COMPREHENSIVE INTERPRETATION OF CENTRAL VENOUS OXYGEN SATURATION AND BLOOD LACTATE LEVELS DURING RESUSCITATION OF PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK IN THE EMERGENCY DEPARTMENT

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ABSTRACT—Objectives: We evaluated central venous oxygen saturation (ScvO2) and lactate levels as a combination measure to predict mortality in patients with severe sepsis or septic shock. Methods: We included patients older than 18 years of age who presented to a single tertiary emergency center with septic shock or severe sepsis and received early goal-directed therapy. We classified the sample into four groups according to lactate (cut-off: 4 mmol/L) and ScvO2 (cut-off: 70%) levels at the time of initial resuscitation: Group 1, high-ScvO2 and low-lactate; Group 2, low-ScvO2 and low-lactate; Group 3, high-ScvO2, and high-lactate; Group 4, low-ScvO2, and high-lactate. The primary outcome was 28-day mortality determined by multivariable Cox-regression analysis. Results: A total of 880 patients were included in this study. The 28-day mortality was 6.7% in Group 1, 15.7% in Group 2, 26.7% in Group 3, and 25.5% in Group 4 (P < 0.01). Compared with Group 1, all other groups showed significant differences in mortality (P < 0.01 by the log-rank test). There was, however, no difference between Groups 3 and 4. Multivariable Cox regression analysis showed that all other groups exhibited significantly increased hazard ratios for 28-day mortality, compared with Group 1. Conclusions: Oxygenation category, as represented by initial ScvO2 and lactate levels, was significantly associated with 28-day mortality in patients with severe sepsis or septic shock. Associations between ScvO2 ≥ 70% and 28-day survival were observed only in patients without severe lactic acidosis.

KEYWORDS—Central venous oxygen saturation, lactate, sepsis, septic shock

INTRODUCTION

Severe sepsis and septic shock are life-threatening conditions associated with inadequate tissue perfusion and hypoxia leading to irreversible organ dysfunction (1–3). To achieve optimal hemodynamic status and improve outcomes, the use of an early resuscitation strategy with fluid administration and vasopressors is an important step in the management of severe sepsis and septic shock (1, 4). Several resuscitation targets can be used during this critical resuscitation period to optimize oxygen delivery and predict outcomes (5–8).

Central venous oxygen saturation (ScvO2) has been widely used as a surrogate marker of the balance between oxygen delivery and consumption since Rivers et al. (9) first proposed early goal-directed therapy (EGDT) (10–12). Lactate is also a useful biomarker of tissue hypoxia and anaerobic metabolism because of cellular decompensation, reflecting disease severity (5, 13), and lactate clearance can be used as a therapeutic target instead of ScvO2 (8, 14, 15). Current clinical trials, however, have shown that EGDT targeting ScvO2 fails to improve outcomes compared with usual care or lactate-based protocols, and that no target or protocol is clearly superior (15–18).

The two general biomarkers, ScvO2 and lactate levels, are currently used during resuscitation of patients with septic shock (19), but more comprehensive interpretations might be required in the clinical context. Dependence on a single index might lead to inappropriate therapeutic decisions or outcome predictions because the values are often nonspecific, and because normal values for these markers do not ensure favorable outcomes in patients with sepsis (3, 11–13, 20, 21). Furthermore, the levels of the two markers can also predict contradictory outcomes (21, 22).

Although there is debate regarding the optimal goal of resuscitation in sepsis, we tried to interpret ScvO2 and lactate as complementary rather than exclusive (6, 23). The aim of this study was to investigate the relationships between global oxygenation status as evaluated by combined assessments of ScvO2-lactate levels and outcomes in patients with severe sepsis and septic shock.

METHODS

We analyzed data from the sepsis registry for patients presenting to the emergency department (ED) at Samsung Medical Center (a 1,960-bed, university-affiliated, tertiary referral hospital with 70,000 annual ED visits in Seoul, South Korea). Data for patients presenting with severe sepsis or septic shock were prospectively collected from August 2008 to September 2014. We used the same sepsis registry in previous studies regarding the management of severe sepsis and septic shock (24–29). This study was approved by the institutional review board of Samsung Medical Center. The requirement for informed consent was waived because of the retrospective, observational, and anonymous nature of the study.

