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The timing of last hemodialysis influences the prognostic value of serum lactate levels in predicting mortality of end-stage renal disease patients with sepsis in the emergency department

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Abstract

Sepsis is a life-threatening condition, and serum lactate levels have been used to predict patient prognosis. Studies on serum lactate levels in patients undergoing regular hemodialysis who have sepsis are limited. This study aimed to determine the predictive value of serum lactate levels for sepsis-related mortality among patients who underwent last hemodialysis at three different times before admission to the emergency department (ED).

This retrospective cohort study was conducted from January 2007 to December 2013 in southern Taiwan. All hemodialysis patients with sepsis, receiving antibiotics within 24 hours of sepsis confirmation, admitted for at least 3 days, and whose serum lactate levels were known were examined to determine the difference in the serum lactate levels of patients who underwent last hemodialysis within 4 hours (Groups A), in 4–12 hours (Group B), and beyond 12 hours (Group C) before visited to the ED. All the continuous variables, categorical variables and mortality were compared by using Kruskal-Wallis test or Mann-Whitney test, the χ^2 or Fisher exact tests, and multiple logistic regression model, respectively.

A total of 490 patients were enrolled in the study, and 8.0% (39), 21.5% (84), and 74.9% (367) of the patients were in Group A, Group B and Group C, respectively; the serum lactate levels (2.91 vs 2.13 vs 2.79 mmol/L, respectively; $P = .175$) and 28-day in-hospital mortality (17.9% vs 14.6% vs 22.9%) showed no statistically significant difference between 3 groups. The association between serum lactate levels and 28-day in-hospital mortality was reliable in Group B ($P = .002$) and Group C ($P < .001$), but it was unreliable in Group A ($P = .629$).

Serum lactate level has acceptable sensitivity in predicting 28-day in-hospital mortality among patients with sepsis who undergo last hemodialysis after 4 hours, but is not reliable when the last hemodialysis takes place within 4 hours.

Abbreviations: 95% CI = 95% confidence interval, AUC = area under the curve, Da = Dalton, ED = emergency department, ESRD = end-stage renal disease, ICD-9 = International Statistical Classification of Diseases and Related Health Problems, Ninth Revision, Q1-Q3 = first quartile to third quartile, ROC = receiver operating characteristic curves.

Keywords: hemodialysis, lactate, mortality, sepsis

1. Introduction

Sepsis is a life-threatening condition that develops in the body in response to infection. It is the second leading cause of death in end-stage renal disease (ESRD) patients.[1] Early recognition and prompt treatment offer the best chance of survival, but early diagnosis of sepsis presents a challenge.

Measurement of serum lactate levels is increasingly being used as a screening tool to assist in the risk stratification of sepsis patients owing to its reliable prognostic value in predicting poor outcomes.[2] In fact, an elevated lactate level (>2.0 mmol/L) is now one of the criteria to be met, as per the most recent consensus definition of septic shock.[3] Hyperlactatemia was found to be a strong independent marker of adverse outcomes in ERSD patients in a previous study.[4]

An increased risk of death has also been reported in association with elevated serum lactate levels in patients with suspected sepsis,[5] and this risk rises exponentially with the increase in lactate levels.[6] In a prospective cohort study, high serum lactate levels (0–2.4 vs 2.5–3.9 vs >4.0 mmol/L) were associated with high 28-day in-hospital mortality (4.9% vs 9.0% vs 28.4, respectively).[7]

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The authors of this work have nothing to disclose

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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However, studies on serum lactate levels in ESRD patients with sepsis are limited, and, to the best of our knowledge, the correlation between serum lactate levels and mortality in patients with sepsis who have undergone hemodialysis recent before admission to the ED has never been studied.

Therefore, this study was conducted to compare the predictive value of serum lactate levels in patients with sepsis who had undergone their last hemodialysis within 4 hours (Groups A), in 4–12 hours (Group B), and beyond 12 hours (Group C) for 28-day in-hospital mortality.

