

Use of plasma lactate level to predict 28-day mortality in non-elderly and elderly sepsis patients based on the MIMIC-III database

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Abstract

Purpose We compared the use of lactate level for predicting 28-day mortality in non-elderly (<65 years) and elderly (≥ 65 years) sepsis patients who were admitted to an intensive care unit (ICU). **Methods** This retrospective study used the Medical Information Mart for Intensive Care III, a publicly available database of ICUs. Eligible sepsis patients were at least 18 years-old, hospitalized for at least 24 h, and had lactate levels measured in the ICU. The relationship of lactate level with 28-day mortality was determined. **Results** The 28-day mortality was 30.9% among the 2482 patients, and was significantly greater in elderly than non-elderly patients. Within each age group, the lactate level was greater for non-survivors than survivors. Among non-survivors, the lactate level was significantly higher for the non-elderly than the elderly. Adjusted logistic regression analysis showed that elderly and non-elderly patients with lactate levels of 2.0–4.0 mmol/L and above 4.0 mmol/L had greater risk of death than those with normal lactate. Cirrhosis, chronic renal failure, and malignancy were independent risk factors for 28-day mortality in each age group. Based on a lactate cut-off level of 2.1 mmol/L, the area under the receiver operating characteristic curve was 0.628 (overall), 0.707 (non-elderly), and 0.585 (elderly). **Conclusion** In our population of sepsis patients, a plasma lactate level above 2.0 mmol/L was an independent risk factor for death at 28-days. The lactate level among elderly non-survivors was about 0.9 mmol/L lower than among non-elderly survivors. Lactate was a better prognostic indicator for non-elderly than elderly patients.

Introduction

The clinical mortality rate of sepsis is now higher than that of myocardial infarction and, except for heart disease, sepsis is the main cause of death in the ICU [1]. The ultimate cause of death from sepsis is organ dysfunction caused by the patient's reaction to the infection [2]. Because of their reduced immune responses and resistance, sepsis more common among the elderly. The prevalence and mortality of severe sepsis have increased significantly over time [3].

The plasma lactate level is an important biomarker that reflects the oxygen metabolism of tissues. The root cause of septic shock is tissue hypoxia, and this leads to an increased level of glucose, anaerobic glycolysis, and lactate production [4]. Persistent hyperlactatemia, which suggests that tissue hypoxia has not been corrected, is associated with adverse outcome. An elevated level of plasma lactate during sepsis is associated with more severe disease and poor prognosis [5]. However, there have been questions about the use of lactate as a risk marker for sepsis and the ability of lactate level to predict 28-day mortality in patients with sepsis.

The rapid development of medical information resources has made a large number of electronic health records available [6]. Analysis of these records has been a focus of significant research in medical research and related fields [7]. The Medical Information Mart for Intensive Care (MIMIC-III), which we used for the present study, is a publicly available database developed by the Laboratory of Computational Physiology at the Massachusetts Institute of Technology. This database integrates comprehensive

clinical data from ICU patients who received care at the Beth Israel Medical Center from 2001 to 2012. It has de-identified data on demography, vital signs, laboratory tests, medical records, imaging reports, drug use, and other clinically significant information [8]. Researchers and institutions around the world have published numerous studies based on analysis of the MIMIC-III database [9-13].

The present study is the first to use the MIMIC-III database to compare the predictive value of plasma lactate level on 28-day mortality of non-elderly and elderly patients with sepsis in the ICU.

Materials And Methods

Study design

The MIMIC-III database was used to identify all adults diagnosed with sepsis, severe sepsis, or septic shock with a first ICU admission. All included patients were at least 18 years-old and were hospitalized for at least 24 h. Patients whose initial lactate levels were not recorded were excluded.

Data collection

All data (including demographic characteristics, major complications, major infection sites, laboratory data, vital signs, and 28-day prognosis) were extracted from MIMIC-III *via* PostgreSQL, a structured query language with Navicat Premium 12.

Plasma venous lactate levels that were recorded upon ICU admission were analyzed. Lactate level was categorized as normal (<2.0 mmol/L), intermediate ($\geq 2.0, <4.0$ mmol/L), or high (≥ 4.0 mmol/L). The primary outcome was 28-day mortality.

Statistical analysis

SPSS 17.0 software was used for data analysis. Continuous variables are expressed as medians and inter-quartile range, and the Mann-Whitney U test was used for comparisons. Categorical variables are expressed as numbers and percentages, and were compared using the chi-square test or Fisher exact test. Multivariate logistic regression was used to identify factors significantly and independently associated with lactate and the prognosis of sepsis. The Hosmer-Lemeshow test was used to evaluate the suitability of the model. Prognosis was evaluated using receiver operating characteristic (ROC) analysis, and the ability of lactate level to predict 28-day mortality was assessed by calculation of the area under the ROC (AUROC). For all analyses, a P value below 0.05 was considered significant.

