Nutritional Biomarkers in Critically Ill Children with Acute Kidney Injury

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Abstract:

Background: Acute kidney injury (AKI) is associated with many short term and long term renal impairments as well as increased morbidity mortality in intensive care unit. Nutritional assessment is an indispensable tool for the evaluation and monitoring of patients with AKI. The use of nutritional biomarkers may prove some usefulness as screening parameters for worse prognosis and higher mortality in AKI patients.

Aim: The current study aimed to evaluate the correlation between Albumin, Cholesterol and Insulin like growth factor- 1 (IGF- 1) as nutritional biomarkers and the clinical outcome of acute kidney injury in critically ill children.

Patients and Methods: Study included 42 critically ill patients with age range from 2 months to 5 years. Serum Albumin, Cholesterol were assayed by spectrophotometric method (Stanbio, USA) at day 3 and 5. IGF- 1 were measured by enzyme- linked immunosorbent assay (R& D systems, USA) at days 3 and 5. Serum creatinine at days 1 and 3 was assayed by spectrophotometric method (Stanbio, USA).

Results: Out of the 42 patients, 31% developed AKI. Serum cholesterol was significantly lower in AKI compared to non- AKI group at days 3 and 5 with mean values 80.08± 32.91 vs 114.41± 41.58 respectively at day 3, and 87.46± 23.36 vs 121.14± 45.49 respectively at day 5. While serum albumin showed no statistically significant difference between both groups. IGF- 1 values at day 3 and day 5 were significantly lower in AKI group compared to non- AKI with a median (IQR) 123 (119- 140) vs 158 (131- 362) in both groups respectively at day 3, and 124 (100- 148) vs 210 (143- 287) respectively at day 5. There was a correlation between serum IGF- 1 and mortality only at day 5 in our study.

Conclusion: Malnutrition is a common finding in patients with AKI and leads to worse outcome. Nutritional biomarkers like Cholesterol and IGF- 1 are possible predictors of worse outcome in AKI patients.

Key Words: Acute Kidney Injury (AKI), Malnutrition, Nutritional Biomarkers, Critically Ill Children.

المؤشرات الحيوية الغذائية للأطفال المصابين بأمراض حرجة مع إصابات الكلى الحادة

الخلفية: ترتبط إصابات الكلى الحادة (AKI) بالعديد من القصور الكلوي قصير المدى وطويل الأجل بالإضافة إلى زيادة معدل الوفيات المرضية في وحدة العناية المركزة. التقييم الغذائي هو أداة لا غنى عنها لتقييم ومراقبة المرضى الذين يعانون من AKI. قد يثبت استخدام المرقمات الحيوية الغذائية بعض النفع كمعلمات فحص لسوء التشخيص وارتفاع معدل الوفيات لدى مرضى AKI.

الهدف: تهدف الدراسة الحالية إلى تقييم العلاقة بين الألبومين والكوليسترول والأنسولين مثل عامل النمو-١ (IGF-1) كمؤشرات حيوية غذائية والنتائج السريرية لإصابة الكلى الحادة لدى الأطفال المصابين بأمراض خطيرة.

النتائج: من بين ٤٢ مريضا، قام ٣١% تطوير AKI كان الكوليسترول في الدم أقل بشكل ملحوظ في AKI مقارنة بالمجموعة غير AKI في اليومين ٣ و٥ مع متوسط القيم ٨٠,٠٨± ٣٢,٩١ مقابل ١١٤,٤١± ٤١,٥٨ على التوالي في اليوم الثالث، و٨٧,٤٦± ٢٣,٣٦ مقابل ١٢١,١٤± ٤٥,٤٩ على التوالي في اليوم ٥. بينما أظهر ألبومين المصل لا يوجد فرق ذو دلالة إحصائية بين المجموعتين. كانت قيم IGF-1 في اليوم ٣ واليوم ٥ أقل بشكل ملحوظ في مجموعة AKI مقارنة بغير AKI مع متوسط (IQR) 123 (119- 140) مقابل ١٥٨ (١٣١- ٣٦٢) في كلا المجموعتين على التوالي في اليوم ٣، و١٢٤ (١٠٠- ١٤٨) مقابل ٢١٠ (١٤٣- ٢٨٧) على التوالي في اليوم ٥. كان هناك ارتباط بين مصل IGF-1 والوفيات فقط في اليوم الخامس في دراستنا.