2. Methods

2.1. Study design

A retrospective cohort study was conducted to evaluate the 28-day mortality predictive value of serum lactate levels obtained at three different timings before admission to the ED. The Institutional Review Board of Chang Cheng Memorial Hospital approved this study, the need for informed consent from the patients was waived.

2.2. Study setting and population

This was a single-center, retrospective, observational cohort study conducted from January 2007 to December 2013 at Kaohsiung Chang Gung Memorial Hospital, a 2300-bed medical center providing primary- and tertiary-level care in southern Taiwan. Every year, >100,000 patients visit its ED. We analyzed the data of all adult patients (≥18 years) who visited the ED with ESRD under regular hemodialysis, received parenteral antibiotics in 24 hours, admitted for at least 3 days, and whose serum lactate levels were known. Electronic medical records including medical charts and nursing documentation were obtained from the ED health information system, which is a computerized database, and reviewed by the authors. All the enrolled patients were divided into 3 groups according to the last hemodialysis timing: within 4 hours (Group A), in 4–12 hours (Group B), and beyond 12 hours (Group C). Other data were retrospectively collected from the electronic medical records of all enrolled patients: demographic characteristics (age, gender), pre-existing major comorbidities (liver cirrhosis, diabetes mellitus, congestive heart failure, cerebrovascular disease, and malignancy), initial vital signs, serum lactate levels, major infection sources, and in-hospital mortality. The infection sites were determined on the basis of the International Statistical Classification of Diseases and Related Health Problems, Ninth Revision (ICD-9) coding, including respiratory tract (481.0–486.9), urinary tract (590.00–590.99, 601.0–601.9), skin and soft tissue (680.0–686.9, 728.86), intra-abdominal sites (562.11, 567.0–567.9, 5761, 574.00–574.19, 574.30–574.49, 574.60–574.89), and other unknown infectious foci or infection sites that do not belong to the 4 categories. The comorbidity of the underlying diseases was also determined using the ICD-9 coding: liver cirrhosis (571.2, 571.5, 571.6), diabetes mellitus (250.00–250.99), chronic renal insufficiency (582.00–589.99), congestive heart failure (428.0–428.9), cerebrovascular disease (430.00–438.99), and malignancy (140.00–199.99). The major outcome measured was 28-day in-hospital mortality.

2.3. Serum lactate testing equipment

Serum lactate levels were initially measured within 2 hours, depending on the ED physician's suspicion of sepsis development. Serum lactate (mmol/L) levels were measured using a serum-based immunoassay (Unicel DxC 880i Synchron; Beckman Coulter Inc., Brea, CA).

2.4. Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY). Continuous variables were expressed as median, first quartile to third quartile (Q1-Q3) and compared using the Kruskal-Wallis test and Mann-Whitney test. Categorical variables, expressed as numbers and percentages, were compared using the χ^2 or Fisher's exact tests. Age, sex, and comorbidities including liver cirrhosis, diabetes mellitus, chronic renal insufficiency, congestive heart failure, cerebrovascular disease, and malignancy, which may affect mortality in sepsis as described in previous articles,[8–11] were incorporated into a multiple logistic regression model, which was also used to calculate the odds ratio of serum lactate levels of over 2 mmol/L for predicting mortality. Goodness-of-fit was analyzed by Hosmer & Lemeshow test. The receiver operating characteristic (ROC) curves for serum lactate levels were generated to predict the 28-day in-hospital mortality, and their area under the curve (AUC) values with 95% confidence interval (95%CI) were compared. Finally, Youden's index was used to identify the optimal cutoff values for clinical use in different groups. P values <.05 were considered statistically significant.

