Differences in Impact of Definitional Elements on Mortality Precludes International Comparisons of Sepsis Epidemiology—A Cohort Study Illustrating the Need for Standardized Reporting

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Objectives: Sepsis generates significant global acute illness burden. The international variations in sepsis epidemiology (illness burden) have implications for region specific health policy. We hypothesised that there have been changes over time in the sepsis definitional elements (infection and organ dysfunction), and these may have impacted on hospital mortality.

Design: Cohort study.

Setting: We evaluated a high quality, nationally representative, clinical ICU database including data from 181 adult ICUs in England.

Patients: Nine hundred sixty-seven thousand ive hundred thirty-two consecutive adult ICU admissions from January 2000 to December 2012.

Interventions: None.

Measurements and Main Results: To address the proposed hypothesis, we evaluated a high quality, nationally representative, clinical, ICU database of 967,532 consecutive admissions to 181 adult ICUs in England, from January 2000 to December 2012, to identify sepsis cases in a robust and reproducible way. Multinomial logistic regression was used to report unadjusted trends in sepsis definitional elements and in mortality risk categories based on organ dysfunction combinations. We generated logistic regression models and assessed statistical interactions with acute hospital mortality as outcome and cohort characteristics, sepsis definitional elements, and mortality risk categories as covariates. Finally, we calculated postestimation statistics to illustrate the magnitude of clinically meaningful improvements in sepsis outcomes over the study period. Over the study period, there were 248,864 sepsis admissions (25.7%). Sepsis mortality varied by infection sources (19.1% for genitourinary to 43.0% for respiratory; $p < 0.001$), by number of organ dysfunctions (18.5% for 1 to 69.9% for 5; $p < 0.001$), and organ dysfunction combinations (18.5% for risk category 1 to 58.0% for risk category 4). The rate of improvement in adjusted hospital mortality was significant (odds ratio, 0.939 [0.934–0.945] per year; $p < 0.001$), but showed different secular trends in improvement between infection sources.

Conclusions: Within a sepsis cohort, we illustrate case-mix heterogeneity using definitional elements (infection source and organ dysfunction). In the context of improving outcomes, we illustrate differential secular trends in impact of these variables on adjusted mortality and propose this as a valid reason for international variations in sepsis epidemiology. Our article highlights the need to determine standardized reporting elements for optimal comparisons of international sepsis epidemiology. (*Crit Care Med* 2016; XX:00–00)

Key Words: epidemiology; healthy policy; heterogeneity; international benchmarking; sepsis

Sepsis is a syndrome defined by life-threatening organ dysfunction due to a dysregulated host response to infection (1). Understanding the true global illness burden generated by sepsis has important implications for both policy and practice (2–4)—as substantial resources are directed toward campaigns to enhance recognition and improve management and outcomes, nationally and internationally. This knowledge might inform region-specific health policy.

Considerable international variation in incidence of (6.0–27.0%) and mortality from (as high as 80.0%) sepsis has been

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reported across ICU cohorts (3–6), with recent trended data indicating a decrease in mortality (7–9). However, interpretation of these data is challenging as it is likely that differences in the timing and trajectories of pre- and within hospital care, enhanced recognition (through campaigns such as the Surviving Sepsis Campaign (10) and the Sepsis Six in the United Kingdom [11]) and available ICU resources (the provision and use of ICU beds), will influence the characteristics of the sepsis population admitted to ICU (3, 12–16). Currently, no international consensus exists for standardised reporting of the characteristics of and outcomes for a sepsis population.

Using a nationally representative, clinical, ICU database to identify sepsis cases in a robust and reproducible way using physiologic and diagnostic data within the first 24 hours of admission, we set out to describe sepsis case mix (by source of infection and by number and combination of systemic inflammatory response syndrome [SIRS] criteria and of organ dysfunctions), its impact on mortality, and to illustrate the potential role that differences in sepsis case mix might play in the interpretation of ICU epidemiology—all with a view to initiating a dialogue for more standardised reporting.

MATERIALS AND METHODS

Data Source

The Case Mix Programme is the national clinical audit for adult general ICUs in England. For consecutive admissions, trained data collectors collect sociodemographic, comorbidity, and physiologic data to precise rules and definitions, during the first 24 hours following admission to ICU, and outcomes. Diagnostic data are determined clinically and coded using the hierarchical Intensive Care National Audit & Research Centre (ICNARC) Coding Method (additional information provided in **S-Methods-1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B941) (17). Collected data undergo extensive local and central validation prior to pooling into the Case Mix Programme Database (CMPD) (18). Support for the collection and use of these data has been obtained under Section 251 of the National Health Service Act 2006 (approval number: PIAG 2–10(f)/2005).

