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Original Contribution

Septic acute kidney injury patients in emergency department: The risk factors and its correlation to serum lactate

Yin-Chou Hsu, Chih-Wei Hsu *

Department of Emergency Medicine, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan

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ABSTRACT

Background: Acute kidney injury (AKI) is a common complication in septic patients, imposing a heavy burden of illness in terms of morbidity and mortality. Serum lactate is a widely used marker predicting the severity of sepsis. A paucity of research has investigated septic AKI in emergency departments (EDs) and its correlation with initial serum lactate level. This study aimed at identifying risk factors for septic AKI and clarifying the link between initial serum lactate level and septic AKI in ED patients.

Methods: A retrospective cohort study was conducted at a single tertiary referral medical center. The medical records of all adult ED patients with measurement of serum lactate and creatinine between January 2012 and December 2016 were reviewed. A total of 696 septic patients were stratified into AKI and non-AKI groups according to Acute Kidney Injury Network (AKIN) criteria for further statistical analysis.

Results: Ninety-nine septic patients (14.2%) had AKI, with AKIN-I, AKIN-II, and AKIN-III in 71.7%, 11.1%, and 17.2% of patients, respectively. Compared with the non-AKI group, the AKI group had a significantly higher mortality rate (71.7% vs. 21.3%, $p < 0.001$). Independent risk factors for septic AKI included liver disease (adjusted odds ratio [AOR] = 2.02, 95% confidence interval [CI] = 1.16–3.52), diabetes mellitus (AOR = 1.73, 95% CI = 1.11–2.69), chronic kidney disease (AOR = 1.68, 95% CI = 1.06–2.66), and initial serum lactate (AOR = 1.08, 95% CI = 1.02–1.14).

Conclusions: Patients with septic AKI had an overwhelmingly higher mortality rate. The comorbidities of liver disease, diabetes mellitus, and chronic kidney disease were correlated with septic AKI and in combination with an elevated initial serum lactate level had predictive regarding AKI and further mortality in ED septic patients.

1. Introduction

Sepsis, which is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1], represents the most common cause of morbidity and mortality among critically ill patients [2]. Sepsis is the leading factor of acute kidney injury (AKI) in critical illness [3], and AKI resulting from sepsis (septic AKI) increases patient length of stay in the hospital and consumes considerable health resources [4]. The diagnosis of septic AKI is mainly based on clinical assessment such as Acute Kidney Injury Network (AKIN) [5] or Kidney Disease Improving Global Outcomes (KDIGO) criteria [6], although the application of several novel biomarkers has gained more attention [7].

Lactate is an important source of energy, particularly during situations of biological stress, such as tissue hypoxia and mitochondrial dysfunction [8]. It was viewed as a marker of tissue hypoperfusion, a risk-stratification tool in septic patients, since elevated lactate levels have been highly associated with in-hospital mortality [9,10]. The initial serum lactate level was also recognized as a predictor of mortality of septic patients in the emergency department (ED) [11].

Most studies relating to septic AKI and its associated novel biomarkers have been conducted in the intensive care unit (ICU) [12-14], with only a few studies [15-17] conducted in the ED setting. Compared with the intensivist, ED physicians encounter these critically ill patients more frequently with subtle beginning signs of septic AKI. Therefore, it is extremely important to ensure that ED physicians are aware of those septic patients at high risk of AKI, because aggressive resuscitation and timely management may prevent disease progression and further mortality. In addition, although serum lactate level has been widely used as a marker and predictor of septic patients, its linkage with septic AKI has seldom been discussed [18].

The goal of our study was to investigate the incidence, characteristics, risk factors, and clinical outcomes of septic AKI in ED patients. We also investigated the link between initial serum lactate level and septic AKI in ED patients to ascertain whether lactate can be used as a risk-

* Corresponding author at: Department of Emergency Medicine, E-Da Hospital, No. 1, Yida Road, Jiao-su Village, Yan-chao District, Kaohsiung City 82445, Taiwan.
E-mail address: saab30002000@gmail.com (C.-W. Hsu).

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stratification marker or predictor so that ED physicians can recognize patients with a high risk of developing septic AKI.

