Sequential Organ Failure Assessment Score as the Determinant of Outcome for Patients with Severe Sepsis

Saulius Vosylius, Jurate Sipylaite, Juozas Ivaskevicius

Clinic of Anesthesiology and Intensive Care, Vilnius University, Vilnius, Lithuania

Aim. To evaluate the impact of organ dysfunction in severe sepsis and determine the effectiveness of organ dysfunction scores to discriminate outcome after admission to the intensive care unit (ICU).

Methods. Patients with a diagnosis of severe sepsis and at least one organ dysfunction on the first day in the ICU (n = 117) were included in the prospective observational study. The presence of organ dysfunction was assessed using a Sequential Organ Failure Assessment (SOFA). The severity of illness was assessed using a Simplified Acute Physiology Score (SAPS) II during the first 24 hours after the admission to the ICU. The main outcome was survival status on day 28 after admission to the ICU.

Results. Most common sites of infection were intra-abdominal and respiratory system (77 and 38 cases, respectively). Median SAPS II score on admission was 47 points (25th-75th quartiles range, 37-57 points). Twenty eight days survival rate was 41%. The best discrimination results were shown for cumulative scores with the highest for the SOFA score on day 3 in the ICU. The ability to discriminate outcome on day 1 was weak for the presence of dysfunction in all organ systems except neurological. The discriminative power of organ dysfunction scores increased during the stay in the ICU. Neurological and cardiovascular dysfunctions were the independent risk factors for mortality.

Conclusion. The SOFA scores showed high accuracy in describing the course of organ dysfunction for the patients with severe sepsis. Evolving organ dysfunction following admission to the ICU strongly affected the outcome. Cumulative SOFA scores were better in discriminating outcome compared to single organ dysfunction scores.

Key words: intensive care units; multiple organ failure; sepsis; treatment outcome; mortality

Severe sepsis became a common condition with steadily increasing incidence rate (1,2). It is present in up to 15% of critically ill patients requiring intensive care, and contributes to the impairments of many organ system functions (3,4). Clinically significant organ dysfunction is the reason for supportive care in the intensive care unit (ICU) (5). The severity of inflammatory response and impairment of organ function are the major determinants of the outcome in critically ill septic patients. A trend in the outcome improvement was noted over last decade in several multicenter studies (1,2,6,7).

The severe sepsis is defined as the presence of sepsis and related organ dysfunction. Clinical trials and observational studies usually use a scoring system for the assessment of the severity of organ function impairment. Most popular among them are Sequential Organ Failure Assessment (SOFA) score (8), Logistic Organ Dysfunction System (LODS) (9), and Multiple Organ Dysfunction Score (MODS) (10). All of these systems rely on the number and degree of organ dysfunction. Similar feature for all systems is the measurement of the type and severity of physiologic function derangement by summing the points of dysfunction from six key organ systems: cardiovascular, respiratory, neurological, renal, hepatic, and coagulation.

The assessment of the impact of each organ dysfunction to the outcome of the patients admitted to the ICU with a diagnosis of severe sepsis was undertaken in this study applying a set of reliable statistical methods. The choice of the SOFA system was made because it was created to describe a sequence of complications in septic patients (8). Some multicenter and multinational studies using SOFA system showed different prognostic value of each organ dysfunction and unequal contribution to outcome in general ICU population (5,8,11). Similar investigations in septic patients are lacking. The objectives of the study were to evaluate the impact of organ dysfunction in severe sepsis and to determine the effectiveness of organ dysfunction scores to discriminate outcome after admission to the ICU.

Methods

A prospective observational cohort study was performed in a single medical-surgical ICU of Vilnius University Emergency Hospital. Data collection took place from February 1, 1998, to
The permission for this study was obtained from the local Hospital Ethics Committee. The cohort of 117 patients (5.2% of 2,261 patients in the database) having a diagnosis of severe sepsis with clinically or microbiologically confirmed infection on the first day in the ICU was selected and included to this study. The patients who were readmitted to the ICU during the same hospitalization or stayed in the ICU less than 24 hours were not included. Severe sepsis was defined as sepsis and related dysfunction of at least one organ system. The presence of 6 organ dysfunctions (cardiovascular, neurological, respiratory, renal, hepatic, coagulation) was assessed using a Sequential Organ Failure Assessment (SOFA) score (Table 1) (5). The presence of each organ dysfunction was defined when degree of dysfunction was equal to 1 and more. The most abnormal value for each clinical and laboratory parameters defined when degree of dysfunction was equal to 1 and more. The SOFA score was calculated daily by summing the worst scores of each of the six organ systems during the stay in the ICU. The SOFA score on day 1 and day 3 in the ICU were found. SOFA scores on day 1 and day 3 in the ICU were selected for the assessment of prognosis.