Study population

We included patients 18 years of age or older who presented to the ED with septic shock or severe sepsis and who received EGDT. Sepsis was defined as suspected or confirmed infection in the presence of two or more systemic inflammatory response syndrome (SIRS) criteria (30). Severe sepsis was defined as sepsis associated with acute organ dysfunction. Septic shock was defined as sepsis that presented with hypotension (systolic blood...
pressure <90 mmHg, mean arterial pressure [MAP] <60 mmHg, or a reduction in systolic blood pressure of >40 mmHg from baseline) despite adequate fluid resuscitation (31).

Exclusion criteria were as follows: terminal malignancy, patients who previously signed “Do Not Resuscitate” orders or refused invasive interventions, patients who did not receive goal-directed therapy targeting ScvO₂, and patients who did not undergo initial paired measurements of lactate and ScvO₂.

We classified patients into four groups according to specific cutoff values of the first lactate and ScvO₂ levels measured at the time of initial resuscitation: Group 1, ScvO₂ ≥70% and lactate <4 mmol/L (high-ScvO₂ and low-lactate); Group 2, ScvO₂ ≥70% and lactate <4 mmol/L (low-ScvO₂ and low-lactate); Group 3, ScvO₂ ≥70% and lactate ≥4 mmol/L (high-ScvO₂ and high-lactate); Group 4, ScvO₂ ≥70% and lactate ≥4 mmol/L (low-ScvO₂ and high-lactate). The cutoff values for lactate and ScvO₂ were determined according to thresholds of tissue hypoperfusion and global hypoxia used by previous studies and that were recommended by SSC guidelines (8, 10–13).

Outcome measurements
The primary endpoint was 28-day mortality, and the secondary endpoint was in-hospital mortality.

Data collection
During the study period, a resuscitation protocol based on the protocol by Rivers et al. (8, 9, 32) and on the 2008 or 2012 Surviving Sepsis Campaign (SSC) guidelines was implemented for patients with severe sepsis or septic shock. Once a patient met the criteria for severe sepsis or septic shock, fluid resuscitation and hemodynamic monitoring were initiated with placement of a central venous catheter for central venous pressure and ScvO₂ monitoring. ScvO₂ levels were intermittently measured by a standard blood gas analyzer in the ED. Serum lactate concentrations were measured by the hospital’s central laboratory when patients arrived at the ED, and subsequent serum lactate measurements were repeated at the time of initial resuscitation.

The following data were obtained from our sepsis registry and electronic medical records: patient characteristics, comorbidities, vital signs, sites of infection, laboratory data, use of vasopressors, mechanical ventilation, and length of stay (LOS) in the intensive care unit (ICU). Sequential Organ Failure Assessment (SOFA) scores were calculated at the time that severe sepsis or septic shock was diagnosed, as were Acute Physiology and Chronic Health evaluation (APACHE) II scores (33, 34).

A total of 880 patients were included in this study (Figure 1). Patients who were missing paired data and were not treated with EGDT were excluded. Compared with excluded patients, included patients had more severe shock (overt shock) and more organ failures, although there were no significant differences in comorbidities or sources of infection. Of the eligible patients, 282 (32.0%) were assigned to Group 1, 249 (28.3%) to Group 2, 165 (18.8%) to Group 3, and 184 (20.9%) to Group 4. Comparisons of lactate and ScvO₂ levels are shown in Table 1. In all 880 patients, the median lactate level was 3.2 mmol/L (IQR, 1.9–5.2) and the median ScvO₂ was 70.1% (IQR, 63.2–76.2).

A comparison of baseline characteristics among the four groups is summarized in Table 2. Among the groups, there were significant differences in age, the presence of metastatic solid cancer, focus of infection, initial MAP, respiratory rate, initial

**Table 1. Initial values of lactate and ScvO₂**

<table>
<thead>
<tr>
<th></th>
<th>Overall group (n = 880)</th>
<th>Group 1 (n = 282)</th>
<th>Group 2 (n = 249)</th>
<th>Group 3 (n = 165)</th>
<th>Group 4 (n = 184)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate (mmol/L)</td>
<td>3.2 (1.9–5.2)</td>
<td>2.0 (1.2–2.9)</td>
<td>2.2 (1.6–3.1)</td>
<td>5.7 (4.7–7.7)</td>
<td>5.7 (4.8–7.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ScvO₂ (%)</td>
<td>70.1 (63.2–76.2)</td>
<td>75.4 (72.7–79.8)</td>
<td>63.7 (58.1–67.0)</td>
<td>77.7 (73.5–82.0)</td>
<td>61.5 (54.2–65.6)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are shown as medians with interquartile ranges.

