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Original Article

# Predictors of mortality in children with acute kidney injury in intensive care unit

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## Abstract

***Background*** Acute kidney injury (AKI) can increase the morbidity and mortality in children admitted to the pediatric intensive care unit (PICU). Previous published studies have mostly been conducted in high-income countries. Evaluations of possible predictors of mortality in children with AKI in low- and middle-income countries have been limited, particularly in Indonesia.

***Objective*** To assess possible predictors of mortality in children with AKI in the PICU.

***Methods*** We conducted a retrospective cohort study at Dr. Sardjito Hospital, Yogyakarta. All children with AKI admitted to PICU for more than 24 hours from 2010 to 2016 were eligible and consecutively recruited into the study. Logistic regression analysis was used to identify independent predictors.

***Results*** Of the 152 children with AKI recruited, 119 died. In order to get a P value of <0.25, multivariate analysis was run to degree AKI, ventilator utilization, primary infection disease, multiple organ failure (MOF), and age. Multivariate analysis showed that ventilator use, severe AKI, and infection were independently associated with mortality in children with AKI, with odds ratios (OR) of 19.2 (95%CI 6.2 to 59.7; P<0.001), 8.6 (95%CI 2.7 to 27.6; P<0.001), and 0.2 (95%CI 0.1 to 0.8; P=0.02), respectively.

***Conclusion*** The use of mechanical ventilation and the presence of severe AKI are associated with mortality in children with AKI admitted to the PICU. Interestingly, the presence of infection might be a protective factor from mortality in such patients. **[Paediatr Indones. 2019;59:92-7; doi: http://dx.doi.org/10.14238/pi59.2.2019.92-7]**.

***Keyword:*** *predictor; death; acute kidney injury; PICU*

Acute kidney injury (AKI) might increase morbidity and mortality in children admitted to intensive care units. These critically ill children are often treated for sepsis using nephrotoxic drugs. Renal ischemia might be related to the development of AKI. The incidence of AKI in children varies from 16.7 to 50%, with a 32% mortality rate.[1]

Early detection of mortality predictors in children with AKI is important in order to improve outcomes. Previous studies have identified predictors of mortality in children with AKI, but studies conducted in children from low- and middle-income countries have been limited. An Indian study reported that age, infection, sepsis, shock, heart disease, mechanical ventilation, PRISM score, hypoxia, and coagulopathy were associated with mortality in children with AKI.[2]

To our knowledge, no studies have been published on the predictors of mortality in children

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with AKI treated in Indonesian PICUs, therefore, we aimed to identify such predictors in Dr. Sardjito Hospital, Yogyakarta, Indonesia.

## Methods

A retrospective cohort study was conducted to determine mortality predictors in children with AKI in the PICU. All severely ill children aged less than 18 years, diagnosed with AKI, admitted to the PICU at Dr. Sardjito Hospital, Yogyakarta, Indonesia for at least 24 hours in 2010-2016, and who met at least one of the risk, injury, failure, loss, end stage renal failure (RIFLE) criteria, were eligible for the study. The dependent variable was mortality. Independent variables, which were the potential predictors of mortality, were identified based on epidemiological and clinical parameters. These factors included a severe condition as determined by RIFLE criteria, age, gender, nutritional status, length of PICU stay, multi-organ failure, ventilator usage, and primary disease.

The RIFLE criteria were used to classify AKI severity, in which the condition was categorized into injury, failure, loss, or end-stage phase. Nutritional state was assessed using the WHO Z-score curve for children aged ≤5 years old or BMI-for-age for children aged >5 years old.[3] Malnutrition was defined as weight/height Z-scores or BMI-for-age of <-2SD or >+2SD. Multi-organ failure was defined as a state of two or more organ system failures (cardiovascular, respiratory, neurological, gastrointestinal, and hematological) characterized by worsening clinical and laboratory parameters. Primary disease was defined as the patient's major diagnosis recorded in the medical record. For complex conditions, we classified the primary disease based on what was written in the medical record by an intensivist who treated the patient as the main reason for PICU admission. Primary diseases were recorded as nominal data, using the following categories: (1) chronic, in which the primary diagnosis was a chronic disease, such as congenital heart disease or autoimmune disease (2) infection, in which the primary diagnosis was infectious disease, such as pneumonia, sepsis, or meningoencephalitis, and (3) malignancy, in which the primary diagnosis was hematological malignancy or solid tumor, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), retinoblastoma, osteosarcoma, neuroblastoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, nasopharyngeal carcinoma, rhabdomyosarcoma, histiocytosis, and nephroblastoma.[4] Data were analyzed using *SPSS 23* software. We used Chi-square bivariate analysis to determine the magnitude and strength of association between independent (predictors) and dependent (mortality) variables. Multivariate analysis was also conducted to determine predictors that were independently associated with mortality. For these analyses, all potential predictive factors were selected, including all variables found to be significant in the univariate analysis ($P<0.25$), and analyzed by multiple logistic regression. Multivariate analysis results are reported as odds ratios.[5]

Preliminary data collection was conducted by looking for ICD-10 code of N.17 (Acute Renal Failure) in patients' medical records starting in 2010. After 2013, data collection was conducted by looking for AKI diagnoses in patients' medical records. For each medical record with an N.17 diagnosis code, the RIFLE criteria were inspected. If the patient met the RIFLE criteria, they were included as research subjects. Patient identity and data were confidential; names and medical record numbers were not included in the study data and only the investigators knew the patient codes.