Case Selection and Definitions

Using contemporaneous physiologic data, definitions for each of the four SIRS criteria and each of five organ dysfunctions were applied and deemed to be met/not met. A sepsis admission was defined as any admission clinically coded as infection and at least one organ dysfunction (additional information provided in S-Methods-1, Supplemental Digital Content 1, http://links.lww.com/CCM/B941).

Analysis

The annual number and proportion of sepsis admissions, between January 2000 and December 2012, were calculated from the CMPD. The primary outcome was hospital mortality. Population incidence for severe sepsis admissions in England was estimated using extrapolation. Actual numbers for participating ICUs were extrapolated to the total number of ICUs in England for each year. Extrapolated numbers were converted to population incidences by dividing by mid-year population estimates obtained from the Office for National Statistics (19).

For each year, "cohort characteristics" were described by age, sex, presence of severe comorbidities, source of admission/surgical urgency, and cardiopulmonary resuscitation within 24 hours prior to admission and illness severity (Acute Physiology and Chronic Health Evaluation [APACHE] II and ICNARC physiology scores). For each year, "sepsis specific case mix" was described by source of infection, by the number and combination of SIRS criteria and by number, type, and combination of organ dysfunctions. Based on the report by Padkin et al (20) (**S-Table-1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B941), we generated four mortality risk categories to illustrate the relationship between number(s) and type(s) of organ dysfunction combinations and associated unadjusted hospital mortality. After summarizing study cohort characteristics, we reported the change over time in proportion of sepsis admissions, unadjusted hospital mortality, and univariate analyses to show the heterogeneity and the associations between definitional elements and unadjusted hospital mortality. Multinomial logistic regression was used to report unadjusted trends for source of infection, number of SIRS criteria, number of organ dysfunctions, and risk categories.

Risk-adjusted trends in hospital mortality were evaluated using a logistic regression model adjusted for "cohort characteristics and sepsis specific case-mix characteristics." To assess the presence of interactions between source of infection, organ dysfunctions, and longitudinal trends, three further logistic regression models were created with interaction terms and adjusted for case-mix characteristics. In the first model, the interaction between sources of infection over time on risk-adjusted mortality was assessed. The second model assessed the interaction between organ dysfunctions (by risk category) over time on risk-adjusted mortality. The third model (model-3) assessed the interaction between both the source of infection and organ dysfunctions (by risk category) over time on risk-adjusted mortality and was also used to generate all the adjusted odds ratios (ORs) reported. Finally, we assessed whether, if the case-mix characteristics had remained the same as in 2000 but all characteristic-specific improvements in mortality had occurred as they did, the sepsis mortality by infection source and risk category had truly improved over time. Postestimation predictive margins were used to estimate the marginal-predicted mortality for each year for sources of infection and risk categories using regression model-3, holding all other covariates at the values observed in 2000. All logistic regression models excluded readmissions of the same patient during the same hospital stay, were fitted with robust SEs to account for clustering by ICU, and were reported as OR with 95% CI.

Sensitivity analyses were performed to check the robustness of the findings for the 62 ICUs contributing data over the complete study period. Reported p values are two sided and p value less than 0.05 was considered to represent a statistically significant result. Continuous data were summarized as mean and SD, where normally distributed, and median and interquartile range, where not. Categorical data were presented as frequency

and percentage. Admissions with unmeasured physiology were assumed not to have met the sepsis case definition. Data completeness exceeded 98% in all fields used for case selection, thus complete case analyses were used. All analyses were performed using Stata/SE Version 13.0 (StataCorp LP, College Station, TX).

RESULTS

Over the study period, 248,864 of the 967,532 admissions to adult general ICUs in England met the sepsis case definition. The proportion and numbers of sepsis admissions increased from 23.5% in 2000 to 25.2% in 2012 (**Table 1**; **S-Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B941). Age and sex of sepsis admissions remained relatively stable. The proportion of sepsis admissions with severe comorbidities increased from 16.1% to 19.2% and nonsurgical admissions formed the majority (from 68.2% in 2000 to 72.9% in 2012). There was a decrease in APACHE II and ICNARC Physiology Scores (**S-Table-2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B941). The unadjusted hospital mortality for sepsis admissions decreased from 45.5% in 2000 to 32.1% in 2012 (Table 1).

Source of Infection and Unadjusted Mortality

For sepsis admissions, the source of infection changed significantly over time (test for homogeneity; $p < 0.001$). Respiratory tract was the most common source of infection, increasing from 40.1% in 2000 to 45.1% in 2012. Relative to admissions with respiratory infections, there was a significant increase in the proportions of admissions with genitourinary and musculoskeletal/dermatologic infections and a significant reduction in the proportions with gastrointestinal, neurologic, and unknown source infections (all $p < 0.001$ for change over time; **Fig. 1*A***; **S-Table-3**, Supplemental Digital Content 1, http://links.lww.com/CCM/B941). Unadjusted hospital mortality varied by source of infection from 19.1% (95% CI, 18.2–20.0%) for genitourinary to 43.0% (95% CI, 42.7–43.4%) for respiratory (**Fig. 1*B***).

