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Original Article

Can Renal Resistive Index Be Used As An Early Predictor of Acute Kidney Injury at Paediatric Intensive Care Units?

Y ***Coban***, D ***Yildizdas***, OO ***Horoz***, N ***Aslan***, AK ***Bayazit***

Abstract The purpose of this study is to assess the predictive ability of renal resistive index (RRI) based on a comparison of RRI measurement values with the Kidney Disease: Improving Global Outcomes (KDIGO) stages in critically ill children. This prospective study included 56 paediatric intensive care patients at high risk of kidney injury, and was conducted between June 2018 and September 2019. The mean age of the 56 study patients was 4.8±5.4 years, with an F/M ratio of 23/33. There were 12 patients in the group without kidney injury based on the KDIGO criteria, and 24 patients with KDIGO stage I, 12 patients with stage II and eight patients with stage III. The mean left kidney resistive index (RI) was 0.68±0.006 in the group without kidney injury according to the KDIGO criteria, 0.59±0.15 in the stage I group, 0.58±0.27 in the stage II group and 0.65±0.06 in the stage III group, while the mean right kidney RI was 0.68±0.10, 0.58±0.13, 0.57±0.02 and 0.65±0.07, respectively. A cut-off point of <0.66 for the left kidney RI had a sensitivity of 92%, a specificity of 72%, and a positive likelihood ratio of 3.4 in detecting all kidney injuries according to KDIGO. A cut-off point of <0.68 for the right kidney RI had a sensitivity of 83%, a specificity of 82% and a positive likelihood ratio of 4.58. The present study found RRI to be highly predictive in the early detection of KDIGO stages I and II in critically ill children.

Key words *Early predictor; Renal injury; Resistive index; Paediatric*

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Background

Acute kidney injury is the most common organ failure during paediatric intensive care stay and follow-up, although there is as yet no early predictor of acute kidney injury.[1] Early-stage acute kidney injury was first assessed based on the risk, injury, failure, loss and end-stage (RIFLE) criteria in 2004, and then by the Acute Kidney Injury Network (AKIN) criteria in 2007. The Kidney Disease: Improving Global Outcomes (KDIGO) classification, based on both the AKIN and RIFLE criteria, was introduced in 2012, offering an assessment based on baseline creatinine and urine output.[2] Before creatinine is elevated, however, several biomarkers are released from the kidney into the blood and urine, the most emphasized of which are neutrophil gelatinase-associated lipocalin (NGAL), cystatin C and kidney injury molecule-1 (KIM-1), although these biomarkers are not yet available in routine practice.[3,4]

The renal resistive index (RRI) is a parameter that can be measured by Doppler ultrasound in a quick and non-invasive manner. The RRI indicates the intrarenal arterial resistance to blood flow, revealing tissue perfusion and oxygenation.[5,6] In a previous study involving adult patients, an RRI of >0.70 in those with intraparenchymal diseases was considered a sign of kidney injury,[7-9] although other studies have demonstrated an association between increased RRI and end-stage renal failure and prognosis.[10,11] There has to date been no study assessing children with kidney injury.

The present study evaluates the efficacy of RRI, measured by bedside Doppler ultrasound, in detecting kidney injury in high-risk paediatric intensive care patients.

Methods

This prospective study included 56 paediatric intensive care patients at high risk of kidney injury, and was conducted between June 2018 and September 2019.

The study included patients with risk factors for acute kidney injury, which were accepted as: use of inotropic agents, diuretics, NSAIDs and nephrotoxic drugs; the presence of hypotension, multiorgan failure (MOFS), coagulopathy, fluid overload (2%) and increased intra-abdominal pressure; and being on mechanical ventilation.[12,13]

The patients' demographic data were recorded, as well as urine output per hour, urea, creatinine and glomerular filtration rate (GFR), according to the Schwartz equation. Acute kidney injury was staged according to the KDIGO criteria,[14] and RRI values were compared based on the KDIGO stages.

