Prognostic value of \( \text{PaO}_2/\text{FiO}_2 \), SOFA and D-dimer in elderly patients with sepsis

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Abstract

Objective: To investigate the prognostic value for predicting mortality of partial pressure of oxygen/fraction of inspired oxygen (\( \text{PaO}_2/\text{FiO}_2 \)), the Sequential Organ Failure Assessment (SOFA) score and D-dimer in elderly patients with sepsis.

Methods: This retrospective cohort study enrolled elderly patients with sepsis admitted to the intensive care unit (ICU) between January 2019 and October 2020. Patients were divided into a survival group and a non-survival group. Biomarkers, SOFA, Acute Physiology and Chronic Health Evaluation II and Glasgow Coma Scale scores were recorded within 24 h after admission to the ICU.

Results: A total of 135 elderly patients with sepsis were enrolled in the study: 89 were in the survival group and 46 were in the non-survival group at 28 days. Univariate and multivariate regression analyses demonstrated that \( \text{PaO}_2/\text{FiO}_2 \), SOFA and D-dimer were independently associated with 28-day mortality. The predictive performance for mortality of the combination of \( \text{PaO}_2/\text{FiO}_2 \), SOFA score and D-dimer (area under the receiver operating characteristic curve of 0.926) was higher than the values for the individual factors (0.761, 0.745 and 0.878, respectively).

Conclusion: The combination of \( \text{PaO}_2/\text{FiO}_2 \), SOFA score and D-dimer represents a promising tool and biomarker for predicting 28-day mortality of the elderly patients with sepsis.

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Introduction

According to population statistics for China, the number of people aged ≥65 years has increased rapidly in China; with 164.5 million people aged ≥65 years and 26 million aged ≥80 years. It is estimated that by 2050 over 365 million people will be aged ≥65 years and they will account for 26.1% of China’s total population. As the ageing population continues to grow, more elderly patients will be admitted to the intensive care unit (ICU).

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The mean mortality rate of sepsis is 33.2%. In elderly patients with sepsis, the mortality rate is much higher. The incidence and mortality rate of elderly patients with sepsis is increasing as the ageing population continues to increase globally. A previous study demonstrated that increased age was an independent predictor of death among sepsis patients, especially in those aged ≥65 years. Diagnosing elderly patients with sepsis is difficult because since they present with few specific signs and symptoms. This poses a challenge for ICU physicians to identify elderly patients with sepsis, especially those at a higher risk of death. The ability to diagnose and predict the clinical symptoms and prognostic outcomes in elderly patients with sepsis is vitally important.

Prognostic indices such as the Sequential Organ Failure Assessment (SOFA) and the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) can be used to predict the outcome of the patients with sepsis, but there is little evidence about their value in elderly patients with sepsis. In addition, biological markers such as procalcitonin (PCT), C-reactive protein (CRP), brain natriuretic peptide precursor, lactate (LAC) and D-dimer have been widely used to predict which patients with sepsis are likely to survive. However, none of these biological markers have a 100% sensitivity or 100% specificity.

The present study compared different prognostic indices and biomarkers in relation to predicting mortality in elderly patients with sepsis admitted to the ICU.

Patients and methods

Patient population

This single-centre retrospective study enrolled consecutive elderly patients with sepsis admitted to the ICU of Hunan Provincial People’s Hospital, Changsha, Hunan Province, China between January 2019 and October 2020. This is a tertiary referral hospital located in the south-central region of China. Elderly patients that were >65 years and diagnosed with sepsis according to SEPSI-3 criteria were recruited. Patients were excluded if they had an end-stage disease such as end-stage renal disease, malignant tumour, liver disease, severe immunodeficiency disease, haematological disease or survived <12 h.

