Difference between elderly and non-elderly patients in using serum lactate level to predict mortality caused by sepsis in the emergency department

Hsien-Hung Cheng, MS[a,b], Fu-Cheng Chen, MS[a], Meng-Wei Change, MD[a], Chia-Te Kung, MS[a], Chi-Yung Cheng, MD[a], Tsung-Cheng Tsai, MS[a], Sheng-Yuan Hsiao, MD[a], Chih-Min Su, PhD[a,b],*

Abstract

Elderly people are more susceptible to sepsis and experience more comorbidities and complications than young adults. Serum lactate is a useful biomarker to predict mortality in patients with sepsis. Lactate production is affected by the severity of sepsis, organ dysfunction, and adrenergic stimulation. Whether the predictive ability of serum lactate will be different between non-elderly and elderly patients is unknown.

A retrospective cohort study was conducted to compare the prognostic value of hyperlactatemia in predicting the mortality between elderly ($\geq$65 years) and non-elderly (<65 years) patients with sepsis.

This is a single-center retrospective observational cohort study conducted from January 2007 to December 2013 in southern Taiwan. All patients with sepsis, who used antibiotics, with blood culture collected, and with available serum lactate levels in the emergency department, were included in the analysis. We evaluated the difference in serum lactate level between the elderly and non-elderly septic patients by using multiple regression models.

A total of 7087 patients were enrolled in the study. Elderly and non-elderly patients accounted for 62.3% (4414) and 40.2% (2673) of all patients, respectively. Statistically significant difference of serum lactate levels was not observed between elderly and non-elderly survivors (2.9 vs 3.0 mmol/L; $P = .57$); however, elderly patients had lower lactate levels than those within the 28-day in-hospital mortality (5.5 vs 6.6 mmol/L, $P < .01$). Multiple logistic regression revealed higher adjusted mortality risk in elderly and non-elderly patients with lactate levels of $\geq$4.0 mmol/L (odds ratio [OR], 4.98 and 5.82; $P < .01$, respectively), and lactate level between 2 and 4 mmol/L (OR, 1.57 and 1.99; $P < .01$, respectively) compared to that in the reference group with lactate levels of <2.0 mmol/L in each group. In receiver operating characteristic curve analysis, sensitivity rates for predicting mortality were 0.80 and 0.77 for non-elderly and elderly patients, respectively, by using serum lactate levels higher than 2.0 mmol/L.

Septic elderly non-survivors had 1 mmol/L lower serum lactate level than those of the non-elderly non-survivors. Lactate >2 mmol/L still could provide enough sensitivity in predicting sepsis mortality in elder patients.

Abbreviations: ED = emergency department, OR = odds ratio, ROC = receiver operating characteristic, SIRS = systemic inflammatory response syndrome.

Keywords: elderly, lactate, mortality, sepsis

[a] Department of Emergency Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, [b] School of Medicine, Chung Shan Medical University, Kaohsiung, Taiwan.

* Correspondence: Chih-Min Su, Department of Emergency Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, No. 123, Ta Pei Road, Niao Sung Hsiang, Kaohsiung City 833, Taiwan (e-mails: mitosu@gmail.com, mito@adm.cgmh.org.tw).

1. Introduction

The number of elderly patients (aged $\geq$65 years according to the World Health Organization) with severe sepsis and septic shock has been increasing continuously.[1,2] This population of elderly patients is characterized by an increased prevalence of chronic illness, comorbidities, frailty, and functional impairment.[1,3] Early identification, broad-spectrum antibiotic administration, and hemodynamic stabilization have been the cornerstones of sepsis management.[4] Elderly patients can also easily experience ambiguous symptoms of sepsis response compared with non-elderly patients, which leads to emergency department (ED) physicians' difficulty in early diagnosis of sepsis.[5] Some biomarkers are necessary to aid in the diagnosis and risk stratification of sepsis among elderly patients.

