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Original Research Article

Prevalence, risk factors and outcomes of acute kidney injury in critically ill children with hematological malignancies

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ABSTRACT

Background: Limited data is available on acute kidney injury (AKI) in critically ill children with hematological malignancies. The aim of this study is to assess the rate, risk factors and outcome of AKI in children with hematological malignancies admitted in the pediatric intensive care unit (PICU) of a large tertiary-care pediatric oncology referral center in Karachi.
Methods: We conducted a retrospective, cross-sectional study on critically ill children with hematological malignancies who developed AKI and were admitted in PICU from July 2017 to June 2019. Demographic data, clinical profile, and outcomes were included. AKI was defined according to the kidney disease: improving global outcomes (KIDGO) criteria.
Results: Of 399 critically ill children with a hematological malignancy, 85 (21.33%) patients developed AKI. The mean age was 7.8±3.8 years and 66% were male. The most common diagnosis was acute lymphoblastic leukemia (ALL) (50%). Dialyitc therapy was initiated in 9 patients (2.3%) only. The risk factors for AKI were tumor lysis syndrome ($p=0.001$), exposure to nephrotoxic drugs ($p<0.001$), septic shock ($p<0.001$), use of mechanical ventilation ($p<0.001$), need of vasoactive drugs ($p<0.001$) and age ($p<0.001$). Kaplan-Meier survival analysis showed that median survival time in children with AKI was 11 days (95% CI 7.6–14.4) while median survival time in children without AKI is significantly higher (log rank test $p<0.001$). By multivariate analysis, AKI is an independent risk factor for mortality [OR 20.02; 95% CI 8.14-49.28; $p<0.001$]. The mortality rate was 63.5% in patients with AKI and 8.6% in patients without AKI ($p<0.001$).
Conclusions: AKI occurred in 21.3% of critically ill children with hematological malignancies and is associated with age, organ dysfunction, sepsis, tumor lysis syndrome and exposure to nephrotoxic drugs. AKI is an independent risk factor for high mortality rate in this population.

Keywords: Hematological malignancy, AKI, PICU, Children

INTRODUCTION

The outcomes of patients with hematological malignancies (HM) have improved significantly over the last several decades, with a mortality risk reduction from 9.9% to 98.9% in some developed countries.[1] Recent advances in technology and monitoring have led to significant improvement in the outcome of children with cancer admitted in pediatric intensive care units.[2] Critically ill children with hematological malignancies (CICHM) are highly vulnerable to the development of acute kidney injury (AKI), and the causes are often multifactorial.[3-5]

AKI is a known life-threatening complication in critically ill children and is independently associated with mortality in the pediatric intensive care unit (PICU).[6] The incidence of AKI is reported in the range of 30-68% of critically ill adults with hematological malignancies, and AKI is

associated with a mortality rate of 60-80%.[5,7,8] It is clinically useful to categorize the cause of AKI as prerenal, intrinsic, and post-renal etiologies. Volume depletion (due to inadequate intake, diarrhea, and vomiting) and hypoperfusion (due to sepsis and cardiac dysfunction) are important causes in the pediatric age group. Intrinsic renal causes include tumor deposits and metabolic disturbance from tumor lysis syndrome (especially with large tumor loads and rapidly growing cancers like Burkitt's lymphoma and exposure to nephrotoxic medications, including exposure to intravenous radio-contrast for computed tomography (CT) scans conducted during evaluation.[9,10] The kidney is the most common extracellular site of leukemic and lymphomatous infiltrates, and tumor cells can be found in up to 30% of patients with lymphoma and up to 60% in the autopsy. Renal infiltration alone rarely causes AKI unless there is tubular compression and disruption of microcirculation. Post-renal causes include obstructive nephropathy related to retroperitoneal lymphadenopathy or tumor masses.[11] There has been a significant limitation in estimating accurate epidemiology of AKI, including in critically ill children, due to the use of more than 30 different AKI definitions in the medical literature. The kidney diseases: improving global outcomes (KIDGO) initiative developed AKI guidelines in 2011 with a standardized AKI definition in critically ill patients that better describe epidemiology.[12] Most studies in pediatric oncology from the intensive care units consider AKI a significant determinant of the overall outcome. In adult patients with malignancies managed in critical care units, clinical reports of AKI are available in the literature.[5,8] These reviews highlight the critical importance of renoprotective strategies for possible prevention and early intervention to reduce the associated morbidity, mortality, and economic cost in these patients. The data is scarce on AKI in critically ill children with hematological malignancies from the PICU setting. This study's objective is to determine the prevalence, risk factors, and outcome of AKI in all critically ill children with HM admitted in our critical care unit.

