Original Article

Early evaluation of severity in patients with severe sepsis: a comparison with "septic shock" — subgroup analysis of the Japanese Association for Acute Medicine Sepsis Registry (JAAM-SR)

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Aim: The purpose of this subgroup analysis of a Japanese multicenter registry, the Japanese Association for Acute Medicine Sepsis Registry Advanced (JAAM-SR-Advanced), was to identify early outcome indicators for severe sepsis that are useful and more objective than "septic shock."

Methods: Among 624 patients with severe sepsis registered in JAAM-SR-Advanced, 554 with valid serum lactate data were retrospectively studied. Hypotension before and after fluid resuscitation and the highest lactate values over the initial 24 h were compared for their ability to predict in-hospital mortality.

Results: Of the study group, 155 (28.0%) patients were non-survivors and had significantly lower systolic blood pressures and higher lactate peaks. The mortality of 364 patients with initial hypotension was higher than those patients without it (32.7% versus 19.1%, $P < 0.01$). Patients with the worst lactate values ≥4 mmol/L had much higher mortality than other patients ($P < 0.001$). In an attempt to predict outcomes, we combined initial hypotension and the worst lactate values. The patient group with initial hypotension and the worst lactate values ≥4 mmol/L (183 patients, 33.0%) had a significantly higher mortality rate of 48.6% than the other groups ($P < 0.01$).

Conclusion: The novel combined criterion of initial hypotension and the worst lactate values ≥4 mmol/L within the initial 24 h is potentially useful as a single outcome predictor for severe sepsis.

Key words: Hypotension, lactate, mortality, outcome, prediction

INTRODUCTION

MORTALITY SECONDARY TO severe sepsis is generally as high as 30–50%, although there is great diversity depending on causative diseases and the nations or districts where it is treated.[1] In 2002, the Surviving Sepsis Campaign was proposed, and worldwide efforts to reduce the mortality associated with severe sepsis have continued since that time.[2,3]

In this context, early diagnosis of severe sepsis, early evaluation of its severity, and early resuscitation to achieve predetermined targets, especially for critical cases, are reported to be important for improving clinical outcomes.[4] Among those three "early" targets, the latter two are more promising and important in the sense that there is room left for development and improvement. In other words, to maximize the outcomes for sepsis, we should try to evaluate the severity of sepsis as early and as precisely as possible and resuscitate patients in an effort to achieve predetermined circulatory and/or oxygenation goals.

Regarding early resuscitation, Rivers *et al.* proposed "early goal-directed therapy" (EGDT) in 2001 and reported a remarkable reduction in mortality rate if several "early goals" were all fulfilled.[5] Since the publication of Rivers' paper, there have been many reports that have described the beneficial and promising effects of a modified EGDT.[6,7]

Regarding early evaluation of severity in septic patients, septic shock has been proved to be the strongest prognostic factor for sepsis in various papers to date.[8] In the Japanese Association for Acute Medicine Sepsis Registry Advanced (JAAM-SR-Advanced), the mortality rate among patients with septic shock was 41.5%, which was significantly higher than the 29.5% seen in the whole cohort.[9] However, other candidates for severity predictors have also been studied widely. Among them, serum lactate, which is a sensitive indicator of systemic tissue oxygenation, has been reported to be a useful marker of patient outcomes with a wide variety of severe diseases, not only for patients with severe sepsis.[7,10–12]

Septic shock is defined as "refractory shock after adequate fluid resuscitation".[13] The definition is far from perfect because it is not objective, in that both therapeutic intervention with "adequate fluid resuscitation" and the diagnosis "after resuscitation" are subjectively determined by clinicians.

To this end, we undertook a subgroup analysis of JAAM-SR-Advanced to find early outcome indicators for severe sepsis that are as useful as, and more objective than, "septic shock."