RRI was calculated at the time of admittance to the intensive care unit, and after 24 h, acute kidney injury was staged according to KDIGO.

Excluded from the study were cases with failed effective measurement due to massive intraabdominal gas, patients with hypotension despite inotropic therapy, patients with renal anomalies and patients with congenital heart disease.

The study was approved by the Local Ethical Committee of the Medical Faculty of Çukurova University, and all patients provided written informed consent for their inclusion in the study.

Renal Resistive Index Measurement Method: Ultrasonographic examination and Doppler ultrasonography (ACUSON S300, Siemens Medical Solutions USA Inc.) were performed using a convex transducer. First, the kidney was localised in the flanks with conventional B-mode ultrasonography, after which, color Doppler images were acquired. The interlobar arteries were visualised, with the wavelength obtained by creating a 90-degree right-angle with the interlobar artery using a power Doppler. After the manual determination of the peak systolic and end-diastolic velocities, the RRI was calculated by the device using the formula: RRI = (peak systolic velocity - end-diastolic velocity) / (peak systolic velocity) (Figure 1).

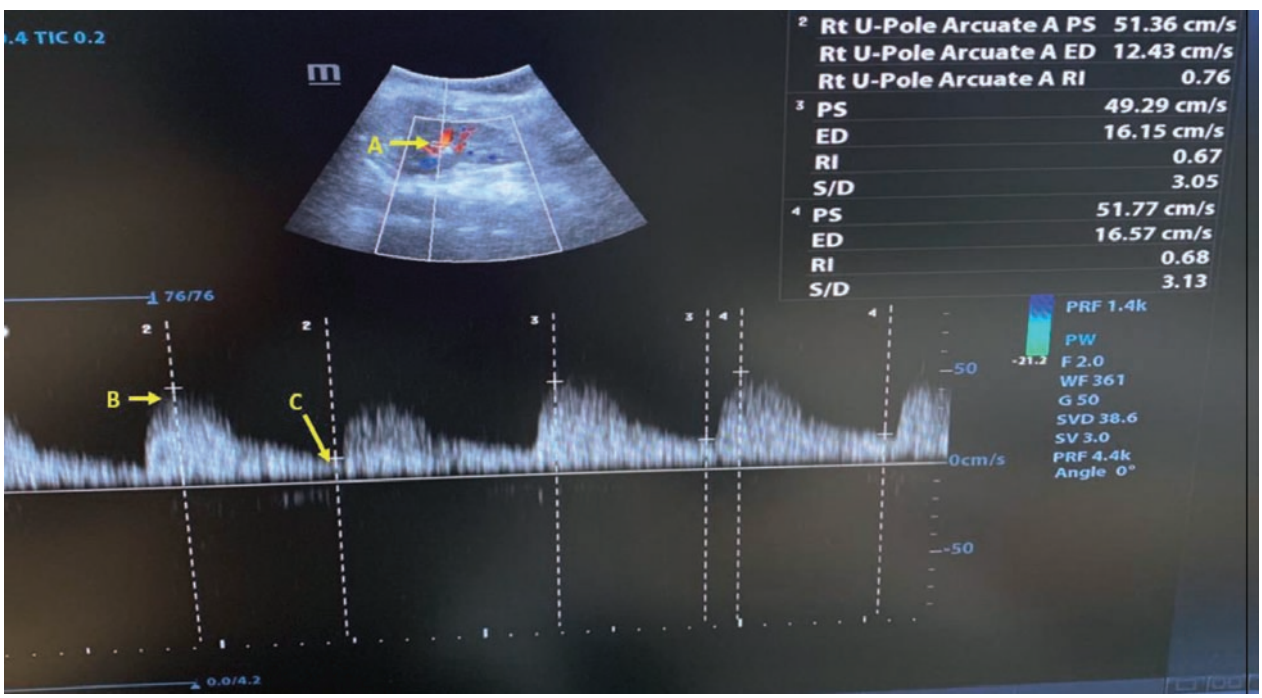

Figure 1 Doppler ultrasonographic assessment of arcuate renal artery. A) Interlober artery; B) Peak systolic velocity; C) End-diastolic velocity

The Doppler measurements of the kidneys were performed at three different kidney positions (upper, middle and lower), three times for each kidney. The Doppler ultrasound measurements were taken at the level of the arcuate artery in the right and left kidneys at three different positions, and the mean RRI values were calculated.

