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Comparison of the sepsis-2 and sepsis-3 definitions in severely injured trauma patients

Jesper Eriksson, MD [a,b,*], Mikael Eriksson, MD PhD [a,b], Olof Brattström, MD PhD [a,b], Elisabeth Hellgren, CCRN MSc [a], Ola Friman, CCRN [a], Andreas Gidlöf, MD PhD [a,b], Emma Larsson, MD PhD [a,b], Anders Oldner, MD PhD [a,b]

[a] Perioperative Medicine and Intensive Care, Karolinska University Hospital, Solna, Stockholm, Sweden
[b] Section of Anaesthesiology and Intensive Care Medicine, Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden

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ABSTRACT

Purpose: To evaluate the performance of the new SOFA-based sepsis definition in trauma patients.
Materials and methods: A single-centre, retrospective, observational study. Primary outcome was 30-day mortality including a censoring analysis for early deaths. The primary outcome was evaluated with logistic regression, receiver operating characteristics (ROC) curves and Kaplan-Meier survival analyses.
Results: 722 severely injured patients were included between 2007 and 2016. 315 patients fulfilled the sepsis-2 criteria and 148 fulfilled the sepsis-3 criteria during the first ten days in the ICU. The odds ratios for 30-day mortality were 0.7 (CI 0.4–1.2) for sepsis-2 and 1.5 (CI 0.8–2.6) for sepsis-3. When censoring patients dying at day 1, sepsis-3 became associated with 30-day mortality whereas sepsis-2 did not. This finding was persistent and enhanced through continuing day-by-day censoring of early deaths. The same pattern was seen for the ROC curves analyses, censoring of early deaths resulted in significant discriminatory properties for sepsis-3 but not for sepsis-2.
Conclusions: The sepsis-3 definition identifies much fewer patients and is more strongly associated with adverse outcomes than the sepsis-2 definition. The sepsis-3 definition seems to be useful in the post trauma setting.

1. Background

Most research in post-injury sepsis to date is based on the 1991 and 2001 international sepsis consensus criteria, sepsis-2 [1], which are based on the presence of systemic inflammatory response syndrome (SIRS). In 2016 Singer et al published new recommendations, sepsis-3, aiming to more accurately differentiate between sepsis and uncomplicated infections [2]. The new definition defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection. SIRS was removed and sepsis was clinically defined as an increase in sequential (sepsis-related) organ failure assessment (SOFA) [3] score of two points or more in conjunction with presence of infection.

The new sepsis definition, sepsis-3, has never been evaluated against the former sepsis-2 definition in trauma patients. These patients typically have a high SOFA score on admission. A circumstance that may affect the accuracy in the operational definition of sepsis-3, which is based on changes in SOFA score. The consequence of trauma patients admitted with high SOFA scores was not addressed in the original definition neither by Singer et al., nor in the validation study by Seymour et al. [4].

In this study we compare the prevalence and 30-day mortality of sepsis based on the new sepsis-3 criteria as well as the 1991 and 2001 consensus criteria (sepsis-2) in a cohort of severely injured ICU-admitted patients.

We study the discriminatory properties of both sepsis definitions for overall 30-day mortality. Since many trauma-related deaths occur early before the patient is at risk of developing sepsis, we also included an analysis censoring early deaths after trauma to account for competing risks. We hypothesized that the new sepsis-3 definition would have a lower incidence due to the fact that it is based on SOFA scoring and would predict mortality better than the sepsis-2 definition.

2. Methods

2.1. Ethical approval and consent to participate

This study was approved by the regional ethical review board in Stockholm, Sweden (approval numbers 2008/249–31/3, 2009/

* Corresponding author at: Perioperative Medicine and Intensive Care, Karolinska University Hospital, Solna SE-171 76, Stockholm, Sweden.
E-mail addresses: jesper.b.eriksson@sll.se (J. Eriksson), mikael.er.eriksson@sll.se (M. Eriksson), olof.brattstrom@sll.se (O. Brattström), elisabeth.hellgren@sll.se (E. Hellgren), ola.friman@sll.se (O. Friman), andreas.gidlof@sll.se (A. Gidlöf), emma.ca.larsson@sll.se (E. Larsson), anders.oldner@ki.se (A. Oldner).

