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DO SEPSIS-3 CRITERIA FACILITATE EARLIER RECOGNITION OF SEPSIS AND SEPTIC SHOCK? A RETROSPECTIVE COHORT STUDY

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ABSTRACT—**Background:** New Sepsis-3 criteria are supposed to "facilitate earlier recognition . . . of patients with sepsis." To test this, we performed novel and direct comparisons of Sepsis-1 vs. Sepsis-3 criteria with respect to time differences of sepsis onset. **Methods:** In a cohort of intensive care unit (ICU) patients prospectively diagnosed with severe sepsis or septic shock according to Sepsis-1 criteria between 01/2010 and 12/2015, the time differences between meeting Sepsis-1 vs. Sepsis-3 criteria as time of sepsis onset and the corresponding differences in illness severity were tested. Similar comparisons were performed for septic shock subset meeting different Sepsis-1 vs. Sepsis-3 criteria. Patients with non-ICU-acquired sepsis and patients with sepsis onset more than 48 h postadmission (ICU-acquired sepsis) were analyzed separately to account for differences in availability of routinely collected organ dysfunction data. **Results:** A total of 10,905 ICU patients were screened; 862 patients met Sepsis-1 criteria, of whom 834 (97%) also met Sepsis-3 criteria. In patients, admitted to the ICU with sepsis, Sepsis-3 criteria compared with Sepsis-1 criteria were more frequently fulfilled within the first 3 h (84% vs. 75%, $P < 0.001$). In patients with ICU-acquired sepsis, sepsis onset was in 50% at least 1 day earlier after application of Sepsis-3 ($P = 0.011$). These patients were systemic inflammatory response syndrome negative at the earlier sepsis onset, but suffered already from organ dysfunction. Sepsis-3 criteria were timely in 86% and 1 day delayed in 7%. Only 7% (8 patients) did not meet Sepsis-3 criteria in this group. These patients had already an increased SOFA score and did develop neither a further increase nor the new septic shock criteria. Classification according to Sepsis-3 reduced the proportion of septic shock (51% vs. 75%, $P < 0.001$). Twenty-eight-day mortality was 38% for new septic shock compared with 33% of Sepsis-1 septic shock ($P > 0.05$). Patients not detected by Sepsis-3 had a 28-day mortality of 11%. **Conclusions:** Sepsis-3 criteria facilitate an earlier and more predictive recognition of sepsis and septic shock in patients with non-ICU and ICU-acquired sepsis primarily diagnosed by Sepsis-1 criteria. These results require further validation with prospectively collected data.

KEYWORDS—Criteria, sepsis onset, septic shock, severe sepsis, severity, SOFA

INTRODUCTION

Sepsis is a major public health problem and incidence of sepsis, and related mortality has remained stable over the last years (1). New sepsis criteria (Sepsis-3) are supposed to "offer greater consistency" for research and "facilitate earlier recognition and timely management [. . .] of patients with sepsis" (2). However, a potentially delayed diagnosis due to elimination of systemic inflammatory response syndrome (SIRS) criteria and the requirement of organ dysfunction or rather hypotension combined with elevated lactate levels for septic shock represents a major criticism (3). This suspicion is based on the assumption that sepsis follows a continuum of infectious SIRS, sepsis, severe sepsis, and finally septic shock, and that organ failure is preceded by SIRS criteria. Since its publication prognostic accuracy, performance and epidemiological impact of Sepsis-3 criteria were analyzed in various comparative studies (4–7).

But direct comparisons of time differences between meeting Sepsis-1 vs. Sepsis-3 criteria as time of sepsis onset have not been previously reported.

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Authors' contributions: CSS, S-OK, and MV performed the data analysis. All authors contributed to the data interpretation. CSS, S-OK, MG, and SR drafted the first version of the manuscript. FB and MS-H contributed to the methodical approach and the data interpretation. All authors amended and approved the final version of the manuscript. S-OK, CSS, and MV have full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. CSS and S-OK assume full responsibility for the integrity of the submission as a whole, from inception to published article.

