ORIGINAL ARTICLE

Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

Kirsi-Maija Kaukonen, M.D., Ph.D., Michael Bailey, Ph.D., David Pilcher, F.C.I.C.M., D. Jamie Cooper, M.D., Ph.D., and Rinaldo Bellomo, M.D., Ph.D.

ABSTRACT

BACKGROUND

The consensus definition of severe sepsis requires suspected or proven infection, organ failure, and signs that meet two or more criteria for the systemic inflammatory response syndrome (SIRS). We aimed to test the sensitivity, face validity, and construct validity of this approach.

METHODS

We studied data from patients from 172 intensive care units in Australia and New Zealand from 2000 through 2013. We identified patients with infection and organ failure and categorized them according to whether they had signs meeting two or more SIRS criteria (SIRS-positive severe sepsis) or less than two SIRS criteria (SIRS-negative severe sepsis). We compared their characteristics and outcomes and assessed them for the presence of a step increase in the risk of death at a threshold of two SIRS criteria.

RESULTS

Of 1,171,797 patients, a total of 109,663 had infection and organ failure. Among these, 96,385 patients (87.9%) had SIRS-positive severe sepsis and 13,278 (12.1%) had SIRS-negative severe sepsis. Over a period of 14 years, these groups had similar characteristics and changes in mortality (SIRS-positive group: from 36.1% [829 of 2296 patients] to 18.3% [2037 of 11,119], P<0.001; SIRS-negative group: from 27.7% [100 of 361] to 9.3% [122 of 1315], P<0.001). Moreover, this pattern remained similar after adjustment for baseline characteristics (odds ratio in the SIRS-positive group, 0.96; 95% confidence interval [CI], 0.96 to 0.97; odds ratio in the SIRS-negative group, 0.96; 95% CI, 0.94 to 0.98; P=0.12 for between-group difference). In the adjusted analysis, mortality increased linearly with each additional SIRS criterion (odds ratio for each additional criterion, 1.13; 95% CI, 1.11 to 1.15; P<0.001) without any transitional increase in risk at a threshold of two SIRS criteria.

CONCLUSIONS

The need for two or more SIRS criteria to define severe sepsis excluded one in eight otherwise similar patients with infection, organ failure, and substantial mortality and failed to define a transition point in the risk of death. (Funded by the Australian and New Zealand Intensive Care Research Centre.)

From the Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University (K.-M.K., M.B., D.P., D.J.C., R.B.), the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (D.P.), and the Department of Intensive Care, Alfred Hospital (D.P.), Melbourne, VIC, and the Intensive Care Unit, Austin Health, Heidelberg, VIC (R.B.) — all in Australia; and the Neurosurgical Unit, Department of Anesthesiology, Intensive Care and Pain Medicine, Helsinki University Central Hospital, Helsinki (K.-M.K.). Address reprint requests to Dr. Bellomo at the Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Level 6, the Alfred Centre, 99 Commercial Rd., Melbourne, VIC 3004, Australia, or at rinaldo.bellomo@austin.org.au.

This article was published on March 17, 2015, at NEJM.org.

N Engl J Med 2015;372:1629-38.
DOI: 10.1056/NEJMoa1415236

Severe sepsis is a major cause of admission to the intensive care unit (ICU) and death.[1,2] The criteria according to the systemic inflammatory response syndrome (SIRS) were described 23 years ago as a clinical expression of the host response to inflammation.[3] In this context and in the presence of symptoms meeting two or more SIRS criteria, severe sepsis was seen as evolving from infection to sepsis, severe sepsis, and septic shock, in order of increasing severity. This approach was codified by the consensus statement of the American College of Chest Physicians and Society of Critical Care Medicine in 1992[3] and has been the predominant approach to classifying sepsis.[4-11]

However, the need for patients to meet two or more SIRS criteria has been criticized because of a low specificity for infection[12,13] within 24 hours after admission to the ICU.[14] Moreover, some patients (the elderly and those taking medications that affect heart rate, respiratory rate, or body temperature) may not have symptoms meeting two or more SIRS criteria, despite having infection and organ failure. Thus, the face validity and sensitivity of two or more SIRS criteria in the diagnosis of severe sepsis remain unclear.[15] The face validity and sensitivity can, however, be indirectly empirically tested by defining the number, characteristics, and outcome of patients in the ICU who have infection and organ failure and who do not have symptoms meeting two or more SIRS criteria but who can be confidently assumed to have severe sepsis on the basis of their presentation. Moreover, the construct validity of the SIRS criteria can be empirically assessed by testing whether the cutoff value of two criteria represents a significant transitional increase in the risk of death to logically justify its choice (in preference to one or three or four criteria) to diagnose or define severe sepsis.