Sepsis-associated hyperlactatemia is a strong independent predictor of mortality in sepsis, and its occurrence and progression are widely observed by clinicians[6] and usually available in the ED.[7] Elevated lactate levels may be due to anaerobic metabolism and oxidative stress, which is a marker of tissue hypoxia, or metabolic changes due to stress reaction by the

release of epinephrine.[8,9] This would lead to our concern regarding their occurrence among elderly patients.

The difference of lactate level between non-elderly and elderly patients with sepsis was still unknown. This is the first study to investigate the prognostic value of hyperlactatemia to predict the 28-day in-hospital mortality among elderly patients with sepsis and if there was any difference with those of the non-elderly.

2. Method

2.1. Study design

A retrospective cohort study was conducted to compare the prognostic value of hyperlactatemia to predict the 28-day in-hospital mortality between elderly (≥65 years) and non-elderly (<65 years) patients with sepsis. The Institutional Review Board of Chang Cheng Memorial Hospital approved this study with a waiver of the patients' informed consent.

2.2. Study setting and population

This is a single-center retrospective observational cohort study from January 2007 to December 2013 in Kaohsiung Chang Gung Memorial Hospital, a 2300-bed medical center providing primary and tertiary level care in southern Taiwan. It receives >100,000 ED visits per year. We analyzed all adult patients (≥18 years) who visited the ED with systemic inflammatory response syndrome (SIRS), receiving parenteral antibiotics, and having their blood culture collected. Only patients with available serum lactate levels checked at the ED were finally included for analysis.

Electronic medical records including chart and nursing documentation were obtained from the ED health information system based on a computerized database and reviewed by the authors. The following data were retrospectively collected from the electronic medical records of all enrolled patients: demographic characteristics, preexisting major comorbidities, initial vital signs, serum lactate level, major infection source, and outcome of septic events.

The underlying disease and infection sites are determined based on the International Statistical Classification of Diseases and Related Health Problems Ninth Revision (ICD-9) coding. The comorbidity on the underlying diseases was defined based on the ICD-9 coding, which is 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). Major infections include 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 (562.11, 567.0–567.9, 5761, 574.00–574.19, 574.30–574.49, 574.60–574.89) infections based on the ICD-9 coding and other unknown infectious focuses or infection sites that does not belong to the 4 categories. The major outcome was 28-day in-hospital mortality.

2.3. Sepsis definitions

The American College of Chest Physicians/Society of Critical Care Medicine definitions were used, and sepsis was defined as infections consisting of ≥2 SIRS criteria: temperature of >38°C or <36°C, heart rate of >90/min, respiratory rate of >20/min or $PaCO_2$ of <32 mmHg, and white blood cell count of >12,000 or <4000 cells/mL (or >10% band forms).[10]

2.4. Serum lactate testing equipment

Serum lactate levels were initially measured within 6 hours based 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).

2.5. Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY). We use PASS (Power Analysis and Sample Size Software) 14.0.7 to calculate power and sample size. Our sample size is enough for our research question and achieve >80% power. Continuous variables were expressed as means ± standard deviations and compared using the Student's t 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 described in previous articles[6,11–13] were incorporated into a multiple logistic regression model. We use Hosmer–Lemeshow test to assess the goodness of fit. We obtain odds ratio (OR) and 95% confidence interval from multiple logistic regression model. Receiver operating characteristic (ROC) curves for serum lactate levels were created to predict the 28-day in-hospital mortality. 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, 902,247 patients visited the ED; 47,553 of them presented with SIRS criteria for sepsis, received parenteral antibiotics, and had an available blood culture collected. A total of 8209 patients were younger than 18 years old, 31,799 were not checked for their serum lactate levels, and 458 were discharged from the ED within 72 hours were excluded. Therefore, a total of 7087 adult patients with sepsis were finally enrolled. The flow chart of patients enrolled is shown in Figure 1.

