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Original article

Role of Urinary Tissue Inhibitor of Metalloproteinase- 2 and Insulin Like Growth Factor Binding Protein-7 in Detection of Acute Kidney Injury in Critically Ill Children in Pediatric Intensive Care Unit

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Abstract:

Background: Acute kidney injury (AKI) is more prevalent in critically sick paediatric patients owing to variables like mechanical ventilation, severe infection and nephrotoxic medications. This study aimed to assess urinary TIMP-2 * IGFBP-7 role as an earlier predictor of AKI in critically ill children. **Methods:** This is case control study included pediatric patients admitted to PICU and at risk for AKI (Group I) and age- and sex- matching control group (Group II) which was split into 2 subgroups: Group II A that included children admitted to PICU without risk of AKI and Group II B as a control group that included healthy children not admitted to PICU. Children were exposed to a comprehensive history taking, clinical examination, and laboratory examinations. Two urine sample 48 hour apart for urinary tissue inhibitor of metalloproteinase-2 (TIMP-2), insulin-like growth factor binding protein-7 (IGFBP-7). **Results:** Cases with risk of AKI showed significantly higher TIMP2 and IGFBP7*TIMP2 those were the substantial AKI predictors, whereas no substantial change was seen among the groups in IGFBP7 levels. The described markers showed no significant differences according to the AKI etiological factors, long term outcome, AKI 30-day mortality or ICU stay length ($p>0.05$). **Conclusions:** The levels of IGFBP-7*TIMP-2 marker in the critically ill pediatric population could be a predictor of AKI risk. The studied markers did not show significant difference according to the mortality. Moreover, they did not show significant correlation with ICU stay length.

Keywords: Urinary biomarkers, AKI detection, pediatric ICU.

Introduction

AKI is among the greatest widespread organ malfunctions and is linked to a significant morbidity and mortality rate in critically sick individuals [(1)]. It is still a major reason for morbidity and mortality in children [(2)].

AKI is particularly prevalent in critically sick paediatric patients owing to variables such as severe infection and mechanical ventilation (MV) usage or nephrotoxic medications; fatality rates for critically ill paediatric patients with AKI severe enough to need dialysis range from 30 to 50 percent. Children with AKI need longer hospitalizations, ICU stays, and mechanical ventilation more often [(3)].

Over the last two decades, several researchers have sought novel biomarkers that are more accurate, particular, inexpensive, and non-invasive, involving AKI-predicting biomarkers. This is crucial for enhancing therapeutic results [(4-6)]. According to studies in adults and children, the combination of ([TIMP-2] •[IGFBP7]) may be accurate in detecting people at AKI or severe AKI risk [(7, 8)].

Several studies addressed the reliability of these markers in adult or neonatal populations [(9-12)], with scarce evidence regarding the paediatric population. To address the aforementioned knowledge gaps and given the crucial sequels of AKI that may persist for life.

This study aimed to assess urinary TIMP-2 & IGFBP-7 role as AKI earlier predictor of acute kidney injury in critically ill children.

Patients and methods:

This case control study was performed on children attending PICU at Kafr El Sheikh General hospital and Benha University hospital, during period of April 2021 to April 2022. Apparently, healthy controls will be picked from an outpatient clinic. Laboratory tests will be undertaken at Benha University, Department of Clinical Pathology.

Inclusion criteria were patient from 1 month to 18 years, both sexes admitted to PICU with acute critical illness defined as patient required mechanical ventilation, patient with more than one system affection, patient who develop hypoxia or patient with. Hypovolemia

Exclusion criteria were previously known renal disease, previous renal transplantation, end-stage renal disease, recent cardiac surgery or multiple congenital anomalies.

Before enrolling the children in the research, ethical approval was acquired from the parents, who were fully informed about all study protocols, and their agreement was secured. This research was authorized by the Benha University Hospitals' faculty of Medicine's ethics committee.