We hypothesized that in the first 24 hours after ICU admission, the presence of symptoms meeting two or more SIRS criteria would have low face and construct validity and sensitivity and that the fulfillment of two criteria would not identify a transitional increase in an otherwise linear increased risk of death that would be logically expected with each additional criterion. We tested these hypotheses by conducting a study of all ICU admissions in Australia and New Zealand over the past 14 years.

Methods

Study Design

We conducted a retrospective study from January 1, 2000, to December 31, 2013, using data from the Australia and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD),[16] a high-quality database run by the ANZICS Centre for Outcome and Resource Evaluation. The ANZICS APD includes information on more than 90% of all ICU admissions in Australia and New Zealand. The Alfred Hospital Human Research Ethics Committee, Melbourne, Australia, approved the study with a waiver of informed consent. The data were gathered as a part of routine quality-assurance benchmarking processes by means of clinical registry surveillance by collectors in the participating ICUs.

Definitions

We defined sepsis, severe sepsis, and septic shock according to the American College of Chest Physicians–Society of Critical Care Medicine consensus definition.[3] We used infection-related diagnoses according to the Acute Physiology and Chronic Health Evaluation (APACHE) III at admission to infer the presence of suspected or proven infection (see the Supplementary Appendix, available with the full text of this article at NEJM.org). We defined organ failure in the first 24 hours after ICU admission as a Sequential Organ Failure Assessment (SOFA) score of 3 or higher (on a scale from 0 to 4, with higher scores indicating more severe organ failure)[2,17,18] (see the Supplementary Appendix).

We diagnosed severe sepsis if a patient had one of the ANZICS APD diagnostic codes for infection and organ failure or one of the following prespecified additional diagnostic categories in the ANZICS APD diagnostic codes for infection: sepsis due to infection other than from the urinary tract with organ failure, sepsis due to urinary tract infection with organ failure, sepsis with shock due to infection other than from the urinary tract, or sepsis with shock due to urinary tract infection. We applied the consensus SIRS criteria to all the data analyses (see the Supplementary Appendix).[3]

All the above criteria were assessed within the first 24 hours after ICU admission. Patient follow-up was available only for the duration of

hospital stay, and the primary outcome was in-hospital mortality.

STUDY POPULATIONS

Patients with SIRS-positive severe sepsis fulfilled the following requirements: symptoms meeting two or more SIRS criteria, an APACHE III diagnosis of infection at admission with at least one organ failure, or an APACHE III diagnosis of severe sepsis or septic shock at admission. Patients with SIRS-negative severe sepsis fulfilled the following requirements: symptoms meeting fewer than two SIRS criteria, and an APACHE III diagnosis of infection at admission with at least one organ failure or an APACHE III diagnosis of severe sepsis or septic shock at admission.

A descriptive analysis was performed on four prespecified subgroups of patients: patients with septic shock, those receiving mechanical ventilation, those with acute renal failure, and those with an APACHE II score of more than 24 (on a scale from 0 to 71, with higher scores indicating more severe disease). An additional post hoc analysis was performed to compare differences between community-acquired sepsis and hospital-acquired sepsis as determined by the ICU admission source.

STATISTICAL ANALYSIS

Data are presented as numbers and percentages, means and standard deviations, medians and interquartile ranges, or proportions with 95% confidence intervals. Accordingly, chi-square tests for equal proportion, Student's t-test, or the Wilcoxon rank-sum test were used to test differences. No assumptions were made for missing data, with multivariable analysis performed on data from patients who had complete data only (see the Supplementary Appendix).