Prior to the present study, a radiologist was given training in RRI measurement, with whom 50 measurements were made. The RRI measurements of all study patients were made by a paediatric intensive care specialist (Y. C.).

Statistical Analysis

The association between the renal resistive indices of the left and right kidneys was evaluated with an analysis of Pearson's correlation coefficient. A one-way analysis of variance (ANOVA) was used for the analysis of parametric data, and a Duncan's multiple range test was applied for multiple comparisons between groups. Non-parametric analyses were conducted using a Chi-square test. A receiver operating characteristic (ROC) curve analysis was performed to determine RRI based on the KDIGO stage. Using the cut-off points, Positive Likelihood Ratios (Sensitivity/1 - Specificity) were calculated. All statistical analyses were conducted using IBM SPSS Statistics (version 20.0. Armonk, NY: IBM Corp.).

Results

The mean age of the 56 study patients was 4.8±5.4 years, with an F/M ratio of 23/33. The mean paediatric logistic organ dysfunction (PELOD II) score was 26.72±1.79, the paediatric risk of mortality (PRISM IV) score was 39.33± 3.38, the GFR was 82.81±4.53 ml/min per 1.73 m^2 and lactate was 2.03±0.17 mg/dl.

In the non-kidney injury group, four patients were ventilator-dependent children with cerebral palsy, two had spinal muscular atrophy, one had Leigh syndrome and sepsis, three had acute respiratory failure and two had encephalitis. In the acute kidney injury group, intensive care units follow-up was required due to sepsis in 20 patients, haemolytic uraemic syndrome in one patient, cystinosis in one patient, rhabdomyolysis in two patients, severe dehydration in four patients, trauma in six patients and surgery in ten patients (Table 1).

There were 12 patients in the group without kidney injury based on the KDIGO criteria, and 24 patients with KDIGO stage I, 12 patients with stage II and eight patients with stage III. The mean age was 2.8±1.5 years in the non-kidney injury group, 4.1±1.4 years in the stage 1 group, 9.6±4.7 years in the stage II group and 6±2.5 years in the stage III group. The F/M ratio in the groups was 7/5, 8/16, 5/7 and 3/5, respectively. The mean PELOD II score was 24±5 in the non-developed kidney injury group, 25±3 in the stage I group, 35±1 in the stage II group, and 30±5 in the stage III group ($p>0.05$). The mean PRISM IV score was 33±5 in the non-developed kidney injury group, 34±7 in the stage I group, 50±20 in the stage II group and 74±9 in the stage III group ($p<0.01$). The mean lactate, in turn, was 1.6±0.3 mg/dL, 2.4±0.4 mg/dL, 2.1±0.2 mg/dL, and 1.3±0.3 mg/dL in the non-kidney injury stage I, stage II and stage III groups, respectively ($p>0.05$) (Table 2).

An examination of the need for diuretic infusion,

Table 1 Underlying diseases according to the presence of kidney injury

	N	Underlying Disease
Non Acute Kidney Injury Group	4	Ventilator-dependent children with cerebral palsy
	2	Spinal muscular atrophy
	1	Leigh syndrome and sepsis
	3	Acute respiratory failure
	2	Encephalitis
Acute Kidney Injury Group	20	Sepsis
	1	Haemolytic uraemic syndrome
	1	Cystinosis
	2	Rhabdomyolysis
	4	Severe dehydration
	6	Trauma
	10	Post-surgery

continuous renal replacement therapy (CRRT), mechanical ventilation and blood product transfusion in the patients was carried out according to the KDIGO stages, and all parameters were found statistically significant, aside from the need for mechanical ventilation ($p<0.01$).