Results

There were 46,476 patients who were first admitted to the ICU, and 3512 had diagnoses of sepsis (ICD 995.91), severe sepsis (ICD 995.92), or septic shock (ICD 785.52; Figure 1). After exclusion of 5 patients who were younger than 18 years-old, 309 patients who were discharged from the ICU within 24 h, 4 patients who did not have chart event data, and 710 patients whose initial lactate levels were not measured, there were 2482 patients. Among these 2482 patients, 1100 were younger than 65 years and 1382 were 65 years or older.

Table 1 shows the baseline clinical and demographic characteristics of the 2482 patients overall and of the elderly and non-elderly groups. The overall 28-day mortality rate was 30.9%, and the rate in elderly patients was 64.8%. Most patients in the non-elderly and elderly groups were male. The average duration in the ICU was 126.07 h for the non-elderly and 101.80 h for the elderly. There were significant differences in the racial composition of the two age groups. In particular, there were higher percentages of black and Hispanic/Latino patients in the non-elderly group. The two age groups also had significant differences in many clinical characteristics, including multiple vital signs, major comorbidities, and major source of infection.

Analysis of major complications indicated the incidence of hypertension, congestive heart failure, chronic renal insufficiency, cerebrovascular disease, and diabetes were greater in elderly patients, but the incidence of cirrhosis was greater in non-elderly patients. The elderly group had more respiratory tract infections (34.2% vs. 29.7%), but the non-elderly group had a greater incidence of skin and soft tissue infections (10.9% vs. 6.9%). The 28-day mortality was significantly greater in the non-elderly group (36.0% vs. 24.5%). The two groups had no significant difference in plasma lactate level.

Analysis of survivors and non-survivors (Table 2) indicated the mortality rate increased with patient age within each age group, and that time in the ICU had a positive association with survivorship only in the non-elderly group. Sex and race had no significant effect in either age group. The incidence of cirrhosis, chronic renal insufficiency, malignancy, and lactate level were significantly greater among non-survivors in each age group. Further analysis (Table 3) showed that the lactate level was similar for elderly and non-elderly survivors (1.8 vs. 1.8 mmol/L, $P = 0.571$), but was greater in non-elderly non-survivors than elderly non-survivors (2.2 vs. 3.1 mmol/L, $P < 0.001$).

We performed multivariate logistic regression analysis to identify factors that were independently and significantly associated with 28-day mortality, in which patients with normal levels of lactate (<2 mmol/L) were used as the reference group (Table 4). The unadjusted and adjusted ORs indicated the risk of death at 28 days in each age group increased with increased lactate level.

We also used multivariate analysis to determine the impact of other clinical factors on mortality among patients overall (Figure 2), the non-elderly group (Figure 3), and the elderly group (Figure 4). In each of these analyses, the adjusted OR for 28-day mortality increased significantly with increased lactate level, and the presence of cirrhosis, chronic renal failure, and malignancy.

We performed ROC analysis to determine sensitivity, specificity, and Youden's index (overall diagnostic performance) for lactate cut-off points of 2.0 and 4.0 mmol/L in the different groups (Table 5). For a lactate cut-off point of 2.0 mmol/L, the sensitivity in predicting 28-day mortality was 0.70 in the non-elderly group and 0.55 in the elderly group ($P < 0.05$). Table 6 shows the AUROC values for 28-day mortality in each age group. The best cut-off point for each group was 2.1 mmol/L. Based on Youden's index, plasma lactate level was a better predictor for non-elderly patients (0.29 vs. 0.15). The AUROC for 28-day mortality was 0.628 in all patients, 0.707 in the non-elderly, and 0.585 in the elderly (Figure 5). At each lactate cut-off point, Youden's index was greater for the non-elderly than the elderly.

Discussion

Sepsis is associated with a high mortality rate, but there are limited objective and effective clinical markers of prognosis. More than half of patients with sepsis in the United States are more than 65 years-old. Relative to the non-elderly, the elderly have a 13.1-fold greater risk of sepsis and 1.56-fold greater risk of death from sepsis [14].

In this study, we retrospectively analyzed the clinical characteristics, 28-day mortality rate, and the relationship of plasma lactate level with the prognosis of sepsis patients in the MIMIC-III database. Most of these patients were from an emergency department, so those with high lactate levels were treated soon after admission. This may have contributed to the lower overall lactate levels in our study than in a previous study [15].

The elderly patients are more likely than the nonelderly to develop sepsis due to Gram-negative bacteria, especially among patients with pneumonia and fungal infections. Respiratory tract infections are also more common causes of sepsis in elderly patients [14]. Relative to the non-elderly, we found that elderly sepsis patients had a higher 28-day mortality rate and that sepsis was more likely to be caused by a respiratory tract infection, in agreement with previous studies [15, 16]. In contrast, we found that sepsis in non-elderly patients was more likely to be caused by skin and soft tissue infections.

Our multivariate adjusted logistic regression analysis showed that lactate level was an independent risk factor for 28-day mortality in non-elderly and elderly sepsis patients. This conclusion is consistent with the results of previous studies of patients admitted to emergency departments [15]. The major indicators of poor prognosis in elderly sepsis patients are shock, elevated plasma lactate, and organ failure (especially of the respiratory system or heart) [17]. In addition, previous research indicated that advanced age is an independent risk factor for severe sepsis and death from sepsis [18].