To identify independent differences at baseline that may exist between patients with SIRS-positive severe sepsis and those with SIRS-negative severe sepsis, we applied multivariable logistic regression to data from all the patients with severe sepsis with SIRS-positive status as the outcome (see the Supplementary Appendix). The multivariable model was developed with the use of the least absolute shrinkage and selection operator (LASSO) method, with variable inclusion determined by the Schwarz–Bayesian information criterion. The resulting prediction equation was then used to generate each patient's probability of being SIRS-positive.

To investigate the similarities of differences in hospital outcomes over time for all the patients with sepsis, logistic-regression models were used (see the Supplementary Appendix), with the Australian and New Zealand calibrated Risk of Death (ANZROD) model.[19] This model has been shown to perform better than the APACHE III in Australia and New Zealand.[20,21]

To further determine the predictive capacity of using two or more SIRS criteria to identify an increase in the risk of death, SIRS was considered first as a dichotomous variable (≥2 SIRS criteria vs. 0 to 1 SIRS criterion) and second as an ordinal variable from 0 to 4, reflecting the number of SIRS criteria met. Because the SIRS criteria are derived from components related to the severity of sepsis in the patient, we determined the predictive capacity of the SIRS criteria by adjusting for the severity markers without SIRS criteria, in conjunction with year, site of admission, and probability of being SIRS-positive. Data were randomly divided into two equal sets, with the first used for model development and the second used for model validation. Model discrimination was determined with the use of the area under the curve (AUC), whereas classification error was determined with the use of integrated discrimination improvement and net reclassification improvement with results reported specifically for the validation data set. Net reclassification improvement was determined first as category-free improvement and second stratified in quartiles of risk.

To determine whether predictors of death differed significantly between SIRS-positive sepsis and SIRS-negative sepsis, a multivariable logistic-regression model for mortality among all the patients with sepsis was developed with the use of the LASSO method, with variable inclusion determined by means of the Schwarz–Bayesian information criterion. Interactions between identified predictors of mortality and SIRS status were then applied to determine whether the nature of the relationship to mortality differed according to SIRS status.

All the data were analyzed with the use of SAS software, version 9.4 (SAS Institute). A two-sided P value of less than 0.01 was considered to indicate statistical significance.

RESULTS

STUDY PATIENTS

We studied data from 1,171,797 patients in 172 ICUs. A total of 1,062,134 patients did not have sepsis, and 109,663 had infection and organ dysfunction. Of the patients with infection and organ dysfunction, 96,385 patients (87.9%) had SIRS-positive severe sepsis and 13,278 (12.1%) had SIRS-negative severe sepsis (Table 1). Patients with SIRS-positive severe sepsis were younger, were more severely ill, and had higher mortality than those with SIRS-negative severe sepsis. They were also more likely to have septic shock or acute kidney injury but less likely to have a surgical admission or to be discharged home (Table 1).

The annual proportions of patients with SIRS-positive severe sepsis or SIRS-negative severe sepsis among all ICU admissions are presented in Figure S1 in the Supplementary Appendix, as are the annual proportions of patients with SIRS-positive severe sepsis or SIRS-negative severe sepsis. Risk factors for SIRS-positive status are presented in Table S1 in the Supplementary Appendix.

SIRS IN SEVERE SEPSIS

The distribution of SIRS criteria is presented in Table 2. The most frequent SIRS criterion that was met in patients with SIRS-positive severe sepsis was an increased heart rate, followed by an increased respiratory rate or a low partial pressure of arterial carbon dioxide ($Paco_2$) and an abnor-

Table 1. Baseline Characteristics and Hospital Outcomes of Patients with Severe Sepsis, According to Status with Respect to Criteria for the Systemic Inflammatory Response Syndrome (SIRS).*

