Journal of Microbiology, Immunology and Infection (2017) xx, 1–8

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

# Risk factors for mortality in patients with low lactate level and septic shock

**Dong Hyun Oh [a], Moo Hyun Kim [b], Woo Yong Jeong [b], Yong Chan Kim [b,c], Eun Jin Kim [b,c], Je Eun Song [d], In Young Jung [b,c], Su Jin Jeong [b,c,*], Nam Su Ku [b,c], Jun Yong Choi [b,c], Young Goo Song [b,c], June Myung Kim [b,c]**

[a] *Department of Internal Medicine, Seoul Medical Center, Seoul, South Korea*
[b] *Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea*
[c] *AIDS Research Institute, Yonsei University College of Medicine, Seoul, South Korea*
[d] *Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, South Korea*

Received 29 April 2017; received in revised form 31 July 2017; accepted 11 August 2017
Available online ■ ■ ■

**KEYWORDS**
Septic shock;
Lactate;
APACHEII;
Score;
SOFA score;
Chronic heart failure;
C-reactive protein

**Abstract** *Background:* According to the new definition of septic shock, vasopressor therapy and hyperlactatemia are essential for diagnosis. However, there is controversy regarding the cutoff value for lactate, and prognostic factors in patients with septic shock and hypolactatemia. This study evaluated the prognostic significance of the cutoff value for lactate level in septic shock patients.
*Methods:* The retrospective observational cohort study enrolled 1043 patients aged ≥18 years who meet the revised definition of septic shock. Clinical outcomes of patients with hyperlactatemia were compared with hypolactatemia.
*Results:* Of the 1022 eligible patients, 369 had an arterial lactate level ≤2 mmol/L. More patients in the high lactate group had poor prognosis than in the low lactate group. A high Sequential Organ Failure Assessment score (SOFA) score group was significant ($p < 0.001$) in predicting lactate levels. On the subgroup analysis of risk factors affecting mortality in the low lactate group, high Acute Physiology And Chronic Health Evaluation II (APACHEII) score ($p = 0.003$), high C-reactive protein ($p = 0.034$), and chronic heart failure ($p = 0.001$) were independently associated with 28-day mortality.

* Corresponding author. Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, 03722, Seoul, South Korea. Fax: +82 2 939 6884.
*E-mail address:* JSJ@yuhs.ac (S.J. Jeong).

http://dx.doi.org/10.1016/j.jmii.2017.08.009

*Conclusion:* Arterial lactate is a very reliable diagnostic and prognostic predictor of septic shock. However, despite low arterial lactate, patients with a high APACHEII score, high C-reactive protein levels, and chronic heart failure had a poorer prognosis.


## Introduction

Sepsis was defined as suspected infection that satisfied diagnostic criteria of the systemic inflammatory response syndrome (SIRS) for the last two decades.[1,2] However, sepsis is now understood as a comprehensive host response to infecting pathogens.[3] Therefore, the definitions of sepsis and septic shock need revision.

To compensate for the fact that inflammation has various courses, while SIRS criteria does not adequately reflect the infection-induced inflammation, new definitions of sepsis and septic shock were announced through Singer et al. in February 2016.[4] Sepsis is defined as life-threatening organ dysfunction caused by a "dysregulated host response" to infection. A Sepsis-related Organ Failure Assessment (SOFA) score $\geq$2 was selected for organ dysfunction.[4,5] Septic shock is a subset of sepsis with underlying "circulatory and cellular metabolic abnormalities" that increase mortality. As index for diagnosis septic shock, 'need for vasopressor therapy' and 'hyperlactatemia' (lactate $>$2 mmol/L despite adequate fluid resuscitation) were selected by the Delphi process.[6]

Lactate has been used as a prognostic marker of sepsis and septic shock. Upon contracting sepsis, patients experience hyperlactatemia caused by lactate overproduction as a consequence of tissue hypoperfusion and sepsis itself, as well as diminished lactate clearance due to hepatic dysfunction and renal dysfunction.[7] In Shankar-Hari et al., the adjusted odds ratio (OR) for hospital mortality increased linearly with increasing lactate levels. Lactate level $>$2 mmol/L was chosen as the cutoff value for diagnosis of septic shock.[6] However, there are many institutions that do not initially measure lactate level.[8] There are patients who with signs of septic shock with hypolactatemia show poor outcomes.[9–11] Therefore, the appropriate cutoff value for lactate level remains controversial.

Our objective was to evaluate the prognostic significance of the cutoff value for lactate through comparison of clinical presentation and outcome between septic shock patients with high and low lactate levels.

