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Original Article

Acute Kidney Injury in Non-critically Ill Children and Correlation With Cystatin C in the Diagnosis of Acute Kidney Injury: A Single Centre Prospective Cohort Study

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ABSTRACT

Background and Aim: Acute kidney injury (AKI) is an acute decline in function and inability to regulate acid, electrolyte, and fluid balance. AKI can be classified as community-acquired AKI (CA-AKI) and hospital-acquired AKI (HA-AKI) depending on the time of onset. Most studies have been conducted on critically ill populations, mainly considering the HA-AKI cases. Limited studies were conducted on CA-AKI, especially in non-critically ill children.

Methods: A prospective cohort study in 505 non-critically ill hospitalized children (1 month to 12 years) after screening 750 children. Baseline creatinine was calculated using a computational method assuming a normal glomerular filtration rate (GFR) for age, hence all communities, as well as hospital-acquired AKI, were included. Kidney disease improving global outcome (KDIGO) criteria was used for classification and also serum cystatin -C levels were done to diagnose AKI.

Results: Fifteen percent (15.64%) of children had AKI, of which 83.54% had CA-AKI and 16.46% had HA-AKI. Of all patients with AKI, 54.43% were exposed to nephrotoxic drugs and 53.49% (23) had received 2 or more nephrotoxic drugs, and 34.18% of patients had sepsis, 35.44% of patients had dehydration. Patients with HA-AKI had a significantly longer duration of stay (15.23±5.42 days) compared to CA-AKI patients (7.48±6.42 days) and were also exposed to nephrotoxic drugs. Cystatin C had a specificity of 88.50% and a negative predictive value of 93.80%.

Conclusion: Non-critically ill hospitalized children are at significant risk for AKI and need more vigilant monitoring. CA-AKI should be detected proactively because they are often underreported. Cystatin-C has good specificity and negative predictive value for diagnosing AKI.

Keywords: Acute kidney injury (AKI), Non-critically ill children, Kidney disease improving global outcome (KDIGO), Cystatin-C

Introduction

Acute kidney injury (AKI) is an acute decline in glomerular filtration rate (GFR), and an inability to regulate acid-base, electrolyte, and fluid balance [1]. Depending on etiology, it can be prerenal, renal, or post-renal [2], and can also be classified as community-acquired AKI (CA-AKI) when a child has AKI within 48 hours of admission or hospital-acquired AKI (HA-AKI) when a child has clinical and or biochemical features of AKI 48 hours after admission [1]. AKI is not only a crucial contributor to increased morbidity with prolonged hospitalization and increased mortality in the acute period but also leads to long-term consequences with residual renal disease (hypertension, reduced GFR, proteinuria), and chronic kidney disease (CKD) and end-stage kidney disease (ESKD) [2, 3] making it worthwhile to prevent its occurrence and progression.

Various definitions and staging systems have been used for AKI in children, including pediatric risk, injury, failure, loss of kidney function, end-stage kidney disease (pRIFLE) criteria, the acute kidney injury network (AKIN) criteria, and the most recently introduced kidney disease improving global outcome (KDIGO) criteria, all of which utilize changing serum creatinine and urine output (UO) to define and stage AKI [4-6]. A wide variability exists in the reported incidence of AKI, ranging from 0.8% to 70% [3, 7-20] attributable to the criteria used to define AKI, settings, and the dynamics of the study population. Most of the available studies in critically ill populations have been in selected and retrospective groups [10, 13, 14, 20]. The prospective studies in non-critically ill children who form the major portion of all hospitalizations are few [8, 9, 11, 12]. Also, studies have used the lowest inpatient serum creatinine as the baseline accounting for only HA-AKI. However, others recommend using the lowest serum creatinine in the last three months or a computational method of back calculation of baseline serum creatinine using the age-estimated GFR if unavailable [21]. In addition, serum creatinine has shortcomings as a marker of kidney function since its levels rise late in AKI, levels are influenced by non-renal factors, such as body weight, race, age, muscle mass, drugs, protein intake, etc [2, 22]. Hence, ideal biomarkers, such as cystatin C, urinary and serum levels for neutrophil gelatinase-associated lipocalin (NGAL), liver fatty acid binding protein (L-FABP), interleukin 10 (IL-18), and kidney injury molecule 1 (KIM-1) etc, are always sought [1]. Out of these, serum cystatin C has been reported for early recognition of AKI, since it is not affected by non-renal factors and is freely filtered by the glomerulus, without tubular secretion [1, 12, 22, 23]. The current study was conducted to determine the incidence, associated risk factors, and outcome of AKI in non-critically ill hospitalized children and to observe the occurrence of cystatin C-based AKI in the same cohort.