There was a very strong positive ($r=0.90$) correlation between the right kidney and left kidney RIs ($p<0.01$).

The mean left kidney resistive index (RI) was 0.68± 0.006 in the group without kidney injury according to the KDIGO criteria, 0.59±0.15 in the stage I group, 0.58±0.27 in the stage II group and 0.65±0.06 in the stage III group, while the mean right kidney RI was 0.68±0.10, 0.58±0.13, 0.57±0.02 and 0.65±0.07, respectively (Figure 2) (Table 3).

The AUC (area under the ROC curve) for the left kidney RI was 0.74 (95% CI 0.62-0.87) and 0.82 for the right kidney RI (95% CI 0.70-0.93) in all groups with kidney injury according to the KDIGO criteria. A cut-off point of <0.66 for the left kidney RI had a sensitivity of 92%, a specificity of 72%, and a positive likelihood ratio of 3.4 in detecting all kidney injuries according to KDIGO. A cut-off point of <0.68 for the right kidney RI had a sensitivity of 83%, a specificity of 82% and a positive likelihood ratio of 4.58 (Figure 2).

When the stage III kidney injury group was removed from the data set due to the increased RRI range of the KDIGO stage III patients, the AUC for the left kidney RI was 0.82 (95% CI 0.69-0.94) and 0.90 for the right kidney RI (95% CI 0.80-1) in the kidney injury group. The left RI of <0.66 for kidney injury had a sensitivity of 92%, a specificity of 80% and a positive likelihood ratio of 4.7. The right RI of <0.66 for kidney injury had a sensitivity of 92%, a specificity of 86% and a positive likelihood ratio of 6.6 (Figure 3).

Discussion

Acute kidney injury (AKI) is one of the most common organ failure syndromes in critically ill children, requiring a prolonged intensive care stay and mechanical ventilation. The incidence of AKI is reported to range from 8% to 89% in paediatric intensive care units, and this broad range can be attributed to the lack of a biological marker or a sufficiently sensitive classification system for the detection of AKI.[15-20] The recent Awareness During Resuscitation (AWARE) study of paediatric patients admitted to paediatric intensive care and cardiac intensive care units in several countries made use of the KDIGO classification, and reported an AKI incidence of 26.9% and 11.6% in turn for KDIGO stages II and III. The study also highlighted such biomarkers as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C and kidney injury molecule-1 (KIM-1) due to the low sensitivity of creatinine and GFR, and the lack of information on the previous creatinine levels of the patients. Although it has been stated that the degree

Table 2 Patients' demographic data according to KDIGO stage

Stage of kidney injury	N	Sex (F/M)	Age (years)	PRISM IV	PELOD II	Lactate (mg/dL)
Non acute kidney injury	12	7/5	2.8±1.5	33±5	24±5	1.6±0.3
KDIGO stage I	24	8/16	4.1±1.4	34±7	25±3	2.4±0.4
KDIGO stage II	12	5/5	9.6±4.7	50±20	35±1	2.1±0.2
KDIGO stage III	8	3/5	6±2.5	74±9	30±5	1.3±0.3
P				<0.01	>0.05	>0.05

Table 3 Mean left and right RRI values according to KDIGO stages

Stage of kidney injury	N	Mean RRI for right kidney	Mean RRI for left kidney
Non acute kidney injury	12	0.68±0.10*	0.68±0.006*
KDIGO stage I	24	0.58±0.13*	0.59±0.15*
KDIGO stage II	12	0.57±0.02*	0.58±0.27*
KDIGO stage III	8	0.65±0.07*	0.65±0.06*
P		0.017	0.032