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862–32). The study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [5].

2.2. Setting

This retrospective cohort study of severely injured trauma patients was conducted at a mixed 13-bed ICU in the trauma centre at the Karolinska University Hospital, Stockholm, Sweden. This is the referral centre for severe trauma cases covering the largest urban region in Sweden with over two million inhabitants.

2.3. Study population and data collection

The study cohort consisted of trauma patients admitted to the ICU following initial resuscitation and, where indicated, interventional surgery. Patients 15 years or older with an expected ICU length of stay (ICU LOS) of >24 h were included between February 2007 and November 2016. All data were entered into a database, ICU-TRAUMAREG. Data were then crosschecked and validated in retrospect by the researchers. Trauma data such as injury severity score (ISS), mechanism of injury, admission blood pressure, admission Glasgow Coma Scale (GCS) were retrieved from the hospital trauma register. Data on comorbidity were collected from the patient charts.

2.4. Outcomes

Patient data were retrieved until ICU day ten, discharge or death, whichever occurred first. Primary outcome was overall 30-day mortality including a censoring analysis for early deaths.

2.5. Definitions

Massive transfusion was defined as administration of ten or more units of packed red blood cells in the first 24 h. Shock upon arrival was defined as systolic arterial blood pressure (SAP) of <90 mmHg. The likelihood of infection was classified as no infection, possible, probable or confirmed infection according to the international sepsis forum (ISF) classification [6]. Further, in the primary analysis, we added a fourth classification. In the few patients where there was an obvious infection to both the attending clinician, the attending infectious disease consultant as well as to the researchers but was not applicable to the ISF classification, we classified the likelihood of infection as "Unknown (ISF N/A)". In the primary analysis, patients fulfilling one of the four classifications were considered infected. Sepsis-2 was defined according to the 1991 [7] criteria modified in 2001 [1]. Sepsis-3 was defined according to the criteria published by Singer et al. [2]. Briefly, sepsis-2 was defined as two or more SIRS criteria and infection on the same day. If less than two SIRS criteria or if the infection resolved, the patient was no longer regarded as septic. Sepsis-3 was defined as an increase in SOFA score of two or more in conjunction with an infection. The neurological component of the SOFA score, even though recorded on a daily basis, was excluded in the primary analysis due to the inherent difficulties in estimating GCS in sedated patients.

If the patients SOFA score returned to the offset level or if the infection resolved, the patient was no longer regarded as septic.

2.6. Statistics

Categorical data are presented as proportions and percentages. Continuous data are presented with median and interquartile ranges. Crude comparisons of proportions were performed using chi-square tests. Comparisons of continuous variables were performed using the Mann-Whitney *U* test. Analyses of the outcome were done with univariate logistic regression and presented as odds ratio (OR) with corresponding 95% confidence intervals (CI). Predictive properties of the two definitions were analysed with receiver operating characteristic curves (ROC) and presented as area under the curve (AUC) with corresponding CI. We tested equality of ROC areas by using the nonparametric approach developed by de Long et al. [8]. Kaplan-Meier survival curves were plotted for 30-day postinjury survival for septic and non-septic patients. The log-rank test was used to examine the difference of survival curves between the groups. In order to account for the competing risk of early trauma-related deaths before being at risk for sepsis a temporal analysis was made by consecutive censoring of patients dying on day 1 and forward. Analyses of risk of death and discriminatory properties were then made for each censoring step.

Where individual components of SIRS criteria or SOFA score were missing, we assigned a normal value (zero points), in accordance with previous reports [9-11]. There were no missing data for the primary outcome. All reported P values are two-sided and P values <.05 were considered statistically significant. Stata/MP 14.2 (StataCorp, College Station, TX) was used for all analyses.