## Material and methods

### Patients and study design

We included critically ill patients who visited the emergency department (ED) of Severance Hospital at Yonsei University College of Medicine, a 2000-bed, tertiary referral hospital in South Korea from November 2007 to March 2016. This retrospective cohort study targeted patients enrolled in a critical pathway (CP) named Early Goal-Directed Therapy, a 6-h bundle established for managing patients with septic shock as quickly and effectively as possible. Protocol of CP was revised to reflect the guidelines of Surviving Sepsis Campaign. The protocol was approved by the institutional review board of Yonsei University Health System Clinical Trial Center. All patients visiting the ED were screened. Patients who satisfied two or more SIRS criteria and showed signs of infection were evaluated for eligibility in CP. Initiation of CP was triggered by one of the following two conditions: a) initial systolic blood pressure $<$90 mmHg despite adequate fluid resuscitation, or b) initial arterial lactate level $\geq$4 mmol/L. These standards followed the Surviving Sepsis Campaign guideline designed by Dellinger et al.[12]

Exclusion criteria included: a) age under 18 years, b) any contraindication to central venous catheterization, c) pregnancy, d) acute cerebrovascular accident, e) acute coronary syndrome, f) active gastrointestinal bleeding, g) trauma, h) drug overdose, i) the need for immediate surgery, j) lack of informed consent, k) transfer to another institution, and l) do-not-resuscitation order. A total of 1043 patients were enrolled in this study.

The resuscitation team consisted of specialists in emergency medicine, division of infectious disease, pulmonology, and anesthesiology. Vital signs, such as blood pressure, heart rate, respiration rate, and body temperature, were checked and recorded when patients visited the ED. In septic patients, fluid resuscitation was initiated via insertion of a central venous catheter into the internal jugular vein or subclavian vein. Per protocol, crystalloids were used as resuscitative fluids and norepinephrine was used for a vasopressor. Central venous pressure (CVP), mean arterial pressure (MAP), and central venous oxygen saturation ($ScvO_2$) were checked every hour for 6 h. The success or failure of CP was analyzed using this data.

### Data collection

Baseline characteristics such as age, sex, height, weight, and preexisting comorbidities, such as, hypertension, diabetes mellitus, chronic kidney disease, chronic heart failure (CHF), coronary disease, dementia, lung disease, autoimmune or connective tissue disease, liver disease, malignancy, human immunodeficiency virus infection, and history of organ transplantation were extracted. Treatment modalities and interventions in the process of treatment such as transfusion, vasopressor therapy, ventilator care, and hemodialysis were also noted.

Laboratory tests were performed according to protocol. Initially, complete blood count, C-reactive protein (CRP),

Please cite this article in press as: Oh DH, et al., Risk factors for mortality in patients with low lactate level and septic shock, Journal of Microbiology, Immunology and Infection (2017), http://dx.doi.org/10.1016/j.jmii.2017.08.009

blood urea nitrogen, creatinine (Cr), estimated glomerular filtration rate (eGFR), total bilirubin, albumin, lactate, prothrombin time (International Normalized Ratio), D-dimer, antithrombin III, fibrinogen, fibrin degradation product, arterial blood gas analysis, and bacterial cultures were obtained from blood, sputum, and urine samples. Severity of disease and degree of organ failure were evaluated using the Acute Physiology and Chronic Health Evaluation (APACHEII) and SOFA scores. Follow-ups continued until patients' death during hospitalization period or their first visit to outpatient clinic after patients being discharged. Occurrence of organ failure in this study was determined by reviewing the patients' medical records as well as results of laboratory tests and special examinations, such as echocardiography, within 28 days after hospitalization. Mortalities were classified as 7-day mortality, 28-day mortality, and mortality after 28 days.

### Definition and resuscitation goals

The high lactate group was defined as the group of patients with arterial lactate >2 mmol/L and the low lactate group was defined as a patient group with arterial lactate 2 mmol/L or less. Thrombocytopenia was defined as the platelet count below $150 \times 10^3$ cells/mm$^3$. Renal failure was defined as serum Cr equal to or above 2.0 mg/dL, or urine output below 500 ml/day.[13] Acute respiratory distress syndrome was defined as the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen below 300 mmHg and bilateral opacities not fully explained by pleural effusion, lung collapse, and nodules on chest imaging.[14] Hepatic failure was defined as serum total bilirubin equal to or above 2.0 mg/dL.[15] Newly developed heart failure (HF) was defined as left ventricular ejection fraction below 50% on echocardiography.[16] Disseminated intravascular coagulation (DIC) was diagnosed based on a score ≥5 according to guidelines of the International Society on Thrombosis and Hemostasis when thrombocytopenia, elevated D-dimer level, prolonged prothrombin time, and decreased fibrinogen level were combined.[17]

Patients were treated according to a CP protocol for at least 6 h, after which monitoring of $ScvO_2$ was discontinued if the initial resuscitation goal was achieved (resuscitation criteria: CVP of 11–15 cm$H_2O$, MAP of 65–90 mmHg, and $ScvO_2$ greater than 70% in the initial 6 h).

### Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Categorical variables were compared using $\chi^2$ analysis, and continuous variables with normal distributions were compared using the Student's *t* test. The Mann–Whitney *U* test was used to compare continuous variables with a skewed distribution. Variables with a $p$ value $< 0.05$ on bivariate analysis were included in the logistic regression model for multivariate analysis of 28-day mortality in the low lactate group.

Adjusted ORs were calculated using a logistic regression model. Kaplan–Meier curves were used to compare 7-day mortality and 28-day mortality between high and low lactate groups. Single linear univariate correlation (Pearson's correlation coefficients) and simple linear regression analyses were performed to evaluate the relationship between SOFA score and serum lactate level. The optimal cutoff value for SOFA score was estimated to maximize the sum of the sensitivity and specificity derived from receiving operating characteristic curves and area under the curve (Youden index) using SOFA scores for 1022 patients. The estimated cutoff value for SOFA score in this study was 7.5 (AUC 0.713, $p < 0.001$). All statistical analyses were performed using the Statistical Package for the Social Sciences 18.0 software (SPSS Inc., Chicago, IL, USA). $p$ values less than 0.05 were considered statistically significant.