METHODS

Patients

THIS STUDY IS a subgroup analysis of results from a multicenter, prospective, observational study (JAAM-SR-Advanced, UMIN000008195) carried out by the JAAM-SR committee.[9] All data were collected under the approval of ethical committees of the JAAM and all of the participating facilities. Written informed consent was not obtained from patients because this was an observational study without any interventions. Over a 1-year period, from 1 June, 2010 to 31 May, 2011, 624 patients diagnosed with severe sepsis from 15 participating facilities were registered to a web-based database, JAAM-SR-Advanced, and among them, 554 patients with valid lactate data were included in this study. As shown in Figure 1, among 364 patients with initial hypotension, 20 were excluded from the analysis due to the lack of fluid resuscitation data. Two patients among 278 with fluid resuscitation were also excluded due to the lack of mean blood pressure (MBP) data after fluid resuscitation.

Definitions

Definitions of severe sepsis and septic shock were according to the 2003 revision of the definitions by the American
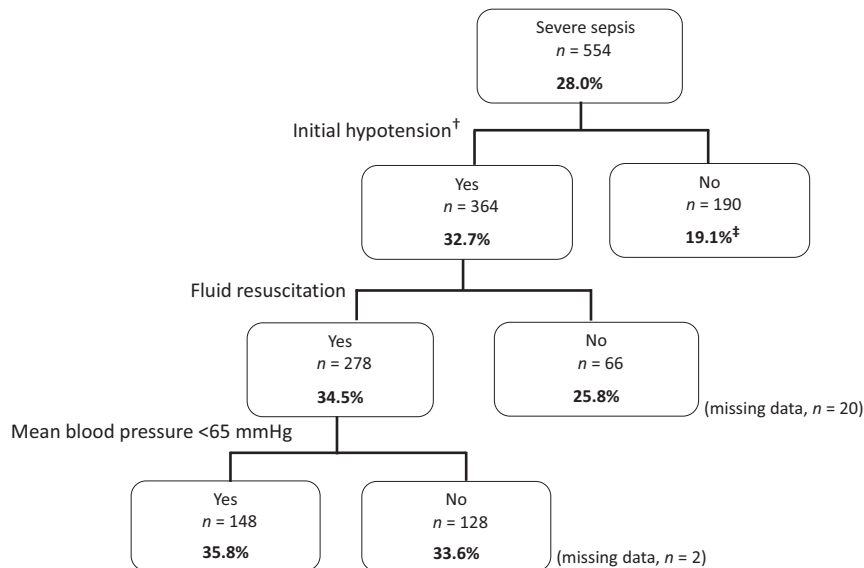
Fig. 1. Comparison of in-hospital mortality related to initial hypotension, fluid resuscitation, and mean blood pressures after resuscitation in patients with severe sepsis. Percentages in the figure show in-hospital mortalities. Patients with initial hypotension had significantly higher in-hospital mortality than those without it, whereas in-hospital mortality did not differ based on whether or not mean blood pressure exceeded 65 mmHg after fluid resuscitation. †Defined as systolic blood pressure <90 mmHg or mean blood pressure <65 mmHg. ‡Compared with patients with initial hypotension, *P* < 0.01.

College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.[13,14] Initial hypotension was defined as a systolic blood pressure (SBP) <90 mmHg or a MBP <65 mmHg.[14]

Methods

Systolic blood pressure, initial MBP, MBP after fluid resuscitation, and the worst lactate values during the initial 24 h were compared for their abilities to predict in-hospital mortality.

Statistics

All statistics were analyzed using the statistical software, Stat Flex, version 6.0 (Arctec, Osaka, Japan). All data are presented as mean ± standard deviation, unless otherwise mentioned. Comparisons between two groups were analyzed by Student's unpaired *t*-test for parametric data and by the Mann–Whitney *U*-test for non-parametric data. The χ^2-test was used for comparisons of proportion. Differences among the three groups were analyzed using one-way ANOVA, followed by post hoc testing using Dunnett's *t*-test, if applicable. A *P*-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

FIVE HUNDRED AND fifty-four patients with severe sepsis with a mean age of 68 years (male : female, 346:208) were included. There were 155 non-survivors (28.0%). Table 1 shows a comparison of patients' demographics between survivors and non-survivors. Non-survivors were significantly older and had significantly lower SBPs and higher lactate peaks during the initial 24 h.