2.7. Sensitivity analyses

We performed the following sensitivity analyses:

1. In patients with missing components of SIRS or SOFA, two approaches were employed: a) Imputation of the median value during the ICU stay for that specific patient and the underlying data value missing. b) Imputation of the highest possible value (i.e. equivalent to assigning 1 point for a missing SIRS component or 4 points for a missing SOFA component).
2. We analysed all patients including the neurological component of the SOFA score.
3. Only confirmed infections were regarded as infection, thus possible, probable and unknown (ISF N/A) infections were assigned as no infection.

3. Results

The study population consisted of 722 severely injured patients (for flowchart of included study patients, see Supplementary Fig. 1) with a median ISS of 26, 84% had an ISS > 15. The median age was 41 (28–58) years and 78% were male. Median admission-SOFA was 5 [3-7], with the exclusion of the neurological component of SOFA score. Overall 30-day mortality in the total cohort was 9.3% (Table 1).

The SOFA score and prevalence of suspected or confirmed infection over time is depicted in Fig. 1. The absolute prevalence of infection increased from day 1 to 4 followed by a gradual decline. Respiratory infections were seen in 75% of the septic patients and the most common pathogen was *Staphylococcus aureus* (for infection specifics, see Supplementary Table 1).

Forty percent of the patients fulfilled the criteria for sepsis-2 during the first ten days of ICU stay, 20% fulfilled the sepsis-3 criteria. All patients with sepsis-3 also met the criteria for sepsis-2 (Fig. 2). ISS > 15 was seen in 89% of the sepsis-2 patients and in 92% of the sepsis-3 patients (Table 1). The changes in SOFA components at the onset of sepsis-3 showed mainly cardiovascular and respiratory failure. No significant differences in 30-day mortality were seen between neither sepsis-2 patients (OR 0.7 (CI 0.4–1.2)) nor sepsis-3 patients (OR 1.5 (CI 0.8–2.6) and their respective non-septic controls (Table 1 and Fig. 3). No apparent differences between the sepsis-2 and 3 groups were seen regarding demography, admittance data and rate of mechanical ventilation. Median ICU LOS was markedly longer in septic patients, 10 days in sepsis-2 and 12 days in sepsis-3 patients, respectively compared with 2–3 days in the non-septic patients (Table 1). The absolute prevalence of sepsis-2 and -3 increased from day 1 and was most prominent on day 3 to 5 (Fig. 4). The proportion of ICU-admitted patients with infection and sepsis-2 and -3 increased over time and was highest at the end of the study period (Fig. 4).

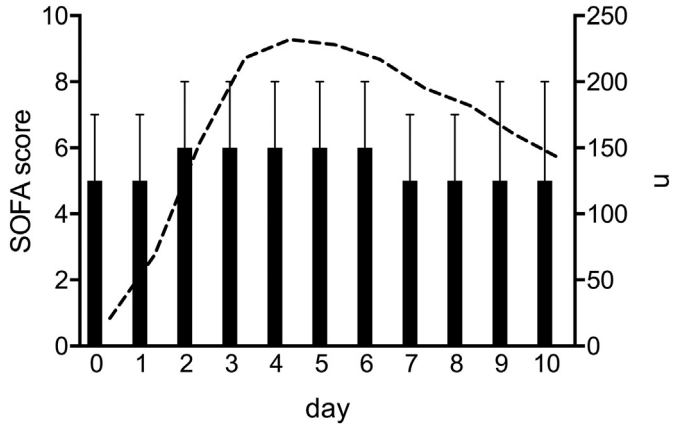

Fig. 1. SOFA score and absolute daily prevalence of infection. Distribution of median and interquartile range of SOFA (black bars) and absolute daily prevalence of infection (dashed line) during the study period for admitted patients. The x-axis represent days since ICU-admission.