Characteristic	All Patients		Patients with SIRS-Positive Sepsis		Patients with SIRS-Negative Sepsis		P Value
	no. of patients with data		*no. of patients with data*		*no. of patients with data*		
Age — yr	109,663		96,385		13,278		<0.001
Median		66.0		65.8		68.3	
Interquartile range		52.2–76.6		51.9–76.4		55.5–77.7	
Male sex — no. (%)	109,663	60,484 (55.2)	96,385	52,932 (54.9)	13,278	7552 (56.9)	<0.001
Surgical admission — no. (%)	109,663	23,630 (21.5)	96,385	18,441 (19.1)	13,278	5189 (39.1)	<0.001
APACHE III score†	105,674	71.7±30.1	93,466	73.7±30.1	12,208	56.7±26.1	<0.001
Risk of death — %‡							
APACHE III	105,320		93,142		12,178		<0.001
Median		22		24		11	
Interquartile range		9–48		10–50		4–26	
ANZROD model							
With SIRS components	105,428		93,251		12,177		<0.001
Median		14		16		8	
Interquartile range		6–33		6–35		3–18	
Without SIRS components	105,428		93,251		12,177		<0.001
Median		15		16		9	
Interquartile range		6–33		7–34		4–22	
Duration of stay							
In ICU — hr	109,579		96,313		13,266		<0.001
Median		80		85		57	
Interquartile range		38–172		40–181		24–128	
In hospital — days	108,565		95,507		13,058		<0.001
Median		12.9		13.1		11.2	
Interquartile range		6.6–25.3		6.7–25.8		5.8–21.9	

Table 1. (Continued.)

Characteristic	All Patients		Patients with SIRS-Positive Sepsis		Patients with SIRS-Negative Sepsis		P Value
	no. of patients with data		*no. of patients with data*		*no. of patients with data*		
Treatment limitations — no. (%)§	109,663	4,928 (4.5)	96,385	4,535 (4.7)	13,278	393 (3.0)	<0.001
Hospital outcome — no. (%)	109,663		96,385		13,278		
Death		25,713 (23.4)		23,577 (24.5)		2136 (16.1)	<0.001
Discharge							
Home		60,292 (55.0)		52,000 (54.0)		8292 (62.4)	<0.001
To rehabilitation or long-term care facility		7,781 (7.1)		6,837 (7.1)		944 (7.1)	0.95
To other hospital		13,168 (12.0)		11,540 (12.0)		1628 (12.3)	0.34
Subgroup — no. (%)							
Septic shock	109,663	61,483 (56.1)	96,385	55,876 (58.0)	13,278	5607 (42.2)	<0.001
Mechanical ventilation	109,643	58,678 (53.5)	96,380	51,359 (53.3)	13,263	7319 (55.2)	<0.001
Acute renal failure	109,556	19,780 (18.1)	96,328	18,229 (18.9)	13,228	1551 (11.7)	<0.001
APACHE II score >24¶	106,621	30,677 (28.8)	94,041	28,778 (30.6)	12,580	1899 (15.1)	<0.001

* Plus–minus values are means ±SD. SIRS-positive status was defined if the patient fulfilled at least two SIRS criteria, and SIRS-negative status if the patient fulfilled zero or one SIRS criterion. ICU denotes intensive care unit.
† Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) III range from 0 to 299, with higher scores indicating a greater severity of illness.
‡ The risk of death was assessed by means of the APACHE III model, which is based on data from 40 U.S. hospitals, and by means of the Australian and New Zealand Risk of Death (ANZROD) model,[19] which has been shown to perform better than the APACHE III in Australia and New Zealand.
§ Patients with treatment limitations are admitted to the ICU with the intention of providing limited treatment, which may include, for example, the withholding of cardiopulmonary resuscitation in case of cardiac arrest, the withholding of dialysis, or the withholding of endotracheal intubation.
¶ Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease.

mal white-cell count. In patients with SIRS-negative severe sepsis, the most frequent single criterion that was met was an abnormal white-cell count, followed by an increased heart rate and increased respiratory rate or a low $Paco_2$ (Table 2). Of the patients with SIRS-negative sepsis, 20% did not fulfill any SIRS criteria, and 80% fulfilled one SIRS criterion (Table 2). The distribution of baseline characteristics among patients with SIRS-negative severe sepsis, stratified according to the presence of zero or one SIRS criterion, is presented in Table S2 in the Supplementary Appendix. The patients with SIRS-positive severe sepsis were significantly more likely than those with SIRS-negative severe sepsis to present with community-acquired infection (38.1% vs. 28.1%, P<0.001) or hospital-acquired infection (28.0% vs. 18.3%, P<0.001) (Tables S1 and S3 in the Supplementary Appendix).

