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Study of Morbidity and Mortality of The Cardio-Renal Syndrome in The Pediatric Intensive Care Unit

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ABSTRACT

Background: Cardio-renal syndrome (CRS) is a term that describes the acute or choric comorbid state of the heart and kidney. Cardio renal axis is of significant importance in pediatric patients in acute conditions as identification and optimum management of this condition improves the survival in the PICU.

Objectives: This study aimed to describe the pattern of CRS in our unit and to compare it with other PICU centers and to highlight the impact of this condition on PICU-admitted children.

Patient and methods: This study was carried out in Benha University Hospital, Egypt on 321 critically ill patients aged from 1 month to 18 years.

Results: In this study, we described 321 children patients admitted to the PICU, out of which 79 (24.9%) acquired cardio-renal syndrome. The primary diagnosis leading to admission to PICU was attributed to CVS causes like heart failure and arrhythmia in 51 patients (15.9%), CNS in 109 cases (34%) with the predominance of CNS infection being the commonest. There was no significant correlation between the severity of kidney injury and the stage of the heart failure in all types of CRS expect in type III. PICU stay significantly longer with CRS III (mean 10.4 ± 5.1 days) compared to other types. The mortality was the highest in type 5 (72.8% compared to other types).

Conclusion: CRS is an important PICU phenomenon that needs to be early recognized and managed to improve the survival of PICU patients and to reduce the mortality.

Keywords: Cardio-renal syndrome, AKI, CKD, PICU, Heart failure.

INTRODUCTION

Acute or chronic malfunction in one organ may cause acute or chronic malfunction in the other organs. In the illness known as CRS, which affects both the heart and the kidneys [1,2].

Heart failure is a clinical illness characterized by elevated venous pressure, early myocardial cells loss, and diminished cardiac output. Acute kidney injury (AKI) is a severe clinical condition characterized by abnormal kidney functioning, with or without testing evidence (often within 48 hours of bilateral renal affections of any degree) [3-5].

CRS was divided into five categories: Acute cardiac failure that results in acute renal damage is a characteristic of type I. Chronic cardiac dysfunction of type II results in chronic renal disease. Acute renal injury that results in heart failure or an arrhythmia as a result of acute cardiac dysfunction characterizes type III. Type IV describes chronic kidney disease leading to chronic cardiac abnormality, while type V is the presence of combined cardiac and renal dysfunction due to systematic disorder [6]**.** There are many mechanisms explaining the heart-kidney interaction including neuro-hormonal activation of renin-angiotensin-aldosterone axis, high abdominal pressure, increased venous pressure and endothelial dysfunction.

Free radical production and cytokine-induced apoptosis are also contributing mechanisms. Defects in perfusion autoregulation pathways contribute to CRS in addition to old well-known theories of abnormal hemodynamics, anemia, hypoxia and hypertension [7].

Although the link between the kidney and heart was studied thoroughly, the CRS is introduced in pediatric literature in 2008 following a cohort study at Cincinnati children hospital in the USA between 2003 and 2005 on children admitted with acute decompensated heart failure [8].

PATIENTS AND METHODS

This was a prospective cohort study that was conducted over a period from 1/10/2013 till 30/9/2017. The study was approved by the ethical committee of Benha University. All admitted cases to the PICU during the aforementioned period who met PICU admission criteria were included in the study. The total number of patients was 321 cases (169 male and 152 female).

Inclusion criteria (PICU admission criteria):

Patients with severe or potentially life-threatening pulmonary or airway disease such as those requiring endotracheal intubation and those with rapidly progressive pulmonary lower or upper airway disease. Those with life-threatening or unstable cardiovascular disease and those with acute or unstable neurological condition. Pediatric patients with acute hematologic/oncologic emergencies like those with severe coagulopathy. Those with GIT, renal, metabolic or multisystem affection were also included [9].

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Exclusion criteria: Patients who were below 1 year or above 18 years. Those who have been discharged or died before accurate cardiac or renal function states were assessed and those with brain stem death.

All patients were subjected to the following:

Thorough history taking (including any current illnesses with emphasis on symptoms suggestive of cardiac decompensation, feeding difficulty, irritability, dyspnea or orthopnea). History suggestive of renal dysfunction was elaborated (oliguria, polyuria, dark urine, or dysuria). Ongoing symptoms of chronic renal or cardiac decompensation were also assessed (pallor or hypertension. These patients were fully examined, and the vital observations were assessed. The weight and height were noted in addition to head circumference as appropriate. The patients were strictly monitored for their clinical progression and for their vital observations (heart rate, respiratory rate, O_2 saturation and blood pressure and temperature monitoring). The patients had investigations during their admission (FBC, CRP, kidney and liver function tests, electrolytes, blood gases and blood sugar in addition to coagulation profile). Specific investigations were requested individually according to the case.