ICU-acquired infection was defined as an infection occurring more than 48 h after the admission to the ICU. In other cases, infections were considered as the infections at the ICU admission. The severity of illness was assessed using the Simplified Acute Physiology Score (SAPS) II during the first 24 hours after the admission to the ICU (13). The SAPS II score is the sum of the points assigned to each of the 17 variables (12 physiological variables, age, type of admission, and 3 underlying diseases) with higher score representing more severe illness. Severe chronic diseases relevant to an infection included: hematological malignancies, metastatic cancer, steroid/immunosuppressive therapy, radio/chemotherapy, chronic renal failure, diabetes mellitus, and cirrhosis. The length of stay in the ICU or hospital was measured as number of days from admission to the ICU to discharge from the ICU and hospital, respectively. The main outcome was the survival status on day 28 after the admission to the ICU. The patients were distributed into two groups according to the 28-day survival status: alive (n = 48) or dead (n = 69).

### Statistical Analysis

Quantitative normally distributed variables were presented as means ± standard deviation (SD) and non-normally distributed variables (age, length of stay, SAPS II score) as medians and the 25th-75th quartiles range. Univariate comparison was performed to compare variables between two groups. The organ dysfunction scores were compared using the unpaired t-test. Categorical variables were expressed as actual numbers and percentages. In all comparisons, p < 0.05 was considered statistically significant. Multivariate logistic regression analysis was applied to determine the independent contribution of organ dysfunction scores to the prediction of the mortality as a dependent variable. The maximum scores for each of the six organ systems were used as independent variables. The regression equation represents how much dependent variable will change with any given change of independent variables constructing a regression line on a scatter diagram. The constant and coefficients (β) for all variables are used in regression equation. Constant signifies the distance above the baseline at which the regression line cuts the vertical axis. The odds ratios with 95% confidence intervals (CI) were used to estimate the association between the independent variables and the dependent variable. The Hosmer-Lemeshow statistic was used to evaluate the calibration, correspondence between observed and predicted mortality, Lower Hosmer-Lemeshow value and higher p value indicate better fit. Good fit was defined as p > 0.05.

The discriminative power of the SOFA scores for the prediction probability of the ICU mortality was tested by the area under the receiver operating characteristic (ROC) curve. The area under the ROC curve summarizes the relationship between sensitivity (number of true positives) and 1-specificity (number of false positives) for all the possible values of the organ dysfunction scores. The area under the ROC curve estimates the ability of the model to assign a higher risk of death to patients who die.

Survival curves were estimated using the Kaplan-Meier method. The patients admitted to the intensive care unit with a diagnosis of severe sepsis were stratified into subgroups according to the number of initial organ dysfunctions. Survival times were measured from the date of the ICU admission until the 28th day. Statistical analysis was performed using the SPSS 10.0 statistical package (SPSS Inc, Chicago, IL, USA).

### Results

Among 117 patients admitted to the ICU with a diagnosis of severe sepsis, the most common sites of infection were intra-abdominal and respiratory (77 and 38 cases, respectively). Urinary tract and soft tissue infection (15 and 8 cases, respectively) and other sites of infections were less common. Forty-two patients had two or more sites of infection on admission. Bacteremia was confirmed in 20 patients. Additionally, ICU-acquired infection was diagnosed in 48 patients. Respiratory and urinary tract infections were diagnosed most frequently (30 and 11 cases, respectively). Intra-abdominal, intra-vascular catheter related, and other sites of infection were less common. Twenty-one patients acquired bloodstream infection during the stay in the ICU.

the hospital 8 (4-25) days. Twenty-eight days survival rate was 41%.

There were 85% of the patients who had two or more organ dysfunctions on day 1. The incidence of organ dysfunction on day 1 was noted more frequently for renal, cardiovascular, and neurological systems (67%, 66%, and 61% of cases, respectively). The abnormalities in respiratory, hepatic, and coagulation function were less common (42%, 41%, and 25% of cases, respectively). During the whole stay in the ICU, cardiovascular (80%), renal (78%), and neurological (76%) dysfunction was the most common.