2. Materials and methods

2.1. Data source

This study was conducted at a 1251-bed, tertiary referral hospital in southern Taiwan that receives approximately 66,000 emergency visits per year. To minimize selection error because of coding method or preference, we extracted and reviewed electronic medical records of all adult ED patients from January 1, 2012, to December 31, 2016, that met the laboratory examination criteria (details below) rather than by disease code (International Classification of Diseases, Ninth Edition, Clinical Modification [ICD-9-CM]). Demographic and clinical characteristics of these patients including age, sex, comorbidities, medications, ED vital signs, and mortality were recorded for further analysis. This observational study was approved by the Institutional Review Board of our hospital, and the requirement of informed consent of patients was waived owing to the retrospective observational nature of the study.

2.2. Study participants

All adult ED patients ≥18 years of age who had initial measurements of serum creatinine and lactate simultaneously followed by a second measurement of serum creatinine within 48–72 h were included in the study. Patients who had already received renal replacement therapy or had a cardiac arrest event before ED arrival were excluded. The enrolled patients were categorized into different causes of shock according to their ED diagnosis by reviewing electronic medical records, and the characteristics of septic patients were analyzed. The sepsis criteria proposed in 1992 (SIRS [systemic inflammatory response syndrome] and infection) [19] were adopted instead of the qSOFA in Sepsis-3 definition [1].

2.3. Definitions

The coding of comorbidities of the eligible patients was acquired from ICD-9-CM diagnostic codes in the electronic medical records of this hospital and the Taiwan Department of Health's cloud medical records. We included liver disease (liver cirrhosis or hepatocellular carcinoma) as comorbidities because of the high prevalence of hepatitis in Taiwan [20,21]. Chronic kidney disease was defined as a baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 [22], which we calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula.

We adopted the AKIN creatinine-based criteria of acute kidney injury staging [5] (stage 1: increase in serum creatinine level > 0.3 mg/dL or a 1.5- to 1.9-fold increase over baseline serum creatinine level; stage 2: 2.0- to 2.9-fold increase over baseline serum creatinine level; stage 3: 3-fold increase over baseline serum creatinine level or increase to a serum creatinine level > 4.0 mg/dL). Anemia was defined