SIRS Criteria and Unadjusted Mortality

The number of SIRS criteria met among sepsis admissions changed significantly over time (test for homogeneity; $p < 0.001$). The proportion meeting all four SIRS criteria decreased from 45.4% in 2000 to 38.4% in 2012. Relative to admissions meeting all four SIRS criteria, there was a significant increase in the proportions of admissions with 0, 1, 2, or 3 SIRS criteria (all $p < 0.001$ for change over time; **Fig. 1*C***; S-Table-3, Supplemental Digital Content 1, http://links.lww.com/CCM/B941). Unadjusted hospital mortality varied by number of SIRS criteria, from 24.7% (95% CI, 21.7–28.1%) for 0 SIRS to 41.2% (95% CI, 40.9–41.6%) for 4 SIRS (**Fig. 1*D***).

Number of Organ Dysfunctions and Unadjusted Mortality

The number of organ dysfunctions among sepsis admissions changed significantly over time (test for homogeneity, $p < 0.0001$). Sepsis admissions with two organ dysfunctions increased from 28.2% in 2000 to 31.0% in 2012. Relative to admissions with two organ dysfunctions, there was a significant increase in the proportions of admissions with one organ dysfunction and a decrease in admissions with three, four, or five dysfunctions (all $p < 0.001$ for change over time; **Fig. 1*E***;

TABLE 1. Numbers of Participating Adult General ICUs in England, Admissions (Total and Sepsis), and Unadjusted Mortality

Parameters	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Adult general ICUs contributing data (*n*)	101	116	132	143	141	141	141	149	158	162	174	179	181
Total ICU admissions (*n*)	35,548	42,261	53,434	62,123	66,294	67,316	67,281	72,820	80,507	85,389	99,688	113,519	121,352
ICU admissions meeting sepsis case definition, *n* (%)	8,366 (23.5)	9,938 (23.5)	12,557 (23.5)	15,108 (24.3)	16,642 (25.1)	17,761 (26.4)	18,086 (26.9)	19,587 (26.9)	21,625 (26.9)	23,066 (27.0)	26,799 (26.9)	28,703 (25.3)	30,626 (25.2)
Extrapolated ICU admissions with sepsis	18,400	20,100	21,100	23,100	25,000	26,900	27,700	29,700	30,700	31,700	33,400	34,100	36,100
ICU mortality for severe sepsis admissions, *n* (%)	2,876 (34.4)	3,337 (33.6)	4,154 (33.1)	5,005 (33.1)	5,374 (32.3)	5,445 (30.7)	5,478 (30.3)	5,601 (28.6)	5,968 (27.6)	6,254 (27.1)	7,031 (26.2)	7,093 (24.7)	7,316 (23.9)
Hospital mortality for sepsis admissions, *n* (%)	3,469 (45.5)	3,968 (44.6)	5,053 (44.1)	6,019 (44.0)	6,527 (43.2)	6,780 (41.6)	6,750 (40.9)	7,020 (39.1)	7,446 (37.3)	7,807 (36.7)	8,772 (35.3)	8,797 (33.2)	9,115 (32.1)

