Predictive accuracy of Sepsis-3 definitions for mortality among adult critically ill patients with suspected infection

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Abstract
Background: Sepsis-3 definitions have been published recently; however, their diagnostic value remains controversial. This study was to assess the accuracy of Sepsis-3 definitions compared to Sepsis-1 definitions by stratifying mortality among adult critically ill patients with suspected infection.

Methods: A multicenter, prospective cohort study was conducted from November 10, 2017 to October 10, 2018, in five Intensive Care Units (ICUs) at four teaching hospitals. Thirty-day mortality was compared across categories for both Sepsis-3 definitions and Sepsis-1 definitions, which were evaluated by logistic regression analysis followed by measurement of the area under the receiver operating characteristic curve (AUROC) for predicting 30-day mortality rates.

Results: Of the 749 enrolled patients, 644 (85.9%) were diagnosed with sepsis according to the Sepsis-1 definitions. Among those patients, 362 were diagnosed with septic shock (362/749, 48.3%). However, according to the Sepsis-3 definitions, there were 483 patients with a diagnosis of sepsis (483/749, 64.5%), among whom 299 patients were diagnosed with septic shock (299/749, 39.9%). According to the Sepsis-3 definitions, sepsis (sepsis and septic shock) patients had higher 30-day mortality (41.8%) than sepsis patients according to the Sepsis-1 definitions (31.8%, \( \chi^2 = 5.552, P = 0.020 \)). The AUROC of systemic inflammatory response syndrome (SIRS) and quick sequential organ failure assessment (qSOFA) scores with regard to 30-day mortality rates were 0.609 (0.566–0.652) and 0.694 (0.654–0.733), respectively. However, the AUROC of SOFA scores (0.828 [0.795–0.862]) were significantly higher than that of SIRS or qSOFA scores (\( P < 0.001 \)).

Conclusion: In adult critically ill patients with suspected infection, the Sepsis-3 definitions were relatively accurate in stratifying mortality and were superior to the Sepsis-1 definitions.

Trial Registration: www.chictr.org.cn (ChiCTR-OOC-17013223).

Keywords: Infection; Critically ill patients; Sepsis-3; Septic shock; Mortality

Introduction
In 1991, the American College of Chest Physicians and Society of Critical Care Medicine convened with the goal of developing a set of sepsis definitions to standardize the definition of sepsis and its spectrum of diseases, including septic shock. The consensus defined sepsis as systemic inflammatory response syndrome (SIRS) resulting from an infection. Sepsis was defined as sepsis-induced hypotension persisting after adequate fluid resuscitation, along with the presence of perfusion abnormalities or organ dysfunction. At the second consensus conference, although some specialists agreed that SIRS was not suitable for the definition of sepsis, the no significant changes made to the definitions of sepsis.

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) were published recently, with significantly revised clinical criteria, adopting sequential organ failure assessment (SOFA) scores and the quick SOFA (qSOFA) screening tool. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The definition of septic shock is clinically identified by the vasopressor requirement to maintain a mean arterial pressure (MAP) of more than 65 mmHg and a serum lactate level of more than 2 mmol/L after initial fluid resuscitation.

Although these new criteria have been validated in large databases, their diagnostic value remains controversial.

Qi-Hong Chen and Jun Shao contributed equally to this work.

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Some retrospective studies have indicated that the new Sepsis-3 definitions were accurate in stratifying mortality and were superior to the previous definitions. However, Sterling suggested that although Sepsis-3 identified a group of patients at greater risk of worse clinical outcomes, it missed a large proportion of patients who may benefit from early resuscitative therapy.

To assess the ability of the Sepsis-1 and Sepsis-3 definitions to predict the primary endpoint, we conducted the present multicenter, prospective cohort study to evaluate the Sepsis-3 definitions and the Sepsis-1 definitions by logistic regression analysis followed by measurement of the area under the receiver operating characteristic curve (AUROC) for predicting 30-day mortality rates.