METHODS

This retrospective-cohort study includes critically ill children (1 month to 16 years) with hematological malignancies admitted in a closed multi-disciplinary PICU associated with a sizeable pediatric oncology unit of a tertiary-care hospital from July 2017 to June 2019. The patient cohort had a hospital-stay >48 hours and had at least two serum creatinine levels measured 48 hours apart. All children with underlying chronic kidney disease were excluded. This study was approved by the institutional ethical review committee (IRD_IRB_2019_09_011). The following information was extracted from the hospital electronic medical record for data analysis: age, gender, height weight, provisional diagnosis (leukemia/lymphoma), and hospital length of stay. The laboratory data included serum creatinine at admission and 48-hours, white cell count (WBC), serum potassium, phosphorus, calcium, and uric acid levels. The treatment data retrieved included the use of mechanical ventilation, inotropes, blood transfusion, nephrotoxic drugs, patient's fluid balance, and dialytic therapy as needed. The pediatric intensivists managed all patients in collaboration with the pediatric oncologist and pediatric nephrologist as a multi-disciplinary team.

Definitions

Hematological malignancy

A neoplastic disease of the hematopoietic and lymphoid tissues with a clinical presentation as leukemia or lymphoma. The disease was confirmed on peripheral smear, bone marrow, or tissue histopathology.[13]

Hyperleukocytosis

It is defined as WBC >100,000/microliter.[9,14]

Acute kidney injury

AKI is defined as a rise in serum creatinine based on KIDGO criteria. Urine output was not used to define or stage AKI in our study. Our laboratory uses a modified Jaffe reaction to measure serum creatinine.[12]

Severe sepsis/septic shock

It was defined by the International Pediatric Sepsis Consensus's definition.[15]

Tumor lysis syndrome

It is defined based on the Carol and Bishop criteria.[16]

Positive fluid balance

It is defined as daily total fluid intake significant higher than total output and accumulation of fluid ≥5%.[17]

Non-dialytic therapy

It includes supportive treatment of AKI, such as fluid restriction, use of diuretics to promote urine output and avoidance of nephrotoxic medications.

Dialytic therapy

It includes renal replacement therapy [peritoneal dialysis (PD), intermittent hemodialysis (IHD), or continuous renal replacement therapy (CRRT)].

Statistical analysis

Data was entered in and analyzed through STATA-version 12. Summary statistics were generated using frequency and percentages for qualitative data and mean±standard deviation for quantitative data. Where

required, Pearson's Chi-square test was applied, and p value ≤0.05 was taken as significant. Binary logistic regression analyses were run for the risk factors of AKI and mortality. A priori recognized exposures (tumor lysis syndrome, nephrotoxic drugs, inotrope use, mechanical ventilation) and co-morbidities (septic shock, mediastinal mass) thought to be associated with AKI and mortality were first to run one at a time – univariate analysis. Variables with a significant association (p value ≤0.20) were included in the final multivariable model. The unadjusted and adjusted associations for these risk factors are reported as odds ratios (OR) with a 95% confidence interval. The Hosmer Lemeshow test ascertained the goodness of fit of the final model. The survival curve has been constructed according to the Kaplan–Meier method. A comparison of mortality across the occurrence of AKI (yes/no) was performed using the log-rank test. All tests were two-sided, and p values ≤0.05 were taken as statistically significant.

