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COMPARISON OF THE PERFORMANCE BETWEEN SEPSIS-1 AND SEPSIS-3 IN ICUS IN CHINA: A RETROSPECTIVE MULTICENTER STUDY

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ABSTRACT—The definition of sepsis was updated to sepsis-3 in February 2016. However, the performance of the previous and new definition of sepsis remains unclear in China. This was a retrospective multicenter study in six intensive care unit (ICUs) from five university-affiliated hospitals to compare the performance between sepsis-1 and sepsis-3 in China. From May 1, 2016 to June 1, 2016, 496 patients were enrolled consecutively. Data were extracted from the electronic clinical records. We evaluated the performance of sepsis-1 and sepsis-3 by measuring the area under the receiver operating characteristic curves (AUROC) to predict 28-day mortality rates. Of 496 enrolled patients, 186 (37.5%) were diagnosed with sepsis according to sepsis-1, while 175 (35.3%) fulfilled the criteria of sepsis-3. The AUROC of systemic inflammatory response syndrome (SIRS) is significantly smaller than that of sequential organ failure assessment (SOFA) (0.55 [95% confidence interval, 0.46–0.64] vs. 0.69 (95% confidence interval, 0.61–0.77], $P = 0.008$) to predict 28-day mortality rates of infected patients. Moreover, 5.9% infected patients (11 patients) were diagnosed as sepsis according to sepsis-1 but not to sepsis-3. The APACHE II, SOFA scores, and mortality rate of the 11 patients were significantly lower than of patients whose sepsis was defined by both the previous and new criteria (8.6±3.5 vs. 16.3±6.2, $P = < 0.001$; 1 (0–1) vs. 6 (4–8), $P = < 0.001$; 0.0 vs. 33.1%, $P = 0.019$). In addition, the APACHE II, length of stay in ICU, and 28-day mortality rate of septic patients rose gradually corresponding with the raise in SOFA score (but not the SIRS score). Sepsis-3 performed better than sepsis-1 in the study samples in ICUs in China.

KEYWORDS—China, ICU, sepsis criteria performance, sepsis-3

ABBREVIATIONS—APACHE II—acute physiology and chronic health evaluation II; AUROC—area under receiver operating characteristic; CRP—C-reactive protein; ER—emergency room; ICU—intensive care unit; LOS—length of stay; PCT—procalcitonin; SD—standard deviation; SOFA—sequential organ failure assessment; SPSS—statistical package for social science; USD—United States dollar

INTRODUCTION

Although sepsis has attracted the attention of physicians and researchers because it is the leading cause of mortality and a major health burden worldwide, the definition of sepsis remains debatable (1–6). Therefore, in February 2016, based on clarity and content validity, and following literature reviews and expert deliberation, the Third International Consensus Task Force convened by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine (the Consensus) redefined sepsis as ''life-threatening organ dysfunction due to a dysregulated host response to infection'' (7, 8). It then revised and validated the new clinical criteria for sepsis (sepsis-3) using US electronic healthcare databases (9).

Intensive care units (ICUs) are rare recourses worldwide. China is a mid-income developing country with limited healthcare resources, so a more precise strategy is needed for admitting very severely ill patients to ICUs (10–12). Sepsis-1, which defined sepsis as a host's systemic inflammatory response syndrome (SIRS) to infection, and the presence of symptoms meeting two or more SIRS criteria as an inflammatory response, was always criticized because of its poor specificity (5, 6, 13–16). In 2001, the Consensus recognized this limitation but failed to offer alternatives because of the lack of supporting evidence (17). Until now, the main diagnostic criteria for sepsis used in ICUs in China are still sepsis-1 (infection plus two or more SIRS). Validation of the more specific sepsis-3 criteria is therefore urgently needed in China.

We conducted the present retrospective multicenter study to evaluate the performance of sepsis-1 and sepsis-3 in China using the area under receiver operating characteristic (AUROC) curves to predict 28-day mortality rates. We also investigated the possibility of using sequential organ failure assessment (SOFA) scores to grade the severity of sepsis.

METHODS

Ethical statement

The Medical Ethical Committee of Zhejiang University approved the study. The need for informed consent was waived because of the retrospective and observational design of the study.