3. Results

During the study period, 9,02,247 patients visited our ED; of them, 627 patients were older than 18 years, had ESRD, underwent hemodialysis, received parenteral antibiotics, and had serum lactate levels available. The timing of the last hemodialysis could not be determined for 69 patients, 57 patients were discharged from the ED within 72 hours, and 11 patients who did not receive antibiotics in 24 hours were excluded. Therefore, a total of 490 ERSD patients with sepsis were finally enrolled and divided into 3 groups according to the last hemodialysis timing. The flow chart on patient enrollment is shown in Figure 1.

The demographic features, presentation at the ED, comorbidities, major sources of infection, serum lactate levels, and outcome are summarized in Table 1. In our cohort, 8.0% (39), 21.5% (84), and 74.9% (367) of the patients were in Group A, Group B and Group C, respectively.

There was no significant difference in age, sex, vital signs in the ED, major comorbidities, and major source of infection between the three groups. The each groups did not show a statistically significant difference in the serum lactate levels (2.35 vs 1.74 vs 1.87 mmol/L for Group A, Group B and Group C, respectively; $P = .175$); however, Group A had the highest serum lactate level. Similarly, the 28-day in-hospital mortality was not significantly different between the 3 groups (17.9% vs 14.6% vs 22.9%, for Group A, Group B and Group C; $P = .338$).

Comparison of lactate levels between survivors and non-survivors in 3 groups were highlighted in Table 2, regarding the predictive value of serum lactate levels for 28-day in-hospital mortality, there was no significant difference between the survivors and non-survivors in Group A (2.22 vs 2.87, respectively, $P = .629$), but the difference was significant in Group B and Group C (1.69 vs 2.67, respectively, $P = .002$; 1.74 vs 3.45, respectively, $P < .001$).