The Medical Ethics Committee of Hunan Provincial People’s Hospital approved the study (no. 2021-37). Informed consent was waived due to the retrospective nature of this
study. All patient data were de-identified. The reporting of this study conforms with STROBE guidelines.\textsuperscript{15}

Data collection

The demographic characteristics of the patients were collected and documented at the time of admission to the ICU department. Infection sites (respiratory tract, gastrointestinal tract, genitourinary tract and others), vital signs (heart rate, breath rates, blood pressure), comorbidities and the ‘do not resuscitate’ status were also collected. SOFA, APACHE II and Glasgow Coma Scale (GCS) scores on admission for all enrolled patients were calculated. PCT, white blood cells (WBC), neutrophils (N), CRP, prothrombin time (PT), D-dimer, fibrinogen degradation product (FDP), N-terminal brain natriuretic propeptide (NT-proBNP), cardiac troponin I (CTnI), creatine kinase (CK), creatine kinase-MB (CK-MB), LAC, platelets (PLT), bilirubin and creatinine were documented from the patient files. All enrolled patients were followed for up to 28 days through their medical records and the 28-day mortality was the clinical endpoint. According to their outcome at 28 days from admission, patients were divided into non-survival and survival groups.

Serum collection

All blood samples were collected within 24 h of admission to the ICU. These samples were used to measure the following using routine laboratory methods: PCT, WBC, N, CRP, PT, D-dimer, FDP, NT-proBNP, CTnI, CK, CK-MB, LAC, PLT, bilirubin and creatinine.

Statistical analyses

All statistical analyses were performed using the SPSS\textsuperscript{®} statistical package, version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows\textsuperscript{®}. Comparisons between the non-survival and survival groups were undertaken using Student’s $t$-test for continuous variables and $\chi^2$-test for categorical variables. Multivariate logistic regression analysis was used to determine the risk factors for 28-day mortality in elderly patients with sepsis. Receiver operating characteristic (ROC) curve analysis was used to compare the prognostic value of partial pressure of oxygen/fraction of inspired oxygen (PaO$_2$/FiO$_2$), SOFA and D-dimer in elderly patients with sepsis. Using the area under the curve (AUC) to assess their predictive values. A $P$-value $<0.05$ was considered statistically significant.

Results

A total of 135 patients were enrolled in this retrospective study. After a follow-up of 28 days, 89 patients had survived and 46 patients had died (Table 1). No significant differences in age, sex, infection sites, comorbidities, ‘do not resuscitate’ status, heart rate, systolic blood pressure, diastolic blood pressure, platelet count, bilirubin, central venous pressure and creatinine were found between the non-survival and survival groups. The respiration rate was significantly higher in the non-survival group compared with the survival group ($P=0.039$). SOFA and APACHE II scores in the non-survival group were significantly higher than in the survival group ($P<0.001$ for all comparisons). The PaO$_2$/FiO$_2$ and GCS scores was significantly lower in the non-survival group compared with the survival group ($P<0.001$ for both comparisons). PT, D-dimer and LAC were significantly higher in the non-survival group compared with the survival group ($P<0.05$ for all comparisons). There were no significant differences between the non-survival and survival groups in terms of PCT, WBC, N, CRP, FDP, NT-proBNP, CTnI, CK and CK-MB.
**Table 1.** Clinical, demographic and biomarker data for elderly patients with sepsis \((n = 135)\) enrolled in a study that compared different prognostic indices and biomarkers in relation to predicting mortality in elderly patients with sepsis admitted to the intensive care unit.

