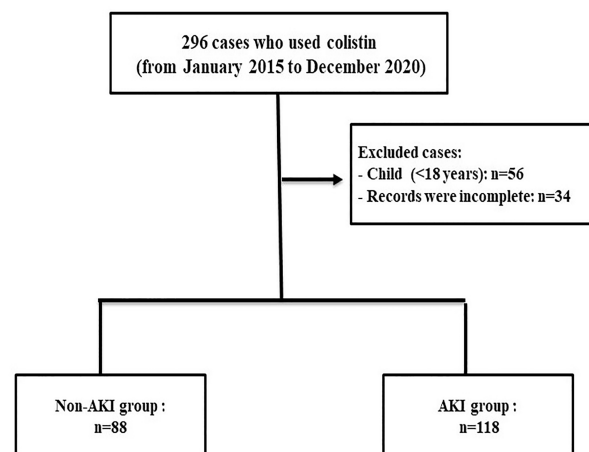

Figure 1. Flowchart of the study population.

Statistical analysis

To compare the main outcome differences of the study, descriptive statistics such as percentage, frequency, average, and standard deviation were utilized to characterize the general features and basic information of the patients. The Chi-square test was used to do an average comparison case of sample basic data. The averages of the other statistical approaches were computed using an independent T-test where the data were normally distributed and a Mann-Whitney U test when the data were not normally distributed, both with a significance level of 0.05.

Covariates with $p \leq 0.25$ in the univariate analysis and additional factors that indicated a trend toward association with outcomes were entered into the logistic regression multivariable model in a backward stepwise elimination to discover independent predictors of AKI in all patients. Finally, the entire model was decreased one element at a time until all remaining factors were statistically significant at a 5% significance level, regardless of their p-values. The logistic regression results were expressed as an adjusted odds ratio (aOR) and 95% confidence interval (CI). In cases where variables exhibit low frequency and wide confidence intervals, we will consider the use of exact logistic regression to address this issue and ensure more precise estimates. The Hosmer-Lemeshow (HL) goodness-of-fit test[13] was used to assess calibration, which determines how well a model fits the data. P-values that are closer to one are often associated with greater model fit.[14] Stata software, version 14 (Stata Corp, College Station, TX, USA), was used to analyze the data.

Results

General characteristics

The study included 206 patients who received colistin between the years 2015 and 2020 (Table 1). Among them, 61.17% were admitted to the intensive care unit, 67.48% required mechanical ventilation, and 33.98% experienced septic shock. The majority of patients had hypertension (40.29%) or cancer (33.98%). The average age was 65.41±15.85 years, with a higher proportion of females (53.40%). The most prevalent reasons for colistin usage were pneumonia (64.56%), followed by other infections (16.02%) and urinary tract infections (12.62%). Table 1 illustrates the baseline characteristics of the study participants. Table 2 presents the subgroup analysis of survival rates in patients with AKI, categorized according to the RIFLE criteria for each patient stage, in comparison to patients without AKI receiving colistin. The odds ratios indicate the likelihood of survival compared to the non-AKI group. The Injury and Failure groups had significantly lower odds of survival, with ORs of 0.44 and 0.43, respectively.

The Table 3 also shows the adjusted odds ratio (aOR) and p-value for the univariate and multivariate analysis, which takes into account the effects of other variables on the occurrence of acute kidney injury. The factors included in the table are vasopressor use, septic shock, ICU status, malignancy, hypertension, combination therapy, aminoglycoside use, vancomycin use, rifampin use, other nephrotoxins, and baseline serum creatinine (Scr) level.