The study included 2 groups; Group I (n=23): including patients admitted to PICU and at risk for acute kidney injury and Group II(n=20) which was subdivided into two groups; Group IIA(n=10) including patients admitted to PICU without risk for AKI and Group II B(n=10) including healthy children not admitted to PICU. Group II was selected age and sex matching to group I.

AKI was identified and classified based on the KDIGO criteria. Stage 1 of AKI was determined when creatinine serum concentration reached 0.3 mg/dL as a minimum within a 48-hour period, or if there was a 1.5-fold rise from the individual's baseline level within 7 days. Stage 2 was identified when the serum creatinine level escalated between 2.0 and 2.9 times the baseline level. Finally,

stage 3 was diagnosed if the serum creatinine level rose more than 3.0 times the baseline level or if it exceeded or equalled 4.0 mg/dL. These classification criteria provided clear guidelines for categorizing the severity of AKI based on the extent of serum creatinine elevation and allowed for a standardized approach to diagnosing and staging this condition [(13)].

Children involved in research were submitted to full history takin, complete clinical assessment and laboratory examinations as; CBC, CRP, Urea, creatinine, ABGs, blood culture and urine analysis.

Two urine sample 48 hour apart for urinary TIMP-2, IGFBP-7 and ([TIMP-2] [IGFBP7]). First Urine samples were acquired instantly following hospital admission and the second sample after 48 h, a 5 ml. Urine collected in a sterile container was centrifuged for twenty min for at 2000-3000. If precipitation formed, the supernatant was removed. Centrifugation was done again. and samples in form of two ml of supernatant collected in two Eppendorf tube (one ml for each) and the four tubes for the two samples stored at -20°C to -80°C. Using Sandwich ELISA Detection, the quantities of TIMP-2 (ng/ml) and IGFBP7 (ng/ml) in urine spots were determined [TIMP-2]•[IGFBP7] is the product (by multiplication) of the corresponding urine concentrations of both bioindicators. The product is divided by 1,000 in order to provide a single numerical test result with the unit (ng/ml)2/1000, which is the unit for all [TIMP-2] •[IGFBP7] attributes cited in this report.

Statistical analysis:

Version 16 of SPSS (Statistical package for social science) was used to record, tabulate, code, and finally analyse the collected data. The following descriptive statistics were computed for the data: Standard deviation (±SD), Mean, Number, and percentage.

Analytical statistics: In order to assess the significance of differences among various groups, several statistical tests were employed. The student's t-test was utilized to compare two groups means when dealing with numerical (parametric) data. When comparing more than 2 numerical data groups, the analysis of variance (ANOVA) test was employed. Inter-group comparisons of categorical data were conducted utilizing the chi-square test (X2-value). To detect the optimal cutoff point and assess each test diagnostic performance, specificity and sensitivity were assessed across different cutoff points by ROC curve assessment. In all analyses, a P-value below 0.05 was regarded substantially significant (S), while a P-value below 0.0001 was regarded highly significant (HS). These thresholds helped determine the level of statistical significance for the observed differences between groups.

Results:

No statistically substantial changes were present among groups in the mean age (p-0.8), sex (p =0.9), and residence (p =0.9), The most common etiology in the AKI group was hemodynamic instability (60.9%), followed by hypoxia (40.4%), septic shock (39.1%), and dehydration (21.4%), Table 1

The TIMP2 1st day and 3rd day levels changed substantially among studied groups ($p<0.001$) with considerably greater mean levels found in the cases with risk of AKI (2.78 ± 0.38 ng/ml and 3.01 ± 0.23 ng/ml, respectively). This was shown also in the IGFBP7*TIMP2 1st day and 3rd day ($p=0.001$ and $p<0.001$, respectively), where

substantially greater mean levels found in the cases with risk of AKI (0.08± 0.14(ng/ml)2/1000 and 0.19 ± 0.26(ng/ml)2/1000, respectively). In contrast, no statistically considerable change was found in the levels of IGFBP7 at the 1st day (p=0.4), or the 3rd day (p=0.1), Table 2

Table 1: AKI group regarding etiology.