Our study is the first to use the MIMIC database to analyze the effect of plasma lactate level on 28-day mortality among sepsis patients in the ICU. Our results indicated that elevated lactate level was associated with increased 28-day mortality in non-elderly and elderly patients, but it was a more reliable prognostic indicator for the non-elderly. A previous study reported that elevated lactate level was associated with poor prognosis for ICU patients after ruptured abdominal aortic aneurysm repair [19].

However, plasma lactate concentration reflects overall changes of the body's metabolism, so its sensitivity often low. In fact, our ROC analysis that lactate level was a fair predictor of 28-day prognosis for the non-elderly (AUROC = 0.707), a poor predictor for patients overall (AUROC = 0.628), and failed to predict mortality for the elderly (AUROC = 0.585). This indicates a need to identify better predictors of 28-day mortality among sepsis patients.

A limitation of this study is that we only examined a relatively small number of patients. In addition, although we examined the effect of ethnicity, patients in the MIMIC-III database were mainly white, and there were very few patients from other ethnic groups. This points to the need for further forward-looking, large sample validation and risk grading studies, and the identification and validation of indicators better than lactate for predicting death from sepsis.

Conclusions

Measurement of plasma lactate level is a simple and inexpensive method that clinicians can use to assess the risk of mortality in patients with sepsis. Our results indicated that lactate level is an independent risk factor for 28-day prognosis in non-elderly and elderly sepsis patients, and that cirrhosis, chronic renal insufficiency, and malignancy were also independently associated with mortality. The lactate level among elderly non-survivors was about 0.9 mmol/L lower than among non-elderly survivors. The ability of elevated plasma lactate (>2.0 mmol/L) to predict 28-day prognosis was better in non-elderly than elderly sepsis patients.

Abbreviations

ICU: Intensive Care Unit; MIMIC-III: the Medical Information Mart for Intensive Care III; ROC: receiver operating characteristic; AUROC: the area under the receiver operating characteristic curve; OR: odd ratio; SpO₂, peripheral capillary oxygen saturation; MICU, medical intensive care unit; CCU, coronary care unit; TSICU, trauma surgical intensive care unit; CSRU, cardiac surgery recovery unit; SICU, surgical intensive care unit.

Declarations

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Availability of data and materials

The datasets analyzed during the current study are available in <https://github.com/MIT-LCP/mimic-code/tree/master/concepts>.

Authors' contributions

YHD designed the methods and experiments, and contributed to the writing of manuscript. XYM and YFH cleaned the data. YYH, JC and YRL provided guidance and reviewed the manuscript critically. JYP supervised the study and revised the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethical consent was not required in this study, since the MIMIC \times data were analyzed namelessly.

Consent for publication

The manuscript does not include individual person's data.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Baseline characteristics and clinical outcomes of all patients, and patients in the two age groups.

Variable	Overall (n=2482)	Non-elderly (n=1100)	Elderly (n=1382)	P value
Age (years)	67.86(55.33-79.93)	53.83(44.82-59.87)	78.67(72.04-84.61)	<0.001*
Sex (male)	1363(54.9%)	637(57.9%)	726(52.5%)	0.007*
ICU length of stay (h)	113.77(58.94-261.29)	126.07(64.72-303.58)	101.80(54.67-222.30)	<0.001*
Ethnicity				
Black	207(8.3%)	121(11.0%)	86(6.2%)	<0.001*
White	1810(72.9%)	745(67.7%)	1065(77.1%)	<0.001*
Asian	78(3.1%)	33(3.0%)	45(3.3%)	0.716
Hispanic or Latino	76(3.1%)	52(4.7%)	24(1.7%)	<0.001*
Other or unknown	311(12.5%)	149(13.5%)	162(11.7%)	0.173
First care unit				
MICU	1708(68.8%)	742(67.5%)	966(69.9%)	
CCU	186(7.5%)	72(6.5%)	114(8.2%)	
TSICU	187(7.5%)	86(7.8%)	101(7.3%)	
CSRU	78(3.1%)	29(2.6%)	49(3.5%)	
SICU	323(13.0%)	171(15.5%)	152(11.0%)	
Admission type				
Emergency	2387(96.2%)	1054(95.8%)	1333(96.5%)	
Elective	95(3.8%)	46(4.2%)	49(3.5%)	
Initial vital signs				
Heart rate (beats/min)	92.56(80.55-106.03)	112.15(102.75-128.29)	88.75(77.02-101.21)	0.005*
Mean blood pressure (mmHg)	71.86(66.78-77.81)	69.49(62.15-82.07)	70.32(65.76-75.75)	0.963
Respiratory rate (breaths/min)	21.13(18.04-24.32)	25.66(20.50-31.72)	20.88(17.95-24.05)	0.027*
Body temperature (°C)	36.88(36.40-37.47)	37.56(36.84-38.42)	36.75(36.29-37.25)	0.015*
SpO ₂	97.22(95.77-98.55)	96.62(94.70-98.91)	97.27(95.86-98.63)	0.622
Major comorbidities				
Hypertension	1293(52.1%)	445(40.5%)	848(61.4%)	<0.001*
Liver cirrhosis	245(9.9%)	175(15.9%)	70(5.1%)	<0.001*
Congestive heart failure	819(33.0%)	210(19.1%)	609(44.1%)	<0.001*
Chronic renal insufficiency	1600(64.5%)	662(60.2%)	938(67.9%)	<0.001*
Cerebrovascular disease	216(8.7%)	76(6.9%)	140(10.1%)	0.005*
Diabetes mellitus	769(31.0%)	284(25.8%)	485(35.1%)	<0.001*
Malignancy	314(12.7%)	126(11.5%)	188(13.6%)	0.11
Major source of infection				
Respiratory tract	800(32.2%)	327(29.7%)	473(34.2%)	0.017*
Urinary tract	70(2.8%)	33(3.0%)	37(2.7%)	0.629
Skin and soft tissue	215(8.7%)	120(10.9%)	95(6.9%)	<0.001*
Intra-abdomen	414(16.7%)	182(16.5%)	232(16.8%)	0.872
Lactate, mmol/L	2.0(1.3-3.1)	2.0((1.3-3.3)	1.9(1.3-3.0)	0.163
28-day mortality	767(30.9%)	270(24.5%)	497(36.0%)	<0.001*

