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Original article

The Effectiveness of Urinary TIMP-2 and L-FABP in Predicting Acute Kidney Injury in Critically Ill Neonates

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Abstract:

Background: Acute kidney injury which is known as (AKI) is correlated with high death and morbidity in critically diseased neonates. Aim: To evaluate the effectiveness of urinary tissue inhibitor of metalloproteinase-2 (TIMP-2) and urinary liver-type fatty acid binding protein (L-FABP) in predicting acute kidney injury. **Methods:** Prospective cohort research was conducted on eighty-eight newborns who were critically diseased were evaluated for the severity of their illness using the score for neonatal acute physiology perinatal extension (SNAPPE), ranging in age from one day to twenty-eight days, then according to Kidney Disease Improving Global Outcomes (KDIGO) staging, they were classified into two groups: Non-AKI group, which were fifty neonates and AKI group, which were divided into two subgroups: KDIGO stage 1, which were twenty-six neonates and KDIGO stage 2, which were twelve neonates. These neonates have been admitted to the Neonatal Intensive Care Unit (NICU) of the Pediatric Department at Benha University Hospital. **Results:** A significant variance has been detected among both groups as regards SNAPPE score, TIMP-2 and L-FABP. There was a significant decrease in hematocrit, hemoglobin and platelets levels at the follow-up of laboratory data, while a significant rise has been detected in CRP, creatinine, urea and serum K. A significant positive association has been detected has been detected between urinary TIMP-2, SNAPPE score, systolic blood pressure (SBP), serum K and L-FABP. Also, there was a significant positive association among urinary L-FABP and SBP, SNAPPE score and Serum K. The results showed that urinary TIMP-2 had the highest sensitivity (84.21%) and specificity (86%) at a cutoff of 4.57 ng/mL, with an area under the curve (AUC) of 0.841. Similarly, ROC analysis of urinary L-FABP revealed the highest sensitivity (81.58%) and specificity (90%) at a cutoff of 6.25 ng/mL, with an AUC of 0.807. Analysis showed that urinary TIMP-2 + L-FABP had 96% sensitivity and 98.9% specificity. SNAPPE score, APGAR score, urinary TIMP-2 and urinary L-FABP can be used as independent factors for predicting AKI. **Conclusion:** Urinary TIMP-2 and L-FABP levels were higher among the AKI group, with levels in the KDIGO stage 2 group being even greater, which were considered as early detectors of AKI.

Key Words: Neonates; u TIMP-2; u L-FABP; AKI.

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Introduction

Acute renal injury, which is one of the most prevalent organ dysfunctions, is correlated with a great rate of morbidity and death in critically diseased neonates [1].

Numerous research has concentrated on the identification of early indicators for the prediction of acute kidney injury, which is essential for the improvement of clinical results [2].

The combination of L-type fatty acid-binding protein with urinary tissue inhibitor of metalloproteinase-2 ([L-FABP] • [TIMP-2]) is proposed to be beneficial for the identification of cases who are at risk for Acute renal injury or severe Acute renal injury, as well as for the prediction of renal injury well in advance of the clinical manifestations, as oliguria and azotemia [3].

Neonates who are critically ill have a much greater probability of developing acute kidney injury due to the presence of factors as severe infection, the utilization of mechanical ventilation (MV) or nephrotoxic medications and perinatal hypoxic asphyxia. Furthermore, the death rate is significantly greater among newborns that have AKI over kids. Because of inter-individual variability in renal maturation and the fact that maternal level, urine output, and serum creatinine (SCr) are unreliable in the newborn period, the identification of neonatal acute kidney injury continues to be difficult when compared to the usual clinical criteria that are utilized in pediatric and adult cases [4].

The purpose of this investigation was to estimate the effectiveness of urinary tissue inhibitor of metalloproteinase-2 and L-FABP in the prediction of acute renal injury in infants who are critically diseased.