*mean values followed by different letters within a column are significantly different ($p<0.05$)

of detection of AKI in critically ill patients is low when these biomarkers are used alone, but that their sensitivity and specificity can increase when used together, they are not considered sufficiently predictive for routine use.[3]

Patients requiring treatment in intensive care units are mostly those with impaired tissue perfusion but without hypotension who may progress to organ failure. To assess tissue perfusion in these patients, clinical parameters such as capillary refill time, urine output, the difference between the peripheral and core temperatures, as well as values such as lactate, cardiac index (CI) and central venous oxygen saturation (ScVO2), are monitored. Prior to the development of these signs, it is believed that renal RI, assessed by Doppler ultrasound, can reveal impaired organ perfusion. Doppler RI assessment especially of the spleen and kidneys is one of the approaches that have been used in recent years.[21]

Among the studies of critically ill patients, Haitsma Mulier et al,[8] in their assessment of RRI, established an RRI of 0.71 (95% CI 0.69-0.73) in a group with AKI and 0.65 (95% CI 0.63-0.68) in a group without AKI, according to KDIGO (p=0.001). Lerolle et al,[9] in turn, evaluated RRI after six hours of inotropic therapy in a group of patients with sepsis, and reported that the RRI increased

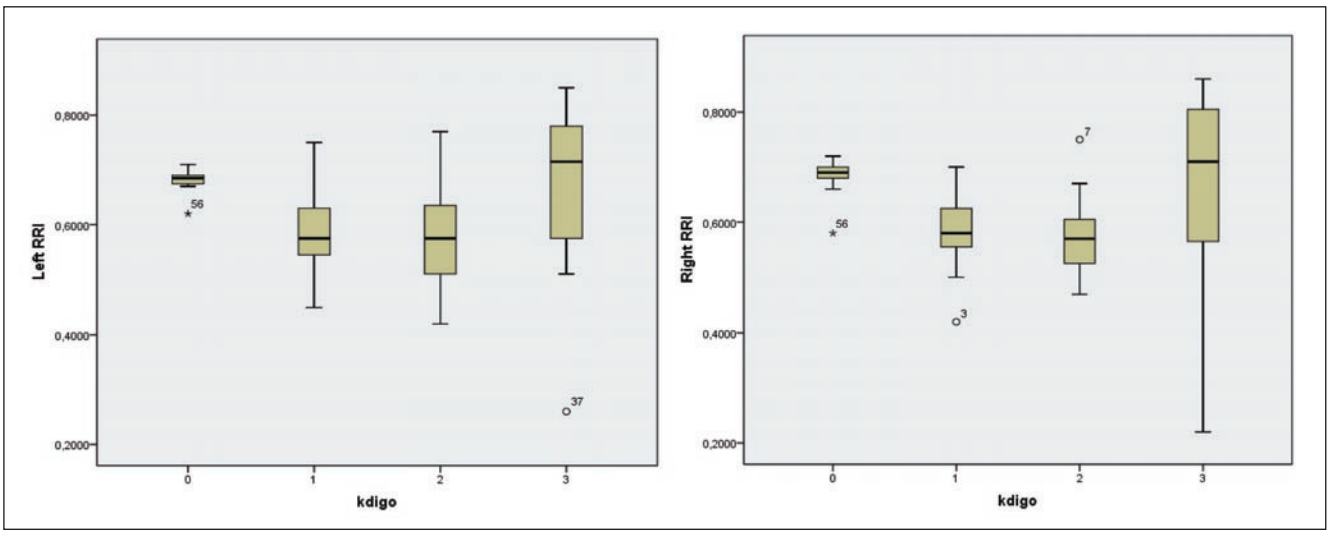

Figure 2 Renal resistive index (mean, 95% CI) for patients without Acute Kidney Injury (AKI) and patients with different stages of AKI.