| Characteristic                      | Survival group \(n = 89\) | Non-survival group \(n = 46\) | \(t/\chi^2\) | Statistical analysis\(^a\) |
|------------------------------------|---------------------------|-------------------------------|--------------|-----------------------------|
| **Demographics**                   |                           |                               |              |                             |
| Age, years                         | 65.38 ± 5.67              | 67.33 ± 8.49                  | -1.584       | NS                          |
| Sex                                |                           |                               |              |                             |
| Male                               | 45 (51%)                  | 27 (59%)                      | 0.801        | NS                          |
| Female                             | 44 (49%)                  | 19 (41%)                      |              |                             |
| **Infection site**                 |                           |                               |              |                             |
| Respiratory tract                  | 54                        | 28                            | 1.334        | NS                          |
| Gastrointestinal tract             | 20                        | 8                             |              |                             |
| Genitourinary tract                | 10                        | 8                             |              |                             |
| Others                             | 5                         | 2                             |              |                             |
| **Comorbidities**                  |                           |                               |              |                             |
| Chronic respiratory disease        | 23                        | 15                            | 0.887        | NS                          |
| Chronic cardiovascular disease      | 18                        | 7                             |              |                             |
| Diabetes mellitus                  | 34                        | 18                            |              |                             |
| Chronic neurological disease        | 16                        | 9                             |              |                             |
| Do not resuscitate status          | 12                        | 7                             | 0.075        | NS                          |
| **Vital signs**                    |                           |                               |              |                             |
| Heart rate, beats/min              | 99.67 ± 18.65             | 106.13 ± 27.02                | -1.452       | NS                          |
| Systolic pressure, mmHg            | 114.78 ± 22.93            | 122.80 ± 33.77                | -1.623       | NS                          |
| Diastolic pressure, mmHg           | 69.86 ± 16.07             | 71.44 ± 16.13                 | -0.537       | NS                          |
| Respiration rate, breaths/min      | 23.64 ± 8.72              | 26.59 ± 5.58                  | -2.080       | \(P = 0.039\)               |
| **SOFA factors**                   |                           |                               |              |                             |
| PaO\(_2\)/FiO\(_2\)               | 195.06 ± 39.92            | 109.69 ± 28.38                | 5.352        | \(P < 0.001\)               |
| Platelets, \(\times 10^9\)/l       | 180.87 ± 96.43            | 153.82 ± 108.95               | 1.477        | NS                          |
| Bilirubin, \(\mu\)mol/l           | 21.75 ± 29.17             | 30.62 ± 50.64                 | -1.096       | NS                          |
| CVP, mmHg                          | 85.42 ± 16.78             | 87.79 ± 20.89                 | -0.700       | NS                          |
| **GCS score**                      | 14.96 ± 0.26              | 13.87 ± 1.94                  | 3.779        | \(P < 0.001\)               |
| **Creatinine, \(\mu\)mol/l**      | 157.08 ± 242.48           | 188.70 ± 231.51               | -0.729       | NS                          |
| **SOFA score**                     | 3.29 ± 1.13               | 6.14 ± 2.36                   | -6.134       | \(P < 0.001\)               |
| APACHE II score                    | 8.55 ± 4.97               | 15.21 ± 6.21                  | -6.773       | \(P < 0.001\)               |
| **Laboratory results**             |                           |                               |              |                             |
| PCT, ng/ml                         | 11.72 ± 25.95             | 21.07 ± 31.72                 | -1.708       | NS                          |
| WBC, \(\times 10^9\)/l             | 14.38 ± 8.75              | 12.90 ± 7.42                  | 0.984        | NS                          |
| N, \(\times 10^9\)/l               | 82.05 ± 17.94             | 83.95 ± 17.49                 | -0.588       | NS                          |
| CRP, mg/l                          | 110.06 ± 73.46            | 121.12 ± 101.73               | -0.722       | NS                          |
| PT, s                              | 15.69 ± 5.39              | 18.45 ± 6.54                  | -2.503       | \(P = 0.014\)               |
| D-dimer, mg/l                      | 3.21 ± 1.66               | 6.86 ± 2.80                   | -8.129       | \(P < 0.001\)               |
| FDP, ng/l                          | 17.84 ± 6.72              | 18.14 ± 4.39                  | -0.297       | NS                          |
| NT-proBNP, fmol/ml                 | 2.94 ± 0.71               | 3.11 ± 0.57                   | -1.455       | NS                          |
| CTnI, \(\mu\)g/l                   | 1.45 ± 0.56               | 1.56 ± 0.64                   | -1.001       | NS                          |
| CK, U/l                            | 167.65 ± 49.70            | 170.26 ± 45.00                | -0.299       | NS                          |