Materials and Methods

This prospective cohort study was conducted in hospitalized children in age group 1 month-12 years of age at a tertiary care centre in north India. Children with short duration of stay (<48 hours), known a case of CKD, serum bilirubin level of >5 mg/dL, those who did not have serum creatinine done within 24 hours of admission or critically ill admitted to pediatric intensive care unit and required mechanical ventilation, and or required dopamine and or dobutamine at a dose >10 ug/kg/min or adrenaline at any dose, fulminant hepatic failure, Glasgow coma scale (GCS) <8 [12] were excluded. Out of 750 patients screened, 505 patients were eligible and enrolled for the study after obtaining written informed consent from the parent/guardian. The study was approved by the Institutional Ethics Review Committee (IEC/2020-11/CC-215). The sample size was calculated using the reference study by Mehta et al., who observed a 9% incidence of AKI in non-critically ill hospitalized patients [12]. The minimum required sample size was 504 patients with a 2.5% margin of error and a significant level of 5%. The following equation (Equation 1) is used:

Equation 1. $N \geq (p\ (1-p)/(ME/z\alpha)^2$

Where Zα is a Z value at two-sided alpha error of 5%, ME is the margin of error, and p is the proportion of patients who had AKI.

$n=((0.09\times(1-0.09))/(0.025/1.96)^2=503.4=504$ (approx)

A pre-designed clinical recording form was used to record demographic, clinical, and laboratory details. UO was documented daily either by diaper weight or by spontaneous void collection. KDIGO criteria were used to diagnose and classify different stages of AKI [4]. Either UO or serum creatinine was used to classify AKI. A 5 mL blood sample was taken to estimate complete hemogram, serum creatinine, serum sodium, potassium, and blood urea nitrogen during hospitalization. The biochemical parameters were measured by a fully automated Beckman Coulter AU analyzer using the kit available at the institution, Jaffe's colorimetric method to measure creatinine levels. Estimated reference GFR values for age were used to calculate normal baseline serum creatinine for age, using the length/height of the children in the age group 1 month-2 years. For older children, an estimated GFR of 120 mL/1.73 m^2/min was taken to calculate baseline serum creatinine using the Schwartz equation [1]. Serum creatinine was repeated every 48 hours till 7 days of admission or discharge/outcome. Serum cystatin

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C was measured once at admission and then at 48 h. Any raised value compared to the reference nomogram was considered abnormal [24]. Based on the development of AKI, all subjects were divided into two groups (with or without AKI). Patients with AKI were further grouped in CA or HA AKI and analyzed and compared based on age, sex, risk factors, duration of illness, and outcome in terms of death or discharge with normal or deranged kidney function test (KFT). All data were entered in the master chart of the Microsoft EXCEL spreadsheet. The categorical variables were presented as numbers and percentages, the quantitative data as the Mean±SD or median with 25th and 75th percentiles (interquartile range). The data normality was checked by using the Kolmogorov-Smirnov test. The quantitative and non-normal data were compared using the Mann-Whitney test (for two groups). The qualitative data were compared using the Chi-square test. If any cell had an expected value of less than 5, Fisher's exact test was used. Sensitivity, specificity, positive predictive value, and negative predictive value of Cystatin C for predicting acute kidney injury were calculated. The receiver operating characteristic (ROC) curve was made to show the predictability of serum cystatin C levels, compared to serum creatinine levels, for the occurrence of AKI. The final analysis was performed using SPSS software, version 21.0. IBM manufacturer, Chicago, USA.

Results

Out of 750 hospitalized children screened, 245 patients were excluded due to various reasons (Figure 1). AKI