When censoring patients dying at the early stage, the risk of 30-day mortality increased and became significant for sepsis-3 already after censoring patients dying on day 1. Sepsis-2 never reached significance. When censoring deaths up until day 3 the OR of 30-day mortality was 3.8 (CI 1.9–7.6) for sepsis-3 and 1.9 (CI 0.9–3.8) for sepsis-2 (Fig. 3).

The discriminatory performances of the two definitions for 30-day mortality were analysed with ROC curves and showed an AUC of 0.46 (CI 0.40–0.52) and of 0.54 (CI 0.48–0.59) for sepsis-2 and -3, respectively. The AUC increased and became significant for sepsis-3, but not for sepsis-2, when censoring patients dying on day 1 and 2 (see Supplementary Fig. 2). Sepsis-3 had significantly larger AUC than sepsis-2, across all levels of censoring.

Kaplan-Meier curves showed no difference in 30-day mortality between either of the sepsis definitions and their respective controls. When censoring patients dying on day 1, sepsis-3 patients had a significant higher mortality than their non-septic counterparts. This was not seen for sepsis-2 (see Supplementary Fig. 3).

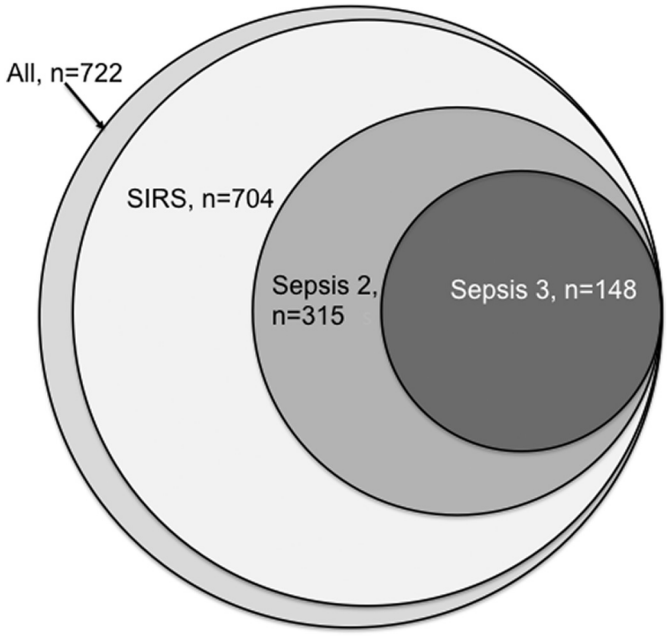

Fig. 2. Diagrammatic distribution of SIRS, sepsis-2 and -3. Venn diagram of systemic inflammatory response syndrome (SIRS), sepsis-2 and sepsis-3.

The SIRS or SOFA component with the most underlying data value missing was bilirubin, which was missing in 4.2% of the cases. All other components had missing values below 2%. As for the sensitivity analyses, imputing the median as well as the highest underlying data value for missing components of SIRS and SOFA showed similar findings as the primary analysis. Inclusion of the neurological component of the SOFA score increased overall SOFA but did not alter the findings (see Supplementary Table 2). Using only confirmed infections as a requisite for sepsis, decreased the number of patients with sepsis, but the pattern remained with increasing and significant odds ratio as well as AUC for 30-day mortality with gradual censoring of early deaths for sepsis-3, but not for sepsis-2 (see Supplementary Table 3).

Table 1
Demographic, admission data and outcomes for all patients, sepsis-2 and sepsis-3 patients respectively.