OUTCOMES

Absolute mortality decreased similarly in the two groups (Fig. 1). The rate of death in SIRS-positive patients decreased from 36.1% (in 829 of 2296 patients) in 2000 to 18.3% (in 2037 of 11,119 patients) in 2013 (P<0.001). Over the same period, in SIRS-negative patients, the rate of death decreased from 27.7% (in 100 of 361 patients) to 8.5% (in 112 of 1315 patients) (P<0.001). These changes represent an annual rate of absolute decrease of 1.3 percentage points in each group, and a reduction in relative risk of 49.3% (45.7 to 52.6%) and 66.5% (57.5 to 73.6%), respectively.

There was a very similar annual decline in adjusted mortality in the two groups (annual odds ratio in the SIRS-positive group, 0.96; 95% confidence interval [CI], 0.96 to 0.97; odds ratio in the SIRS-negative group, 0.96; 95% CI, 0.94 to 0.98; P<0.001 for both comparisons) (P=0.12 for

Table 2. Distribution of Signs Meeting SIRS Criteria in Patients with Severe Sepsis, According to SIRS-Positive and SIRS-Negative Status.*

Variable	All Patients (N=109,663)	Patients with SIRS-Positive Severe Sepsis (N=96,385)	Patients with SIRS-Negative Severe Sepsis (N=13,278)
SIRS criterion met — no. (%)†			
Abnormal temperature	64,365 (58.7)	62,430 (64.8)	1,935 (14.6)
High	33,059 (30.1)	32,605 (33.8)	454 (3.4)
Low	36,130 (32.9)	34,599 (35.9)	1,531 (11.5)
Increased heart rate	83,493 (76.1)	80,747 (83.8)	2,746 (20.7)
Increased respiratory rate or decreased $Paco_2$	76,558 (69.8)	74,043 (76.8)	2,515 (18.9)
Abnormal white-cell count	76,823 (70.1)	73,365 (76.1)	3,458 (26.0)
High	64,720 (59.0)	61,602 (63.9)	3,118 (23.5)
Low	12,967 (11.8)	12,616 (13.1)	351 (2.6)
No. of SIRS criteria met			
Median	3	3	1
Interquartile range	2–4	2–4	1–1
Distribution			
>1	96,385 (87.9)	96,385 (100)	0
0	2,624 (2.4)	0	2,624 (19.8)
1	10,654 (9.7)	0	10,654 (80.2)
2	26,820 (24.5)	26,820 (27.8)	0
3	41,315 (37.7)	41,315 (42.9)	0
4	28,250 (25.7)	28,250 (29.3)	0

* P<0.001 for all comparisons between the SIRS-positive group and the SIRS-negative group. $Paco_2$ denotes partial pressure of arterial carbon dioxide.
† SIRS criteria are defined in the Supplementary Appendix. Patients may have more than one criterion.

between-group difference) (Fig. 1 and Table 3). The proportion of patients discharged home increased in the same way in the two groups (Fig. S2 in the Supplementary Appendix). The adjusted annual odds for discharge home increased significantly in the SIRS-positive group (annual odds ratio, 1.02; 95% CI, 1.01 to 1.02; P<0.001) but not in the SIRS-negative group (annual odds ratio, 1.01; 95% CI, 0.99 to 1.02; P=0.29) (Table 3). However, there was no significant difference between the two groups in the adjusted rate of increase (P=0.17). The unadjusted rate of discharge to another hospital appeared to increase similarly in the two groups (Fig. S2 in the Supplementary Appendix). However, in the adjusted analysis, there was no significant change over time in either group (Table 3). The adjusted rate of discharge to a rehabilitation or long-term care facility increased significantly in each group (P<0.001 for both comparisons), but there was no significant between-group difference (P=0.20) (Table 3).

