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Renal angina index in pediatric septic patients as a predictor of acute kidney injury in remote area

Nugroho Setia Budi, Bambang Pujo Semedi, Arie Utariani, Ninik Asmaningsih

Abstract

***Background*: One of the most common sepsis comorbidities is severe acute kidney injury (AKI), which occurs in about 20% of pediatric patients with severe sepsis and is independently associated with poor outcomes. Many studies have shown the ability of renal angina index (RAI) with a cut-off point of 8 to predict the risk of AKI grade 2 and 3, but with varying sensitivity and specificity. Therefore, this study aims to identify a RAI cut-off point to predict the incidence of AKI in pediatric septic patients in the setting of a regional hospital in Indonesia.**

***Methods*: An observational analytic study with a prospective longitudinal design was conducted on 30 pediatric patients in the Resuscitation Room of Dr. Soetomo General Hospital Surabaya. Patients who met the inclusion criteria were given 1-hour standardized resuscitation, then were observed. Every action taken to the patient was recorded, fluid input and output were measured, and mechanical ventilation and vasopressor administration were documented until the third day to determine factors influencing the incidence of AKI.**

***Results*: In this study, 56.7% of pediatric septic patients had AKI. The Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score in this study had a median of 11, in accordance with the pediatric sepsis guideline. RAI, with a cut-off point of 8 as a predictor for AKI grade 2-3, had a sensitivity of 100% and a specificity of 68% (area under the curve [AUC]=0.912). In terms of AKI risk tranche, the majority of patients (93.1%) had mechanical ventilation, while in terms of AKI injury tranche, the majority met the fluid overload criteria (79.3%).**

***Conclusion*: RAI, with a cut-off point of 8, can be used as a predictor for severe AKI in pediatric septic patients.**

Key words: Pediatric sepsis, acute kidney injury, renal angina index.

From Department of Anesthesiology and Intensive Therapy, Faculty of Medicine Airlangga University, Dr. Soetomo General Academic Hospital Surabaya, Indonesia (Nugroho Setia Budi, Bambang Pujo Semedi, Arie Utariani) and Department of Paediatric, Faculty of Medicine Airlangga University, Dr. Soetomo General Academic Hospital Surabaya, Indonesia (Ninik Asmaningsih).

Address for correspondence:
Arie Utariani
Department of Anesthesiology and Intensive Therapy, Faculty of Medicine - Dr. Soetomo General Academic Hospital, Airlangga University Surabaya
Mayjend Prof. Dr. Moestopo Street No. 6-8, Airlangga, Gubeng, Surabaya 60285, East Java, Indonesia
Tel: (+6231) 5501503, 5501504
Handphone: (+62) 8123306281
Email: arie.utariani@fk.unair.ac.id

Introduction

One of the most common severe sepsis comorbidities in global studies is severe acute kidney injury (AKI). Based on SPROUT study, which involved 128 pediatric intensive care units (PICU) in 26 countries, AKI was reported to occur in about 20% of pediatric patients who had severe sepsis (569 patients) and was independently correlated with poor outcome. (1,2) Sepsis-associated acute kidney injury commonly occurs within 24 hours after admission to PICU. (3)

Prompt recognition of AKI is hampered by classic functional markers such as serum creatinine and urine output, in which abnormalities of either is a late sign of the injury. (4) AKI severity is marked by the increase of serum creatinine (SCr) and AKI stratification based on urine output (UOP) is corre-

lated with mortality incidence. (5) Moreover, a small increase of SCr (0.3 mg/dl) reflects significant kidney damage and is associated with poor outcome. (6)

Limitation of SCr for accurate and real-time AKI diagnosis has prevented prompt therapeutic interventions. (7) The incidence of AKI in pediatric patient, within the first 48 hours, had the highest risk of having poor clinical outcomes, including prolonged hospital stay, need for renal replacement therapy (RRT), and death. (8) Identifying patients at risk of severe and prolonged AKI in PICU, is very important because risk stratification enables AKI assessments to encourage prompt therapeutic interventions, improve predictive performance and cost-effectiveness. It can also help clinicians to optimize resuscitation time and supportive therapy. (9) Therefore, an index to predict the occurrence of acute kidney injury, called the renal angina index (RAI), was created.

