ACUTE KIDNEY INJURY (AKI) IN CRITICALLY ILL CHILDREN: INCIDENCE, DIAGNOSIS & OUTCOME AMONG PATIENTS OF ONE OF EGYPTIAN DISTRICTS (BENHA UNIVERSITY HOSPITAL)

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ABSTRACT

***Background**: Acute kidney injury is characterized by sudden and generally revertible renal function impairment involving inability to maintain homeostasis. In pediatrics, the main causes of acute kidney injury are sepsis, use of nephrotoxic drugs and renal ischemia in critically ill patients. The incidence of acute kidney injury in these patients ranges from 20 to 30%, resulting in increased morbid-mortality, a 40 to 90% rate. **Objectives**: This study aimed to evaluate the incidence of acute kidney injury in intensive care unit patients, to categorize the severity of the acute kidney injury according to the Pediatric Risk (R), Injury (I), Failure (F), Loss, End-Stage (pRIFLE), and to analyze outcome predictors. **Methods**: A prospective study of the patients admitted to the pediatric intensive care unit of Benha University Hospital was conducted between June 2012 and July 2013. Patients were evaluated daily for urine output and serum creatinine, and the patients were categorized according to the pRIFLE criteria. **Results**: During the follow-up period, 241 children were admitted, 61 patients were excluded due to exclusion criteria. The incidence of acute kidney injury was 61 cases out of 180 cases (33%), and the maximal pRIFLE score during hospitalization was 36% for (R), 44% for (I) and 20% for (F). The mortality rate was 34.4% in AKI cases. Patients with acute kidney injury had a twice times higher risk of death versus the not exposed patients. **Conclusions**: Acute kidney injury is frequent in critically ill patients. Early diagnosis and prompt and appropriate therapy for each clinical aspect may change this condition's course and severity, and reduce the patients' morbidity and mortality.*

INTRODUCTION

Acute kidney injury (AKI) is characterized by a sudden and generally revertible renal function impairment, involving inability to maintain the homeostasis, and may or not be accompanied by reduced diuresis.Usually, AKI may be categorized as pre-renal, related to reduced renal blood flow (RBF) from inappropriate cardiac output or intravascular volume; intrinsic renal disease, from an insult to the renal parenchyma including ischemic, vascular, tubular or glomerular disorders; and post-renal, due to urinary tract obstruction either in single kidney or both kidneys, during the childhood, the main AKI causes are sepsis, nephrotoxic drugs, and renal ischemia in critically ill patients. [(1)] These patients, particularly those staying in intensive care units (ICUs), are exposed to a number of conditions which may result in renal impairment, thus significantly increasing the morbidity-mortality rate. [(2)]

Among the main causes we should mention: hypovolemia leading to hypoperfusion and consequent hypoxia; inflammatory and thrombotic events caused by sepsis; systemic inflammation from trauma, major surgeries, extracorporeal circulation ;use of vasodilator drugs such as phosphordiesterase inhibitors, sedatives, epidural blockade; vasopressors; and use of nephrotoxic drugs as aminoglycosides, amphotericin B, radiological contrasts, and drugs interfering with the renal hemodynamics such as angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. [(1)] Sepsis, and specially the septic shock, is one of the main causes of AKI. AKI prevalence in sepsis ranges from 9% to 40%, involves poor prognosis, and is associated with a 70% mortality rate. [(3)] Among critically ill renal impaired patients, about 6% may need renal replacement therapy (RRT), with a mortality rate increased by 50 to 80%, particularly associated with sepsis, septic shock, and multiple organ and systems dysfunction MODS. [(4)]

The AKI diagnosis methods include: clinical evaluation of the urinary output and laboratory tests as urinalysis, blood urea nitrogen, and creatinine, however with low sensitivity and specificity. (5) Biomarkers for early AKI detection are currently under investigation ,among them neutrophil gelatinase associated lipocalin(NGAL), cystatin C, interleukin 18, and kidney injury molecule-1 (KIM-1), although these markers have good sensitivity and specificity, they are not routinely used due to their low availability and high costs. (6) In this context, the Acute Dialysis Quality Initiative(ADQI), which involves the participation of nephrologists and intensivists, held in 2002 in the city of Vicenza the Second International Consensus Conference of the ADQI (7) where adult AKI diagnosis criteria were proposed and decided, and detailed published in 2004 with the name RIFLE criteria. These are currently under scientific community evaluation.The RIFLE criteria define three grades of increasing AKI severity (R – Risk of renal dysfunction; I – Injury of the kidney; F –