## Results

During the study period, we enrolled 1043 patients. We excluded 21 patients due to missing data. The high lactate group included 653 (63.9%) patients (Fig. 1). Mean age of participants was 65.7 ± 14.4 years, and total mortality rate was 16.0% (164/1022). Proportion of patients who received vasopressor was 95.8% (979/1022).

Table 1 shows the baseline characteristics and laboratory data of patients with high and low lactate levels. The mean age of patients in the high lactate group was higher than the low lactate group (66.9 ± 13.4 *vs.* 63.6 ± 15.8 years, $p = 0.010$). Male sex had a significant impact on the differences between the two groups (56.0 *vs.* 42.5%, $p < 0.001$). In addition, the incidence of diabetes mellitus (36.8 *vs.* 27.1%, $p = 0.002$) and malignancy (36.4 *vs.* 30.1%, $p = 0.040$) were statistically different between the two groups. Initial $ScvO_2$ (80.2 [72.0–88.3] *vs.* 83.8 [76.0–94.5]%, $p < 0.001$) was higher in the low lactate group than in the high lactate group.

Platelet count (159.0 [87.5–247.5] *vs.* 214.0 [156.3–290.0] $\times 10^3$ cells/mm$^3$, $p < 0.001$), eGFR (39.0 [22.2–60.7] *vs.* 53.0 [32.2–75.0] mL·min$^{-1}$·1.73 m$^{-2}$, $p < 0.001$), and serum albumin level (3.0 ± 0.7 *vs.* 3.3 ± 0.7 g/dL, $p < 0.001$) were lower in the high lactate group than in the low lactate group.

Regarding the severity of illness at the time of admission to the ED and pre-CP, the SOFA score (9.08 ± 3.03 *vs.* 6.97 ± 2.32, $p < 0.001$) and APACHEII score (18.56 ± 7.15 *vs.* 14.02 ± 5.97, $p < 0.001$) were higher in the high lactate group than in the low lactate group (Table 1).

Table 2 shows the results of resuscitation, incidence of organ failure, and mortality in the two groups. The MAP, 6 h after initiation of CP was higher in the low lactate group than in the high lactate group (81.3 ± 14.1 *vs.* 84.4 ± 14.6 mmHg, $p = 0.028$). Six-hour CVP and $ScvO_2$ were not significantly different between the two groups. The high lactate group had a significantly high percentage of CP goal achievement (50.8 *vs.* 43.9%, $p = 0.037$). Organ failure was significantly more frequent in the high lactate group than in the low lactate group. Seven-day mortality (10.3 *vs.* 1.6%, $p < 0.001$) and 28-day mortality (15.6 *vs.* 4.9%, $p < 0.001$) were significantly higher for the high lactate group than the low lactate group (Fig. 2a).

On multivariate analysis, SOFA score of 7.5 was used as the cutoff between groups. Independent predictive factors for high levels of serum lactate in the patients with septic

Please cite this article in press as: Oh DH, et al., Risk factors for mortality in patients with low lactate level and septic shock, Journal of Microbiology, Immunology and Infection (2017), http://dx.doi.org/10.1016/j.jmii.2017.08.009