**Statistical analysis**
Data are presented as medians with interquartile ranges (IQR) for numeric data and numbers with percentages for categorical data. Continuous variables were compared using the Kruskal–Wallis rank test or the Wilcoxon rank-sum test according to the number of groups. Categorical variables were compared with the chi-square test. A multivariable Cox regression analysis was used to evaluate independent predictive factors for mortality, with an adjustment for variables that were found to be statistically significant at P < 0.02 using univariate analysis. Collinearity between variables was assessed to ensure that no significant collinearity was present. The results were described as the hazard ratio (HR) with a 95% confidence interval (CI).

Kaplan–Meier curves were plotted to show survival trends, and the log-rank test was used. P-values less than 0.05 were considered significant. For all multiple comparisons, P-values were calculated by applying a Bonferroni correction. STATA 11.0 (STATA Corporation, College Station, TX) was used for statistical analysis.

**RESULTS**

**Baseline characteristics**
A total of 880 patients were included in this study (Figure 1). Patients who were missing paired data and were not treated with EGDT were excluded. Compared with excluded patients, included patients had more severe shock (overt shock) and more organ failures, although there were no significant differences in comorbidities or sources of infection. Of the eligible patients, 282 (32.0%) were assigned to Group 1, 249 (28.3%) to Group 2, 165 (18.8%) to Group 3, and 184 (20.9%) to Group 4. Comparisons of lactate and ScvO₂ levels are shown in Table 1. In all 880 patients, the median lactate level was 3.2 mmol/L (IQR, 1.9–5.2) and the median ScvO₂ was 70.1% (IQR, 63.2–76.2).
presentation with septic shock, use of mechanical ventilation, SOFA score, APACHE II score, and ICU LOS. Patients who initially presented with septic shock were more frequent in Groups 1 and 2, but there were no differences among the groups in use of vasoppressors. Initial SOFA scores were higher in Groups 1 and 2, but there were no differences among the groups initially presented with septic shock were more frequent in Groups 1 and 2, but there were no differences among the groups in use of vasopressors. Initial SOFA scores were higher in Groups 1 and 2, but there were no differences among the groups initially presented with septic shock were more frequent in Groups 1 and 2, but there were no differences among the groups in use of vasopressors. Initial SOFA scores were higher in Groups 1 and 2, but there were no differences among the groups.

Crude mortality

The overall 28-day mortality was 16.9% and in-hospital mortality was 18.1%. The 28-day mortality was 6.7% in Group 1, 15.7% in Group 2, 26.7% in Group 3, and 25.5% in Group 4 (P < 0.01) (Figure 2). Compared with Group 1, all other groups showed significantly higher rates of mortality. The mortality of Group 3 was the highest, although Group 3 included patients with values of ScvO₂ > 70%.

Figure 3 shows the survival curves of the four groups. There were significant differences in survival times between groups (P < 0.01 by the log-rank test). Compared with Group 1, all other groups showed significant differences in survival (P < 0.01 by the log-rank test). There was, however, no significant difference between Groups 3 and 4.

Regression analysis adjusting for potential confounders

Multivariable Cox regression analysis showed that all groups exhibited increased hazard ratios for 28-day mortality, compared with Group 1 (Table 3). The adjusted HRs were 2.02 (95% CI, 1.16–3.52; P = 0.02) in Group 2, 3.21 (95% CI, 1.86–5.73; P < 0.01) in Group 3, and 3.17 (95% CI, 1.85–5.45; P < 0.01) in Group 4.