PREDICTION OF MORTALITY

When the analysis included a modified risk of death (with SIRS components removed), the probability of being SIRS-positive, year of admission, study site, and SIRS status (positive or negative) as covariates in the logistic-regression analysis, being SIRS-positive independently increased the risk of death by 26% (odds ratio, 1.26; 95% CI, 1.18 to 1.34; P<0.001). In a similar model that included the number of SIRS criteria from 0 to 4, a 13% linear increase in mortality was associated with each additional SIRS criterion (odds ratio for each additional criterion, 1.13; 95% CI, 1.11

to 1.15; P<0.001) (Table S4 in the Supplementary Appendix) without any transitional increase in risk when two criteria were met (Fig. 2). When a comparison of discrimination and reclassification was performed between SIRS criteria as a binomial variable (≥2 criteria vs. <2 criteria) and SIRS criteria as a continuous variable (0 to 4 criteria), there were modest but significant improvements noted for the continuous model in the AUC, integrated discrimination improvement, and net reclassification improvement when patients were stratified into quartiles of risk (Table S4 in the Supplementary Appendix).

PREDICTION OF MORTALITY ACCORDING TO SIRS-POSITIVE OR SIRS-NEGATIVE STATUS

There were several predictors of mortality among patients with SIRS-positive sepsis or SIRS-severe sepsis (Table S5 in the Supplementary Appendix). Of 16 identified predictors of mortality, the only variable that differed significantly between the two groups was illness severity (Table S5 in the Supplementary Appendix).

DISCUSSION

We studied the sensitivity, face validity, and construct validity of the rule of using two or more SIRS criteria for the diagnosis of severe sepsis in the first 24 hours after ICU admission. We found that the SIRS-criteria rule missed one patient in eight with severe sepsis. Such patients with SIRS-negative severe sepsis had lower but still substantial mortality, as compared with patients with SIRS-positive sepsis, and the incidence, proportion, and mortality decreased over time almost identically to the rates among patients with SIRS-positive sepsis. In addition, their unadjusted and adjusted discharge rates to a rehabilitation or long-term care facility were also similar, as were predictors of mortality. Finally, in the adjusted analysis, mortality increased linearly with each additional SIRS criterion from 0 to 4 without any transitional increase in risk at a threshold of two criteria.

SIRS criteria were described more than two decades ago, and the signs meeting these criteria have been assumed to indicate a clinical response to inflammation.[3] Infection was seen to require the presence of such signs to help define the transition to sepsis, severe sepsis, and septic shock.[15,22,23] This approach was supported by the observation that an increase in the number of SIRS criteria met was associated with a worse outcome in critically ill patients, regardless of infection status.[15,22]

The presence of signs meeting two or more SIRS criteria is common in all patients in the ICU but is not specific for infection.[15] Among patients in the emergency department, 38% of those with SIRS-positive severe sepsis have an