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BC and XF designed the study. BC and GX drafted the manuscript. ZL, LC, and JZ collected the data. BC, XL, and ZX analyzed the data. YY critically revised the manuscript. All authors read and approved the final manuscript.

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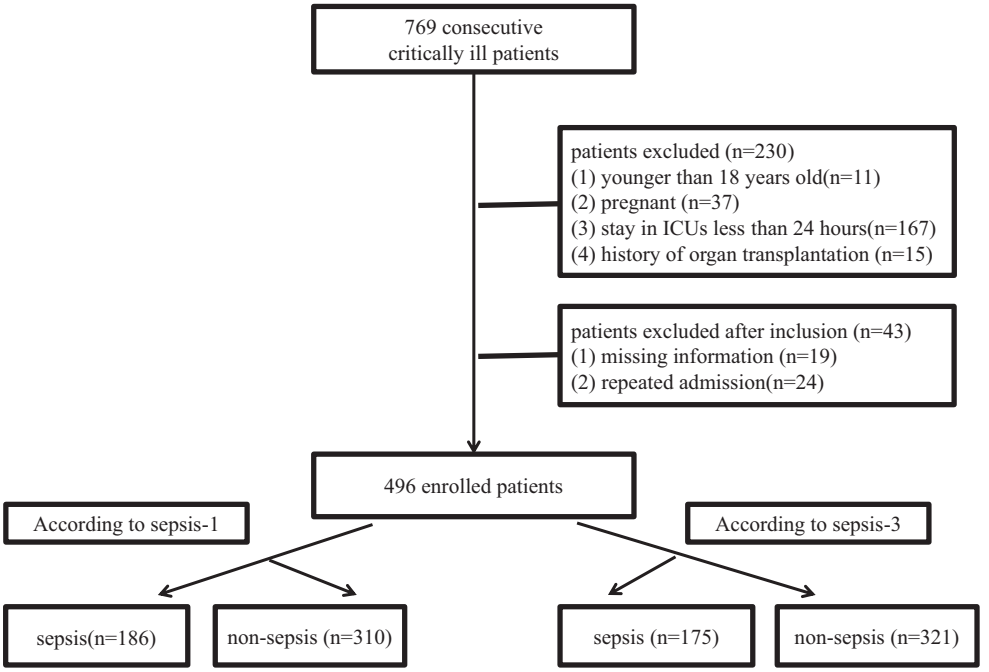

Fig. 1. **Flowchart of enrollment in the present study.** Of the 769 critically ill patients admitted to the study ICUs between May 1, 2016 and June 1, 2016, 496 patients were enrolled and 273 patients were excluded for the following reasons: ICU stays of less than 24 h, missing information, pregnancy, or not adult. According to the criteria for infection, 186 patients were diagnosed as infected patients. We used this group to test the performance of sepsis-1 and sepsis-3. ICU indicates intensive care unit.

Settings

The present study was conducted at six intensive care units with approximately 100 beds in total in five Zhejiang University teaching hospitals (approximately 10,000 hospital beds). All the septic patients were treated according to the International guidelines for the management of severe sepsis and septic shock (2012) (18).

Patients

In total, 769 critically ill patients were consecutively admitted to the study ICUs between May 1, 2016 and June 1, 2016. Patients were excluded from the study for the following reasons: younger than 18 years old, ICUs stays of less than 24 h, history of organ transplantation, for those patients are cared by another group of specialists, pregnancy, information missing but needed to fulfill the sepsis-1 or sepsis-3 criteria. If patients were admitted to the same ICU more than once for the same episode of sepsis, only the first ICU admission was counted. The final number of patients enrolled in the study was 496. Figure 1 shows details of inclusion and exclusion criteria for the study.

Diagnosis

Infection was suspected in all patients who had cultures submitted and who were started on antibiotics within a 24 h window.

Sepsis-1 defines sepsis as infection-induced SIRS (13). The clinical criterion is suspected infection plus SIRS. A diagnosis of SIRS is appropriate where at least two of the following signs are present: heart rate faster than 90 beats per min; respiratory rate faster than 20 breaths per min; leukocyte count greater than 12,000/μL or less than 4,000/μL; temperature less than 36°C or greater than 38°C. The present study assessed the SIRS criteria within the first 24 h of admission to ICU.