Patients and Methods

In this prospective cohort research, 88 newborns who were critically diseased were evaluated for the severity of their illness using the score for neonatal acute physiology perinatal extension (SNAPPE) [5], then according to Kidney Disease Improving Global Outcomes (KDIGO) staging [6]. They were classified into two groups: Non-AKI group, which were 50 neonates and AKI group, which were divided into two subgroups: KDIGO stage 1, which were 26 neonates and KDIGO stage 2, which were 12 neonates. These neonates ranged in age from one day to twenty-two days and were brought to the Intensive Care Unit of the Pediatric Department at Benha University Hospital due to their critical condition. The study was conducted in the neonatal intensive care unit (NICU), Pediatric Department, Benha University Hospital, from December 2022 to December 2023. The research has been approved by the Research Ethics Committee of the Faculty of Medicine at Benha University {Approval code: M.S.5.10.2022}. Informed written consent was obtained from the parents of the newborns involved in the study prior to its commencement.

Inclusion criteria: Full term and preterm neonates. Neonates admitted to NICU from the age of one day to 28 days. Critically ill neonates by assessment of illness severity by the score for neonatal acute physiology perinatal extension (SNAPPE).

Exclusion criteria: Neonates aged more than one month. Mortality or discharge within twenty-four hours of Neonatal Intensive Care Unit admission. Parental refusal to participate in the study.

Methods

All studied neonates were subjected to full history taking, complete clinical examination including anthropometric measurements: head circumference, weight and length. Vital signs assessment including heart rate, respiratory rate (RR), temperature and capillary refill time. Full systemic examination including cardiac, chest and abdominal examination with urine output assessment in 24 hours, APGAR score: Breathing effort, heart rate, muscle tone, grimace response or

reflex irritability, skin color and laboratory assessment as:

Complete blood count (CBC), C- reactive protein (CRP), Arterial blood gases (ABG), serum Sodium, Potassium and Kidney functions (urea and creatinine).
Urinary level of biomarkers (TIMP-2 and L-FABP) were established utilizing enzyme-linked immunosorbent assay (ELISA) kits employed a double-antibody sandwich technique.

Assessment of illness severity

Critically ill neonates were evaluated for the severity of their illness using the score for neonatal acute physiology perinatal extension (SNAPPE).

Table 1 SNAPPE score.

Variable	Measure	Point
Lowest Mean Blood Pressure	>29 mmHg	0
	20-29 mmHg	9
	<20 mmHg	19
Lowest temperature	> 35.6°C	0
	35-35.6°C	8
	<35°C	15
Ratio PO_2/FiO_2	>2.49	0
	1.0-2.49	5
	0.3-0.99	16
Lowest serum pH	>7.19	0
	7.10-7.19	7
	<7.10	16
Seizure	No	0
	Multiple	5
Urine output (ml/BW/hour)	> 0.9 ml/BW/hour	0
	0.1-0.9 ml/BW/hour	5
	< 0.1 ml/BW/hour	18
Birth weight (g)	> 999 g	0
	750-999 g	10
	< 750 g	17
Small for gestational age	> 3rd percentile	0
	< 3rd percentile	12
Apgar score at 5 min	> 7	0
	< 7	18

Newborn with SNAPPE less than ten have only a death of five percent, but SNAPPE greater than sixty was suggestive of poor results with a death of hundred percent [5] **[table 1]**

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Diagnosis of AKI

The Kidney Disease Improving Global Outcomes (KDIGO) staging system has been utilized to estimate the diagnosis and severity of acute renal injury [6].

Since all AKI neonates most probably developed within the first 15 days after NICU admission, urine samples collected during the first 2 weeks and the follow up of developing AKI was done in the following second 2 weeks.

Urine samples were obtained from participating neonates under complete aseptic conditions.

One urine sample was collected from each neonate, a 5 ml urine collected in a sterile container was centrifuged for 20 minutes at 1000×g. If precipitation formed, the supernatant was removed. Samples in form of two ml of supernatant collected in two Eppendorf tubes (one ml for each), one tube for each biomarker and the two tubes stored at -20°C to -80°C. Using sandwich ELISA detection, the quantities of TIMP-2 (ng/ml) and L-FABP (ng/ml) in urine spots were determined, which is manufactured by (Develop Company and has the catalog No: DLR-TIMP2-Hu) [7] and the kit (Develop Company, Catalog No: DLR-FABP1-Hu).