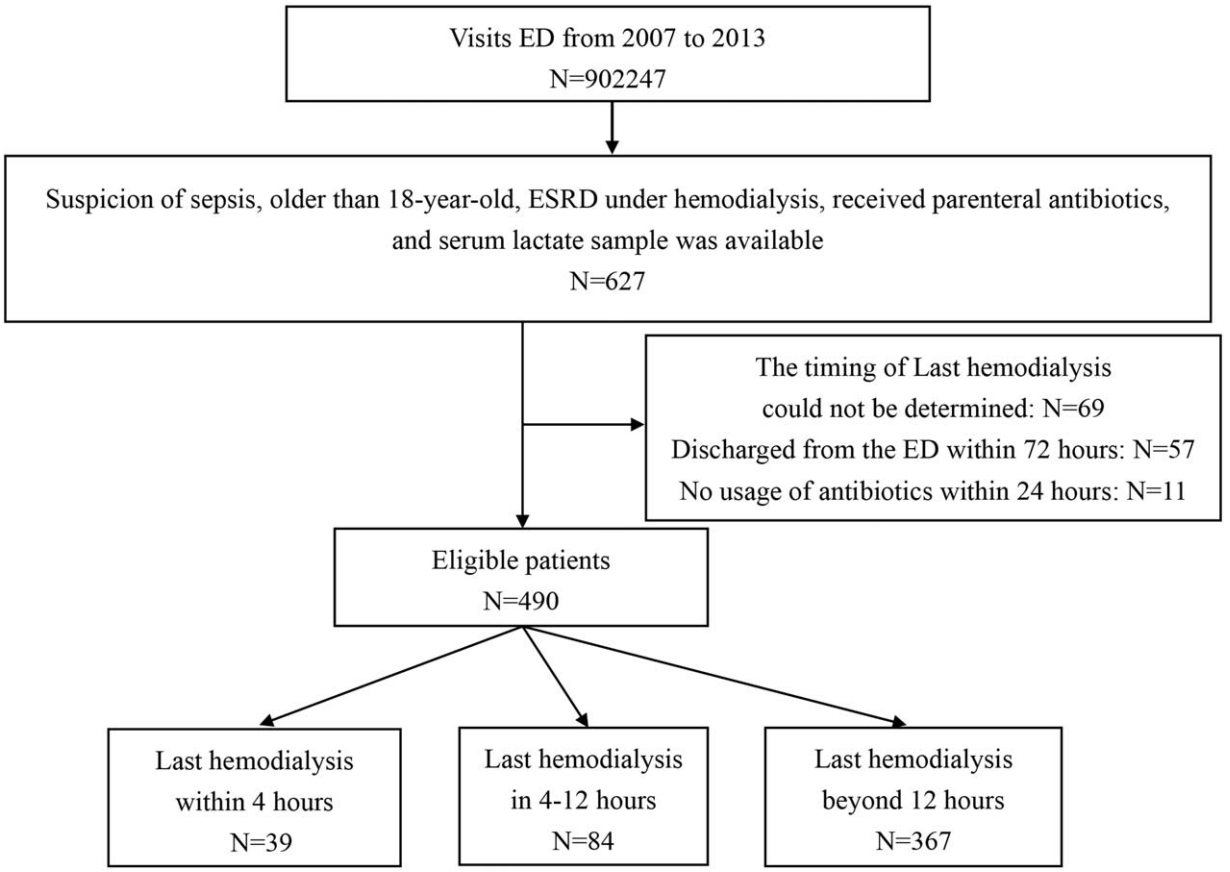

Figure 1. Study flow chart.

Table 1

Patient demographics and clinical characteristics.

	All patients (N = 490)	H/D within 4 h (N = 39)	H/D in 4–12 h (N = 84)	H/D beyond 12 h (N = 367)	*P* value
Age (years old)	67.4 ± 12.1	68.5 ± 11.9	68.7 ± 10.8	67.0 ± 12.4	.707
Gender (male) (N(%))	226 (46.1%)	20 (51.3%)	44 (52.4%)	162 (44.1%)	.602
Vital signs in the ED (Mean ± SD)					
Body temperature, °C	37.4 ± 1.2	37.3 ± 1.1	37.4 ± 0.9	37.4 ± 1.2	.845
Heart rate, beats/min	101.4 ± 23.1	106.4 ± 21.2	101.9 ± 18.2	100.8 ± 24.3	.326
MAP, mmHg	94.5 ± 29.2	88.7 ± 35.7	94.4 ± 25.3	95.1 ± 29.2	.415
RR, breaths/min	20.1 ± 3.7	19.2 ± 1.7	19.6 ± 2.0	20.4 ± 4.2	.160
Major comorbidities (N(%))					
Liver cirrhosis	48 (9.8%)	4 (10.2%)	12 (14%)	32 (8.7%)	.521
Diabetes mellitus	253 (51.6%)	22 (56.4%)	33 (39.3%)	198 (54.0%)	.112
Heart failure	55 (11.2%)	3 (7.7%)	6 (7.1%)	46 (125%)	.582
Stroke	75 (15.3%)	4 (10.3%)	11 (13.1%)	60 (16.3%)	.588
Malignancy	59 (12.0%)	1 (2.6%)	19 (22.6%)	39 (10.6%)	.077
Major source of infection (N(%))					
Respiratory tract	183 (37.3%)	10 (25.6%)	30 (35.7%)	143 (39.0%)	.245
Urinary tract	62 (12.7%)	3 (7.7%)	11 (13.1%)	48 (13.1%)	.613
Soft tissue	60 (12.2%)	5 (12.8%)	16 (19.0%)	39 (10.6%)	.292
Intra-abdomen	68 (13.9%)	12 (30.8%)	8 (9.5%)	48 (13.1%)	.819
Other	172 (35.1%)	14 (35.9%)	41 (48.8%)	127 (34.6%)	.958
Lab data (Median,(Q1–Q3))					
Lactate, mmol/L	1.87 (1.29–3.11)	2.35 (1.50–4.07)	1.74 (1.30–2.58)	1.87 (1.27–3.13)	.196
WBC, $10^3/mm^3$	12.2 (8.4–16.8)	12.9 (9.9–19.5)	12.0 (7.6–16.8)	12.1 (8.5–16.6)	.235
Segment, %	82.5 (75.9–87.4)	84.8 (79.5–90.0)	83.7 (78.5–88.9)	82.0 (75.0–87.0)	.112
Band form, %	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–0.1)	.756
28-day mortality (n (%))	102 (20.8%)	7 (17.9%)	11 (13.1%)	84 (22.9%)	.338

