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Research Article

Risk Factors for Mortality in Septic Children with Acute Kidney Injury in the Pediatric Intensive Care Unit

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Abstract

Acute Kidney Injury (AKI) and sepsis are major causes of morbidity and mortality in pediatric intensive care units (PICUs), especially when they occur concurrently. Despite advancements in critical care, the identification of risk factors remains essential to improve survival outcomes in children. To determine the risk factors associated with mortality in children diagnosed as sepsis with treated in the PICU. This was an observational analytic study with a case-control design, conducted in the PICU of Prof. Dr. I. G. N. G. Ngoerah Hospital from 2022 to 2024. Pediatric patients aged 1 month to <18 years with diagnoses of AKI and sepsis were included. Variables analyzed included nutritional status, duration of PICU stay, requirement of mechanical ventilation, involvement of a pediatric nephrologist, history of nephrotoxic drug use, and the number of nephrotoxic drugs used. Bivariate and multivariate analyses were performed using logistic regression. Total of 126 patients were analyzed. Bivariate analysis showed a significant relationship between mortality and the need for mechanical ventilation (OR 6.2; p 0.001) and the absence of pediatric nephrology care (OR 2.1; p = 0.047). In multivariate analysis, the need for mechanical ventilation (OR 16.5; 95% CI 3.5-77.2; p = 0.001) and pediatric nephrology care (OR 6.7; 95% CI 1.6-28.0; p = 0.009) were independently associated with mortality. The need for mechanical ventilation and the lack of pediatric nephrology consultation are significant risk factors for mortality in septic children with AKI treated in the PICU.

Keywords

Aki, Sepsis, Pediatric, Mortality, Picu, Risk Factors

1. Introduction

Acute Kidney Injury (AKI) is a sudden and reversible decline in kidney function, ranging from mild biochemical abnormalities to severe cases requiring renal replacement therapy (RRT). It is a common complication in critically ill children, with the AWARE study reporting AKI in 26.9% of PICU patients and severe AKI in 11.6% within the first 7 days. AKI is strongly associated with increased mortality and long-term risk of chronic kidney disease. Despite its clinical importance, no effective pharmacological therapy exists, highlighting the need for early identification of risk factors to improve outcomes.

In septic children with AKI, several clinical factors have

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been explored as contributors to mortality. Malnutrition compromises immune function and healing, increasing vulnerability to infection and sepsis, though studies show mixed results regarding its association with mortality. Mechanical ventilation and prolonged hospitalization have also been linked to poor outcomes, with some studies reporting significantly increased risk of death among ventilated AKI patients. Delayed pediatric nephrology consultation and the use of multiple nephrotoxic drugs have further been implicated in worsening renal outcomes and prognosis.

Given the rapid clinical deterioration seen in septic pediatric patients with AKI, identifying modifiable mortality risk factors is essential. This study aims to evaluate the role of nutritional status, duration of mechanical ventilation, length of PICU stay, pediatric nephrology consultation, and nephrotoxic drug exposure in influencing mortality among septic children with AKI at Prof. Dr. I. G. N. G. Ngoerah Hospital, Denpasar.

2. Materials and Methods

This study employs an analytical retrospective design with case-control approach to identify the correlation of risk factors in septic pediatric patient with AKI, in a tertiary referral hospital serving Eastern Indonesia. Secondary data were collected from septic pediatric patient with AKI treated at PICU ward of Prof. Dr. I. G. N. G. Ngoerah Hospital. The study was conducted from January 2022 to April 2024. The inclusion criteria consisted of children aged 0-18 years diagnosed as sepsis with AKI, while the exclusion criteria included children with incomplete medical records, children with congenital kidney disease, chronic kidney disease, urogenital diseases, kidney transplant, diagnosed with AKI prior to PICU admission, congenital or acquired heart disease, and multiple congenital anomaly.

AKI is defined as a sudden decline in kidney function, indicated by a decrease in the glomerular filtration rate (GFR) of at least 25% or a reduction in urine output to less than 0.5 ml/kg/hour for at least 8 hours. The severity of AKI is classified according to the pRIFLE criteria. Data were collected from medical records. The results were categorized as follows: (1) mild AKI (if classified as AKI risk), and (2) severe AKI (if classified as AKI injury, failure, loss, or end-stage). Sepsis is diagnosed based on the presence of infection and organ dysfunction. Data were also obtained from medical records.