Sepsis-3 defines sepsis as a life-threatening organ dysfunction due to a dysregulated host response to infection (7–9). The clinical criterion is suspected infection plus SOFA $\geq$2. In the present study, SOFA scores were recorded within the first 24 h of admission to ICU. The different criteria of sepsis-1 and sepsis-3 to candidate sepsis in patients with suspected infection are listed in Table 1.

Data collection

Two trained research assistants retrospectively collected the following data from the electronic clinical records: gender, age, admission origin (from emergency room or not), relevant information about infection (clinical, imaging, and microbiological signs), procalcitonin (PCT), and C-reactive protein levels, length of ICU and hospital stays, and 28-day mortality outcome (survival or death). We recorded the whole medical cost from the electronic clinical records of the hospitals, and converted them to US dollar according to the current exchange rate on June 26, 2016 when we analyzed the data. We also extracted information for SIRS, Acute Physiology and Chronic Health Evaluation (APACHE) II and SOFA scores within the first 24 h of admission to ICU.

The data were stored in a Microsoft Access database. Another two trained research assistants randomly extracted 10% of cases from the database to check the completeness, accuracy, and relevance of the information.

Statistical analysis

Variables with a normal distribution were presented as mean $\pm$ standard deviation (SD); variables with a skewed distribution were presented as medians and quartiles. Numerical data were presented as numbers and percentages, as appropriate. Groups were compared with *t* tests or non-parametric Kruskal–Wallis tests, where applicable. The chi-square test was used for comparison of frequencies. The Jonckheere–Terpstra test was used for comparison of continuous variables. AUROC of SIRS and SOFA scores were plotted and used to predict 28-day mortality rates of the groups. Binary multivariable logistic regression (forward LR) was used to determine the contribution of the SOFA score to the sepsis outcome. All tests were two-sided with a significance level of $P < 0.05$. All statistical analysis was conducted using the Statistical Package for the Social Sciences (IBM SPSS 20.0).

RESULTS

Demographics

Of 769 patients admitted to the six ICUs during the study period, 496 patients were enrolled in the study. The average age of the 496 patients was 58.3 $\pm$ 17.1 years old; 59.1% were male, and the mean APACHE II score was 13.5 $\pm$ 6.4. The total 28-day mortality rate was 20.4%, and patients' ICU and hospital stays were 6 (4–12) and 21 (11–34) days, respectively. The enrollment process is summarized in Figure 1.

Of the 496 patients, 186 (37.5%) were considered to have suspected infection at admission to ICU. There were 170 (91.4%)

TABLE 1. **The different criteria to candidate sepsis among patients with suspected infection in present study**

Sepsis-1	Sepsis-3					
	Sequential (sepsis-related) organ failure assessment (SOFA) ≥2 scores					
Systemic inflammatory response syndrome (SIRS) ≥2 criteria	System	Scores				
		0	1	2	3	4
Respiratory rate >20/min or $PaCO_2$ <32 mm Hg (4.3 kPa)	Respiration (PaO2/FIO2, mm Hg (kPa))	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Temperature >38°C or <36°C	Coagulation (platelets, $\times 10^3/\mu L$)	≥150	<150	<100	<50	<20
Heart rate >90/min	Liver (bilirubin, mg/dL[μmol/L])	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
White blood cell count >12,000/mm^3 or <4,000/mm^3 or >10% immature bands	Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
	Central nervous system (Glasgow Coma Scale score)	15	13–14	10–12	6–9	<6
	Renal (creatinine, mg/dL (μmol/L))	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
	Urine output, mL/d				<500	<200

cases that have positive culture. The most common infection was pneumonia (91/186, 48.9%), followed by blood stream infections (38/186, 20.4%) and abdominal infections (18/186, 9.70%). All infected patients fulfilled the sepsis-1 criteria, while 175 (94.1%) were diagnosed as sepsis according to the sepsis-3 criteria. And all the 175 patients identified using Sepsis-3 were among the 186 septic cases identified by Sepsis-1.

