Original article:

Sequential organ failure assessment (SOFA) scores as a tool to assess the outcome in patients with acute respiratory distress syndrome due to acute febrile illness

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Abstract:

Context: Early identification, treatment and outcome prediction remains a challenge in the management of acute respiratory distress syndrome (ARDS). The sequential organ failure assessment (SOFA) score may be useful to stratify patients and assess the outcome of ARDS patients.

Aims: To evaluate the mortality outcomes in ARDS patients using the SOFA score.

Settings and Design: A prospective observational study conducted in Medical Intensive Care Unit of King Edward Memorial Hospital, Mumbai, India.

Methods and Material: Twenty five ARDS patients were studied. Berlin criteria were used diagnose ARDS. A detailed history and relevant clinical examination was done. Arterial blood gas analysis, complete blood counts, liver and renal function tests, chest X-ray, blood cultures were studied. Ventilator support was provided to patients. Outcome data recorded as survivors and non-survivors using SOFA score was analysed.

Statistical analysis used: Descriptive statistics and Fischer's Exact test was employed appropriately using SPSS version 20. A ‘p’ value of < 0.05 was considered statistically significant.

Results: The presenting symptoms were fever and breathlessness with an average duration of 6 days and 2 days respectively. Diagnosis ARDS could not be established eight subjects. The median SOFA score was comparable between the survivors and non-survivors except for the PaO2/FiO2 ratio. Creatinine was higher in the non-survivor group. The overall mortality in the MICU was 36%.

Conclusions: ARDS due to AFI has 30% mortality rate. SOFA score assesses severity of organ dysfunction and delta SOFA score is a better predictor of survival outcome than SOFA-0 in ARDS patients. A rough estimate of mortality risk may be made by SOFA score that describes a sequence of complications in the critically ill.

Key-words: ARDS, organ dysfunction, SOFA score, mortality rate, survival outcome.

Introduction

Acute respiratory distress syndrome (ARDS) is a clinical entity characterised by severe dyspnoea of rapid onset, hypoxemia and diffuse pulmonary infiltrates leading to respiratory failure. It accounts for approximately 20% of patients with acute respiratory failure (ARF). ARDS can be due to both direct as well as indirect causes with severe infections and trauma being the most common cause. In spite of the advances in treatment, ARDS still has a mortality rate
of 26-44%. Early identification, treatment and outcome prediction remains a challenge in the management of ARDS. Scoring systems for predicting mortality outcome in critically ill patients are multiple. However, they have been developed in the mixed intensive care unit (ICU) population and their applicability in disease specific subgroups is unknown. Most scoring systems in use are often complex, assess disease severity only on admission and predict outcome. The sequential organ failure assessment (SOFA) score is different from other scoring systems in that it describes sequence of complications in critically ill patients and also assesses the effect of new therapies on the course of organ dysfunction/failure. It is also used for predicting mortality outcomes. The score assigns 1 to 4 points daily to each of the following six organ systems (circulatory, respiratory, renal, hepatic, coagulation and central nervous system) depending on the level of dysfunction. The initial SOFA score is used to quantify the degree of organ dysfunction or failure at the time of admission, the delta SOFA score to assess the degree of organ dysfunction developing during the ICU stay, and total SOFA score to represent the cumulative organ dysfunction experienced by the patient. Thus, SOFA score may be a useful tool to stratify patients in the clinical setting and therefore to assess the outcome in patients with ARDS/Acute Lung Injury (ALI) due to acute febrile illness (AFI).

**Material and methods**

This is a prospective observational study conducted in Medical Intensive Care Unit (MICU) of King Edward Memorial Hospital (KEMH), Mumbai, India. The study was conducted during a 6 months period between April 2015 and September 2015 after obtaining the institute’s ethics committee approval. The primary objective of the study was to evaluate the mortality outcomes in patients admitted to ICU with ARDS/ALI due to AFI using the SOFA score. The specific objectives of the study was to

1. evaluate the clinical profile of patients with AFI who develop ARDS/ALI.
2. study the Investigation profile in the above group of patients.
3. assess the survival outcome of patients with ARDS/ALI due to AFI.
4. correlate SOFA 0 and SOFA 48 scores after admission with the outcome of study.
5. study the effect of multi-organ system failure in patients of AFI with ARDS / ALI and apply SOFA score in the above group of patients.