Parameter	All ($n = 722$)	Sepsis-2 ($n = 315$)	Non Sepsis-2 ($n = 407$)	P value	Sepsis-3 ($n = 148$)	Non Sepsis-3 ($n = 574$)	P value
Gender							
Male n (%)	561 (77.7)	251 (79.7)	310 (76.2)	0.260	117 (79.1)	444 (77.4)	0.657
Age Years	41 (28–58)	43 (29–59)	39 (26–56)	0.023	46 (29–63)	40 (27–56)	0.007
History of comorbidity n (%)	369 (51)	169 (53.7)	200 (49.1)	0.229	86 (58.1)	283 (49.3)	0.056
Mechanism of injury n (%)							
Traffic related	302 (41.8)	140 (44.4)	162 (39.8)		68 (46.0)	234 (40.8)	
Fall	123 (17.0)	44 (14.0)	79 (19.4)		27 (18.2)	96 (16.7)	
Assault	86 (11.9)	30 (9.5)	56 (13.8)	0.031	10 (6.8)	76 (13.2)	0.161
Self-inflicted	120 (16.6)	63 (20.0)	57 14.0)		28 (18.9)	92 (16.0)	
Others	91 (12.6)	38 (12.0)	53 (13.0)		15 (10.1)	76 (13.2)	
Penetrating injury n (%)	88 (12.2)	35 (11.1)	53 (13.0)	0.436	13 (8.8)	75 (13.1)	0.156
Admission SAP < 90 n (%)	115 (15.9)	76 (24.1)	39 (9.6)	0.000	42 (28.4)	73 (12.7)	0.000
Massive transfusion n (%)	125 (17.3)	78 (24.8)	47 (11.6)	0.000	40 (27.0)	85 (14.8)	0.000
ISS score	26 (18–38)	33 (22–43)	24 (17–33)	0.000	34 (23–43)	25 (17–35)	0.000
ISS > 15 n (%)	605 (83.8)	279 (88.6)	326 (80.1)	0.002	136 (91.9)	469 (81.7)	0.003
AIS head ≥ 3 n (%)	298 (41.3)	150 (47.6)	148 (36.4)	0.002	66 (44.6)	232 (40.4)	0.357
SOFA admission score (without GCS)	5 (3–7)	7 (5–8)	4 (2–6)	0.000	7 (5–9)	5 (3–7)	0.000
SOFA admission score (including GCS)	7 (4–10)	9 (6–11)	5 (3–8)	0.000	9 (6–11)	6 (4–9)	0.000
Mechanical ventilation n (%)	573 (79.4)	304 (96.5)	269 (66.1)	0.000	146 (98.7)	427 (74.4)	0.000
SIRS n (%)	704 (97.5)	315 (100)	389 (95.6)	0.001	148 (100)	556 (96.9)	0.029
SOFA total max score	8 (5–10)	10 (8–12)	5 (4–8)	0.000	11 (9–13)	6 (4–9)	0.000
ICU LOS days	3.7 (2.0–8.4)	9.7 (5.5–16.5)	2.3 (1.5–3.3)	0.000	11.9 (7.1–19.2)	2.9 (1.8–5.1)	0.000
30-day mortality n (%)	67 (9.3)	24 (7.6)	43 (10.6)	0.176	18 (12.2)	49 (8.5)	0.175

Table 1. Systolic arterial blood pressure (SAP, mmHg), injury severity score (ISS), sequential organ failure assessment (SOFA), Abbreviated Injury Score (AIS), Glasgow Coma Score (GCS), systemic inflammatory response syndrome (SIRS), intensive care unit length of stay (ICU LOS). SOFA total max is the sum of each SOFA-domains maximum score during the study period. Data on SOFA, SIRS and ventilation during the study period. Continuous parameters presented as median (inter quartile range, IQR), categorical parameters as count and per cent.