ED = emergency department, H/D = hemodialysis, MAP = mean arterial pressure, N = number, Q1 = first quartile, Q3 = third quartile, RR = respiratory rate, SD = standard deviation, WBC = white blood cell.

Table 2

Lactate levels in survivors and non-survivors in 28 days.

	H/D within 4 h			H/D in 4–12 h			H/D beyond 12 h		
	Survivors	Non-survivors	*P* value	Survivors	Non-survivors	*P* value	Survivors	Non-survivors	*P* value
Serum lactate ((Median,(Q1–Q3)))	2.22 (1.47–4.11)	2.87 (1.53–4.06)	.629	1.69 (1.23–2.33)	2.67 (1.97–5.06)	.002*	1.74 (1.16–2.46)	3.45 (1.72–5.85)	<.001*

H/D = hemodialysis, Q1 = first quartile, Q3 = third quartile.
* $P < .05$.

Table 3

ROC curve analysis to predict the 28-day in-hospital mortality in the 3 groups.

Group	AUC	95%CI	Cutoff point	Sensitivity	Specificity	Youden's index
All patients	0.74*	0.69–0.80	2.0	0.70	0.62	0.32
			4.0	0.39	0.90	0.29
H/D within 4 h	0.56*	0.34–0.78	2.0	0.71	0.43	0.14
			4.0	0.29	0.75	0.04
H/D in 4–12 h	0.79*	0.66–0.93	2.0	0.73	0.64	0.37
			4.0	0.36	0.66	0.02
H/D beyond 12 h	0.75*	0.69–0.81	2.0	0.69	0.63	0.32
			4.0	0.41	0.90	0.31

AUC = area under the curve, CI = confidence interval, H/D = hemodialysis, ROC = receiver operating characteristic.
* $P < .05$

3.1. Effectiveness of serum lactate level in predicting 28-days in-hospital mortality

Table 3 and Figure 2 shows the results of the ROC analysis. Youden's index was used to calculate the sensitivity and specificity based on the serum lactate level cutoff points of 2.0 mmol/L and 4.0 mmol/L, respectively. The AUC values were 0.79 (95%CI, 0.66–0.93) and 0.75 (95%CI, 0.69–0.81) for Group B and Group C, respectively. Group A had the lowest AUC value of 0.56 (95%CI, 0.34–0.78). Serum lactate levels higher than 2.0 mmol/L had similar sensitivity rates of 0.71, 0.73, and 0.69 in predicting the 28-day in-hospital mortality of Group A, Group B and Group C, respectively, but relatively lower specificity for Group A (0.43) than for the other 2 groups (0.64 and 0.63, respectively). For the cutoff point of 4.0 mmol/L, Group A had the lowest sensitivity of 0.29 as compared to the other 2 groups (0.36 and 0.41, respectively).