3.1. Risk factors of septic patients

Table 1 shows these patients' demographics, presentation at the ED, comorbidities, major sources of infection, serum lactate levels, outcomes of sepsis, and difference between elderly and non-elderly patients. Elderly patients accounted for 62.3% of the patients, and both non-elderly and elderly groups were
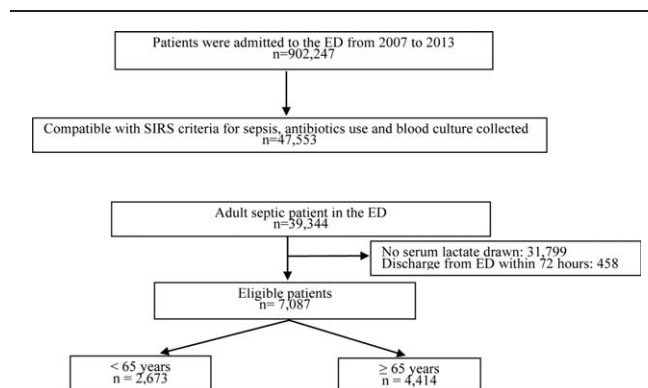

Figure 1. Study flow chart. ED = emergency department.

Table 1

Patient demographics and clinical characteristics.

Variable	All patients (n=7087)	<65 years (n=2673)	≥65 years (n=4414)	P
Age	67.3±15.8	50.4±10.6	77.5±7.3	<.001[*]
Sex, male	4084 (57.6%)	1647 (61.6%)	2437 (55.2%)	<.001[*]
Vital signs in the ED				
Body temperature, °C	37.7±2.1	37.8±1.9	37.7±2.2	.072
Heart rate, beats/min	114.4±26.3	117.1±22.3	112.7±28.4	<.001[*]
Mean arterial pressure, mmHg	94.9±30.1	93.8±29.4	96.2±30.1	<.001[*]
Respiratory rate, breaths/min	21.4±4.6	21.0±4.1	21.7±4.9	<.001[*]
Major comorbidities				
Liver cirrhosis	619 (8.7%)	348 (13.0%)	271 (6.1%)	<.001[*]
Diabetes mellitus	2450 (34.6%)	739 (27.6%)	1711 (38.8%)	<.001[*]
Chronic renal insufficiency	1520 (21.4%)	571 (21.4%)	949 (21.5%)	.905
Congestive heart failure	562 (7.9%)	112 (4.2%)	450 (10.2%)	<.001[*]
Cerebral vascular disease	1111 (15.7%)	218 (8.2%)	893 (20.2%)	<.001[*]
Malignancy	1701 (24.0%)	777 (29.1%)	924 (20.9%)	<.001[*]
Major source of infection				
Respiratory tract	3377 (47.7%)	948 (35.5%)	2429 (55.0%)	<.001[*]
Urinary tract	2033 (28.7%)	559 (20.9%)	1474 (33.4%)	<.001[*]
Skin and soft tissue	537 (7.6%)	255 (8.7%)	295 (6.4%)	<.001[*]
Intra-abdomen	791 (11.2%)	363 (13.6%)	428 (9.7%)	<.001[*]
Other infection	1606 (22.7%)	836 (31.3%)	770 (17.4%)	<.001[*]
Lactate, mmol/L	3.7±3.8	3.8±4.4	3.6±3.4	.041[*]
Blood culture-positive rate	1440 (20.3%)	569 (21.3%)	871 (19.7%)	.120
Septic shock	1394 (19.7%)	536 (20.1%)	858 (19.4%)	.538
Metformin use	187 (2.6%)	59 (2.2%)	128 (2.9%)	.079
28-day mortality	1673 (23.6%)	569 (21.3%)	1104 (25.0%)	<.001[**]

ED = emergency department.

[*] P < .05.

predominantly composed of men. Significantly different physiological changes such as lower heart rate, higher mean arterial pressure, and respiratory rate were observed in elderly patients with sepsis. Renal insufficiency, blood culture positive rate, septic shock rate, and metformin usage were not significantly different between these 2 groups.

