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Renal Angina Index As A Predictor of Acute Kidney Injury Development in Critically Ill Children Admitted to Pediatric Critical Care Units: A Prospective Observational Study

Pediatrik Yoğun Bakım Ünitelerine Kabul Edilen Kritik Durumdaki Çocuklarda Akut Böbrek Hasarı Gelişiminin Öngörücüsü Olarak Renal Anjina İndeksi: Prospektif Gözlemsel Bir Çalışma

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Abstract

Introduction: Acute kidney injury (AKI) is a major cause of morbidity and mortality in critically ill children. The incidence of AKI is approximately 10%, with mortality of 11-40%. Traditional methods delay the diagnosis of AKI, and it is essential to combine clinical and laboratory parameters. Renal angina index (RAI) scoring aids in the early recognition of the risk of developing AKI. There are few studies on RAI in children; hence, the present study was undertaken. To determine the proportion of children with positive RAI who develop AKI on day 3. The secondary objective was to measure the association between positive RAI scores and short-term outcomes.

Methods: This hospital-based prospective observational study. All children who met the inclusion criteria and were admitted to the pediatric intensive care unit were included. RAI was calculated on day 0 and AKI development was monitored on day 3. An RAI score of 8 was considered positive.

Results: Of the 93 children, 26 were RAI-positive, among whom 21 (80.77%) developed AKI. The sensitivity of RAI in predicting the development of AKI on D3 was 65.38% [95% confidence interval (CI) 44.33-82.79%], specificity was 88.06% (95% CI 77.82-94.7%) and accuracy was 81.72%. A positive RAI score is independently associated with an increased need for mechanical ventilation and increased mortality.

Conclusion: The RAI score obtained upon admission is a simple yet reliable tool for predicting the development of severe AKI. Positive RAI is also an independent predictor of morbidity and mortality in critically ill children.

Keywords: Acute kidney injury, creatinine, critically ill children, mortality and morbidity

Öz

Giriş: Akut böbrek hasarı (ABH), kritik durumdaki çocuklarda önemli bir morbidite ve mortalite nedenidir. ABH sıklığı yaklaşık %10, mortalite oranı ise %11-40'tır. Geleneksel yöntemler ABH tanısını geciktirir ve klinik ve laboratuvar parametreleri birleştirmek esastır. Renal anjina indeksi (RAI) skorlaması, ABH gelişme riskinin erken tanınmasına yardımcı olur. Çocuklarda RAI ile ilgili az sayıda çalışma olduğu için bu çalışma yapılmıştır. RAI pozitif olan ve 3. günde ABH gelişen çocukların oranını belirlemek ve ikincil olarak da pozitif RAI skorları ile kısa vadeli sonuçlar arasındaki ilişkiyi ölçmek amaçlanmıştır.

Yöntemler: Bu çalışma hastane tabanlı ileriye yönelik gözlemsel bir çalışmadır. Dahil edilme ölçütlerini karşılayan ve çocuk yoğun bakım ünitesine kabul edilen tüm çocuklar çalışmaya dahil edildi. RAI 0. günde hesaplandı ve ABH gelişimi 3. günde izlendi. RAI skorunun 8 olması pozitif olarak kabul edildi.

Bulgular: Doksan üç çocuktan 26'sında RAI pozitifti ve bunların 21'inde (%80,77) ABH gelişti. D3'te ABH gelişimini öngörmede RAI'nın duyarlılığı %65,38 [%95 güven aralığı (CI) %44,33-82,79], özgüllüğü %88,06 (%95 CI %77,82-94,7) ve doğruluğu %81,72 idi. Pozitif bir RAI skoru bağımsız olarak mekanik ventilasyon ihtiyacının ve mortalitenin artmasıyla ilişkilidir.

Sonuç: Başvuru sırasında elde edilen RAI skoru, şiddetli ABH gelişimini öngörmek için basit ancak güvenilir bir araçtır. Pozitif RAI aynı zamanda kritik durumdaki çocuklarda morbidite ve mortalitenin bağımsız bir belirleyicisidir.

Anahtar Kelimeler: Akut böbrek hasarı, kreatinin, kritik hasta çocuklar, mortalite ve morbidite

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Introduction

The prevalence of acute kidney injury (AKI) among critically ill children is increasing. The reported incidence of AKI in pediatric intensive care units is 10%.[1,2] There is an incremental increase in the morbidity and mortality rates with an increase in the severity of AKI. Mortality from AKI is reported to range from 11-40%.[3-6] There is improvement in patient outcomes with early prediction of AKI.