*P<0.05

SpO₂, peripheral capillary oxygen saturation; MICU, medical intensive care unit; CCU, coronary care unit; TSICU, trauma surgical intensive care unit; CSRU, cardiac surgery recovery unit; SICU, surgical intensive care unit.

Table 2. Comparison of survivors and non-survivors in the two age groups.

Variable	Non-elderly (n=1100)			Elderly (n=1382)		
	Survivors (n=830)	Non-survivors (n=270)	P value	Survivors (n=885)	Non-survivors (n=497)	P value
Age (years)	53.15(43.46-59.44)	55.26(48.71-61.07)	<0.001*	78.14(71.90-84.23)	80.03(72.18-85.54)	0.023*
Sex (male)	476(57.3%)	161(59.6%)	0.51	451(51.0%)	275(55.3%)	0.118
ICU length of stay (h)	132.42(65.95-319.86)	122.88(57.36-258.84)	0.016*	96.84(53.92-227.84)	113.93(58.00-216.25)	0.651
Ethnicity						
Black	96(11.6%)	25(9.3%)	0.293	63(7.1%)	23(4.6%)	0.066
White	563(67.8%)	182(67.4%)	0.897	696(78.6%)	369(74.2%)	0.062
Asian	27(3.3%)	6(2.2%)	0.388	32(3.6%)	13(2.6%)	0.315
Hispanic or Latino	44(5.3%)	8(3.0%)	0.116	16(1.8%)	8(1.6%)	0.468
Other or unknown	100(12.0%)	49(18.1%)	0.011*	78(8.8%)	84(16.9%)	<0.001*
Major comorbidities						
Hypertension	343(41.3%)	102(37.8%)	0.302	556(62.8%)	292(58.8%)	0.136
Liver cirrhosis	77(9.3%)	98(36.3%)	<0.001*	33(3.7%)	37(7.4%)	0.003*
Congestive heart failure	154(18.6%)	56(20.7%)	0.427	381(43.1%)	228(45.9%)	0.31
Chronic renal insufficiency	463(55.8%)	199(73.7%)	<0.001*	569(64.3%)	369(74.2%)	<0.001*
Cerebrovascular disease	58(7.0%)	18(6.7%)	0.857	83(9.4%)	57(11.5%)	0.216
Diabetes mellitus	220(26.5%)	64(23.7%)	0.361	304(34.4%)	181(36.4%)	0.439
Malignancy	71(8.6%)	55(20.4%)	<0.001*	85(9.6%)	103(20.7%)	<0.001*
Lactate, mmol/L	1.8(1.2-2.9)	3.1(1.8-5.4)	<0.001*	1.8(1.3-2.8)	2.2(1.5-3.4)	<0.001*

*p<0.05

Table 3. Lactate levels in survivors and non-survivors of the two age groups.

Variable	Survivors (n=1715)			Non-survivors (n=767)		
	Non-elderly (n=830)	Elderly (n=885)	P value	Non-elderly (n=270)	Elderly (n=497)	P value
Lactate mmol/L	1.8(1.2-2.9)	1.8(1.3-2.8)	0.571	3.1(1.8-5.4)	2.2(1.5-3.4)	<0.001*

*P<0.05

Table 4. Multivariable logistic regression analysis[†] of the relationship of lactate level with 28-day mortality in the two age groups.