	No.	%
Septic shock	9	39.1
Dehydration	5	21.4
Hemodynamic instability	14	60.9
Hypoxia	7	40.4

Table 2: Comparison of study groups regarding markers.

		N	Mean	SD	Min	Max	Test of sig	p-value
TIMP2 ng/ml	Group I	23	2.78	0.38	2.12	3.41	24.6	<0.001*
(1st day)	Group IIA	10	2.19	0.13	2.03	2.41		
	Group IIB	10	2.09	0.21	1.77	2.44		
IGFBP7 ng/ml	Group I	23	20.32	2.79	16.75	26.65	0.8	0.4
(1st day)	Group IIA	10	20.40	2.94	15.55	24.55		
	Group IIB	10	19.07	2.33	15.10	22.25		
IGFBP7*TIMP2	Group I	23	0.08	0.14	0.04	0.71	14.5	0.001*
(ng/ml)2/1000	Group IIA	10	0.04	0.01	0.03	0.05		
(1st day)	Group IIB	10	0.04	0.01	0.03	0.05		
TIMP2 ng/ml	Group I	20	3.01	0.23	2.57	3.39	70.7	<0.001*
(3rd day)	Group IIA	10	2.38	0.14	2.17	2.64		
	Group IIB	10	2.20	0.16	1.98	2.51		
IGFBP7 ng/ml	Group I	20	21.40	2.14	17.25	25.25	2.3	0.1
(3rd day)	Group IIA	10	23.32	2.29	20.15	28.05		
	Group IIB	10	21.56	2.95	17.50	26.40		
IGFBP7*TIMP2	Group I	20	0.19	0.26	0.04	0.77	19.5	<0.001*
(ng/ml)2/1000	Group IIA	10	0.06	0.01	0.05	0.07		
(3rd day)	Group IIB	10	0.05	0.01	0.03	0.06		

On comparison of studied markers regarding the etiological factors in cases with risk of AKI. It is evident that no significant difference presents in either marker according to the AKI etiological factors (p>0.05), Table 3

On comparison of studied markers regarding the 30-day mortality in cases with risk of AKI. It is evident that no significant difference presents in either marker according to the AKI 30-day mortality (p>0.05), Table 4

No considerable association was present among the studied markers with ICU stay length in cases with risk of AKI, Table 5

Table 3: Comparison of studied markers regarding the etiological factors in cases with risk of AKI.

		N	Mean	S. D	Min	Max	Test of sig	p-value
TIMP2	Septic shock	9	2.65	0.50	2.12	3.33	1.3	0.3
ng/ml	AGE & Dehydration	4	3.06	0.25	2.83	3.41		
(1st day)	RF	3	2.66	0.12	2.57	2.80		
	hemodynamic instability	7	2.85	0.26	2.65	3.37		
IGFBP7nglml	Septic shock	9	20.45	3.50	16.75	26.65	0.1	0.9
(1st day)	AGE & Dehydration	4	19.74	2.42	18.10	23.30		
	RF	3	20.02	2.18	18.45	22.50		
	hemodynamic instability	7	20.61	2.70	16.80	23.55		
IGFBP7*TIMP2	Septic shock	9	0.13	0.22	0.04	0.71	0.4	0.7
(ng/ml)2/1000	AGE & Dehydration	4	0.06	0.013	0.052	0.08		
(1st day)	RF	3	0.05	0.008	0.047	0.06		
	hemodynamic instability	7	0.06	0.012	0.045	0.08		
TIMP2	Septic shock	7	2.87	0.24	2.57	3.27	1.6	0.2
ng/ml (3rd day)	AGE & Dehydration	4	3.09	0.23	2.86	3.36		
	RF	2	3.17	0.31	2.95	3.39		
	hemodynamic instability	7	3.07	0.16	2.87	3.24		
IGFBP7 ng/ml	Septic shock	7	20.59	2.53	17.25	25.25	0.9	0.5
(3rd day)	AGE & Dehydration	4	22.15	1.10	21.10	23.20		
	RF	2	23.13	1.52	22.05	24.20		
	hemodynamic instability	7	21.27	2.23	18.45	25.00		
IGFBP7*TIMP2	Septic shock	7	0.24	0.32	0.04	0.77	0.6	0.6
(ng/ml)2/1000	AGE & Dehydration	4	0.07	0.004	0.063	0.073		
(3rd day)	RF	2	0.07	0.002	0.07	0.074		
	hemodynamic instability	7	0.25	0.31	0.057	0.75		