الخلاصة: سوء التغذية هو اكتشاف شائع في المرضى الذين يعانون من AKI ويؤدي إلى نتائج أسوأ المؤشرات الحيوية الغذائية مثل الكوليسترول وIGF-1 هي مؤشرات محتملة لنتيجة أسوأ في مرضى AKI.

Introduction:

Acute kidney injury (AKI) is associated with many short term and long term renal impairment as well as increased morbidity mortality in intensive care unit (Kaddourah et.al., 2017). The incidence of AKI following admission to PICU varies from 4.5 to 82%, being higher in children requiring invasive mechanical ventilation, patients with septic shock and patients on vasopressor medications (McCaffrey et.al., 2015). Changes in serum creatinine and/ or urine output form the basis of diagnostic and staging criteria for AKI (Kellum et.al., 2016- Westhoff et.al., 2015). Nutritional assessment is an indispensable tool for the evaluation and monitoring of patients with acute kidney injury (AKI). Acute loss of renal function affects the metabolism of all macronutrients, responsible for pro- inflammatory, pro- oxidative and hypercatabolic situations. The major nutritional disorders in AKI patients are hyper-catabolism, hyperglycemia, and hypertriglyceridemia (Berbel et.al., 2011).

Previous studies showed the association of some nutritional parameters with clinical outcomes (Berbel et.al., 2014; Guimaraes et.al., 2008 and Ficcadori et.al., 1999). The current study aimed to evaluate the use of nutritional biomarkers like Albumin, Cholesterol and Insulin Like Growth Factor- 1 (IGF- 1) as screening parameters for worse outcome of AKI in critically ill children.

Subjects And Methods:

A prospective study was conducted on forty- two patients recruited from pediatric intensive care unit (PICU), Children's Hospital, Ain-Shams University during the period from August 2016 to May 2017. Ethical approval from the ethical committee of the Institute of Postgraduate Childhood Studies and the National Research Centre was taken, with commitment to the ethical considerations. Then informed consents were obtained from the parents after explanation of the aim of the study and its possible benefits for early detection of acute kidney injury.

The study included critically ill children from 2 months to 5 years of age. Patients who were considered eligible included mechanically ventilated patients, sepsis/ septic shock and patients on vasopressor medications. Cases with known acute and chronic Kidney diseases were excluded. All the enrolled children were subjected to: Full medical history: (Demographic data including age and sex; Clinical data including causes of PICU admission and days of PICU stay, A thorough clinical examination: (Anthropometric assessment including weight (Kg), height (cm) and calculation of body mass index [weight (kg)/ height (m^2)]; As well as neurological, cardiac, chest and abdominal examination).

Laboratory Investigations:

Blood samples: 5 ml of venous blood from each child were collected by venipuncture, allowed to clot then serum was separated by centrifugation at room temperature and stored at- 80 until assay. Samples were withdrawn at days 3 and 5 respectively to measure: serum albumin, cholesterol using spectrophotometric methods (Stanbio, USA) and IGF- 1 using enzyme linked immunosorbent assay (R& D systems, USA); and at days 1 and 3 respectively to measure serum creatinine by spectrophotometric method (Stanbio, USA).

Statistical Analysis:

All statistical calculation were done using computer programs and SPSS [statistical package for the social science] version 16. Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Mean± Standard deviation (± SD) were used for parametric numerical data, while Median and Interquartile range (IQR) for non- parametric numerical data. Frequency and percentage of non- numerical data. Student t- test was used to assess the statistical significance of the difference between two study group means. Pearson's correlation analysis was used to assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically (r) defines the strength and direction of the linear relationship between two variables. Paired t- test was used to assess the statistical significance of the difference between two means measured twice for the same study group.

Results:

The descriptive data of the studied group are shown in table (1). The current study included 42 patients. Age ranged from 2 months to 5 years. Body weight ranged from 3- 21 kg. 59.5% of the studied group were males while 40.5% were females. The mean height of the studied patients was 68.9± 15.19, and the mean body mass index (BMI) was 13.5± 2.20. Of the studied patients, 26.2% were admitted post- operative, 23.8% with chest infection, 19% with sepsis, 14.3% with shock, 11.9% with heart failure, and 2.4% with metabolic disorders and post cardiac arrest. 71.4% of the studied group needed mechanical ventilation, while only 28.6% of them were not ventilated. By follow up of the patients, 57.1% improved and were discharged from ICU, while 42.9% died.