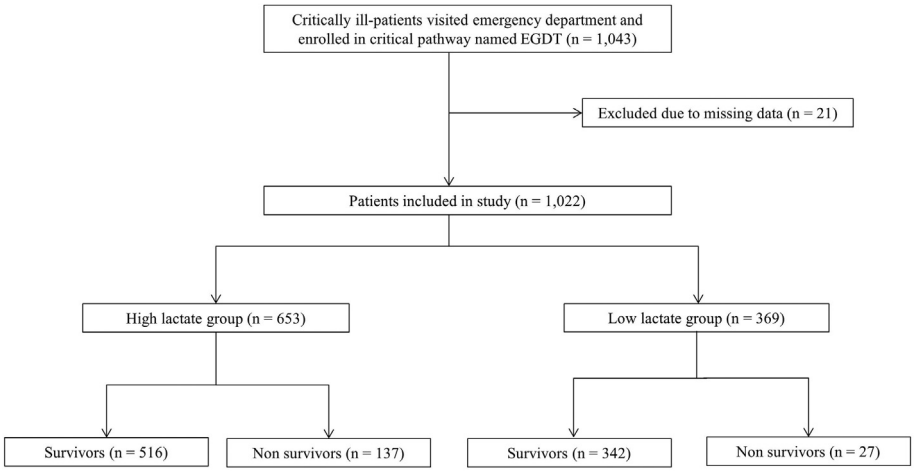


**Figure 1.** Flowchart of patient selection and clinical outcome.

**Table 1** Baseline data of study participants.

| Characteristic | High lactate (n = 653) | Low lactate (n = 369) | *p*-value |
|---|---|---|---|
| Age, years | 66.9 ± 13.4 | 63.6 ± 15.8 | 0.010[a] |
| Male, (%) | 366 (56.0) | 157 (42.5) | <0.001[b] |
| Underlying disease, yes (%) | | | |
| Malignancy | 238 (36.4) | 111 (30.1) | 0.040[b] |
| Transplantation | 8 (1.2) | 6 (1.6) | 0.780[b] |
| Chronic heart failure | 44 (6.7) | 31 (8.4) | 0.602[b] |
| Cardiovascular attack | 101 (15.5) | 61 (16.5) | 0.657[b] |
| Hypertension | 355 (54.4) | 175 (47.6) | 0.049[b] |
| Dementia | 34 (5.2) | 15 (4.1) | 0.449[b] |
| HIV infection | 0 (0.0) | 1 (0.3) | 0.361[b] |
| Chronic kidney disease | 98 (15.0) | 55 (14.9) | 0.533[b] |
| Chronic liver disease | 61 (9.3) | 25 (6.8) | 0.162[b] |
| Chronic lung disease | 82 (12.6) | 57 (15.5) | 0.216[b] |
| Autoimmune disease | 24 (3.7) | 19 (5.1) | 0.330[b] |
| DM | 240 (36.8) | 100 (27.1) | 0.002[b] |
| SOFA score | 9.08 ± 3.03 | 6.97 ± 2.32 | <0.001[a] |
| APACHEII score | 18.56 ± 7.15 | 14.02 ± 5.97 | <0.001[a] |
| MAP initial, mmHg | 66.4 ± 16.0 | 65.5 ± 12.9 | 0.369[a] |
| CVP initial, $cmH_2O$ | 9.6± 5.3 | 9.6 ± 5.0 | 0.919[a] |
| $ScvO_2$ initial, % | 80.2 (72.0–88.3) | 83.8 (76.0–94.5) | <0.001[c] |
| Laboratory test | | | |
| Lactate, mmol/L | 5.55 ± 3.27 | 1.27 ± 0.44 | <0.001[a] |
| Platelet, $\times 10^3$ cells/$mm^3$ | 159.0 (87.5–247.5) | 214.0 (156.3–290.0) | <0.001[c] |
| CRP, mg/L | 130.0 (59.2–234.0) | 119.0 (59.8–198.3) | 0.152[c] |
| D-dimer, ng/mL | 2589 (1013–6566) | 756 (470–1631) | <0.001[c] |
| BUN, mg/dL | 28.7 (19.2–44.4) | 23.0 (15.6–36.1) | <0.001[c] |
| eGFR (mL $min^{-1} \cdot 1.73\ m^{-2}$) | 39.0 (22.2–60.7) | 53.0 (32.2–75.0) | <0.001[c] |
| Albumin, g/dL | 3.0 ± 0.7 | 3.3 ± 0.7 | <0.001[a] |

[a] Student's *t*-test.
[b] Pearson's $\chi$-test.
[c] Mann–Whitney *U*-test, median (interquartile range).

ED, emergency department; CAOD, coronary artery occlusive disease; HIV, human immunodeficiency virus; DM, diabetes mellitus; SOFA, sepsis-related organ failure assessment; APACHEII, acute physiology and chronic health evaluation II; MAP, mean arterial pressure; CVP, central venous pressure; $ScvO_2$, central venous $O_2$ saturation; CRP, C-reactive protein; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate.
The data were expressed as number (percentage), mean ± SD or number (%) or median (interquartile range).

Please cite this article in press as: Oh DH, et al., Risk factors for mortality in patients with low lactate level and septic shock, Journal of Microbiology, Immunology and Infection (2017), http://dx.doi.org/10.1016/j.jmii.2017.08.009

**Table 2** Clinical response and rate of organ failure in study participants.

| Variables | High lactate (n = 653) | Low lactate (n = 369) | *p*-value |
|---|---|---|---|
| MAP 6h, mmHg | 81.3 ± 14.1 | 84.4 ± 14.6 | 0.028[a] |
| CVP 6h, $cmH_2O$ | 9.5 ± 4.5 | 8.9 ± 4.6 | 0.217[a] |
| $ScvO_2$ 6h, % | 79.6 (71.8–84.8) | 79.2 (74.1–85.3) | 0.664[c] |
| $ScvO_2$ goal, success | 585 (89.6) | 340 (92.1) | 0.221[b] |
| CP goal, success | 332 (50.8) | 162 (43.9) | 0.037[b] |
| Organ failure | | | |
| Renal | 285 (43.6) | 94 (25.5) | <0.001[b] |
| Liver | 107 (16.4) | 13 (3.5) | <0.001[b] |
| Heart | 37 (5.7) | 10 (2.7) | 0.019[b] |
| ARDS | 24 (3.7) | 5 (1.4) | 0.032[b] |
| DIC | 85 (13.0) | 11 (3.0) | <0.001[b] |
| Use of vasopressor | 621 (95.1) | 358 (97.1) | 0.314[b] |
| Hemodialysis | 115 (17.5) | 23 (6.3) | <0.001[b] |
| Ventilator care | 179 (27.4) | 35 (9.5) | <0.001[b] |
| Use of Steroid | 309 (47.3) | 122 (33.0) | <0.001[b] |
| 7-day mortality | 67 (10.3) | 6 (1.6) | <0.001[b] |
| 28-day mortality | 102 (15.6) | 18 (4.9) | <0.001[b] |
| Hospital stay (days) | 13 (7–25) | 10 (7–18) | 0.020[c] |