Assessment of kidney function was according to RIFLE score and estimated GFR was calculated (**Error! Reference source not found.**) (Table 1).

Table (1): RIFLE score in AKI [10]

RIFLE	Serum creatinine	Urine output
End stage renal disease (E)	Loss of kidney functions > 3 months	
Loss (l)	Loss of kidney functions > 4 weeks but < 3 months	
Failure (F)	Serum creatinine increase to 3 folds or GFR decreased >75% from baseline, or Serum creatinine (≥ 4mg/dl)	Anuria for 12 hours
Injury (I)	Serum creatinine increase to 2 folds or GFR decreased >50% from baseline	<0.5ml/kg/for 12 hours
Risk (R)	Serum creatinine increase to 1.5 folds or GFR decreased >25% from baseline	<0.5ml/kg/for 6 hours

Staging of chronic kidney disease if present according to Kidney Disease Outcomes Quality Initiative (KDOQI) grading as following (Table 2):

Table (2): Staging of chronic kidney disease [11]

Stage	Description	GFR (ml/min/1.73m^2)
1	Kidney Damage with normal or ↑GFR	90≤
2	Kidney damage with mild GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	< 15

Evaluation of cardiac functioning and heart failure scanning:

On the basis of a combination of dyspnea and tachycardia, heart failure was identified (Heart rates more than >160, >150, >140, >120, and >100 beats per minute for newborns, kids in the 1-3, 4-5, 6-12 years, and adults over 12, respectively), Tachypnoea is defined as having a breathing rate of > 60, > 40, > 34, > 30, and > 20 breaths/minute for newborns, kids, and adults, respectively, dietary issues, painful hepatomegaly, and chests X-rays evidences of cardiomegaly (abnormal cardiothoracic ratios > 60% in youngsters under the age of five and > 55% in older kids). The updated Ross heart failure categorization for kids was used to evaluate and classify HF degree [12].

Grade I heart failure is asymptomatic. Grade II heart failure indications include mild tachypnea or diaphoresis with feeding in infants, or dyspnea with exertions in older kids. Infants feeding indications such as tachypnea, retractions, grunts, or diaphoresis, severe dyspnea with exertion, and longer feeding periods with growth failures are all examples of grade III heart failure indications. Tachypnea, retractions, grunting, and diaphoresis during resting are examples of grade IV heart failure indications. According to the 7th ADQI consensus committee reports, CRS was assigned (6).

Ethical approval:

This study was performed in line with the principles of the Declaration of Helsinki. All the patients gave their consents for the study. Approval was granted by the Ethics Committee of Benha University.

Statistical analysis

Using SPSS V-26, the gathered data were displayed and examined. Numbers and percentages were used to express qualitative data. Means and standard deviations were used to represent quantitative results. For data that are not normally distributed, the median was given. The Kolmogorov-Smironov analysis was employed to determine whether the distribution of the data was normal.

The significance level within two populations with a normal distribution of data was evaluated using the Student's t test. The qualitative data was compared across independent group sampling using the Chi-square analysis. Mann-Whitney U test was utilized for two independent groups with aberrant data distribution. The Kruskall-Wallis analysis was used to compare the aberrant data distributions of more than two independent cohorts. The correlation between two variables was examined using the coefficient of correlation (r). P value ≤ 0.05 was considered significant. - P value > 0.05 was considered non-significant.

RESULTS

A total of 321 patients admitted to the PICU in our institute were assessed. The demography and primary pathology is described below. There was 42 out of 170 male children acquired CRS, and 37 out of 151 females developed CRS (a total of 24.6% children had CRS who were admitted) as shown in table (3).

Table (3): Demographic characteristics of the studied group

Category	Number	Percentage
Male	169	52.6%
Female	152	47.4%
Age		
1 month- 1 year	170	53%
1-2 years	44	14%
2-5 years	42	13%
5-12 years	46	14%
12-18 years	19	6%
PICU admission period		
1-7 days	219	68.2
8-14	56	17.4
15-21	22	6.9
21-30	8	2.5
> 1month	16	5
Primary diagnosis on PICU admission:	51	15.9%
CVS	109	34%
CNS	89	27.7%
Respiratory	10	3.1%
Renal	15	4.7%
Endocrinal	19	5.9%
Gastrointestinal	6	1.9%
Inborn error of metabolism	8	2.5%
Post Arrest	9	2.8%
Polytrauma	5	1.6%
Poisoning		

79 patients CRS and 242 non CRS (Added to the table below)

Table (4): Comparing CRS and non-CRS groups in regard to demography and PICU stay

This table demonstrates the duration of stay of both groups and the siginificant difference in PELOD score between both groups. It also highlights the intense requirement of inotropes and oxygen support in the CRS group compared to the non CRS one.