Lactate	n(%)	28-day mortality n(%)	Unadjusted OR (CI _{95%})	P value	Adjusted OR (CI _{95%})	P value
Non-elderly						
<2.0 mmol/L	532(48.4%)	74(13.9%)	Reference ¹		Reference ¹	
2.0-3.9 mmol/L	354(32.2%)	89(25.1%)	2.08(1.47-2.93)	<0.001*	1.73(1.21-2.48)	0.003*
≥4.0 mmol/L	214(19.5%)	107(50.0%)	6.19(4.30-8.90)	<0.001*	4.05(2.73-6.01)	<0.001*
Elderly						
<2.0 mmol/L	703(50.9%)	210(29.9%)	Reference ²		Reference ²	
2.0-3.9 mmol/L	477(34.5%)	194(40.7%)	1.61(1.26-2.05)	<0.001*	1.56(1.22-2.00)	<0.001*
≥4.0 mmol/L	202(14.6%)	93(46.0%)	2.00(1.45-2.76)	<0.001*	1.76(1.27-2.45)	0.001

†Adjusted for age and major comorbidities (congestive heart failure, liver cirrhosis, chronic renal insufficiency, malignancy)

¹Reference group: lactate level<2.0mmol/L and age<65 years²Reference group: lactate level<2.0mmol/L and age≥65years

*p<0.05

Table 5. Receiver operating characteristic analysis of 28-day mortality of all patients, and patients in the two age groups for different lactate cut-off points.

Group	Lactate cut-off (mmol/L)	Sensitivity(CI _{95%})	Specificity(CI _{95%})	Youden's index(CI _{95%})
Overall	2.0	0.60 (0.57-0.64)	0.59 (0.57-0.61)	0.19 (0.13-0.25)
	4.0	0.26 (0.23-0.29)	0.88 (0.87-0.90)	0.14 (0.09-0.19)
Non-elderly	2.0	0.70 (0.64-0.75)	0.59 (0.56-0.62)	0.29 (0.20-0.38)
	4.0	0.39 (0.33-0.45)	0.88 (0.86-0.90)	0.27 (0.19-0.35)
Elderly	2.0	0.55 (0.50-0.59)	0.59 (0.56-0.62)	0.14 (0.06-0.21)
	4.0	0.18 (0.15-0.22)	0.88 (0.86-0.91)	0.06 (0.01-0.13)

Table 6. Receiver operating characteristic analysis of 28-day mortality of all patients, and patients in the two age groups for a lactate cut-off point of 2.1 mmol/L.

Group	AUROC (CI _{95%})	Cut-off point (mmol/L)	Sensitivity(CI _{95%})	Specificity(CI _{95%})	Youden's index(CI _{95%})
Overall	0.628 (0.609-0.647)	2.1	0.58 (0.55-0.62)	0.62 (0.59-0.64)	0.20 (0.14-0.26)
Non-elderly	0.707 (0.679-0.734)	2.1	0.68 (0.62-0.74)	0.61 (0.58-0.64)	0.29 (0.20-0.38)
Elderly	0.585 (0.558-0.611)	2.1	0.53 (0.48-0.57)	0.62 (0.59-0.65)	0.15 (0.07-0.22)