RESULTS

There were 399 patients included, with a mean age of 7.81±3.9 years, and 259 (65%) patients were male. Acute leukemia was the underlying diagnosis of malignancies in 77.4% (n=309) patients. Acute kidney injury developed in 21.3% (n=85) patients. The frequencies of stage 1, 2 and 3 were 54% (n=46), 27% (n=23) and 19% (n=16) respectively. Renal replacement therapy (4 underwent-CRRT and 5 underwent-IHD) was used in 9/19 (47.3%) children with stage 3 AKI. Of all, mechanical ventilation was needed in 89 (22.3%), inotropic support in 95 (23.8%), and dialysis in 9 (2.3%). Among all children with AKI, 10.5% patients needed renal replacement therapies. Renal replacement therapy (4 underwent-CRRT and 5 underwent-IHD) was used in 9/19 (47.3%) children with stage 3 AKI. Overall mortality was 20.3% (n=81) in the study cohort. The characteristics of AKI (n=85) and non-AKI (n=314) groups are compared in Table 1. Children in the AKI group children were significantly older than the non-AKI group (9.34±3.9 versus 7.39±3.7, p value <0.001). The use of mechanical ventilation (51% versus 14.7%), inotropes (53.6% versus 16%) and dialysis (10% versus 0%) was significantly higher (p value <0.001) in the AKI group compared to the non-AKI group. The mortality rate was higher in the AKI group compared to the non-AKI group (63.5% versus 8.6%, p value <0.001). The proportion of nephrotoxic drugs use (21% versus 10%), presence of positive fluid balance (42% versus 2%) and septic shock (21.7% versus 7%) were significantly higher in the AKI group (p value 0.004, <0.001 and <0.001 respectively) compared to the non-AKI group (Table 1). By multivariate logistic regression analysis, the independent predictors of AKI in our cohort were age [OR 1.16, 95% CI 1.06-1.26, p <0.001], positive fluid balance [OR 25.40, 95% CI 8.04-80.24, p<0.001], use of mechanical ventilation [OR 2.73, 95% CI 1.14-6.54, p=0.024], administration of blood products [OR 6.35, 95% CI 1.29-31.20, p-0.023)] and presence of TLS [OR 3.96, 95%CI 1.88-8.34; p< 0.001]. The independent predictors of mortality in our study were presence of AKI [OR 20.02, 95% CI-8.14-49.28, p<0.001], exposure to nephrotoxic agents [OR 4.48, 95% CI 1.64-12.26, p=0.004], use of mechanical ventilatory support [OR 5.08, 95% CI 1.88-13.71, p<0.001] and need of vasoactive support [OR-7.48 95% CI 2.65-21.07, p<0.001]. The Kaplan-Meier survival estimates showed that median survival time in children with AKI was 11 days (95% CI 7.6-14.4), and the median survival time of children without AKI was significantly high (log-rank test; p<0.001) (Figure 1).

Table 1: Characteristics of critically ill children with malignancy (n=399) with (n=85) and without AKI (n=314).