Table 4: Comparison of study groups regarding 30-day mortality.

		N	Mean	S. D	Min.	Max.	Test of sig	p-value
TIMP2 ng/ml	survived	19	2.59	0.45	2.06	3.41	0.2	0.8
(1st day)	died	14	2.62	0.40	2.03	3.33		
IGFBP7 ng/ml	survived	19	20.35	2.86	15.55	24.55	0.1	0.9
(1st day)	died	14	20.34	2.80	16.75	26.65		
IGFBP7*TIMP2(ng/ml)2/1000	survived	19	0.09	0.15	0.03	0.71	0.9	0.4
(1st day)	died	14	0.05	0.01	0.04	0.09		
TIMP2 ng/ml	survived	19	2.77	0.39	2.24	3.39	0.7	0.4
(3rd day)	died	11	2.87	0.31	2.17	3.24		
IGFBP7 ng/ml	survived	19	22.48	2.01	19.65	28.05	1.3	0.2
(3rd day)	died	11	21.27	2.76	17.25	25.25		
IGFBP7*TIMP2(ng/ml)2/1000	survived	19	0.13	0.20	0.05	0.75	0.5	0.6
(3rd day)	died	11	0.18	0.27	0.04	0.77		

Table 5: Correlation between Length of ICU stay and marker.

	r	p-value
TIMP2 ng/ml (1st day)	-0.143	0.427
IGFBP7 ng/ml (1st day)	0.015	0.935
IGFBP7*TIMP2(ng/ml)2/1000 (1st day)	-0.1	0.578
TIMP2 ng/ml (3rd day)	0.115	0.546
IGFBP7 ng/ml (3rd day)	-0.181	0.339
IGFBP7*TIMP2(ng/ml)2/1000 (3rd day)	-0.009	0.964

The significant predictors of AKI cases were the TIMP levels at the 1st day (a cutoff value of 2.33 showed an AUC of 0.96, sensitivity of 90%, and specificity of 80%, p<0.001), and at the 3rd day (a cutoff value of 2.61 showed an AUC of 0.995, sensitivity of 95%, and specificity of 90%, p<0.001), the IGFBP7*TIMP2 at the 1st day (a cutoff value of 0.046 showed an AUC of 0.838, sensitivity of 85%, and specificity of 70%, p=0.003), and at the 3rd day (a cutoff value of 0.062 showed an AUC of 0.803, sensitivity of 65%, and specificity of 80%, p=0.008), while the IGFBP7 at the 1st or 3rd days showed no clinical significance (p>0.05),Figure 1& Table 6

The significant predictors of AKI cases were the TIMP levels at the 1st day (a cutoff value of 2.49 showed an AUC of 0.96, sensitivity of 85%, and specificity of 90%, p<0.001), and at the 3rd day (a cutoff value of 2.54 showed an AUC of 1, sensitivity of 100%, and specificity of 100%, p<0.001), the IGFBP7*TIMP2 at the 1st day (a cutoff value of 0.044 showed an AUC of 0.893, sensitivity of 90%, and specificity of 80%, p=0.001), and at the 3rd day (a cutoff value of 0.056 showed an AUC of 0.952, sensitivity of 90%, and specificity of 90%, p<0.001), while the IGFBP7 at the 1st or 3rd days showed no clinical significance (p>0.05), Figure 2&Table 7

Table 6: ROC analysis for discrimination of Group I from Group IIA.