Relationship between blood pressure and in-hospital mortality

Among 554 patients with severe sepsis, 364 (65.7%) with initial hypotension defined as SBP <90 mmHg or MBP <65 mmHg had a mortality rate of 32.7%, whereas 190 (34.3%) without hypotension had a mortality rate of 19.1% (*P* < 0.01) (Fig. 1). Among 344 patients with initial hypotension, fluid resuscitation was initiated for 278 (80.8%). In 276 patients with blood pressure data after fluid resuscitation, 148 (53.6%) remained in a hypotensive state, defined as MBP <65 mmHg, and the other 128 (46.4%) recovered from initial hypotension. There was no statistically significant difference in mortality between the two groups.

Worst lactate values during the initial 24 h and in-hospital mortality

As shown in Figure 2, mortality rates were compared among the three groups separated according to the worst lactate values during the initial 24 h. The groups with the worst lactate values ≥4 mmol/L (235 patients, 42.4%), those with the worst lactate values ≥2 and <4 (200, 36.1%), and those with the worst lactate values <2 (119, 21.5%) had in-hospital mortality rates of 43.8%, 18.0%, and 13.4%, respectively (*P* < 0.001). Furthermore, because sensitivity and specificity curves of the worst lactate values for the prediction of in-hospital deaths crossed at approximately 4 mmol/L, we used this number as a cut-off value in further analysis (Fig. 3).

Outcome prediction using initial hypotension and worst lactate values

In an attempt to predict outcomes by combining initial hypotension and the worst lactate values, the patient

Table 1. Comparison of age, gender, initial blood pressures, and lactate values between non-survivors and survivors with severe sepsis

	Non-survivor *n* = 155	Survivor *n* = 399	*P*-value
Age, years	71 ± 16	67 ± 17	<0.05
Gender, male/female	102/53	244/155	NS
Systolic blood pressure, mmHg	80 ± 32	91 ± 30	<0.001
Mean blood pressure, mmHg	56 ± 22	65 ± 21	<0.001
Lactate, mmol/L	5.4 (2.9–9.8)	3.0 (1.9–4.6)	<0.001

All data are expressed as mean ± standard deviation, except median (interquartile range) for lactate.
Blood pressures are initial values; lactate values are the worst during the initial 24 h.
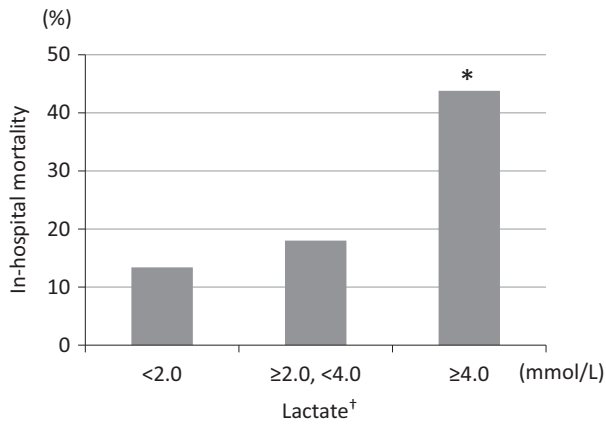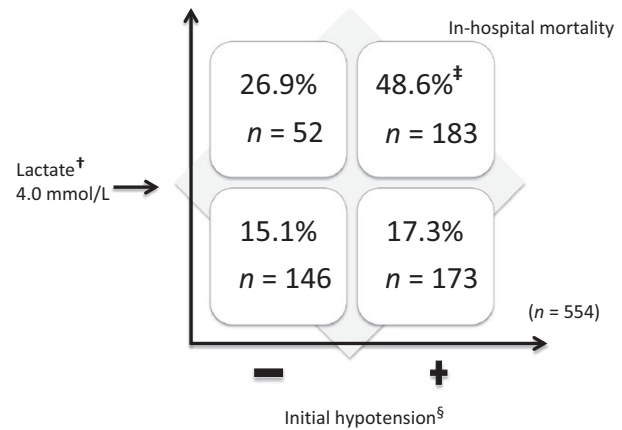
Fig. 2. Relationship between the worst lactate values during the initial 24 h and in-hospital mortality in patients with severe sepsis. The group with the worst lactate values ≥4 mmol/L had significantly higher in-hospital mortality than the other groups. †Worst values during the initial 24 h. *Compared with the other groups, $P < 0.001$.
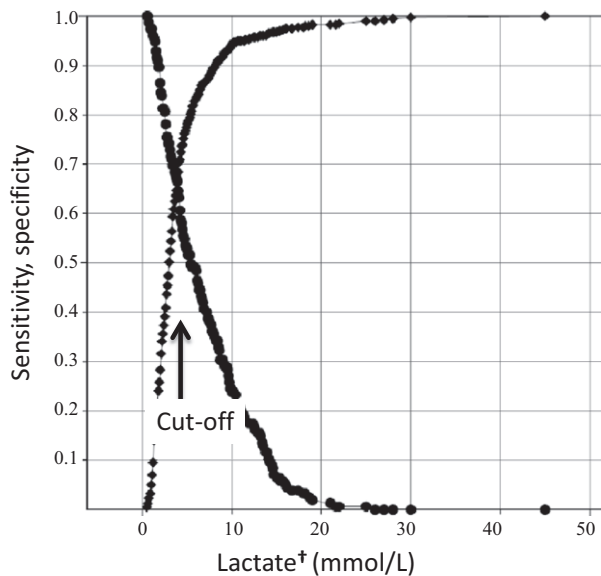
Fig. 3. Sensitivity and specificity curves of lactate values (worst values during the initial 24 h) for the prediction of in-hospital death among patients with severe sepsis. Sensitivity and specificity curves crossed at a lactate value of approximately 4 mmol/L. †Worst values during the initial 24 h.