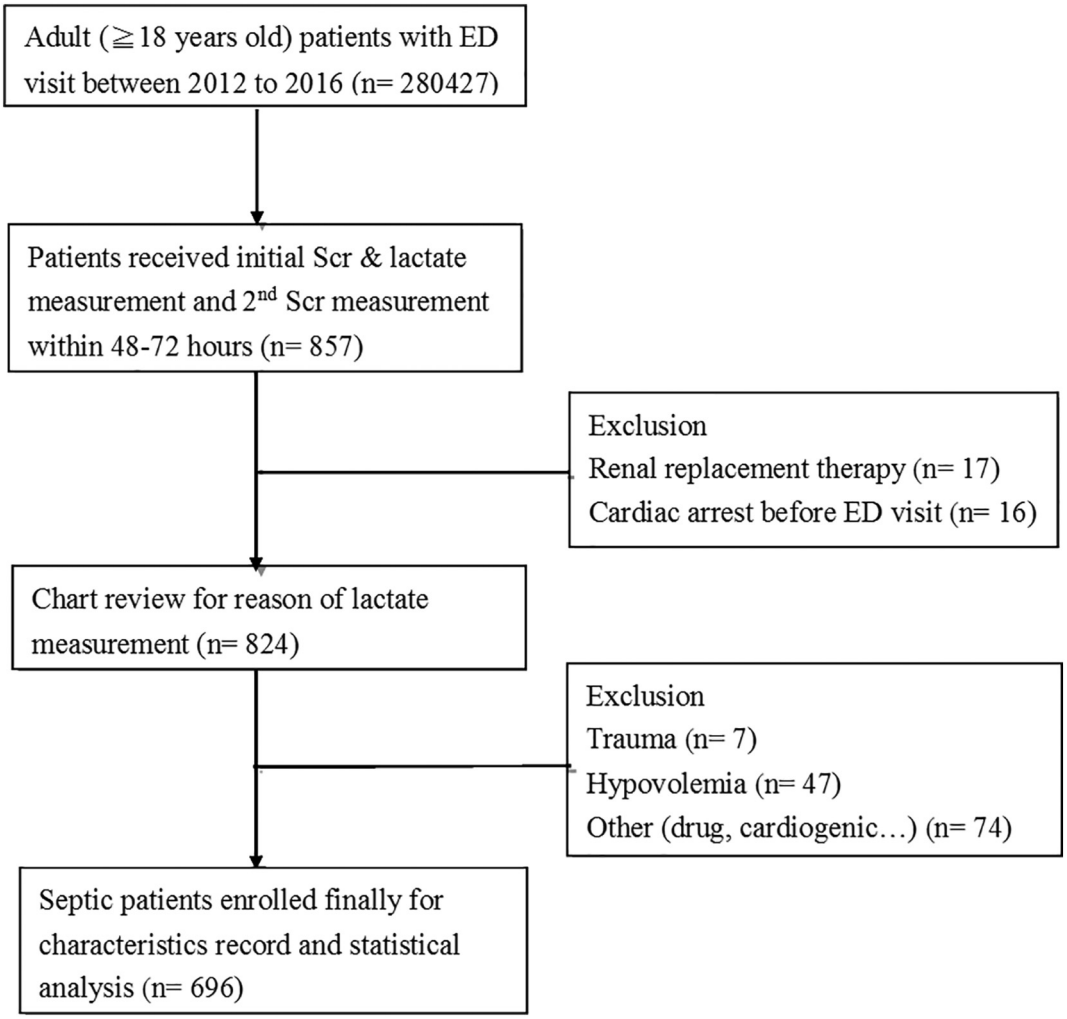

Fig. 1. Flow chart of patient enrollment. ED: emergency department; SCr: serum creatinine.

according to the World Health Organization (WHO) as a baseline hematocrit value <39% and <36% for men and women, respectively [23]. Shock was defined as a requirement of vasopressors despite adequate fluid administration during the ED stay.

2.4. Statistical analysis

Data are presented as mean ± standard deviation or median with interquartile range for continuous variables, and number (percentage) for categorical variables. Paired *t*-tests and chi-square tests were used to compare continuous variables and categorical variables, respectively. Multivariate logistic regression was used to identify independent risk factors of septic AKI and to estimate odds ratios. A two-tailed *p* value of <0.05 was considered statistically significant. SPSS version 22.0 statistical software (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis.

3. Results

During the study period, 280,427 adult patients visited the ED, of whom 857 met the selection criteria. After excluding 161 patients meeting the exclusion criteria (previously receiving renal replacement therapy, cardiac arrest event, or non-sepsis-related disease), the remaining 696 septic patients were analyzed (Fig. 1). The overall incidence of AKI in septic patients was 14.2% (99/696), of whom 71 (71.7%) were stage 1, 11 (11.1%) were stage 2, and 17 (17.2) were stage 3 according to the AKIN criteria. The overall mortality rate of septic patients was 28.4% (198/696). We divided the 696 septic patients into an AKI group, including stage 1, 2, and 3, and a non-AKI group and compared the demographic and clinical characteristics between the two groups (Table 1).

There were no differences in demographic variables (age and sex) between the AKI and non-AKI groups. Regarding comorbidities, the proportion of patients with diabetes mellitus, liver disease, and chronic kidney disease in the AKI group was significantly higher than that in the non-AKI group. It is noteworthy that the median level of initial serum lactate in the AKI group was significantly higher than in the non-AKI group (3.25 vs. 2.23 mmol/L, $p = 0.004$). Regarding acute illness, there was no significant difference in the proportion of patients with shock between the two groups. On the other hand, the AKI group had an overwhelmingly higher mortality rate than the non-AKI group (71.7% vs. 21.3%, $p < 0.001$, odds ratio [OR] = 9.38, 95% confidence interval [CI] = 5.81–15.16). Multivariate logistic regression analysis revealed that liver disease (adjusted odds ratio [AOR] = 2.02), diabetes mellitus (AOR = 1.73), chronic kidney disease (AOR = 1.68), and serum lactate level (AOR = 1.08) were independently associated with a higher risk of AKI in septic patients (Table 2).