[a] Student's *t*-test.
[b] Pearson's $\chi$-test.
[c] Mann–Whitney *U*-test, median (interquartile range).
MAP, mean arterial pressure; CVP, central venous pressure; $ScvO_2$, central venous $O_2$ saturation; CP, critical pathway; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation.
The data were expressed as number (percentage), mean ± SD or number (%) or median (interquartile range).

shock were thrombocytopenia and low eGFR were independent (Table 3). The SOFA score was a significant variable for predicting arterial lactate, and it showed a marked positive correlation with serum lactate in simple correlation analysis (r = 0.394, $p < 0.001$) and linear regression ($R^2 = 0.155$, $p < 0.001$; Fig. 2b).

Subgroup analysis of predictive factors for 28-day mortality in the low lactate group was performed. Nine factors were significantly associated with 28-day mortality in univariate analysis: low MAP ($p = 0.009$), low initial $ScvO_2$ ($p = 0.037$), low eGFR ($p = 0.028$), low serum albumin ($p = 0.013$), high CRP ($p = 0.012$), high arterial lactate ($p = 0.037$), high SOFA score ($p < 0.001$), high APACHEII score ($p < 0.001$), and CHF ($p = 0.005$). On multivariate analysis, high APACHEII score (OR, 1.141; 95% CI, 1.047–1.243, $p = 0.003$), high CRP (OR, 1.006; 95% CI, 1.000–1.011, $p = 0.034$) and CHF (OR, 10.244; 95% CI, 2.763–37.980, $p = 0.001$) were significant independent predictive factors for 28-day mortality in patients with low lactate levels (Table 4).

## Discussion

Sepsis is a clinical syndrome of pathophysiologic and biochemical abnormalities induced by infection. The increasing incidence and high mortality rate associated with sepsis is a major public health concern worldwide.[18] The new definition for sepsis emphasizes organ dysfunction and suggests that lactate is an important marker of tissue damage even without hypotension.[4]

As an index for monitoring treatment and predicting prognosis, several variables were proposed such as MAP, lactate level, $ScvO_2$, and CRP. Serum lactate levels and $ScvO_2$ were found to be good prognostic factors in several studies.[19,20] Mikkelsen et al. reported that initial lactate was independently associated with mortality in patients with severe sepsis.[21] Thus, lactate is an important factor in predicting the severity and outcome of septic shock patients, but controversy remains regarding the optimal cut-off value. The universally accepted lactate level representing tissue hypoxia is 4 mmol/L and is often applied when initiating resuscitation in patients with septic shock.[12] However, Bakker and colleagues reported lactate >2 mmol/L to be an independent predictor of mortality in septic shock.[22] In 2015, Casserly et al. reported that patients with lactate >2 mmol/L had significantly higher mortality (42.3% [95% CI, 41.2–43.3]) in risk-adjusted comparisons with other subgroups.[6,23]

Patients in the high lactate group had more severe clinical characteristics and poorer outcomes than those in the low lactate group. Patients in the high lactate group also had higher SOFA score and APACHEII score, and their organ failure was more frequent than those in the low lactate group. In addition, 7-day and 28-day mortality rates were higher in the high lactate group than in the low lactate group. A number of recent studies have shown that high lactate levels are associated with poor clinical outcomes.[21,24] However, a secondary analysis study comparing the prognosis of patients who met the new definition of septic shock to patients who do not meet the new diagnostic criteria, but met the previous diagnostic criteria, was recently published. In this study, low lactate level was the main reason why patients did not meet the new diagnostic criteria. Although patients with high lactate level fulfilled the new diagnostic criteria and had significantly high mortality, patients with lower lactate level also had a mortality rate of 14.4%. This mortality rate was significantly higher than the rates of severe illness, such as stroke and heart diseases.[25] Additionally, several studies were performed on the high mortality rate of patients with hypolactatemia. Nichol and colleagues found that hospital mortality was significantly increased when patients had lactate concentrations >0.75 mmol/L and surviving patients had a median blood lactate concentration of 1.2 mmol/L, while non-survivors had a median lactate concentration of 1.3 mmol/L ($p < 0.001$).[10] Wacharasint et al. reported an increase in mortality with lactate levels >1.4 mmol/L.[11] Therefore, it is necessary to use other variables to substitute for lactate and predict the prognosis of septic shock.

Analysis of the low lactate group revealed high APACHEII score, high CRP, and CHF to be independent prognostic factors for 28-day mortality. Many investigators have demonstrated that the APACHEII score is a prognostic factor influencing mortality in septic shock patients.[11,26] APACHEII score is a significant prognostic factor for mortality because it is result of the calculation includes the main physiologic factors of critically ill patients.[27] CRP is a traditional and frequently used marker of sepsis and its management.