Table (1) Descriptive data of the studied children

N= 42		Median/Mean	Range
Age (Years) Median (Iqr)		0.50 (0.25- 1.50)	0.2- 5 (2 m- 5 y)
Weight (Kg) Median (Iqr)		5.50 (4.00- 8.00)	3- 21
Height Mean± Sd		68.9± 15.19	54- 115
Body Mass Index Mean± Sd		13.5± 2.20	10.2- 18.7
		Number	Percent
Sex	Male	25	17
	Female	59.5%	40.5%
Cause Of ICU Admission	Post Operative	11	26.2%
	Chest Infections	10	23.8%
	Sepsis	8	19%
	Shock	6	14.3%
	Heart Failure	5	11.9%
	Post Cardiac Arrest	1	2.4%
	Metabolic Disorders	1	2.4%
Mechanical Ventilation	Ventilated	30	71.4%
	Not Ventilated	12	28.6%
[ASI] Outcome	Survived	24	57.1%
	Died	18	42.9%

From the total studied cases (42 patients), 13 children (31%) developed AKI wile 29 of them (69%) did not develop AKI Figure (1).

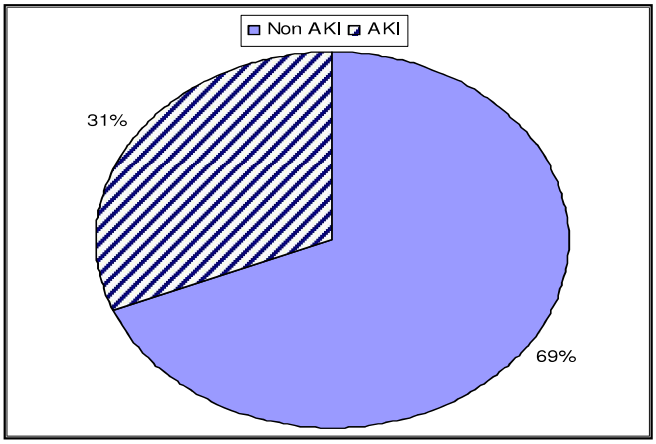

Figure (1) Subgroups of studied population (AKI and Non AKI)

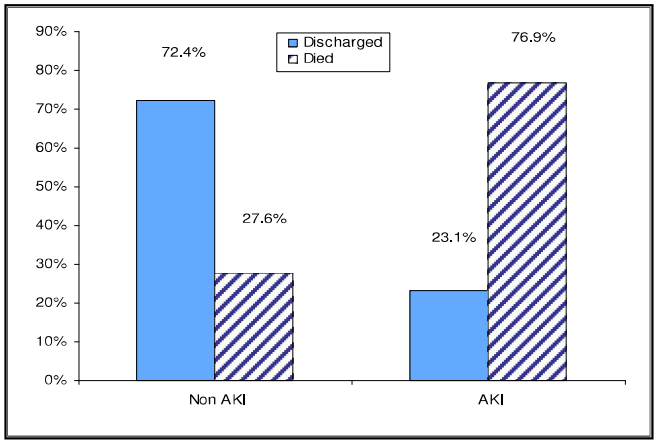

Figure (2) Comparison of outcome in both groups (AKI and Non- AKI patients)

Patients with AKI had significantly lower body weight compared to non- AKI patients, with a Median (IQR) body weight 4 (4.5- 5) in AKI and 7 (4.7- 10) in non- AKI groups. There was no statistical significance in the height and body mass index measurements between the 2 studied groups (Not tabulated).

Serum creatinine levels at day 1 showed no statistical significance between both groups with mean values 0.38± 0.14 and 0.38± 0.08 in AKI and Non- AKI groups. However, at day 3, their levels showed high statistical significance between both groups, with mean values 0.59± 0.16 and 0.37± 0.10 in AKI and non- AKI groups respectively. Serum cholesterol was significantly lower in AKI compared to non- AKI group at days 3 and 5 with mean values 80.08± 32.91 and 114.41± 41.58 respectively at day 3, and 87.46± 23.36 and 121.14± 45.49 respectively at day 5. While serum albumin showed no statistically significant difference between AKI and Non- AKI groups at days 3 and 5 with mean values 3.25± 0.76 and 3.07± 0.56 respectively at day 3 and values 3.03± 0.53 and 3.08± 0.51 respectively at day 5. IGF- 1 values at day 3 and day 5 were significantly lower in AKI group compared to Non- AKI with a median (IQR) values 123 (119- 140) and 158 (131- 362) in both groups respectively at day 3, and values 124 (100- 148) and 210 (143- 287) respectively at day 5 Table (2).