Risk factors associated with acute kidney injury

Univariate analysis found that diabetes (OR = 2.82, 95% CI: 1.21–6.59, p = 0.016) and malignancy (OR = 2.06, 95% CI: 1.12–3.77, p = 0.020) were significantly associated with an increased risk of acute kidney injury but baseline Scr level is associated with a significantly decreased risk (OR=0.71, 95% CI: 0.51–0.99, p=0.048) (Table 3). However, multivariate analysis shows that patients with diabetes (adjusted OR (aOR) = 3.09, 95% CI: 1.20–7.96, p = 0.019), malignancy (aOR = 2.31, 95% CI: 1.18–4.52, p = 0.015), septic shock (aOR = 2.80, 95% CI: 1.02–7.69, p = 0.045) and vasopressor (aOR = 2.85, 95% CI: 1.12–7.23, p = 0.028) use were significantly associated with an increased risk of acute kidney injury while baseline serum creatinine (Scr) is associated with a significantly decreased risk (aOR=0.54, 95% CI: 0.36–0.82, p=0.004). Aminoglycoside use, vancomycin use, rifampin use, combination therapy and other nephrotoxins were not significantly associated with an increased risk of acute kidney injury (p > 0.05) (Tables 3 and 4). Hypertension and ICU status were also not significantly associated with an increased risk, although the OR for ICU status was relatively high (Table 3 and Figure 2). The obtained model in Figure 3 demonstrated a receiver operating characteristic curve (ROC curve) with an area under the curve (AUC) of 0.728. The Hosmer-Lemeshow test produced a nonsignificant P-value of 0.9201, indicating satisfactory calibration power.

Discussion

The present study aimed to investigate the risk factors associated with AKI in patients receiving colistin therapy. The results of the univariate analysis revealed that diabetes and malignancy were significantly associated with an increased risk of AKI, while baseline serum creatinine (Scr) level was associated with a decreased risk. However, the multivariate analysis demonstrated that diabetes, malignancy, septic shock, and vasopressor use remained as significant risk factors for AKI, while baseline Scr level continued to be associated with a decreased risk. Notably, the use of aminoglycosides, vancomycin, rifampin, combination therapy, and other nephrotoxins did not show a significant association with an increased risk of AKI. Hypertension and ICU status were also not significantly associated with an increased risk, although the odds ratio for ICU status was relatively high.

The results of this study identified several risk factors that were significantly associated with an increased risk of AKI. Diabetes and malignancy were found to be independent risk factors for colistin-induced nephrotoxicity. These findings are consistent with previous studies that have demonstrated the association between diabetes and nephrotoxicity.[15,16] The underlying mechanisms for this association may include impaired renal function and

Table 1. Demographic and clinical characteristics of patients with non-AKI group compared to AKI group.

Characteristics	Non-AKI group (n= 88)	AKI group (n= 118)	P-value
Sex, n (%)			
Male	41 (46.59)	55 (46.61)	0.998
Female	47 (53.41)	63 (53.39)	
Age, years, mean±SD	64.13± 17.00	66.35±14.93	0.321
Duration of hospitalization, days, mean±SD	37.14± 24.92	38.67± 24.92	0.697
Duration of treatment, days, mean±SD	8.43± 5.44	9.38± 5.84	0.232
Comorbidities*, n (%)	76 (86.36)	109 (92.37)	0.159
Hypertension	30 (34.09)	53 (44.92)	0.118
Cardiovascular disease	25 (28.41)	35 (29.66)	0.845
Diabetes mellitus	8 (9.09)	26 (22.03)	0.016
Chronic obstructive pulmonary disease	12 (13.64)	16 (13.56)	0.987
Malignancy	22 (25.00)	48 (40.68)	0.020
Chronic liver disease	4 (4.55)	8 (6.78)	0.498
ICU status	44 (50.00)	70 (59.32)	0.183
Septic shock	27 (30.68)	43 (36.44)	0.388
Mechanical ventilation	57 (64.77)	82 (69.49)	0.475
Charlson score, mean±SD	3.57±1.24	3.31±1.21	0.133
APACHE II score[a], mean±SD	12.28±4.11	12.81± 4.12	0.362
Baseline SCr, mg/dL, mean±SD	1.26±0.97	1.02±0.74	0.048
Baseline GFR, mL/min, mean±SD	60.82±41.29	70.09±41.97	0.116
Combination therapy*	40 (45.45)	44 (37.29)	0.239
Co-contaminants of nephrotoxic medications, n (%)			
Aminoglycosides	1 (1.14)	5 (4.24)	0.222
Diuretics	71 (80.68)	95 (80.51)	0.975
Amphotericin B	13 (14.77)	11 (9.40)	0.236
Vasopressors	44 (50.00)	70 (59.32)	0.184
Vancomycin	47 (53.41)	67 (56.78)	0.630
Rifampin	1(1.14)	3 (2.54)	0.481
Other nephrotoxins	8 (8.33)	6 (4.84)	0.292
Site of Gram-negative infection			
Pneumonia	58 (65.91)	75 (63.56)	0.727
Bacteraemia	5 (5.68)	9 (7.63)	0.583
UTI	11 (12.50)	15 (12.71)	0.964
Other	14 (15.91)	19 (16.10)	0.970