Age was calculated as the difference between the date of AKI diagnosis and the patient's birthdate, recorded in months, and categorized into two groups: (1) ≤5 years and (2) >5 years. Gender was determined based on the patient's phenotype, recorded as male or female in the medical records. Acute malnutrition was assessed using weight-for-height (W/H) or weight-for-length (W/L) indices for children aged 0-60 months, and body mass index-for-age (BMI/A) for children aged 5-18 years. Acute malnutrition was defined as W/H or W/L < -2 SD for 0-60 months, and BMI/A < -2 SD for 5-18 years. Acute malnutrition was categorized as yes or no. Mechanical ventilation requirement was assessed based on the need for a ventilator during PICU admission. The duration of PICU stay was measured in days, categorized as <14 days or >14 days. Renal consultation was defined as cases where the patient was referred to pediatric nephrologist for AKI management. History of nephrotoxic drug use, including medications such as acyclovir, amikacin, and others, was assessed based on medical records, with a yes/no scale. The number of nephrotoxic drugs used was categorized as single or multiple medications.

This study was approved by the Research and Development Unit (Litbang) of Prof. Dr. I. G. N. G. Ngoerah Hospital with ethical protocol number 2682/UN14.2.2. V. 1/PT.01.01/2024 from the Ethics Committee of the Faculty of Medicine, Udayana University/ Prof. Dr. I. G. N. G. Ngoerah Hospital, and research permit number LB.02.01/XIV.2.2.2/40293/2022. Data were analyzed using the Statistical Product and Service Solution (SPSS) software version 25.0 for Windows. The proportion difference test compares mortality rates across categories of each independent variable. This analysis is conducted by creating a cross-tabulation, with the dependent variable in the table columns and the independent variables in the rows, presented as column percentages. Multiple logistic regression is used to assess clinical characteristics as risk factors for mortality, analyzing all risk factors simultaneously. The association is measured using odds ratios, with inference based on a 95% confidence interval and a p-value, where $p < 0.05$ is considered significant.

3. Results

The study was conducted in the PICU at RSUP Prof. dr. I G. N. G. Ngoerah, Denpasar, including subjects who met the inclusion and exclusion criteria from January 2022 to December 2024.

All eligible subjects underwent the study procedures. Total of 126 subjects were enrolled, with characteristics detailed in Table 1. The study involved pediatric sepsis patients with AKI aged 1 month to less than 18 years, with a median age of 9 months. The distribution of subjects by sex and AKI severity was nearly balanced.

Table 1. Characteristics of study subjects based on case-control groups.

Characteristics	Outcome	
	Death (n=63)	Survived (n=63)
Age (month), median (IQR)	9 (2-93)	9 (2,25-57)
Gender, n (%)		
Male	32 (50,8)	33 (52,4)
Female	31 (49,2)	30 (47,6)
AKI severity, n (%)		
Mild AKI	8 (12,7)	55 (87,3)
Severe AKI	55 (87,3)	8 (12,7)

Bivariate analysis of factors affecting mortality in septic children with AKI is shown in Table 2. Most subjects had acute malnutrition (53%), were treated in the PICU for less than 14 days (74.6%), required mechanical ventilation during PICU stay (60.3%), did not receive nephrology care (58.7%), and were administered nephrotoxic drugs during treatment (57.9%). Among those receiving nephrotoxic drugs, 72.6% received a single nephrotoxic agent.

Table 2. Distribution of risk factors based on case-control groups.

Characteristics	Outcome		RO	95% CI	p
	Death	Survived			
Acute malnutrition, n (%)					
Yes	37 (58,7)	29 (46,0)	2,0	0,8-3,3	0,154
No	26 (41,3)	34 (54,0)			
PICU care, n (%)					
≥ 14 days	18 (26,5)	12 (19,0)	1,7	0,7-3,9	0,209
< 14 days	45 (71,4)	51 (81,0)			
Ventilator requirement, n (%)					
Yes	50 (79,4)	24 (38,1)	6,2	2,8-13,8	0,001
No	13 (20,6)	39 (61,9)			
Nephrologist care, n (%)					
Yes	21 (33,3)	32 (50,8)	2,1	1,0-4,2	0,047
No	42 (66,7)	31 (49,2)			
History of nephrotoxic drugs administration, n (%)					
Yes	41 (65,1)	29 (46,0)	2,1	1,1-4,4	0,031
No	22 (34,9)	34 (54,0)			

