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ORIGINAL RESEARCH

Urinary Liver-Type Fatty Acid Binding Protein (L-FABP) in Early Detection and Outcome Prediction of Sepsis-Associated Acute Kidney Injury

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Abstract: **Introduction:** Acute kidney injury (AKI) is one of the most frequent complications in septic shock cases, and has a high mortality rate. The aim of this study was to determine the value of urinary liver-type fatty acid binding protein (L-FABP) in early detection and outcome prediction of AKI in patients with sepsis and septic shock. **Methods:** This prospective cohort study was conducted on patients who presented to the emergency department (ED) with sepsis or septic shock. Urinary L-FABP levels were measured at the time of admission and patients were classified into AKI and non-AKI groups within 7 days according to the KIDGO Criteria. The screening performance characteristics of urinary L-FABP in early detection of AKI within seven days of admission and need for renal replacement therapy (RRT) were calculated and reported. **Results:** 212 patients with the mean age of 66.5 ± 16.2 (range 18-99) years were included (60.4% male). 54 (25.5%) patients had sepsis, and septic shock was developed in 158 (74.53%) cases. 143 (67.5%) patients were complicated with AKI. The area under the receiver operating characteristic (ROC) curve (AUC) of urinary L-FABP in early detection of sepsis-associated AKI was 0.94 (95% confidence interval (CI): 0.90 - 0.97), compared to the AUC of 0.64 (95% CI: 0.54-0.74) for serum creatinine. The sensitivity and specificity of urinary L_FABP at its best cutoff point (13.90 μg L-FABP/g Cr) were 89.9% and 86.3%, respectively. The area under the ROC curve of urinary L-FABP in predicting the need for RRT in sepsis-associated AKI patients was 0.74 (95% CI: 0.64-0.85), compared to the AUC of 0.53 (95% CI: 0.41-0.64) for serum creatinine. The sensitivity and specificity of urinary L-FABP at its best cutoff point (22.05 μg L-FABP/g Cr) were 63.6% and 71.4%, respectively. **Conclusion:** It seems that, L-FABP could be considered as a valuable biomarker for early detection and predicting the severity of AKI in septic patients.

Keywords: Acute kidney injury; Fatty acid binding proteins; Sepsis; Shock, Septic

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1. Introduction

Sepsis occurs when a dysregulated host response to infection, results in potentially life-threatening tissue damage and organ dysfunction. Although any organ system can be affected by sepsis, six organ systems are typically evaluated in clinical practice and have received the most attention: cardiovascular, respiratory, renal, neurological, hematological, and hepatic. Acute kidney injury (AKI) is one of the most frequent problems occurring in patients with sepsis. It occurs in 51% - 64% of patients with septic shock, with 50-70% mortality rate (1). Besides increasing mortality, AKI also increases medical costs and increases the risk of chronic kidney disease (CKD). According to Coca et al. (2012), AKI increased the risk of CKD by 8-fold and the risk of end-stage kidney disease by 3-fold (2).

Early detection of individuals at risk of AKI, or at risk of advancing to severe and/or chronic AKI, is critical for the commencement of appropriate supportive interventions, such as minimizing subsequent renal insults. However, the early recognition of AKI remains a challenge due to the lack of unified criteria for diagnosing AKI, which is still mainly based on blood creatinine and urine output. The discovery of biomarkers associated with AKI that can aid in its early detection is an area of intensive investigation. The ideal biomarker for AKI should possess the following characteristics: high sensitivity and specificity for the early detection of AKI, as well as allowing for effective differentiation between prerenal, intrarenal, and postrenal AKI. Additionally, it should help determine whether the primary cause of AKI is ischemia, toxins, or infection, and distinguish AKI from other acute kidney conditions such as glomerulonephritis, interstitial nephritis, and acute pyelonephritis. Furthermore, the biomarker should be able to predict the severity of kidney injury, facili-

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tate monitoring of AKI progression, assess responses to therapeutic interventions, and provide insights into AKI prognosis. For clinical applicability, such biomarkers need to fulfill specific requirements, including non-invasive or minimally invasive sample collection methods (e.g., through urine or blood), ease of implementation at the bedside or in standard clinical labs, and the capability to deliver reliable, rapid results with high diagnostic sensitivity and specificity (3).