AKI is defined as an abrupt loss of kidney function, leading to a rapid decline in the glomerular filtration rate (GFR). Over the last decade, various classification systems have been developed to define and assess AKI severity. The kidney disease improving global outcome (KDIGO) and pediatric risk injury failure loss of function criteria were the most widely accepted.

Traditionally, AKI was diagnosed based on elevated serum creatinine (SCr) levels. However, the levels of SCr remains normal, till most of the renal injury has occurred.[1,7,8] Also the values of SCr levels are affected by various factors, such as age, height, gender, body mass index, and hydration status.[9] To avoid delays in the recognition of AKI, combined clinical and laboratory parameters can help in the early prediction of the development and severity of AKI.

The renal angina model proposed by Goldstein and Chawala[10] provided risk stratification for the development of AKI in critically ill children. RAI was validated in children by Basu et al.[2] The renal angina index (RAI) combines risk factors (admission to intensive care unit, solid organ or stem cell transplantation, mechanical ventilation and use of inotropes) and early signs of loss of function (increase in SCr and extent of fluid accumulation).

The RAI is a simple and easy index of the onset of AKI in critically ill children and aids in the early detection of AKI, thereby allowing for timely intervention. This scoring system is particularly valuable in developing countries because of its minimal requirement for additional laboratory investigations. The RAI demonstrates greater discriminative accuracy than the traditional creatinine-based indicators of renal injury.

Materials and Methods

We conducted a prospective single-center observational study from August 2022 to August 2023. The study was approved by the Ethics Committee of the research. The study was conducted at the SDM College of Medical Sciences and Hospital, Dharwad, India (SDMIEC/2022/359) after obtaining informed consent from the parents or legal guardians of all participants.

Children aged between 1 month and 14 years who met the criteria for PICU admission (paediatrics index of mortality-3 criteria)[11] were included in the study. Children who had AKI stage 2 at the time of admission to the PICU, children who are known to have chronic kidney disease, and children with a duration of PICU stay of less than 72 hours were excluded from the study.

Children who met the inclusion criteria were enrolled in the study. All relevant data, including anthropometry, demographic parameters, admission diagnosis, comorbidities, vital signs, and other clinical and laboratory parameters, were recorded in a predesigned proforma.

Baseline SCr levels were calculated using Jefery's method on day 0 of admission (within 8 hours admission to PICU). Repeat SCr was performed on day 3, between 72 and 96 hours of admission to the PICU, to assess the severity of AKI. The RAI was determined for all enrolled subjects between 8 and 12 hours from the time of PICU admission on day 0.

The RAI was defined as the product of the risk group score and renal injury score.[2] RAI score given in Table 1. RAI score ranges from 1 to 40. The RAI was calculated by multiplying the risk and injury scores assigned (risk score × FO% score or risk score × GFR score), whichever was worse. The index RAI ≥8 was considered positive for renal angina positive (RA +) and a score of less than 8 considered as RA negative (RA-). Both groups were compared for primary outcome parameters, such as the development and severity of AKI, and risk factors for AKI development. The secondary outcome parameters were the duration of PICU stay, need for mechanical ventilation, development of acute respiratory distress syndrome (ARDS), and mortality. Fluid overload (FO) was calculated using the following formula:

FO = total intake (Lt) total output 100

Weight at admission to the PICU

Table 1. Renal angina index in children

Risk strata		
Risk criteria		**Score**
Admission to the ICU		1
Solid organ or stem cell transplantation		3
Mechanical ventilation or inotrope		5
Injury strata		
S creatinine level relative to baseline	**Fluid accumulation (%)**	
Decreased or unchanged	<5	1
>1-1.49*	5-10	2
1.5-1.99*	11-15	4
>2*	>15	8

ICU: Intensive care unit

All children were closely monitored for AKI development. The severity of AKI is defined using KDIGO staging.[12] According to KDIGO guidelines, AKI is defined as any of the following: An increase in SCr by 0.3 milligrams per deciliter (mg/dL) or more within 48 hours, an increase in SCr to 1.5 times the baseline within the last 7 days, or urine output less than 0.5 milliliters/kilogram/hour (mL/kg/h) for 6 hours. The AKI classification is shown in Table 2. Both the RA+ and RA groups were compared for the following outcome parameters: development of AKI and its severity. The RAI score was also co-correlated with risk factors for the development of AKI and short-term outcomes in these children in terms of duration of PICU stay, need for mechanical ventilation, development of ARDS, and mortality. Based on the KDIGO guidelines, stage 3 AKI is defined as an increase in SCr up to 3 times from baseline, a SCr level of >4.0 mg/dL (354 micromol/L), or the initiation of renal replacement therapy.

