Predictive Value of Frailty Index in Comparison to Traditional Markers of Sepsis in Predicting Mortality among Elderly Admitted in Tertiary Care Hospital

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ABSTRACT

Introduction: The frailty index’s potential as a prognostic marker of sepsis is so far been untapped. Here we studied the predictive value of frailty index in the elderly with sepsis.

Methods: This prospective cohort study was conducted in a tertiary level hospital in North India. The duration of the study was 18 months starting from January 2020 to July 2021. The frailty index was calculated along with traditional markers of sepsis such as sequential organ failure assessment (SOFA), quick sequential organ failure assessment (qSOFA), and systemic inflammatory response syndrome (SIRS) within 24 hours of admission in elderly patients suspected to have sepsis. The area under the receiver operating characteristic (AUROC) of frailty index, SOFA, qSOFA, and SIRS was compared for in-hospital and 3-month mortality.

Results: There was no significant difference between the performance of the frailty index and SOFA (DeLong’s test p = 0.242) in predicting in-hospital mortality, but there was a statistical difference between the AUROC of SOFA score (AUC = 0.548) and frailty in predicting 3-month mortality (DeLong’s test p ≤ 0.001).

Conclusion: The frailty index had greater sensitivity and negative predictive value among the other scores in predicting in-hospital mortality, whereas SOFA had higher specificity in predicting in-hospital mortality. The frailty index was superior to SOFA and the other prognostic markers of sepsis in predicting 3-month mortality.

INTRODUCTION

The mean age of patients being admitted in hospitals in India with sepsis is increasing gradually. The mean age of patients admitted with sepsis in a tertiary care hospital was 59.4 ± 17.9 years.1 In the same study, 85% of the total in-hospital mortality was attributable to sepsis. Sensitive the medical fraternity and providing them with tools to handle this increasing population of elderly with sepsis is thus the need of the hour.

Traditional prognostic markers and scores in critical illness rely excessively on derangements in acute physiologic state at or within 24 hours of admission—such as Acute Physiology and Chronic Health Evaluation II,2 SOFA,3 and Simplified Acute Physiology Score II. The abovementioned scores equate illness severity with the outcome of the patient.4 They do not include sociodemographic characteristics like age, social support, and education. Nor do they integrate important elements like prehospital functional status, severity of comorbid illness, disability, or frailty. However, in elderly patients, if considering short-term mortality and morbidity outcomes, addressing these limitations is particularly important following critical illness.

The elderly with their unique physiology have a widely varying response to sepsis and are more severely affected by insults, such as infection, than young adults. Therefore, generalizing the same conclusions derived from other landmark studies like sepsis-3 on elderly patients with sepsis would be unfair.

In our study, we compared the frailty index with traditional markers of sepsis such as SOFA, SIRS, and qSOFA for the prediction of in-hospital mortality and 3-month mortality in elderly patients admitted with sepsis.

METHODS

A prospective cohort study was conducted in a tertiary healthcare facility in North India after the approval of the Institutional Ethics Committee. The study duration was 18 months which coincided with the peak of the COVID era. Patients were enrolled from January 2020 to July 2021. As per the World Health Organization, people equal to or older than 60 years are considered elderly. In the study, elderly patients with suspected sepsis were enrolled. Those patients were suspected to have sepsis whose blood culture, urine culture, or other infection-specific investigations (bacterial, viral, fungal, and parasitic) were sent within 72 hours of admission by the primary treating physician. The elderly with a history of prior antibiotic therapy (30 days) and localized infection were excluded. As frailty assessment requires a degree of mobility and intact cognition, elderly with Parkinson’s disease, previous stroke, cognitive impairment, and depression were also excluded. Those with a documented terminal illness (established life expectancy ≤6 months) were excluded. Since there is a lack of epidemiological data from India depicting in-hospital mortality for elderly patients with sepsis, a multicenter study conducted in Italy provided the expected in-hospital mortality for the study which was set at 12.5%.6 An AUROC curve for frailty equal to at least the lower limit of the 95% confidence interval (CI) of the AUROC for SOFA prediction of in-hospital mortality (outside intensive care unit) detected in sepsis-3,6 which was 0.79; 95% CI (0.78–0.80) would demonstrate the non-inferiority of frailty from SOFA. Therefore, the assumed AUROC for frailty was 0.78. A sample of 24 elderly participants in sepsis with eventual mortality led us to reach a statistical power of 81% to detect a statistically significant difference (p < 0.05) between the assumed AUROC of frailty and SOFA (calculation performed with PASS-14).