RAI is made to stratify patient's risks of having AKI and early signs of renal impairment. A RAI value ≥8 was reported to be able to predict the occurrence of severe AKI on the third day better than Kidney Disease : Improving Global Outcomes (KDIGO)'s evaluation. (10) Another study also found that RAI had superior sensitivity compared to serum biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), matrix metalloproteinase-8 (MMP-8), and elastase-2. (4) RAI consists of two factors, namely risk and injury, as is ilustrated in **Figure 1**. Injury factors consist of an increase in serum creatinine and fluid overload accumulation whose value is shown in **Figure 1**. (4) Therefore, this research aimed to study RAI according to the settings that can be used in remote regional hospitals in Indonesia.

Material and methods

Study design and setting

This research was a prospective observational study, the data was processed analytically, and an association test was conducted. We evaluated each pediatric patient who admitted to the Resuscitation Room of Dr. Soetomo General Hospital from October to December 2019. The Resuscitation Room only accepts blue coded patients based on Canadian Triage Criteria. Ethics Section Dr. Soetomo General Hospital has granted an approval for this research. Risk factors were assessed during triage and patients were considered for transfer to intensive care unit after stabilized in the Resuscitation Room. Injury factor criteria for an increase in serum creatinine was assessed on the following day due to the hospital's protocol that on the second day each intensive care unit patient has to be checked the routine blood tests such as complete blood, electrolytes, blood sugar, and serum creatinine. On the third day and the following days, only necessary examinations were done. Criteria for injury fluid overload were not directly measured after patients' stabilization, because some patients were not immediately transferred to the intensive care unit due to limited space. Therefore, fluid overload assessment, which should be assessed when the patient had stabilized and transferred into the intensive care unit, was carried out at 12 hours after admission to the Resuscitation Room. Twelve hours after Resuscitation Room admission, patient was considered to be stable, then 12 hours was considered as the point zero from fluid overload assessment as ilustrated in **Figure 2**. Meanwhile, to measure serum creatinine increase, patient's lowest serum creatinine results during the last three months before hospital admission were selected (4) and compared to the serum creatinine levels measured in the next day to determine the RAI score.

Participant selection criteria

Inclusion criteria included: 1) age three months to 18 years, 2) Pediatric Logistic Organ Dysfunction-2 (PELOD-2) scores of more than seven according to the Consensus on Sepsis Management in Pediatrics, (11) 3) no history of kidney disease.

Patients received a standard protocol for pediatric sepsis management. Documentations included: 72 hours fluid balance, inotropic drugs and vasopressors, ventilator use, and laboratory values during follow-up.

Exclusion criteria in this study were: 1) history of previous heart disease, 2) malignancy.

Exposure and outcome

Patients admitted to the Resuscitation Room were sorted for suspected sepsis from the physical examination. After that, intubation was performed if there was respiratory failure or shock. Then, an assessment of risk factors from RAI was obtained, such as: admission to intensive care (patients treated in Resuscitation Rooms were intensive care patients), patients with a history of transplants, and patients using ventilators or inotropic. Afterwards, the injury factor of the patient was determined by calculating fluid overload starting from 12 hours after the patient was resuscitated for up to 24 hours. Patient's serum creatinine increase was obtained within 24 hours and the highest value was selected. Patients were then followed and evaluated for grade 2 and 3 AKI according to KDIGO criteria.

Statistical analysis

Statistical analysis was performed using SPSS statistics software version 25. Continuous variables were expressed by median (interquartile range) and compared using Mann-Whitney test. Categorical variables were expressed using absolute values and proportions (%) and compared using the chi-square or Fisher's exact test. Descriptive assessment was carried out. RAI's diagnostic ability to predict the occurrence of grade 2 and 3 AKI was calculated using the receiver operator characteristic (ROC) curve, and the cut-off value was calculated to achieve the best sensitivity and specificity.

Results

From 30 pediatric patients with sepsis in Dr. Soetomo General Hospital, who were admitted into this study, the incidence of severe AKI was 16.7%. Patients' demographic, early assessment, therapy characteristic, and outcome are presented in **Table 1**. There was a statistically insignificant difference in diuretic administration between patients with mild and severe AKI (p=0.023).

Majority of the patients admitted in this study met the criteria of a decrease in creatinine clearance with a significant p value (p<0.001) (**Table 2**). Even in patients who met both criteria, decreased creatinine clearance criteria also dominated.