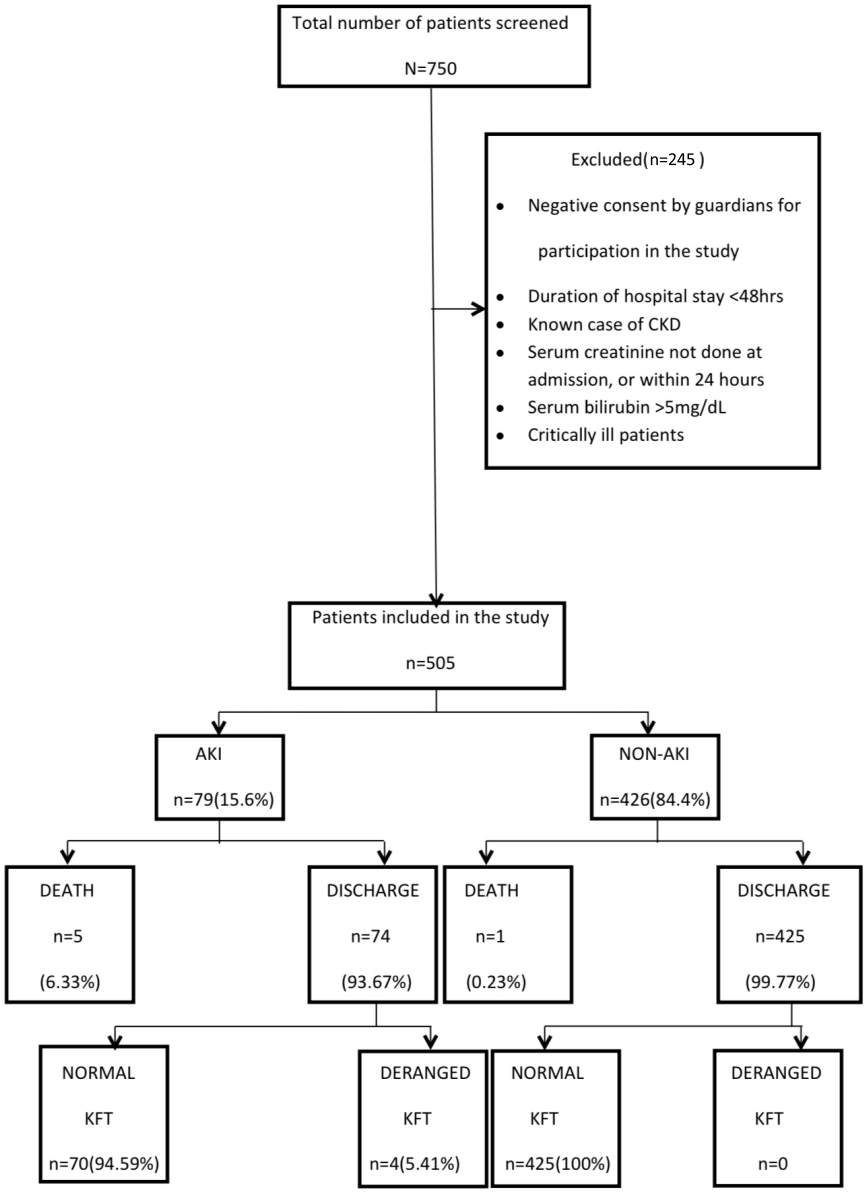

Figure 1. Study flow chart

and non-AKI groups were analyzed and compared. Out of 505 patients enrolled, 62.38% were males and the mean age was 4.43±3.9 years and the majority of patients were 2 to 12 years old. Most patients stayed for a short duration (<7 days) with the mean duration of stay at 6.56±4.59 days. The majority (99%) of discharge and mortality was observed in 1% (Table 1). Out of 505 included subjects, 15.6% (79) patients had AKI, of which 13.2% patients had CA-AKI, and 2.5% patients had HA-AKI (Figure 1).

No significant difference was observed in gender or age group among children with or without AKI. Patients in the AKI group had a longer duration of stay (8.76±6.87 days) compared to patients without AKI (6.15±3.9 days) (P<0.05). In terms of risk factors, more patients in the AKI group (53.5%) were exposed to multiple nephrotoxic drugs, compared to 27% in the non-AKI group (P<0.05). Other factors, such as sepsis and dehydration were also more significantly observed in the AKI group (34% vs 9.6% and 35% vs 4.5%, respectively). In terms of outcome, the AKI group had a higher incidence of death at 6%, compared to 0.23% in the non-AKI group. Around 6% of patients in the AKI group had deranged KFT on discharge (Table 2).