Test Result Variable(s)	Area	p-value	95% Confidence Interval		Sensitivity	Specificity	Cut-off
			Lower Bound	Upper Bound			
TIMP2 ng/ml (1st day)	0.960	0.000	0.898	1.000	90	80	2.33
IGFBP7 ng/ml (1st day)	0.525	0.826	0.296	0.754	50	50	20.7
IGFBP7*TIMP2 (ng/ml)2/1000 (1st day)	0.838	0.003	0.695	0.980	85	70	0.046
TIMP2 ng/ml (3rd day)	0.995	0.000	0.979	1.000	95	90	2.61
IGFBP7 ng/ml (3rd day)	0.283	0.056	0.090	0.475	30	30	22.6
IGFBP7*TIMP2 (ng/ml)2/1000 (3rd day)	0.803	0.008	0.643	0.962	65	80	0.062

Table 7: ROC analysis for discrimination of Group I from Group IIB.

Test Result Variable(s)	Area	p-value	95% Confidence Interval		Sensitivity	Specificity	Cut-off
			Lower Bound	Upper Bound			
TIMP2 ng/ml (1st day)	0.960	0.000	0.898	1.000	85	90	2.49
IGFBP7 ng/ml (1st day)	0.670	0.135	0.469	0.871	60	60	19.13
IGFBP7*TIMP2(ng/ml)2/1000 (1st day)	0.893	0.001	0.772	1.000	90	80	0.044
TIMP2 ng/ml (3rd day)	1.000	0.000	1.000	1.000	100	100	2.54
IGFBP7 ng/ml (3rd day)	0.493	0.947	0.244	0.741	60	40	20.5
IGFBP7*TIMP2(ng/ml)2/1000 (3rd day)	0.952	0.000	0.879	1.000	90	90	0.056

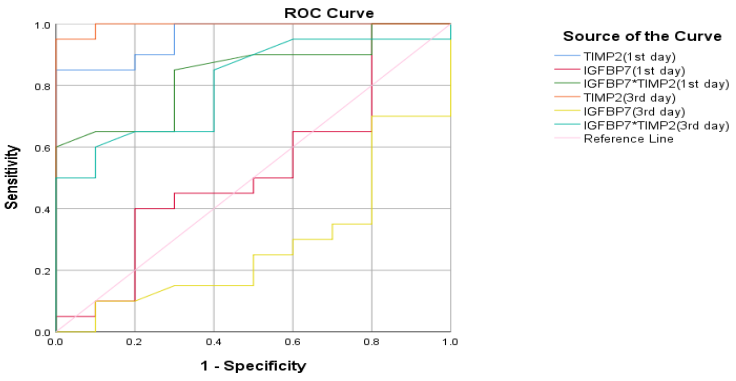

Figure 1: ROC curve for discrimination of Group I from Group IIA.

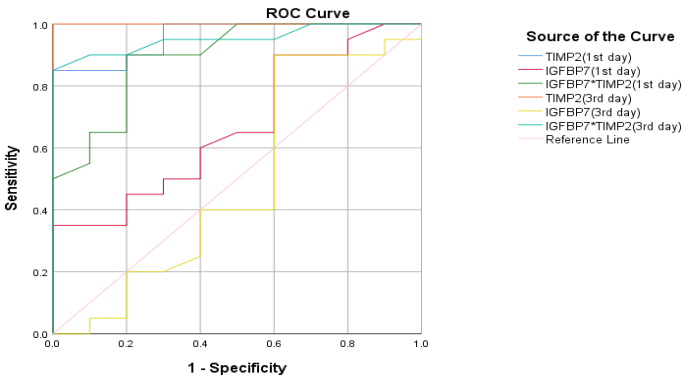

Figure 2: ROC curve for discrimination of Group I from Group IIB.