Variables	All (n=399)	AKI (n=85)	Non-AKI (n=314)	P value
Age (years)	7.81±3.9	9.34±3.9	7.39±3.7	< 0.001
Gender (male)	259 (65)	62 (72.94)	197 (62.74)	0.12
Underlying malignancy				
Acute leukemia	309 (77.4)	64 (75.3)	245 (78.0)	0.59
Lymphoma	90 (22.6)	21 (24.7)	69 (22.0)	
Organ support therapy				
MV	89 (22.3)	43 (51.2)	46 (14.7)	<0.001
Inotrope	95 (23.8)	45 (53.6)	50 (16.0)	<0.001
Dialysis	9 (2.3)	09 (10.6)	00 (00)	<0.001
Risk factors				
TLS-L	120 (30.1)	49 (57.6)	71 (22.6)	<0.001
TLS-C	19 (4.8)	16 (18.8)	03 (0.9)	<0.001
Hyperurecemia (>8.0)	123 (30.8)	48 (56.5)	75 (23.9)	<0.001
Hyperphosphatemia (>6.5)	44 (11)	29 (34.1)	15 (17.6)	<0.001
Hyperkalemia (>5.3)	20 (5.0)	12 (14.1)	08 (2.5)	<0.001
Elevated creatinine (>2.0)	23 (5.8)			
Nephrotoxic drugs	49 (12.3)	18 (21.2)	31 (9.9)	0.004
Positive FB	41 (10.3)	35 (42.2)	06 (1.9)	<0.001
Blood therapy	348 (87.2)	78 (92.8)	270 (86.3)	0.13

Continued.

Variables	All (n=399)	AKI (n=85)	Non-AKI (n=314)	P value
Hyperleukocytosis (>100,000)	110 (27.6)	28 (32.9)	82 (26.1)	0.21
Mediastinal mass (+)	59 (14.8)	17 (20.5)	42 (13.4)	0.11
Septic shock	40 (10)	18 (21.7)	22 (7.0)	<0.001
MODS (inotrope+ MV)				
Outcome				
Mortality	81 (20.3)	54 (63.5)	27 (8.6)	<0.001

Table 2: Independent predictors of AKI in critically ill children with hematological malignancy (n=399).

Variables	OR	95% CI	P value
Age (years)	1.16	1.06-1.26	0.001
Positive fluid balance (yes)	25.40	8.04-80.24	0.000
Mechanical ventilation (yes)	2.73	1.14-6.54	0.024
Blood transfusion (yes)	6.35	1.29-31.20	0.023
Lab. TLS (yes)	3.96	1.88-8.34	0.000
Clinical TLS (yes)	47.20	5.41-411.98	0.000
Nephrotoxic exposure (yes)	2.46	0.88-6.89	0.086

Table 3: Independent predictors of mortality in critically ill children with hematological malignancy (n=399).

Variables	OR	95% CI	P value
AKI (yes)	20.02	8.14-49.28	0.001
Nephrotoxic exposure (yes)	4.48	1.64-12.26	0.004
Mechanical ventilation (yes)	5.08	1.88-13.71	0.001
Inotropes (yes)	7.48	2.65-21.07	0.001

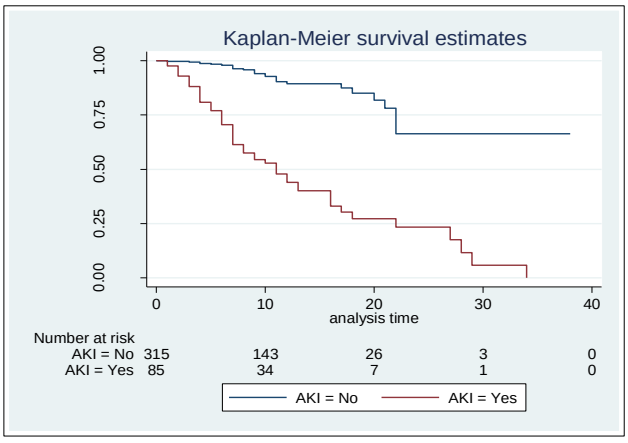

Figure 1: Cumulative survival analysis of critically-ill children with hematological malignancies in presence or absence of AKI.

DISCUSSION

AKI is common in pediatric cancer patients.[18,19] In this study, we described the frequency, risk factors, and outcomes of AKI in critically ill children with hematological malignancies admitted in our PICU. We found that 20.3% of patients developed AKI in our cohort.