Many novel biomarkers in blood and urine can help early detection of AKI such as Liver-type fatty acid binding protein (L-FABP), Cystatin C, Neutrophil gelatinase associated lipocalin (NGAL), Kidney injury molecule – 1, and IL-18. L-FABP is a 15 KDa protein that belongs to the family of fatty acid binding proteins. This small protein is involved in cellular long chain fatty acid metabolism and is abundantly expressed in tissues with an active fatty acid metabolism like heart and liver. Following cell damage, FABA is quickly released into the interstitium and plasma (4-8).

Although some urinary biomarkers are used to assess the acute phase of kidney injury, urinary L-FABP is used to evaluate AKI, the progression from AKI to CKD, and CKD (9). Additionally, urinary L-FABP serves as a predictive marker for the progression of age-associated renal fibrosis (10). Early application of L-FABP as a prognostic tool may enhance patient outcomes by improving early detection and predicting the outcome of AKI cases (9). This study aimed to determine the accuracy of urinary L-FABP in early detection and predicting the outcome of sepsis-associated AKI.

2. Methods

2.1. Study design and setting

The prospective cohort study investigated the diagnostic and prognostic accuracy of urinary L-FABP within the first hour of emergency department (ED) admission in patients with sepsis-associated AKI. The screening performance characteristics of urinary L-FABP in early detection of AKI within seven days of admission and need for renal replacement therapy (RRT) were calculated and reported.

The researchers adhered to the principles of Helsinki Declaration and confidentiality of patients' information throughout the study and the protocol of the study was approved by the Ethical committee of 108 Military Central Hospital (number 340/QD-BV).

2.2. Participants

Patients admitted to the Emergency Department of 108 Military Central Hospital, from January 2021 to August 2023, diagnosed with sepsis or septic shock according to the SCCM/ESICM 2016 guidelines, and aged over 18 years, were included in the study. Patients who were admitted in a state of cardiac arrest or brain death, those whose course of treatment was less than 24 hours, and those who did not receive the mandated level of monitoring and testing as per the established protocol were excluded from the study.

2.3. Measurements

After reaching diagnosis of sepsis or septic shock in ED, urine L-FABP was measured within the first hour of admission. Then patients were sent to Intensive Care Unit (ICU), where they were managed according to the treatment protocol for sepsis and septic shock in accordance with the 2016 Surviving Sepsis Campaign (SSC) guidelines. Patients were monitored and treated daily. Clinical signs and symptoms were recorded, blood creatinine tests conducted, and urine output measured daily for the first seven days of the study. Patients with AKI were followed to have urine output and normal blood creatinine levels. The patients' response to treatment was assessed throughout their stay in the intensive care unit (ICU) until they were either discharged or passed away.

2.4. Definitions

- Sepsis and Septic shock according to the Society of Critical Care Medicine/the European Society of Intensive Care Medicine (SCCM/ESICM) 2016:

Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total Sequential Organ Failure Assessment (SOFA) score ≥2 points consequent to the infection.

Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain Mean Arterial Pressure (MAP) ≥65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation (11).

- Definition and staging of AKI were according to Kidney Disease: Improving Global Outcomes (KDIGO) 2012 (12).
- Treatment and monitoring protocol was done according to SSC 2016 (11).

2.5. Data gathering

The following data were gathered for all patients included in this study:

- Demographic data: sex, age.
- Infection entry route, culture results.
- Every 6 hours, measurement of urine output till discharge from ICU.
- Urinary L-FABP were measured on admission. Urine samples were collected by sterile methods in sterile urinary cup.

The data mentioned above were collected from electronic medical records using a predesigned checklist. A trained intern, under the direct supervision of the emergency medicine attending, was responsible for data collection and patient follow-up. The intern strictly adhered to the protocol, ensuring no interference, and only filled out the pre-prepared checklists.

2.6. Outcomes

The outcomes evaluated in the study included the development of AKI based on KDIGO 2012 criteria and the requirement for renal replacement therapy (RRT).

2.7. Statistical analysis

Data were analyzed using the Statistical Program for Social Sciences (SPSS) version 23. Quantitative variables were expressed as mean ± standard deviation for normally distributed data, median and interquartile range for non-normally distributed data, while qualitative variables were presented as frequency and percentage. The Chi-square (X^2) test was employed to compare proportions between qualitative parameters, with a p-value greater than 0.05 considered statistically insignificant, a p-value less than 0.05 considered significant, and a p-value below 0.01 considered highly significant. Area under the Receiver Operating Characteristic (ROC) curve was used to evaluate the accuracy of urinary L-FABP in early detection of AKI within seven days of admission. ROC curves were generated, and the area under the curve (AUC) was calculated to assess the accuracy. Sensitivity and specificity values of urinary L-FABP were calculate and reported in the optimal cutoff points, which were determined based on Youden's Index.