Discussion:

Multiple aetiologies and risk factors contribute to the complexity of the pathophysiology of AKI. It may happen in a variety of situations, including severe cardiac or transplant operations, shock, and sepsis [14]. Present study showed that the most common etiology in the AKI group was hemodynamic instability, followed by hypoxia, septic shock, and dehydration. The possible explanation for these findings is that renal ischemia is the major reason for AKI and may be caused by several processes, including cytokines, oxygen-free radicals and enzymes creation; endothelial stimulation and leukocyte adhesion; coagulation activation and apoptosis induction. All these predisposing molecular mechanisms could be encountered in critically ill patients [15].

Diverse studies have aimed to describe AKI risk factors in critically ill children. In agreement with our findings, previous study [16] found that sepsis and hypoxia were the most prevalent AKI risk factors in pediatric patients admitted to ICU. Also, other researchers [17] reported hemodynamic instability as the most prevalent AKI risk factor in PICU patients. Recent study [18] highlighted septic shock and dehydrations as commonly incriminated reasons for AKI occurrence in these patients.

Our study clearly explored a significant elevation in TIMP2 levels as well as the IGFBP7*TIMP2 at 1st day and 3rd day of admission. The same parameters were found to be the significant predictors of AKI cases. These findings are supported by the studies which have noted that IGFBP-7 and TIMP-2 are engaged in G1 cell cycle arrest at the first stages of cellular injury and inhibit cell division development until DNA issue was resolved [19]**.** IGFBP-7 and TIMP-2 are molecules that participate in cell apoptotic, inflammatory, and ischemic events in response to a range of stressors [20]. It has been claimed that IGFBP-7*TIMP-2 indicates AKI in both septic and nonseptic severely ill individuals [21]. Our study clearly explored this association since we found significant elevation in TIMP2 levels as well as the IGFBP7*TIMP2 at 1st day and 3rd day of admission. The same parameters were found to be the significant predictors of AKI cases.

In congruence with our findings, A prospective multicentre observational study of 94 babies, [22] detected that Patients with AKI had substantially increased urine IGFBP-7*TIMP-2 levels. Other researchers [23] reported that IGFBP-7*TIMP-2 may reliably assess AKI development in neonates after cardiac operation. IGFBP-7*TIMP-2 usefulness in high-risk patients having major non-cardiac surgery has also been studied. In a single-centre study [24], This biomarker was evaluated in 107 high-risk patients on ICU admission around four hours following major surgery and was shown to indicate AKI risk.

In neonates, a few studies assessed this marker value [1, 5, 25, 26] found that TIMP-2 and IGFBP-7 combination exhibited independent discriminatory utility for AKI in severely ill newborns. Another study [27] evaluated ([TIMP-2]•[IGFBP7]) using a commercially available immunoassay (NephroCheckTM) in a prospective cohort study involving 133 subjects aged 0–18 years, including 46 patients with established AKI, 27 patients without AKI (non-AKI group I), and 60 apparently healthy neonates and children (non-AKI group II). Patients in the "Failure" stage showed median urine [TIMP-2] •[IGFBP7] levels 3.7-fold greater than non-AKI participants.

So far, only two studies assessed IGFBP-7*TIMP-2 marker in the pediatric population to explore its role as an AKI risk indicator. In a prospective cohort study [24] IGFBP-7*TIMP-2 capacity to detect AKI risk in 51 children having CPB surgery was investigated. Another study [20] found that IGFBP-7*TIMP-2 was a good indicator for AKI in children injected with intravenous contrast medium.

As G1 cell cycle arrest is a recognised result of AKI, it is hypothesised that TIMP-2 and IGFBP7 upregulation in AKI patients reflects their growth inhibitory activities [19].