The variable “number of nephrotoxic drugs” was excluded from multivariate analysis due to its high correlation with

"use of nephrotoxic drugs," which could cause multicollinearity, as seen in Table 3. Children with severe AKI, ventilator use, and lack of nephrology care had a significantly higher risk of mortality. AKI severity was the strongest risk factor in the model. Children with severe AKI had a 63.3 times greater risk of death compared to those with mild AKI.

Table 3. *Subgroup analysis.*

Characteristics	Outcome		RO	95% CI	P
	Death	Survived			
Nephrotoxic drugs types, n (%)					
Single drug	32 (78,0)	19 (65,5)	0,53	0,1-1,5	0,245
Multiple drugs	9 (22,0)	10 (34,5)			

Table 4. *Analysis of Mortality Risk Factors in Pediatric Sepsis Patients with AKI.*

Characteristics	Adjusted RO (exp B)	95% CI	p
Gender, n (%) Male Female	0,7	0,1-2,5	0,595
Age, n (%) ≤ 5 years old > 5 years old	0,5	0,1-2,2	0,380
AKI severity, n (%) Severe Mild	63,3	16,1-247,6	0,001
Acute malnutrition, n (%) Yes No	2,0	0,8-3,3	0,154
PICU care, n (%) ≥ 14 days < 14 days	1,7	0,7-3,9	0,209
Ventilator requirement, n (%) Yes No	6,2	2,8-13,8	0,001
Nephrologist care, n (%) No Yes	2,1	1,0-4,2	0,047
History of nephrotoxic drugs administration, n (%) Yes No	2,1	1,1-4,4	0,031

4. Discussion

Sepsis with AKI is a common condition in children admitted to the PICU and contributes to increased morbidity and mortality. This study involved subjects aged 1 month to less than 18 years diagnosed as sepsis with AKI treated in the PICU at RSUP Prof. Dr. IGNG Ngoerah, Denpasar. Our data showed higher mortality in children with severe AKI, age ≤ 5 years, acute malnutrition, PICU stay less than 14 days, ventilator use, no nephrologist care, exposure to nephrotoxic agents, and single nephrotoxic drug use.

Among six tested hypotheses, ventilator requirement and pediatric nephrologist consultation were significantly associated with mortality, while acute malnutrition, PICU duration, nephrotoxic drug history, and drug number were not statistically significant. Previous studies reported lower proportions of severe AKI and associated mortality risk, but our findings indicated a higher proportion of severe AKI in deceased children, linked to impaired kidney perfusion, systemic inflammation from sepsis, and nephrotoxic medication effects. [1].

In this study, AKI severity, age, and sex were identified as confounding variables and controlled in multivariate analysis to clarify the true relationship between risk factors and mortality. After adjustment, severe AKI remained significantly associated with higher mortality, consistent with previous literature. Ventilator use and nephrologist care also showed significant associations with mortality, highlighting their importance in managing sepsis with AKI. Although higher mortality was observed in children with acute malnutrition, shorter PICU stays, and nephrotoxic drug exposure, these factors did not reach statistical significance, suggesting possible influence from uncontrolled variables. Further research with larger samples or better variable control is needed to confirm these findings.

This study found no significant association between acute malnutrition and increased mortality in pediatric septic patients with AKI. Multivariate analysis showed that acute malnutrition did not significantly affect mortality (adjusted OR = 1.1, p = 0.823). Although malnutrition was more common in patients who died, after controlling for factors such as ventilator use and AKI severity, its impact on mortality was not statistically significant. This suggests that while acute malnutrition may worsen patient condition, other dominant factors influence mortality more strongly. Previous research shows mixed results, but this study supports the need to monitor and manage nutritional status in critically ill septic children with AKI. [2-4].