In terms of AKI risk tranche, all patients were admitted to PICU and majority were in mechanical vetilation, but none of them underwent transplantation (**Table 3**). While in terms of AKI injury tranche, patients who met both criteria were dominating over patients with decreased creatinine clearance criteria and only fluid overload criteria (**Table 4**).

This study performed an ROC curve to determine area under the curve (AUC) for RAI with a cut-off value of 8 as a predictor for AKI in pediatric sepsis patients (**Table 5**). The analysis obtained significant p value for AKI grade 1, 2, and 3 (p=0.008), and AKI grade 2 and 3 (p=0.004). AUC for predicting AKI grade 2-3 was higher than AKI grade 1-3. Meanwhile, it turned out that RAI as a predictor for AKI grade 3 did not has a significant p value.

A binary logistic analysis was performed to determine the capabilities of RAI with cut-off 8 as an AKI predictor. **Table 6** shows that RAI with cut-off 8 only can significantly predict severe AKI with OR of 1.179.

This study also performed an ROC curve to determine AUC for KDIGO as a predictor for AKI in pediatric sepsis patients, but the result was not statistically significant (p>0.05) (**Table 7**).

Furthermore, this study found that an RAI with a cut-off value of 8 has a sensitivity of 100% and specificity of 68% to predict severe AKI in pediatric sepsis patients (**Table 8**).

Discussion

RAI is one of the tools to determine whether pediatric septic patients will experience severe AKI. Sepsis itself is a severe comorbidity, but the presence of AKI increases mortality rate even more. (12) With this predicting tool, clinicians are expected to be more aware of the patient's condition during the treatment.

In this study, all of the patients included were having high Pediatric Risk of Mortality-3 (PRISM-3) score, which meant that they had high disease severity and mortality rate, as shown in **Table 1**. (13) On the other hand, a previous study by Basu, et al demonstrated lower median PRISM-3 score compared to median PRISM-3 score on this study. (10)

In this study, risk factor from RAI that was mostly experienced by patients was admission to PICU, followed by the use of ventilators and inotropic agents, which corresponded to a study by Basu, et al. (10)

The proportion of patients with mild AKI and severe AKI in this study was similar to the global research of AKI as a predictor of pediatric sepsis by Fitzgerald, et al, in which the incidence of severe AKI was 21%. (14)

The median age of the patients who experienced severe AKI was 12 months, which was younger compared to the patients with mild AKI with the median age of 14 months. This study was different from a global study where the patients with mild AKI had an average age of 3 years and the patients with severe AKI had an average age of 5 years. (14) However, the discrepancy can be explained because patients aged less than one year old are more prone to get infections, sepsis and even septic shock. (15) A study by Hanson, et al demonstrated that the median age of patients who experienced AKI was significantly younger than the patients without AKI. (16)

Male gender dominated most patients in this study, and it corresponded to global studies where the frequency of male children was higher than female ones. (1,2)

The median PELOD-2 score and lactate on admission in this study showed higher values in patients with severe AKI than in mild AKI as in the study by Fitzgerald, et al even though the p value was not significant. (14)

The duration of ventilator use in pediatric septic patients with severe AKI were longer than patients

with mild AKI. This result was also related to the length of ventilator-free days, in which the patients with mild AKI had a median of 11 days free of the ventilator while the patients with severe AKI had a median of 0 day. Moreover, this condition was almost the same as the results reported by global research where the length of the ventilator-free days was longer in pediatric septic patients with mild AKI than those who experienced severe AKI. (1,16)

Mortality in pediatric septic patients with severe AKI was higher than in patients with mild AKI. Mortality in a study by Fitzgerald, et al also showed the same results where mortality in pediatric septic patients with severe AKI was three times greater than patients with mild AKI (64% vs 20%, p=<0.001). (1)

The results of this study with the cut-off point 8 had the highest AUC than other studies, (10,17) and regarding other sample study characteristics, this study had similar sample characteristic with the Montreal Children's Hospital (MCH) retro validation study. (17)

Conclusion

In this prospective observational study, we found that the use of RAI as a predictor for the occurrence of severe AKI on pediatric septic patients was reliable compared to using serum creatinine increase based on KDIGO criteria.