Fig. 4. Comparison of in-hospital mortality among four groups of patients with severe sepsis separated based on initial hypotension and the worst lactate values during the initial 24 h. The group with initial hypotension and the worst lactate values ≥4 mmol/L had a significantly higher mortality rate than the other groups. †Worst values during the initial 24 h. ‡Compared with the groups with or without initial hypotension and the worst lactate values <4 mmol/L, $P < 0.001$, and with the group with no initial hypotension and the worst lactate values ≥4 mmol/L, $P < 0.01$. §Defined as systolic blood pressure <90 mmHg or mean blood pressure <65 mmHg.

DISCUSSION

IN THIS SUBGROUP analysis ($n = 554$) of results from the multicenter, prospective, JAAM-SR-Advanced, we found that, by selecting patients with initial hypotension (SBP <90 mmHg or MBP <65 mmHg) and the worst lactate values ≥4 mmol/L within the initial 24 h (which consisted of 33.0% of the whole patient population with severe sepsis), we were able to select the most critical patient group with an in-hospital mortality rate as high as 48.6%. This mortality rate was comparable with the 41.5% mortality rate of the septic shock group (45.2% of the whole patient population),[9] and this novel criterion is potentially useful as a powerful outcome predictor for severe sepsis (Table 2).

The production rate of lactate sensitively reflects regional oxygen debt because it is produced in the course of anaerobic metabolism. Therefore, lactate values themselves, their clearances, or clearance rates during certain intervals have often been reported to be useful for evaluating systemic tissue oxygenation and for predicting patient outcome.[5–7,10–12] Aduen *et al.* reported that lactate values ≥4 mmol/L were indicators of worse outcomes for patients being treated in intensive care units,[11] and Rivers *et al.* adopted hypotension or lactate values ≥4 mmol/L after adequate fluid resuscitation as selection criteria for

group with initial hypotension and the worst lactate values ≥4 mmol/L (183 patients, 33.0%) had a significantly higher mortality rate (48.6%) than the other groups (Fig. 4).