Failure of kidney function) and two outcome variables (L - Loss of kidney function and E - End-stage kidney disease). For the first three categories, the RIFLE criteria aimed to standardize AKI definition by patients' stratification according to serum creatinine and urinary output changes from baseline. (7) Recently, Akcan-Arikan et al. provided a pediatric patients-modified RIFLE version (pRIFLE), based on a 12 months single center study where 150 critically ill children were prospectively analyzed. (8) The proposed pRIFLE criteria are based on the estimated creatinine clearance (ECC) calculated by means of the Schwartz formula (9) or on the urinary output reduction, in abody weight per hour basis, as detailed on Table 1.

Table (1): pediatric RIFLE classification system

RIFLE	SERUM CREATNINE	URINE OUT PUT
Risk (R)	Serum creatinine increase to 1.5 fold or GFR decreased >25% from baseline	<0.5ml/kg/for 6 hours
Injury (I)	Serum creatinine increase to 2 fold or GFR decreased >50% from baseline	<0.5ml/kg/for 12 hours
Failure (F)	Serum creatinine increase to 3 fold or GFR decreased >75% from baseline, or Serum creatinine(> 4mg/dl)	anuria for 12 hours

AIM OF THE WORK

To evaluate incidence of AKI according to pRIFLEcriteria, associated risk factor and outcome in the PICU.

PATIENTS & METHODS

All consecutive admissions to the Benha university hospital PICU (a twelve beds pediatric ICU) were included in prospective study, from July 2012 to last of June 2013, this study was approved by the Institution's Ethics Committee. This study was explained to the patients' parents or legal representatives, before they were asked to sign the Informed Consent Form.

The exclusion criteria were: Less than one month of age, more than 18 years of age, Less than 24 hours stay in PICU, brain death at admission, chronic kidney disease (GFR is less than 60ml/min/1.73m, for more than 3 months) & end stage renal disease on regular hemodiaysis. The included patients were followed from admission to discharge or death on daily biases for clinical, laboratory parameters, certain risk factors and outcome according to arranged protocol with consideration of exclusion criteria, each readmission after more than 24 hours after discharge is considered as a new admission.

The cases were divided in to two major groups. **Group (A):** PICU cases with AKI (Acute kidney injury), and this group were subdivided into 3 subgroups according to RIFLE classification (Risk group , injury group and failure group).**Group (B):** PICU case without AKI (Acute kidney injury).For kidney injury degree (pRIFLE) **Akcan-Arikan et al.,**[8] categorization, were analyzed daily: depending on serum creatinine level, and the estimated creatinine clearance was calculated according to the Schwartz formula.[9]The patients admitted with missing baseline renal function data had the normal clearance value of 100mL/1.73 m/24h considered as reference, as proposed by Akcan-Arikan et al., [9]

The data collected were statistically analyzed. The quantitative variables were expressed as means and standard deviations, and median values .The categorical variables were described by their absolute (n) and relative (%) frequencies. The association between the different variables was analyzed by appropriate hypothesis testing (Pearson's Chi-square, exact Fisher's, Mann-Whitney's, and Kruskall-Wallis tests(The relative risks (RR) for patients' complications & outcomes for either with or without acute renal failure were calculated, as well as their respective 95% Confidence Intervals (95%CI). P values $\leq$ 0.05were considered significant. [10] The analysis was performed using the SPSS version 16.

RESULTS

During this 12 months period 241 children were admitted to the PICU, being 61 of them excluded for presence of exclusion criteria. Of the 180 children in this study, (60.5%) were male, the age group range was from one month up to 14 years , of 180 patients 61 patients were AKI (33%) according to pRIFLE . Regarding to diagnosis at admission the most common admission diagnosis was infection 51.1% then DKA (8.3)%, neurological conditions(7.8)% & cardiac failure(7.8)%.The comparison between group (A) & (B) regarding to risk factors which may predispose to acute kidney injury (AKI),

the group (A) was significantly associated with mechanical ventilation, infection, nephrotoxic drugs, shock, haemato- oncological pathologies, and intrinsic renal disease ($p<0.05$) see table (2**).Regarding duration of PICU admission**, in the Group (A) the Median value of duration of PICU admission was 7days while in Group (B) was 5days.There was significant difference between the group A & B regarding admission duration in days as group A was associated with longer PICU admission ($P<0.05$) .Regarding mortality in group A Survived /died cases was (65.6 / 34.4)% and in group (B) was (84.8/15.2)% with significant difference between the two groups as group (A) was associated with higher mortality with Relative risk (RR) was 1.9.

