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EDITORIALS

Severe sepsis in the UK and the case volume-outcome association

High standards of care in low volume critical care units may have reduced differences between centres

David J Wallace *research fellow, critical care medicine*, Jeremy M Kahn *associate professor of critical care medicine, medicine, and health policy and management*

University of Pittsburgh School of Medicine, Pittsburgh, PA 15261, USA

The association between case volume and outcome in healthcare was first described more than 30 years ago.[1] Since then, multiple studies have confirmed that for many high risk surgical conditions, larger hospital case loads are associated with better patient outcomes.[2] More recently, researchers have shown volume-outcome associations for high risk medical conditions as well, including mechanical ventilation for acute respiratory failure[3] and severe sepsis,[4-6] the critical illness syndrome characterised by infection, inflammation, and systemic organ failure.

However, new data suggest that volume-outcome relations in intensive care are not universal. In a linked study (doi:10.1136/bmj.e3394), Shahin and colleagues report equivalent outcomes for patients with severe sepsis who were treated in low volume and high volume critical care units in the United Kingdom.[7] Similar outcomes were found among patients who needed mechanical ventilation and patients with the highest severity of illness, subgroups of patients for whom a volume-outcome association is most likely to exist. The data came from the case mix programme of the Intensive Care National Audit and Research Centre (ICNARC), a rich clinical data source that allows for detailed risk adjustment between high volume and low volume centres. The findings of this study challenge the notion that higher volume hospitals always provide better care for critically ill patients.

Two limitations of the study make it possible that the absence of a volume-outcome association in patients with severe sepsis in the UK is spurious. Firstly, despite its large sample size, the study may be underpowered to detect important differences between high volume and low volume hospitals. Indeed, the confidence intervals for the subgroup analyses do not exclude clinically meaningful effects and contain the point estimates of other volume-outcome studies that demonstrated significant association. Secondly, the study might be affected by exposure misclassification, because even low volume hospitals had relatively high annual case loads. For example, in recent studies of patients with septic shock and severe sepsis, high volume units cared for medians of 77 and 96 cases a year,[4 6] compared with 70 for the lowest volume group in the current study. This suggests that most NHS hospitals have annual volumes that may exceed the volume-outcome inflection point for severe sepsis.

Despite these limitations, a more compelling interpretation of this study is that the findings are real and indicative of consistent high quality care within NHS critical care units for patients with sepsis. In an ideal healthcare system, sick patients at low volume and high volume hospitals would fare equally well, either through the systematic transfer of the sickest patients to regional referral centres or through targeted quality improvement efforts that overcome the lack of clinical experience at low volume hospitals. In the UK, audit and feedback of hospital quality via ICNARC may stimulate quality improvement at low volume providers, especially when coupled with active dissemination of evidence based practice guidelines to give hospitals the tools needed to improve sepsis care.[8] Low volume hospitals that participate in ICNARC might be adept at providing early adequate resuscitation or preventive care to avert complications, which can reduce mortality in patients with sepsis. In short, critical care units in the UK may be figuring out how to narrow an important quality gap, with the lack of a volume-outcome association testifying to their success.

In addition to providing a roadmap for quality improvement, this study has important policy implications. The existence of volume-outcome relations in critical care has prompted calls to regionalise care for critically ill patients. If regionalisation efforts proceed, hospital volume should not be the sole criterion for designating hospitals as regional referral centres, because high quality care can clearly be achieved at lower volume centres.[9] Instead, designation as a referral centre should be based on demonstrated outcomes, or on the presence or absence of care processes and structures that may not be implemented at all hospitals, such as extracorporeal membrane oxygenation or comprehensive trauma care.[10 11]

kahnjm@upmc.edu

Most importantly, this study should prompt researchers to investigate ways to move beyond volume-outcome relations in critical care. Although it is important to consider volume-outcome relations, Shahin and colleagues' findings remind us that they can and should be reduced. Taking a cue from this study, health services researchers need to go beyond volume-outcome reporting and focus on how both large and small centres provide high quality care. What practices that are common to large volume hospitals can be exported to small volume hospitals? Or, as in the case of severe sepsis in the UK, what are small volume hospitals doing to provide high quality care? Finding out what drives the volume-outcome mechanism is the only way we can leave it behind us.