Methods

Ethical approval
The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Northern Jiangsu People’s Hospital (2017KY-021) and was registered in the Chinese Clinical Trial Registry with a registration number ChiCTR-OOC-17013223. Written informed consent was obtained from each participant/guardian prior to their enrollment in this study.

Study design and population
The present study was conducted at five Intensive Care Units (ICUs) with more than 180 beds in a total of four Jiangsu province teaching hospitals. This was a prospective cohort study of adult patients with suspected infection admitted to ICUs over an approximate 1-year span from November 10, 2017 to October 10, 2018, in ICUs of four teaching hospitals containing Northern Jiangsu People’s Hospital, Jiangdu People’s Hospital of Yangzhou, Affiliated Hospital of Yangzhou University, and Taizhou People’s Hospital. The patients, who were less than 18 years of age or having any of the following primary conditions: trauma, epilepsy, cardiogenic pulmonary edema, stroke, or active bleeding, were excluded.

Definition of suspicion of infection
Suspicion of infection was defined as clinical documentation of this suspicion based on clinical presentation and radiological or laboratory examination by the attending physician on the first day of ICU admission with the subsequent administration of antimicrobials. This approach was carried out by following the definition of suspicion of infection used by Finkelsztein and colleagues.

Sepsis-3 definitions
The Sepsis-3 categories are defined as follows: Sepsis is identified as an acute change in the total SOFA score ≥2 points that is a result of the infection. The baseline SOFA score is assumed to be 0 in patients not known to have preexisting organ dysfunction.

Septic shock is identified with a clinical construct of sepsis if the patient has persistent hypotension that requires vasopressors to maintain a MAP >65 mmHg and if they have a serum lactate level >2 mmol/L despite adequate fluid resuscitation.

Sepsis-1 definitions
The Sepsis-1 categories (sepsis and septic shock) were defined according to previously published consensus. Sepsis was identified with documented or as suspected infection and ≥2 signs of SIRS. Septic shock was defined as suspected infection, ≥2 SIRS signs and persistent hypotension that required vasopressors to maintain a MAP >65 mmHg despite adequate fluid resuscitation.

Assessment of qSOFA and SIRS
Patients with suspected infection were identified with the qSOFA score, including alterations in mental status, systolic blood pressure ≤100 mmHg, or a respiratory rate ≥22 breaths/min.

SIRS was identified with ≥2 of the following four signs: temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, and white blood cell count >12,000/mm³ or <4000/mm³ or >10% immature forms. As proposed by Bone et al, one point was awarded for each of the four conditions, and the score ranged from 0 to 4.

Data Collection
To ensure data validity and reliability, two data collectors were supported by a continuous online webchat. We provided important study information through emails and online training, including the protocol, answers to questions and a description of the electronic case report form (eCRF) on the electronic tablets. We collected data from medical and nursing records, including age; gender; worst and best vital signs through emails and online training, including the protocol, answers to questions and a description of the electronic case report form (eCRF) on the electronic tablets. We collected data from medical and nursing records, including age; gender; worst and best vital signs; etiological diagnosis; Infection source; ICU length of stay (LOS); organ support measures; and initial lactate level on the first ICU day; Acute Physiology and Chronic Health Evaluation (APACHE) II score; first day total SOFA score; etiologic diagnosis; Infection source; ICU length of stay (LOS); organ support measures; and initial lactate level on the first day. Laboratory variables were retrieved from the electronic health database. Patient visits were performed 30 days after enrollment through telephone interviews. The primary end point was all-cause 30-day mortality.

Statistical analysis
Continuous variables are presented as the mean ± standard deviation (SD), and compared using independent sample t-test. Differences in proportions were compared using Chi-square test or Fisher exact test. We evaluated Sepsis-3 definitions and Sepsis-1 definitions by logistic regression analysis followed by measurement of the AUROC for predicting 30-day mortality rates. AUROCs were compared using DeLong test. All statistical analyses were performed using SPSS version 16.0 (SPSS Inc.,
Chicago, IL, USA). A P < 0.05 (two-tailed) was considered as statistically significant.