Twenty five (25) consecutive male and female patients aged 18 years and above with ARDS/ALI due to AFI admitted to the MICU were recruited for the study by universal sampling method. Patients with MICU stay less than 48 hours were not included in the study. Informed consent from the recruited patients/patients’ relatives was obtained. The study was conducted in compliance with the protocol and regulatory requirements of the hospital. The Berlin criteria was used to make the diagnosis of ARDS that included, i) an appropriate clinical setting, ii) the development of bilateral alveolar and/or interstitial infiltrates of acute onset (<72hrs) on chest radiograph, iii) a ratio of PaO2/FiO2 <300 and iv) no clinical evidence that left ventricular failure or intravascular volume overload as the principle cause of acute radiographic pulmonary infiltrates. At baseline, the demographic data, a detailed history and relevant clinical examination findings were recorded. Arterial blood gas (ABG) analysis was done at admission to MICU to confirm diagnosis of.
ARDS/ALI. Other investigations included complete blood counts, complete liver function test, renal function test, chest X-ray, blood cultures and tropical panel test (H1N1, Dengue NS 1 antigen test by ELISA, MP smear and card test) as a part of AFI evaluation. During the MICU stay, the mode of ventilator support needed and treatment given to each patient was also recorded. From the data collected, SOFA score were determined at baseline i.e. 0 hours and at 48 hours after admission. Delta SOFA score which is the difference between 48 hour SOFA score and admission SOFA score was calculated. The delta SOFA score over 48hrs revealed that a decrease in score meant improvement in organ function while an unchanged or increasing score meant worsening organ function and thus clinical deterioration. Outcome data was recorded as in-MICU survivors and non-survivors.

Statistical analysis
The data was analysed by using SPSS software version 20. Descriptive statistics was used for presenting the epidemiological data. The baseline SOFA score was categorized into less than or equal to 3 and more than 3 that was correlated with survival outcome. The delta SOFA score was categorised into two as decreased and unchanged/or increased and was correlated with survival outcome. Fischer's Exact test was used for correlating significance. A’p’ value of less than 0.05 (two sided) was considered statistically significant.

Results
Twenty five patients were included in the study with a median age of 32 years (14-60 years). Eight of the patients had history of cigarette smoking. The median duration of MICU stay was 6 days (range-3-12 days). The presenting symptoms were fever and breathlessness with an average duration of 6 days and 2 days respectively. Aetiology of ARDS due to AFI was seen in various clinical forms as shown in Table1. However in 8 of them, the diagnosis of AFI causing ARDS could not be established.

Table1. Clinical manifestations of ARDS in AFI patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td></td>
</tr>
<tr>
<td>Male: n, (%)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Female: n, (%)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Causes of AFI:</td>
<td>n, (%)</td>
</tr>
<tr>
<td>Malaria</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Dengue</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>2 (8)</td>
</tr>
<tr>
<td>H1N1</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (32)</td>
</tr>
</tbody>
</table>
The overall mortality in the MICU was 36% (9 out of 25 patients – non-survivors) and 64% of the patients survived (16 out of 25 patients – survivors).

The median age in the survivors was 27 years while it was 44 years in the non-survivors. The average duration of hospital stay of survivor and non-survivor group in MICU was 3.5 days and 4 days respectively.

The median organ dysfunction parameters used for SOFA score analysis were comparable between the survivors and non-survivors except for the PaO2/FiO2 ratio which was higher in the survivor group than non-survivors. Creatinine was higher in the non-survivor group. Further details are shown in Table 2.