Table (2) Comparison of Serum measurments of creatinine and nutritional biomarkers in AKI and Non- AKI groups at days 1, 3 and 5.

	AKI		Non AKI		Test Value	P Value	Sig
	Mean± SD	Range	Mean± SD	Range			
Creatinine D1	0.38± 0.14	0.2- 0.6	0.38± 0.08	0.2- 0.6	- 0.053•	0.958	NS
Creatinine D3	0.59± 0.16	0.3- 0.9	0.37± 0.10	0.2- 0.6	5.599•	0.000	HS
Albumin D3	3.25± 0.76	2.4- 5.5	3.07± 0.56	1.9- 4.3	- 0.833•	0.410	NS
Albumin D5	3.03± 0.53	2.2- 4.2	3.08± 0.51	1.9- 4	0.262•	0.795	NS
Cholesterol D3	80.08±32.91	42- 134	114.41±41.58	52- 245	2.625•	0.012	S
Cholesterol D5	87.46±23.36	63- 139	121.14±45.49	69- 266	2.513•	0.016	S
Igf- 1 D3 (Median/IQR)	123 (119- 140)	60- 186	158 (131- 362)	105- 486	-2.327**	0.020	S
Igf- 1 D5 (Median/IQR)	124 (100– 148)	57 – 480	210 (143– 287)	94– 556	-2.762**	0.006	HS

hly significant (HS)

A highly significant statistical difference was found between the outcomes in both groups, with a mortality of 76.9% of AKI patients, and only 27.6% in Non- AKI patients Figure (2).

There was a positive correlation between serum IGF- 1 and mortality only at day 5 in our study Table (3)

Table (3) Correlation between serum IGF- 1 and patient survival at day 3 and day 5

	Discharged		Died		R Value	P Value	Sig
	Median (IQR)	Range	Median (IQR)	Range			
Igf- 1 D3	147 (122.5- 226)	105- 486	130 (120- 186)	60- 476	- 0.674	0.500	NS
Igf- 1 D5	233 (140.5- 294)	103- 556	137 (100- 180)	57- 514	- 2.364	0.018	S

<0.05= Significant (S); P value< 0.001= Highly significant (HS).

Discussion:

Critically ill children are at high risk of having acute kidney injury (AKI). AKI is associated with many short term and long term renal impairments as well as increased morbidity mortality in intensive care unit (McCaffrey et.al., 2015). Nutritional assessment is an essential tool for the evaluation and monitoring of patients with AKI (Berbel et.al., 2011).

The current study aimed to evaluate the correlation of nutritional biomarkers like Albumin, Cholesterol and Insulin like growth factor- 1 (IGF- 1) with the morbidity and mortality of critically ill children with acute kidney injury. Thirteen patients of the studied population (31%) developed AKI, while 29 patients (69%) did not develop AKI or have any changes in kidney functions. These results are inline with Bell et.al., 2015 who found in their study on 94 patients, that (20%) only developed AKI within 48 hours of admission while (80%) did not develop AKI. Yamashita et.al., 2014 in their study on critically ill adults, found that (42.9%) of patients developed AKI. Likewise, Gocze et.al., 2015 in their study on 107 patients found that (42%) developed AKI.

In the current study study, the difference in serum creatinine levels at day 1 showed no statistical significance between both groups, with mean values 0.38± 0.14 and 0.38± 0.08 in AKI and Non- AKI groups respectively. However, at day 3, serum creatinine showed high statistically significant difference between both groups, with mean values 0.59± 0.16 and 0.37± 0.10 in both groups respectively. Andreoli 2009 mentioned that the concentration of serum creatinine is a measure of decreased kidney function following AKI. Westhoff et.al., 2015 in their study found that serum creatinine on study enrollment was significantly higher in the AKI group compared to the non- AKI group with mean values 1.7 and 0.3 mg/dl respectively and a p value< 0.001. This means that serum

creatinine is a significant marker for diagnosing AKI.