Statistical Analysis

All data were entered in Microsoft Excel version 2023 and analyzed using SPSS software version 23.0 for Windows (IBM Corp., Armonk, NY, USA). The categorial variables are presented as percentages, and the continuous variables are presented as the mean ± standard deviation (SD) or median. RAI score predictive ability was assessed by calculating sensitivity, specificity, positive predictive value, and negative predictive value. To predict the severity of AKI on day 3, receiver operating characteristic curves for day 0 RAI score and SCr were constructed. Other risk factors associated with AKI development were assessed using univariate and multivariate logistic regression. The categorical variables are presented as percentages. The numerical variables were compared using Student's t-test and the chi-square test. A p-value of 0.05 was considered statistically significant.

Results

As shown in Figure 1, out of the 125 children admitted to the PICU during the study period, 93 children who met the inclusion criteria were included in the study. Seven out of 125 children had elevated serum creatinine at admission, 12 children had PICU stay for less than 72 hours, 4 did not give consent for the study, day 3 serum creatinine was not measured in 4 children, and 5 who took discharge against medical advice were excluded from the study.

In present study 63.44% (n=59) were male. The majority of children aged less than 1 year (27.54%), as depicted in Figure 2. The mean age of the participants was 3.8 years (SD=4.05). The median height of the participants was 80 cm (QR=52) and median weight was 9 kg (QR=10.3).

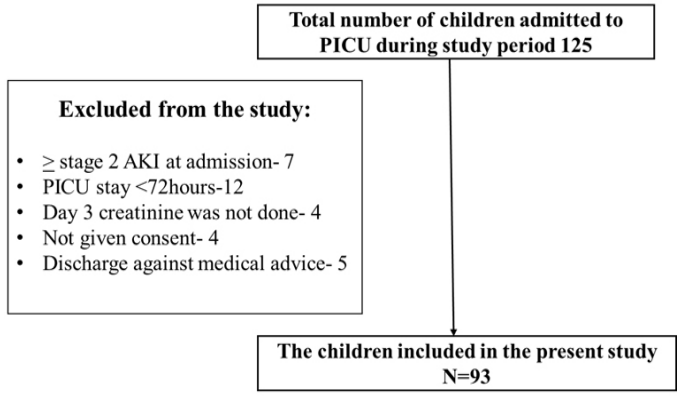

Figure 1. Flow chart of study participants
AKI: Acute kidney injury, PICU: Pediatric critical care unit

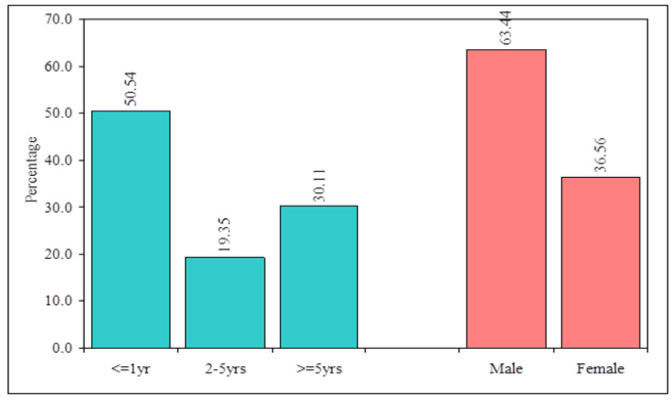

Figure 2. Demographic profile of the participants

Table 2. KDIGO staging of AKI in children

Stages	Serum creatinine	Urine output
Stage 1	1.5-1.9 times baseline Or >0.3 mg/dL increase	<0.5 mL/kg/hr for 6-12 hours
Stage 11	Increase >2-2.9 times baseline	<0.5 mL/kg/hr for >12 h
Stage 111	3.0 times the baseline Or >4 mg/dL initiation of renal replacement therapy in patients <18 hours, decrease in eGFR to <35 mL/min/1.73 m	<0.3 mL/kg/h for 24 hours or anuria for 12 hours

eGRF: Estimated glomerular filtration rate, AKI: Acute kidney injury, KDIGO: Kidney disease improving global outcome

In the present study, the prevalence of AKI was 22.58% (n=21). A positive RAI score was observed in 27.96% (n=26). Among children with positive RAI, 80.77% (n=21), 80.77% developed AKI. Of 72.04% (n=67), children were RAI negative, and none developed AKI. The association between positive RAI and AKI development is statically significant.