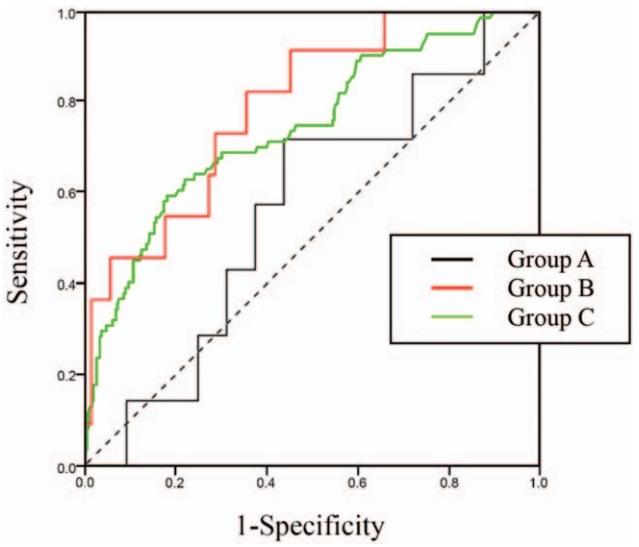

Figure 2. ROC curve of serum lactate level in predict 28 days in-hospital mortality in patients underwent hemodialysis within 4 hours (Group A), within 4–12 hours (Group B) and beyond 12 hours (Group C).

The data were further analyzed with multiple logistic regression including all possible factors associated with the 28-day in-hospital mortality for sepsis patients. Table 4 shows the odds ratios for the possible clinical factors. Goodness-of-fit were 0.943, 0.882, 0.917 and 0.630 in all patients, A, B and C groups, respectively. The data shows that the odds ratio of mortality significantly increased when the serum lactate levels were higher than 2 mmol/L: 5.19 ($P = .037$) and 4.50 ($P < .001$) for Group B and Group C, respectively. However, there was no significant increase in the odds ratio of mortality when the serum lactate levels were higher than 2 mmol/L in Group A (OR = 2.16, $P = .487$). Malignancy was significantly associated with the 28-day in-hospital mortality for Group C (OR = 3.11, $P = .003$). There was no significant increase in the odds ratio of mortality for age >65 years, sex, and other major comorbidities in the 3 groups.

4. Discussion

Sepsis is an important comorbidity in ESRD patients in the ED; these patients are predisposed to infections because of the presence of intravenous lines and vulnerable to invading organisms because of impaired phagocytic function.[12] As per the United States Renal Data System, the adjusted all-cause mortality rate for hemodialysis patients per 1,000 patient-years was 172, and infectious disease accounted for 15.6% of the mortality in 2013.[13] In a retrospective study, the in-hospital mortality of ESRD patients with sepsis was 26.7%.[14] Meanwhile, our study showed that the 28-day in-hospital mortality was 20.8% in ESRD patients with sepsis. Owing to the high mortality in the ESRD population, early determination of the severity of sepsis and adequate resuscitation are important and challenging aspects. As per our results, serum lactate levels may have enough sensitivity in predicting the 28-day in-hospital mortality of patients with sepsis who have undergone last hemodialysis after 4 hours.

Table 4

Multivariate logistic regression for 28-day in-hospital mortality in the 3 groups.

	All 490 patients		H/D within 4 h		H/D in 4–12 h		H/D beyond 12 h	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Age >65	1.29 (0.78–2.12)	0.318	0.59 (0.06–5.89)	.654	0.70 (0.13–3.70)	.678	1.57 (0.90–2.76)	.113
Gender (male)	1.34 (0.84–2.13)	0.217	0.73 (0.09–6.17)	.773	1.54 (0.37–6.36)	.551	1.56 (0.92–2.66)	.099
Liver cirrhosis	1.37 (0.67–2.80)	0.395	Null	.992	0.79 (0.10–6.29)	.825	1.58 (0.68–3.70)	.290
Diabetes mellitus	0.84 (0.52–1.34)	0.455	0.54 (0.06–4.67)	.572	0.88 (0.21–3.71)	.862	0.82 (0.48–1.41)	.477
Congestive heart failure	0.84 (0.40–1.78)	0.655	15.3 (0.90–26.7)	.059	1.03 (0.09–11.8)	0984	0.54 (0.22–1.30)	.166
Cerebral vascular disease	1.37 (0.72–2.59)	0.336	Null	.992	Null	Null	1.94 (0.96–3.91)	.064
Malignancy	2.11 (1.09–4.08)	0.026	Null	Null	0.86 (0.15–4.91)	.868	3.11 (1.44–6.72)	.003*
Lactate > 2 mmol/L	4.05 (2.49–6.60)	<0.001*	2.16 (0.25–18.8)	0.487	5.19 (1.11–24.3)	.037*	4.50 (2.58–7.84)	<.001*
Goodness-of-fit	*P*=.943		*P*=.882		*P*=.917		*P*=.630	

95%CI = 95% confidence interval, H/D = hemodialysis, OR = odds ratio.
* $P < .05$.