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METHODS

This study represents a retrospective analysis of septic patient previously identified within a quality improvement program at the University Hospital of Greifswald, Germany (8). All intensive care unit (ICU) patients between January 2010 and December 2015 with severe sepsis or septic shock according to the Sepsis-1 definition of the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) (9) were included. Briefly, Sepsis-1 severe sepsis was diagnosed if at least 2 SIRS criteria were met and organ dysfunction plus clinical suspicion or evidence of infection were present (Supplement Table S1, http://links.lww.com/SHK/A752). Sepsis-1 septic shock was defined as severe sepsis and persistent arterial hypotension or the need for vasopressors despite adequate fluid resuscitation (Supplement Table S1, http://links.lww.com/SHK/A752).

Patients fulfilling Sepsis-1 criteria were assigned to two subgroups (Fig. 1):

1. *Non-ICU-acquired sepsis*: Patients were admitted with sepsis to the ICU or developed sepsis within the first 48 h after ICU admission. This group included patients from the emergency department, the ward, or the operating room.
2. *ICU-acquired sepsis*: Patients already admitted at the ICU because of other reasons than sepsis (e.g., trauma, postoperative) and developed sepsis at least 48 h after ICU admission.

After that charts of the electronic patient data management system (PDMS) were retrospectively analyzed and new Sepsis-3 criteria were applied. For patients with non-ICU-acquired sepsis, we analyzed the SOFA scores within the first 3 h after ICU admission and again for the first 24 and 48 h after admission. The first time point, when the respective criteria were met, was defined as sepsis onset. For patients with ICU-acquired sepsis, we analyzed the SOFA scores and signs of infection back to 3 days before the original sepsis onset. In this group, we also identified the time point, when the respective criteria were met and defined as sepsis onset. Data for quick SOFA (qSOFA) were not gathered in the original database. For both groups, we compared the differences of time points.

According to Sepsis-3 criteria, sepsis onset was defined as a Sequential/Sepsis-related Organ Failure Assessment score (SOFA) at least2 points at ICU admission or a SOFA score increase at least 2 points during ICU stay and suspected or confirmed infection. Sepsis-3 septic shock was diagnosed in case of an additional vasopressor therapy combined with lactate levels more than 2 mmol/L (Supplement Table S1, http://links.lww.com/SHK/A752). Glasgow Coma Scale (GCS) for the SOFA score calculation was not available for all patients at ICU admission because the awareness of these patients was determined partly by other scores. SOFA scores were calculated excluding the GCS for this group analogous to the study of Freund et al. analyzed the prognostic accuracy of Sepsis-3 criteria (5). For patients with ICU-acquired sepsis, data for GCS were available and SOFA scores were completely calculated. There were no patient-related exclusion criteria to achieve a realistic reflection of daily practice and to reduce bias. The study represents a subset of our local quality improvement program which was approved by the local ethics committee (Ethikkommission an der Universitätsmedizin Greifswald; identifier: BB 133/10). The article was written in consideration of the *Standards for Reporting of Diagnostic Accuracy* (STARD) guidelines (10).