As shown in Table 3, the mean SCr level on day 0 was 0.40 and that on day 3 was 0.57; this difference in mean SCr was not statistically significant (p-value =0.1421).

Table 4 shows that RAI performed at the time of admission to predict the subsequent development of AKI on day 3 of admission had a specificity of 88.06%, sensitivity of 65.38%, and accuracy of 81.72%.

Figure 3 depicts the receiver operating characteristic curve constructed for assessing the individual values of day 0 RAI for predicting AKI on day 3, with an area under curve of 0.7672.

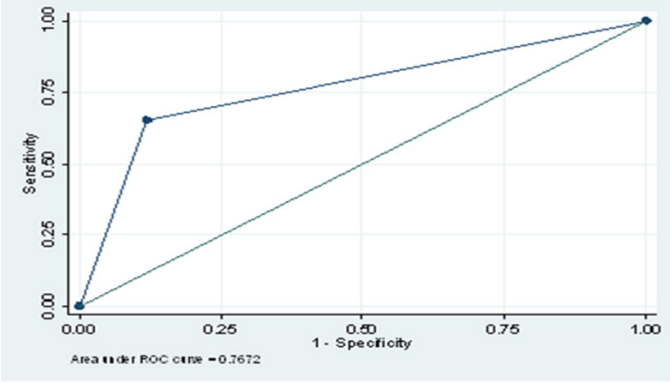

Figure 3. ROC curve for RAI and day 3 serum creatinine
RAI: Renal angina index, ROC: Receiver operating characteristic, area under curve =0.7672

Univariate regression analysis performed to evaluate the effect of individual parameters showed that the use of mechanical ventilation, inotrope, nephrotoxic drugs, presence of ARDS, and day 0 positive RAI score were significantly associated with the occurrence of severe AKI on day 3. Multivariate analysis showed that a positive day 0 RAI score was independently associated with the occurrence of Severe AKI on day 3, nephrotoxic drug usage, and need for mechanical ventilation, is show in Table 5.

Table 6 shows significant correlation between RAI score and elevated SCr level on day 3 and the development of AKI on day 3.

In the present study, the mortality rate was 23.6% (n=22). Among the 26 children who were RAI-positive, the mortality rate was 69.2% (n=18). The RAI was associated with increased mortality, and this association was statistically significant.

Discussion

The present study is a hospital-based prospective observational study. Results showed that a positive RAI obtained at admission was useful in predicting the development of AKI by day 3. RAI outperformed conventional baseline SCr level predicting AKI. The study, which included children with a similar range of disease severity (as accessed using PIM-3 score at admission), had a notably higher proportion of younger children in the RAI-positive group than in the RAI-negative group.

In the present study, 22.58% of children admitted to the PICU developed AKI on day 3 admission. Compared with previous studies done by Gawadia et al.[1], Basu et al.[2], Mehta et al.[13] and Naik et al.[4], the incidences of AKI were 70%, 13.6%,

Table 3. Compression of serum creatinine levels on days 0 and 3

Sr. Cr.	Mean	SD	Median	Quartile range
Sr. Cr. day 0	0.40	0.18	0.37	0.25*
Sr. Cr. 3	0.57	0.56	0.36	0.34*
Z-value	1.4680			
P-value	0.1421			

Data expressed as median (min-max), and mean, SD: Standard deviation, *Wilcoxon's matched-pair test

Table 4. Sensitivity, specificity, accuracy, and positive and negative predictive values of RAI

Statistic	Value	95% CI for OR
Sensitivity	65.38%	44.33% to 82.79%
Specificity	88.06%	77.82%-94.70%
Positive likelihood ratio	5.48	2.70 to 11.11
Negative likelihood ratio	0.39	0.23-0.67
Positive predictive value	68.00%	51.15%-81.18%
Negative predictive value	86.76%	79.33%-91.80%
Accuracy	81.72%	72.35% to 88.98%

CI: Confidence interval, OR: Odds ratio, RAI: Renal angina index

36.1%, and 90%, respectively. This variation in the incidence of AKI may be attributed to several factors, such as diagnosis at admission, presence of FO, use of nephrotoxic drugs, presence of sepsis, and MODS. The incidence of AKI increases with increasing severity of illness.