Results

Characteristics

Of the 993 ICU patients with suspected infection during the study period, 244 patients were excluded. The remaining 749 patients were enrolled in the study [Figure 1]. The mean age of these 749 patients was 63.4 ± 12.3 years; 74.8% were male, and the mean APACHE II score was 21.4 ± 8.2. The most common infection was respiratory infections (429/749, 55.8%), followed by urinary tract infections (167/749, 20.9%) and abdominal infections (69/749, 8.7%; Table 1).

According to the Sepsis-1 definitions, there were 644 patients diagnosed with sepsis (644/749, 85.9%), among whom 362 patients were diagnosed with septic shock (362/749, 48.3%). According to the Sepsis-3 definitions, there were 483 patients diagnosed with sepsis (483/749, 64.5%), among whom 299 patients were diagnosed with septic shock (299/749, 39.9%) [Figure 1]. Among the 749 patients enrolled in the study, 170 (22.6%) patients only met the Sepsis-1 definitions, while nine (1.2%) patients only met the Sepsis-3 definitions. A total of 474 (63.3%) patients met both definitions. The remaining 96 (12.8%) met neither definitions. The APACHE II and SOFA scores were significantly higher in patients who met both sets of criteria than those in the other groups [Table 1].

Mortality

Of the 749 enrolled patients, the total 30-day mortality rate was 29.1% [Table 1]. The mortality of patients who met both definitions (38.2%) was significantly higher than those of patients who met Sepsis-1 definitions alone (15.3%, $\chi^2 = 16.919, P < 0.010$) or who met neither criteria (9.3%, $\chi^2 = 17.537, P < 0.010$) [Table 1]. The Sepsis-1 definitions and Sepsis-3 definitions showed significant differences in 30-day mortality among the three categories (non-sepsis, sepsis, and septic shock; all $P < 0.001$) [Figure 2]. Additionally, according to the Sepsis-3 definitions, sepsis (sepsis and septic shock) patients had higher 30-day mortality (41.8%) than sepsis patients according to the Sepsis-1 definitions (31.8%, $\chi^2 = 5.552, P = 0.020$).

Logistic regression analysis

The patients were divided into survival group ($n = 531$) and non-survival group ($n = 218$) depending on outcome. Many demographic and other variables were collected from the patient medical records. The single variable analysis showed that there were significant differences in APACHE II score, qSOFA score, SOFA score, SIRS score, initial serum lactate level and the percentage of sepsis or septic shock patients between the two groups ($P < 0.05$) [Table 2]. Table 3 shows the associations of sepsis definitions with the 30-day mortality in the binary logistic regression, indicating that sepsis (odd ratio [OR]: 2.205, 95% confidence interval [CI]: 1.160–4.192, $P < 0.05$) and septic shock (OR: 7.321, 95% CI, 3.985–13.450, $P < 0.001$) and septic shock patients according to the Sepsis-1 or Sepsis-3 definitions were two independent risk factors for the 30-day mortality.

Sensitivity analyses

There is no gold standard for sepsis diagnosis. Therefore, this study evaluated the performance of Sepsis-1 and Sepsis-3 definitions in predicting the 30-day mortality.
using ROC curves. The AUROC of the Sepsis-3 model with regard to the 30-day mortality rates was 0.746 (0.710–0.783). However, the AUROC of the Sepsis-1 model [0.620 (0.577–0.663)] was significantly lower than that of the Sepsis-3 model [0.746 (0.710–0.783), \( P < 0.01 \); Table 3]. Additionally, the sensitivity (72.8%) and the specificity (69.0%) of the Sepsis-3 model with respect to the 30-day mortality were higher than those of the Sepsis-1 model (63.3% and 57.8%, respectively).