Receiver operating characteristics curves were used to depict the correlation among lactate level, acute kidney injury (Fig. 2a), and in-hospital mortality (Fig. 2b). As shown in Fig. 2, the area under the curve was 0.591 (95% CI = 0.528–0.653) for lactate and acute kidney injury and 0.625 (95% CI = 0.579–0.671) for lactate and in-hospital mortality. We further calculated the cutoff value and found that an initial lactate level of 2.80 and 2.79 mmol/L had the best discriminative ability in predicting acute kidney injury and all-cause in-hospital mortality, respectively.

4. Discussion

Our study was the largest single-center study investigating septic AKI in ED patients. In this retrospective study including 696 septic patients, we evaluated the incidence, characteristics, and clinical outcomes of septic AKI in ED patients and identified independent risk factors for its occurrence. We also investigated the correlation between serum lactate level and septic AKI. To the best of our knowledge, this was the first study regarding septic AKI and serum lactate in ED patients.

Table 1
Demographic and characteristics of septic patients (n = 696).

Characteristics	AKI (n = 99)	non-AKI (n = 597)	*p* value**
Age (y, SD)	68.8 ± 16.1	68.3 ± 15.5	0.788
Male (n, %)	63 (63.6)	366 (61.3)	0.659
Comorbidities (n, %)[a]			
Hypertension	58 (58.6)	343 (57.5)	0.833
Diabetes mellitus	58 (58.6)	265 (44.4)	0.009*
Liver disease[b]	21 (21.2)	75 (12.6)	0.021*
Left heart failure	15 (15.2)	80 (13.4)	0.638
Coronary artery disease	9 (9.1)	81 (13.6)	0.219
Chronic kidney disease[c]	65 (65.7)	324 (54.3)	0.035*
Anemia[d]	71 (71.7)	416 (69.7)	0.682
Stroke	17 (17.2)	130 (21.8)	0.299
Laboratory result			
Initial SCr (mg/dl, median & IQR)	2.00 (1.30–3.20)	1.80 (1.20–2.70)	0.055
Initial eGFR (mL/min/1.73m^2)	31 (20–52)	36 (22–57)	0.079
Initial lactate (mmol/L)	3.25 (1.57–5.58)	2.23 (1.40–3.96)	0.004*
Acute illness (n, %)			
Shock[e]	52 (52.5)	290 (48.6)	0.467
All-cause mortality	71 (71.7)	127 (21.3)	<0.001*

AKI: acute kidney injury, based on the criteria of Acute Kidney Injury Network/Kidney Disease Improving Global Outcomes; SD: standard deviation; SCr: serum creatinine; eGFR: estimated glomerular filtration rate; IQR: Interquartile range.

* *p* value < 0.05.

** Chi-square test was used for categorical variable comparison; paired *t*-test or Mann–Whitney *U* test was used for continuous variable comparison; statistical significance was determined by *p* value < 0.05.

[a] Based on ICD-9-CM diagnostic codes and admission diagnosis from previous hospitalization or index ED visit.

[b] Liver cirrhosis or Hepatocellular Carcinoma.

[c] Based on the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guideline (baseline eGFR <60 mL/min/1.73 m^2).

[d] According to World Health Organization (WHO) definition: baseline hematocrit male < 39%, female < 36%.

[e] Requirement of vasopressors during ED (Emergency Department) stay.

Most previous studies about AKI in septic patients were conducted in an ICU, which revealed the incidence of septic AKI ranging widely from 22.2% to 64% [24-28]. Only a very few studies addressed this issue in ED patients [17,29]. As in the ICU studies, obvious differences in the incidence of septic AKI in ED patients among previous studies (57.7% and 70%) and our present study (14.2%) were noticed. The wide range of the incidence of septic AKI among ED and ICU studies may have resulted from the different classification of AKI. Many septic AKI studies used the RIFLE classification [30] instead of the AKIN criteria. The detection rate of AKI using these two classifications remains controversial [31]. One study showed no difference in predictive ability and sensitivity between these two classification after first 24 h of ICU admission [25], and the other study reported that RIFLE showed better robustness and higher early AKI detection ability (35.5% vs. 28.5%) [26]. Although we used serum creatinine level rather than a combination of serum creatinine and urine output to define AKI owing to missing urine output data during the ED stay, concordance between serum creatinine and urine output was found in a previous study [32]. Nevertheless, our study was strengthened by a longer observational period (5 years versus 1 year) [29] and a larger cohort number (696 versus 200 patients) [17] compared with previous ED studies.