Patients with AKI had significantly lower body weight than non- AKI patients, with a Median (IQR) body weight 4 (4.5- 5) in AKI and 7 (4.7- 10) in non- AKI groups. Also the mean weight for age centiles were lower in AKI group compared to Non- AKI being on the 18th and 23rd centiles respectively. On the other hand, there was no statistical significance in the height and body mass index measurements between the 2 studied groups. Berbel et.al., 2011 stated that anthropometric parameters, such as body mass index, arm circumference, and thickness of skin folds, are difficult to interpret due to changes in hydration status in those patients.

Although there are no prospective data about the behavior of nutritional markers, some authors demonstrated associations of some parameters with clinical outcomes. The use of markers like albumin, cholesterol, IGF- 1, seem to be useful as screening parameters for worse prognosis and higher mortality in AKI patients (Berbel et.al., 2011).

In this study, serum cholesterol at day 3 was significantly lower in AKI compared to non- AKI group with mean values 80.08 and 114.4 respectively. This was also the case at day 5 with mean values 8.46 and 121.14 in both groups respectively. This was in accordance with Obialo et.al. 1999 who identified a 50% reduction in survival of AKI patients who had cholesterol levels lower than 150 mg/ dL on admission. Then Guimarães et.al., 2008 in a study with 56 AKI patients admitted to the ICU, demonstrated that cholesterol levels below 96 mg/dL reduced significant and independently the rate if survival in those patients. The ISRNM Expert Panel proposed cholesterol levels below 100 mg/dL among the criteria of biochemical assessment for the clinical diagnosis of protein energy wasting (PEW) in AKI (Berbel et.al., 2011).

As for IGF- 1 in our studied population, values at day 3 and day 5 were significantly lower in AKI group compared to non- AKI with a median value at day 3 of 123 and 158 and at day 5 of 124 and 210 in both groups respectively. Guimarães et.al 2008 stated that Insulin- like growth factor 1 (IGF- 1) is a peptide analogous to insulin whose synthesis is influenced by hormonal and nutritional factors. Its reduction is associated to a lower survival in AKI patients. Moreover, by evaluating 56 AKI patients, Berbel et.al., 2011 observed that IGF- 1 levels lower than 50.6 ng/mL showed a significant association to decreased survival regardless of the presence of sepsis. They also stated that malnutrition in AKI patients is associated with increased incidence of complications, longer hospitalization, and higher hospital mortality.

Conversely, serum albumin in the studied patients, showed no statistically significant difference between both groups at day 3 and day 5. Ficcadori et.al., 2011 stated that albumin, the classic malnutrition marker, can lose its accuracy in AKI patients, since the reduction in its levels is not always a consequence of the limited energy and protein substrate intake. They also stated that the presence of inflammation, which prioritizes the production of acute- phase proteins, can be intense in those patients, making albumin of little value as a nutritional marker.

In the current study, a highly significant statistical difference was found between the outcomes of both groups, with a mortality of 76.9% of AKI patients, and only 27.6% in Non- AKI patients. Pajenda et.al., 2015 and Sanchez- Gonzalez 2011 stated that acute kidney injury as such is known to be a poor prognostic factor in terms of mortality. Westhoff et.al., 2015 also found that Seven patients (15.2%) died within 3 months following study enrollment, six of them (13.0%) within the first 30 days. Causes of death included septic shock with coexisting AKI. Moreover, they stated that in critically ill children, the reported mortality from AKI is still as high as 60%.

In the current study, serum IGF- 1 was correlated to mortality of patients at day 5 where serum levels were significantly lower in the deceased group. This was highlighted by Berbel et.al., 2011 who stated that the use of markers like albumin, cholesterol, and IGF- 1, seem to be useful as screening parameters for worse prognosis and higher mortality in AKI patients.

Conclusion:

1. Acute kidney injury (AKI) is common in critically ill children especially in patients with sepsis and patients on mechanical ventilation.
2. Malnutrition is a common finding in patients with AKI and leads to wore outcome.
3. Nutritional assessment is an indispensable tool in managing AKI patients.
4. Nutritional biomarkers like Cholesterol and IGF- 1 are possible predictors of worse outcome in AKI patients.

Recommendations:

Further studies must be conducted on a larger scale in this field to further prove the correlation between nutritional biomarkers and outcome of acute kidney injury in critically ill children.

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