3. Results

3.1. Baseline characteristics of studied cases

A total of 243 patients were evaluated, of whom 31 were excluded: 7 were admitted in a state of cardiac arrest or brain death, and 24 had incomplete data. Consequently, 212 patients with the mean age of 66.5 ± 16.2 (range 18-99) years were included (60.4% male). Table 1 compares the baseline characteristics of studied patients between cases with and without sepsis-associated AKI.

54 (25.5%) patients had sepsis, and septic shock was developed in 158 (74.53%) cases. 143 (67.5%) patients were complicated with AKI. The AKI group exhibited a higher overall positive rate of blood cultures and other pathogens compared to the non-AKI group. The most common site of infection was the gastrointestinal (GI) tract, accounting for 40.6% of cases in non-AKI patients and 46.2% in AKI patients.

Additionally, E. coli was the most common bacterial agent, accounting for 39.0% of cases in non-AKI patients and 26.3% in AKI patients (Table 1). In AKI patients, approximately two-thirds were classified as stage 1 (61.5%), 21.0% as stage 2, and 17.5% as stage 3 according to KDIGO 2012, and 19.6% required RRT. The median urinary L-FABP concentrations were 30.9 [IQR: 17.29-56.32] μg L-FABP/g Cr in the AKI group and 3.93 [IQR: 2.18-8.13] μg L-FABP/g Cr in the non-AKI group, with a statistically significant difference ($p < 0.001$, Table 1).

3.2. Urinary L-FABP in early detection of AKI

In our study, 90 patients presented with AKI on the first day. To use L-FABP for predicting AKI development, these patients were excluded, focusing only on the 122 patients who did not have AKI on admission. 53 patients developed AKI from the 2nd day to the 7th day after admission. The area under the ROC curve of urinary L-FABP in early detection of sepsis associated AKI was 0.94 (95% CI: 0.90 - 0.97), compared to the AUC of 0.64 (95% CI: 0.54-0.74) for serum creatinine (figure 1). Table 2 summarizes the screening performance characteristics of urinary L-FABP in early detection of sepsis-associated AKI. The sensitivity and specificity of urinary L-FABP at its best cutoff point (13.90 μg L-FABP/g Cr) were 89.9% and 86.3%, respectively.

3.3. Urinary L-FABP in predicting the need for RRT

The median urinary L-FABP concentrations were 18.22 [IQR: 4.88- 36.60] μg L-FABP/g Cr in the 'No need for RRT' group and 57.22 [IQR: 15.07 – 182.86] μg L-FABP/g Cr in the 'Need for RRT' group, showing a statistically significant difference. The area under the ROC curve of urinary L-FABP in predicting the need for RRT in sepsis-associated AKI patients was 0.74 (95% CI: 0.64-0.85), compared to the AUC of 0.53 (95% CI: 0.41-0.64) for serum creatinine (figure 2). Table 2 summarizes the screening performance characteristics of urinary L-FABP in predicting the need for RRT in sepsis-associated AKI patients. The sensitivity and specificity of urinary L-FABP at its best cutoff point (22.05 μg L-FABP/g Cr) were 63.6% and 71.4%, respectively.

4. Discussion

This study evaluated the utility of urinary L-FABP in early detection of AKI and its prognosis among septic patients in the emergency department. The findings demonstrated that urinary L-FABP was more effective than admission serum creatinine in detecting AKI, with an AUC of 0.94, sensitivity of 89.9 %, and specificity of 86.3% at a cutoff value of 13.9 μg L-FABP/g Cr, compared to an AUC of 0.64 for serum creatinine. Additionally, urinary L-FABP levels measured upon emergency admission can predict the requirement for renal replacement therapy with an AUC of 0.74 at a cutoff value of 22.05 μg L-FABP/g Cr, with a sensitivity of 63.6% and specificity of 71.4%.