All consecutive elderly meeting the inclusion criteria were enrolled after taking their written informed consent (Fig. 1). Baseline demographic characteristics and clinical details of the population were entered on a predesigned Performa. Frailty index,
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**Fig. 1:** Flow chart showing the participants of the study

SOFA, SIRS, and qSOFA were calculated at the time of admission.

The Fried frailty index was used to assess frailty. It has five dimensions that reflect the impaired regulation of different systems of the body. These five dimensions are:

- **Unintentional weight loss:** It was assessed by asking the amount of weight loss in the last year, not because of dieting or exercise. If the answer was more than 4.5 kg then the criterion was met and a score of 1 was given to this item.

- **Exhaustion:** Exhaustion was measured by asking “How often did you feel that everything you did was an effort?” and “How often did you feel that you could not get going?” This was taken from the Center for Epidemiologic Studies Depression scale. Response options were “rarely or never,” “some or a little of the time (1–2 days),” “a moderate amount of the time (3–4 days),” and “most of the time” in Fried’s version. If the answer to at least one or two questions was “always or most of the time” then this criteria was met.

- **Muscle weakness:** Grip strength/muscle weakness was measured by asking the question from the Tilburg frailty indicator “Do you experience difficulties in daily life because of low grip strength?” Yes would count as a point.

- **Slowness while walking:** 6-minute walk test was used to assess the slowness of walking. In healthy adults, 6-minute walk distance has been reported to range from 400 to 700 m. Test was performed by making the subject walk on a 10-m strip, marked on the ground at a regular pace wearing his/her usual footwear. Distance covered in 6 minutes was noted. If the subject could walk for 6 minutes and cover a distance of more than 400 m, a score of 1 was given. If the walking distance was less than 400 m or the subject could not walk for 6 minutes, a score of 0 was given.

- **Low levels of activity:** Kilocalories per week were calculated by using the Minnesota leisure time activity questionnaire. Patients were stratified as per their gender and their physical activity. The calculated value was compared with the cutoff as described by Fried et al. (men 383 kcal/week and women 270 kcal/week). If the calculated value fell below this cutoff then this criterion was met.

Interpretation of Fried frailty index: Patients with a score of 0 are classified as robust or not frail. A score of 1 or 2 is at intermediate risk for adverse outcomes and is considered to be pre-frail. A score of 3–5 indicates that someone is frail.

SOFa and qSOFA are scores that are used to quantify the degree of organ dysfunction and are helpful in stratifying patients with sepsis. Initially they were proposed as a tool to assess the complications of sepsis but then they were repurposed as a tool that will predict mortality as well. It comprises six organ system assessments of respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems each scored from 0 to 4.

Patients were followed, and the outcome of in-hospital and 3-month mortality was noted through hospital records and by telephonic contacts, respectively.

Data were analyzed with SPSS statistical software (version 25). For normally distributed variables, data were reported as mean and standard deviation, median and interquartile range for non-normal distributed variables, or as a percentage for discrete variables. In addition, ROC curves and AUCs were calculated for SOFA, qSOFA, SIRS, and Fried frailty index to predict the primary outcome pooled 3-month mortality and in-hospital mortality. A pairwise comparison of ROC curves was performed using DeLong’s test. Patients who were lost to follow-up were excluded from the analysis.

**RESULTS**

Sixty patients were sequentially enrolled and followed, of which 10 were excluded (two previous strokes, five previously on antibiotics, and three lost to follow-up). The mean age of the study population was 68.98 ± 7.18 years. Females comprised 46%. Diabetes followed by chronic obstructive pulmonary disease was the most common comorbidity in the study population at 34% and 28%, respectively. The most common site of infection was the respiratory tract (62%) followed by urinary tract and abdominal sepsis. Of the total patients followed, 13 (26%) were admitted to the critical care units.