Objectives

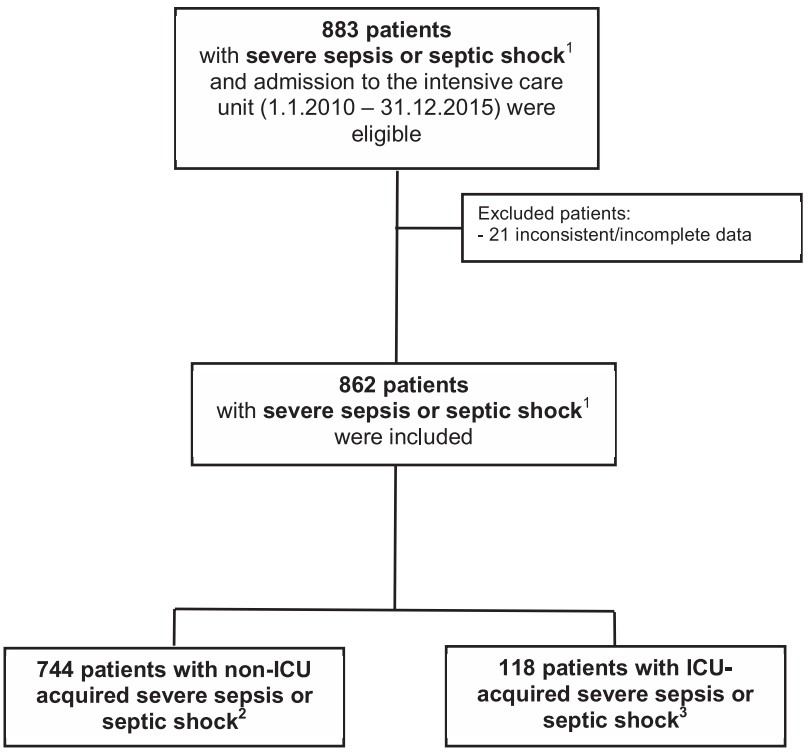
The objective of this study was to determine whether Sepsis-3 criteria result in a time difference of sepsis onset in patients originally classified according to Sepsis-1 criteria.

Secondary objectives included the disease severity based on SOFA scores and lactate levels for the different sepsis severity entities at Sepsis-1- and Sepsis-3 onsets (Sepsis-1 severe sepsis vs. Sepsis-3 sepsis and Sepsis-1 septic shock vs. Sepsis-3 septic shock) as well as the proportion of sepsis severity entities and 28-day mortality.

Statistical Analysis

Statistical analysis was performed using GraphPad and R Studio. Based on the retrospective exploratory design with lack of knowledge about time differences, a sample size calculation was not performed.

Time differences of sepsis onset were identified by analyzing the time point when the respective sepsis criteria (Sepsis-1 or Sepsis-3) were met. For patients originally diagnosed with severe sepsis or septic shock within the first 48 h after ICU admission, the number of patients who met the respective criteria (Sepsis-1 vs. Sepsis-3) within the first 3, 24, and 48 h after ICU admission were compared by two-sided tests of equal proportions with Yates' continuity correction.



[1] Data from the local sepsis quality improvement program: Severe sepsis and septic shock were prospectively identified according to ACCP/SCCM consensus conference criteria of 1992 (Sepsis-1).
[2] Severe sepsis or septic shock onset < 48h after ICU-admission.
[3] Severe sepsis or septic shock onset ≥ 48h after ICU admission.

Fig. 1. **Flow chart of the analyzed patients.**

For patients who developed ICU-acquired sepsis, the null hypothesis for the time difference of sepsis onset was an unknown distribution around zero. We conducted a one-sided binomial test to check the hypothesis given by the Third International Consensus Definitions that "these updated definitions and clinical criteria should replace previous definitions [. . .] [to] [. . .] facilitate earlier recognition [. . .] of patients with sepsis" (2). Regarding the secondary objectives, we calculated the mean SOFA scores and mean lactate levels including standard deviation for the respective time points. Severity entities of Sepsis-1 (severe sepsis or septic shock) and Sepsis-3 (sepsis or septic shock) were compared by chi-square test of homogeneity. Twenty-eight-day mortality was compared by two-sided tests of equal proportions with Yates' continuity correction. To guarantee independence of the random samples, a splitting procedure was used. A P value < 0.05 was classified as statistical significant.

RESULTS

A total of 10,905 ICU patients were screened for sepsis. A total of 883 adult ICU patients with severe sepsis or septic shock according to the ACCP/SCCM Sepsis-1 criteria were eligible. Twenty-one patients were excluded because of incomplete data. The remaining 862 patients were classified as non-ICU-acquired sepsis (86.3%, 744/862 patients) and ICU-acquired sepsis (13.7%, 118/862 patients), respectively (Fig. 1). Baseline characteristics are presented in Table 1.