Despite advancements in laboratory science and critical care medicine, currently, AKI is diagnosed via monitoring changes in serum creatinine levels, with or without the presence of oliguria. However, serum creatinine is relatively insensitive and nonspecific for detecting early kidney injury, which hampers timely diagnosis and intervention, ultimately affecting patient outcomes. Over the past decade, considerable efforts have been made to identify an ideal biomarker for early AKI detection and to assess the prognostic capabilities of various candidate biomarkers, including kidney injury molecule-1 (KIM-1), N-acetyl--d-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), and Liver type fatty binding protein (L-FABP). Hypoxia induces the expression of L-FABP genes through HIF-1 and HIF-2 (hypoxia-inducible factors) (13). To assess the response of L-FABP to hypoxic stress, researchers measured L-FABP gene expression in the pig LLC-PK1 cell line, derived from proximal tubule cells, after culturing these cells under hypoxic conditions. The results showed increased

expression of L-FABP genes in response to hypoxic stress, indicating that L-FABP is a hypoxia-inducible protein in proximal tubule cells. (14). Yamamoto T et al. investigated the relationship between peritubular capillary blood flow and urinary L-FABP excretion during reperfusion after living donor kidney transplantation. They found that L-FABP had an inverse correlation with peritubular capillary blood flow. This result demonstrates that L-FABP is secreted into the proximal tubular lumen in response to ischemic and oxidative stress (15).

The understanding of L-FABP's response to oxidative and ischemic stress has led to the hypothesis that L-FABP may play an antioxidant role. When examining the relationship between the production of reactive oxygen species and L-FABP gene expression, results indicated that L-FABP exhibits antioxidant activity independently of the antioxidant actions of superoxide dismutase, glutathione peroxidase, and catalase (16, 17).

The kidneys contain large amounts of fatty acids, making them prone to lipid peroxide formation. Since L-FABP binds with high affinity to long-chain fatty acids, particularly those with double bonds or fatty acid peroxides, it is suggested that L-FABP may protect the kidneys by removing lipid peroxides from the proximal tubules (18). Urinary L-FABP acts as an antioxidant and is secreted into urine in response to oxidative and ischemic stress. In sepsis patients, oxidative stress caused by endotoxins has been associated with acute kidney injury (19). Thus, L-FABP may be secreted into the urine during sepsis. Doi K and colleagues reported that in patients treated with polymyxin B, both urinary L-FABP levels and endotoxin concentrations decreased among survivors (20). This finding suggests that urinary L-FABP levels may reflect the severity of oxidative stress in sepsis patients and could represent a new avenue for research into using urinary L-FABP as a biomarker to monitor treatment efficacy in the future.

This study showed that urinary L-FABP predicts AKI (with an AUC of 0.94) more effectively than serum creatinine (AUC: 0.64). Serum creatinine levels can be influenced by age, gender, race, dietary protein intake, and muscle mass. Creatinine levels may remain within the normal reference range in individuals with reduced kidney function if they have low muscle mass. Therefore, serum creatinine has low sensitivity for early kidney disease detection and is not a reliable prognostic factor in elderly individuals (21, 22). Acute kidney injury (AKI) is prevalent among critically ill patients, with strong links to increased disability, mortality, and long-term kidney dysfunction. Currently, AKI is diagnosed and staged using serum creatinine levels, divided into three stages (12). However, serum creatinine lacks sensitivity for early tubular injury, as it does not rise until glomerular filtration is reduced (23, 24). Urinary L-FABP, a novel biomarker and endogenous antioxidant expressed in renal tubular cells, is released quickly in response to ischemic and oxidative stress (15, 25). Research by Nakamura found no correlation between elevated urinary L-FABP and serum creatinine (r = 0.28, P = 0.135), indicating that urinary L-FABP may increase independently of serum creatinine, especially in septic shock (26). Due to its early and rapid increase, urinary L-FABP has greater sensitivity than serum creatinine, making it a superior predictor of AKI.

In our analysis, urinary L-FABP serves as a reliable prognostic marker for severity of AKI as demonstrated in the following aspects: urinary L-FABP levels measured upon emergency admission can predict the requirement for renal replacement therapy, achieving an AUC of 0.74 at a cutoff value of 22.05 μg L-FABP/g Cr, with a sensitivity of 63.6% and specificity of 71.4%. These results align with findings from previous studies. Although it is now recognized that, in critically ill patients, an early renal replacement therapy strategy compared to standard does not correlate with a reduction in 90-day mortality risk (27), early renal replacement therapy still has certain benefits. These include the rapid improvement and stabilization of acid-base balance, fluid and electrolyte balance, thereby preventing severe complications of acute kidney injury and potentially removing toxic substances (28).