Mortality according to ScvO₂ values by quartiles

Figure 4 shows the 28-day mortality according to ScvO₂ values by quartile and the presence of severe lactic acidosis. The highest survival was observed in the third quartile of the ScvO₂ (70.2 to 76.2%) in the sample as a whole, and in patients with lactate concentrations <4 mmol/L. In patients with lactate concentrations <4 mmol/L, the 28-day mortality was 6.7% in Group 1, 15.7% in Group 2, 26.7% in Group 3, and 25.5% in Group 4 (P < 0.01) by the log-rank test. Compared with Group 1, all other groups showed significantly higher mortality rates.

Figure 4 shows the 28-day mortality according to ScvO₂ values by quartile and the presence of severe lactic acidosis. The highest survival was observed in the third quartile of the ScvO₂ (70.2 to 76.2%) in the sample as a whole, and in patients with lactate concentrations <4 mmol/L. In patients with lactate concentrations <4 mmol/L, the 28-day mortality was 6.7% in Group 1, 15.7% in Group 2, 26.7% in Group 3, and 25.5% in Group 4 (P < 0.01) by the log-rank test. Compared with Group 1, all other groups showed significantly higher mortality rates.

FIG. 2. Comparison of 28-day mortality and in-hospital mortality (\(P < 0.05\) compared with Group 1 after Bonferroni correction).
concentrations <4 mmol/L, there was a significant difference in 28-day mortality between the lower two quartiles and the higher two quartiles (P < 0.01). In patients with lactate concentrations ≥4 mmol/L, however, the fourth quartile (76.3 to 98.2%), showing hyperoxia, as well as the first quartile (12.7 to 63.1%), showing hypoxia, had higher rates of 28-day mortality.

**DISCUSSION**

ScvO₂ and lactate are widely used as targets of initial resuscitation in patients with severe sepsis and septic shock (5, 8, 23). These targets, however, have inherent limitations because of their nonspecific natures, and there can be discrepancies between outcomes predicted by the two biomarkers (3, 21–23). We found that categorization of patients by the complementary use of the two global indexes for tissue oxygenation provided useful information about patient outcomes.

Recent clinical trials have shown that strict adherence to the EGDT protocol, including optimization of ScvO₂ ≥70%, does not lead to better outcomes compared with usual care (16–18). The sepsis bundles according to the SSC Committee have been revised, and the importance of ScvO₂ as a resuscitation target has been deemphasized (19). ScvO₂, however, can be used as an alternative index together with other modalities because there is

### TABLE 3. Cox regression analysis for mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td><strong>Subgroup</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>2.42 (1.40–4.20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Group 3</td>
<td>4.48 (2.61–7.67)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Group 4</td>
<td>4.29 (2.52–7.31)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>1.11 (0.80–1.54)</td>
<td>0.51</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.01 (0.73–1.40)</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.88 (0.62–1.25)</td>
<td>0.47</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.02 (0.69–1.51)</td>
<td>0.91</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1.53 (0.97–2.41)</td>
<td>0.07</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1.36 (0.72–2.59)</td>
<td>0.35</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>1.13 (0.52–2.41)</td>
<td>0.76</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>1.24 (0.67–2.28)</td>
<td>0.50</td>
</tr>
<tr>
<td>Metastatic solid cancer</td>
<td>1.74 (1.24–2.43)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>1.02 (0.59–1.77)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Suspected infection focus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-abdominal infection</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.61 (1.11–2.36)</td>
<td>0.01</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0.24 (0.09–0.67)</td>
<td>0.01</td>
</tr>
<tr>
<td>Others</td>
<td>1.45 (0.91–2.27)</td>
<td>0.12</td>
</tr>
<tr>
<td>Use of vasopressors</td>
<td>2.01 (1.25–3.44)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>3.30 (2.27–4.81)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SOFA score (+1)</td>
<td>1.18 (1.13–1.24)</td>
<td>&lt;0.01</td>
</tr>
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</table>

CI, confidence interval; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment.
no outstanding marker of need for initial resuscitation, and no definite harmful effects of ScvO₂ measurements were demonstrated in a previous trial (19). We find that ScvO₂ during resuscitation has some limitations as a single target and can predict mortality only in patients without severe lactic acidosis.