Notably, our study showed that IGFBP-7 alone was elevated, but not to a significant level in the AKI group. In partial alignment, other researchers [28] reported that TIMP-2 was better than IGFBP-7 in sepsis-induced AKI. These discrepancies may imply modest but significant mechanistic differences between various AKI etymologies, and the 2 biomarkers are implicated in processes that are somewhat distinct.

Less emphasis was dedicated to the search for relevant biomarkers predictive of AKI prognosis, particularly renal recovery, requirement for RRT, and patient mortality, in comparison to the progression of new AKI biomarkers onset prediction. In the present study, comparison of the studied markers regarding the long-term outcome in cases with risk of AKI revealed that no significant difference presents in either marker according to the AKI long term outcome (need for dialysis). Similar to our results, another study [29] did not find correlation between these markers and the need for renal replacement therapy in patients before elective cardiac surgery. However, as significant difference was shown after surgery. Importantly, severely sick individuals cannot be compared to the patients in this research who had elective heart surgery. Patients attended to the ICU for a range of medical causes, such as sepsis, coma, and respiratory insufficiency, and including emergency admissions, constitute a diverse community of critically ill patients. On the other side, a previous study [27] showed that good diagnostic performance of urine [TIMP-2] •[IGFBP7] in identifying poor results in newborn and paediatric AKI of diverse aetiology. Indeed, we believe that the results reliability is impacted by the small number of cases that required dialysis (n=3).

In this study, the studied markers did not show significant difference according to the mortality. Moreover, they did not show significant correlation with ICU stay length. Data on the predictive value of both biomarkers with regard to mortality is

scarce. Another study [30] found that [TIMP-2] [IGFBP7] did not enhance the clinical model predicting a composite result of death or dialysis in critically ill patients within 9 months. On the other side, other researchers [31] TIMP-2 predicted stage 3 AKI and 7-day death in 98 individuals with severe illness.

Overall, our study indicates that Pediatric practitioners should use IGFBP-7*TIMP-2 with caution in circumstances where it has not been used before. This biomarker should not be used in ambulatory practices, and it should not be considered as a substitute for measurement of serum creatinine. A repeat measurement in a critically sick patient may be evaluated if a variation in a stable patient's clinical state (e.g., tachycardia, acidosis, blood loss, etc.) places the patient at AKI risk.

The present work is limited by the relatively small sample size, and the short-term follow-up period. Also, it is single-center research with inherent limitations in generalizability to larger groups. Finally, we evaluated TIMP-2 and IGFBP7 independently using ELISA kits since NephroCheck is not accessible outside the United States. Consequently, it is difficult to draw a direct comparison and it may not be suitable to employ non-standard ELISA findings in clinical practise. However, our study emphasizes the value of adopting new markers to predict AKI risk in critically ill children.

Conclusion:

The levels of IGFBP-7*TIMP-2 marker in the critically ill paediatric population could be a predictor of AKI risk. In this study, the studied markers did not show significant difference according to the mortality. Moreover, they did not show significant correlation with the length of stay in ICU.

Recommendations:

Implementation of IGFBP-7*TIMP-2 analysis, in adjunct with other routine tests, as a feasible reliable screening test for prediction of AKI risk. Further multicenter long-term prospective studies on a larger population with variable causes of ICU admission are needed to clarify further roles of the IGFBP-7*TIMP-2 in the prediction of AKI risk and prognosis of disease. More in-depth studies are needed to shed light on the molecular pathologic background of the association between IGFBP-7*TIMP-2 and the AKI risk.

Abbreviations

ABG	Arterial BloodGas
AKI	Acute Kidney Injury
ANOVA	A one-way Analysis of Variance
CBC	Complete Blood Count
CRP	C-Reactive Protein
ELISA	Enzyme Linked Immunosorbent Assay
G1	Gap 1
IGFBP7	Insulin-Like Growth Factor Binding Protein-7
PICU	Pediatric Intensive Care Unit
ROC	Receiver Operating Characteristic Curve
TIMP2	Tissue Inhibitor of Metalloproteinase-2

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