(continued)
As shown in Table 2, multivariate logistic regression analysis showed that PaO2/FiO2, SOFA and D-dimer were risk factors for the 28-day mortality of elderly patients with sepsis. Receiver operating characteristic curves were used to evaluate the prognostic value of the three factors in elderly patients with sepsis (Figure 1). The results showed that the AUCs of PaO2/FiO2, SOFA and D-dimer were 0.761 (95% confidence interval [CI], 0.669, 0.853), 0.745 (95% CI, 0.663, 0.827) and 0.878 (95% CI, 0.822, 0.934), respectively (Table 3). The sensitivity and specificity of the cut-off values were calculated according to ROC curve analysis. The prognostic value of the combined PaO2/FiO2, SOFA and D-dimer levels in elderly patients with sepsis was higher than the values for the individual factors ($P < 0.001$).

**Discussion**

Sepsis has become one of the main causes of death in the geriatric population. Elderly patients with sepsis account for 58–65% of
all patients with sepsis.\textsuperscript{17–19} Studies have shown that the incidence and mortality of sepsis increase with age.\textsuperscript{20,21} For example, the mortality rate of sepsis in children is 10%, but it is 26% in those aged 60–64 years and 38% in patients aged ≥85 years.\textsuperscript{20,21} Previous studies have shown that most elderly patients with sepsis are prone to acute renal failure, respiratory failure and multiple organ dysfunction syndrome (MODS) because of the deterioration in their physical function and poor organ compensatory function.\textsuperscript{22} Compared with adult patients, elderly patients have fewer signs and symptoms of infection and more easily develop septic shock.\textsuperscript{9} Therefore, the early detection and prognostic evaluation would be more meaningful in this population.

**Figure 1.** Receiver operating characteristic (ROC) curve analysis of the prognostic value of partial pressure of oxygen/fraction of inspired oxygen (PaO\textsubscript{2}/FiO\textsubscript{2}), the Sequential Organ Failure Assessment (SOFA) score and D-dimer for 28-day mortality of elderly patients with sepsis (n = 135). The colour version of this figure is available at: http://imr.sagepub.com.

**Table 3.** Receiver operating characteristic curve (ROC) analysis of the prognostic value of partial pressure of oxygen/fraction of inspired oxygen (PaO\textsubscript{2}/FiO\textsubscript{2}), the Sequential Organ Failure Assessment (SOFA) score and D-dimer for 28-day mortality of elderly patients with sepsis (n = 135).

| Factor                  | Area under the ROC | Sensitivity | Specificity | Cut-off | 95% CI       | P-value |
|-------------------------|--------------------|-------------|-------------|---------|--------------|---------|
| PaO\textsubscript{2}/FiO\textsubscript{2} | 0.761             | 63.0%       | 83.1%       | 227.27  | 0.669, 0.853 | <0.001  |
| SOFA                    | 0.745             | 97.8%       | 38.2%       | 1.5     | 0.663, 0.827 | 0.004   |
| D-Dimer                 | 0.878             | 87.0%       | 71.9%       | 4.16    | 0.822, 0.934 | <0.001  |
| PaO\textsubscript{2}/FiO\textsubscript{2} & SOFA & D-dimer | 0.926 | 0.89.1%   | 86.5% | –   | 0.881, 0.971 | <0.001  |
The present study evaluated the values of biological markers and prognostic indices in predicting mortality in elderly patients with sepsis. The results showed that PaO2/FiO2, SOFA and D-dimer in the non-survival group were significantly higher compared with the survival group. The prognostic value of the combined PaO2/FiO2, SOFA and D-dimer levels in elderly patients with sepsis was higher than the values for the individual factors.