Admission location, platelet count (lakh per mm$^3$), PaO$_2$/FiO$_2$ ratio category, serum lactate (mmol/L), SOFA score, frailty index, frailty status, duration of hospital stay (days), requiring a higher level of care, and upgradation of antibiotics were found to be significantly associated ($p < 0.05$) with in-hospital mortality. The AUROC for frailty index, SOFA, qSOFA, and SIRS in predicting in-hospital mortality was 0.888 (95% CI: 0.797–0.947) ($p < 0.001$), 0.768 (95% CI: 0.592–0.944) ($p = 0.016$), 0.531 (95% CI: 0.288–0.775) ($p = 0.731$), 0.549 (95% CI: 0.33–0.769) ($p = 0.657$), respectively. SOFA and frailty showed good diagnostic performance and were statistically significant. Pairwise comparison using DeLong’s test showed that there was no significant difference between frailty index and SOFA (DeLong’s test $p = 0.242$). However, frailty performed better than SIRS ($p = 0.013$) and qSOFA score ($p = 0.006$). Table 1 shows an association between in-hospital mortality, 3-month mortality, and various clinical parameters among the study participants.

Platelet count (lakh per mm$^3$), PaO$_2$/FiO$_2$ ratio category, frailty index, frailty status, and duration of hospital stay (days) were significantly associated ($p < 0.05$) with 3-month mortality.

The AUROC for frailty index, SOFA, qSOFA, and SIRS for predicting 3-month mortality was 0.844 (95% CI: 0.74–0.947) ($p ≤ 0.001$), 0.548 (95% CI: 0.387–0.709) ($p = 0.562$), 0.513 (95% CI: 0.382–0.644) ($p = 0.850$), 0.502 (95% CI: 0.346–0.659) ($p = 0.984$), respectively (Fig. 2). The diagnostic performance of frailty index (AUC = 0.844) was significantly better than that of SOFA score (AUC = 0.548) (DeLong’s test $p ≤ 0.001$), qSOFA Score ($p ≤ 0.001$), SIRS score ($p ≤ 0.001$) in predicting 3-month mortality (Fig. 3).

Table 2 shows the Frailty Index (cutoff 4) is best parameter in term of sensitivity and negative predictive value whereas SOFA score is best in terms of diagnostic accuracy.
The present study compared the predictive value of the frailty index with traditional markers of sepsis such as SOFA, SIRS, and qSOFA in predicting in-hospital mortality and 3-month mortality. We observed that the frailty index had the highest sensitivity and negative predictive value for mortality in the elderly with sepsis. However, SOFA had the highest positive predictive value and specificity among all the scores tested. Our study did not find any difference in the AUROC of SOFA and frailty in predicting in-hospital mortality but the frailty index was far superior to SOFA in predicting 3-month mortality. No significant difference was found in the AUROC of SOFA, qSOFA, and SIRS for 3-month mortality.

The mean age of presentation in our study was 68.98 ± 7.18 years, which is slightly younger compared to other studies conducted in developed countries with elderly with sepsis, probably reflecting the increased life expectancy in the developed countries. However, age was not found to be a good predictor of in-hospital mortality or 3-month mortality. In our study, the number of males was slightly more than females, 54 vs 46%, which could be attributed to fewer women seeking medical care in India.

### DISCUSSION

The present study compared the predictive value of the frailty index with traditional markers of sepsis such as SOFA, SIRS, and qSOFA in predicting in-hospital mortality and 3-month mortality. We observed that the frailty index had the highest sensitivity and negative predictive value for mortality in the elderly with sepsis. However, SOFA had the highest positive predictive value and specificity among all the scores tested. Our study did not find any difference in the AUROC of SOFA and frailty in predicting in-hospital mortality but the frailty index was far superior to SOFA in predicting 3-month mortality. No significant difference was found in the AUROC of SOFA, qSOFA, and SIRS for 3-month mortality.