This study was approved by the Ethics Committee of Medical Research of the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada/ Dr. Sardjito Hospital, Yogyakarta prior to conducting the research.

## Results

A total of 2,630 children were treated in the PICU of Dr. Sardjito Hospital, Yogyakarta, Indonesia for a minimum of 24 hours from 2010 -2016. Among these patients, 152 were diagnosed with AKI according to medical records. Of the 152 children with AKI, 119 (78.3%) died. The baseline characteristics of all the AKI patients are presented in **Table 1**.

Of 10 possible predictors of mortality in children with AKI, the bivariate analysis identified 5 potentially significant associations including age, degree of severity, multi-organ failure, ventilator use,

**Table 1.** Characteristics of children with AKI

| Characteristics | Died (n = 119) | Survived (n = 33) |
|---|---|---|
| Median age, years (range) | 3 (0-17) | 8 (0-15) |
| Male, n (%) | 67 (56.3) | 22 |
| Nutritional status, n (%) | | |
| Well-nourished | 68 (57.1) | 21 |
| Malnourished | 29 (24.4) | 2 |
| Severely malnourished | 15 (12.6) | 0 |
| Excessively nourished | 7 (5.9) | 0 |
| AKI level, n (%) | | |
| Mild-to-moderate (risk) | 79 (66.4) | 8 |
| Severe (injury, failure, loss, end stage) | 40 (33.6) | 25 |
| Mean PICU length of stay (SD), days | 7.4 (6.4) | 7.06 (3.0) |
| <7 days PICU length of stay, n (%) | 74 (62.2) | 18 |

**Table 2**. Bivariate and multivariate analyses of predictors of mortality in children with AKI

| Predictors | Bivariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| Age | | | | |
| ≤ 5 years old | 1.87 (0.8 to 4.1) | 0.11 | 1.5 (0.5 to 4.4) | 0.50 |
| >5 years old | | | | |
| Gender | | | | |
| Male | 0.64 (0.3 to 1.4) | 0.28 | | |
| Female | | | | |
| Multi-organ failure | | | | |
| Yes | 3.39 (0.7 to 15.3) | 0.09 | 2.9 (0.5 to 17.4) | <0.001 |
| No | | | | |
| AKI severity level | | | | |
| Mild | | | | |
| Severe | 6.17 (2.5 to 14.9) | 0.00 | 8.6 (2.7 to 27.6) | <0.001 |
| Length of stay | | | | |
| < 7 days | | | | |
| ≥ 7 days | 0.73 (0.3 to 1.6) | 0.43 | | |
| Ventilator usage | | | | |
| Yes | 15 (6.0 to 37.4) | 0.001 | 19.2 (6.2 to 59.7) | <0.001 |
| No | | | | |
| Nutritional status | | | | |
| Well-nourished | | | | |
| Malnourished | 1.03 (0.5 to 2.3) | 0.94 | | |
| Primary disease | | | | |
| Infection | | | | |
| Yes | 0.40 (0.2 to 0.9) | 0.03 | 0.2 (0.1 to 0.8) | 0.02 |
| No | | | | |
| Malignancy | | | | |
| Yes | 0.83 (0.1 to 8.2) | 1.0 | | |
| No | | | | |
| Chronic disease | | | | |
| Yes | 0.67 (0.2 to 2.3) | 0.51 | | |
| No | | | | |

and lack of infectious primary disease. Multivariate analysis revealed that multi organ failure, the degree of severity, ventilator use, and lack of infection remained independently associated with mortality in children with AKI (**Table 2**).

## Discussion

Various criteria have been used to diagnose AKI. The amount of urine production, urinalysis data, blood urea nitrogen (BUN) level, and serum creatinine have been used as laboratory parameters, however, these examinations have low sensitivity and specificity.[1] A Denpasar, Indonesia study reported an incidence of 16.77% of AKI in the PICU, lower than in Cincinnati, Ohio, USA (30%-50%). In addition, a Puerto Rico study noted a 27.4% AKI incidence in the PICU within the first 72 hours of treatment.[1,6-8]

Some studies showed that severe AKI, as determined using pRIFLE criteria, is an indicator of poor prognosis. The Denpasar, Indonesia study found a 32% mortality rate due to AKI,[1] while a Brazilian study found a 24.6% mortality rate, 10 times higher than that of patients without AKI. The mortality rate in patients with various levels of AKI was 5 times higher than that in patients without AKI.[9] The risk of dying in patients with AKI was 10 times higher than in patients without AKI. Furthermore, a study in Spain also found 32.6% mortality due to AKI in the PICU.[10] Moreover, a study in a Brazilian PICU found that 82% of patients with AKI met pRIFLE classification with 15.1% mortality rate.[11]