Table (2): Statistical comparison between groups (A)&(B)regarding risk factors

Item	Group A No = 61		Group B No = 119		Chi-square	P - value
	No	%	No	%		
Mechanical ventilation	24	39.3	20	16.8	11	**<0.01***
Associated Organ dysfunction	21	34.4	18	15.1	8.8	**<0.01***
Shock	14	22.9	9	7.5	8.5	**<0.01***
Bleeding	8	13.1	1	0. 8	12.7	**0.00***
Nephrotoxins	17	27.8	14	11.7	7.3	**<0.01***
Infection	30	49.1	29	24.3	11.2	**<0.01***
Onco- haematological pathology on admission	3	4.9	0	0	2.4	**<0.05***
Intrinsic renal disease on admission	5	8.2	1	0.8	2.6	**<0.05***
Survived	40	65.6	101	84.8	10.1	**> 0.01**
Died	21	34.4	18	15.2		

In this study the different **AKI classes incidences** at maximal RIFLE were as the followings: Class (R) was 22 cases out of 61 (36%),class (I) was 27 cases out of 61 (44%) and Class (F) was 12 cases out of 61 (20%).In this study when the three classes of AKI were compared regarding the **selected risk factors** for AKI (mechanical ventilation , shock , nephrotoxins and sepsis) to obtain data which refer to if these risk factors affect the severity of AKI level or not , we found statistically significant difference regarding sepsis , haemto –oncological pathologies and intrinisic renal disease($p<0.05$) and no statistical significant difference regarding nephrotoxins & shock among AKI classes.

AKI onset on admission Class (R) cases of AKI onset on admission were (1) case out of 22 (4.5%),class (I) were (9) cases out of 27 (33.3%) and class (F) were (12) cases out of 12 (100%).With comparison of these subgroups, there was significant difference among the AKI classes regarding AKI onset on admission ($p< 0.05$), as class (F) was significantly associated with larger number of cases of AKI onset on admission than in other classes, and this reveals that the sever AKI cases were associated with early onset of AKI.

Regarding AKI onset in the 1st week of admission Class (R) cases of the 1st week AKI onset of admission were (20) cases out of 22 (90.9%),Class (I) cases of the 1st week AKI onset of admission were (26) cases out of 27 (96.3%) and Class (F) cases of the 1st week AKI onset of admission were (12) cases out of 12 (100%).With comparison of these subgroups, there was no significant difference among the AKI classes regarding AKI onset on the first week of admission ($p > 0.05$).

AKI etiology (primary versus secondary causes) among AKI classes Class (R) the primary / secondary cause's ratio was (3/19) (13.6/86.4)%, class (I) was (1/26) (4/96)% and class (F) was (8/4) (67/33)%. With comparison of the AKI classes regarding the primary to secondary etiology we found a highly statistically significant difference as classes (R) & (I) were highly significantly associated with secondary AKI in comparison to class (F) which was significantly associated to primary AKI ($p<0.01$) , this refer to the vast majority of AKI etiology in the PICU were related to secondary causes more that primary causes .

Complicated cases among AKI classes. The complicated cases distribution among AKI classes. Class (R) the complicated cases were (6) out of 22, (27.3%), Class (I): were (17) out of 27, (63%) and Class (F) were (11) out of 12, (91.7%).the class (F) & (I) were Highly significantly associated with larger number of complicated cases than class (R) ($P<0.01$).

Therapy mode among AKI classes, Class (R) conservative/ RRT ratio was (22/0) (100% / 0%), class (I) was (27/0) (100% / 0%) &Class (F) was (6/6) (50% / 50%). In comparison of AKI classes regarding therapy, the class (F) was absolute significantly associated with cases which received replacement therapy in comparison with classes (R) or (I).

For reversal of renal function (prognosis) with 1st 48 hours of admission Class (R) cases that had early reversal of renal function were (19) cases out of 22 (86.3%), Class (I) were (18) cases out of 27 (66.6%) and Class (F) were (2) cases out of 12 (16%). In comparison of three classes of AKI we found that class (R) & (I) were significantly associated with improved renal function with 1st 48 hours of

admission in comparison to class (F) with p value of (0.00) which refer to absolute significant difference

Regarding survival among AKI classes Class (R): survived / died cases ratio was (21/1) - (95.4/4.6)%, Class (I): was (20/7) -(74/26)% and Class (F)was (5/7) - (41.7/58.3)%. The comparison of the three classes regarding survived / died ratio revealed statistically significant difference among the three classes as the class (F) had significant larger number of died cases than the other classes (P<0.05).