The SOFA score is a better tool for predicting in-hospital mortality than quick SOFA, Systemic Inflammatory Response Syndrome and APACHE II scores.23,24 A previous study demonstrated that the SOFA score can be used as a tool to predict the outcomes of patients with sepsis and it had the strongest association with 28-day mortality in patients with sepsis compared with the Overt-Disseminated Intravascular Coagulation score and the Japanese Association for Acute Medicine Disseminated Intravascular Coagulation Score.25 Research has demonstrated that the SOFA score was significantly higher in non-survivor groups than those that survived and it could predict the prognosis of septic patients.24–26 The current findings demonstrated that the SOFA score was significantly higher in the non-survival group compared with the survival group and was superior to the APACHE II score, which was consistent with previous studies.23–26 The ROC curve analysis demonstrated an AUC of 0.745 for the SOFA score, which suggests that the SOFA score may predict the short-term prognosis of the mortality in elderly patients with sepsis. The SOFA score may be better than the APACHE II score because sepsis is a life-threatening acute organ dysfunction caused by an imbalance in the inflammatory response. When compared with the APACHE II scoring system, the SOFA score more accurately reflects the overall acute state of the body and is more suitable for the evaluation and prognosis of elderly patients with sepsis.

A previous study demonstrated that high levels of D-dimer can reflect a hypercoagulable state and secondary hyperfibrinolysis.27 Some studies reported that the concentration of D-dimer in non-survival groups was higher than in survival groups and that using a combination of the SOFA score and high levels of D-dimer predicted 28-day mortality of sepsis patients.28,29 These previous results were in agreement with the current findings that D-dimer was superior to the other biomarkers evaluated. The pathophysiological processes that occur in sepsis involve the release of inflammatory mediators, cytokines and endothelial cells, thereby activating and promoting the coagulation cascade, especially in disseminated intravascular coagulation.30 Coagulation biomarkers accelerate the coagulation cascade, so the concentration of D-dimer and other coagulation-related biomarkers increases significantly.31 Sepsis is a systemic inflammatory reaction that occurs during infection, severe burns, multiple injuries and other diseases; and sepsis is the basis for the pathogenesis of MODS.30 The lungs are commonly affected when multiple organ injuries are complicated by sepsis, resulting in acute respiratory distress syndrome (ARDS).32 The Berlin diagnostic criteria can distinguish the severity of ARDS and PaO2/FiO2 is the most important feature of the criteria, which divides ARDS into mild, moderate and severe.33 PaO2/FiO2 reflects the severity of the disease and the degree of lung damage in ARDS patients with sepsis.34 A previous study found that PaO2/FiO2 is related to the occurrence of ARDS sepsis and PaO2/FiO2 in the non-survival group was significantly lower than that in the survival group.35 PaO2/FiO2 was an independent risk factor for death in patients with sepsis.35 These results were consistent with the current findings that PaO2/FiO2 had...
prognostic value for predicting mortality in patients with sepsis.

The current study also had several limitations. First, it was a single-centre study undertaken at a tertiary referral hospital. Secondly, the current study only included a small number of elderly patients with sepsis, so the results may not be representative of the geriatric population. Thirdly, it was retrospective and not a prospective study, so the inherent bias of this study could not be avoided. Finally, some of the older patients that were transferred to the ICU had received prior sepsis management, such as fluid resuscitation, antibiotics and mechanical ventilation. Prospective controlled multi-centre studies are needed in the future.

In conclusion, this current study demonstrated that PaO₂/FiO₂, SOFA score and D-dimer can be used as prognostic makers for mortality in elderly patients with sepsis. The prognostic value of the combined PaO₂/FiO₂, SOFA and D-dimer levels in elderly patients with sepsis was higher than the values for the individual factors.

Author contributions
H.R.G. and Z.Y.S. provided the idea. X.L. collected data. W.Q.H., J.P.Z. and L.Z.T wrote the manuscript. L.X.Y. contributed to the scientific discussion. T.L. provided the design of the article, statistical consulting and data analysis.

Declaration of conflicting interest
The authors declare that there are no conflicts of interest.

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