**Table 2. Comparison of various features of survivors and non-survivors**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivors (n=16)</th>
<th>Non-survivors (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years: median, (range)</td>
<td>27 (14-52)</td>
<td>44 (22-60)</td>
</tr>
<tr>
<td>Gender: n, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (56)</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (44)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Duration of MICU stay in days: median, (range)</td>
<td>3.5 (3-11)</td>
<td>4 (3-12)</td>
</tr>
</tbody>
</table>

**Organ dysfunction parameters: median, (range)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Survivors</th>
<th>Non-survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm of Hg)</td>
<td>83 (70-110)</td>
<td>80 (70-110)</td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td>15 (13-15)</td>
<td>15 (6-15)</td>
</tr>
<tr>
<td>Pao2/Fio2 rtio</td>
<td>239 (75-500)</td>
<td>82 (62-430)</td>
</tr>
<tr>
<td>Platelet count (10^9/L)</td>
<td>160 (20-400)</td>
<td>160 (20-330)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.0 (0.5-7.8)</td>
<td>1.3 (0.8-10.4)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>1.0 (0.8-11.2)</td>
<td>1.0 (1.0-2.1)</td>
</tr>
</tbody>
</table>

Different types of respiratory support like Non Re-Breathing Mask (NRBM), Non-Invasive Ventilation (NIV) and Mechanical Ventilation (MV) were used in the study, the details of which are shown in Table 3.
Table 3. Respiratory support used in the study.

<table>
<thead>
<tr>
<th>Type of Respiratory support</th>
<th>All n, (%)</th>
<th>Survivors n, (%)</th>
<th>Non-survivors n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRBM</td>
<td>9 (36)</td>
<td>9 (56)</td>
<td>0</td>
</tr>
<tr>
<td>NIV</td>
<td>9 (36)</td>
<td>7 (44)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>MV</td>
<td>4 (16)</td>
<td>0</td>
<td>4 (45)</td>
</tr>
<tr>
<td>NIV+MV</td>
<td>3 (12)</td>
<td>0</td>
<td>3 (33)</td>
</tr>
</tbody>
</table>

Duration of respiratory support needed in days: n, (range).

- NRBM: 3 (1-7)
- NIV: 3 (1-4)
- MV: 4 (2-7)
- NIV+MV: 3 (1-7)

The average SOFA score at 0 hrs (SOFA-0) and SOFA score at 48 hrs (SOFA-48) and the change in SOFA score over 48 hrs referred to as delta SOFA score is shown in Table 4.

Table 4. Average SOFA scores of the study population.

<table>
<thead>
<tr>
<th>SOFA score</th>
<th>All median, (range) (n=25)</th>
<th>Survivor median, (range) (n=16)</th>
<th>Non survivor median, (range) (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA-0</td>
<td>4 (0-14)</td>
<td>3.5 (0-10)</td>
<td>7 (2-14)</td>
</tr>
<tr>
<td>SOFA-48</td>
<td>5 (0-19)</td>
<td>3 (0-11)</td>
<td>9 (3-19)</td>
</tr>
<tr>
<td>Delta SOFA</td>
<td>n, (%)</td>
<td>n, (%)</td>
<td>n, (%)</td>
</tr>
<tr>
<td>Decreased</td>
<td>6 (24)</td>
<td>6 (37)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>5 (20)</td>
<td>4 (26)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Increased</td>
<td>14 (56)</td>
<td>6 (37)</td>
<td>8 (89)</td>
</tr>
</tbody>
</table>
The survival outcomes in relation to SOFA score at 0 hrs and delta SOFA score is shown in Figure 1 and Figure 2 respectively. Using the Fischer Exact test, the correlation between Initial SOFA scores (SOFA-0) and survival outcome and the correlation between delta SOFA score with survival outcome were analysed. There was no correlation between initial SOFA score and outcome (p=0.67). However, a borderline statistical significance (p=0.057) was obtained between delta SOFA score and outcome as depicted in Figure 3 and Figure 4 respectively.

Figure 1. Survival outcomes in relation to SOFA score at 0 hrs.