The serum lactate level was significantly lower in elderly septic group. Elderly patients seem to have more respiratory tract infection (55.0% vs 35.5%) and urinary tract infections (33.4% vs 20.9%) and the mortalities in each group are higher. The 28-days in-hospital mortality of ≥65 group with respiratory infection is 20.7% (504/2429) compare with <65 group with respiratory infection is 19.3% (183/948). The 28-days in-hospital mortality of ≥65 groups with urinary tract infection is 13.0% (191/1474) compare with <65 group with urinary tract infection is 9.5% (53/559). Non-elderly patients had significantly high

incidences of liver cirrhosis, malignancy, skin and soft tissue infection, and intra-abdominal infection, whereas elderly patients with sepsis had high incidences of diabetes mellitus, congestive heart failure, cerebral vascular disease, respiratory tract infection, urinary tract infection, and 28-day in-hospital mortality.

3.2. Difference of serum lactate levels in non-survival septic patients

Table 2 demonstrates the subgroup analysis based on the 28-day in-hospital mortality. Increasing age was significantly more frequent in non-survival patients with sepsis in both non-elderly and elderly groups. Liver cirrhosis, chronic renal insufficiency, and malignancy were significantly more frequent in non-survivors in both non-elderly and elderly group. Otherwise, diabetes mellitus as a predictive factor was significantly more

Table 2

Subgroup analysis based on 28-day in-hospital mortality.

Variables	< 65 years (n=2673)			≥ 65 years (n=4414)		
	Survivors (n=2104)	Non-survivors (n=569)	P	Survivors (n=3310)	Non-survivors (n=1104)	P
Age	50.0±10.9	52.3±9.2	<.001[*]	77.3±7.3	78.1±7.4	.002[*]
Sex, male	1227 (58.3%)	420 (73.8%)	<.001[*]	1812 (54.7%)	625 (56.6%)	.294
Liver cirrhosis	247 (11.7%)	101 (17.8%)	<.001[*]	160 (4.8%)	111 (10.1%)	<.001[*]
Diabetes mellitus	613 (29.1%)	126 (22.1%)	.001[*]	1364 (41.2%)	347 (31.4%)	<.001[*]
Chronic renal insufficiency	398 (18.9%)	173 (30.4%)	<.001[*]	616 (18.6%)	333 (30.2%)	<.001[*]
Congestive heart failure	85 (4.0%)	27 (4.7%)	.479	340 (10.3%)	110 (10.0%)	.818
Cerebral vascular disease	174 (8.3%)	44 (7.7%)	.730	744 (22.5%)	149 (13.5%)	<.001[*]
Malignancy	510 (24.2%)	267 (46.9%)	<.001[*]	590 (17.8%)	334 (30.3%)	<.001[*]
Lactate, mmol/L	3.0±3.1	6.6±6.7	<.001[*]	2.9±2.5	5.5±4.9	<.001[*]

[*] P < .05.

Variables	Survivors (n=5414)			Non-survivors (n=1673)		
	<65 years (n=2104)	≥65 years (n=3310)	P	<65 years (n=569)	≥65 years (n=1104)	P
Lactate, mmol/L	3.0±3.1	2.9±2.5	.565	6.6±6.7	5.5±4.9	<.001*

* $P<.05$.

frequent in survivors in both non-elderly and elderly patients. The serum lactate levels in survival elderly and non-elderly patients with sepsis were similar, with 2.9 and 3.0 mmol/L, respectively. Elevated serum lactate level was significantly more frequent in the non-survival group in both elderly and non-elderly patients with sepsis, with 5.5 and 6.6 mmol/L, respectively. Compared with the non-elderly, the serum lactate level of the elderly is statistically significant different with about lower 1 mmol/L in non-survivors. Multiple logistic regression revealed higher adjusted mortality risk in elderly and non-elderly patients with lactate levels of ≥4.0 mmol/L (OR, 4.98 and 5.82; $P<.01$, respectively) compared to that in the reference group of non-elderly patients with lactate levels of <2.0 mmol/L (OR, 1.57 and 1.99; $P<.01$, respectively).

In Table 3, we compare lactate levels between survivors and non-survivors in <65 years and ≥65 years groups, lactate levels in elderly are lower than non-elderly only in non-survivors (5.5 vs 6.6 mmol/L, $P<.001$) not in survivors (2.9 vs 3.0 mmol/L, $P=.565$).