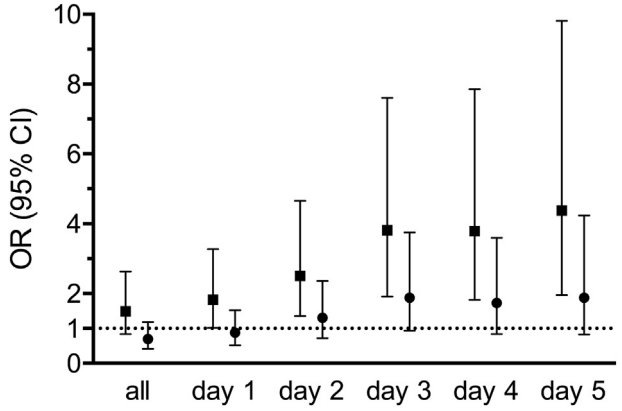

Fig. 3. Temporal analyses of odds ratio for 30-day mortality. Logistic regression analyses exploring 30-day mortality consecutively censoring patients dying at the early stages. Odds ratio (OR) and 95% confidence intervals (CI) for 30-day mortality for sepsis-2 (circles) and sepsis-3 (squares). The x-axis depicts all patients and subsequently censoring patients dying on day 1 and on, up until day 5.

4. Discussion

4.1. Key findings

We conducted the first study comparing the former sepsis definition with the present in the same cohort of severely injured trauma patients. The new sepsis-3 criteria identify fewer patients than the previous sepsis-2 criteria, the incidence of sepsis-3 was less than half than that of sepsis-2. Both definitions showed poor discriminatory properties for 30-day mortality. However, when censoring patients dying at the early stage sepsis-3 became associated with mortality and the discriminatory properties became significant for this outcome. This was not seen for sepsis-2.

4.2. Relationship with previous studies

In the original sepsis-3 definition, baseline SOFA was suggested to be zero in patients without prior organ dysfunction. In our cohort the median admission SOFA, excluding the neurological component of SOFA, was five, and with the majority of the patients without any prior organ dysfunctions. Therefore, we chose to use a change in SOFA-score with two or more points from the previous day together with infection as the sepsis-3 definition.

In our study, fewer patients fulfilled the sepsis-3 criteria than the sepsis-2 criteria. Previous non-trauma studies have shown a more equal distribution between the two definitions [4,9,12-15]. The reason for the difference in incidence between the two definitions in our study might be twofold. Firstly, the incidence of SIRS, being an unspecific entity, was very high in our cohort. Secondly, the difference may also reflect the difficulty of increasing the SOFA score by two points or more in trauma patients with organ dysfunction already at admittance. Thus, to be diagnosed with sepsis-3, a typical trauma patient need not only to increase their SOFA score by two or more but also override the natural decline in SOFA when recovering from trauma-related organ dysfunction. This aspect of the sepsis-3 definition could arguably be extrapolated to all severely ill patients primarily admitted for non-infectious causes.

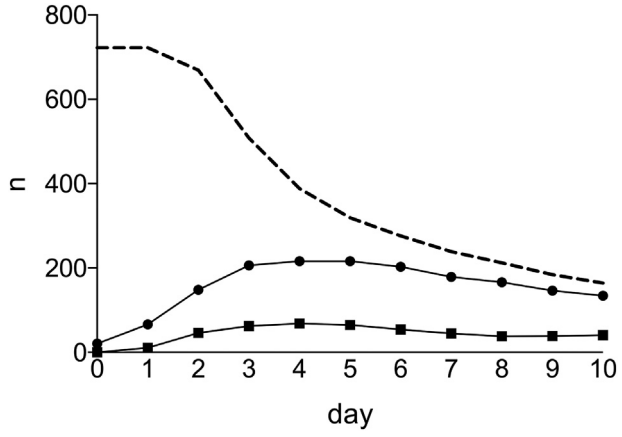

Fig. 4. Daily prevalence of sepsis and infection. Absolute daily prevalence of sepsis-2 (circles), sepsis-3 (boxes). Number of admitted patients (dashed line). The x-axis represent days since ICU-admission.

Very few patients had a suspicion of infection on admission. In contrast, after day five a majority of still admitted patients were regarded as infected. Previous studies in trauma victims have reported various rates of post-traumatic infections up to 57%, although with differing injury severities [16,17]. In our cohort 47% had a suspicion of infection during the study period. A recent study showed that infections are more common in the more severely injured patients [17]. In comparison with many previous trauma studies, our cohort was severely injured at admission, which may explain our relatively high infection rate. Pneumonia was by far the most common infection site and *Staphylococcus aureus* the most frequent pathogen, a finding similar to several previous reports [14,18].