Figure 2. Survival outcomes in relation to delta SOFA score.
Discussion

Fever is a frequently presenting complaint of patients attending emergency departments of most hospitals. Febrile illness can be localized to organ systems or non-localized (commonly referred to as ‘acute undifferentiated febrile illness’ (AUFI); sometimes as ‘acute febrile illness (AFI). AUFI is characterised by acute onset of fever more than 38°C lasting for less than 2 weeks and no cause found after full history and physical examination. In order to identify the cause of AUFI, most emergency departments have their own protocols. The Indian Society of Critical Care Medicine (ISCCM) recommends a 'syndromic' approach to diagnose tropical fevers. The five major clinical syndromes are: undifferentiated fever, fever with rash/thrombocytopenia, fever with ARDS, fever with encephalopathy and fever with multi-organ dysfunction syndrome.

AFI poses diagnostic and therapeutic challenges to the health workers, particularly in limited resource settings. Some fever syndromes have better developed guidelines for their management. On the other hand, AUFI syndromes have overlapping aetiologies which make their diagnosis and management even more challenging. According to some reports, the cause of AUFI is driven by malaria in 5 - 50% cases; scrub typhus/Rickettsial fevers in 4 - 49% cases; enteric fever in 7 - 30% cases; dengue in 4 - 19% cases; leptospirosis in 3 - 10% cases; and influenza in 8 - 12% cases. Such conditions are referred to as tropical illness including tuberculosis and Japanese encephalitis. According to a systematic
review in 2014, the proportion of undiagnosed AUFI ranges between 8% and 80%\textsuperscript{5}. Indian studies report an incidence ranging from 1 to 30% and up to 5% patients with uncomplicated falciparum malaria and 20% – 30% with severe and complicated malaria going on to develop ARDS\textsuperscript{10,11}.

In a study by Bajpai and team, a significant population of patients with tropical fever syndrome had ARDS (30% clinically and 50% post-autopsy)\textsuperscript{12}. In the present study, the cause of AFI with ARDS was found to be one of the tropical infections in 68% of the total patients. Two thirds of the patients had a diagnosis while in one third of the group the cause for AFI could not be confirmed. Among the diagnosed cases, dengue fever (32%) constituted majority of cases. This was followed by influenza (H1N1) -16%, malaria 12% - and leptospirosis - 8%.

In a study by Bhadade and co-researchers\textsuperscript{13} the aetiology of ARDS was malaria in 28%, leptospirosis in 20%, dengue fever in 5% and undiagnosed fever in 30% of patients. In another study, maximum patients suffered from dengue fever (and other infections in order of frequency were malaria, typhoid and scrub typhus)\textsuperscript{14}. In our study, dengue fever and H1N1 were predominant causes of AFI causing ARDS. This is probably because the study was influenced by seasonal variations and endemic nature of these infections.

Analysis of variables between survivors and non-survivors was done to compare the demographic profile and organ dysfunction involvement. The median age of non-survivor group was 44yrs as compared to the median age of 27 yrs in the survivor group. The duration of MICU stay was similar in the two groups. Six organ systems (cardiovascular, respiratory, coagulation, central nervous, renal and hepatic) involvement were assessed. The average values of mean arterial pressure and Pao2/Fio2 ratio were lower and serum creatinine was higher in the non-survivor group (Table 3).

Other studies have reported a higher mortality (40%-60%) with Pao2/Fio2 ratio of less than 200 as compared to PaO2/FiO2 ratio of more than 200\textsuperscript{13}. Refractory hypoxemia accounts for 16% of ARDS-related deaths. Karman et al\textsuperscript{15} observed that a rise in serum creatinine over 2 mg/dl in patients of ARDS led to 80% mortality. Risk factors for mortality include increasing age, worsening multi-organ dysfunction and presence of pulmonary and non-pulmonary comorbidities, higher Acute Physiology and Chronic Health Evaluation (APACHE) II score, acquisition of illness in ICU, longer time for resolution of lung, use of systemic corticosteroids and acidosis. Most ARDS related deaths are due to multi-organ failure. Thus, as seen in our study, multiple organ involvement was associated with higher mortality. Accordingly, the overall mortality from ARDS due to AFI was 36% that is comparable with other studies\textsuperscript{17-19}.