*Colistin plus carbapenem

Table 2. Subgroup analysis of survival rate in patients with AKI, according to the RIFLE criteria for each patient stage, compared to patients without AKI receiving colistin.

Severity outcome	Stage of AKI based on RIFLE criteria criteria	Number of patients n/N (%)	OR (95% CI)	P-value
	Non-AKI	54/88 (61.36)	1 (reference)	
Survival rate	Injury	17/41 (41.46)	0.44 (0.21-0.95)	0.036
	Failure	15/37 (40.54)	0.43 (0.20-0.94)	0.035
	Loss	21/40 (52.50)	0.70 (0.33-1.48)	0.346

increased susceptibility to drug-induced toxicity in patients with diabetes. Malignancy, on the other hand, can contribute to nephrotoxicity through various mechanisms, such as direct renal infiltration, paraneoplastic syndromes, or the effects of chemotherapy.[17] The presence of septic shock and the use of vasopressors were also identified as significant risk factors for AKI. Septic shock is known to be associated with renal dysfunction due to hemodynamic

Table 3. Univariate and multivariate logistic regression analysis of clinical factors associated with the occurrence of acute kidney injury.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	aOR (95% CI)	*P*-value
Diabetes	2.82 (1.21–6.59)	0.016	3.09 (1.20–7.96)	0.019
Septic shock	1.29 (0.72–2.33)	0.388	2.80 (1.02–7.69)	0.045
ICU status	1.46 (0.84–2.54)	0.183	3.44 (0.85–13.93)	0.083
Malignancy	2.06 (1.12–3.77)	0.020	2.31 (1.18–4.52)	0.015
Hypertension	1.57 (0.89–2.79)	0.118	1.84 (0.93–3.63)	0.078
Combination therapy*	0.71 (0.41–1.25)	0.239	0.59 (0.32–1.11)	0.105
Aminoglycosides	3.85 (0.44–33.55)	0.222	6.42 (0.58–71.28)	0.130
Vasopressors	1.46 (0.84–2.54)	0.184	2.85 (1.12–7.23)	0.028
Vancomycin	1.15 (0.66–1.99)	0.630	2.20 (0.83–5.839)	0.114
Rifampin	2.27 (0.23–22.19)	0.481	5.63 (0.43–74.16)	0.188
Other nephrotoxins	1.12 (0.90–1.39)	0.292	0.62 (0.35–1.09)	0.100
Baseline Scr	0.71 (0.51–0.99)	0.048	0.54 (0.36–0.82)	0.004

*Colistin plus carbapenem

alterations, endothelial dysfunction, and inflammatory responses.[18] Vasopressor use, which is commonly required in septic shock, can further exacerbate renal perfusion and contribute to nephrotoxicity.

The findings of this study are consistent with previous research conducted in different settings. Alotaibi *et al.*[15] conducted a retrospective study in a tertiary care hospital in Saudi Arabia and found that vasopressors were significant risk factors for colistin-induced nephrotoxicity. Moreover, Inci *et al.*[16] conducted a study in an adult ICU and identified chronic obstructive pulmonary disease, malignancy, and advanced age as risk factors for nephrotoxicity in colistin-treated patients. Özkarakaş *et al.*[17] evaluated the risk factors for colistin-associated nephrotoxicity and mortality in critically ill patients. They found that aging, hypoalbuminemia, and the use of vasopressors were risk factors for nephrotoxicity. Among these, the use of vasopressors had the highest positive predictive value. They also found that the use of vasopressors was the only significant risk factor for mortality in patients who developed nephrotoxicity. These findings highlight the importance of careful monitoring and management of vasopressor use in critically ill patients receiving colistin. These studies[15-19] collectively emphasize the importance of patient factors, such as comorbidities, age, and vasopressor use, in determining the risk of nephrotoxicity in colistin-treated patients.