Figures

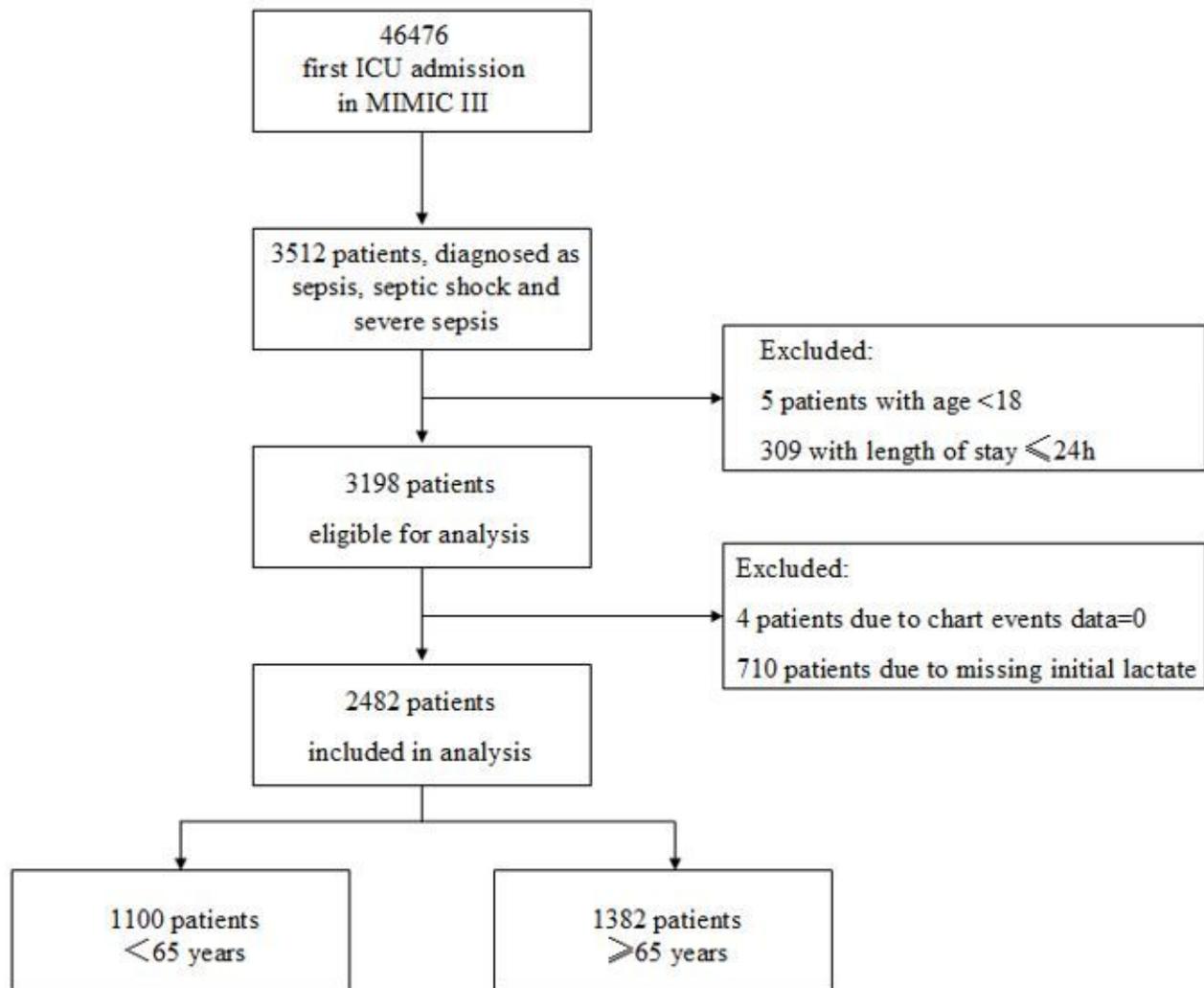


Figure 1

Patient disposition.

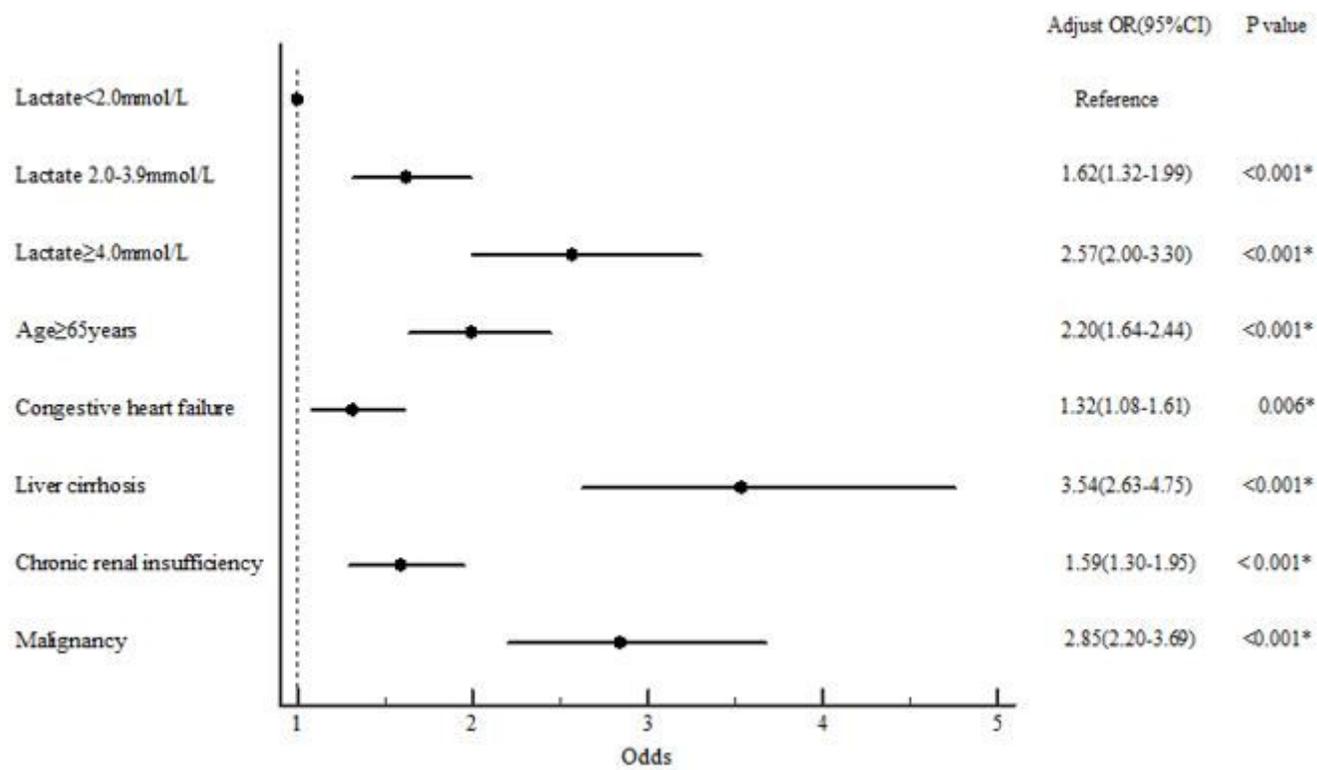


Figure 2

Multivariable logistic regression model of 28-day mortality in all patients, with adjustment for age and major comorbidities (congestive heart failure, liver cirrhosis, chronic renal insufficiency, and malignancy).