Patients with non-ICU-acquired sepsis

A total of 744 patients met Sepsis-1 criteria within the first 48 h after ICU admission and were classified as non-ICU-acquired severe sepsis or septic shock. Within the first 3 h after admission, 74.9% of these patients met Sepsis-1 criteria, whereas 84.4% already met Sepsis-3 criteria ($P < 0.001$). Considering the first 24 h, 97.6% of these patients met Sepsis-1 criteria and 96.6% met Sepsis-3 criteria at this stage (Fig. 2A). Twenty-five patients (3.4%) did not meet the Sepsis-3 criteria within the first 24 h. These patients had SOFA scores between 0 and 1 points (mean SOFA score: 0.7 points) and lactate levels below 2 mmol/L (mean lactate level 1.8 mmol/L) at this time (Fig. 2B). Five more patients were detected within 48 h after admission. Twenty-eight-day mortality of the 20 (2.7%) remaining patients not detected by Sepsis-3 was 5.0%.

Patients with ICU-acquired sepsis

A total of 118 patients suffered from sepsis during their ICU stay and were classified as ICU-acquired sepsis. After application of Sepsis-3 criteria, sepsis onset was at least 1 day earlier in 59 patients (50%) ($P = 0.011$) (Fig. 3A). These patients were SIRS negative at the time when Sepsis-3 criteria were already met, but had organ dysfunction. Eight (7%) patients met Sepsis-3 criteria with 1 day delay.

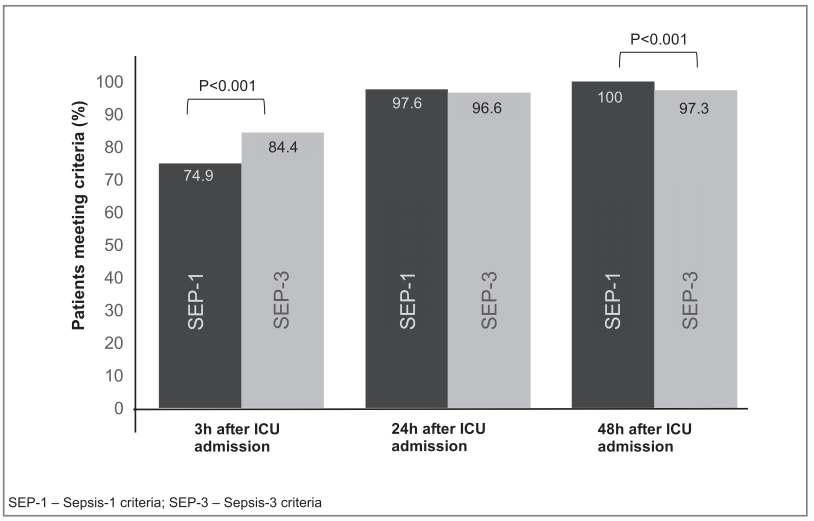
Only 8 (7%) patients formerly diagnosed with severe sepsis or septic shock by Sepsis-1 criteria did not meet Sepsis-3 criteria. These patients neither had a SOFA score increase at least 2 points nor lactate level more than 2 mmol/L. Twenty-eight-day mortality of these 8 patients was 25% (Table 2).

TABLE 1. **Characteristics of patients formerly diagnosed as severe sepsis or septic shock according to Sepsis-1 criteria**