We also evaluated the performance of SIRS, qSOFA, and SOFA in predicting the 30-day mortality using ROC curves. The results showed that the AUROC of SIRS and qSOFA with regard to the 30-day mortality were 0.609 (0.566–0.652) and 0.694 (0.654–0.733), respectively. However, the AUROC of SOFA (0.828 [0.795–0.862]) was significantly higher than that of SIRS (0.609 [0.566–0.652]) or qSOFA (0.694 [0.634–0.733]; all \( P < 0.001 \) [Figure 3].
In the present study, we demonstrated that the Sepsis-3 definition was better than the Sepsis-1 definition at stratifying mortality among adult critically ill patients with suspected infection. Logistic regression showed that sepsis and septic shock were two independent risk factors for the 30-day mortality. According to the Sepsis-3 definition, the 30-day mortality was higher in septic shock patients than that according to the Sepsis-1 definition. Furthermore, the AUROC of the Sepsis-3 model was significantly higher than that of the Sepsis-1 model when used to predict 30-day mortality in patients with suspected infection.

A higher specificity and a better distinction between sepsis and non-sepsis have always been demanded in the past. In the present study, 85.9% of the patients with suspected infections admitted to the ICUs met the Sepsis-1 definition. A total of 22.6% of the patients were diagnosed with sepsis according to the Sepsis-1 definition but were excluded according to the Sepsis-3 definition, which differed from a previous study. The main probable reason was that the

Table 2: General characteristics and support measures of patients according to outcome.

| Variables                  | Whole group (n = 749) | Survivors (n = 531) | Non-Survivors (n = 218) | $F/\chi^2$ | $P$  |
|----------------------------|----------------------|---------------------|-------------------------|------------|------|
| Age (years)                | 63.4 ± 12.3          | 62.8 ± 12.4         | 64.8 ± 11.9             | 4.024      | 0.045|
| Male                       | 560 (74.8)           | 388 (73.7)          | 172 (78.9)              | 0.396      | 0.542|
| APACHE II score            | 21.4 ± 8.2           | 19.1 ± 7.1          | 26.9 ± 7.9              | 176.015    | <0.001|
| Initial lactate (mmol/L)   | 3.4 ± 2.1            | 2.8 ± 1.7           | 4.7 ± 2.4               | 152.386    | <0.001|
| Initial SIRS score         | 2.6 ± 1.1            | 2.4 ± 1.1           | 2.8 ± 0.8               | 26.712     | <0.001|
| Initial qSOFA score        | 2.0 ± 0.9            | 1.8 ± 0.9           | 2.5 ± 0.7               | 87.787     | <0.001|
| SOFA score                 | 5.7 ± 4.7            | 4.0 ± 3.7           | 9.7 ± 4.3               | 318.240    | <0.001|
| Infection source           |                      |                     |                         |            |      |
| Pneumonia                  | 429 (55.8)           | 308 (58.0)          | 121 (55.5)              |            |      |
| Urinary tract              | 167 (20.9)           | 116 (21.8)          | 51 (23.4)               |            |      |
| Abdominal                  | 69 (8.7)             | 51 (9.6)            | 18 (8.3)                |            |      |
| Skin and soft tissue       | 20 (1.6)             | 14 (2.6)            | 6 (2.7)                 |            |      |
| Catheter related           | 40 (5.7)             | 28 (5.3)            | 12 (5.5)                |            |      |
| Primary bloodstream infection| 17 (2.3)            | 10 (1.9)            | 7 (3.2)                 |            |      |
| Unidentifiable source      | 5 (0.7)              | 3 (0.6)             | 2 (0.9)                 |            |      |
| Others                     | 2 (0.3)              | 1 (0.2)             | 1 (0.5)                 |            |      |
| Sepsis-1 definition        |                      |                     |                         | 32.402     | <0.001|
| Non-Sepsis                 | 105 (14.1)           | 92 (17.3)           | 13 (6.0)                |            |      |
| Sepsis                     | 282 (37.6)           | 215 (40.4)          | 67 (30.7)               |            |      |
| Septic shock               | 362 (48.3)           | 224 (42.2)          | 138 (63.3)              |            |      |
| Sepsis-3 definition        |                      |                     |                         | 141.992    | <0.001|
| Non-Sepsis                 | 266 (35.5)           | 250 (47.1)          | 16 (6.9)                |            |      |
| Sepsis                     | 184 (24.6)           | 128 (24.1)          | 56 (93.1)               |            |      |
| Septic shock               | 299 (39.9)           | 153 (28.8)          | 146 (67.4)              |            |      |
| ICU length of stay (days)  | 7.3 ± 5.7            | 7.3 ± 5.9           | 7.4 ± 5.1               | 0.081      | 0.775|
| Duration on mechanical ventilation (h) | 63.3 ± 51.1 | 62.7 ± 53.6 | 64.6 ± 43.6 | 0.173      | 0.677|