Statistical methods

The statistical analysis and data administration have been performed utilizing SPSS version 23 (IBM, Armonk, New York, States). Comparing quantitative data between the research groups was accomplished utilizing either the one-way analysis of variance (ANOVA) or the Kruskal Wallis test, depending on whether the numerical variables in question had a distributed normally or non-normal distribution. For the purpose of comparing categorical data, either the Fisher's exact test or the Chi-square test has been utilized. In order to examine the sensitivity and specificity of quantitative diagnostic measures that classify patients into one of 2 categories, ROC analysis has been utilized to create a prediction of acute kidney injury. Calculations have been made to determine the best cut-off point, diagnostic indices, and Area Under Curve (AUC) with a confidence interval of ninety-five percent Every single statistical test is comprised of two distinct sides. The significance of the P values was determined to be less than 0. 05.

Results

There were insignificant variances between the groups under investigation as regards age, gender, age at admission, or natal history. However, statistically significant variances has been detected between the two groups as regards APGAR score and follow-up weight; as medians of APGAR score and follow-up weight were lower among the AKI group.

(Table **2)** shows a statistically significant difference between the two groups in terms of the SNAPPE score, with the mean SNAPPE score being higher in the AKI group (P-value < 0.001).

(Table **3**) demonstrates a statistically significant difference between the two groups regarding TIMP-2 and L-FABP levels, with both TIMP-2 and L-FABP levels being higher in the AKI group (P-value < 0.001).

(Table **4**) demonstrates a statistically significant difference between the two groups regarding TIMP-2 and L-FABP levels, with both TIMP-2 and L-FABP levels being higher in the KDIGO stage 2 group (P-value < 0.001).

Table 2 score for acute neonatal physiology perinatal extension among studied groups

Variables		**Non-AKI (number=fifty)**	**AKI (number=38)**	**P Value**
SNAPPE score	*Mean ± SD*	12 ± 6.37	24.5 ± 9.27	
	Range	(5 – 23)	(5 – 47)	**<0.001**

* Student's T test, Non-significant: P -value greater than 0.05, Significant: P-value not more than 0.05

Table 3 Specific investigations among studied 2groups: the no-AKI group and AKI group

Variables		**Non-AKI (number=fifty)**	**AKI (number=38)**	**P Value**
TIMP-2*(ng/ml)*	*Mean ± SD*	2.17 ± 2.02	6.08 ± 2.65	
	Range	(0.54 – 8.73)	(0.7 – 9.88)	**<0.001**
L-FABP	*Mean ± SD*	3.51 ± 2.14	7.63 ± 3.05	
(ng/ml)	*Range*	(1.37 – 11.22)	(1.44 – 12.3)	**<0.001**

Table 4 Comparison of TIMP-2 and L-FABP as regards outcomes among studied patients in the AKI group

Variables		**TIMP-2** *(ng/ml)*	**L-FABP** *(ng/ml)*
KDIGO	*Mean ± SD*	5.39 ± 2.19	6.81 ± 2.34
stage 1 AKI	*Range*	(0.7 – 8.5)	(1.46 – 9.2)
KDIGO	*Mean ± SD*	7.58 ± 3.03	9.43 ± 3.71
stage 2 AKI	*Range*	(0.93 – 9.88)	(1.44 – 12.3)
P Value		**<0.001**	**<0.001**

(Table **5**) demonstrates a significant positive correlation between urinary TIMP-2 and several variables: SNAPPE score (r = 0.458, P < 0.001), SBP (r = 0.297, P = 0.01), serum K (r = 0.630, P = 0.001), and L-FABP (r = 0.844, P = 0.001). A significant negative correlation was observed between urinary TIMP-2 and both APGAR score (r = -0.297, P = 0.02) and urine output (r = -0.310, P = 0.003). Additionally, urinary L-FABP showed a significant positive association with SBP (r = 0.258, P = 0.02), SNAPPE score (r = 0.396, P = 0.001), and serum K (r = 0.601, P < 0.001), while a significant negative correlation was found with APGAR score (r = -0.300, P = 0.02) and urine output (r = -0.230, P = 0.03).