Study limitations

RAI score in this study was addressed to determine the occurrence of severe AKI. However, RAI was able to distinguish between AKI and non-AKI significantly with AUC-ROC, as shown in **Table 5**. On the other hand, we chose the use of RAI as a determinant for the occurrence of severe AKI because the AUC-ROC was highest in the event of severe AKI than AKI alone. Moreover, the cut-off point for the occurrence of AKI and severe AKI was the same. Furthermore, other studies are still needed in determining the benefit of RAI as a tool to predict the event of severe AKI. (10,17)

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Table 1. Patients' demographic, early assessment, therapy characteristic, and outcome

	Mild AKI (n=25)	Severe AKI (n=5)	p value
Demographic			
- Age (months)	14 (5-86)	12 (3-38)	0.759*
• 3 months-1 yo	11 (36.7)	3 (10)	0.710***
• 1-5 yo	12 (40)	2 (6.7)	
• 5-10 yo	2 (6.7)	0 (0)	
- Male	17 (68)	4 (80)	0.521**
- PELOD-2 score	11 (7-17)	14 (9-17)	0.179*
- PRISM-3	19 (7-33)	23 (13-35)	0.189*
- Early lactate level	1.85 (0.64-7.6)	3 (0.8-4.6)	0.867*
Early assessment			
- Pneumonia	9 (36)	2 (40)	1.000**
- Shock	14 (56)	2 (40)	0.642**
- Meningo/encephalitis	12 (40)	4 (13.3)	0.336**
- Gastroenteritis/diarrhea	18 (72)	3 (60)	0.622**
Therapy characteristic			
- Ventilator	23 (92)	5 (100)	1.000**
- Fluid resuscitation	22 (88)	5 (100)	1.000**
- Inotropic	9 (36)	4 (80)	0.138**
- Diuretic	0 (0)	2 (40)	0.023**
Outcome			
- MV usage (days)	4 (0-34)	5 (1-32)	0.236*
- MV free (days)	11 (0-27)	0 (0-75)	0.176*
- PICU LOS (days)	4 (2-34)	5 (1.5-32)	0.955*
- Total LOS (days)	12 (2-37)	8 (1.5-32)	0.468*
- Mortality	8 (32)	4 (80)	0.128**

Legend: AKI=acute kidney injury; PELOD-2=Pediatric Logistic Organ Dysfunction-2; PRISM-3=Pediatric Risk of Mortality-3; MV=mechanical ventilation; PICU=non-cardiac pediatric intensive care unit; LOS=length of stay.
*Mann-Whitney test; **Fischer's exact test; ***chi-square test. Age, PELOD-2 score, PRISM-3, early lactate level, MV usage, MV free, and LOS are expressed as median (interquartile range).

Table 2. Comparison of AKI diagnosis based on KDIGO criteria

AKI	n (%)	p value
Met decreased creatinine clearance criteria only	8 (47.1)	<0.001*
Met urine output criteria only	5 (29.4)	
Met both criteria	4 (23.5)	
- Decreased creatinine clearance criteria dominating	2 (11.8)	
- Urine output criteria dominating	1 (5.9)	
- Same score in both criteria	1 (5.9)	

Legend: AKI=acute kidney injury; KDIGO=Kidney Disease : Improving Global Outcomes. *chi-square test.

Table 3. AKI risk tranche according to RAI

AKI risk tranche	n (%)	Chosen, n (%)
PICU admission	30 (100)	1 (3.3)
Transplantation	0 (0)	0 (0)
Mechanical ventilation and inotropic	29 (96.7)	29 (96.7)

Legend: AKI=acute kidney injury; RAI=renal angina index; PICU=non-cardiac pediatric intensive care unit.

Table 4. AKI injury tranche according to RAI

AKI injury tranche	n (%)
Met decreased creatinine clearance criteria	11 (36.7)
Met fluid overload criteria	2 (6.7)
Met both criteria	17 (56.7)

Legend: AKI=acute kidney injury; RAI=renal angina index.

Table 5. AUC-ROC based on RAI

RAI 8	AUC	p value
Predict AKI grade 1, 2, 3	0.787 (0.625-0.949)	0.008
Predict AKI grade 2, 3	0.912 (0.791-1.000)	0.004
Predict AKI grade 3	0.802 (0.617-0.988)	0.090

Legend: AUC=area under the curve; ROC=receiver operator characteristic; RAI=renal angina index; AKI=acute kidney injury.