Patients diagnosed with sepsis-3 were significantly older than the non-sepsis patients; however, there was no difference in age between sepsis patients diagnosed with sepsis-1 and non-sepsis patients. The APACHE II and SOFA scores in the first 24 h after admission to ICU were significantly higher in sepsis patients as defined by both sepsis-1 and sepsis-3. Sepsis patients diagnosed using sepsis-1 or sepsis-3 stayed longer in ICU than non-sepsis patients. The mortality of sepsis-1 patients was 31.2% (58/186), and of sepsis-3 patients 33.1% (58/175). Detailed characteristics are shown in Table 2.

SIRS in infected patients

All suspected infection patients fulfilled two or more SIRS criteria. It has been reported that disease severity and mortality rise as the number of SIRS criteria fulfilled increases (19). However, there were no significant differences in APACHE II or SOFA scores, PCT levels, length of stay (LOS) in ICU/hospital, or 28-day mortality rates of infected patients based on the number of SIRS criteria present at admission. Table 3 shows the details.

SOFA in suspected infection patients

A SOFA score of ≥2 was recorded in 94% of patients in the first 24 h after infection. SOFA has been used to grade disease severity in many critically ill populations (20). In the present study, we found a gradual and significant increase in APACHE II scores, PCT levels, LOS in ICUs, and 28-day mortality rates corresponding to the increase in SOFA score. Table 4 shows the details.

Patients excluded by sepsis-3

Using sepsis-1, 11 (5.9% infected patients) patients were diagnosed with sepsis but they did not fulfill the criteria of sepsis-3. The characteristics of those 11 excluded patients are listed in Table 5. The culture positive rate of those 11 cases is significantly lower than the sepsis patients who fulfilled both the sepsis 1.0 and sepsis 3.0 criteria (54.5% vs. 93.7%, $P = 0.001$). The APACHE II and SOFA scores and LOS in ICU of the 11 patients were significantly lower than of patients whose sepsis was defined by both the previous and new criteria. Moreover, the SOFA scores were even lower than that for non-sepsis patients. All 11 patients survived. The mean cost of each patient is 12033.1 ± 7221.8 USD.

Performance of sepsis-1 and sepsis-3

As discussed in the sepsis-3 development paper, there is no gold standard for sepsis diagnoses (7–9). Therefore, we also evaluated the performance of sepsis-1 and sepsis-3 using a ROC curve to predict 28-day mortality rates. All the decedents had two or more SOFA and 91.4% (117/128 cases) of survivors had less than 2 SOFA points. And all the 186 cases had two or more SIRS

Table 2. **Demographics and clinical characteristics of patients**

		Sepsis-1			Sepsis-3		
	Total	Non-sepsis	Sepsis	P^*	Non-sepsis	Sepsis	$P^\dagger$
Patients (n, %)	496	310, 62.5	186, 37.5	—	321, 64.7	175, 35.3	—
Age (years, mean ± SD)	58.3 ± 17.1	57.3 ± 16.1	59.9 ± 18.4	0.111	57.0 ± 16.6	60.6 ± 17.7	0.026
Gender/male (n, %)	293, 59.1	167,53.8	126,67.7	0.002	175,54.5	118,67.4	0.005
Origin/from ER (n, %)	259, 52.2	136, 43.9	123, 66.1	<0.001	143,44.5	116,66.3	<0.001
PCT (ng/mL, median [quartiles])	0.8 (0.4–4.2)	0.6 (0.4–2.8)	1.0 (0.5–4.9)	0.227	0.6 (0.4–2.1)	1.0 (0.5–5.2)	0.090
CRP (mg/L, median [quartiles])	15.2 (3.8–54.5)	11.0 (3.0–33.4)	35.0 (9.9–121.5)	<0.001	8.8 (2.4–29.1)	36.7 (11.3–121.5)	0.000
APACHE II (mean ± SD)	13.5 ± 6.4	12.1 ± 6.0	15.8 ± 6.3	<0.001	12.0 ± 6.0	16.3 ± 6.2	<0.001
SOFA (median [quartiles])	4 (3–7)	4 (2–6)	6 (4–8)	<0.001	4 (2–6)	6 (4–8)	<0.001
Respiration	1 (0–2)	1 (0–2)	2 (1–3)	<0.001	1 (0–2)	2 (1–3)	<0.001
Cardiovascular	0 (0–3)	0 (0–3)	0 (0–4)	0.597	0 (0–3)	0 (0–4)	0.215
Liver	0 (0–1)	0 (0–1)	0 (0–1)	0.277	0 (0–1)	0 (0–1)	0.117
Renal	0 (0–0)	0 (0–0)	0 (0–1)	<0.001	0 (0–0)	0 (0–1)	<0.001
Coagulation	0 (0–1)	0 (0–1)	0 (0–1)	0.231	0 (0–1)	0 (0–1)	0.067
Central nervous system	0 (0–2)	0 (0–0)	0 (0–3)	0.004	0 (0–0)	0 (0–3)	0.001
LOS in hospital (days, median [quartiles])	19 (12–30)	17 (13–28)	22 (12–35)	0.141	17 (13–28)	22 (12–36)	0.114
LOS in ICU (days, median [quartiles])	4 (3–8)	4 (2–6)	6 (4–12)	<0.001	3 (2–6)	6 (4–12)	<0.001
Cost (USD, mean ± SD)	14,467.1 ± 12,914.5	14,441.0 ± 12,951.1	14,513.9 ± 12,890.8	0.955	14,364.7 ± 12,808.2	14,668.9 ± 1,3164.4	0.818
28-day mortality (n, %)	101, 20.4	43, 13.9	58, 31.2	<0.001	43, 13.4	58, 33.1	<0.001