ROC analysis was conducted to determine the optimal cutoff values for distinguishing AKI patients from non-AKI patients. The results showed that urinary TIMP-2 had the highest sensitivity (84.21%) and specificity (86%) at a cutoff of 4.57 ng/mL, with an area under the curve (AUC) of 0.841. Similarly, ROC analysis of urinary L-FABP revealed the highest sensitivity (81.58%) and specificity (90%) at a cutoff of 6.25 ng/mL, with an AUC of 0.807 (Table **6** and Figure **1**).

On conducting ROC analysis (Receiver operation Curve) to discriminate AKI patients from non-AKI patients, the analysis showed that urinary TIMP-2 + L-FABP had (96%) sensitivity and (98.9perent) specificity with the area under the curve was (0.942) (figure **2**).

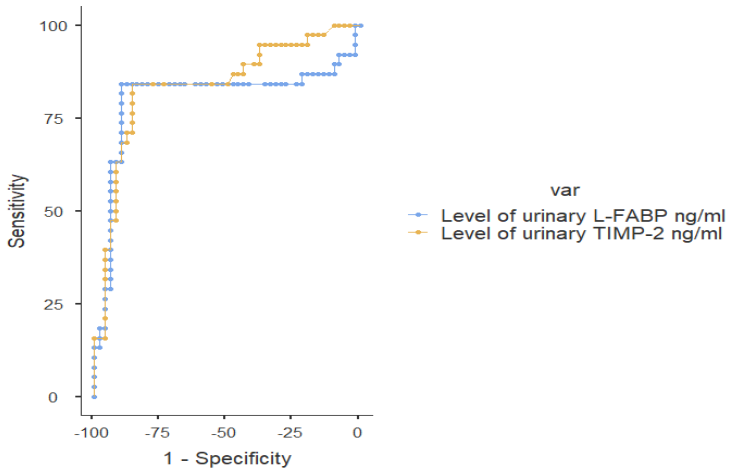

Figure 1: ROC curve analysis of TIMP-2 & L-FABP in differentiating acute kidney injury from non- acute kidney injury.

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Table 5: Correlation of urinary TIMP-2 and L-FABP with different variables among groups under investigation

	TIMP-2		L-FABP	
Variable	***R***	***P***	***R***	***P***
Age	0.033	0.76[2]	0.025	0.82[2]
APGAR score	-0.297	**0.02[1]**	-0.300	**0.02[1]**
Birth weight	-0.090	0.69[1]	-0.049	0.65[1]
Recent weight	-0.158	0.15[1]	-0.110	0.32[1]
SBP	0.297	**0.01[1]**	0.258	**0.02[1]**
Urine output	-0.310	**0.003[2]**	-0.230	**0.03[2]**
SNAPPE score	0.458	**<0.001[1]**	0.396	**0.001[1]**
CRP	0.145	0.32[2]	-0.66	0.65[2]
Creatinine	-0.019	0.86[1]	-0.081	0.45[1]
Urea	0.045	0.68[2]	0.114	0.29[2]
Serum K	0.630	**<0.001[2]**	0.601	**<0.001[1]**
L-FABP	0.844	**<0.001[2]**	-	-

*[1]Pearson correlation, [2]Spearman rank correlation test

Table 6 ROC curve analysis of TIMP-2 and L-FABP in differentiating acute kidney injury from non-AKI among studied patients

Variables	Cut-off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPP (%)	AUC (%)	P Value
TIMP-2	**4.57**	84.21%	86%	82.05%	87.76%	0.841	**<0.001**
L-FABP	**6.25**	81.58%	90%	86.11%	86.54%	0.807	**<0.001**

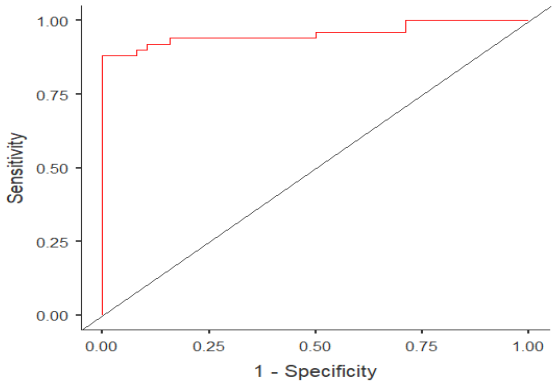

Figure 2: ROC curve analysis of the added value of TIMP-2 with L-FABP in differentiating AKI from non-AKI.