The lowest scores and small contribution of the coagulation and hepatic systems to the overall SOFA score was noted. SOFA score on day 1 and day 3 were significantly higher in non-survivors than those in survivors (Table 2). There were minor differences in the severity of organ dysfunction on day 1 between two groups of patients. Significant changes in the course of organ dysfunction were observed during the stay in ICU. The non-survivors compared with the survivors had higher organ dysfunction scores for all organ systems (p<0.01), except hepatic.

The trend of the mean SOFA score for the first seven days of ICU stay showed a progressive decrease in the total number of patients and the significant difference of SOFA scores between survivors and non-survivors in each day over the first week in the ICU (Fig. 1). Non-survivors had stable higher SOFA scores on day 1 (p=0.001), and on each subsequent day (p<0.001). SOFA scores were significantly higher in non-survivors on day 1 (p=0.001), and on each subsequent day (p<0.001). SOFA scores are expressed as means ± standard error. Open bars – SOFA score, survivors; closed bars – SOFA score, non-survivors; triangles – number of survivors; squares – number of non-survivors.

Figure 1. Sequential organ failure assessment score as the determinant of outcome for patients with severe sepsis. The trends in daily Sequential Organ Failure Assessment (SOFA) scores for the patients with a diagnosis of severe sepsis over the first seven days in the intensive care unit. The patients are divided in two groups according to 28-day survival status. The SOFA scores were significantly higher in non-survivors on day 1 (p = 0.001), and on each subsequent day (p < 0.001). SOFA scores are expressed as means ± standard error. Open bars – SOFA score, survivors; closed bars – SOFA score, non-survivors; triangles – number of survivors; squares – number of non-survivors.

Table 2. Sequential Organ Failure Assessment (SOFA) scores in severe sepsis patients during stay in the intensive care unit*

<table>
<thead>
<tr>
<th>Organ dysfunction</th>
<th>Day 1</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA score</td>
<td>alive (n=48)</td>
<td>dead (n=69)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>5.2 ± 2.9</td>
<td>7.4 ± 3.4</td>
</tr>
<tr>
<td>Neurological</td>
<td>2.0 ± 1.5</td>
<td>2.0 ± 1.5</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1.8 ± 1.5</td>
<td>3.2 ± 1.4</td>
</tr>
<tr>
<td>Coagulation</td>
<td>0.0 ± 1.4</td>
<td>0.1 ± 1.4</td>
</tr>
<tr>
<td>Renal</td>
<td>0.9 ± 1.4</td>
<td>1.3 ± 1.3</td>
</tr>
<tr>
<td>Hepatic</td>
<td>0.7 ± 0.9</td>
<td>0.8 ± 1.0</td>
</tr>
</tbody>
</table>

*The outcome used was 28-day survival status. Data are expressed as means ± standard deviation.

The discriminative power of organ dysfunction degree defined by Sequential Organ Failure Assessment (SOFA) scores for 117 patients admitted to the intensive care unit with a diagnosis of severe sepsis* is shown in Table 3. The SOFA score on day 1 was weak for the presence of dysfunction in all organ systems except for neurological. However, the discriminative power of organ dysfunction scores increased over the stay in ICU. The mortality became significantly related to the severity of dysfunction in each organ system during stay in the ICU except for hepatic system with most significant values for cardiovascular and neurological system. The best discriminative results were shown for cumulative scores with the highest for the SOFA score on day 3, less for the SOFA score on day 1. The discriminative power of the Sequential Organ Failure Assessment (SOFA) scores daily during the first week in the ICU. In survivors, organ dysfunction declined gradually as reflected by decreasing mean daily SOFA scores over the first week.

In the evaluation of the discriminative power of the SOFA scores, the area under the ROC was used (Table 3). The ability to discriminate outcome on day 1 was weak for the presence of dysfunction in all organ systems except for neurological. However, the discriminative power of organ dysfunction scores increased over the stay in ICU. The mortality became significantly related to the severity of dysfunction in each organ system during stay in the ICU except for hepatic system with most significant values for cardiovascular and neurological system. The best discriminative results were shown for cumulative scores with the highest for the SOFA score on day 3, less for the SOFA score on day 1. The discriminative power of the Sequential Organ Failure Assessment (SOFA) scores daily during the first week in the ICU. In survivors, organ dysfunction declined gradually as reflected by decreasing mean daily SOFA scores over the first week.