*Comparison between sepsis and nonsepsis patients according to sepsis-1.
†Comparison between sepsis and nonsepsis patients according to sepsis-3.
APACHE II indicates acute physiology and chronic health evaluation II; CRP, C-reactive protein; ER, emergency room; ICU, intensive care unit; LOS, length of stay; PCT, procalcitonin; SD, standard deviation; SOFA, sequential organ failure assessment; USD, United States dollar.

criteria no matter they survived or not. The AUROC value of SIRS is significantly lower than that of SOFA (0.55 [95% confidence interval, 0.46–0.64] vs. 0.69 [95% confidence interval, 0.61–0.77], $P = 0.008$). The curves are shown in Figure 2. The data regarding overlap between Sepsis-1 and Sepsis-3 indicates that the false positive rate for Sepsis-1 is nearly 50%.

DISCUSSION

The present retrospective multicenter study demonstrated that sepsis-3 performed better than sepsis-1 in China and was comparable with its performance in the primary derived and validated population. The AUROC value of SOFA is significantly higher than that of SIRS when used to predict 28-day

Table 3. **Characteristics and outcomes of infected patients according to number of SIRS criteria on admission (n = 186)**

	SIRS 2	SIRS 3	SIRS 4	*P*
Patients (n, %)	104, 55.9	60, 32.3	22, 11.8	—
APACHE II (mean ± SD)	15.22 ± 6.23	16.22 ± 6.28	17.36 ± 6.72	0.112
PCT (ng/mL, median [quartiles])	0.69 (0.29–4.14)	1.45 (0.49–5.94)	1.12 (0.67–10.87)	0.054
SOFA (median [quartiles])	5.00 (3.00–8.00)	6.00 (4.00–8.00)	6.00 (4.00–10.25)	0.104
LOS in hospital (days, median [quartiles])	19.50 (12.00–34.00)	22.00 (11.25–35.25)	23.00 (11.00–43.50)	0.698
LOS in ICU (days, median [quartiles])	6.00 (4.00–13.00)	6.00 (4.00–12.00)	6.00 (3.75–11.00)	0.834
28-day mortality rate (%)	28.9	38.3	31.8	0.315

APACHE II indicates acute physiology and chronic health evaluation II; ICU, intensive care unit; LOS, length of stay; PCT, procalcitonin; SD, standard deviation; SOFA, sequential organ failure assessment.

Table 4. **Characteristics and outcomes of infected patients according to SOFA scores on admission (n = 186)**

	SOFA<2	SOFA 2–10	SOFA≥10	*P* value
Patients (n, %)	11, 5.9	147, 79.0	28, 15.1	
APACHE II (mean ± SD)	8.6 ± 3.5	15.0 ± 5.6	22.7 ± 5.2	<0.001
PCT (ng/mL, median [quartiles])	0.4 (0.3–0.6)	0.8 (0.4–4.3)	3.5 (1.0–13.3)	0.003
LOS in hospital (days, median [quartiles])	18 (12–25)	22 (12–36)	20 (5–41)	0.692
LOS in ICU (days, median [quartiles])	3 (2–4)	6 (4–12)	8 (4–18)	0.005
28-day mortality rate (%)	0.0	27.9	60.7	<0.001

APACHE II indicates acute physiology and chronic health evaluation II; ICU, intensive care unit; LOS, length of stay; PCT, procalcitonin; SD, standard deviation; SOFA, sequential organ failure assessment.