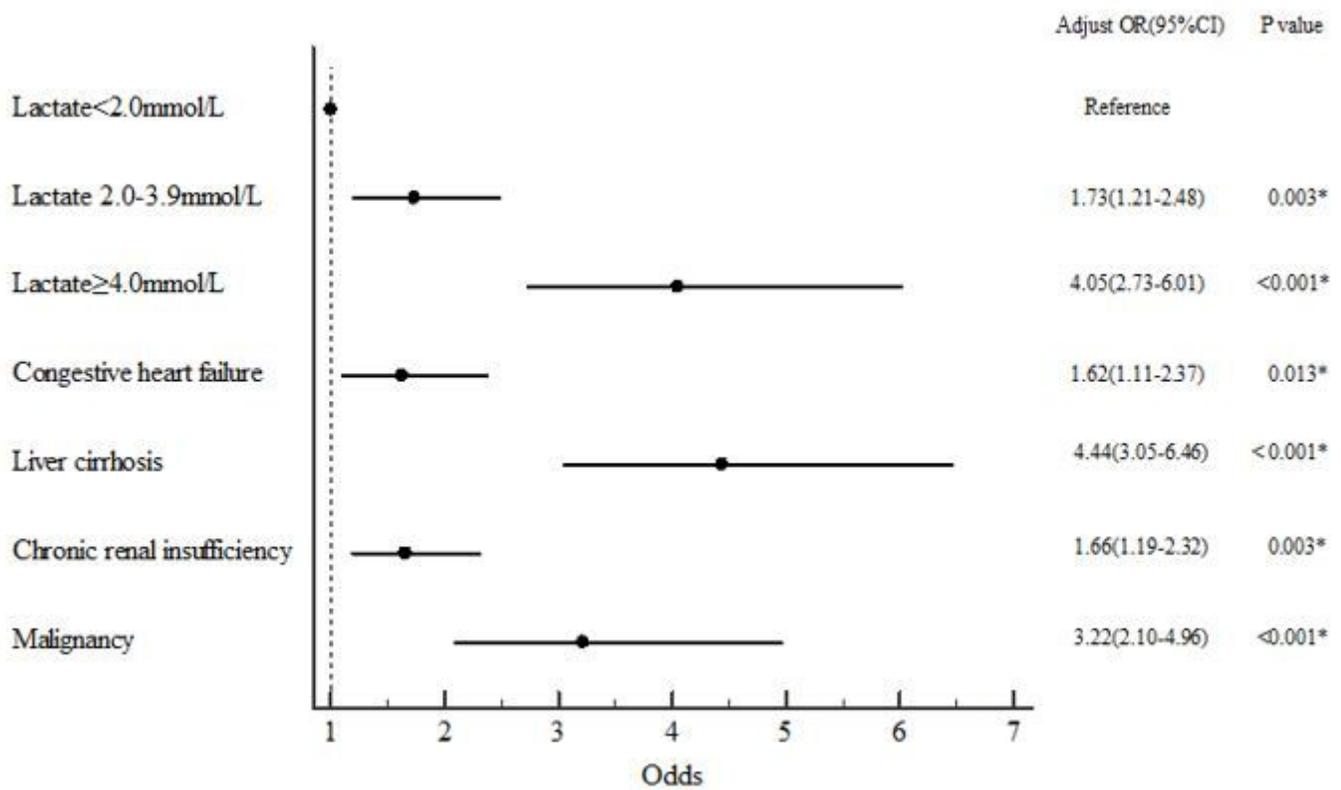


Figure 3

Multivariable logistic regression model of 28-day mortality rate in non-elderly patients, with adjustment for age and major comorbidities (congestive heart failure, liver cirrhosis, chronic renal insufficiency, and malignancy).