Of the 79 patients with AKI, the majority i.e. 83.5% (66) were CA-AKI. Based on the KDIGO staging, it was observed that most patients had AKI stage 1 (77.21%), followed by stage 2 (16.45%) and stage 3 (6.32%). This trend was also observed in CA-AKI and HA-AKI groups individually, where most patients had developed stage 1 AKI (83.3% and 46.15%, respectively). The mean age of patients in both groups (CA vs HA) was similar and also had similar gender distribution with the majority being males (72% and 69%, respectively). Patients with HA-AKI had a significantly longer duration of stay compared to the CA-AKI group (15.23±5.42 vs 7.48±6.42 days). HA-AKI group also had a higher frequency of exposure to 2 or more nephrotoxic drugs (69% vs 47%), although this was not statistically significant. HA-AKI group had a higher (54%) incidence of sepsis compared

Table 1. Baseline demographic and clinical characteristics of study subjects (n=505)

Baseline Characteristics		No. (%)/ Mean±SD
Age (y)	1 month-<2	182(36.04)
	2-12	323(63.96)
		4.43±3.9
Gender	Female	190(37.62)
	Male	315(62.38)
Duration of stay (d)	≤7	368(72.87)
	8-14	106(20.99)
	15-21	28(5.54)
	>21	3(0.59)
		6.56±4.59
Nephrotoxic drugs	<2	164(68.33)
	≥2	76(31.67)
Dehydration	Negative	458(90.69)
	Positive	47(9.31)
Sepsis	Negative	437(86.53)
	Positive	68(13.47)
Outcome	Death	6(1.19)
	Discharged	499(98.81)

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Table 2. Baseline demographic and clinical characteristics in AKI and non-acute kidney injury groups

Variables	Baseline Characteristics	Mean±SD/No. (%)			P
		Acute Kidney Injury	No Acute Kidney Injury	Total	
Age (y)		4.3±4.06	4.45±3.84	4.43±3.87	0.458‡
	Median (25th-75th percentile)	3(0.5-8)	3.5(0.83-7)	3.5(0.75-8)	
Gender	Female	22(27.85)	168(39.44)	190(37.62)	0.051†
	Male	57(72.15)	258(60.56)	315(62.38)	
Duration of stay (d)	7	43(54.43)	325(76.29)	368(72.87)	<0.0001*
	8-14	24(30.38)	82(19.25)	106(20.99)	
	15-21	9(11.39)	19(4.46)	28(5.54)	
	>21	3(3.80)	0(0)	3(0.59)	
		8.76±6.87	6.15±3.91	6.56±4.59	0.001‡
Nephrotoxic drugs	<2	20(46.51)	144(73.10)	164(68.33)	0.0007†
	2	23(53.49)	53(26.90)	76(31.67)	
Dehydration	Negative	51(64.56)	407(95.54)	458(90.69)	<0.0001†
	Positive	28(35.44)	19(4.46)	47(9.31)	
Sepsis	Negative	52(65.82)	385(90.38)	437(86.53)	<0.0001†
	Positive	27(34.18)	41(9.62)	68(13.47)	
Outcome Death/discharged	Death	5(6.33)	1(0.23)	6(1.19)	0.0004*
	Discharged	74(93.67)	425(99.77)	499(98.81)	
Discharged	Discharged with deranged KFT	4(5.41)	0(0)	4(0.80)	0.0005*
	Discharged with normal KFT	70(94.59)	425(100)	495(99.20)	

‡ Mann Whitney test, * Fisher's exact test, † Chi square test.

KFT: Kidney function test.

to 30% in the CA-AKI group. On the other hand, the CA-AKI group had a significantly higher incidence of dehydration (42% vs 0%). In terms of outcome, most patients were discharged from both groups, and the death rate was also similar. Ninety-two percent of patients in the HA-AKI group were discharged with normal KFT and 8% had deranged KFT on discharge. Whereas, in the CA-AKI group, 5% of patients were discharged with deranged KFT, and 95% were discharged with normal KFT (Table 3).

Serum cystatin C levels in the study population were measured at admission and 48 hours. Serum cystatin C was raised in 20% (103) cases. Out of the 79 patients with KDIGO-based AKI, 68.35% had raised serum cystatin C levels (Table 4).

On the receiver operating characteristic (ROC) curve, the discriminatory power of cystatin C (area under the curve [AUC] 0.784; 95% confidence level [CI]: 0.746 to 0.819) was acceptable and cystatin C is a good predictor of AKI with 78.40% chances of correctly predicting AKI. Cystatin C had a sensitivity of 68.35%, a specificity of 88.50%, and a negative predictive value of 93.80%.