TABLE 5. **Characteristics and outcomes of patients (n = 11) diagnosed with sepsis according to sepsis-1 but excluded according to sepsis-3**

	Only sepsis-1	Sepsis-3 and sepsis-1	P^*	Non-sepsis	$P^\dagger$
Age (years, mean ± SD)	48.2 ± 26.4	60.6 ± 17.7	0.153	57.3 ± 16.1	0.279
APACHE II (mean ± SD)	8.6 ± 3.5	16.3 ± 6.2	<0.001	12.1 ± 6.0	0.053
SOFA (median [quartiles])	1 (0–1)	6 (4–8)	<0.001	4 (2–6)	<0.001
LOS in ICU (days, median [quartiles])	3 (2–4)	7 (5–11)	0.002	4 (3–10)	<0.001
LOS in hospital (days, median [quartiles])	18 (12–25)	20 (11–35)	0.520	22 (13–32)	0.258
28-day mortality rate (%)	0.0	33.1	0.019	13.9	0.371

*Comparison between "only sepsis-1" patients who were diagnosed with sepsis according to sepsis-1 but not according to sepsis-3, and sepsis-3 and sepsis-1 patients who were diagnosed with sepsis according to sepsis-1 and sepsis-3.
†Comparison between "only sepsis-1" patients who were diagnosed with sepsis according to sepsis-1 but not according to sepsis-3, and non-sepsis patients who were not diagnosed with sepsis either according to sepsis-1 or sepsis-3.
APACHE II indicates acute physiology and chronic health evaluation II; ICU, intensive care unit; LOS, length of stay; SOFA, sequential organ failure assessment.

mortality rates in infected patients. The "sepsis-3" excluded 11 extremely slightly ill cases from "sepsis patients" defined by "sepsis-1." The APACHE II and SOFA scores and LOS in ICU of the 11 patients were significantly lower than of patients whose sepsis was defined by both the previous and new criteria. All 11 patients survived, and all received antibiotic treatment. The APACHE II scores, PCT levels, LOS in ICU, and 28-day mortality rates increased gradually and significantly corresponding with the rise in SOFA score but not SIRS score. Despite obviously distinct characteristics between the ICU in the present study and those in the derived settings, there was no impact on the performance of sepsis-3.

In the present study, all the suspected infection patients admitted in ICUs met two or more SIRS criteria, and 11 (5.9% infected patients) less ill patients were still diagnosed as having sepsis according to sepsis-1 but not to sepsis-3. The disease severity of those 11 patients is significantly slighter than that of patients whose sepsis was defined by both the previous and new criteria. And all of them survived. So the characteristics of 11 patients did not support them as real "sepsis" patients. However, all those 11 cases were treated as sepsis patients according to surviving sepsis guidelines and eight of them were treated by broad-spectrum antibiotics. All the 11 "less ill patients" should not have received antibiotics and those over-treatments have brought considerable burden to our ICUs with limited resource. Only in 1 month on around 100 ICU beds, we spend over 130,000 USD on those "sepsis" patients. According to the data from official website of "Chinese Society of Critical Care Medicine," there are around 4,000 ICUs in China in 2010 with around 80,000 beds. It could be estimated that we spend over 1.2 billion USD annually on those "less ill sepsis" patients nationally.