5. Limitations

While our prospective study offers valuable insights, it has several limitations. Firstly, it was conducted at a single center with a relatively small sample size. Secondly, the AKI group in our study included both newly developed and pre-existing AKI cases. Due to the limited sample size, we were unable to fully evaluate the predictive ability of urinary biomarkers for early AKI detection compared to serum creatinine. Thirdly, as with other biomarker studies, urinary L-FABP was compared to serum creatinine, which, although widely used in clinical practice to define AKI, is neither sensitive nor specific for kidney injury. Lastly, serial measurements of urinary biomarkers could provide more comprehensive data for future applications, even though obtaining a single urine sample at the time of admission is the simplest method for clinical use.

6. Conclusions

It seems that, urinary L-FABP is a promising biomarker for early detection and predicting the prognosis of sepsis-associated AKI. High levels of L-FABP are associated with the early onset of AKI, greater severity of renal injury, and worse clinical outcomes. As such, urinary L-FABP has potential clinical utility in improving the diagnosis, risk stratification, and management of patients with sepsis-associated AKI. Its use alongside other biomarkers could enhance the overall accuracy of AKI prediction and help in tailoring more effective treatment strategies.

7. Declarations

7.1. Acknowledgments

None.

7.2. Ethics approval

The study was approved by 108 Military Center Hospital ethics committee in biomedical research, number 310/QĐ-BV.

7.3. Author contribution statement

All authors listed have significantly contributed to the investigation, development, and writing of this article.

• Conceptualization: Duong Le Xuan, Ghi Nguyen Hai, , Anh Duong Duc.

• Data curation: Duong Le Xuan, Hoa Do Thanh, Cuong Nguyen Thai, Ghi Nguyen Hai.

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• Supervision: Duong Le Xuan, Gia Binh Nguyen.

• Writing – original draft: Anh Duong Duc, Duc Vu Anh, Ghi Nguyen Hai.

• Writing – review & editing: Duong Le Xuan, Anh Duong Duc, Ghi Nguyen Hai.

• All authors read and approved the final version of manuscript.

7.4. Funding statement

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7.5. Data availability statement

Data will be made available on request.

7.6. Declaration of competing interest

The authors declare no conflict of interest.

7.7. Using artificial intelligence chatbots

None.

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Table 1: Baseline characteristics of included patients (n = 212)

Characteristics	Non-AKI (n=69)	AKI (n=143)	P value
Age (years)			
Mean ± SD	64.78 ± 17.02	67.34 ± 15.76	0.28
Sex			
Male	37 (53.6)	91 (63.6)	0.18
Source of the infection			
Respiratory System	19 (27.5)	36 (25.2)	0.74
Digestive System	28 (40.6)	66 (46.2)	0.46
Urinary System	8 (11.6)	19 (13.3)	0.83
Skin and Soft Tissues	8 (11.6)	6 (4.2)	0.07
Other	6 (8.7)	16 (11.2)	0.64
Positive cultures			
Blood	17 (24.6)	49 (34.3)	0.21
Other	28(40.6)	47 (32.9)	0.44
Both	41 (59.4)	80 (55.9)	0.66
Bacterial agent			
Klebsiella	9 (22.0)	17 (21.3)	1.0
E. Coli	16 (39.0)	21 (26.3)	0.21
Pseudomonas	1 (2.4)	2 (2.5)	1.0
Acinetobacter	3 (7.3)	7 (8.8)	1.0
Enterobacter	2 (4.9)	6 (7.5)	0.72
Staphylococcus	7 (17.1)	10 (12.5)	0.58
Streptococcus	1 (2.4)	7 (8.8)	0.26
Other	2 (4.9)	10 (12.5)	0.22
AKI stage			
1	0	88 (61.5)	-
2	0	30 (21.0)	-
3	0	25 (17.5)	-
Renal replacement therapy			
Yes	0	28 (19.6)	<0.001
Urinary L-FABP (μg L-FABP/g Cr)			
Median (IQR)	3.93 (2.18-8.13)	30.90 (17.29-56.32)	<0.001

Data are presented as mean ± standard deviation (SD), median and interquartile range (IQR), or frequency (%).
AKI: Acute kidney injury; L-FABP: liver-type fatty acid binding protein.