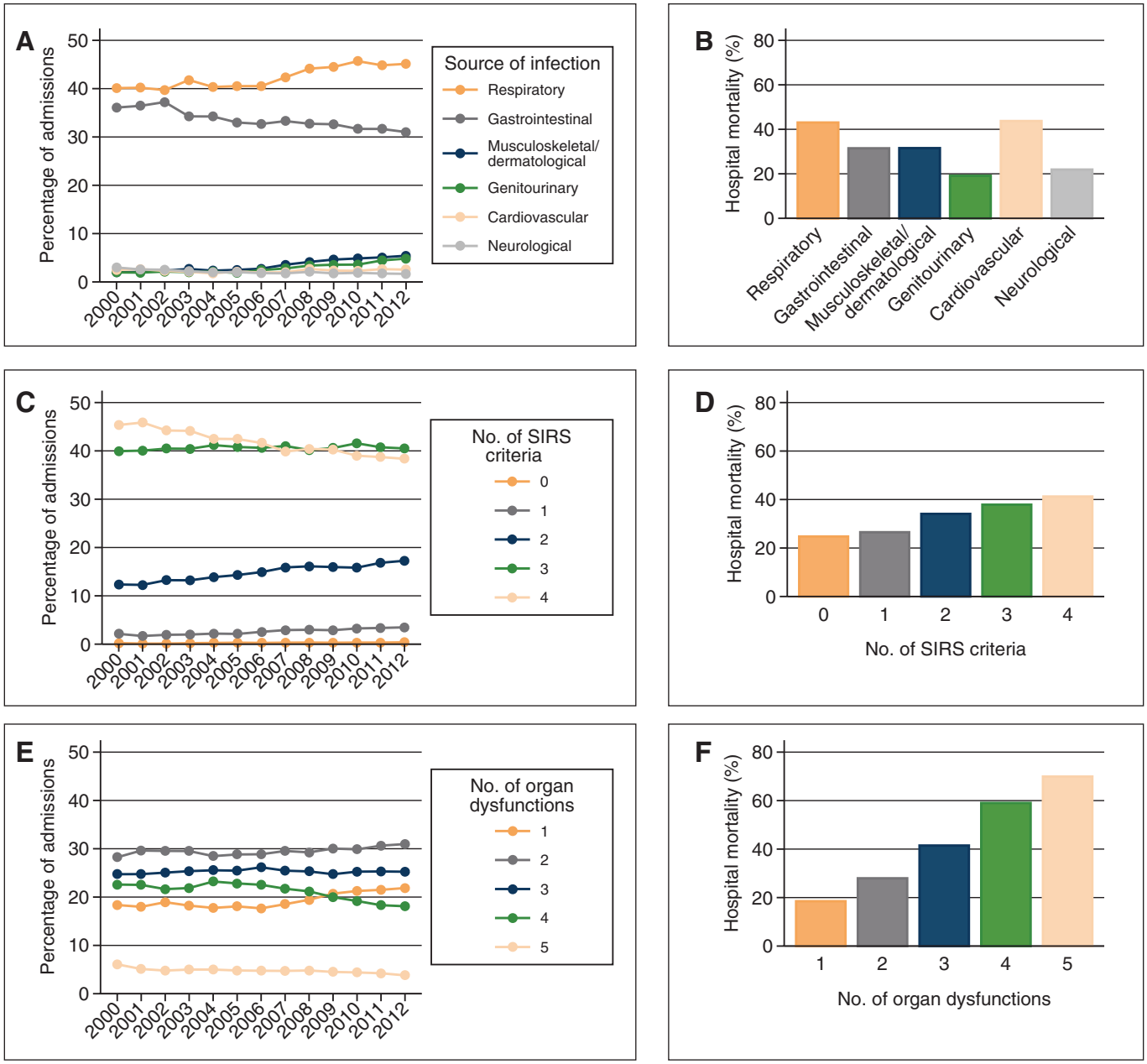

Figure 1. Sepsis specific case-mix. Trends in sepsis admissions to adult general ICUs in England by source of infection (**A**) and hospital mortality by source of infection (**B**), by number (No.) of systemic inflammatory response syndrome (SIRS) criteria (**C**) and hospital mortality by number of SIRS criteria (**D**), number of organ dysfunctions (**E**) and hospital mortality by number of organ dysfunctions (**F**). **A**, **C**, and **E**, show the changes over the study period. **B**, **D**, and **F**, show the overall hospital mortality over study period by each sepsis definitional element.

S-Table-3, Supplemental Digital Content 1, http://links.lww.com/CCM/B941). Unadjusted hospital mortality varied by number of organ dysfunctions from 18.5% (95% CI, 18.1–18.9%) for one organ dysfunction to 69.9% (95% CI, 69.1–70.8%) for five organ dysfunctions (**Fig. 1*F***).

Illustration of Organ Dysfunction Number and Combinations Trends Using Risk Category and Relationship to Unadjusted Mortality

Overall hospital mortality by different combinations of number(s) and type(s) of SIRS criteria and of organ dysfunctions was variable (**Fig. 2**, ***A*** and ***B***).

The risk category distribution among sepsis admissions changed significantly over time ($p < 0.0001$). Risk categories 2 and 3 each constituted one quarter of the cohort, every year over the study period and were stable. Between 2000 and 2012, the proportion of sepsis admissions categorized as risk category 1 increased from 18.4% to 21.9% while those categorized as risk category 4 decreased from 31.0% to 27.3%. Relative to admissions in risk category 2, the changes in risk categories 1 and 4 were statistically significant (both $p < 0.001$ for change over time), whilst for risk category 3 it was not ($p = 0.47$). As anticipated, unadjusted hospital mortality increased across risk categories from 18.5% (95% CI, 18.1–18.9%) to 58.0% (95% CI,