Malnutrition directly impairs the immune system by reducing lymphocyte, neutrophil, and macrophage function, weakening the body's ability to fight severe infections like sepsis and complications such as AKI. [5] It also reduces muscle mass and energy reserves, which are critical during sepsis and AKI to maintain homeostasis, increasing the risk of organ dysfunction and kidney failure. Furthermore, malnutrition compromises gut mucosal barriers, facilitating bacterial and endotoxin translocation that worsens systemic inflammation and sepsis. [6, 7] Although this study's results were not statistically significant, the higher mortality observed in malnourished children aligns with previous theories emphasizing malnutrition's detrimental role in critical illness outcomes. Variations in study populations and clinical factors may explain differing findings across regions, indicating a complex relationship that warrants further investigation.

This study found that most survivors had shorter PICU stays (less than 14 days), with 79.6% of survivors in this group compared to 29.2% of non-survivors. However, analysis showed no statistically significant correlation between PICU length of stay and mortality, indicating that duration of PICU stay did not directly influence mortality risk in septic children with AKI. Previous research by Rakhmawati et al similarly found no association between length of stay and mortality in pediatric AKI patients, possibly due to clinical and socio-economic factors unique to the population. [1] Longer PICU stays may not adequately reflect the main risk factors affecting mortality in this group. Some studies, however, such as Odetola et al, reported that longer stays were associated with greater severity and higher mortality, highlighting differing findings in other settings. [8].

The length of PICU stay may not directly represent treatment effectiveness or patient condition after hospitalization. Some patients may require longer stays for stabilization but still have good outcomes, while others with more severe illness might have shorter stays due to rapid deterioration. Sepsis along with AKI are complex conditions often involving multi-organ failure, and factors like intensive care quality, resource availability, and clinical management likely have a larger impact on outcomes. This complexity might explain why length of stay was not significantly linked to mortality in this study. Therefore, PICU duration alone is not a strong predictor of mortality in septic children with AKI.

Multivariate logistic regression analysis showed that ventilator use is a strong predictor of mortality in pediatric septic patients with AKI. Children requiring mechanical ventilation had a 16.5 times higher risk of death compared to those not on ventilators (adjusted OR 16.5; 95% CI: 3.5-77.2; p = 0.001), reflecting more severe illness such as respiratory failure, multiorgan dysfunction, or systemic complications [9]. Ventilators are typically used in cases of respiratory failure, ARDS, or severe septic shock, indicating a high severity of disease. The greater the severity, the higher the mortality risk, as multiple organs including lungs, heart, kidneys, and the central nervous system are often affected. [10] Ventilator use also increases the risk of nosocomial infections in immunocompromised patients, further raising the risk of secondary sepsis and death. [11].

These findings align with previous studies, such as Rusmawatiningtyas et al, which reported that 96.4% of PICU sepsis mortality was associated with mechanical ventilation, with significantly lower survival rates in ventilated patients

(HR 2.7, 95% CI 1.6-4.6, p < 0.001). [1] Similarly, Miklaszewska et al found that 92% of AKI patients in PICU required mechanical ventilation, correlating with increased mortality risk. [12] However, de Akker et al noted that while invasive mechanical ventilation increased AKI risk threefold, variations in ventilator settings (such as tidal volume and PEEP) did not affect this risk. [13] Overall, ventilator dependency in sepsis with AKI is a critical marker of poor prognosis.

The analysis showed that pediatric nephrology care is associated with reduced mortality in pediatric septic patients with AKI, with an adjusted odds ratio of 6.7 (95% CI: 2.72-21.05, p = 0.009). Patients who did not receive nephrology care had a significantly higher risk of death compared to those who did. This finding aligns with Pinheiro et al, who reported that nephrologist monitoring and management improve patient outcomes by reducing complications and mortality in AKI-sepsis cases. [14] Wu et al also demonstrated benefits of nephrology care in lowering congestive heart failure exacerbations and mortality among adults receiving acute dialysis. [15] Conversely, Rusmawatiningtyas et al found that absence of nephrology consultation correlated with increased mechanical ventilation use and mortality in AKI-sepsis patients. [1].

Further supporting this, Flannery et al noted that AKI-sepsis patients face higher mortality and long-term complications such as chronic kidney disease or need for renal replacement therapy, which appropriate nephrology care can help mitigate. [16] Pinheiro et al also found that more intensive nephrology care reduces mortality risk by improving complication management and decreasing ventilator dependency. [14] Early and focused nephrology intervention may lower the need for mechanical ventilation and improve survival in septic children with AKI, highlighting its critical role in patient management.