Table 3. Association of baseline characteristics and outcome with community acquired (CA) and hospital acquired AKI

Variables		No. (%)/Mean±SD			P
Baseline Characteristics		CA AKI	HA AKI	Total	
Stage	1	55(83.3)	6(46.15)	61(77.21)	
	2	8(12.12)	5(38.46)	13(16.45)	
	3	3(4.54)	2(15.38)	5(6.32)	
Age (y)		4.06±3.96	5.53±4.52	4.3±4.06	0.236‡
Gender	Female	18(27.27)	4(30.77)	22(27.85)	0.748*
	Male	48(72.73)	9(69.23)	57(72.15)	
Duration of stay (d)	7	42(63.64)	1(7.69)	43(54.43)	<0.0001*
	8-14	20(30.30)	4(30.77)	24(30.38)	
	15-21	2(3.03)	7(53.85)	9(11.39)	
	>21	2(3.03)	1(7.69)	3(3.80)	
		7.48±6.42	15.23±5.42	8.76±6.87	<0.0001‡
Nephrotoxic drugs	<2	16(53.33)	4(30.77)	20(46.51)	0.203*
	≥2	14(46.67)	9(69.23)	23(53.49)	
Dehydration	Negative	38(57.58)	13(100)	51(64.56)	0.003*
	Positive	28(42.42)	0(0)	28(35.44)	
Sepsis	Negative	46(69.70)	6(46.15)	52(65.82)	0.102†
	Positive	20(30.30)	7(53.85)	27(34.18)	
Outcome Death/discharged	Death	4(6.06)	1(7.69)	5(6.33)	1*
	Discharged	62(93.94)	12(92.31)	74(93.67)	
Discharged	Discharged with deranged KFT	3(4.84)	1(8.33)	4(5.41)	0.515*
	Discharged with normal KFT	59(95.16)	11(91.67)	70(94.59)	

‡ Mann Whitney test, * Fisher's exact test, † Chi square test.

KFT: Kidney function test.

Table 4. Association of cystatin C levels with KDIGO based AKI

Cystatin C Levels	No. (%)			P
	Acute Kidney Injury (n=79)	No Acute Kidney Injury (n=426)	Total	
Raised	54(68.35)	49(11.50)	103(20.40)	<0.0001
Normal	25(31.65)	377(88.50)	402(79.60)	
Total	79(100)	426(100)	505(100)	

† Chi square test.

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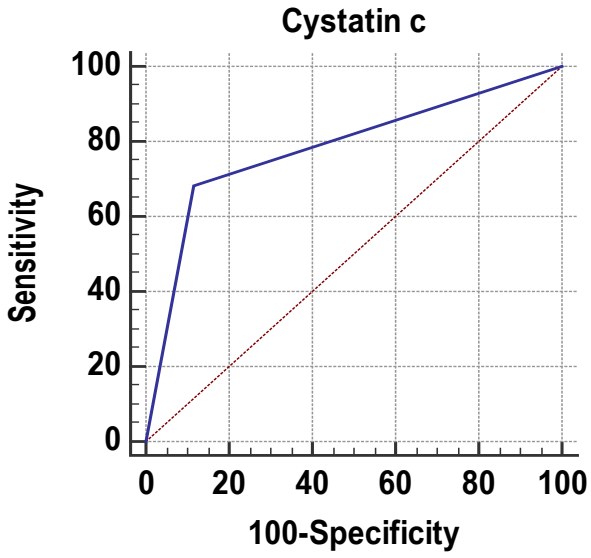

Figure 2. ROC curve of cystatin C for predicting AKI

Discussion

Most studies on AKI are in critically ill hospitalized children who have multiple risk factors (sepsis, shock, fluid overload, use of multiple nephrotoxic drugs, mechanical ventilation, etc.) mainly for hospital-acquired cases, including the recent multinational, multicentric AWARE study [14] or are in selected cohorts [16, 17]. In this prospective study incidence of CA as well as HA-AKI was analyzed in the non-critically ill pediatric population. Out of 505 patients, 15.64% (79) patients developed AKI using the KDIGO criteria. Previously documented reports vary from 0.5% to 30% [7-9, 11, 12, 15, 20]. However, most of the studies are in the adult population or retrospective in nature using data records. Krishnamurthy et al. in their prospective observational study among 2376 children (1 m-13 years) reported an incidence of 5.2% using AKIN criteria [9], while Nawaz et al. (AKIN) in their study reported it to be 17% similar to our study [11]. Others have also reported an incidence of 9%-10% [12, 13]. Variability in data may be explained due to the difference in criteria used as well as baseline creatinine taken in various studies. Also, in the current study UO or serum creatinine, either of these was used to identify and classify AKI, resulting in increased incidence. In a retrospective cohort study by McGregor et al. using KDIGO, AKI criteria were met in 30% of patients [20]. A recent AWARE study analyzed that the use of serum creatinine alone can lead to misdiagnosis in about two-thirds of patients, also stage III AKI defined by UO criteria predicted higher mortality than stage 3 AKI defined by serum creatinine criteria [14] hence emphasizing the importance of urine output monitoring in these children. Increased incidence of AKI in the adult population is well reported and attributed to more aggressive therapies in the aging population and multiple co-morbidities [7]. Similar data obtained in the future in children also require more vigilant monitoring in non-critically ill admitted children.