Table 2. Comparison of frequency, in-hospital mortality, sensitivity†, and specificity† between septic shock and initial hypotension‡ plus hyperlactate in patients with severe sepsis

	Septic shock§	Initial hypotension‡ and lactate¶ ≥4.0 mmol/L
Frequency, %	45.2	33.0
In-hospital mortality, %	41.5	48.6
Sensitivity†, %	63.6	57.4
Specificity†, %	62.5	76.4

†For the prediction of in-hospital deaths.
‡Defined as systolic blood pressure <90 mmHg or mean blood pressure <65 mmHg.
§Ogura *et al.*[9]
¶Worst values during the initial 24 h.

critically ill patients in their 2001 paper in which they proposed EGDT.[5] More recently, there have been several papers reporting that an improvement in outcome could be realized for critical patients with diseases such as severe sepsis by navigating therapy using lactate clearance in the early resuscitation phase.[6,7,10]

Because this is a retrospective study, the lactate values in this study are the worst values during the initial 24 h and they were not all measured at the same time. Generally speaking, lactate values tend to improve gradually as therapies such as volume resuscitation and respiratory management are undertaken adequately. Therefore, the worst lactate values during the initial 24 h are expected to be the first measurements in most of the cases. In this regard, if a new prospective study is planned to examine initial lactate values instead of the worst values during the initial 24 h, similar results to those of this study would be expected, and the initial lactate value would be the most promising candidate as a predictive outcome measure in the earliest stage of treatment.

The relationship between hypotension and the outcome of severe sepsis has been extensively examined in several reports because the definition of septic shock includes hypotension after fluid resuscitation.[8,9,15] Nevertheless, as far as we know, there have been no reports similar to the current one that focus on initial hypotension as the predictive outcome measure for patients with severe sepsis. Most initial hypotension in patients with severe sepsis is more often caused by hypovolemia than by cardiogenic dysfunction and is treatable by sufficient volume replacement. Patients with initial hypotension are thought to be in a combination of a temporarily hypovolemic state and true shock state from sepsis, and those two situations completely differ

from each other with regard to their probable outcomes. If we can stratify these two different patient groups, we may be able to more easily target patients for intensive resuscitation therapy. The present study shows that, among 356 patients with initial hypotension, 183 patients with the worst lactate values ≥4 mmol/L showed a mortality rate as high as 48.6%, and the other 173 patients had a mortality rate of only 17.3% (Fig. 4). Although we cannot deduce any solid conclusions from this retrospective study, it is probable that the patient subgroup with both initial hypotension and hyperlactemia is showing a true shock state with oxygen debt.

"Septic shock" has been reported to be one of the most potential and useful outcome predictors for severe sepsis.[8] JAAM-SR-Advanced also reported that the mortality rate of patients with septic shock was twice as high as those without it.[9] Nevertheless, the definition of septic shock is "refractory hypotension remaining after adequate fluid resuscitation,"[14] and there is subjective discretion with regard to the amount and interval of "adequate fluid resuscitation." Based on our results, this new outcome indicator, which combines initial hypotension and hyperlactemia ≥4 mmol/L, is thought to be objective and potentially more reliable and useful than the term "septic shock." Furthermore, if we can utilize the initial lactate values instead of the worst lactate values over 24 h, it would be possible to predict patient outcomes more precisely at the time of admission.

Although the results obtained in this retrospective study are promising, they should be interpreted carefully, particularly with regard to the following points. The blood pressures in some cases might be affected by inotropes being used before the diagnoses for severe sepsis. Additionally, as the lactate values were the worst ones during the initial 24 h, there might be a time gap between initial blood pressures and the worst lactate values. We believe that future prospective studies involving patients with severe sepsis should be organized to ensure the reproducibility and usefulness of this new outcome indicator. The incidence rate of severe sepsis is not very high, but there are possibilities for every hospital to have patients diagnosed with severe sepsis during their hospital stay or to accept them as incoming emergent patients. Because the mortality rate of severe sepsis is very high, it is important to collect as much patient data as possible from multiple institutes, similar to the method in the current study, and to undertake further clinical studies as needed. If the usefulness of the new outcome predictor in this study is confirmed in future studies, it will be possible for clinicians to select the most severely ill patients in the early stages of treatment for severe sepsis so that outcomes can be improved.

DISCLOSURE

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