In a retrospective cohort study of children with AML, 64% patients developed AKI based on the KIDGO AKI definition.[20] In another pediatric study, AKI developed in 52.6% of their 1868 children with cancer, two-third children had hematological malignancies, and the highest incidence (84.4%) of AKI was in those with AML.[18] Our findings corroborate the results of adult critically ill patients with hematological malignancies.[5,8] In ICU settings, adult patients with hematological malignancy have a higher risk of AKI than other critically ill adult patients, ranging from 10-30% adult who needed RRT in ICU.[21-23] However in our cohort only 2.3% of all CICHM required dialysis compared to 10-30% of adult critically ill patients with hematological malignancies in ICU who needed RRT.[7,8]

It is evident from published literature that AKI is also a widespread organ dysfunction in the general medical or surgical critically ill child. The incidence of AKI based on KIDGO definition varies from 20-33% in multi-disciplinary PICUs in published literature.[24,25] The emergence of biomarkers for early diagnosis of AKI will undoubtedly help in early recognition and prevention of AKI in critically ill children.[26,27] Many studies have demonstrated that AKI is an independent risk factor for mortality in PICUs and is associated with poor outcomes. An extensive database is available on the high incidence (20-86%) and severity of AKI in neonates and infants after cardiac surgeries.[24,28,29]

AKI is also common in children after hematopoietic stem cell transplantation (HSCT) with a reported incidence of 21-84% based on the type of population and criteria used to define AKI.[30,31] Children with severe sepsis is another high-risk population especially in low-resource setting, associated with high AKI rates and mortality. Fitzgerald et al reported a 46% incidence of AKI in severe pediatric sepsis, and 26% had severe AKI stages.[32,33]

Most of the patients in our cohort had multiple causes present in combination leading to AKI in our cohort and which were often present in combination. The risk factors associated with AKI in our cohort were similar to other critical-oncology reports.[3,9,11] Shock and sepsis are the major contributory factors. Volume depletion is widespread in these patients, as they often experience reduced oral intake, vomiting, and diarrhea, as well as poor cardiac reserve, and almost 50% of children with AKI needed vasoactive medications to support perfusion. TLS, either spontaneous or following chemotherapy, is a common risk factor for AKI, was the underlying cause of AKI in 58% in children with AKI in our cohort ($p<0.001$) similar to reported rates of 10-60%.[34,35] We found nephrotoxicity had an odds ratio of 2.46 (0.88-6.89) for the development of AKI similar to Darmon et al.[5] A recent study on the implementation of reno-protective strategies including high vigilance and restricting the use of nephrotoxic medication improved kidney function surveillance by decreasing 45% episodes of AKI (from 3.48 to 1.92 per 1000 patient days).[36] A positive fluid balance was associated with 25 times the odds of associated AKI in our cohort like other published reports.[37]

Adult patients with AKI and underlying hematological malignancy have high mortality rates ranging from 40-77%.[7,8] Our pediatric cohort also showed a similar high in-hospital mortality (63.5%). We found that AKI is a significant and independent predictor of mortality in children with hematological malignancy admitted in PICU like adult critically ill patients with cancer. Children with AKI and a hematologic malignancy had 20 times the odds of death within 11 days of admission despite supportive critical care.

Limitations

The present study has several limitations. The first limitation is the single-center design which makes it un-generalizable. Secondly, on account of the retrospective design, there were missing elements of data from electronic medical records. Further limitations were inability to define the score of severity of illness based on PRISM-III as well as phases of chemotherapy. An important strength of the study is the utilization of a standardized definition of AKI.

CONCLUSION

AKI occurred in 21.3% of critically ill children with hematological malignancies and is associated with age, organ dysfunction, sepsis, tumor lysis syndrome, and exposure to nephrotoxic drugs. AKI is an independent risk factor for high mortality rate among CICHM. Preventive measures, including avoidance of hypoperfusion, overhydration and nephrotoxins, prompt sepsis, and TLS management in this high-risk group, will result in better outcome and cost savings in our low resource settings.

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