The majority of subjects in this study had stage I AKI (77%) compared to stage II (16.5%) or stage III (6.3%) which is similar to previously observed data [8, 11, 12]. The majority (83.5%) had CA-AKI defined by those with deranged AKI on admission (baseline serum creatine calculated from normal estimated GFR using Schwartz equation). Wonnacot et al. in their analysis of the adult population reported similar observations of higher incidence of CA-AKI compared to HA-AKI (67.3% vs 32.7%, respectively) [7]. Most of the available literature does not differentiate AKI in CA and HA-AKI. In this study, no significant difference was observed in the age and sex between the two groups (Table 3), similar to observation by others [7, 19]. HA-AKI patients were observed to have a significantly longer duration of stay (15.23±5.42 days), compared to CA-AKI patients (7.48±6.42 days), although mortality in both groups was similar (6.06% vs 7.7%). Wonnacott et al. also observed a longer duration of stay in HA-AKI [7], however, previous studies found poor survival rates in HA-AKI compared to CA-AKI [7, 19].

The majority (55.70%) of the patients who had developed AKI were in the age group of 2 to 12 years, with a mean age of 4.3±4.06 years similar to previous observation [9, 20]. No significant relationship was observed

between the gender of the patient and AKI incidence similar to others [11]. AKI patients in this study were observed to have significantly longer duration [7, 11-14, 16, 17] and also had significantly higher mortality compared to the non-AKI group (6.33% vs 0.23%) in sync with previous observations. Out of 79 subjects with AKI, 5.41% [4] had persistent deranged KFT values at discharge (Table 3, Figure 2). Many previous studies have shown persistent kidney dysfunction in patients developing AKI [3, 13, 18]. A significant relationship was observed between factors, such as sepsis, dehydration, and the development of AKI (Table 2). Sepsis leads to AKI by reduced renal blood flow as in septic shock or sepsis-induced hypotension, along with cytokine-induced damage to tubular cells [1]. A significant relationship was also observed between the use of two or more nephrotoxic drugs and the development of AKI (Table 2). Nephrotoxic drugs, such as aminoglycosides cause renal injury by various mechanisms which can lead to reduced renal function over a while as reported in studies from 11% to 33% [2, 16, 17, 25]. Among the two groups (CA vs HA-AKI), a significant difference was observed in the occurrence of dehydration but not for sepsis and use of nephrotoxic drugs, although 70% of the patients in HA-AKI were exposed to two or more nephrotoxic drugs compared to 46% in CA-AKI group (Table 3).

Serum cystatin C was measured at two time periods (admission and at 48 h) and raised values at any point compared to normal reference value were considered abnormal for age and were observed in 20.4% of patients. Out of all patients who had AKI, 68.3% also had raised serum cystatin C levels (Table 4). It was observed that serum cystatin C levels had a significant discriminatory power to predict AKI (Figure 3) and a high negative predictive value (93.80%). It had a sensitivity of 68.35%, and a specificity of 88.50% (area under the curve [AUC] 0.784; 95% confidence interval [CI]: 0.746-0.819). Similar results were observed by others [26, 27]. Filler et al. compared the serum creatinine-based Schwartz equation and serum cystatin C in 536 children with various renal pathologies to accurately predict the GFR. It was observed that the Schwartz equation tends to overestimate GFR in patients with lower GFR, with a mean deviation of +10.8%, while the formula based on serum cystatin C (Equation 1):

1. (log [GFR]=1.962+[1.123×log(1/Cystatin C)])

showed a deviation of +0.3%, making it significantly more accurate [28]. Serum cystatin C levels in AKI rise earlier than creatinine and decrease in UO and can be a good alternative for early diagnosis [29].