In our study, the incidence of AKI varied and significantly increased after 2013. This observation might have been because the strict application of RIFLE criteria for diagnosing AKI started that year. The incidence of AKI in 2016 was 40%, which was consistent with previous studies that showed incidences of AKI in low- and middle-income countries (e.g., India, Jordan, and others) ranging from 1 to 58%,[10] and in high-income countries (e.g., USA, others) ranging from 5.4% to 30%.[1,12-15]

In our study, approximately three-quarters of children with AKI died. A Hong Kong study conducted in a PICU reported a mortality rate of 41%.[16] Cabral *et al.* in Portugal showed that severe AKI (injury and failure phases) had a mortality rate of 21% compared to other phases of AKI.[17] In addition, an Indian study found that the injury phase of AKI had the highest mortality (50%) compared to other phases.[13] The mortality rate in our study was higher compared to previously published studies, perhaps due to differences in patient characteristics, risks, types of treatment, and severity of illness.

In our study, more severe AKI was significantly associated with mortality. Multivariate analysis revealed that severe AKI increased mortality risk by 8.6 times compared to mild-to-moderate AKI. This result was consistent with a Jordanian study, which noted an OR of 6.3 (95%CI 5.6 to 7.4; $P<0.001$).[15] The failure phase of AKI upon PICU admission was reported to be an independent predictor of mortality in the PICU.[15] Also, the mortality rate of AKI patients in the injury and failure phases was twice as high compared to those in the risk phase.[18] The failure phase of AKI represents the most severe form of AKI, which might have been accompanied by severe organ dysfunction and reduced reversibility of health status. Similarly, Soler *et al.* found that the injury and failure phases of AKI, as well as length of stay, were related to morbidity and mortality.[8]

The majority of our patients used mechanical ventilation, which was associated with an increased risk of death by 19.2 times compared to those without ventilator use. This finding was comparable to studies conducted in Jordan, Hong Kong, Brazil and Taiwan, which noted that ventilator use was associated with 6.7 to 80 times higher mortality among children with AKI.[11,13,15,19] The use of endotracheal tubes and mechanical ventilation was associated with increased mortality due to alteration of bacterial colonies in the respiratory tract, aspiration of oropharyngeal secretions, or impaired clearance of lung secretions, all of which subsequently can lead to the development of ventilator-associated pneumonia.[20,21]

Infection was the most common primary disease in our subjects. However, multivariate analysis showed that infection was a protective against mortality in children with AKI. This result was inconsistent, as infections tend to worsen the condition of patients, subsequently leading to death.[17] As such, an explanation might be that our patients with acute infection had no chronic disease or they were in relatively good condition prior to being treated in the PICU, therefore, adequate treatment for acute

infection might HAVE resulted in good recovery or prognosis.

Multivariate analysis revealed no significant association between age and increased risk of death in AKI patients. However, previous studies noted that younger age was associated with mortality,[2,8,19] except for an indian study showed that age more than 5 years was a significant risk factor for severe AKI.[13] Differences of PICU patient characteristics may account for these discrepancies.[15]

No association was found between gender and increased risk of death, consistent with previously published studies.[2,8,18] About half of our AKI patients had wellnourished, nonetheless, malnutrition was also not associated with an increased risk of mortality. Similarly, Imani *et al.* showed that nutrition was not associated with AKI (OR 1.8; 95%CI 1.2 to 2.7).[6] However, a Puerto Rican study found that low body weight was a predictor of AKI mortality.[8] These different results might be due to different characteristics of PICU patients, such as age, type of diseases, and morbidity.

Multivariate analysis also revealed no association between length of stay and increased risk of death, unlike previous studies where AKI increased the risk of longer hospitalization in PICU (OR 3.73; 95%CI 1.89 to -7.38),[8] and longer length of stay increased mortality, especially among those with multi-organ failure.[15]

In our study, multi-organ failure was associated with a three-fold increase in mortality in children with AKI. This finding was in general agreement with a previous study, which stated that children with AKI who developed multi-organ failure had a survival rate of 43% (6/14).[22] Multi-organ failure also served as an independent risk factor of AKI mortality in the PICU (OR 3.21; 95%CI 2.08 to 4.94).[2] In addition, multi-organ failure increased mortality risk by 10-57%.[23] As such, multi-organ failure was a significant variable for the development of severe AKI.[8,13]

To our knowledge, this study was the first from Indonesia to report on predictors of mortality in children with AKI who were admitted to the PICU. Our findings might provide guidelines to prevent mortality in this population. However, there were some limitations to this study. We used a retrospective cohort design to collect data from medical records, in which information bias might have occurred. A selection bias could also occur due to the fact that only patients diagnosed with AKI based on medical records were included in the study.

In conclusion, ventilator usage, severe AKI, multi-organ failure, and lack of infection are associated with mortality in severely ill children with AKI. Our findings suggest that early diagnosis of AKI and identification of those particular mortality predictors in children admitted to the PICU might reduce mortality rates and give better outcomes.

## Conflict of Interest

None declared.

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