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1 Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. *N Engl J Med* 1979;301:1364-9.
2 Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med* 2002;137:511-20.
3 Kahn JM, Goss CH, Heagerty PJ, Kramer AA, Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. *N Engl J Med* 2006;355:41-50.
4 Peelen L, de Keizer NF, Peek N, Scheffer GJ, van der Voort PHJ, de Jonge E. The influence of volume and intensive care unit organization on hospital mortality in patients admitted with severe sepsis: a retrospective multicentre cohort study. *Crit Care* 2007;11:R40.
5 Powell ES, Khare RK, Courtney DM, Feinglass J. Volume of emergency department admissions for sepsis is related to inpatient mortality: results of a nationwide cross-sectional analysis. *Crit Care Med* 2010;38:2161-8.
6 Zuber B, Tran T-C, Aegerter P, et al. Impact of case volume on survival of septic shock in patients with malignancies. *Crit Care Med* 2012;40:55-62.
7 Shahin J, Harrison DA, Rowan KM. Relation between volume and outcome for patients with severe sepsis in United Kingdom: retrospective cohort study. *BMJ* 2012;344:e3394.
8 Ferrer R, Artigas A, Levy MM, González-Díaz G, Garnacho-Montero J, et al. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *JAMA* 2008;299:2294-303.
9 Glance LG, Osler TM, Mukamel DB, Dick AW. Estimating the potential impact of regionalizing health care delivery based on volume standards versus risk-adjusted mortality rate. *Int J Qual Health Care* 2007;19:195-202.
10 Noah M, Peek G, Finney S, Griffiths MJ, Harrison DA, Grieve R, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A (H1N1). JAMA 2011;306:1659-68.
11 MacKenzie EJ, Rivara FP, Jurkovich GJ, Nathens AB, Frey KP, Egleston BL, et al. A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med* 2006;354:366-78.

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RESEARCH

Relation between volume and outcome for patients with severe sepsis in United Kingdom: retrospective cohort study

Jason Shahin *assistant professor*[1] *clinical research associate*[2], David A Harrison *senior statistician*[2], Kathryn M Rowan *director*[2]

[1]McGill University, Department of Critical Care, Department of Medicine, Respiratory Division, 1650 Cedar Avenue, Montreal, Quebec, Canada H3G 1A4; [2]Intensive Care National Audit & Research Centre (ICNARC), London WC1H 9HR, UK

Abstract

Objective To evaluate whether a relation exists between volume and outcome for admissions with severe sepsis to adult general critical care units in the United Kingdom.

Design Retrospective cohort study using data from a pooled case mix and outcome database.

Setting Adult general critical care units participating in the case mix programme.

Participants Consecutive admissions to participating units for the years 2008-09 meeting objective, standardised criteria for severe sepsis.

Main outcome measures Mortality at ultimate discharge from acute hospital.

Results The primary exposure was volume of admissions with severe sepsis per unit per year. A multivariable logistic regression analysis, using generalised estimating equations, was used to assess the association between volume, modelled using fractional polynomials, and ultimate acute hospital mortality while adjusting for potential confounders. No relation was seen between volume and outcome for admissions with severe sepsis to adult, general critical care units in the UK. Subgroup analyses tested for interactions between the effect of volume and acute severity of illness or receipt of mechanical ventilation. No significant interactions were found.

Conclusions This study showed no relation between volume and outcome in admissions with severe sepsis treated in adult general critical care units in the UK.

Introduction

Over the past three decades, studies have evaluated the relation between the volume of cases treated and patients' outcomes for a variety of surgical and medical conditions.[1] A strong association was found for complex surgical procedures, such as repair of abdominal aortic aneurysms and surgery for specific cancers and paediatric cardiac conditions. For medical conditions such as AIDS and myocardial infarction, treatment in high volume centres has also been associated with improved outcome.[1] Several studies have evaluated the volume-outcome relation for critically ill patients.[2] These studies have included all critically ill patients, as well as selected groups of patients, such as those who were mechanically ventilated and those with severe sepsis. Two alternative hypotheses have been put forward to explain the underlying mechanism for volume-outcome relations: "practice makes perfect" and "selective referral."[3] In the case of acutely ill patients in critical care units, the most likely mechanism would be "practice makes perfect," as little scope exists for critically ill patients to choose where they are treated.