The strength of the study is the prospective cohort taken in exclusively non-critically ill hospitalized children to categorize AKI patients in CA and HA groups as it has an etiologic and prognostic difference and measures cystatin C to predict its diagnostic power. While limitations exist, such as a relatively small sample size and lack of follow-up serum cystatin C till 7 days because it can increase the diagnostic yield. Also, long-term follow-up of children with residual kidney dysfunction was not done.

Conclusions

Non-critically ill hospitalized children are at significant risk for developing AKI and need more vigilant monitoring. CA-AKI should be detected proactively because they are often underreported. Since serum cystatin C has a significant discriminatory power to predict AKI, it can be explored in a larger group of populations for early detection for its practical utility.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization: Shobha Sharma; Methodology and Resources: Anita Rani and Kanika Kapoor; Software: Gunjan Gupta; Validation: Anita Rani and Rani Gera; Formal analysis: Gunjan Gupta, Shobha Sharma and Anita Rani; Investigation: Gunjan Gupta and Anita Rani; Data curation: Rani Gera and Gunjan Gupta; Writing—original draft preparation: Gunjan Gupta and Shobha Sharma; Writing—review, and editing: Shobha Sharma, Gunjan Gupta and Kanika Kapoor; Visualization: Shobha Sharma and Anita Rani; Supervision: Rani Gera.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Devarajan P. Acute kidney injury: Prevention and diagnosis. In: Geary D, Schaefer F, editors. Pediatric kidney disease. Heidelberg: Springer; 2016. [DOI:10.1007/978-3-662-52972-0_46]

[2] Srivastava RN, Bagga A. Pediatric nephrology. New Delhi: JP Medical Ltd; 2011. [Link]

[3] Menon S, Kirkendall ES, Nguyen H, Goldstein SL. Acute kidney injury associated with high nephrotoxic medication exposure leads to chronic kidney disease after 6 months. J Pediatr. 2014; 165(3):522-7.e2. [DOI:10.1016/j.jpeds.2014.04.058] [PMID]

[4] Disease KJ. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group: KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012; 2(1):1-38. [Link]

[5] Mehta RL, Kellum JA, Shah SV, Molitoris BA,Ronco C, Warnock DG, et al. Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007; 11(2):R31. [DOI:10.1186/cc5713] [PMID] [PMCID]

[6] Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007; 71(10):1028-35. [DOI:10.1038/sj.ki.5002231] [PMID]

[7] Wonnacott A, Meran S, Amphlett B, Talabani B, Phillips A. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. Clin J Am Soc Nephrol. 2014; 9(6):1007-14. [DOI:10.2215/CJN.07920713] [PMID] [PMCID]

[8] Ashraf M, Shahzad N, Hussain A, Tak SA, Bukhari ST, Kachru A. Incidence of pediatric acute kidney injury in hospitalized patients. Saudi J Kidney Dis Transpl. 2016; 27(6):1188-93. [DOI:10.4103/1319-2442.194608] [PMID]

[9] Krishnamurthy S, Mondal N, Narayanan P, Biswal N, Srinivasan S, Soundravally R. Incidence and etiology of acute kidney injury in southern India. Indian J Pediatr. 2013; 80(3):183-9. [DOI:10.1007/s12098-012-0791-z] [PMID]

[10] Prodhan P, McCage LS, Stroud MH, Gossett J, Garcia X, Bhutta AT, et al. Acute kidney injury is associated with increased in-hospital mortality in mechanically ventilated children with trauma. J Trauma Acute Care Surg. 2012; 73(4):832-7. [DOI:10.1097/TA.0b013e31825ab14f] [PMID]

[11] Nawaz S, Afzal K. Pediatric acute kidney in North India: A prospective hospital-based study. Saudi J Kidney Dis Transpl. 2018; 29(3):689. [DOI:10.4103/1319-2442.235172] [PMID]

[12] Mehta P, Sinha A, Sami A, Hari P, Kalaivani M, Gulati A, et al. Incidence of acute kidney injury in hospitalized children. Indian Pediatr. 2012; 49(7):537-42. [DOI:10.1007/s13312-012-0121-6] [PMID]

[13] Bhojani S, Stojanovic J, Melhem N, Maxwell H, Houtman P, Hall A, et al. The Incidence of paediatric acute kidney injury identified using an AKI e-alert algorithm in six english hospitals. Front Pediatr. 2020; 8:29. [DOI:10.3389/fped.2020.00029] [PMID] [PMCID]