4.1. Lactate level in ESRD patients with sepsis

First, we need to determine the lactate metabolism in the body and the effect of hemodialysis on serum lactate levels. Lactic acidosis is often attributed to tissue hypoperfusion because of the shift toward anaerobic glycolysis, although it can result from various other mechanisms, such as changes in the activity of sodium potassium adenosine triphosphatase[15] or mitochondrial process dysfunction and inhibition.[16] Indeed, patients with ischemic tissue often manifest markedly elevated serum lactate values. Lactate has a molecular weight of 90 Dalton(Da), similar to urea (60 Da), and as such is easily eliminated by dialysis.[17]

In a prospective study involving a regular hemodialysis population, the rapid fluid shift during hemodialysis was thought to cause relative hypoperfusion and an increase in lactate levels. In fact, lactate levels increased in only 16% of the patients after dialysis, whereas they decreased in 80%. Lactate levels decreased by 27% after hemodialysis, with a greater percentage of decline among patients with high pre-hemodialysis lactate levels.[18]

Thus, post-hemodialysis serum lactate levels may underestimate the elevation of lactate levels and illness severity, potentially reducing its ability to screen patients for severe sepsis.

4.2. Lactate level in different timing of last hemodialysis

This study demonstrates the ability of serum lactate level in predicting the mortality of patients with sepsis for different timings of last hemodialysis. The mean lactate levels were higher than 2 mmol/L in 3 groups.

According to a previous study,[18] we expected the Group A to have the lowest lactate levels; contrastingly, this group had the highest lactate levels. These patients were possibly sent to ED right after completion of hemodialysis or during hemodialysis due to severe clinical conditions or unstable vital signs (such as hypotension, dyspnea, fever . . .), which could have resulted in high lactate levels. However, the mortality rate showed no significant increase in this group.

We compared the serum lactate levels of survivors and non-survivors within 28 days for each group. The serum lactate level was not reliable in predicting the 28-day in-hospital mortality for Group Abut was reliable in doing so for the other 2 groups. Per the ROC analysis, the AUC was 0.56 for Group A, showing no validity in predicting mortality. However, acceptable validity was noted for the other groups.

Lactate levels higher than 2 mmol/L were independent predictors of the 28-day in-hospital mortality in Group B and Group C. Serum lactate level did not show any predictive value inGroup A. In sum, this indicates that serum lactate level may not be a useful tool for predicting the 28-day in-hospital mortality for patient who undergo their last hemodialysis within 4 hours.

4.3. Limitations

Our study design includes several limitations. First, some patients were excluded initially for lack of precise timing of hemodialysis in the chart or because the serum lactate levels were not available in the ED, which could have led to selection bias. Second, Group A had very few patients. Third, since sepsis is a diverse disease and patients may come to the ED at different stages of sepsis, without information on pre-hemodialysis serum lactate levels of Group A, we could not determine the true effect of hemodialysis on serum lactate levels but found its predictive ability concerning sepsis-related mortality after different timing of hemodialysis. Finally, all of our study groups consisted of Asian patients. Different ethnicities may have led to different outcomes. Since no study has compared the impact of ethnic differences on sepsis outcomes, future studies could consider this topic.

5. Conclusions

Serum lactate level has acceptable sensitivity in predicting the 28-day in-hospital mortality of patients with sepsis who undergo their last hemodialysis after 4 hours. However, serum lactate level is not reliable in predicting the 28-day in-hospital mortality of patients who undergo their last hemodialysis within 4 hours.

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