Severe AKI was observed in 80.77% of RAI-positive children. These study results are in line with the studies conducted by Gawadia et al.[1] and Menon et al.[14], where severe AKI was observed in 72% and 80% respectively. In present study, approximately 80% of children with positive RAI developed AKI on day 3 of admission. These results are in good agreement with the studies of Gawadia et al.[1] and Basu et al.[2] However, predictive value was lower in studies by Sethi et al.[16] and Kaur et al.[17] The predictive ability of RAI in the development of severe AKI on day 3 was AUC 0.76 with 95% confidence interval (CI) of 0.72-0.88, which was similar to the studies by Basu et al.[15] (AUC=0.86, with 95% CI of 0.75-0.86) and Sethi et al.[16] (AUC =0.73, 95% CI of 0.61-0.82).

In the present study, 26 children were RAI positive, among whom 10 (38.46%) developed ARDS, 24 (92.3%) required mechanical ventilation, and 18 (69.23%) required one or more inotropic supports. The study by Gawadia et al.[1] showed that among children with positive RAI, 71% required mechanical ventilation and 78% needed inotropic support. In another

Table 5. Association between individual parameters and positive RAI using univariate analysis

Factors	RAI <8	%	RAI ≥8	%	Total	%	Chi-square	p-value
Duration of stay								
<7 days	45	67.16	18	69.23	63	67.74	0.0370**	0.8480
≥7 days	22	32.84	8	30.77	30	32.26		
Sepsis								
Absent	46	68.66	14	53.85	60	64.52	1.7950**	0.1800
Present	21	31.34	12	46.15	33	35.48		
ARDS								
Absent	59	88.06	16	61.54	75	80.65	8.4410**	0.0040*
Present	8	11.94	10	38.46	18	19.35		
Nephrotoxic drugs								
No	25	37.31	4	15.38	29	31.18	4.1970**	0.0400*
Yes	42	62.69	22	84.62	64	68.82		
Inotropes								
No	57	85.07	8	30.77	65	69.89	26.2510**	0.0001*
Yes	10	14.93	18	69.23	28	30.11		
Mechanical ventilation								
No	49	73.13	2	7.69	51	54.84	32.3910**	0.0001*
Yes	18	26.87	24	92.31	42	45.16		
Stages of AKI								
Stage 0	67	100.0	5	19.23	72	77.42	69.8990**	0.0001*
Stage 1	0	0.00	21	80.77	21	22.58		
Mortality								
Recovered	63	94.03	8	30.77	71	76.34	41.5070**	0.0001*
Death	4	5.97	18	69.23	22	23.66		
Total	67	100.0	26	100.0	93	100.00		

**: Chi-square test, *: Independent t-test and p-value is <0.05, univariate regression analysis performed to evaluate the effect of individual parameters on positive AKI, AKI: Acute kidney injury, RAI: Renal angina index, ARDS: Acute respiratory distress syndrome

Table 6. Correlation between serum creatinine levels on days 0 and 3 and AKI stage with RAI

Variables	Correlation between RAI scores and			
	n	Spearman R	t-value	p-value
Serum creatinine level at day 0	93	0.0451***	0.4306	0.6678
Serum creatinine level on day 3	93	0.5751**	6.7059	0.0001*
Stage of AKI on day 3	93	0.7405**	10.5113**	0.0001*

***: Spearman's rank correlation,**: Student's t-test, *: Independent t-test, p-value <0.05 is taken as statistically significant, AKI: Acute kidney injury, RAI: Renal angina index

study by Menon et al.[14] showed 1.68% required mechanical ventilation, and 8.6% had a prolonged hospital stay among RAI-positive children.

The present study observed that there was increased mortality among RAI-positive children, accounting for 68.23% (p=0.0001). These results co-relate with the study by Gawadia et al.[1] and Menon et al.[14] where the mortality rates were 24% and 18.3% respectively.

In the present study, positive AKI was associated with increased severity of AKI on day 3. These children tended to have an increased incidence of ARDS, shock requiring inotropic support, need for mechanical ventilation, and increased mortality. Furthermore, logistic regression suggested that there was an independent association between positive RAI performed at admission, severity of AKI, increased need for mechanical ventilation, and mortality. These results are in parallel with those of Gawadia et al.[1] and Kaur et al.[17]

Study Limitations

The study should have included a large sample. Only short-term outcomes were analyzed; long-term follow-up of these children had not been done.