Discussion

AKI is among the greatest widespread organ malfunctions and is linked to a significant morbidity and mortality rate in critically sick individuals. It is still a major reason for morbidity and mortality in neonates [9].

This study showed insignificant variance among the groups under investigation in terms of age, gender or age at admission.

In agreement with our results, Sun et al [10] found that there were insignificant differences in gender and age.

A statistically significant variance has been demonstrated by this research among both groups as regards APGAR score as the median of APGAR score was lower among the acute kidney injury group (P-value less than 0.001).

This is in line with the research of Bansal et al. [11], who found a significant relationship between AKI and low APGAR scores at one and five minutes.

This research showed a statistically significant variance among both groups in terms of SNAPPE score as the mean of SNAPPE score was higher among the AKI group (P-value less than 0.001).

This agrees with Naunova-Timovska & co-workers [12] who found neonates with AKI and lethal outcome had severe SNAPPE score. The high score level was significantly associated with the severity of the disease.

In terms of platelets, CRP, and serum potassium, this research demonstrated a statistically significant distinction among both groups in the follow-up laboratory data. CRP and serum K^+ levels were greater in the acute kidney injury group (P-value equals 0.001), whereas platelet levels were greater in the non-AKI group (P-value equal to 0.003).

The results of Gabri and colleagues [13] further showed C-reactive protein was positive in more than half of the cases.

These results were also supported by Lyu and Fu [14] who noticed Low platelet count was correlated with the high odds of AKI in the NICU.

This study showed insignificant variance among both groups as regards baseline laboratory data regarding CBC, CRP, urea, creatinine, Na^+, K^+.

In agreement with our research, Sun 7 co-workers [10] found insignificant variances in Na^+, K^+, PLT, WBC, and baseline creatinine; the same as Paramastuty [15] who detected that creatinine at zero hour at birth demonstrated statistically insignificant variance among their group under investigation (P value greater than 0.05).

A statistically significant variance has been demonstrated by this investigation among both groups as regards TIMP-2; as TIMP-2 level was higher among the acute kidney injury group (P-value less than 0.001).

In accordance with our outcomes, Sobeih and colleagues [7] found that the TIMP2 1st day and 3rd day levels changed substantially among studied groups with considerably greater mean levels found in the cases with risk of AKI.

This was consistent with the outcomes of Pajenda [16], who observed a rapid rise in urine TIMP-2 following renal tubular insult in most cases who have acute kidney injury, and who found that a significant reduction suggested an improvement in renal function.

A statistically significant variance has been detected by this investigation among both groups as regards L-FABP as L-FABP level was greater among the acute kidney injury group (P-value less than 0.001).

This finding agrees with Sun and colleagues [10] who found that the median L-type fatty acid-binding protein concentration was significantly higher in acute kidney injury cases than non-AKI cases and the results showed that L-type fatty acid-binding protein was a potential predictor of AKI.

As regards results among studied patients, a statistically significant variance has been demonstrated by this investigation among both groups as regards TIMP-2 and L-FABP as TIMP-2 and L-FABP levels were significantly higher among the KDIGO stage 2 group.

In agreement with Sun et al [10] who found that the median concentration of L-type fatty acid-binding protein in cases with non-acute kidney injury was remarkably lower than in those with acute kidney injury stage I, acute kidney injury stage II, and acute kidney injury stage III. The development of acute kidney injury was detected by an increasing concentration of L-FABP.