3.3. Serum lactate level is an independent risk factor in sepsis with different trend characteristics based on age

The data were further analyzed with multiple logistic regression as the joint influence of the factors possibly associated with mortality in sepsis. Table 4 shows the OR of 28-day in-hospital mortality rate based on the serum lactate level divided into 3 groups, <2.0, 2.0 to 3.9, and >4.0 mmol/L. The crude OR of the mortality rate significantly increased with elevated serum lactate level and was 2.06, 5.99 for non-elderly patients and 1.54, 4.71 for elderly patients in the second and third lactate level groups, respectively. The same trend of significantly increased adjusted mortality risk based on the elevated lactate level was also found in either non-elderly or elderly group. Multiple logistic regression analysis revealed that the highest lactate level was associated with

highest mortality risk, and the OR was 5.82 for non-elderly and 4.98 for elderly group.

The results of the multiple logistic regression analysis in the complete cohort, in <65 years cohort and in ≥65 years cohort are shown in Figures 2–4, respectively. The adjusted OR of the mortality rate is significantly increased with elevated serum lactate level and is 1.85 and 5.64 for all septic patients in the second and third lactate level groups, respectively. The serum lactate level, chronic renal insufficiency, and malignancy are significantly associated with 28-day in-hospital mortality rate in each cohort (OR > 1, $P<.05$). In contrast, diabetes mellitus is significant associated with survival in all septic cohort (OR < 1, $P<.05$).

3.4. Serum lactate level in high-risk group

Table 5 shows the ROC curve analysis, and Youden's index was used to calculate the sensitivity and specificity based on the cutoff point 2.0 and 4.0 mmol/L of the serum lactate level, respectively. Sensitivity rates of 0.80 and 0.77 for non-elderly and elderly patients with sepsis were higher on 2.0 mmol/L, respectively, whereas the specificity rate of 0.81 for non-elderly and elderly patients with sepsis were higher on 4.0 mmol/L.

4. Discussion

A 6-year retrospective analysis of >7000 ED admissions was conducted to evaluate the clinical characteristics, 28-day in-hospital mortality rate, and association between the serum lactate level and sepsis. In this study, elderly patients with sepsis were more likely to have respiratory and urinary tract infections and higher 28-day in-hospital mortality rate, which is similar to the findings reported in previous studies.[12,14] However, non-elderly patients with sepsis were more likely to have soft tissue and intra-abdominal infections.

Lactate	n (%)	28-day mortality n (%)	Crude OR (95% CI)	P	Adjusted† OR (95% CI)	P
<65 years						
<2.0 mmol/L	1096 (41.0%)	115 (10.5%)	Reference‡		Reference‡	
2.0–3.9 mmol/L	901 (33.7%)	175 (19.4%)	2.06 (1.60–2.65)	<.001*	1.99 (1.53–2.59)	<.001*
≥4.0 mmol/L	676 (25.3%)	279 (30.8%)	5.99 (4.69–7.67)	<.001*	5.82 (4.48–7.55)	<.001*
≥65 years						
<2.0 mmol/L	1698 (38.5%)	252 (14.8%)	Reference§		Reference§	
2.0–3.9 mmol/L	1553 (35.2%)	328 (21.1%)	1.54 (1.28–1.84)	<.001*	1.57 (1.30–1.89)	<.001*
≥4.0 mmol/L	1163 (26.3%)	524 (45.1%)	4.71 (3.94–5.61)	<.001*	4.98 (4.14–5.99)	<.001*

CI = confidence interval, OR = odds ratio.
† Adjusted for age, sex, metformin use and comorbidities (liver cirrhosis, diabetes mellitus, chronic renal insufficiency, congestive heart failure, cerebral vascular disease, and malignancy).
‡ Reference group: lactate level ≤2.0 mmol/L and age <65 years
§ Reference group: lactate level ≤2.0 mmol/L and age ≥65 years
* $P<.05$.

Table 5

Receiver operating curve analysis to predict the outcome of 28-day in-hospital mortality.