	CRS (79 patients)	Non-CRS (242 patients)	P Value
Age in years (median)	0.8	1.2	NS
PICU stay (in days)	6	5	NS
Survival Survived Died	 45 34	 194 48	Highly significant
PELOD Score (Median)	11	1	Highly significant
O2 requirement	78 (98.7%)	159 (65.7%)	Highly Significant
Inotropes	24 (30.4%)	6 (2.5%)	HS
Diuretics	37 (46.8%)	9 (3.7%)	HS
Mechanical ventilation	43 (54.4%)	57 (23.6%)	HS
Hemodialysis	10 (12.7%)	0 (0%)	HS
Peritoneal dialysis	5 (6.3%)	0 (0%)	HS

Table (5): Comparing different types of CRS in terms of length PICU stay and survival
This table shows the differences between different subgroups of CRS and survival being the highest in CRS type1 and lowest in group 5.

	CRS I	CRS II	CRS III	CRS IV	CRS V	P Value
PICU Stay in days (median)	6	5	11	5	6	< 0.05
Survival • Survived • Died	 18 5	 8 5	 7 4	 6 4	 6 16	 < 0.05
PELOD Score	10	1	11	21	11	< 0.05

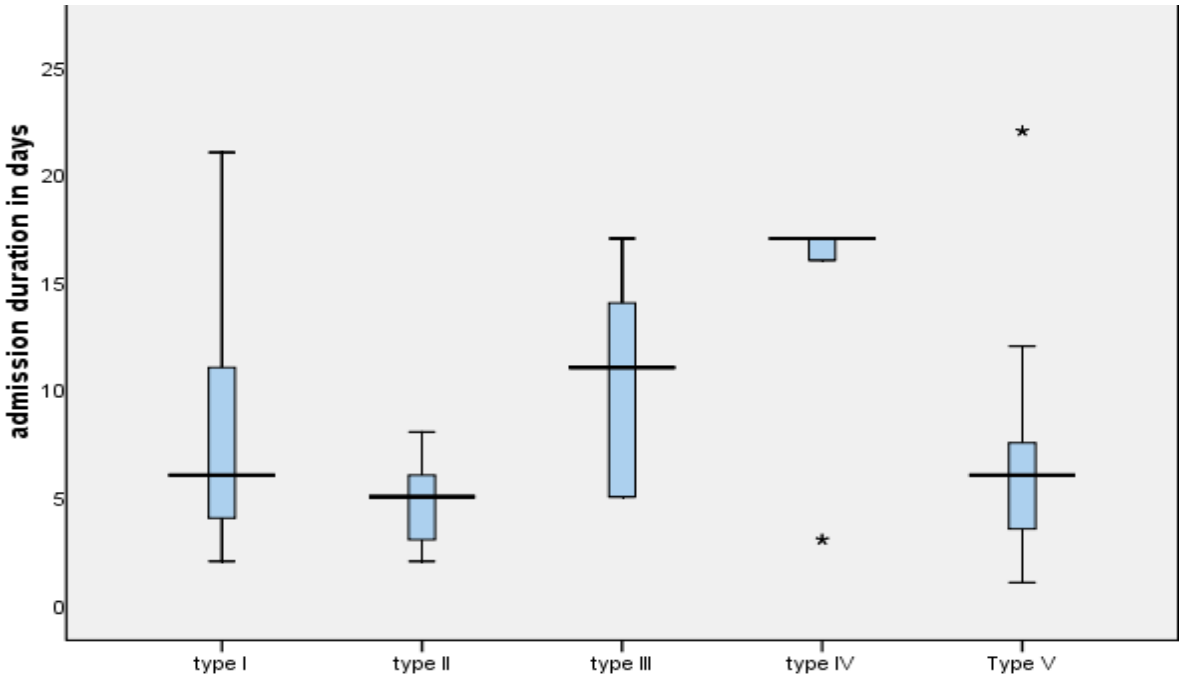

Figure (1): Stay in PICU for children with CRS

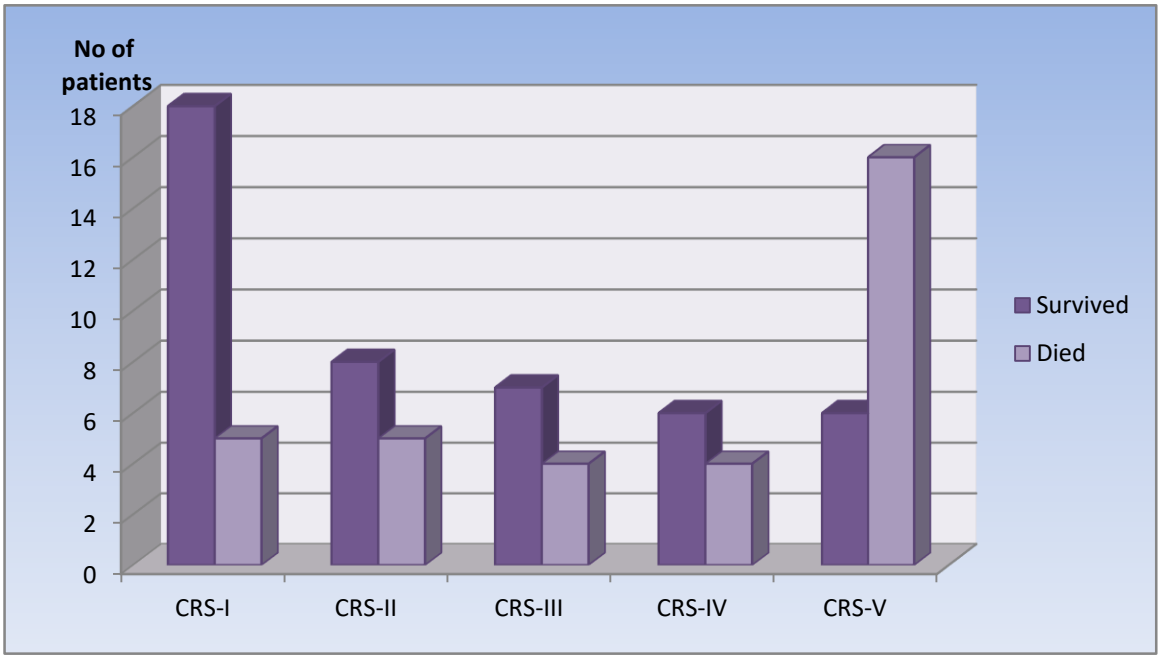

Figure (2): Survival of children with different types of CRS**.**

DISCUSSION

The phrase "cardio-renal syndrome", which was just coined, refers to the long-known and commonly treated comorbid condition of the heart and kidneys, which can be acute or chronic [13].

The cardio-renal axis is of essential importance to pediatric patients in different conditions and it was found that optimum management leads to substantial improvement in PICU survival [14]. **Ronco and Ronco [6]** classified it into 5 different categories depending on the primary affection and secondary organ involvement. This study involved 321 paediatric patients admitted to the PICU in the period between October 2013 and September 2017 with age ranged from 1 month to 18 years of age. Detailed history and clinical examination and essential investigations were carried out. Acute kidney injury was classified according to RIFLE scoring [10], while chronic kidney disease was classified according to KDOQI grading CKD [11]. Grading of heart failure was based on modified Ross score for heart failure [12]. The aim was to describe the pattern of CRS in our unit and to compare it with other PICU centres and to highlight the impact of this condition on PICU admitted children.