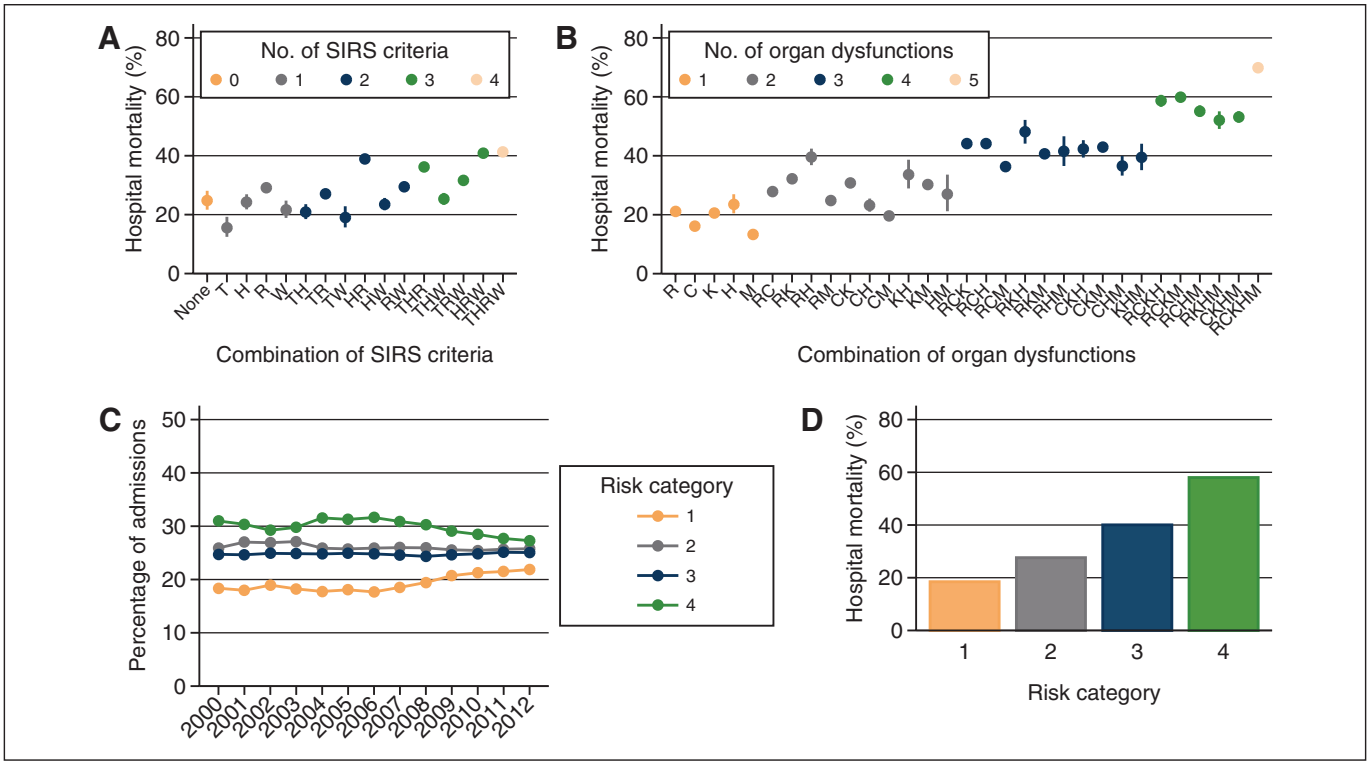

Figure 2. Simple illustration of heterogeneity using number and combinations of organ dysfunction (risk categories) and systemic inflammatory response syndrome (SIRS) combinations. Trends in sepsis admissions to adult general ICUs in England by SIRS combinations (**A**); heterogeneity within number and combinations of organ dysfunctions (**B**); risk category (**C**) and hospital mortality by risk category (**D**). For description of risk-categories please refer to methods and S-Table-1 (Supplemental Digital Content 1, http://links.lww.com/CCM/B941) for further details. **A**: H = heart rate, R = respiratory rate, T = temperature, W = white cell count. **B**: C = cardiovascular; H = hematologic; K = renal; M = metabolic, R = respiratory.

57.7–58.4%) (**Fig. 2**, ***C*** and ***D***; S-Table-3, Supplemental Digital Content 1, http://links.lww.com/CCM/B941).

Adjusted Trends in Hospital Mortality by Infection and Organ Dysfunction

The adjusted trend for improvement in hospital mortality for sepsis admissions was significant (OR, 0.939; 95% CI, 0.934–0.945 per year; $p < 0.001$). Adjusted hospital mortality decreased significantly within each category of infection source and the rate of change over time varied significantly by infection source (respiratory, OR for risk category, 1, 0.947 [95% CI, 0.938–0.956] per year; cardiovascular, 0.937 [0.918–0.957] per year; gastrointestinal, 0.941 [0.933–0.950] per year; genitourinary, 0.938 [0.918–0.959] per year; musculoskeletal/dermatologic, 0.943 [0.925–0.962] per year; neurologic, 0.939 [0.919–0.960] per year; unknown, 0.919 [0.907–0.932]; all individual trends and test of homogeneity $p < 0.001$).