	Total n = 862 (%)	Non-ICU acquired* n = 744 (%)	ICU acquired† n = 118 (%)
Gender male	542 (62.9)	455 (61.2)	87 (73.7)
Age (mean, SD)	68.8 ± 12.4	68.9 ± 12.5	68.3 ± 11.8
Systemic inflammatory response syndrome (SIRS) (positive criteria)			
Heart rate	732 (84.9)	638 (85.8)	94 (79.7)
Respiratory rate	505 (58.6)	403 (54.2)	102 (86.4)
Temperature	461 (53.5)	376 (50.5)	85 (72.0)
White blood cell count	590 (68.4)	520 (69.9)	70 (59.3)
Organ dysfunction (positive criteria)			
Cardiovascular	651 (75.5)	563 (75.7)	88 (74.6)
Encephalopathy	213 (24.7)	179 (24.1)	34 (28.8)
Renal	261 (30.3)	239 (32.1)	22 (18.6)
Acidosis	302 (35.0)	283 (38.0)	19 (16.1)
Platelets	110 (12.8)	98 (13.2)	12 (10.2)
Respiratory	517 (60.0)	426 (57.3)	91 (77.1)
Lactate, mmol/L (mean ± SD)‡	4.3 ± 4.5	4.5 ± 4.7	3.0 ± 2.9
Severe sepsis§	216 (25.1)	180 (24.2)	36 (30.5)
Septic shock§	646 (74.9)	564 (75.8)	82 (69.5)
APACHE II (mean ± SD)‖	20.1 ± 7.1	20.1 ± 7.1	19.7 ± 6.7
Origin of infection			
Respiratory tract	183 (21.2)	131 (17.6)	52 (44.1)
Abdominal	387 (44.9)	354 (47.6)	33 (28.0)
Bone and soft part	66 (7.7)	64 (8.6)	2 (1.7)
Urogenital	60 (7.0)	56 (7.5)	4 (3.4)
Catheter infection	24 (2.8)	21 (2.8)	3 (2.5)
Other¶	142 (16.5)	118 (15.9)	24 (20.3)
Mortality			
28-day mortality	260 (30.2)	221 (29.7)	39 (33.1)
90-day mortality	360 (41.8)	300 (40.3)	60 (50.8)

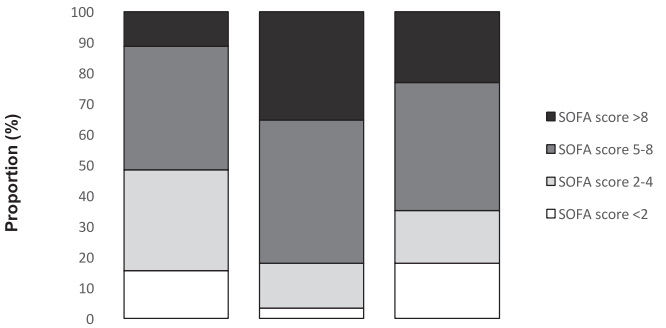
*Severe sepsis or septic shock onset less than 48 h after ICU admission.
†Severe sepsis or septic shock onset at least 48 h after ICU admission.
‡Highest value during first 24 h after sepsis onset.
§Severe sepsis and septic shock according to ACCP/SCCM consensus conference criteria of 1992 (Sepsis-1).
‖Acute Physiology and Chronic Health Evaluation II (during first 24 h after sepsis onset).
¶Endocarditis, meningitis, unknown focus.

A Time point when sepsis criteria were met in ICU patients admitted with sepsis or developing sepsis within the first 48 hours after admission. Bar diagram representing the cumulative percentage of patients meeting the respective criteria at the indicated time point.



SEP-1 – Sepsis-1 criteria; SEP-3 – Sepsis-3 criteria

B Stacked bar diagram showing the SOFA severity at the indicated time points. Tabulated the mean SOFA score and lactate level at the indicated time points.



	3h after ICU admission	24h after ICU admission	48h after ICU admission
SOFA score* mean (±SD)	5.0 (±3.0)	7.4 (±3.0)	5.8 (±3.7)
Lactate mmol/L mean (±SD)	3.4 (±3.2)	4.7 (±4.7)	3.3 (±4.2)

SOFA – Sepsis/Sequential Organ Failure Assessment (excluding Glasgow Coma Scale); SD – standard deviation

FIG. 2. **Time point of sepsis onset and corresponding severity among patients with non-ICU-acquired sepsis.**