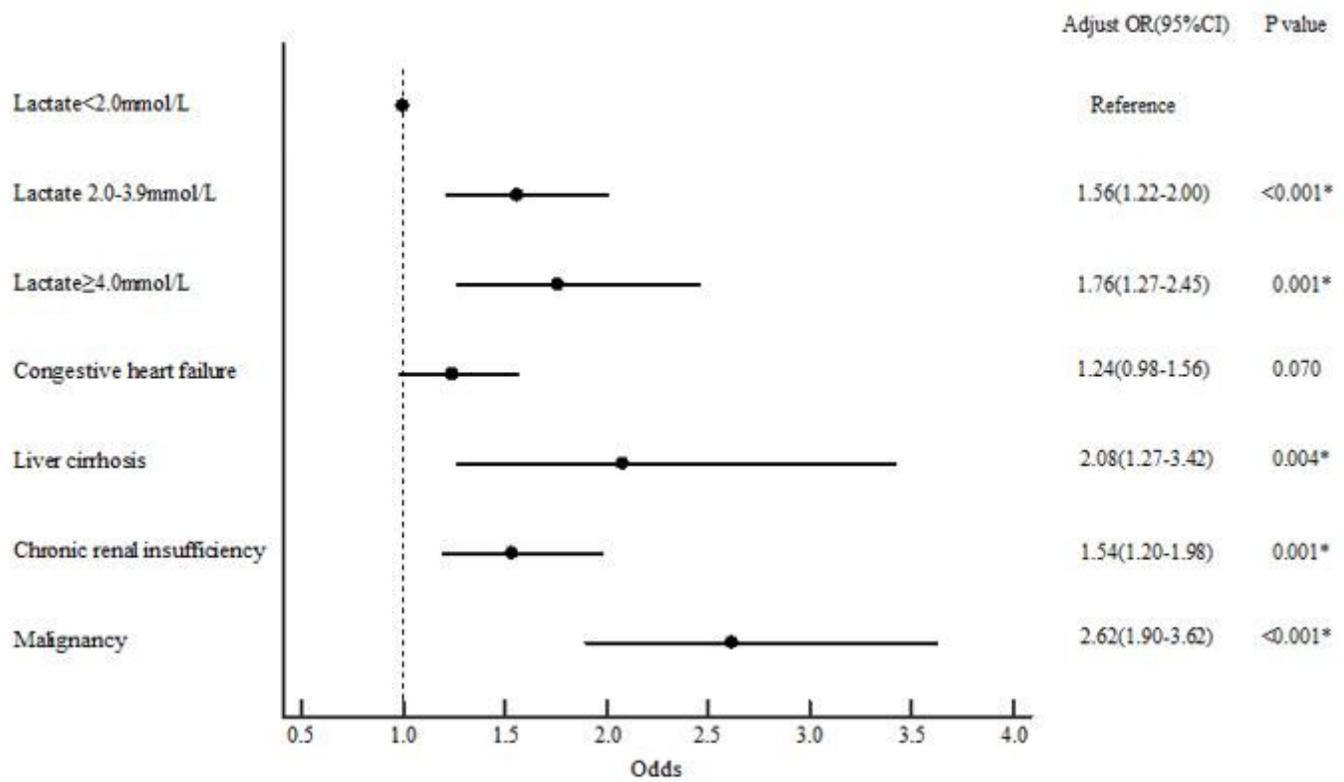


Figure 4

Multivariable logistic regression model of 28-day mortality rate in elderly patients with adjustment for age and major comorbidities (congestive heart failure, liver cirrhosis, chronic renal insufficiency, and malignancy).

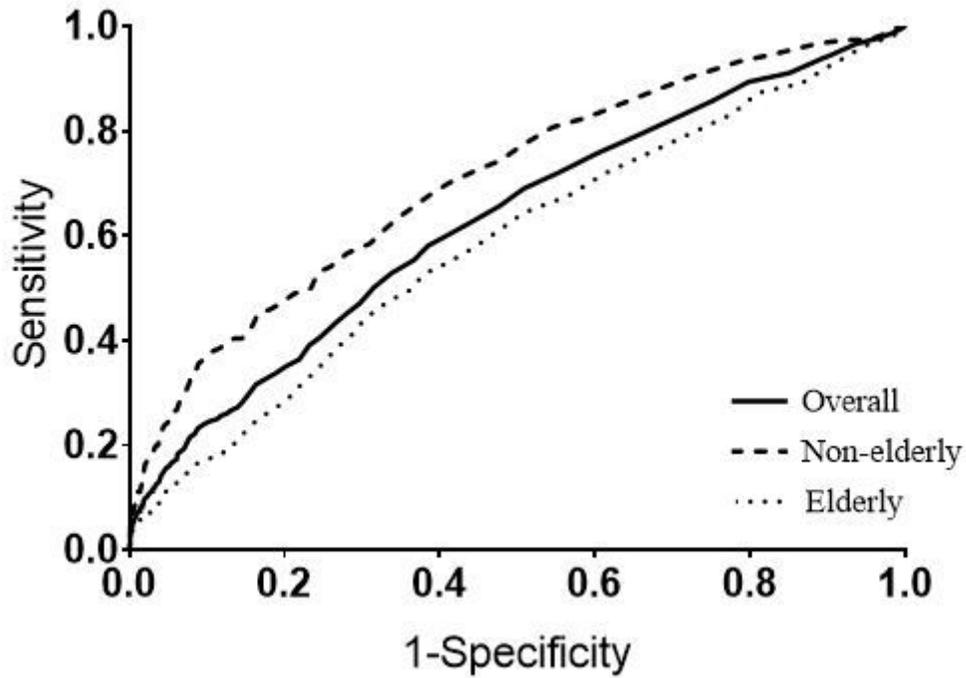


Figure 5

Receiver operating characteristic curves for 28-day mortality. The AUROC for all patients was 0.628 (95% CI = 0.609 to 0.647, $P < 0.01$), for non-elderly patients was 0.707 (95% CI = 0.679 to 0.734, $P < 0.01$), and for elderly patients was 0.585 (95% CI = 0.558 to 0.611, $P < 0.01$)