Group	AUC	95% CI	Cutoff point	Sensitivity	Specificity	Youden's index
All patients	0.70[*]	0.68–0.71	2.0	0.78	0.45	0.23
			4.0	0.48	0.81	0.29
<65 years	0.72[*]	0.69–0.74	2.0	0.80	0.46	0.26
			4.0	0.49	0.81	0.30
≥65 years	0.69[*]	0.67–0.71	2.0	0.77	0.44	0.21
			4.0	0.48	0.1	0.28

AUC = area under the curve, CI = confidence interval.
[*] $P < .05$.

4.1. Sepsis and lactate

Sepsis is defined as a systemic inflammatory response secondary to an acute infection and is a disease of great importance to ED physicians because of its potential rapid progression.[4,10] There is no reliable single objective test and diagnosis based on clinical features and investigation in septic patients.[7] Poor prognostic factors in elderly patients with sepsis include shock, elevated serum lactate levels, and organ failure.[15,16]

Elevated lactate level was a risk factor and a predictor of mortality in patients with sepsis independent of covariates, such as comorbidities in this study and subgroup patients in the previous study.[6,17,18] Evaluating the lactate levels has been proposed as an effective method to determine the adequacy of resuscitation and the nature of response to the initial treatment of sepsis.[8,19]

As shown in Figures 2–4, lactate level is an independent predictors for 28-days in-hospital mortality. This study demonstrates the ability of serum lactate level in predicting the mortality

of patients with sepsis in the ED with an increased risk if the lactate level is >2.0 and 4.0 mmol/L in non-elderly and elderly patients, respectively. Many clinical scores existed regarding the severity and risk of sepsis.[11,20] The lactate level provides a simple and cheaper way for ED physicians to estimate the risk of mortality in patients with sepsis in both young adults and elderly.

### 4.2. Serum lactate level in elderly septic patients

An elderly body is physiologically different from that of a younger adult, and during old age, deterioration of various organ systems becomes evident. The characteristics of diseases in elderly persons may be vague and non-specific with lower body temperature, lower heart rate, and higher mean arterial pressure in sepsis, as shown in Table 1. Elderly patients have more multiple disorders and missed or delayed diagnosis.[21] Elderly patients with sepsis have an increased mortality as compared to their younger counterparts as evidenced by about 60% mortality rate in severe sepsis and septic shock.[12,20] Few observational studies have addressed the lactate level differences between non-elderly and elderly patients with sepsis.