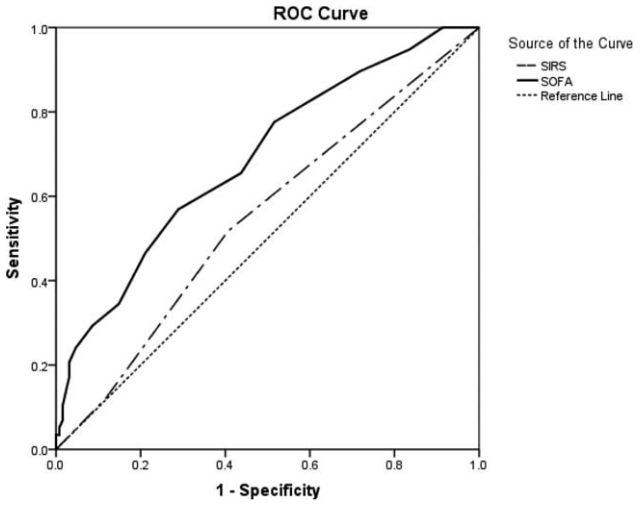

FIG. 2. **Receiver operating characteristic (ROC) curves for SIRS and SOFA scores to predict 28-day mortality rates of infected patients.** The area under ROC curve of the SIRS score is significantly smaller than that of the SOFA score (0.55 [95% CI, 0.46–0.64] vs. 0.69 [95% CI, 0.61–0.77], $P = 0.008$). 95% CI indicates 95% confidence interval; ROC, receiver operating characteristic; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

The AUROC (95% confidence interval, 0.61–0.77) of SOFA with regard to 28-day mortality rates is 0.69 (95% confidence interval, 0.61–0.77) in the present study, which is comparable to the performance in the primary cohort (AUROC = 0.74 [95% confidence interval, 0.73–0.76]) (9). In ICUs of typical tertiary hospitals in China, all the variables are available and most doctors working in these settings prefer to calculate SOFA scores to evaluate organ dysfunction. Collectively, we validated and recommended SOFA score as the defining criterion for organ dysfunction for sepsis-3 in ICUs in China. qSOFA has been validated in patients with pneumonia in China very recently (21), it was developed to scan for sepsis in non-ICU settings, and, like SIRS, only three items may be challenged by its specificity. SOFA scores have performed well for critically ill patients in China in previous studies. It is valuable to validate qSOFA in the present dataset to confirm the conclusion in the Sepsis-3 datasets or identify another arena where qSOFA might be useful in another arena. However, we only recorded the SOFA scores of every organ system but not the values for qSOFA. We have conducted another investigation to validate qSOFA in ICUs in smaller hospitals in China.

We found that the number of SIRS criteria present could not be used to stratify the severity of illness. Kaukonen et al. (22) also documented the inability of SIRS to stratify the severity of illness. SOFA score has been used as a front-line tool to grade disease severity in ICUs (20, 23, 24). We investigated the possibility of grading sepsis according to SOFA scores. APACHE II score, LOS in ICU/hospital, and mortality increased as the SOFA score rose. In infected patients, adjusted for age and gender, SOFA is an independent factor contributing to bad outcome. Further studies could grade sepsis as "mild," "moderate," and "severe" according to SOFA score, in a way

similar to that described in the new Berlin ''ARDS'' criteria (25).

The present study has its strengths and limitations. Strengths include: the first multicenter study to validate the use of sepsis-3 in ICUs in China and also in low- or mid-income countries; evidence that SOFA score may be used to grade the severity of sepsis. Limitations include: the retrospective design; further prospective studies are needed to confirm the results; only 28-days mortality as the endpoint. In the study that developed and validated Sepsis-3 criteria, the outcome assessed was death or an ICU stay > 3 days. But the ICU resources are limited in China, so the strategies that how to admit and discharge from ICUs are quite different compared with developed countries. The length of stay in ICUs is always influenced by many other factors as financial factors, insurance, and limited ICUs beds. We only used death as the endpoint to avoid the deviation; a focus solely on criteria that evaluate the host response to infection, but not on makers to enable precise diagnosis of infections. As reported, between one third and one quarter of patients with signs of clinical infection do not have positive culture results (5–6). We found culture positive infection in 65.1% of 186 patients with infection. Some of the most recently investigated biomarkers, such as elements originating from microorganism or alarmins from the host, may inform development of a further, more precise diagnosis of sepsis in the sepsis-3 era (26).

CONCLUSION

The present study was the first multicenter study conducted in ICUs in China to validate the performance of the new sepsis criteria developed in the US population. We found that sepsis-3 worked well in the study sample. These results may also inform the application of sepsis-3 in various settings or populations, especially in low- and mid-income countries. Further studies are needed to confirm whether SOFA scores can be used to grade the severity of sepsis, which would help to improve the clinical management of sepsis and the allocation of resources in ICUs.