Treatment of ARDS primarily includes mechanical ventilation along with nutritional support. ARDS in dengue has been rarely reported and has good outcome with an early initiation of mechanical ventilation and supportive therapy\textsuperscript{20}. Patients on ventilators should be encouraged to participate in mobilization therapy. This therapy has been associated with decreased days on the ventilator in the ICU and in the hospital for patients with acute respiratory failure\textsuperscript{21}. As per MICU treatment protocol for ARDS, all patients received intravenous antibiotics, intravenous methylprednisolone, non-invasive or invasive ventilator and other support. In our study it was observed that non-invasive ventilation in the form of NRB M and NIV was sufficient in two thirds of the patients. The survivor
group was maintained only on non-invasive ventilation but more than two thirds of the non-survivor group required invasive ventilation. This goes in hand with the fact that the non-survivors had severe forms of ARDS. However, the average duration of respiratory support used was not different between the two groups.

Scoring systems used in critically ill patients can be broadly divided into those that are specific for an organ or disease. The SOFA was initially validated in a mixed, medical surgical ICU population and has since been validated and applied in various patient groups. There are two major applications of such a SOFA score. 1) To improve our understanding of the natural history of organ dysfunction/failure and the interrelation between the failure of the various organs.2) To assess the effects of new therapies on the course of organ dysfunction/failure. This could be used to characterize patients at entry or to evaluate the effects of treatment.

Some studies have reported a maximum total SOFA score greater than 15 that correlated with a mortality rate of 90% and an increase in SOFA score during the first 48 hours independent of the initial score, predicted a mortality rate of at least 50% while a decrease was associated with an ICU mortality rate of just 27%. Another study on patients with multiple organ dysfunction syndrome reported 100% mortality for patients with an age over 60 years, a total maximum SOFA greater than 13 on any of the first 5 days of ICU admission, minimum SOFA greater than 10 at all times, and a positive or unchanged SOFA trend over the first 5 days of ICU admission.

The average SOFA-0 and SOFA-48 recorded were 4 and 5 respectively in the entire study group. When the study population was grouped as survivor and non-survivors, we found that the SOFA-0 and SOFA-48 were considerably higher in those who died. In the total population, one half of them had an increasing delta SOFA score and in the other half, the delta SOFA score decreased or remained unchanged equally. In the survivor group, approximately there were one third patients in each of those who had Delta SOFA score decreased, increased or remained unchanged. Whereas, in the non-survivor group none of them had a decrease in delta SOFA score. Rather approximately 90% of them had an increase in their Delta SOFA score. It was thus concluded that there was no correlation between SOFA-0 and survival outcome (p=0.67) and there was borderline statistical significance (p=0.057) between the delta SOFA score and the survival outcome.

In our study we found the delta SOFA score to be a better predictor of mortality than the initial SOFA score which was similar to findings of other reports. Though, the results of our study are not statistically significant, we attribute such an observation to the small size of our study population.

Although there is no direct conversion of SOFA score to mortality, a rough estimate of mortality risk may be made. It is important to realize that the SOFA score is designed not to predict the outcome but to describe a sequence of complications in the critically ill. SOFA score does not compete with the existing severity indices but complements them.

The findings of this study can thus be concluded as below.

- ARDS/ALI due to AFI is associated with approximately 30% mortality rates.
- Survivors of ARDS/ALI due to AFI required only Non-invasive type of ventilation.
SOFA score is a useful tool to assess severity of organ dysfunction in these patients. Delta SOFA score is a better predictor of survival outcome than the initial SOFA score.

Abbreviations:
ABG: Arterial blood gas
AFI: Acute febrile illness
ALI: Acute Lung Injury
ARDS: Acute respiratory distress syndrome
ARF: Acute respiratory failure
ICU: Intensive care unit
ISCCM: Indian Society of Critical Care Medicine
KEMH: King Edward Memorial Hospital
MICU: Medical Intensive Care Unit
MV: Mechanical Ventilation
NIV: Non-Invasive Ventilation
NRBM: Non Re-Breathing Mask
PaO2/FiO2: Aarterial oxygen partial pressure to fractional inspired oxygen
SOFA: Sequential organ failure assessment

References


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