[14] Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL. Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med. 2017; 376(1):11-20. [DOI:10.1056/NEJMoa1611391] [PMID] [PMCID]

[15] Segarra A, Del Carpio J, Marco MP, Jatem E, Gonzalez J, Chang P, et al. Integrating electronic health data records to develop and validate a predictive model of hospital-acquired acute kidney injury in non-critically ill patients. Clin Kidney J. 2021; 14(12):2524-33. [DOI:10.1093/ckj/sfab094] [PMID] [PMCID]

[16] Schaffzin JK, Dodd CN, Nguyen H, Schondelmeyer A, Campanella S, Goldstein SL. Administrative data misclassifies and fails to identify nephrotoxin-associated acute kidney injury in hospitalized children. Hosp Pediatr. 2014; 4(3):159-66. [DOI:10.1542/hpeds.2013-0116] [PMID]

[17] Moffett BS, Goldstein SL. Acute kidney injury and increasing nephrotoxic-medication exposure in noncritically-ill children. Clin J Am Soc Nephrol. 2011; 6(4):856-63. [DOI:10.2215/CJN.08110910] [PMID] [PMCID]

[18] Shalaby MA, Sawan ZA, Nawawi E, Alsaedi S, Al-Wassai H, Kari JA. Incidence, risk factors, and outcome of neonatal acute kidney injury: a prospective cohort study. Pediatr Nephrol. 2018; 33(9):1617-24. [DOI:10.1007/s00467-018-3966-7] [PMID]

[19] Hsu CN, Chen HL, Tain YL. Epidemiology and outcomes of community-acquired and hospital-acquired acute kidney injury in children and adolescents. Pediatr Res. 2018; 83(3):622-9. [DOI:10.1038/pr.2017.262] [PMID]

[20] McGregor TL, Jones DP, Wang L, Danciu I, Bridges BC, Fleming GM, et al. Acute kidney injury incidence in noncritically ill hospitalized children, adolescents, and young adults: a retrospective observational study. Am J Kidney Dis. 2016; 67(3):384-90. [DOI:10.1053/j.ajkd.2015.07.019] [PMID] [PMCID]

[21] Siew ED, Matheny ME, Ikizler TA, Lewis JB, Miller RA, Waitman LR, et al. Commonly used surrogates for baseline renal function affect the classification and prognosis of acute kidney injury. Kidney Int. 2010; 77(6):536-42. [DOI:10.1038/ki.2009.479] [PMID] [PMCID]

[22] Newman DJ. Cystatin c. Ann Clin Biochem. 2002; 39(2):89-104. [DOI:10.1258/0004563021901847] [PMID]

[23] Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: A systematic review. Kidney Int. 2008; 73(9):1008-16. [DOI:10.1038/sj.ki.5002729] [PMID]

[24] Finney H, Newman DJ, Thakkar H, Fell JM, Price CP. Reference ranges for plasma cystatin C and creatinine measurements in premature infants, neonates, and older children. Arch Dis Child. 2000; 82(1):71-5. [DOI:10.1136/adc.82.1.71] [PMID] [PMCID]

[25] Zappitelli M, Moffett BS, Hyder A, Goldstein SL. Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare centre: A retrospective cohort study. Nephrol Dial Transplant. 2011; 26:144-50. [DOI:10.1093/ndt/gfq375] [PMID]

[26] Elmas AT, Tabel Y, Elmas ON. Serum cystatin C predicts acute kidney injury in preterm neonates with respiratory distress syndrome. Pediatr Nephrol. 2013; 28(3):477-84. [DOI:10.1007/s00467-012-2331-5] [PMID]

[27] Yong Z, Pei X, Zhu B, Yuan H, Zhao W. Predictive value of serum cystatin C for acute kidney injury in adults: A meta-analysis of prospective cohort trials. Sci Rep. 2017; 7(1):1-11. [DOI:10.1038/srep41012] [PMID] [PMCID]

[28] Filler G, Lepage N. Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? Pediatr Nephrol. 2003; 18(10):981-5. [DOI:10.1007/s00467-003-1271-5] [PMID]

[29] Nakhjavan-Shahraki B, Yousefifard M, Ataei N, Baikpour M, Ataei F, Bazargani B, et al. Accuracy of cystatin C in prediction of acute kidney injury in children; serum or urine levels: Which one works better? A systematic review and meta-analysis. BMC Nephrol. 2017; 18(1):1-3. [DOI:10.1186/s12882-017-0539-0] [PMID] [PMCID]