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REFERENCES

1. Martin GS, Mannino DM, Eaton S, Moss M: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 348:1546–1554, 2003.
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR: Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 29:1303–1310, 2001.
3. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D, Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 34:344–353, 2006.
4. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K: International forum of acute care trialists. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med* 193:259–272, 2016.
5. Vincent JL, Mira JP, Antonelli M: Sepsis: older and newer concepts. *Lancet Respir Med* 4:237–240, 2016.
6. Vincent JL, Opal SM, Marshall JC, Tracey KJ: Sepsis definitions: time for change. *Lancet* 381:774–775, 2013.
7. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, et al.: The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 315:801–810, 2016.
8. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, Angus DC, Rubenfeld GD, Singer M, Sepsis Definitions Task Force. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 315:775–787, 2016.
9. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, et al.: Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 315:762–774, 2016.
10. Du B, Xi X, Chen D, Peng J, China Critical Care Clinical Trial Group (CCCCTG). Clinical review: critical care medicine in mainland China. *Crit Care* 14:206, 2010.
11. Robert R, Coudroy R, Ragot S, Lesieur O, Runge I, Souday V, Desachy A, Gouello JP, Hira M, Hamrouni M, et al.: Influence of ICU-bed availability on ICU admission decisions. *Ann Intensive Care* 5:55, 2015.
12. Sakr Y, Moreira CL, Rhodes A, Ferguson ND, Kleinpell R, Pickkers P, Kuiper MA, Lipman J, Vincent JL, Extended Prevalence of Infection in Intensive Care Study Investigators. The impact of hospital and ICU organizational factors on outcome in critically ill patients: results from the extended prevalence of infection in intensive care study. *Crit Care Med* 43:519–526, 2015.
13. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. ACCP/SCCM Consensus Conference Committee; American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 101:1644–1655, 1992.
14. Shetty AL, Brown T, Booth T, Van KL, Dor-Shiffer DE, Vaghasiya MR, Eccleston CE, Iredell J: Systemic inflammatory response syndrome-based severe sepsis screening algorithms in emergency department patients with suspected sepsis. *Emerg Med Australas* 28:287–294, 2016.
15. Vincent JL: Dear SIRS, I'm sorry to say that I don't like you. *Crit Care Med* 25:372–374, 1997.
16. Klein Klouwenberg PM, Ong DS, Bonten MJ, Cremer OL: Classification of sepsis, severe sepsis and septic shock: the impact of minor variations in data capture and definition of SIRS criteria. *Intensive Care Med* 38:811–819, 2012.
17. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G, SCCM/ESICM/ACCP/ATS/SIS. 2001SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 31:1250–1256, 2003.
18. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, et al.: Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 41:580–637, 2013.
19. Sprung CL, Sakr Y, Vincent JL, Le Gall JR, Reinhart K, Ranieri VM, Gerlach H, Fielden J, Groba CB, Payen D: An evaluation of systemic inflammatory response syndrome signs in the Sepsis Occurrence in Acutely Ill Patients (SOAP) study. *Intensive Care Med* 32:421–427, 2006.
20. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S: Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on ''sepsis-related problems'' of the European Society of Intensive Care Medicine. *Crit Care Med* 26:1793–1800, 1998.
21. Chen YX, Wang JY, Guo SB: Use of CRB-65 and quick Sepsis-related Organ Failure Assessment to predict site of care and mortality in pneumonia patients in the emergency department: a retrospective study. *Crit Care* 20:167, 2016.
22. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R: Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med* 372:1629–1638, 2015.
23. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL: Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 286:1754–1758, 2001.
24. Cour M, Bresson D, Hernu R, Argaud L: SOFA score to assess the severity of the post-cardiac arrest syndrome. *Resuscitation* 102:110–115, 2016.
25. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS, The ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 307:2526–2533, 2012.
26. Cartwright M, Rottman M, Shapiro NI, Seiler B, Lombardo P, Gamini N, Tomolonis J, Watters AL, Waterhouse A, Leslie D, et al.: A broad-spectrum infection diagnostic that detects pathogen-associated molecular patterns (PAMPs) in whole blood. *EBio Med* 9:217–227, 2016.