This study found that most patients who died (65.1%) had received nephrotoxic drugs, compared to 46% of survivors, while more survivors (54%) did not receive these drugs compared to non-survivors (34.9%). However, analysis showed no significant association between nephrotoxic drug use and increased mortality (adjusted OR 3.0; 95% CI: 0.8-10.3; p = 0.078). Although mortality was higher among patients with a history of nephrotoxic drug use, this may reflect the severity of illness since such drugs are often necessary to treat severe infections or critical conditions. These findings highlight the importance of close kidney function monitoring and careful risk-benefit evaluation when using nephrotoxic agents in this population.

The lack of significant association may be due to physicians balancing risks and benefits, timing of drug administration, and variation in drug types, doses, and durations—all factors not fully captured in this study. Prior research supports the link between nephrotoxic drugs and increased mortality or AKI severity in pediatric ICU patients. [14, 17, 18] However, Flannery et al suggest that while nephrotoxic drugs are related to AKI, their direct impact on sepsis mortality needs further exploration. [16] This underscores the need for ongoing research on the long-term effects of nephrotoxic agents and reinforces the critical role of monitoring to prevent complications and reduce mortality in sepsis and AKI management.

This study found no significant association between the use of one or more nephrotoxic drugs and increased mortality risk (OR 0.53, 95% CI: 0.1-1.5, p = 0.245). Although descriptively more patients who died had received a single nephrotoxic drug, there was no statistical evidence that using multiple nephrotoxic drugs directly increases mortality. This may be explained by physicians' rational risk-benefit considerations, where nephrotoxic drugs are used in critical conditions like sepsis to control severe infection and prevent organ dysfunction, potentially reducing mortality despite their renal risks. Moreover, the severity of the patient's condition likely plays a greater role in mortality than the number of nephrotoxic drugs used, emphasizing optimal management and appropriate drug selection to stabilize the patient.

Supporting studies show mixed findings: Almeida et al reported that multiple nephrotoxic drugs significantly increased AKI and mortality risk in PICU patients, especially with combinations like furosemide, vancomycin, acyclovir, and ganciclovir. [17] Pinheiro et al highlighted increased ventilator use and mortality in AKI-sepsis patients without nephrology monitoring, with nephrotoxic drug combinations contributing to AKI risk. [14] Totapally et al found higher AKI incidence and worse renal damage markers in patients on nephrotoxic drugs. [18] Despite potential risks, the use of multiple nephrotoxic agents may be justified if carefully indicated, closely monitored, and individualized with nephrology collaboration to maximize benefits and minimize harm in septic children with AKI.

5. Study Limitations

This study has several limitations that need to be considered when interpreting the results. First, the retrospective study design carries a risk of information bias due to reliance on secondary data from medical records. Errors in documentation or inconsistencies in data entry by healthcare personnel with varying backgrounds and experience may affect data quality. Since the data were collected from a past period, it was not possible to conduct training or standardization of medical record documentation directly, which potentially led to errors in data collection.

6. Conclusions

The need for mechanical ventilation and care without pediatric nephrology consultation are significantly associated with mortality in septic children with AKI treated in the PICU, whereas acute malnutrition, duration of PICU stay, history of nephrotoxic drug use, and the number of ne-

phrotoxic drugs are not associated with mortality in these patients.

Abbreviations

AKI	Acute Kidney Injury
ARS	Artificial Renal Support
BMI/A	Body Mass Index-for-Age
CI	Confidence Interval
GFR	Glomerular Filtration Rate
IQR	Interquartile Range
LOS	Length of Stay
OR	Odds Ratio
PICU	Pediatric Intensive Care Unit
pRIFLE	Pediatric Risk, Injury, Failure, Loss, and End-Stage Kidney Disease (Classification Criteria for AKI)
OR	Odds Ratio
SD	Standard Deviation
SPSS	Statistical Product and Service Solutions
WHO	World Health Organization

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Author Contributions

Putu Satya Pratiwi: Data curation, Formal Analysis, Investigation, Project administration, Resources, Software, Visualization, Writing – original draft

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Data Availability Statement

The data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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