Please cite this article in press as: Oh DH, et al., Risk factors for mortality in patients with low lactate level and septic shock, Journal of Microbiology, Immunology and Infection (2017), http://dx.doi.org/10.1016/j.jmii.2017.08.009

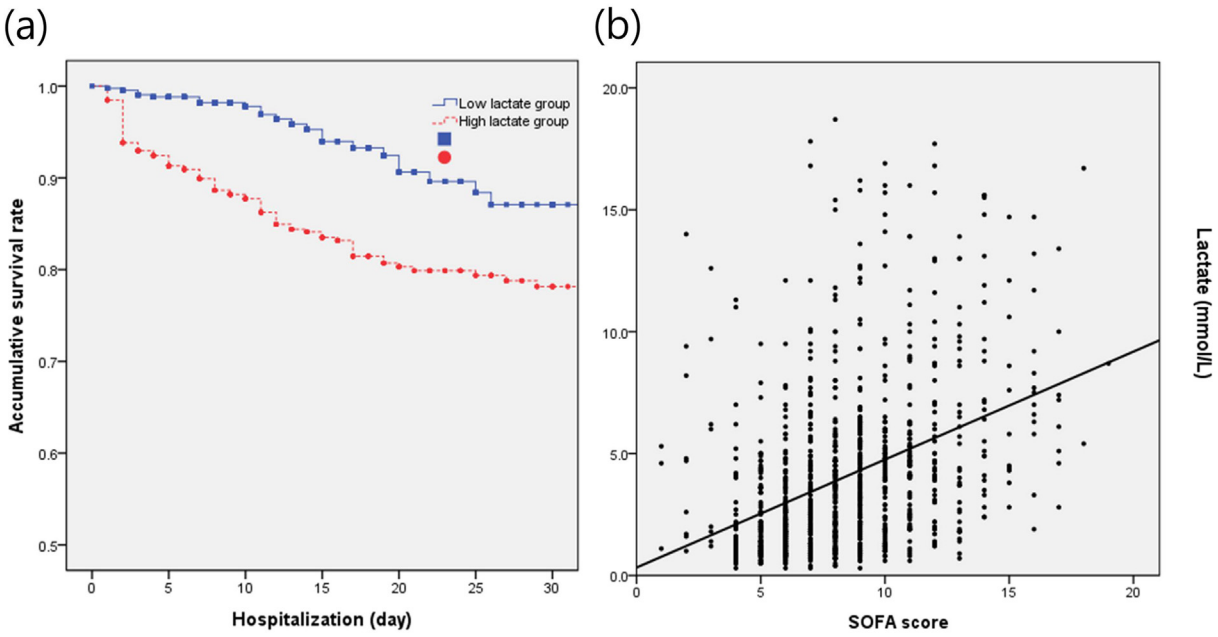


**Figure 2.** (a) Comparison between the high lactate group and low lactate group in 28-day mortality($p < 0.001$) by Kaplan–Meier method, and (b) correlation between serum lactate and SOFA score ($R^2 = 0.155$, $p < 0.001$ by linear regression).

**Table 3** Multivariate analysis of predictive factors for a high level of serum lactate in patients with septic shock.

| Variables | Odds ratio (95% CI) | *p*-value |
|---|---|---|
| Thrombocytopenia[a] | 3.279 (1.374–7.824) | 0.007 |
| eGFR, (mL $min^{-1} \cdot 1.73\ m^{-2}$) | 0.982 (0.969–0.995) | 0.008 |
| High SOFA score group[b] | 2.830 (1.249–6.411) | 0.013 |

[a] Thrombocytopenia is defined as a platelet count under 150,000/$mm^3$.
[b] A SOFA score of 7.5 on the receiver operating characteristic curve was used as the cutoff.
eGFR, estimated glomerular filtration rate; .SOFA, sepsis-related organ failure assessment.

Yentis et al. reported that daily estimation of CRP is very useful in monitoring the success of failure of therapy.[28] The relationship between CHF and the outcomes of septic shock remains unclear; however, decreased heart function negatively affects the outcome of septic shock. Patients in septic shock require more oxygen transport. Therefore, decreased heart function can lead to insufficiency in meeting increased oxygen demands despite decreased systemic vascular resistance resulting from septic shock.[29] The prognostic value of a positive response to dobutamine challenge in septic shock has been demonstrated in several studies.[30,31] In another study, diastolic dysfunction was a strong independent predictor of mortality of septic shock after adjusting for other independent predictors such as age, diabetes mellitus, hypertension, APACHEII score, and concurrent coronary heart disease.[32]

Since lactate cannot be measured in some medical environments, especially outside of critical care settings, and as there were many cases that did not check a lactate at the time of suspected infection, even if measurement thereof was possible, we analyzed variables predicting lactate to evaluate the severity of septic shock in patients in these situations.[6,8] Participants were divided into high and low SOFA score groups based on a cutoff value 7.5. As a result, thrombocytopenia, low eGFR, and high SOFA score group were significant risk factors based on our evaluation. Thiery-Antier et al. reported thrombocytopenia within the first 24 h of septic shock onset as a prognostic marker of 28-day mortality in intensive care unit patients. In multivariate Cox regression, a platelet count $\leq 100.0 \times 10^3$ cells/$mm^3$ was independently associated with significantly increased 28-day mortality. Mortality increased with the severity of thrombocytopenia.[33] In our analysis, incidence of thrombocytopenia was significantly high in the high lactate group and it is a one of the significant risk factor of hyperlactatemia, but not a prognostic marker of 28-day mortality in the subgroup analysis of the low lactate group. Reflecting the pathogenesis of lactic acidosis, decreased renal function can contribute the hyperlactatemia. The kidneys contribute to lactate clearance via excretion, gluconeogenesis, and oxidation, even though they may not be a major component in lactate clearance.[34] SOFA score is of diagnostic value according to the new sepsis definition, and correlates with lactate.[4,19] In our analysis, SOFA score showed a positive correlation with lactate, and was similar to former studies. SOFA score may play an important role in institutions that cannot measure lactate for management of septic shock. A SOFA score of 8 can be a reference point upon consideration of our analysis.