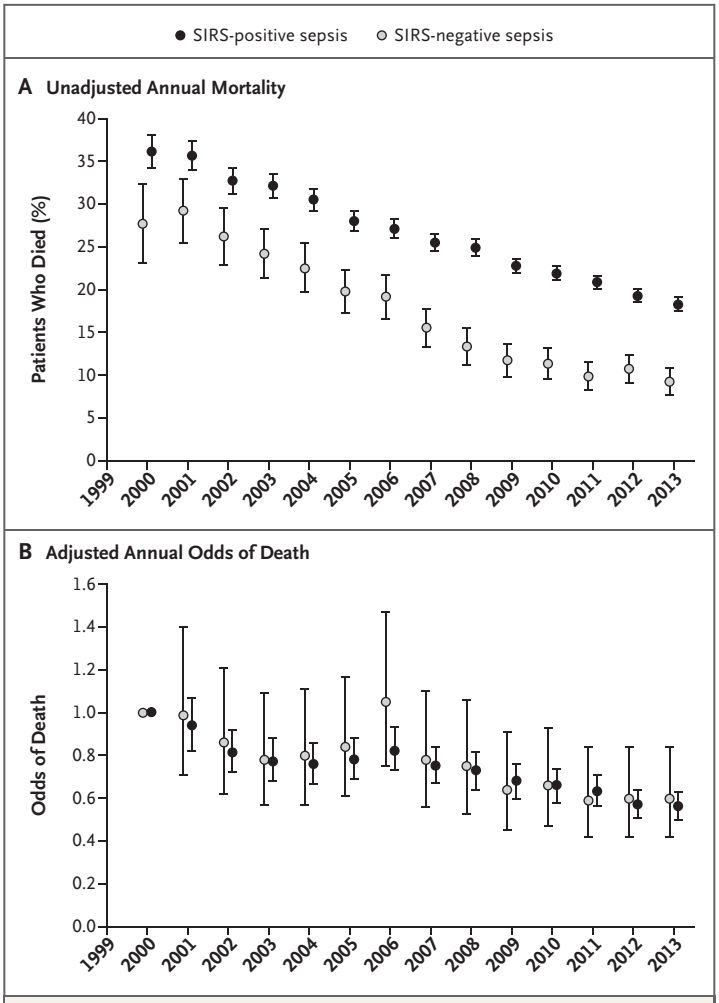

Figure 1. Mortality among Patients with Severe Sepsis, According to Status with Respect to Criteria for the Systemic Inflammatory Response Syndrome (SIRS).

Patients were categorized according to whether they had symptoms meeting two or more SIRS criteria (SIRS-positive sepsis) or symptoms meeting less than two SIRS criteria (SIRS-negative sepsis). Panel A shows the unadjusted annual mortality among patients in the two groups from 2000 through 2013, and Panel B shows the adjusted annual odds of death. The bars represent 95% confidence intervals.

Table 3. Annual Change in Hospital Outcomes from 2000 through 2013 and Between-Group Differences.

Hospital Outcome	Patients with SIRS-Positive Severe Sepsis		Patients with SIRS-Negative Severe Sepsis		P Value for Between-Group Comparison
	Adjusted Odds Ratio (95% CI)	P Value for Change over Study Period	Adjusted Odds Ratio (95% CI)	P Value for Change over Study Period	
Death	0.96 (0.96–0.97)	<0.001	0.96 (0.94–0.98)	<0.001	0.12
Discharge					
Home	1.02 (1.01–1.02)	<0.001	1.01 (0.99–1.02)	0.29	0.17
To other hospital	1.00 (1.00–1.01)	0.50	1.00 (0.98–1.02)	0.86	0.88
To rehabilitation or long-term care facility	1.06 (1.05–1.07)	<0.001	1.07 (1.05–1.09)	<0.001	0.20
To other hospital	1.00 (1.00–1.01)	0.50	1.00 (0.98–1.02)	0.86	0.88

infection,[24] as compared with 21% of those with SIRS-negative severe sepsis.[24] In our patients with SIRS-positive severe sepsis, the most frequent signs meeting SIRS criteria were an increased heart rate and increased respiratory rate, which is in agreement with the results of a prospective study of SIRS prevalence among patients with infection in the ICU.[15] These observations support the external validity of our study. Our study, however, assessed the prevalence of signs meeting individual SIRS criteria. Among our patients who had infection and organ failure, signs meeting two or more SIRS criteria occurred in 87.9% of patients within 24 hours after ICU admission, supporting their presence in the majority of patients with severe sepsis. Regardless of how we assess their sensitivity, these criteria fail to identify one in eight patients with severe sepsis. Moreover, we found that the cutoff point of two SIRS criteria does not define any specific transition point for risk.

The presence of symptoms meeting two or more SIRS criteria is believed to have excellent sensitivity but low specificity for severe sepsis.[15] Our study showed that it may also have limited sensitivity. The application of the criteria in the first 24 hours after ICU admission (the period when recruitment into sepsis trials is most common) would exclude approximately one in eight ICU patients with infection and organ failure. However, it may also decrease the specificity of these criteria. These patients have substantial mortality and their epidemiologic data are identical to these of patients with classic SIRS-positive severe sepsis,[25] which suggests that these two groups represent different clinical phenotypes of the same process. Moreover, on adjusted analysis, mortality increased linearly with each additional SIRS criterion from 0 to 4, with no transitional increase in risk at two criteria to justify the use of two criteria as definitional cutoff point.

Our study has several strengths. It investigates the effect of SIRS criteria within the first 24 hours after ICU admission on the diagnosis of severe sepsis over a period of 14 years. Second, the study is large. Third, the SIRS data consist of physiological or laboratory measurements that were prospectively collected for routine quality-surveillance purposes and are therefore unlikely to be biased. Fourth, our findings are broadly consistent with the limited existing literature and include data from 172 ICUs, which increases external validity, and data obtained in 2013, which increases contemporary relevance.