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Table 3. Discriminative power of organ dysfunction degree defined by Sequential Organ Failure Assessment (SOFA) scores for 117 patients admitted to the intensive care unit with a diagnosis of severe sepsis*

<table>
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<tr>
<th>Organ dysfunction</th>
<th>Day 1</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA score</td>
<td>alive (n=48)</td>
<td>dead (n=69)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.60 (0.49-0.66)</td>
<td>0.092</td>
</tr>
<tr>
<td>Neurological</td>
<td>0.63 (0.53-0.74)</td>
<td>0.011</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0.56 (0.46-0.67)</td>
<td>0.248</td>
</tr>
<tr>
<td>Coagulation</td>
<td>0.59 (0.49-0.69)</td>
<td>0.097</td>
</tr>
<tr>
<td>Renal</td>
<td>0.59 (0.49-0.69)</td>
<td>0.100</td>
</tr>
<tr>
<td>Hepatic</td>
<td>0.51 (0.41-0.62)</td>
<td>0.790</td>
</tr>
</tbody>
</table>

*The outcome used was 28-day survival status. ROC – receiver operating characteristic.

SAPS II score was 0.691 (95% CI 0.594-0.787, standard error 0.049, p<0.001).

A multivariate logistic regression analysis was used to evaluate the relative independent contribution to the outcome. Among different organ system scores on day 1, only neurological dysfunction carried the highest significant correlation with risk of mortality (odds ratio, 1.490; 95%CI 1.057-2.099; p=0.023). The contribution of the maximum score of each organ system dysfunction during stay in the ICU is shown in Table 4. Neurological and cardiovascular dysfunction were associated with the highest contribution to the outcome (p<0.001).

Kaplan-Meier survival analysis showed that the subgroups of patients with three and higher number of organ systems with dysfunction had a lower survival rate than the subgroups of patients with one or two organ systems with dysfunction (Fig. 2).
Table 4. Relative contribution of the maximum value of organ dysfunction to the outcome during stay of 117 patients with a diagnosis of severe sepsis in the intensive care unit for each of the six components of the Sequential Organ Failure Assessment (SOFA).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nagelkerke R²</th>
<th>Odds ratio (95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>0.561</td>
<td>2.492 (1.621-3.833)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2.111 (1.435-3.105)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>1.143 (0.798-1.636)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>1.119 (0.744-1.682)</td>
<td></td>
</tr>
<tr>
<td>Coagulation</td>
<td>1.269 (0.726-2.217)</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>1.333 (0.793-2.309)</td>
<td></td>
</tr>
</tbody>
</table>

The outcome used was 28-day survival status.

Figure 2. Sequential organ failure assessment score as the determinant of outcome for patients with severe sepsis. Kaplan-Meier estimates of the cumulative probability of survival stratified by the number of initial organ dysfunction for patients admitted to the intensive care unit with a diagnosis of severe sepsis. Comparison of the cumulative survival estimates over the hospital stay for patients with one (n=1), two (n=2), three (n=3), or four and more (n≥4) organ dysfunctions.

**Discussion**

The results of the present study showed that the changes in the severity of organ dysfunction were closely related to the outcome of the patients admitted to ICU with diagnosis of severe sepsis. Initial and daily scores outlined the baseline and evolution in the severity of disease. Increasing organ dysfunction scores and cumulative SOFA scores reflected the worsening function in organ systems during the course of severe sepsis mostly in non-surviving patients. The SOFA score on day 3 was better compared with SOFA score on day 1 as the tool for outcome prediction.

Some degree of organ dysfunction necessitating active treatment is frequently present in a majority of critically ill patients. The assessment of organ dysfunction scores are often used to determine the baseline severity of illness and the pattern of changes in organ function over the course of various critical illnesses. In this study we evaluated organ dysfunction using the SOFA system. This system was developed as a tool for sepsis-related organ failure assessment (8). Further, it was validated in general ICU population in subsequent multicenter studies showing the best results (5,8,11). The SOFA system was also applied to many other diagnostic groups of the ICU patients (medical, cardiac, trauma, pancreatitis, acute renal failure, and hematological malignancy) (14-18). When comparisons were made among organ dysfunction systems in the predictive ability of outcome, SOFA system showed highest values (18-20). The results of our study confirmed that the SOFA score is a good tool for assessing the impact of organ dysfunction in severe sepsis.