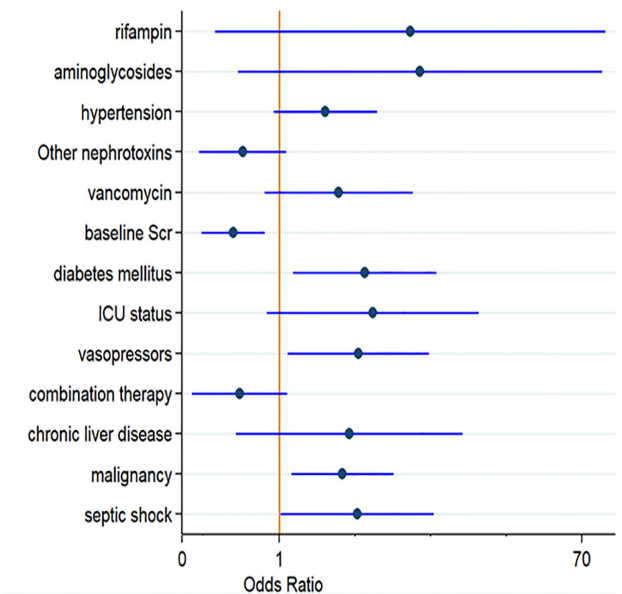The findings of this study have important clinical

Figure 2. illustrates the predictors associated with the development of acute kidney injury in patients receiving intravenous colistin.
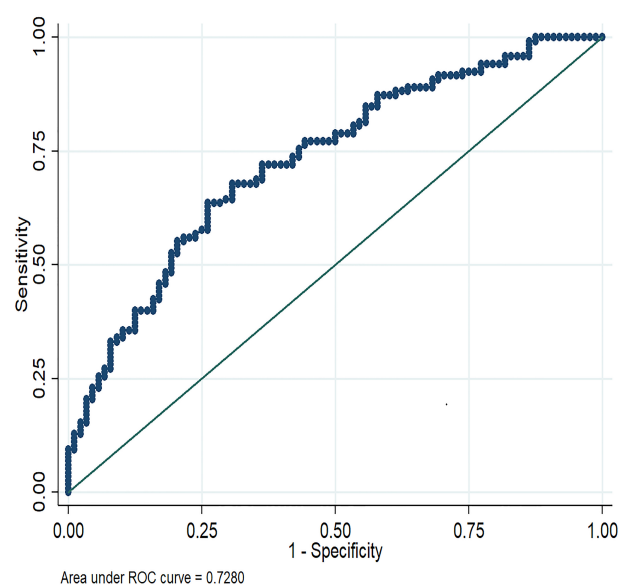

Figure 3. The generated model demonstrated a receiver operating characteristic curve (ROC) with an area under the curve (AUC) of 0.728.

Table 4. Univariate and multivariate exact logistic regression analysis of clinical factors associated with the occurrence of acute kidney injury.

Variable	Univariate exact analysis		Multivariate exact analysis	
	OR (95% CI)	*P*-value	aOR (95% CI)	*P*-value
Aminoglycosides	3.82 (0.42–184.13)	0.379	3.88 (0.42– 187.00)	0.369
Rifampin	2.26 (0.18–120.49)	0.855	2.34 (0.18– 124.54)	0.829

implications. Identifying diabetes, malignancy, septic shock, and vasopressor use as significant risk factors underscores the need for close monitoring and cautious use of colistin in patients with these conditions.

Interestingly, the study found that baseline serum creatinine (Scr) levels were associated with a decreased risk of AKI. This contradicts the common notion that pre-existing renal dysfunction is a risk factor for colistin-induced nephrotoxicity. However, it's important to note that baseline Scr levels may not accurately reflect underlying renal function, as they can be influenced by various factors such as hydration status and muscle mass.[20] Moreover, there are several limitations to utilizing levels of creatinine in the blood to estimate glomerular filtration rate, such as their influence on gender, age, nutrition, and body mass.[20]

Furthermore, the protective effect of a lower baseline Scr level highlights the importance of assessing renal function before initiating colistin therapy, particularly in patients with compromised renal function. Monitoring renal function throughout treatment and adjusting colistin dosages accordingly can help mitigate the risk of nephrotoxicity.