Consistent with previous septic AKI studies [3,4,17,24,27-29], the overall in-hospital mortality rate in the AKI group (71.7%) was drastically higher than that in the non-AKI group (21.3%) in our current study. However, there was no significant difference in age or sex between the AKI and non-AKI groups in our study. The impact of demographic characteristics on septic AKI varied in different studies. An Australian study of septic AKI in the ICU revealed female and older-age patients were more prone to develop AKI [24], whereas other ICU observational studies showed no significant difference in age or sex

Table 2
Logistic regression models of factors associated with acute kidney injury in septic patients

Variable	Adjusted OR	95% CI of OR	*p* value
Liver disease	2.02	1.16–3.52	0.013
Diabetes mellitus	1.73	1.11–2.69	0.015
Chronic kidney disease	1.68	1.06–2.66	0.028
Initial lactate (mmol/L)	1.08	1.02–1.14	0.013

OR: odds ratio; CI:confidence interval.

[27,28].These inconsistent findings indicate the complexity of multiple factors contributing to the development of AKI.

One previous ED study demonstrated that the development of septic AKI was associated with prior chronic kidney disease, use of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and shock status [29]. Another ED study revealed diabetes mellitus and the presence of shock, defined as a mean blood pressure of <65 mm Hg, as independent risk factors [17]. In agreement with these studies, our study identified diabetes mellitus and chronic kidney disease as risk factors for septic AKI. We also demonstrated that liver disease (liver cirrhosis or hepatocellular carcinoma) was also an independent risk factor, which has not been mentioned in previous ED septic AKI studies. Compared with these two studies, shock status in our study statistically failed to become a predictor of AKI (OR = 1.17, 95% CI = 0.77–1.80), a discrepancy that may be explained by the different definitions of shock status, as we defined shock status as patients administered vasopressor rather than low blood pressure measured during the ED stay.

In recent years, Sepsis-3 had revised the definition of sepsis and septic shock, defining an elevated serum lactate level (>2 mmol/L) as a component of septic shock [1], and the Surviving Sepsis Campaign suggested guiding resuscitation to normalize lactate in patients with hyperlactatemia, since an increased lactate level and reduced lactate clearance is associated with higher mortality [10,33]. Sepsis-associated hyperlactatemia was viewed as a marker of tissue hypoxia and generated by anaerobic glycolysis, but growing evidence supported that it was more associated with increased aerobic glycolysis secondary to stress response activation, such as β-adrenergic stimulation [8,33,34]. Since serum lactate is considered a sensitive biomarker of either systemic or regional hypoperfusion [35], it is reasonable that serum lactate might be used to predict ongoing renal hypoperfusion, which contributes to the development of AKI. Only two ICU studies addressed the issue and demonstrated identical findings that serum lactate in septic patients with AKI was higher than in those patients without AKI [18,27]. Our present study found that the initial serum lactate level in the septic AKI group was significantly higher than in the non-AKI group and was an independent risk factor of septic AKI in ED patients after we adjusted for other variables. Our results supported the previous ICU study exploring the role of serum lactate as a predictor of septic AKI (AOR = 1.03, 95% CI = 1.01–1.06) [18]. However, the evidence in our study to use initial serum lactate level as a sole predictive factor for development of AKI was insufficient (Fig. 2).

Many studies revealed that the possible pathophysiology of septic AKI is profoundly different from AKI of other etiologies. Sepsis results in profound macrocirculation and microcirculation alterations, decreased peripheral vascular resistance, tissue blood flow maldistribution, and microcirculatory derangement [36]. These alterations result in an increment in heterogeneity of regional blood flow [37]. Septic AKI was viewed as a result of decreased renal blood blow in the past [38], but growing evidence from human and animal studies revealed that the renal blood blow was maintained or even increased during a hyperdynamic sepsis state [39,40]. Despite the renal hyperemia condition, AKI developed during sepsis, indicating the dissociation between the renal blood flow and glomerular function [7,41]. Furthermore, the heterogeneous distribution of renal blood flow caused by microcirculation shunting is complicated by hypoxia and hypoperfusion [7,36], resulting in ischemia and tubular cell injury. In histopathology, septic AKI is characterized by simple renal tubular epithelial cell injury, mostly focal leukocyte infiltration, or apoptosis, which is different from renal-ischemia reperfusion injury characterized by a necrotic appearance [7,36,42]. Since septic AKI is a unique form of AKI with increased renal blood flow and few histology changes, multifactorial factors including microcirculation injury and inflammatory renal tubular cell injury could possibly contribute to it [7]. The role of lactate in predicting septic AKI development may need more human and animal studies to elucidate.