Adjusted hospital mortality also decreased significantly within each risk category but the rate of change was consistent across the risk categories (risk category 1, OR for respiratory source, 0.947 [95% CI, 0.938–0.956] per year; risk category 2, 0.947 [95% CI, 0.939–0.955] per year; risk category 3, 0.943 [95% CI, 0.935–0.950] per year; risk category 4, 0.947 [95% CI, 0.940–0.955] per year; all individual trends $p < 0.001$; test of homogeneity $p = 0.48$).

Finally, the improving trends in hospital mortality appeared truly representative of sepsis mortality improvements when the case mix (in terms of all other variables in the model) was held constant at the values observed in 2000 (**Fig. 3**; and **S-Table-4**, Supplemental Digital Content 1, http://links.lww.com/CCM/B941).

Sensitivity Analyses

Results from the sensitivity analyses (by restricting analyses to the same 62 ICUs contributing data over the complete study period) were consistent with the primary analyses (**S-Table-5**, Supplemental Digital Content 1, http://links.lww.com/CCM/B941; and **S-Fig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B941).

DISCUSSION

Main Findings

We report an increase in incidence and significant improvements in adjusted hospital mortality among adult critical care admissions with sepsis in England between 2000 and 2012. Sepsis admissions represented a heterogeneous population, and a population that was changing over time as highlighted by differential trends in definitional elements (infection source, SIRS, number and type of organ dysfunctions). The independent impact of these definitional elements on mortality was also different. Postestimation predictive margins used to estimate the marginal predicted mortality show clinically relevant improvement in sepsis outcomes between risk categories (such

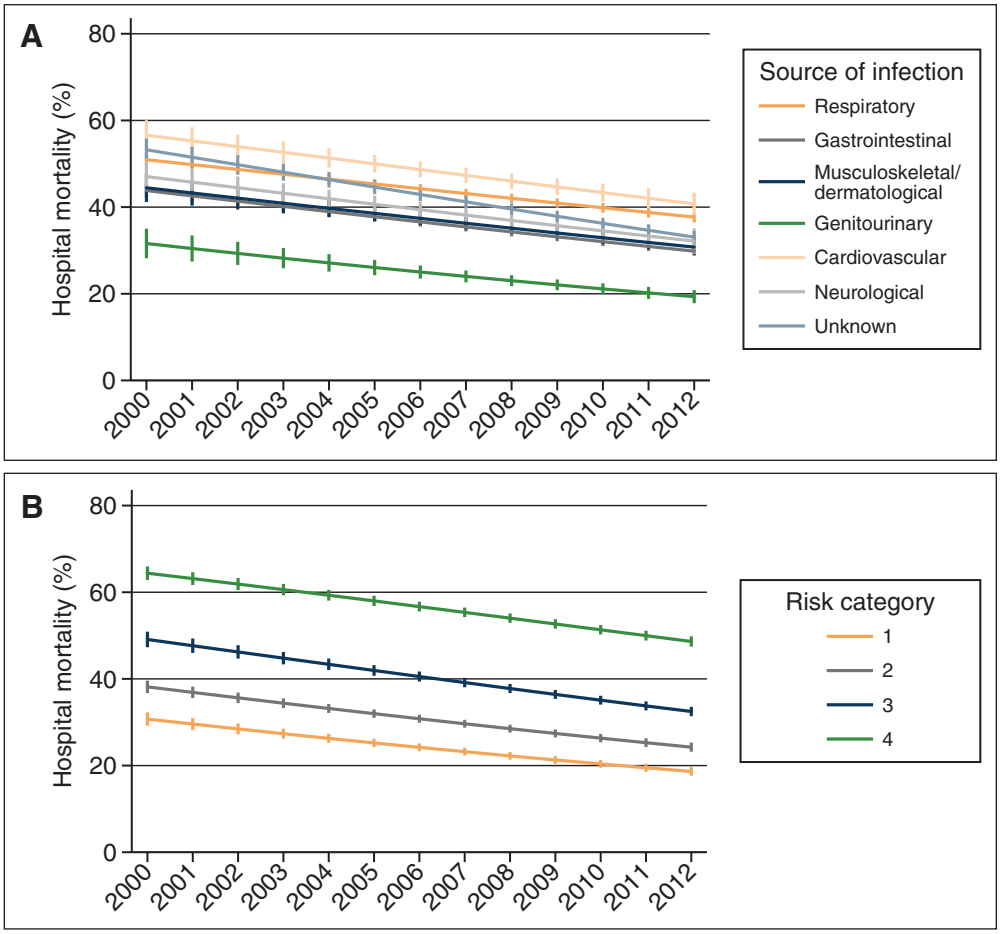

Figure 3. Postestimation predictive margins to estimate the marginal predicted mortality. Yearly trends in mortality by infection source (**A**) and by risk category (**B**) among the sepsis admissions with year 2000 as the referent year are shown. Year 2000 and 2012 characteristics are shown in S-Table-4 (Supplemental Digital Content 1, http://links.lww.com/CCM/B941).

as 12.1% for risk category 1; 15.8% for risk category 4) and between infection sources (such as 13.2% for respiratory infection; 12.3% for urinary infections), despite differences in baseline mortality (year 2000) in these sepsis definitional elements.