In our study, the majority of stay for children with CRS or non-CRS was less than a week in the PICU, which is similar to finding by **Krmpotic and Lobos** [15]. We reported 109 patient with unstable neurological status or disease (34%), which is similar to a study by **Lopez *et al***. [16] who documented 32% of PICU admissions due to similar neurological problems. Respiratory diseases contributed to 27% and cardiovascular disorders were 15% of cases.

In this study; we divided our cohort in to two groups; one with CRS (79 children) and the other group did not develop CRS. The median age of those who developed CRS were 0.8 year compared to a median age of 1.2 in the non-CRS group. This agrees with the study by **Jefferies and Goldstein** [17].

The overall survival was significantly lower in the CRS group (56%) compared to the non-CRS group (80%), which reflects the severity of the disease impact. The CRS group had a much higher PELOD score compared to the non-CRS group, with 98% of the former group required oxygen compared to only 65% were in different modes of oxygen therapy. 30% of the CRS group required inotropes while only 2.5% of the non-CRS group required oxygen. Supportive therapy is a main aspect in patient care in PICU and frequency of patient needs for it can be used as a complementary parameter in assessment of patient severity [18].

Half of the CRS children required mechanical ventilation compared to under quarter of the non-CRS group requiring ventilation. Comparing different subtypes of CRS syndromes, the longest PICU stay was in CRS type III, and the best survival was in CRS I.

CONCLUSION

The pathogenesis of the cardio-renal syndrome is related to many factors beside the hemodynamic derangement. These factors include the role of RAAS, inflammatory mediators and cytokines. Oxidative stress and stimulation of apoptosis process contributes also to the progress of these symptoms. Diagnosis of the cardio renal syndrome depends mainly on accurate diagnosis of

heart failure and kidney failure with application of diagnostic criteria. Prompt diagnosis and early management is crucial to improve the survival of these children and further studies are required to address these aspects.

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