The data were shown as mean ± SD or n (%). $F$ values, otherwise $\chi^2$ values. APACHE II: Acute physiology and chronic health evaluation II; ICU: Intensive care unit; qSOFA: Quick sequential organ failure assessment; SD: Standard deviation; SIRS: Systemic inflammatory response syndrome.

Table 3: Multivariate regression models using 30-day mortality as a dependent variable.

| Items                  | Model predictive value | Model accuracy |
|------------------------|------------------------|----------------|
|                        | OR (95% CI)            | AUC (95% CI)  |
|                        |                        | Sensitivity   |
|                        |                        | Specificity   |
| Sepsis-3 model         |                        |               |
| Constant               | 0.06                   | 0.746 (0.710–0.783) | 72.8% | 69.0% |
| Sepsis                 | 2.211 (1.501–3.256)    | <0.001        |               |
| Septic shock           | 7.321 (3.985–13.450)   | <0.001        |               |
| Sepsis-1 model         |                        |               |
| Constant               | 0.141                  | 0.620 (0.577–0.663) | 63.3% | 57.8% |
| Sepsis                 | 1.997 (1.398–2.796)    | <0.001        |               |
| Septic shock           | 2.205 (1.160–4.192)    | <0.001        |               |

$^* P < 0.010$, Sepsis-3 model vs. Sepsis-1 model. AUC: Area under curve; CI: Confidence interval; OR: Odds ratio.

**Discussion**

In the present study, we demonstrated that the Sepsis-3 definition was better than the Sepsis-1 definition at stratifying mortality among adult critically ill patients with suspected infection. Logistic regression showed that sepsis and septic shock were two independent risk factors for the 30-day mortality. According to the Sepsis-3 definition, the 30-day mortality was higher in septic shock patients than that according to the Sepsis-1 definition. Furthermore, the AUROC of the Sepsis-3 model was significantly higher than that of the Sepsis-1 model when used to predict 30-day mortality in patients with suspected infection.

A higher specificity and a better distinction between sepsis and non-sepsis have always been demanded in the past. In the present study, 85.9% of the patients with suspected infections admitted to the ICUs met the Sepsis-1 definition. A total of 22.6% of the patients were diagnosed with sepsis according to the Sepsis-1 definition but were excluded according to the Sepsis-3 definition, which differed from a previous study. The main probable reason was that the
patients included in this study were different from those in the previous study. All patients in this study were admitted to the ICU, while only 37.5% of patients in the study of Cheng et al[15] were admitted to the ICU. Furthermore, according to the Sepsis-3 definition, 64.5% of the suspected infection patients were diagnosed with sepsis. Thus, relative to the results with the Sepsis-1 definitions, fewer patients with suspected infection were classified as having sepsis according to the Sepsis-3 definitions. Additionally, this study indicated that sepsis patients as defined by the Sepsis-3 definitions had a higher mortality rate. Therefore, the findings supported the use of the Sepsis-3 definition to identify critically ill patients with suspected infection who are at high risk of death.