Table 6. Binary logistic analysis of RAI with cut-off 8

RAI 8	OR (CI 95%)	p value*
Predict AKI grade 1, 2, 3	1.394 (0.998-1.948)	0.051
Predict AKI grade 2, 3	1.179 (1.033-1.346)	0.015
Predict AKI grade 3	1.062 (0.975-1.157)	0.164

Legend: RAI=renal angina index; AKI=acute kidney injury; OR=odd ratio; CI=confidence interval.
*Regression binary logistic.

Table 7. AUC-ROC based on KDIGO

KDIGO 24	AUC	p value
Predict AKI grade 1, 2, 3	0.676 (0.485-0.868)	0.103
Predict AKI grade 2, 3	0.764 (0.482-1.000)	0.066
Predict AKI grade 3	0.562 (0.210-0.914)	0.730

Legend: AUC=area under the curve; ROC=receiver operator characteristic; KDIGO=Kidney Disease : Improving Global Outcomes; AKI=acute kidney injury.

Table 8. Comparison of sensitivity, specificity, PPV, NPV, and AUC of every study

	CCHMC sepsis 1 derivation (10)	MCH pro validation 1 (10)	MCH retro validation 2 (10)	CCHMC sepsis 2 validation 3 (10)	AWARE (13)	This study
Cut-off	8	8	8	8	8	8
RAI (+), n (%)	51 (35)	18 (15)	38 (35)	145 (68)	286 (18)	13 (43)
Severe AKI, n (%)	28 (19)	12 (10)	11 (10)	29 (13)	368 (23)	5 (17)
Sensitivity, % (95% CI)	75 (55-89)	58 (28-85)	91 (59-100)	93 (76-99)	67 (59-75)	100 (100-100)
Specificity, % (95% CI)	73 (68-81)	90 (82-95)	71 (61-80)	36 (33-37)	87 (85-88)	68 (50-86)
PPV, % (95% CI)	40 (27-55)	39 (17-64)	26 (13-43)	18 (15-19)	31 (28-35)	38 (12-65)
NPV, % (95% CI)	92 (85-97)	95 (89-98)	99 (92-100)	97 (90-99)	97 (96-97)	100 (100-100)
AUC	0.77	0.74	0.81	0.80	0.83	0.912

Legend: PPV=positive predictive value; NPV=negative predictive value; AUC=area under the curve; CCHMC=Cincinnati Children's Hospital Medical Center; MCH=Montreal Children's Hospital; pro=prospective; retro=retrospective; AWARE=Assessment of Worldwide Acute Kidney Injury and Epidemiology (a multicenter study of renal angina index); RAI (+)=renal angina index≥8; AKI=acute kidney injury; CI=confidence interval.

Figure 1. The renal angina index

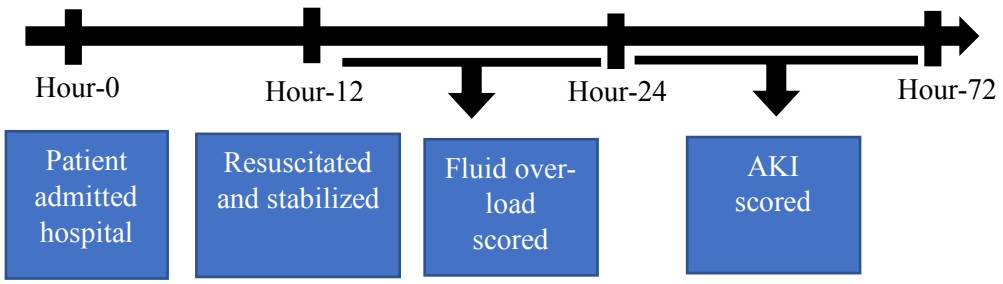
Risk criteria		Score
Admission to intensive care unit		1
Solid organ or stem-cell transplantation		3
Mechanical ventilation or vasoactive support or both		5
Injury criteria		
Serum creatinine relative to baseline	FO accumulation (%)	Score
Decrease or no change	<5	1
>1x-1.49x	5-10	2
1.5x-1.99x	11-15	4
≥2x	>15	8

Risk x injury

Scores: 1-40

Legend: FO=fluid overload.

Figure 2. Fluid calculation time line



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