Table (3): Statistical comparison among AKI classes regarding risk factors , etiology , complications , prognosis , therapy & outcome

Item	Risk (R) NO=22		Injury (I) NO=27		Failure (F) NO=1K2		p
	No	%	No	%	No	%	
MV	5	22.7	13	48	6	50	>0.05
Shock	3	13.6	8	30	3	25	>0.05
Organ dysfunction	7	32	8	30	6	50	>0.05
Coagulopathy	0	0	5	18	3	25	<0.05*
Nephrotoxins	5	23	9	33	3	25	>0.05
Sepsis	6	27	14	52	10	83	<0.01*
Onco-haematological	0	0	0	0	3	25	0.00*
Intrinsic renal	0	0	0	0	5	41.6	0.00*
Primary AKI	3	13.6	1	4	8	67	<0.01*
Secondary AKI	19	86.4	26	96	4	33	
Complicated AKI	0	0	3	11	11	91.7	<0.01*
Improvement with conservative therapy	19	86.3	18	66.6	2	16	0.00*
Conservative	22	100	27	100	6	50	0.00*
RRT	0	0	0	0	6	50	
Survived	21	95.4	20	74	5	41.7	<0.05*
Died	1	4.6	7	26	7	58.3	

DISCUSSION

AKI has a known catastrophic impact on critically ill patients. It is common among them, and its cause is mostly multifactor. AKI may progress to renal failure, preventing the kidneys to play their most important role, homeostasis. The incidence of AKI in this study was (33%), which 61 cases out of 180 cases admitted to the PICU. As regard to the incidence of AKI in various studies, the incidence was variable as Hoste et al., (11) reported incidence of 67.2% while Ostermann & Chang (2) reported AKI incidence of 35.8% and Bagshaw et al.,(12) reported incidence of 36.1%, This variation can be explained by specific epidemiological characteristics according to the area of study

Regarding duration of PICU admission, there was significant difference between the group A & B regarding admission duration in days as group A was associated with longer PICU admission (P<0.05) .This agree with Akcan-Arikan et al., (8) , Duzova et al., (13) as they reported the AKI cases which diagnosed on basis of RIFLE criteria were associated with longer PICU stay in comparison with non AKI group and it means that AKI cases consume prolonged time in intensive care units and so resources consuming , but plotz et al ., (14) reported that there was no significant difference between the AKI cases & non AKI cases regarding the admission PICU duration and this was explained by variation of diseases which admitted to PICU which associated with prolonged admission length without presence of AKI .

For mortality & survival, the group A was highly significantly associated with higher mortality and lower survival (P<0.01) with relative risk (RR) of 1.9 than group B and this means that the AKI cases were twice times higher in mortality than that of non AKI cases .This agree with keina et al., (15) who reported that the mortality in AKI cases was ten times higher than that in non AKI cases also plotz et al .,(14) identified a five times higher mortality in AKI cases than that in Non AKI cases ,Hoste et al., (11) identified three times higher mortality rates in the exposed group, Ostermann & Chang(2) identified that AKI patients had a four times higher mortality versus non-AKI patients. This was explained by AKI is associated with a number of life-threatening complications, which increase the mortality rate in these cases,

In this study the different AKI classes incidences at maximal RIFLE were as the followings: Class (R) was 22 cases out of 61 (36%), class (I) was 27 cases out of 61 (44%) and class (F) was 12 cases out of 61 (20%). The incidence was variable at different studies as keina et al., reported that the maximal RIFLE score found during the patients stay was 39.1% for class (R), 39.1% for class (I) and 21.8% for class (F) while Akcan-Arikan et al., (8) found 48.8%, 26% and 25.2%, respectively, and plotz et al ., (14) reported incidences of 52%, 37% and 11%, respectively .This variability of incidences can be explained by keina et al., (15) who reported that the cause of this variability was due to different populations studied, and also by the different ICU characteristics.