An initial wave of dysfunction due to the presence of infection on admission to the ICU is most commonly observed in main vital organ functions (cardiovascular, respiratory, and neurological). All our patients with severe sepsis had at least one organ dysfunction. A significant proportion of the patients acquired infection during stay in the ICU. An inflammatory response to new acquired infection episodes additionally to the initial septic insult or inadequate resuscitation is the most likely mechanism causing a second wave of organ dysfunction. The emergence of more severe organ dysfunction was strongly associated with mortality. So measurements of sepsis-related evolving organ dysfunction are clearly needed during the course of intensive care (on admission, daily, maximal scores) to follow organ function over time (21-23).

The incidence of organ dysfunctions varies according to the definition and the case-mix. For the patients with severe sepsis cardiovascular, respiratory, neurological, and renal dysfunctions were most common. Hematological and hepatic dysfunction was less common. Respiratory dysfunction, especially its mild form, was found less frequently than expected in our study. It could be related to the existing practice to take arterial blood samples for blood gas analysis routinely only for most severe cases. In the multicenter study of working group on sepsis-related problems of the European Society of Intensive Care Medicine which involved all ICU patients the incidence rate of organ dysfunction was highest also for respiratory, neurological, and renal systems (5). SOFA system was successfully applied and helped to assess morbidity in severe sepsis clinical trial managed with and without recombinant human activated protein C (23).

Discriminatory power in outcome prediction as estimated by the area under ROC was excellent for cumulative SOFA scores on day 1, day 3, and for all organ dysfunctions, except hepatic. However, the initial degree of individual organ dysfunction scores were less useful for outcome analysis compared with discriminative capability of increasing severity of acquired organ dysfunction during intensive care. The measurement of organ dysfunction daily during the ICU stay provided additional prognostic information compared to baseline measures. The discriminative capability of the SOFA score was the highest on day 3. Similarly, Ferreira et al (22) determined that, regardless of the initial score, an increase in SOFA score during the first 48 hours in the ICU predicts a mortality rate of at least 50%.

The weight of each organ score in cumulative SOFA scores was not equal. The most severe impair-
ment was noted in cardiovascular system, followed by renal, neurological, and respiratory systems. Multivariate logistic regression analysis, including maximum values of organ dysfunction, revealed that two organ systems independently associated with ICU mortality were the neurological and cardiovascular ones. The predictive power of other organ dysfunctions was relatively less important which may be due to a small proportion of more severe dysfunctions.

In the European Sepsis Study, Alberti et al (24) found that acute organ dysfunction and shock were among the prognostic factors of hospital mortality. Jacobs et al (25) described a cohort of critically ill patients who developed septic shock during stay in the ICU. The development of septic shock was associated with the progression of organ dysfunction resulting in higher maximal and delta multiple organ dysfunction scores, reflecting new organ dysfunction arising following ICU admission. The majority of our patients underwent abdominal surgery and had intra-abdominal source of infection. Some of them had chronic liver function impairment. The hepatic dysfunction was assessed by bilirubin level in serum, which lacks specificity for acute hepatic dysfunction and has limited ability to reflect the full spectrum of liver dysfunction in sepsis.

This study included only patients admitted to a single ICU institution. We selected survival status on day 28 after ICU admission as the main outcome measure and did not take into account the later changes in clinical course. In original SOFA studies, the ICU mortality was chosen as the outcome measure (5,8). The assessment of ICU outcome is readily available without any additional effort. However, the discrimination power (area under ROC) of SOFA scores was even slightly higher when using ICU mortality and lower for hospital mortality as the end point of outcome (our unpublished data). Mortality rate in our study was high but within reported ranges in recently conducted multicenter study in the European countries, Canada, and Israel (26).

In summary, the severity of organ dysfunction proved to be a good factor in discriminating outcome for the patients with severe sepsis. The SOFA scores showed high accuracy describing the course of organ dysfunction in these patients. Evolving organ dysfunction following admission to the ICU strongly affected the outcome. Cumulative SOFA scores, particularly on day 3, were better in predicting outcome compared to single organ dysfunction score. Cardiovascular, neurological, and respiratory dysfunctions were the independent risk factors for mortality. The assessment of organ dysfunction should be used for risk stratification in clinical trials including critically ill patients with severe sepsis.

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References


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Correspondence to:
Juozas Ivaskevicius
Clinic of Anesthesiology and Intensive Care
Vilnius University Emergency Hospital
Siltnamiu 29
04130 Vilnius-43, Lithuania
juozas.ivaskevicius@mf.vu.lt