Relevance

Our study introduces the concept that differences in the contribution of each sepsis definitional element such as source of infection and type and number of organ dysfunctions potentially contributes to the international variation observed across ICU cohorts. This concept was implicitly seen when different administrative database algorithms were applied (7, 9) but has not been formally tested before. Consistent with the published literature, we report an association between sepsis mortality with source of infection (21) and with type and number of organ dysfunctions (22). We also show that, within a number of organ dysfunction group, mortality varies by organ dysfunction combinations (Fig. 2*B*).

Illustrative Direct Comparison

To further illustrate this issue, we compared the sepsis mortality over from 2000 to 2012 and the 2012 case-mix characteristics reported by Kaukonen et al (8) for sepsis and septic shock admissions from Australia/New Zealand (ANZ). The rationale for this comparison includes use of a national ICU database similar to ours over the same time period (between 2000 and 2012), the similarities in per capita healthcare spending (~ US$3,000) and life expectancy at birth (~ 80 yr), albeit there are uncertainties around critical care bed provision per 100,000 population (3.5–7.4 in United Kingdom vs 8.0–8.9 in ANZ) (23). Both studies also show similar improvements in adjusted hospital mortality for sepsis admissions over time (OR, 0.94 per year).

However, sepsis mortality in our study was 1.5 times higher and mortality curves of the two studies are parallel over the entire study period. The mortality comparisons when done using the simple risk categories, the ANZ study mortality is similar to group two unadjusted mortality. With case-mix comparisons, as shown by our study, the mortality in the ANZ study varies by infection source and other case-mix characteristics, which also change with time. In all the case-mix comparisons using 2012 data, the hospital mortality in our study was higher than the ANZ study (**Fig. 4**, ***A*** and ***B***; and **S-Table-6**, Supplemental Digital Content 1, http://links.lww.com/CCM/B941). The SIRS negative population was much lower in our dataset (3.0% compared with 12.1% reported by the ANZ study [24]) (**Fig. 4*C***). These simple illustrative comparisons neither explain the reasons for the observed differences in outcomes nor imply that the sepsis outcomes are worse in England, but support our study hypothesis of heterogeneity in sepsis case mix and the need for standardization of reporting elements to aid direct international comparisons. However, this needs to be confirmed using simultaneous direct comparison of similar databases using the same criteria to identify sepsis cases.

Strengths

The strengths of our study are in the use of a high quality clinical database to identify sepsis admissions using accurate, raw physiologic data (for SIRS criteria and for organ dysfunction variables) and synchronous, clinically coded diagnostic data to identify infection for consecutive ICU admissions. Our approach addresses many of the key limitations often