In this study the overall mortality was low and most prominent in the early phase of the ICU stay. Patients dying at this stage typically succumbed to brain injury, major bleeding and other trauma-related causes of death. Admission GCS was notably lower in this group as compared with patients dying at a later stage (data not shown). In this early phase very few patients had sepsis, which generally presented at a later stage. Due to these anticipated competing risks, a temporal mortality analysis was performed. When censoring patients dying on day 1 sepsis-3 became associated with 30-day mortality whereas sepsis-2 did not. This relationship was maintained after continued, day-by-day, censoring of early deaths. These findings suggest that sepsis-3 is associated with late death in trauma victims whereas sepsis 2 is not.

The fact that early death, not related to sepsis, may confound the association between any sepsis definition and the outcome death applies to other patient categories as well. Patients admitted to an ICU for potentially lethal but non-infectious causes may display significant early mortality before being at risk for sepsis. This may be expected in conditions like cardiac arrest, severe burns, intracranial haemorrhage etc.

In the literature the previous sepsis definition has been criticised for having high sensitivity but too low specificity making it a less reliable tool [19,20]. This is reflected in our study where 80% of patients still admitted after day 6 had sepsis-2 but not an increased mortality. In contrast, an increased fatality was seen for patients with sepsis-3 at this stage. Concerns have also been raised regarding the new sepsis definition. One is that organ failure is part of the definition, something that may lead to delayed recognition of a severe infection and therefore late treatment [21]. How should a sepsis definition be used? Clearly any patient with signs of a serious infection should be diagnosed and treated appropriately regardless of formal sepsis criteria. Over the last decade most large interventional trials in septic patients have been neutral, a fact that has fuelled the debate of the sepsis-2 criteria being too unspecific, allowing for broad inclusions of patients, generating heterogenous cohorts with different clinical courses. This may in part explain why several of the large trials on potentially important interventions have failed to show beneficial effects. Hopefully the new definition, generally targeting fewer patients but with a higher risk of adverse outcome and therefore more likely to benefit from therapeutic interventions, may become a useful tool for future trials in septic patients [22,23].

4.3. Strength and weaknesses

This is to our knowledge, the first study to date evaluating the new sepsis criteria with the previous in trauma victims. It is also one of few

studies investigating the new definition in patients primarily admitted for non-infectious causes.

Strengths include data extraction from a high-resolution ICU trauma database. Moreover, all data were retrospectively validated by the researchers. Missing data was minimal for the variables used in the analysis. There was no loss to follow up regarding the end points and all data was collected prospectively.

Despite the above strengths, our study has several limitations. It is not possible to completely distinguish between an increase in SOFA due to a dysregulated host response secondary to infection, or to other reasons. We can only state that the change in SOFA occurred in direct temporal connection with infection. The inclusion rate was reduced due to shortage of research staff. At the present time there are no clear guidelines defining baseline SOFA in trauma patients developing sepsis-3 after admission. The approach used in the current study could be debated. A recent study on sepsis-3 in post cardiac surgery, however, used a similar approach as the current study [24].

The data were collected during a relatively long period. We cannot rule out changes in clinical practice during this time. However, the data used for the categorisation of sepsis-2 and 3 were retrieved with the same protocol over the entire study period. Further, changes in clinical practice might affect the number of patients with septic complications after trauma, but it is less likely that it would change the ratio between the two definitions.

5. Conclusion

Our findings imply that in traumatically injured ICU patients the change from the old sepsis-2 definition to the new sepsis-3 definition cuts sample size in half. This needs to be accounted for in the design of future studies regarding post-injury sepsis. Both definitions showed poor discriminatory properties for overall 30-day mortality. However, sepsis-3 had significant discriminatory properties and was associated with death, when censoring patients dying early after trauma before being at risk for sepsis. This was not seen for sepsis-2 definition implying that the sepsis-3 definition is more useful in a post trauma setting.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.08.019.

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