In this study, we illustrated that there was a positive association among urinary TIMP-

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2 and SNAPPE score, SBP, Serum K and L-FABP, while a significant negative association has been detected with APGAR score and urine output and no correlation with gestational age and birth weight.

The contrary was shown by Chen and co-workersl [17], who discovered that being born small for gestational age (SGA) continued to be strongly related with elevated 1st urine TIMP-2 levels.

On conducting ROC analysis (Receiver operation Curve) to determine the optimal cutoff value to discriminate AKI patients from non-AKI patients, the analysis showed that urinary TIMP-2 had the highest sensitivity (84.21%) and specificity (86%) at 4.57 nanogram per milliliter with the area under the curve of 0.841 which was a good accuracy.

These results are supported by Sobeih and colleagues [7] who showed that TIMP on the 1st day had a sensitivity of 90% and specificity of 80% at 2.33 with the AUC of 0.96; and at a cutoff value of 2.49, it had sensitivity of 85% and specificity of 90% with the AUC of 0.96. On the 3rd day, it had sensitivity of 95% and specificity of 90% at 2.61 with the AUC of 0.995; and at a cutoff value of 2.54, it had sensitivity of hundred percent and specificity of hundred percent with the AUC 1.

On conducting ROC analysis on urinary L-FABP, the analysis showed that L-FABP had the highest sensitivity (81.58%) and specificity (90%) at 6.25 nanogram per milliliters with the area under the curve of 0.807 which was a good accuracy.

Also, Sun et al [10] demonstrated that the diagnostic sensitivity and specificity were 71.8 percent and 92.5 percent, respectively, which is consistent with these findings.

The ROC curve analysis has been utilized for estimating the predictive power of L-type fatty acid-binding protein for acute kidney injury which revealed L-FABP was a biomarker that can predict acute kidney injury. They suggested that clinical application of quick and sensitive detection methods of L-FABP could provide cases with advantages. It was possible that L-FABP might be utilized as a diagnostic and predictive biomarker for acute kidney injury.

Similarly, Elnady and co-workers [18] discovered that urinary L-type fatty acid-binding protein has the ability to identify acute kidney injury with an area under the curve of 0.743, a sensitivity of 90.5 percent, and a specificity of ninety percent. This finding agreed with their findings.

After applying logistic regression analysis for predictors of AKI; urinary TIMP-2 can be used as independent factors for predicting AKI.

In accordance with the results of Abouhadid and colleagues [19], who discovered that urine TIMP-2 could have a role in the early prediction of acute kidney injury prior to the rise in serum creatinine and the further deterioration in renal functions, this would be beneficial for the early treatment of the illness and would also improve the prognosis.

Conducting ROC analysis (Receiver operation Curve) to discriminate AKI patients from non-acute kidney injury cases revealed that the combination of L-type fatty acid-binding protein and urinary tissue inhibitor of metalloproteinase-2 achieved 96% sensitivity and 98.9 percent specificity, with an AUC of 0.942, indicating excellent accuracy.

This finding demonstrates that combining TIMP-2 and L-FABP provides superior predictive performance compared to using each biomarker individually. Consequently, this strong performance may reduce the need for additional diagnostic investigations.

There are no existing studies examining the combination of TIMP-2 and L-FABP. Our hypothesis aimed to demonstrate that this combination could serve as an independent predictor of AKI occurrence in critically diseased newborns, offering the highest sensitivity, specificity and accuracy.

Conclusion

Based on our findings, urinary TIMP-2 may serve as a valuable biomarker for predicting acute kidney injury (AKI) in critically ill neonates. Additionally, urinary L-FABP levels showed a statistically significant correlation with the prediction of AKI development. The combination of urinary TIMP-2 and L-FABP demonstrated independent discriminative values, further enhancing their potential as early detectors of AKI. Logistic regression analysis revealed that the SNAPPE score, APGAR score, urinary TIMP-2, and urinary L-FABP can all act as independent predictors of AKI. Notably, TIMP-2 and L-FABP levels were higher in the AKI group, with levels in the KDIGO stage 2 group being even greater, further supporting their role as early biomarkers for AKI detection.

Conflict of interest

None of the contributors declared any conflict of interest

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