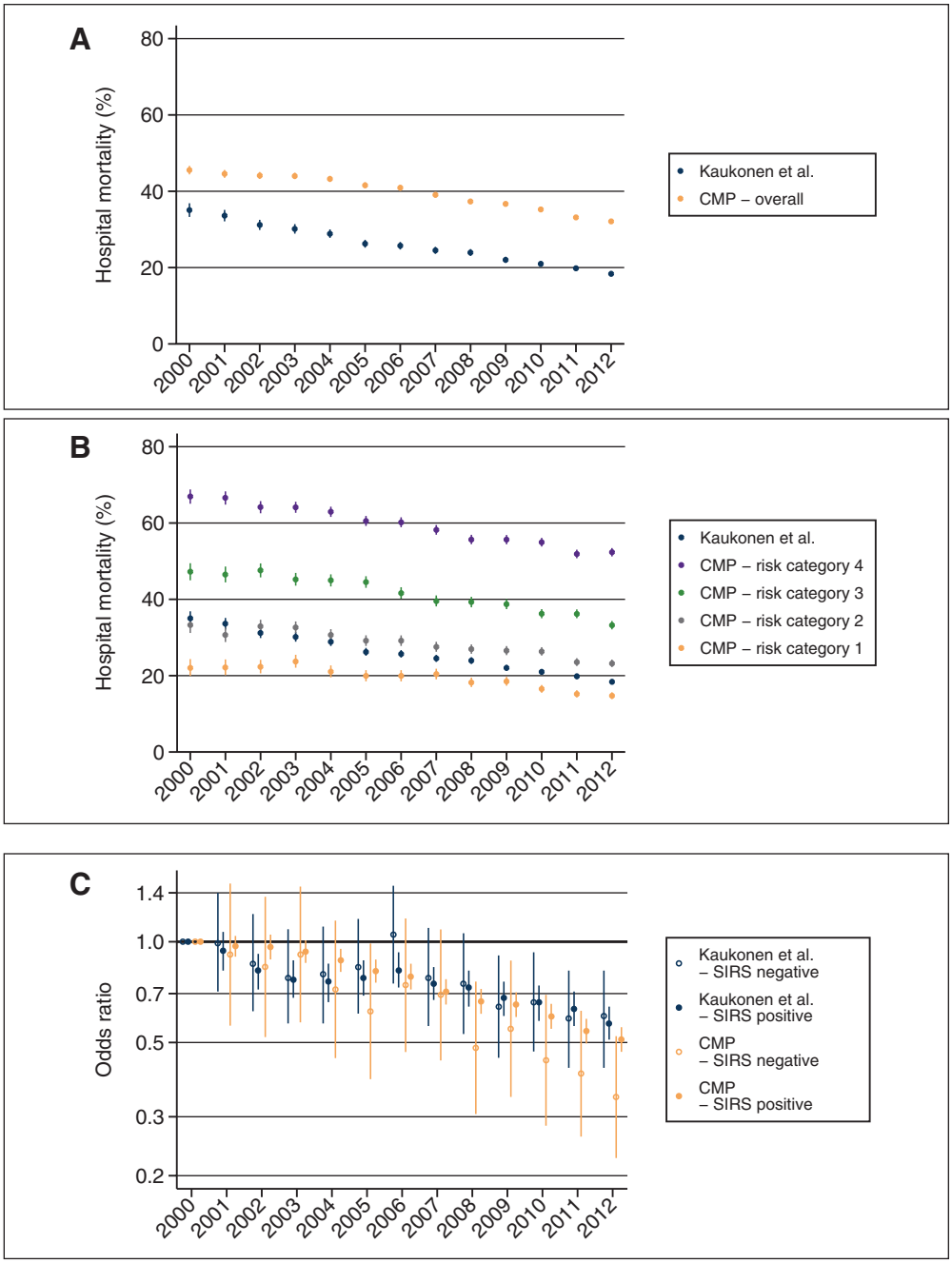

Figure 4. Comparisons of current study with Kaukonen et al (8). Unadjusted sepsis outcomes to adult general ICUs in England and in Australia and New Zealand (**A**); by number and type of organ dysfunction (risk category) (**B**) and adjusted sepsis mortality by systemic inflammatory response syndrome (SIRS) positive and negative status (**C**). CMP = case mix programme.

highlighted in studies of sepsis epidemiology (7, 9, 25–30) namely, reliance on administrative/insurance claims data and use of either subjective sepsis codes (highly likely influenced by awareness campaigns, influential studies, and reimbursement formulae) or separate but asynchronous codes for infection and organ dysfunction, often coded at discharge.

Limitations

There are limitations to our study. First, our database was not primarily designed for ICU sepsis epidemiology, and therefore, the overall incidence of sepsis may be underestimated (i.e., some admissions may develop sepsis after the first 24 hours in ICU). However, given the relatively low provision of ICU beds in England (higher threshold for admission) (23, 31) and with 80% of the study cohort having two or more organ dysfunctions in the first 24 hours, the impact would likely be minimal. Second, the ICUs contributing to the dataset varied over time, which we addressed in our sensitivity analyses. Third, the organ dysfunction assessment was cross sectional. Fourth, the dataset contains planned and unplanned ICU admissions, where the physiology-modified secondary to interventions such as fluid management that would not be similarly captured by the organ dysfunction assessment (32) that is a common limitation of large database based epidemiology reports (33). Finally, changes to the health care system and increasing awareness of sepsis could have influenced some of the observed improvements in outcome (34); however, assessment of effects of these changes was not the research question addressed by this study.

Future Research

Definitions are descriptions of illness and criteria provide the variables to identify a case (6). To-date, there are neither universally agreed standardized criteria nor reporting elements for sepsis epidemiology, which when interpreted with lack of gold-standard diagnostic tests for sepsis potentially introduces heterogeneity in epidemiology (6, 35). By contrasting our results to similar national database publications (8, 24) over the same study period and in the context of a global need for more accurate measurement of sepsis (4), our study makes a case for research into directed international sepsis epidemiology comparisons using national databases. Global ecologic studies will help provide incidence density and identify higher risk areas, which would help design regional health policies to tackle sepsis.

CONCLUSIONS

The characteristics of our sepsis ICU population changed over time and so did the impact of definitional elements on hospital mortality, which we propose preclude direct international comparisons of incidence and mortality. We illustrate a case for developing an international consensus on standardized reporting of sepsis epidemiology. This has important implications, both for health policy and benchmarking.

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