5. Limitations

There were several limitations in our study, including its monocentric and retrospective design. First, we identified septic patients with serum lactate level, which may have missed septic patients

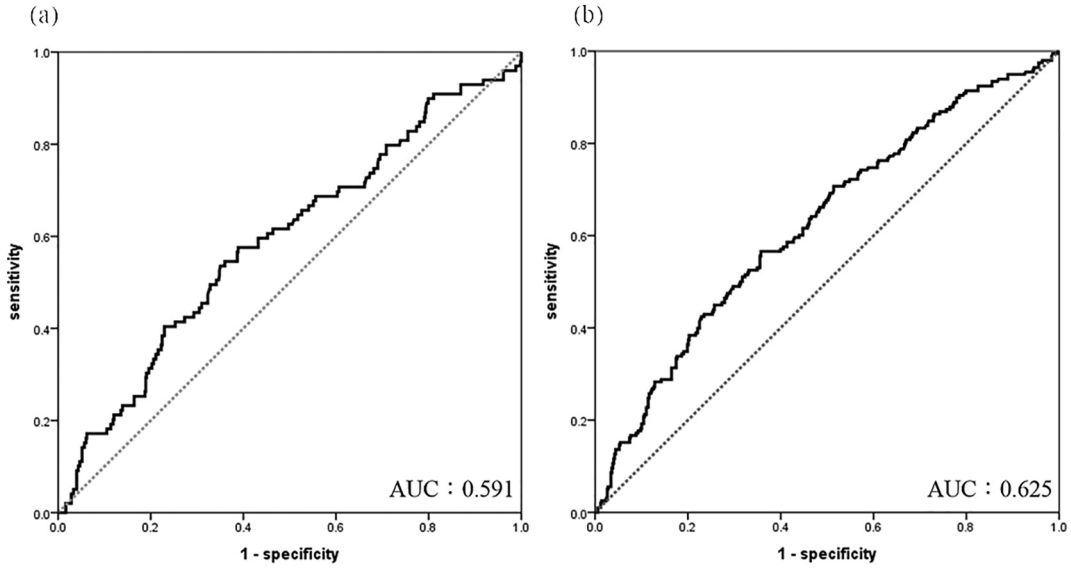

Fig. 2. ROC curves regarding the predicting ability of initial serum lactate level in different outcomes in 696 septic patients. (a) ROC curve of lactate and development of acute kidney injury. AUC = 0.591 (95% CI = 0.528–0.653, $p = 0.004$), the cutoff value of lactate was 2.80 (mmol/L). (b) ROC curve of lactate and mortality. AUC = 0.625 (95% CI = 0.579–0.671, $p < 0.001$), the cutoff value of lactate was 2.79 (mmol/L). AUC: area under the curve; CI: confidence interval; ROC: receiver operating characteristics.

without measurement of lactate and included false septic patients with elevated serum lactate level affected by clinical conditions other than sepsis, resulting in selection bias. Second, we did not research the precise etiology of AKI, as a histopathological study was not conducted in our patients. Finally, stratification of AKI in the present study was based on serum creatinine level alone without considering urine output data as defined by the AKIN criteria [5] because urine output data was not available in the ED. However, patients whose AKI status was defined according to serum creatinine level were more severely ill than patients whose AKI status was defined according to urine output, so that the inclusion of urine output data may not have changed the results [32].

6. Conclusions

In summary, the complication of AKI in ED septic patients resulted in a higher mortality rate and was more likely to develop in patients with liver disease, diabetes mellitus, and chronic kidney disease as well as in patients with higher initial serum lactate levels. A future prospective, multicenter study is warranted to confirm these findings.

Author contributions

YCH: conceived and designed the study, performed data analysis, drafted manuscript.

CWH: conducted data extraction, critically revised manuscript.

Source of support

None declared.

Conflicts of interest

None declared.

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