Admissions with severe sepsis make up roughly one quarter of all admissions to adult general critical care units in the United Kingdom. Over the past decade, the incidence of severe sepsis in the UK increased from 46 per 100 000 to 60 per 100 000 in 2009 (personal correspondence from the Intensive Care National Audit & Research Centre).[4] As the incidence of admissions with severe sepsis increases, the costs of caring for these critically ill patients, in terms of infrastructure, personnel, and therapeutics, will put an enormous strain on the healthcare system. With this and other increased demand for critical care beds, alternative models for organising critical care services are being considered. One such model calls for centralisation of care, whereby critically ill patients at higher risk are routinely transferred from smaller to larger designated centres for more specialised care.[2] Centralisation has been successfully carried out in the UK for paediatric critical care and, more recently, for trauma,[5-9] but it does not exist for adult general critical care. The rationale behind centralisation is twofold. Firstly, by focusing

Correspondence to: J Shahin Jason.shahin@mcgill.ca

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allocated healthcare funds on only a smaller number of specialised centres, the financial burden can be contained; secondly, health outcomes are potentially improved by treating patients in high volume facilities.[6 10]

Two previous studies have assessed the volume-outcome relation for admissions with severe sepsis to adult general critical care and showed a lower hospital mortality for admissions treated in units with higher annual volume.[11 12] These studies, however, were done outside the UK and included relatively few critical care units and admissions. Therefore, the existence of a relation between volume and outcome for admissions with severe sepsis to adult general critical care units in the UK remains unclear. In view of the need for the NHS to understand volume-outcome relations to inform service delivery and organisation of care,[13] this study evaluated whether a volume-outcome relation exists for admissions with severe sepsis in adult general critical care units in the UK.

Methods

Study design

We did a secondary analysis of the case mix programme database.[13] This database contains pooled case mix and outcome data on consecutive admissions to adult general (mixed medical/surgical) critical care units (that is, stand alone intensive care units and combined intensive care/high dependency units) in England, Wales, and Northern Ireland that are collected as part of the national clinical audit coordinated by the Intensive Care National Audit & Research Centre (ICNARC). The database contains raw physiological and diagnostic data needed for the acute physiological and chronic health evaluation (APACHE) II and ICNARC risk prediction models,[14 15] together with demographic, outcome, and activity data. Trained data collectors collect case mix programme data prospectively and abstract them retrospectively. Data undergo extensive validation, both locally and centrally, before being pooled in the central database. Details of data collection and validation have been reported previously,[16] and the case mix programme database has been independently assessed to be of high quality.[17]

Patient selection

We extracted data for 2008-09, selecting patients aged 16 years or older who met the criteria for severe sepsis in the first 24 hours after admission to a critical care unit. Using raw physiological and diagnostic data, we considered severe sepsis to be present if the admission had data indicating evidence of three or more systemic inflammatory response syndrome criteria, infection, and evidence of at least one organ dysfunction (see supplementary table A for precise definitions).

We excluded critical care units with less than six months of data in 2008-09 and admissions transferred either directly into a unit from another critical care unit or transferred out of a unit directly to another critical care unit within 24 hours. In addition, we excluded subsequent readmissions to the same critical care unit during the same acute hospital stay.

Exposure, outcome, and confounding variables

The primary exposure of interest was volume of admissions with severe sepsis per unit per year. We included all admissions with severe sepsis (that is, before above exclusions) in the calculation of volume. For critical care units contributing less than one year of data (but more than six months) in 2008-09, we extrapolated the number of admissions with severe sepsis per year from available data. For the primary analysis, we used fractional polynomials (degree 2) to model volume. For reporting descriptive statistics and for secondary analyses, we grouped volume both by quarters of critical care units and by quarters of admissions. The primary outcome was ultimate acute hospital mortality, defined as death before final discharge from the acute hospital, and included deaths after direct transfer to another acute hospital from the acute hospital housing the critical care unit.