Conclusion

The RAI is a simple yet reliable predictor of the development of AKI in critically ill children. A positive RAI score emerges as a superior tool to help in the early reorganization of development AKI. This score is more useful in developing countries because it requires fewer investigations and can be easily applied in resource settings. The discriminative accuracy of RAI surpasses that of traditional creatinine-based renal injury parameters. Additionally, RAI has an independent predictive value for AKI severity, morbidity, and mortality in critically ill children.

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Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the research. The study was conducted at the SDM College of Medical Sciences and Hospital, Dharwad, India (SDMIEC/2022/359).

Informed Consent: Informed consent from the parents or legal guardians of all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.S., K.D.S., D.P., Concept: A.S., K.D.S., D.P., Design: A.S., K.D.S., D.P., Data Collection or Processing: A.S., K.D.S., D.P., Analysis or Interpretation: A.S., K.D.S., D.P., Literature Search: A.S., K.D.S., D.P., Writing: A.S., K.D.S., D.P.

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References

1. Gawadia J, Mishra K, Kumar M, Saikia D. Prediction of severe acute kidney injury using renal angina index in a pediatric intensive care unit. Indian Pediatr. 2019;56:647-52.
2. Basu RK, Zappitelli M, Brunner L, Wang Y, Wong HR, et al. Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children. Kidney Int. 2014;85:659-67.
3. Sadeghi-Bojd S, Noori NM, Mohammadi M, Teimouri A. Clinical characteristics and mortality risk prediction in children with acute kidney injury. Niger Med J J Niger Med Assoc. 2015;56:327-32.
4. Naik S, Sharma J, Yengkom R, Kalrao V, Mulay A. Acute kidney injury in critically ill children: Risk factors and outcomes. Indian J Crit Care Med Peer-Rev Off Publ Indian Soc Crit Care Med. 2014;18:129-33.
5. Prasad Devarajan. Acute kidney injury. Nelson Test Book Paediatrics. 21st ed. volume 2 Elsevier; p. 2769-2774.
6. R N Srivastava AB. Acute kidney injury. Paediatric Nephrology, 5th edition 235-259.
7. Waikar SS, Betensky RA, Bonventre JV. Creatinine as the gold standard for kidney injury biomarker studies. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2009;24:3263-5.
8. Honore P, Jacobs R, Joannes-Boyau O, Verfaillie L, De Regt J, et al. Biomarkers for early diagnosis of AKI in the ICU: ready for prime time use at the bedside Ann Intensive Care. 2012;2:24.
9. Mishra OP. Predictive ability of renal angina index alone or in combination with biomarkers for detection of acute kidney injury in children. Pediatr Nephrol Berl Ger. 2022;37:1171-4.
10. Goldstein SL, Chawla LS. Renal Angina. Clin J Am Soc Nephrol. 2010;5:943.
11. Jung JH, Sol IS, Kim MJ, Kim YH, Kim KW, et al. Validation of pediatric index of mortality 3 for predicting mortality among patients admitted to a pediatric intensive care unit. Acute Crit Care. 2018;33:170-7.
12. KDIGO AKIWG: Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury. 2012. Available from: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf
13. Mehta P, Sinha A, Sami A, Hari P, Kalaivani M, et al. Incidence of acute kidney injury in hospitalized children. Indian Pediatr. 2012;49:537-42.

14. Menon S, Goldstein SL, Mottes T, Fei L, Kaddourah A, et al. Urinary biomarker incorporation into the renal angina index early in intensive care unit admission optimizes acute kidney injury prediction in critically ill children: a prospective cohort study. Nephrol Dial Transplant. 2016;31:586-94.
15. Basu RK, Wang Y, Wong HR, Chawla LS, Wheeler DS, et al. Incorporation of biomarkers with the renal angina index for prediction of severe AKI in critically ill children. Clin J Am Soc Nephrol CJASN. 2014;9:654-62.
16. Sethi SK, Raghunathan V, Shah S, Dhaliwal M, Jha P, et al. Fluid overload and renal angina index at admission are associated with worse outcomes in critically ill children. Front Pediatr. 2018;6.
17. Kaur R, Dhooria GS, Pooni PA, Bhat D, Bhargava S, et al. Utilization of the renal angina index in PICU of a developing country for prediction of subsequent severe acute kidney injury. Pediatr Nephrol. 2018;33:2185-91.