In this study, 28-day mortality was relatively lower than the mortality rates reported in other recent studies.[20,26] In this study, 28-day mortality was 11.7% in all patients. However, total mortality rate in this study was 16.0%. After dividing total mortality by range of lactate, we found that total mortality was 25.6% (103/403) in the patient group

Please cite this article in press as: Oh DH, et al., Risk factors for mortality in patients with low lactate level and septic shock, Journal of Microbiology, Immunology and Infection (2017), http://dx.doi.org/10.1016/j.jmii.2017.08.009

**Table 4** Multivariate analysis of predictive factors for 28-day mortality in patients with low levels of serum lactate.

| Variables | Unadjusted OR (95% CI) | *p*-value | Adjusted OR (95% CI) | *p*-value |
|---|---|---|---|---|
| MAP, mmHg[a] | 0.939 (0.896–0.985) | 0.009 | | |
| $ScvO_2$ initial | 0.964 (0.932–0.998) | 0.037 | | |
| eGFR, (mL $min^{-1} \cdot 1.73\ m^{-2}$) | 0.980 (0.962–0.998) | 0.028 | | |
| Albumin, mg/dL | 0.431 (0.222–0.835) | 0.013 | | |
| CRP, mg/L | 1.006 (1.001–1.010) | 0.012 | 1.006 (1.000–1.011) | 0.034 |
| Lactate, mmol/L | 3.366 (1.073–10.555) | 0.037 | | |
| SOFA score | 1.446 (1.198–1.745) | <0.001 | | |
| APACHEII score | 1.156 (1.074–1.243) | <0.001 | 1.141 (1.047–1.243) | 0.003 |
| Chronic heart failure | 4.808 (1.591–14.531) | 0.005 | 10.244 (2.763–37.980) | 0.001 |

[a] At the time of admission to the emergency department.
MAP, mean arterial pressure; $ScvO_2$, central venous $O_2$ saturation; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; APACHEII, acute physiology and chronic health evaluation II; OR, odds ratio; CI, confidence interval.

with lactate >4 mmol/L, which was significantly higher than mortality of the patient group with lactate <1 mmol/L (5.8%, 8/138, $p < 0.001$). Additionally, the relatively high number of patients with urinary tract infection who were known to have a good prognosis could be a reason (n = 294, 28.8%). In other words, these results indicate that lactate is a reliable prognostic marker in septic shock patients.

This study had several limitations. First, the clinical and biological data used in this study were collected from a single center. Second, nosocomial infections were excluded due to the collection of data from ED admissions. For the same reason, there is a possibility for selection bias. Since the initiation of CP was mainly dependent on the decision of physicians at the ED, their subjective judgment may have interfered with CP enrollment. Third, patients who needed emergency surgery with a high likelihood of septic shock were excluded from the study. Patients who needed emergency surgery were excluded in CP protocol design since the initial 6-h management bundle was difficult to apply in the same environment as other patients. However, it is not necessary to maintain the existing 6-h bundle when managing patients with septic shock according to the recently revised SSC guideline.[35] Therefore, it may be possible to enroll patients who require emergency surgery in CP in future protocol revision and research design. Finally, since this was a long-term period study, changes in medical devices, techniques, and antibiotics over time were not entirely reflected. However, this study has been carefully conducted and includes a significant number of participants while considering strict definition of septic shock. In addition, we found that the predictive power for key variables was sufficiently high in the final multivariate logistic regression model.

Our study demonstrates that arterial lactate level is a very reliable diagnostic and prognostic predictor of septic shock. SOFA score correlated well with arterial lactate. However, there were not inconsiderable cases of mortality in patients without hyperlactatemia. In the low lactate group, high APACHEII score, high CRP, and CHF affected the mortality rate independently. Re-examination of arterial lactate should be considered when treating patients with suspected septic shock and low arterial lactate, if the patient has high APACHEII score, high CRP, and CHF. Further studies are needed that will identify other predictive factors for high-risk cases of septic shock without hyperlactatemia.

## Disclosure of interest

All authors reported no conflict of interest.

## Acknowledgements

We appreciate to all critical care physicians and medical staffs of the Sevrance hospital, Yonsei University College of Medicine.

## References

1. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;**101**:1644–55.
2. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;**31**:1250–6.
3. Deutschman CS, Tracey KJ. Sepsis: current dogma and new perspectives. *Immunity* 2014;**40**:463–75.
4. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;**315**:801–10.
5. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;**315**:762–74.
6. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;**315**:775–87.
7. Suetrong B, Walley KR. Lactic acidosis in sepsis: it's not all anaerobic: implications for diagnosis and management. *Chest* 2016;**149**:252–61.
8. Rhee C, Murphy MV, Li L, Platt R, Klompas M. Lactate testing in suspected sepsis: trends and predictors of failure to measure levels. *Crit Care Med* 2015;**43**:1669–76.