Table 2: Screening performance characteristics of urinary liver-type fatty acid binding protein (L-FABP) in early detection of acute kidney injury (AKI) and predicting the need for renal replacement therapy (RRT)

Characteristics	AKI detection	Need for RRT
Sensitivity	86.3 (86.3 - 93.3)	71.4 (51.3 - 86.8)
Specificity	89.9 (80.2- 95.8)	63.6 (56.2 - 70.5)
Positive predictive value	86.3 (75.5- 92.8)	23.0 (18.1 - 28.8)
Negative predictive value	89.9 (81.6 - 94.7)	93.6 (89.0 - 96.4)
Positive likelihood ratio	8.50 (4.18 - 17.31)	1.96 (1.45 - 2.65)
Negative likelihood ratio	0.14 (0.09 - 0.22)	0.45 (0.25 - 0.82)
Accuracy	0.88 (0.81 – 0.94)	0.65 (0.58 – 0.71)

All measures are presented with 95% confidence interval.

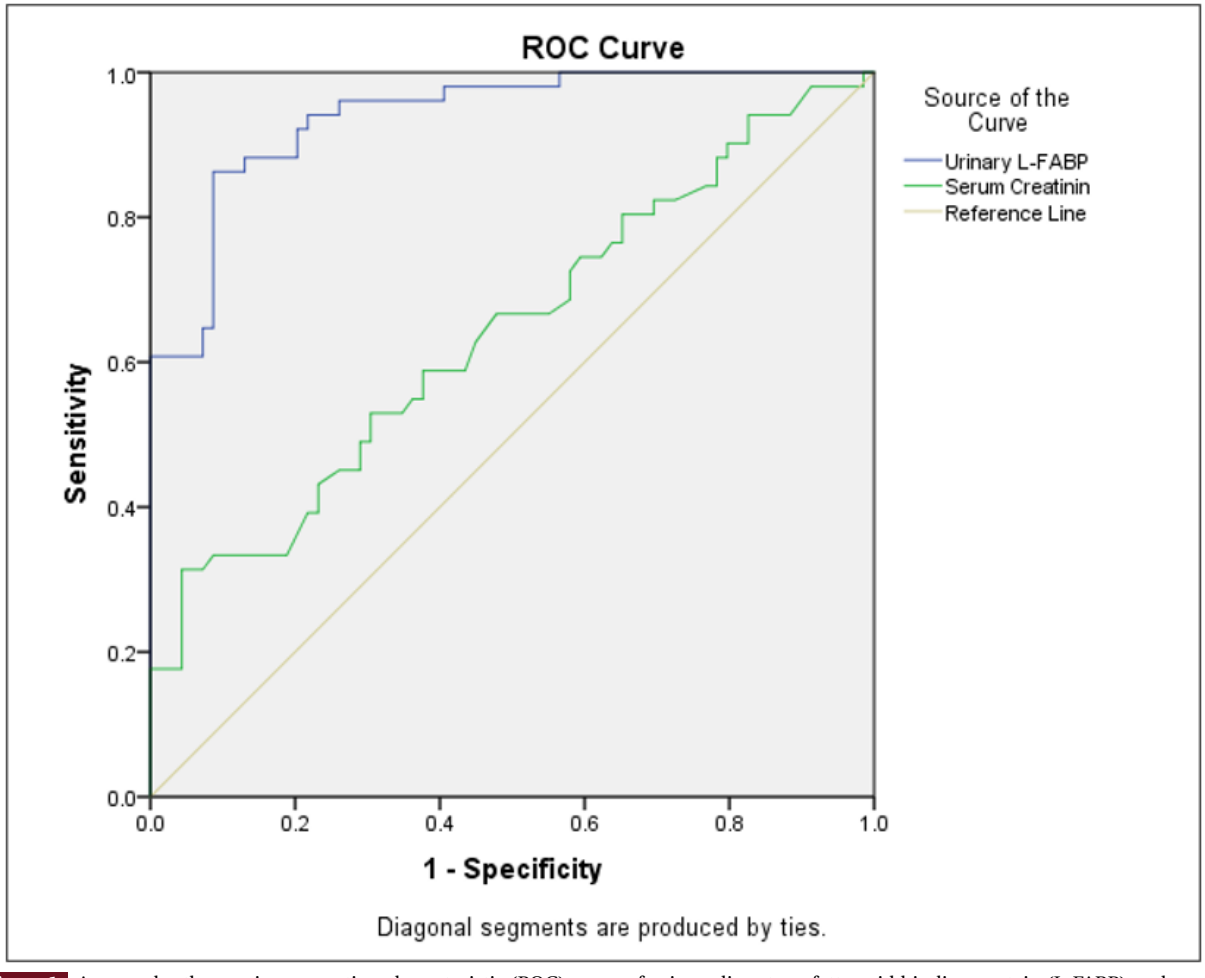

Figure 1: Area under the receiver operating characteristic (ROC) curve of urinary liver-type fatty acid binding protein (L-FABP) and serum creatinine in early detection of sepsis-associated acute kidney injury (AKI).