Our study also has some limitations. The data were collected primarily for quality-control purposes and not for study purposes. We could study symptoms meeting SIRS criteria only during the first 24 hours in the ICU as recorded either every 30 minutes or every 60 minutes on the observation charts. Thus, we cannot comment on their absence or presence before or after this period or for short intervals between observations. We cannot define a population at risk for sepsis to assess the SIRS criteria for their diagnostic value. However, this was not the aim of our study. The accuracy of specific diagnostic coding of infections was not independently monitored. However, on-site audits of data quality, validation rules built into data-collection software, and regular education sessions

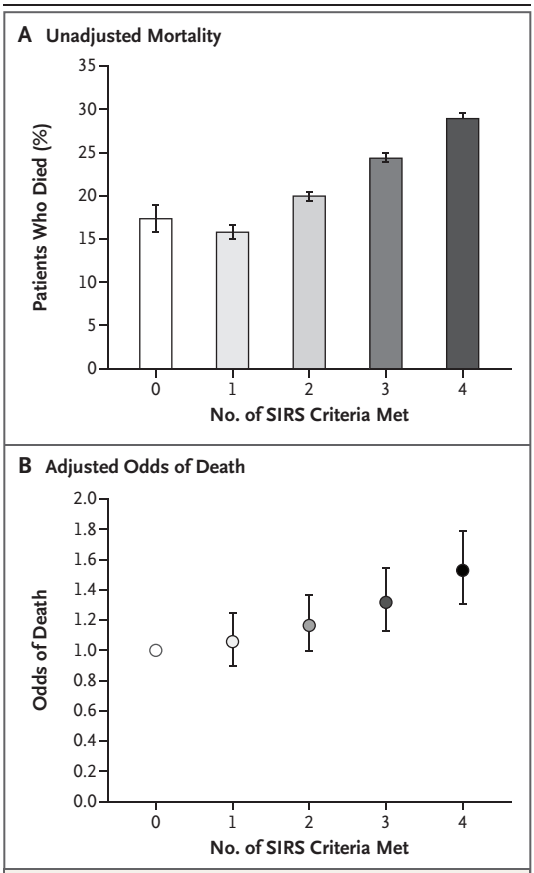

Figure 2. Mortality among Patients with Severe Sepsis, According to Number of SIRS Criteria Met.

The bars represent 95% confidence intervals.

make systematic bias in diagnostic coding unlikely. Some of the patients who had severe sepsis after surgery may have had SIRS because of the surgery rather than because of sepsis. However, this problem would apply to such patients in any clinical context. Our definition of organ failure related only to the first 24 hours. Thus, patients who might have had organ failure on the second day of the ICU stay were missed. Our definition of organ failure was based on the SOFA score. Other definitions exist,[26] which we did not have sufficient data to assess. Our definition of cardiovascular failure relied on the presence of hypotension and a diagnosis of shock and did not include the use of vasopressor drugs. However, such criteria were applied equally to both groups, which makes bias unlikely.

In this epidemiologic study, the requirement of two or more SIRS criteria for the diagnosis of severe sepsis excluded a sizable group of patients in the ICU with infection and organ failure. These patients with SIRS-negative severe sepsis had substantial mortality and, over a period of more than a decade, had epidemiologic characteristics and changes that were essentially identical to those of patients with SIRS-positive severe sepsis, providing indirect empirical evidence that these two groups of patients represent separate phenotypes of the same condition. Moreover, the risk of death in the two groups increased linearly with each additional SIRS criterion from 0 to 4, without a transitional increase in risk at two criteria that would justify this consensus cutoff point. Our findings challenge the sensitivity, face validity, and construct validity of the rule regarding two or more SIRS criteria in diagnosing or defining severe sepsis in patients in the ICU.

Supported by the Australian and New Zealand Intensive Care Research Centre, which is supported by an enabling grant (0606978) from the Australian National Health and Medical Research Council.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Mountain Bluebird, Colorado Brian Shaw, M.D.