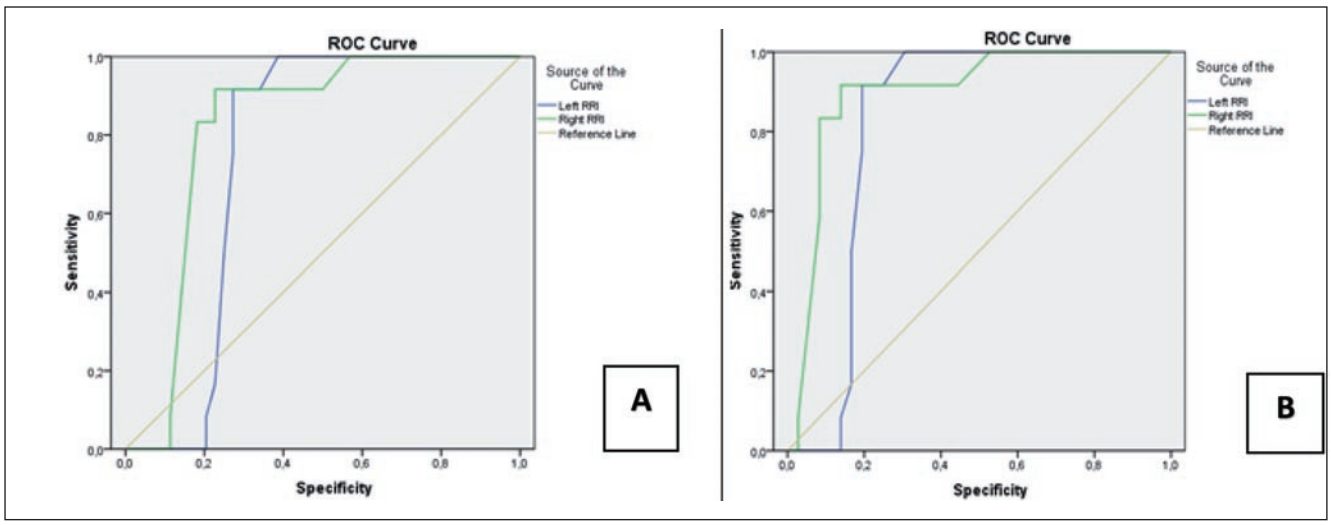

Figure 3 A) ROC curve of RRI for AKI stage 0, 1, 2 and 3; B) ROC curve for AKI stage 0, 1 and 2 RRI.

significantly from the risk group towards injury and failure in the group with renal failure according to the RIFLE criteria on day five. When the risk group and the healthy group were evaluated together in the same study, the RRI was statistically significantly higher than in the injury group. The authors determined that an RRI of >0.74 was significant in detecting renal failure, although they were unable to establish a relationship with the dose of inotropic agents. The mean arterial pressure was found to be inversely proportional to RRI, leading the authors to believe that RRI increased as a compensatory mechanism, aiming to increase GFR when the mean arterial pressure decreased. Only in this study, the authors identified a decreased RI in the group with acute prerenal kidney injury (RI: 0.68) than in others (RI: 0.77) in the prerenal kidney injury patient group.[9]

The study by Örmeci et al of infants undergoing cardiac surgery compared RRIs with renal and brain near-infrared spectroscopy (NIRS), lactate and urine output, and serum creatinine, and identified a strong negative correlation with NIRS in the two groups, a high level of lactate in the group with RRI > 0.8 ($p<0.05$) and low urine output ($p<0.05$), but no association with creatinine. AKI was not staged in the said study.[22] Aside from this research,[22] no studies of on critically ill patients in the paediatric age group could be identified.