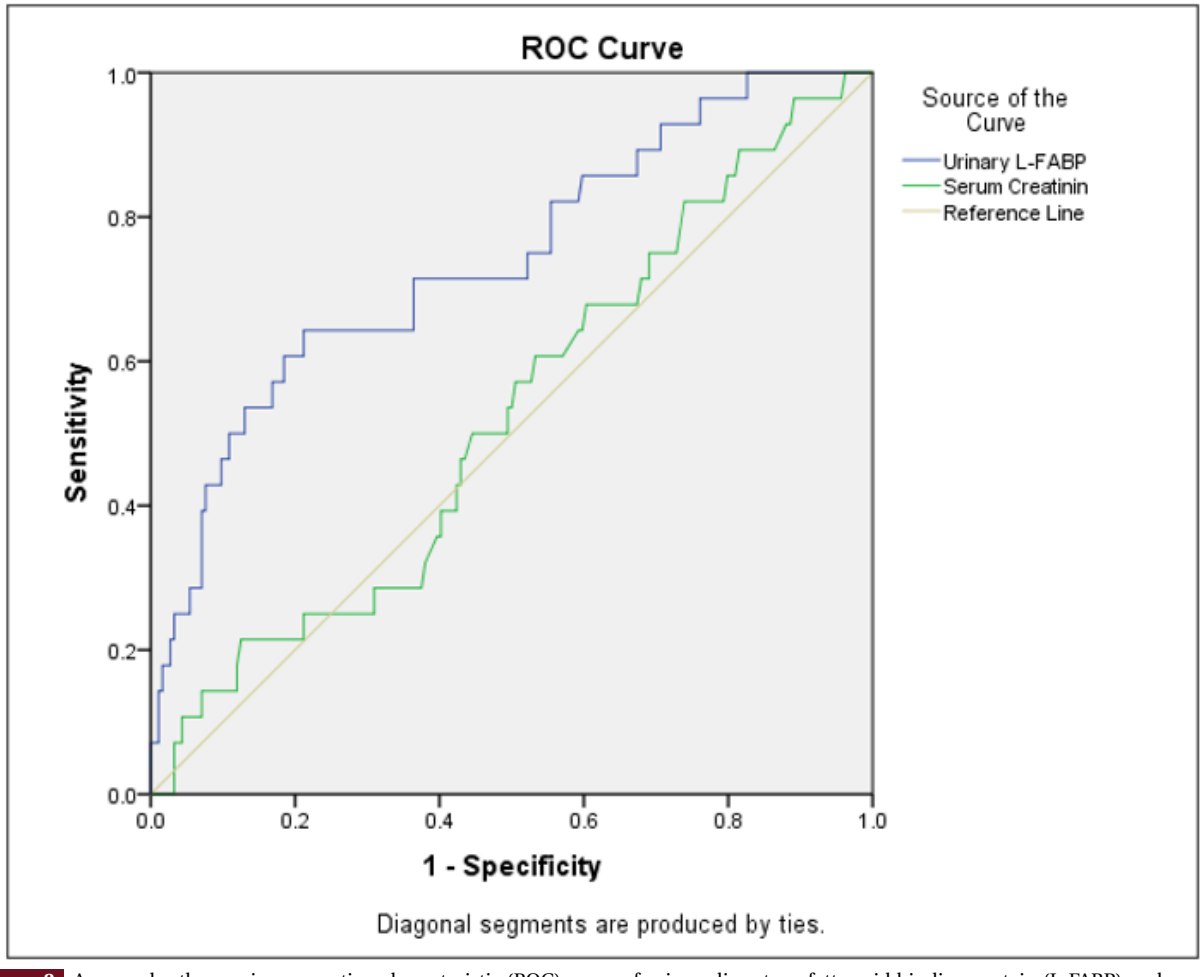

Figure 2: Area under the receiver operating characteristic (ROC) curve of urinary liver-type fatty acid binding protein (L-FABP) and serum creatinine in predicting the need for renal replacement therapy (RRT).