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Table 2: The various diagnostic parameters and the best performance of their scores

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Best score</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The best parameter in terms of AUROC</td>
<td>Frailty index</td>
<td>0.888 (0.797–0.98)</td>
</tr>
<tr>
<td>The best parameter in terms of sensitivity</td>
<td>Frailty index (cutoff 4)</td>
<td>100.0% (63–100)</td>
</tr>
<tr>
<td>The best parameter in terms of specificity</td>
<td>SOFA score (cutoff 6)</td>
<td>95.2% (84–99)</td>
</tr>
<tr>
<td>The best parameter in terms of positive predictive value</td>
<td>SOFA score (cutoff 6)</td>
<td>66.7% (22–96)</td>
</tr>
<tr>
<td>The best parameter in terms of negative predictive value</td>
<td>Frailty index</td>
<td>100.0% (86–100)</td>
</tr>
<tr>
<td>The best parameter in terms of diagnostic accuracy</td>
<td>SOFA score</td>
<td>88.0% (76–95)</td>
</tr>
</tbody>
</table>

Fig. 2: Comparison of the diagnostic performance of SOFA, qSOFA, SIRS, and frailty index in predicting in-hospital mortality

Fig. 3: Comparison of the diagnostic performance of SOFA, qSOFA, SIRS, and frailty index in predicting 3-month mortality

Langlais et al. found that frailty index was not an independent risk factor in predicting mortality. However, in the same study, frailty was significantly associated with mortality and clinical frailty score (CFS) of less than five was excellent in predicting survival. Hence, if a patient is found to be not frail, it is predictive of a good outcome. This mirrors the finding of our study where the sensitivity of the frailty index was superior to that of SOFA and that there was no significant difference between the AUROC in SOFA and the frailty index in predicting in-hospital mortality. However, SOFA had the highest positive predictive value and specificity among all the scores tested. So, if a patient has a high SOFA value, it is fairly accurate in predicting mortality and is an excellent tool to diagnose sepsis, as proven in sepsis-3. SOFA showed poor diagnostic ability (AUROC 0.543) in predicting 3-month mortality. This was expected as SOFA is a tool to help diagnose and predict in-hospital mortality with sepsis. Instead, frailty index and length of hospital stay were significantly associated with 3-month mortality in another study that compared frailty with qSOFA and SIRS in predicting in-hospital mortality. Rookwood’s clinical frailty scale was superior to SIRS, but no significant difference was seen between qSOFA and Rookwood’s clinical frailty scale. The deviation from our results could be explained as qSOFA showed a poor diagnostic value (AUROC 0.531) in our study, perhaps because of the small sample size of our study.

In another prospective study conducted in France, frailty (assessed by CFS and phenotype model) was an independent risk factor for both in-hospital and 6-month mortality. Our results also showed that frailty was superior to SOFA, SIRS, and qSOFA in predicting 3-month mortality. Thus, we can assume that frailty status is more representative of an admission’s immediate short-term outcome (3- and 6-month mortality). The traditional scores calculated in patients with sepsis at the time of admission reflect their status during hospitalization; they focus more on organ involvement and vitals than the patient’s pre-existing reserves. Therefore, any outcome will depend on the condition at admission and pre-existing status, which could explain why the frailty index performed so well in predicting mortality, especially at 3 months.

**Conclusion**

Our study found that frailty was a good predictor of both in-hospital and 3-month mortality. There was no significant difference between SOFA and frailty in predicting in-hospital mortality; however, frailty performed better in predicting 3-month mortality.

Frailty has all the attributes of an excellent triaging tool. Its high sensitivity makes it easy to identify all those at high risk, even if it means over triaging a few. India is a country with varying distribution of wealth and resources, and such a tool can prove extremely useful to the physician to risk stratify the elderly and determine the level of care required in the management of acute illness.

**Limitations**

- The sample size for the study was calculated using western hospital records and data.
- In-hospital mortality was more than predicted in our study population. This could be attributed to the COVID-19 pandemic or merely representative of the mortality rate of the elderly in a tertiary hospital in India.
• Larger studies evaluating the use of the frailty index in the assessment of an acutely ill elderly should be conducted considering the unique physiology of an elderly patient.

**Ethics Approval**
Institutional Ethics Committee approval has been taken via letter no AIIMS/IEC/19/1035.

**Acknowledgments**
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**References**