It is noteworthy that certain commonly used antibiotics and other nephrotoxins, including aminoglycosides, vancomycin, rifampin, combination therapy, and other nephrotoxins, were not found to be significant risk factors for AKI in this study. This finding contrasts with some previous studies[20,21] that have reported associations between these agents and nephrotoxicity. However, it is important to consider that the lack of significant associations in this study may be due to factors such as the relatively small sample size or differences in patient populations and treatment protocols. Further research with larger sample sizes and standardized protocols is necessary to confirm these findings and clarify the potential risk factors associated with nephrotoxicity in colistin-treated patients.

This study contributes to advancing the understanding of AKI risk factors during colistin therapy and has the potential to reshape clinical practices in the use of this important antibiotic. The identification of diabetes, malignancy, septic shock, and vasopressor use as significant risk factors for AKI during colistin therapy holds immediate clinical relevance. Contrary to established beliefs, the identification of lower baseline serum creatinine levels as a protective factor challenges the prevailing notion that pre-existing renal dysfunction significantly contributes to colistin-induced nephrotoxicity. These findings underscore the importance of tailored monitoring and cautious use of colistin in patients with these conditions, contributing

directly to the improvement of patient care.

Despite the valuable insights provided by this study, several major limitations preclude its practical application. Firstly, the study's specific setting raises concerns about the generalizability of the findings to broader populations or healthcare settings. The need for replication in diverse settings with larger sample sizes is essential to validate the results and ensure their broader relevance.

Secondly, the study's retrospective design introduces inherent limitations. Retrospective studies rely on medical records, which may contain gaps or inaccuracies that affect the data's reliability. Furthermore, the retrospective nature limits the ability to capture all relevant variables or potential confounding factors that could influence the observed associations.

Thirdly, the study primarily focuses on identifying risk factors for acute kidney injury (AKI) related to colistin therapy, but it doesn't delve into the underlying mechanisms or assess the impact of different colistin dosing regimens or treatment durations on nephrotoxicity. Additional research is necessary to clarify these mechanisms and optimize colistin treatment strategies.

Moreover, the study, despite its multivariate analysis, cannot completely rule out residual confounding. Unmeasured variables or factors not considered in the analysis may still contribute to the observed associations.

Additionally, the study relies on clinical criteria and serum creatinine levels to assess acute kidney injury. The inclusion of additional biomarkers or more sensitive diagnostic methods, such as urinary biomarkers or renal imaging, would provide a more comprehensive evaluation of kidney injury. Lastly, as with any observational study, the findings establish associations rather than causality. While the identified risk factors offer critical insights, further prospective studies or randomized controlled trials are needed to establish a causal relationship between colistin therapy and nephrotoxicity, accounting for potential confounders and mediating factors.

Despite these limitations, this study contributes to the existing body of knowledge on the risk factors associated with acute kidney injury in patients receiving colistin therapy. Further research with rigorous study designs and comprehensive assessments is warranted to address these limitations and enhance our understanding of nephrotoxicity in colistin-treated patients.

Conclusion

In conclusion, this study provides insights into the risk factors associated with AKI in patients receiving colistin

therapy. The identification of diabetes, malignancy, septic shock, and vasopressor use as significant risk factors highlights the importance of close monitoring and cautious use of colistin in patients with these conditions. The protective effect of a lower baseline Scr level emphasizes the importance of assessing renal function before initiating colistin therapy. Clinicians should carefully consider these risk factors and implement appropriate monitoring strategies to optimize patient management and minimize the risk of nephrotoxicity.

Ethical Issues
The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Nakornping Hospital (093/65).

Author Contributions
Wasan Katip: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing - Review & Editing. Peninnah Oberdorfer: Validation, Supervision. Puntapong Taruangsri: Data curation, Supervision. Teerapong Nampuan: Formal Analysis, Data Curation.

Conflict of Interest
The authors declare no conflict of interest.

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