Predictive Validity

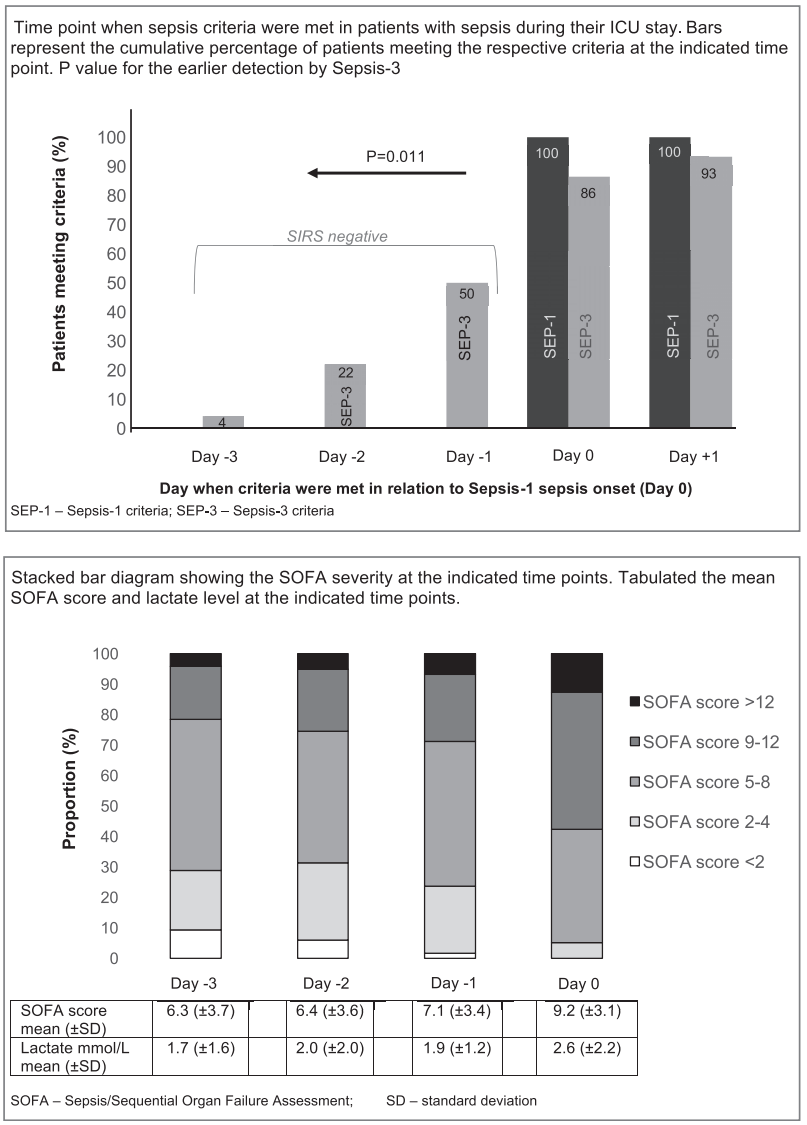
A total of 834 patients (96.8%) formerly diagnosed with severe sepsis or septic shock according to Sepsis-1 criteria met the new Sepsis-3 criteria, whereas 28 patients (3.2%) did not. Sepsis-3 criteria resulted in an altered proportion of sepsis severity entities. The proportion of septic shock decreased from 75% (Sepsis-1) to 51% (Sepsis-3) ($P < 0.001$).

Twenty-eight-day mortality was 38% for new septic shock compared with 33% of Sepsis-1 septic shock ($P > 0.05$). Patients not detected by Sepsis-3 had a 28-day mortality of 11%.

DISCUSSION

The present study demonstrates a 97% overlap between patients diagnosed with Sepsis-3 sepsis/septic shock and Sepsis-1 severe sepsis/septic shock. For both, non-ICU and ICU-acquired sepsis, sepsis onset was earlier with Sepsis-3 criteria compared with Sepsis-1. Despite some missing values due to the use of data from daily practice, Sepsis-3 recognized septic patients earlier. In patients, ICU admitted with sepsis, 84% met already Sepsis-3 criteria within the first 3 h, whereas Sepsis-1 criteria were only met in 75% at this stage. In ICU-acquired sepsis, 50% of the patients fulfilled Sepsis-3 criteria at least 1 day earlier. All earlier recognized patients were SIRS negative at the earlier time point, but suffered already from organ dysfunction. These results suggest a potentially faster identification of Sepsis-3 sepsis, which is different from concerns highlighted in the literature (3).