Please cite this article in press as: Oh DH, et al., Risk factors for mortality in patients with low lactate level and septic shock, Journal of Microbiology, Immunology and Infection (2017), http://dx.doi.org/10.1016/j.jmii.2017.08.009

9. Shankar-Hari M, Bertolini G, Brunkhorst FM, Bellomo R, Annane D, Deutschman CS, et al. Judging quality of current septic shock definitions and criteria. *Crit Care* 2015;**19**:445.
10. Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. *Crit Care* 2010; **14**:R25.
11. Wacharasint P, Nakada TA, Boyd JH, Russell JA, Walley KR. Normal-range blood lactate concentration in septic shock is prognostic and predictive. *Shock* 2012;**38**:4—10.
12. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;**41**:580—637.
13. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001;**286**:1754—8.
14. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;**307**:2526—33.
15. Craig DG, Reid TW, Wright EC, Martin KG, Davidson JS, Hayes PC, et al. The sequential organ failure assessment (SOFA) score is prognostically superior to the model for end-stage liver disease (MELD) and MELD variants following paracetamol (acetaminophen) overdose. *Aliment Pharmacol Ther* 2012;**35**:705—13.
16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;**28**. 1-39e14.
17. Taylor Jr FB, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001;**86**:1327—30.
18. Vincent JL, Marshall JC, Namendys-Silva SA, Francois B, Martin-Loeches I, Lipman J, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. *Lancet Respir Med* 2014;**2**:380—6.
19. Houwink AP, Rijkenberg S, Bosman RJ, van der Voort PH. The association between lactate, mean arterial pressure, central venous oxygen saturation and peripheral temperature and mortality in severe sepsis: a retrospective cohort analysis. *Crit Care* 2016;**20**:56.
20. Lee YK, Hwang SY, Shin TG, Jo IJ, Suh GY, Jeon K. Prognostic value of lactate and central venous oxygen saturation after early resuscitation in sepsis patients. *PLoS One* 2016;**11**, e0153305.
21. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med* 2009;**37**:1670—7.
22. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg* 1996;**171**:221—6.
23. Casserly B, Phillips GS, Schorr C, Dellinger RP, Townsend SR, Osborn TM, et al. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the surviving sepsis Campaign database. *Crit Care Med* 2015;**43**:567—73.
24. Goyal N, Taylor AR, Rivers EP. Relationship between central and peripheral venous oxygen saturation and lactate levels: a prospective study. *J Emerg Med* 2016. http://dx.doi.org/10.1016/j.jemermed.2016.03.021.
25. Sterling SA, Puskarich MA, Glass AF, Guirgis F, Jones AE. The impact of the Sepsis-3 septic shock definition on previously defined septic shock patients. *Crit Care Med* 2017. http://dx.doi.org/10.1097/CCM.0000000000002512.
26. Huang CT, Tsai YJ, Tsai PR, Yu CJ, Ko WJ. Severe sepsis and septic shock: timing of septic shock onset matters. *Shock* 2016; **45**:518—24.
27. Ho KM, Dobb GJ, Knuiman M, Finn J, Lee KY, Webb SA. A comparison of admission and worst 24-hour acute physiology and chronic health evaluation II scores in predicting hospital mortality: a retrospective cohort study. *Crit Care* 2006;**10**:R4.
28. Yentis SM, Soni N, Sheldon J. C-reactive protein as an indicator of resolution of sepsis in the intensive care unit. *Intensive Care Med* 1995;**21**:602—5.
29. Kimmoun A, Ducrocq N, Mory S, Delfosse R, Muller L, Perez P, et al. Cardiac contractile reserve parameters are related to prognosis in septic shock. *Biomed Res Int* 2013;**2013**, 930673.
30. Hayes MA, Timmins AC, Yau EH, Palazzo M, Watson D, Hinds CJ. Oxygen transport patterns in patients with sepsis syndrome or septic shock: influence of treatment and relationship to outcome. *Crit Care Med* 1997;**25**:926—36.
31. Kumar A, Schupp E, Bunnell E, Ali A, Milcarek B, Parrillo JE. Cardiovascular response to dobutamine stress predicts outcome in severe sepsis and septic shock. *Crit Care* 2008; **12**:R35.
32. Ognibene FP, Parker MM, Natanson C, Shelhamer JH, Parrillo JE. Depressed left ventricular performance. Response to volume infusion in patients with sepsis and septic shock. *Chest* 1988;**93**:903—10.
33. Thiery-Antier N, Binquet C, Vinault S, Meziani F, Boisrame-Helms J, Quenot JP, et al. Is thrombocytopenia an early prognostic marker in septic shock? *Crit Care Med* 2016;**44**: 764—72.
34. Luft FC. Lactic acidosis update for critical care clinicians. *J Am Soc Nephrol* 2001;**12**(Suppl. 17):S15—9.
35. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017. http://dx.doi.org/10.1097/CCM.0000000000002255.

Please cite this article in press as: Oh DH, et al., Risk factors for mortality in patients with low lactate level and septic shock, Journal of Microbiology, Immunology and Infection (2017), http://dx.doi.org/10.1016/j.jmii.2017.08.009