In the validation of clinical criteria for sepsis, the Sepsis-3 definition for identifying sepsis patients has been extensively questioned since its publication.[3,4,11-13] Retrospective cohort studies showed a better discriminative performance of the Sepsis-3 definition in predicting mortality compared to the Sepsis-1 or Sepsis-2 criteria.[6,14,15] In this multicenter, prospective cohort study, we further evaluated the Sepsis-3 and Sepsis-1 definitions by logistic regression analysis followed by measurement of the AUROC for predicting 30-day mortality rates. The AUROC of the Sepsis-3 model was significantly higher than that of the Sepsis-1 model when used to predict 30-day mortality rates in patients with suspected infection. Furthermore, the sensitivity and specificity of the Sepsis-3 model for predicting the 30-day mortality were relatively low (72.8% and 69.0%, respectively) but were higher than those of the Sepsis-1 model (63.3% and 57.8%, respectively). Therefore, the Sepsis-3 definition was more accurate in stratifying mortality and superior to the Sepsis-1 definition in adult critically ill patients with suspected infection.

The Sepsis-3 definition summarizes two conditions: sepsis and septic shock.[16-17] The additional request for a lactate level of ≥ 2 mmol/L in the septic shock definition enables the identification of a high-risk group.[18] The present study suggested that, by applying the Sepsis-3 definition, the proportion of septic shock decreased 8.4%, with a 9% mortality increase compared to the Sepsis-1 definitions. The Sepsis-3 definitions identified sepsis and septic shock patients as having higher mortality, while the non-sepsis patients had lower mortality compared to the Sepsis-1 definition. Thus, the critically serious patients were identified by the new definition. This also suggested that Sepsis-3 definition was better than Sepsis-1 definition at stratifying mortality among septic patients admitted to the ICU.

Previous studies indicated that the number of SIRS criteria present could not be used to stratify the severity of illness.[19] The Sepsis-3 definition exclude the concept of SIRS since this term is no longer considered useful.[20] The SOFA and qSOFA scores have been used as two diagnostic tools to identify sepsis with the Sepsis-3 definition.[3,4] We further evaluated the performance of SIRS and qSOFA and SOFA scores using an ROC curve to predict the 30-day mortality. The AUROC of SIRS and qSOFA scores with regard to 30-day mortality rates were 0.609 (0.566–0.652) and 0.694 (0.654–0.733), respectively. However, the AUROC of SOFA scores (0.828 [0.795–0.862]) was significantly higher than that of SIRS or qSOFA scores. This meant that the SOFA score was an excellent tool and superior to SIRS or the qSOFA score for predicting mortality in critically ill patients with suspected infection.

The present study had strength and some limitations. The strength was that the size of the cohort was relatively large. Our study had several limitations. First, we followed our patients for only 30 days and did not collect data beyond that point. Long-term survival rates will be explored in the future. Second, we evaluated only patients admitted to the ICU; thus, our findings could not be generalized to patients treated in regular wards and in the emergency room. Third, the validity of the Sepsis-3 definition in this study was assessed based on the 30-day mortality. Although the 30-day mortality is widely used, the 28-day mortality and ICU mortality were used as endpoints in some studies, possibly causing deviations in results among studies.[14,15,20,23,25]

In conclusion, this study showed that the new clinical criteria of sepsis proposed in the Sepsis-3 definitions predicted the 30-day mortality in adult critically ill patients with suspected infection. The Sepsis-3 definition was relatively accurate and superior to the Sepsis-1 definition in stratifying mortality. Our findings supported the translation of the Sepsis-3 definitions into sepsis definitions in adult critically ill patients with suspected infection.

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