As single indexes, static lactate levels or clearance might be better predictors of outcomes than other biomarkers (1, 13, 14). There are, however, potential pitfalls in the interpretation of lactate levels because normal lactate levels are common in patients with septic shock, despite considerable risk of mortality, and lactate kinetics can be affected by many factors (5, 23, 35–37). Therefore, the complementary interpretation of lactate and ScvO₂ might lead to more accurate predictions of underlying pathophysiologic conditions and oxygen delivery than information from a single index. For example, in our study, Group 1 patients might represent relatively normal or compensated metabolic status, Group 2 oxygen deficit status, Group 3 microcirculatory dysfunction status, and Group 4 oxygen debt status (6, 23, 35). The combined use of biomarkers may be a good predictor of early outcomes and a potential indicator for additional therapeutic interventions.

We observed that patients with high ScvO₂ showed mortality comparable to that of patients with low ScvO₂, if both groups had severe lactic acidosis. The results were also similar when we performed additional analyses according to the presence of severe organ failure (higher SOFA scores). This finding is consistent with those of previous studies, showing that high ScvO₂ was associated with mortality (11, 12, 20). When patients remain in this category after initial treatment, it could be interpreted as a status refractory to resuscitation and involve impaired oxygen extraction because of microcirculatory failure or cellular dysfunction (6, 23). What is challenging is that currently, there are no therapeutic options supported by both human trials and experimental studies. Targeting microcirculation and cellular metabolic pathways including mitochondrial function might be beneficial, but these approaches must be validated in future research.

We found that low ScvO₂ is a potential predictor of poor outcomes. In particular, when combined with high lactate levels suggesting poor tissue perfusion, low ScvO₂ was associated with worse outcomes. This is unsurprising, because low ScvO₂ is often associated with pathologic conditions including cardiac dysfunction, pulmonary dysfunction, severe volume depletion, and high tissue oxygen requirements. Low ScvO₂, however, also requires cautious interpretations in the clinical context because low ScvO₂ is often nonspecific.

In a previous study of ICU patients, a lactate cut-off level of 2.2 mmol/L was used to interpret the relationship to ScvO₂ (11). In the present study, in which ScvO₂ and lactate levels were measured earlier in the ED, we used a high cutoff value for lactate (≥4 mmol/L), although intermediate lactate levels (2.0–3.9 mmol/L) are also associated with poor outcomes (13, 29). This method was used because the differences in mortality according to ScvO₂ level were similar between patients with intermediate lactate levels and normal lactate levels, and no differences were observed in patients with higher lactate levels (≥4 mmol/L).

We detected differences in the distribution of septic shock between groups. We suggest two explanations for these findings. First, septic shock is an indication for aggressive resuscitation even in patients with low lactate levels, according to the SSC guidelines (8, 32). High lactate levels ≥4 mmol/L despite the absence of septic shock is another main indication. Second, patients in Group 1 and 2 might have been responders to initial treatment before obtaining paired values of lactate and ScvO₂.

This study has some limitations that should be considered. First, it was conducted at a single center, and the EGDTS was not performed in all eligible patients. Compared with the excluded patients, included patients had more severe shock. These findings might represent real practice, considering current evidence that all patients with septic shock require central venous access and invasive monitoring, but remains one of main limitations of this study (1, 16–18). Therefore, there is a risk of selection bias, and our findings may not be generalizable to other settings. In particular, the cutoff points and the main findings were not validated by internal or external data. Second, we used initial static values of ScvO₂ and lactate for analysis. Dynamic changes of oxygenation category during resuscitation were not analyzed. Third, we were unable to fully evaluate clinical factors that might affect levels of ScvO₂ and lactate, and might have neglected potential confounders including detailed foci of infection. Fourth, we used conventional cutoff values for ScvO₂ and lactate levels, but optimal cutoffs for the study population were calculated using maximum Youden’s indexes and were slightly different from conventional values (4.3 mmol/L of lactate and 71.3% of ScvO₂). Our main findings, however, were not changed by reclassification. Finally, cutoff values should be interpreted in the context of individual patients’ conditions because they may vary depending on the clinical status of patients, including age and comorbidities.

In conclusion, global oxygenation status evaluated by complementary assessments of initial lactate and ScvO₂ levels was significantly associated with 28-day mortality in patients with severe sepsis or septic shock. ScvO₂ ≥70% was a favorable outcome predictor of 28-day mortality in patients without severe lactic acidosis. In patients with severe lactic acidosis, however, ScvO₂ ≥70% had no discriminative value for 28-day mortality.

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