Regarding AKI etiology, with comparison of the AKI classes regarding the primary to secondary etiology we found that classes (R)& (I) were highly significantly associated with secondary AKI in comparison to class (F) which was significantly associated with primary AKI , this refer to the vast majority of AKI etiology in the PICU were related to secondary causes more that primary causes, and this agrees with Paula Dennen et al.,(16) who reported that the cause of AKI in the ICU is frequently

develops from a combination of hypovolemia, sepsis, medications, and hemodynamic perturbations.

Regarding AKI onset on admission there was significant difference among the AKI classes regarding AKI onset on admission ($p< 0.05$), as class (F) was significantly associated with larger number of cases of AKI onset on admission than in other classes, and this reveals that the sever AKI cases were associated with early onset of AKI. Regarding AKI onset in the 1st week of admission ,Class (R) cases of the 1st week AKI onset of admission were (20) cases out of 22 (90.9%),Class (I) cases of the 1st week AKI onset of admission were (26) cases out of 27 (96.3%) and Class (F) cases of the 1st week AKI onset of admission were (12) cases out of 12 (100%).With comparison of these subgroups, there was no significant difference among the AKI classes regarding AKI onset on the first week of admission ($p > 0.05$), and means that the vast majority of AKI cases onset was in the first week of admission and AKI was unlike to develop after first week of admission This agree with Akcan-Arikan et al., (8) who reported that the AKI occurred very early in the PICU course most often within the first week of admission and patients who did not develop AKI with in the first week of admission were very unlikely to develop AKI later .this data support previous pediatric studies demonstrating that children develop their maximum number of organ failure early in the intense care unit (ICU) course.

In this study Incidence of RRT versus Conservative was: 55 cases out of 61 (90%) received conservative therapy &6 cases (10%) received renal replacement therapy .This refers to the majority of cases of AKI in the PICU received conservative therapy. These results agree with keina et al., (15) who reported that renal replacement therapy was required by 11.6% patients and Akcan-Arikan et al., (8) who reported that 8.9% of patients needed renal replacement therapy.

Therapy mode among AKI classes, the class (F) was absolute significantly associated with cases which received replacement therapy in comparison with classes (R) or (I). This agree with keina et al., (15) who reported that the vast majority of cases which needed renal replacement therapy were in class (F), representing 40% of this subgroup also Akcan-Arikan et al., (8) found 71% of the class (F) level patients received renal replacement therapy while plotz et al ., (14) reported incidence of 14.3% of class F needed replacement therapy . The difference in values and incidences of RRT for Class F in the previous studies can be explained by keina et al., (15) who reported that the difference in these studies was due to lack of specific criteria for RRT indications and probably due to different population characteristics, although all were critically ill patients.

For reversal of renal function with 1st 48 hours of admission Class (R) cases that had early reversal of renal function. In comparison of the three classes of AKI we found that class (R) & (I) were significantly associated with improved renal function with 1st 48 hours of admission in comparison to class (F), this agree with Akcan-Arikan et al., (8) who reported that early reversal of AKI was likely to occur in patients with class R than in those in class I & F.

Regarding survival among AKI classes, there was statistically significant difference among the three classes as class (F) had significant larger number of died cases than the other classes, this agrees with Hoste et al., (11) , Akcan-Arikan et al., (8) & keina et al., (15) who reported that mortality increased in parallel with the AKI severity groups, which was also identified by other authors .A similar mortality rate was found for AKI R and I levels (14.8%). (keina et al., 2010) also reported that the level R has increased progression to more severe levels, and high mortality rates in this level similar to level I (more severe), emphasize the relevance of the early diagnosis and therapy. It is thus suggested that early AKI diagnosis will result in improved prognosis and, specially, reduced mortality , Yet patients categorized as level F had a substantially higher mortality rate (60%) versus other AKI levels, showing that the level F represents a severe insult condition, with severe functional impairment and decreased reversibility, nevertheless the best of the therapeutic efforts.

CONCLUSION

In this study the incidence of AKI in critically ill patients was high. AKI was directly related to increased mortality, with a twice times higher risk of death versus patients without AKI.. The time of hospital stay was determinant. It was seen that patients with AKI staying longer. Regarding the AKI-associated prognostic factors, it was identified that infection, bleeding, haemato-oncological pathology, intrinsic renal disease on admission lead to more severe AKI, and dialysis was required more frequently in the patients with more severe AKI. The pRIFLE criteria were shown to be important for early AKI risk patients detection, suggesting that, with its use, earlier diagnosis will imply more careful and less delayed therapy, which in long term will lead to reduction in this disease related morbidity and mortality.

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