Our study found RRI to be higher in patients without kidney injury, according to the KDIGO staging, and lower in stage I and stage II patients, while an increase and a greater variation were noted in stage III patients. Similarly, when the first ROC curve analysis (including all KDIGO stages) and the second analysis (after the removal of KDIGO stage III) were compared, the explanatory power of the model, as well as its specificity and sensitivity, were found to be increased, despite the similar cut-off points. In contrast to previous studies involving adults, a decreased RRI was noted in stage I and stage II patients, but this could either increase or decrease in KDIGO stage III patients. The decreased RRI in stage I and stage II patients established in the present study, unlike in previous studies involving adults, suggests relative hypovolemia, regardless of the underlying cause other than cardiac failure and anuric renal failure. We think that the lower total body fluid ratio and smaller volume of cardiac output in children than in adults may lead to a decrease in vascular resistance to organ perfusion in children, in contrast to the increase seen in adults. The only study carried out to date with children was conducted by Örmeci et al,[22] in which cardiogenic shock was prominent. Vasoconstriction is seen more common in cardiogenic shock. In addition, Örmeci et al did not mention the level of inotropic agents taken by the patients in this study.[22] Perhaps their patients had received high dose inotropic agents. Therefore, they found higher RRI compared to our study secondary to vasoconstriction. The patients in the present study developed acute kidney injury mostly secondary to sepsis or hypovolaemic shock, and it was thus concluded that the decreased RRI was due to different physiopathologies. In addition, only one study was found which compared prerenal and renal injury in terms of RRI. In that study, RRI was lower in prerenal injury group than those renal injury group.[9] Our study was consistent with these studies.[9,22]

RRI appears to either increase or decrease in the KDIGO stage III kidney injury group in the present study, and it was concluded that RI cannot be determined based only on systemic or intraparenchymal factors, but may also increase or decrease depending on the underlying cause. In a case report by Anile et al,[23] it was reported that RRI increased first before the development of hypotension, with no changes noted in ScVO2, CI or lactate levels in an adult patient with septic shock. The authors reported that RRI increased when oxygen excretion increased in the initial period before macrovascular deterioration was observed in sepsis or shock. The authors stated, however, that the splenic artery resistive index should be examined, being affected by such systemic and intrarenal factors as age, vascular disease, pulse pressure, systemic vascular compliance, heart rate, cardiac function, end-stage renal failure or renal capillary wedge pressure.

No clear values for RRI have been reported in previous studies of healthy children.[24-27] At the outset of the our study, no healthy group was included, as no optimal value could be determined in the healthy and awake patient group as a result of both abdominal breathing and the cooperation problems associated with paediatric patients. The study by Murat et al[24] provided measurement ranges together with median values for four age groups in which the RRI ranges were very wide, and so this parameter cannot be considered reliable in the awake child patient group. However, since critically ill children hospitalised in the intensive care unit are mostly immobile on mechanical ventilator or sedated, we think that this parameter can be evaluated more accurately than those healty children.

We are aware that kidney injury scores and new biomarkers for kidney injury in critically ill children may not be appropriate for every patient for present knowledge, but believe that ultrasound, as a non-invasive method and a routine part of a physical examination for intensive care

professionals, can provide an early warning in assessments of renal function through RRI in the determination of a treatment modality.

The limitations of our study include the small sample size, and the lack of multiple comparisons of the risk factors and the underlying causes of kidney injury. Further studies are needed involving larger patient groups to facilitate clearer determinations in this area.

This is the first study which evaluated RRI for the identification of acute kidney injury in critically ill children. Renal RI had higher sensitivity and specificity, especially in detecting KDIGO stages I and II. We believe that there is a need for further studies should be conducted into this issue involving larger patient groups.

Conclusion

Our study is the first to evaluate RRI for the identification of acute kidney injury in critically ill children. Renal RI had higher sensitivity and specificity, especially in detecting KDIGO stages I and II, although further studies should be conducted into this issue involving larger patient groups. We wanted in the present study to underline that renal resistive index is a potential parameter for use in acute kidney injury.

Ethics Committee Approval

Ethical approval for this study was received from the Çukurova University Faculty of Medicine Clinical Research Ethics Committee (April 2018; 80).

Conflict of Interest

No conflict of interest is declared by the authors.

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