This study shows that higher lactate levels are associated with higher risk of mortality, and age is a predictor of the 28-day in-hospital mortality among patients with sepsis. Multiple logistic regression revealed higher adjusted mortality risk in elderly and non-elderly patients with lactate levels of ≥4.0 mmol/L compared to that in the reference group of non-elderly patients with lactate levels of <2.0 mmol/L.
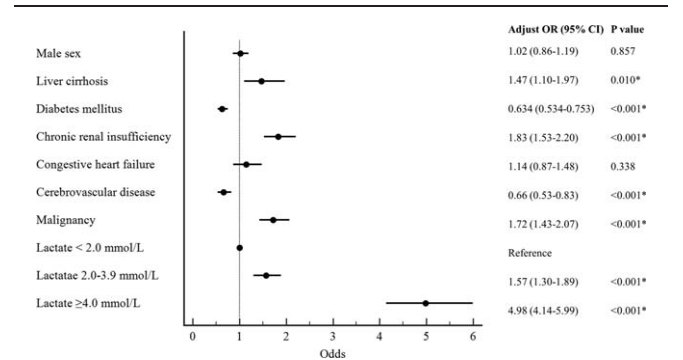
However, the difference of the serum lactate level was not observed between elderly and non-elderly survivors in this study. Compared with non-elderly patients, elderly patients with sepsis had a significantly lower lactate level, about 1 mmol/L (6.6 vs 5.5) in the non-survival group. There is no previous study about serum lactate level between non-elderly and elderly patients with sepsis. Further
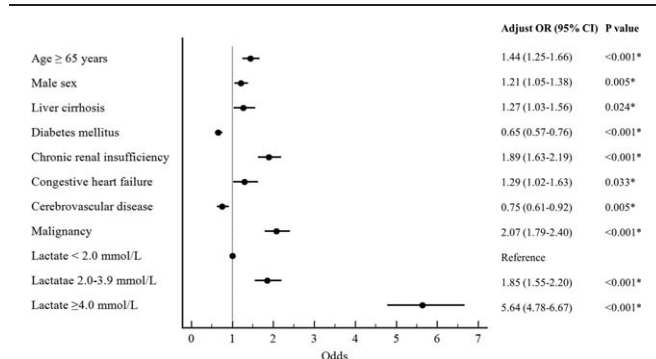
Figure 2. Multiple logistic regression model of 28-day in-hospital mortality rate in complete cohort. CI = confidence internal, OR = odds ratio. [*]$P < .05$.
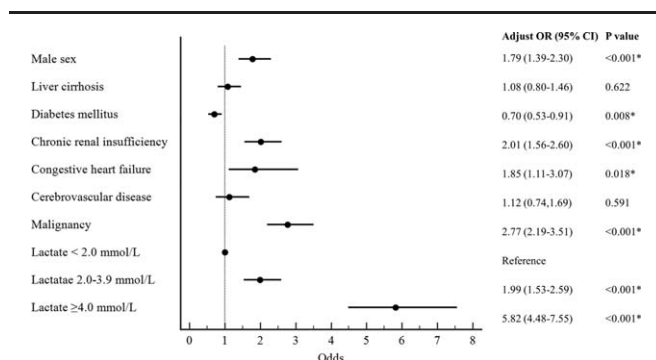
Figure 3. Multiple logistic regression model of 28-day in-hospital mortality rate in <65 years cohort. CI = confidence internal, OR = odds ratio. [*]$P < .05$.

Figure 4. Multiple logistic regression of 28-day in-hospital mortality rate in ≥65 years cohort. CI = confidence internal, OR = odds ratio. [*]$P < .05$.

effort to clarity and eliminate the gap of lactate levels between non-elderly and elderly patients with sepsis in the non-survival group would improve the risk prediction of sepsis in the ED.

4.3. Limitations

This study has several limitations. First, a number of patients with lactate samples not drawn in the ED were excluded. The 28-day mortality of patients who did not undergo lactate measurement was 6.5% (2075/31799) and much lower than our study patients (23.6%). The infection of these patients should be less serious. If patients who did not undergo lactate measurement are included, the difference of lactate level between survivors and non-survivors will be more significant. We minimized the limitation impact by using large size of cohort and non-imputed data. Second, although the design of our study excluded the problems of data missing, there may be key-in errors in electric medical record. Since the distribution of the key-in errors is randomized in both groups, it would not interfere our major results. Thirdly, although different serum lactate levels were found between non-elderly and elderly patients with sepsis in non-survivors, a detailed explanation of this finding was beyond the scope of this study and required further investigation. Finally, all of our study groups are composed of Asians. Differences in ethnicity of patient groups may have consequences but there have been no studies to date comparing the impact of ethnic differences on sepsis outcomes. More studies of different ethnic groups are required to solve this problem.

5. Conclusion

Although elderly septic patients had more co-morbidities and severity of disease, elderly non-survivors had 1 mmol/L lower serum lactate level than those of the non-elderly non-survivors. Lactate >2 mmol/L still could provide enough sensitivity in predicting sepsis mortality in elder patients.

Acknowledgments

Author contributions

Conceptualization: C-M. Su.
Data curation: C-Y. Cheng, C-T. Kung, F-C. Chen, M-W. Change, S-Y. Hsiao, T-C. Tsai.
Formal analysis: F-C. Chen, H-H. Cheng.
Investigation: C-M. Su.
Methodology: F-C. Chen, H-H. Cheng.
Supervision: C-M. Su.
Validation: M-W. Change.
Writing – original draft: F-C. Chen, H-H. Cheng.
Writing – review & editing: C-M. Su.

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