A potentially earlier sepsis recognition by applying Sepsis-3 criteria, as suggested by the present data, presumable offers a time advantage toward completing the early sepsis care, as recommended by the Surviving Sepsis Campaign guidelines (11, 12). As Sepsis-3 also identifies patients with higher illness severity and greater organ dysfunction, this time advantage may be valuable. As our study is a retrospective observation and not a clinical decision tool analyses, we can only hypothesize that



	Day -3	Day -2	Day -1	Day 0
SOFA score mean (±SD)	6.3 (±3.7)	6.4 (±3.6)	7.1 (±3.4)	9.2 (±3.1)
Lactate mmol/L mean (±SD)	1.7 (±1.6)	2.0 (±2.0)	1.9 (±1.2)	2.6 (±2.2)

Fig. 3. **Time point of sepsis onset and corresponding severity among patients with ICU-acquired sepsis.**

there might be potential outcome benefit of an earlier therapy initiated by an earlier diagnosis with Sepsis-3 criteria.

We observed a 97% overlap between Sepsis-1 and Sepsis-3. A recent comparison between Sepsis-2 and Sepsis-3 observed a similar overlap of 92% in 197,000 septic patients (7). Patients not diagnosed with Sepsis-3 might represent a risk to overlook septic patients, as supposed previously (3). However, 28-day mortality of these patients was only 11% which is consistent with a recent study evaluating Sepsis-1 and Sepsis-3 performance in China (6) and average mortalities of general ICU patients (13, 14). An improved predictive validity of Sepsis-3 criteria is further supported by a reduced proportion of shock

Table 2. **Characteristics of patients with ICU-acquired sepsis not meeting Sepsis-3 criteria**

	Age	Reason for ICU admission	Focus of infection	SOFA score			Day of Sepsis-1 sepsis onset	Sepsis-1 severity	28-day mortality
				Day 3	Day 2	Day 1			
1	65	Acute abdomen	Urogenital	7	7	8	8	S. shock	Living
2	73	Trauma	Pneumonia	7	5	5	5	S. shock	Dead
3	49	Trauma	Bone and soft tissue	5	6	6	6	S. shock	Living
4	51	Hemorrhagic shock	Catheter infection	17	17	18	17	S. shock	Living
5	29	Esophageal resection	Abdominal	7	6	7	7	S. shock	Living
6	82	Intracranial hemorrhage	Pneumonia	5	4	4	5	S. sepsis	Living
7	49	Limb fracture	Pneumonia	4	3	3	4	S. shock	Living
8	52	Pancreatic resection	Pneumonia	NA	6	5	5	S. sepsis	Dead

These patients had no SOFA score increase at least 2 points and do not met shock criteria (vasopressor need + lactate >2 mmol/L) according to Sepsis-3. S. sepsis indicates severe sepsis; S. shock, septic shock; SOFA, Sequential Organ Failure Assessment.

patients and higher mortality in the new septic shock group. These results were also seen in a much larger analysis of Shankar-Hari et al. (7).

The present study has some limitations. First, the retrospective design of the analysis could be criticized. However, prospective investigations are only possible after the new sepsis definition has been released for a certain time period. Second, this study investigated only sepsis onset at ICU admission and the recognition during ICU stay because the database did not include data prior ICU admission. As data about qSOFA were not assessed and SOFA scores were not available outside the ICU, the present study cannot make any conclusions about the time before ICU admission.

CONCLUSION

The present results suggest an earlier and more specific recognition of sepsis and septic shock in ICU patients by applying the Sepsis-3 diagnostic criteria. As a consequence, there is a potential for an earlier treatment initiation by using Sepsis-3. Based on the retrospective design of the present study, however, no conclusions about potential improvements in outcome can be made. Future trials need to consider the lower ratio of septic shock patients and the increased mortality in this subgroup according to Sepsis-3 criteria as compared with the shock patients identified by Sepsis-1 criteria.

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