For critical care admissions, data were available on age, sex, ethnicity, acute severity of illness, severe medical history, location before admission, mechanical ventilation, length of stay, and hospital discharge location. We categorised ethnicity as white or non-white. We used the ICNARC physiology score from the ICNARC model to measure acute severity of illness.[14 15] We defined medical history by severe comorbidities, using the APACHE II method (severe cardiovascular disease, severe respiratory disease, renal disease, chronic liver disease, haematological malignancy, metastatic disease, immunological dysfunction), in the six months before admission[14]; by activities of daily living in the six months before admission; and by cardiac arrest in the 24 hours before admission. We categorised location before admission as operating theatre, hospital ward, high dependency unit, or emergency department. We further categorised admissions from the operating theatre as following emergent/urgent or elective/scheduled surgery. We defined mechanical ventilation by receipt of mechanical ventilation either at admission to or in the first 24 hours after admission to the critical care unit. We divided length of stay into critical care unit and hospital stay, where hospital stay included continuous stay in acute hospital, even if transferred. We defined hospital discharge location as discharge to home, residential place of work/education, or non-health related institution; nursing home/nursing home equivalent; short term rehabilitation; long term rehabilitation; other health related institution; or hospice/hospice equivalent. Finally, hospital type was available, defined by the hospital's reported university affiliation. We used age, sex, acute severity of illness, severe medical history, location before admission, and hospital type to adjust for confounding.

Sample size

After adjustment for the cluster effect, at least 26 500 admissions and 42 critical care units per group would be needed to detect a difference in mortality of 5% from a baseline mortality of 40% with an α level of 0.05 and 90% power. This sample size assumes an exposure variable with four groups and a design effect of 3.3 (intra-cluster correlation coefficient 0.014), which was calculated from case mix programme data from 2007.

Statistical analysis

We analysed baseline characteristics by quarters of volume. We explored all variables with frequency distributions and cross tabulation of exposure with outcome.

We used Stata version 10.1 for statistical analyses. We did a multivariable analysis to assess the effect of volume (admissions with severe sepsis per unit per year) on outcome (ultimate acute hospital mortality) while adjusting for a priori selected confounders. All of the variables were entered into the model simultaneously with no statistical selection process applied. A logistic regression model was fitted with generalised estimating equations and robust standard errors to adjust for clustering of outcome at the critical care unit level. We did hypothesis tests using Wald tests. We used multivariable fractional polynomial

modelling (degree 2) to select the best functional form for continuous factors (volume, ICNARC physiology score, and age).[18]

We used interaction tests to explore two subgroup analyses, selected a priori. The first, between volume and acute severity of illness, tested the hypothesis that sicker admissions may have derived greater benefit from being treated in higher volume units. The second, between volume and mechanical ventilation, tested the hypothesis that mechanically ventilated admissions may have derived greater benefit from being treated in higher volume units. We used the "MPFIgen" procedure to explore interactions with continuous variables.[18] Briefly, we constructed multiplicative interaction terms between the fractional polynomial transformations selected in the main model without interactions. The model was then refitted with the interaction terms added and all interaction terms jointly tested using a Wald test.

As secondary analyses, and in the absence of a gold standard for defining volume,[3] we repeated the above analyses with volume groups divided into quarters both by number of critical care units and by number of admissions and with ICNARC physiology score and age also fitted as categorical variables. The secondary analyses used random effects logistic regression models.

Results

Between 1 January 2008 and 31 December 2009, the case mix programme database contained 162 648 admissions to 181 adult, general critical care units in 181 acute hospitals; raw data for 33 955 (20.9%) admissions met the standard objective definition used for determining severe sepsis (fig 1⇓). After exclusion of 11 units contributing less than six months' worth of data, 33 538 admissions from 170 units were available for calculating the volume of admissions with severe sepsis per unit per year. Following the calculation of volume, we excluded readmissions within the same hospital stay (n=995, 2.9%), direct transfers into a unit from another critical care unit (n=1692, 5.0%), and direct transfers out to another critical care unit within 24 hours (n=124, 0.4%). The final study sample available for analysis was 30 727 admissions with severe sepsis to 170 units, representing more than 80% of adult general critical care units in the UK.

The proportion of all admissions that met systemic inflammatory response syndrome, infection, and organ dysfunction criteria did not vary markedly across quarters of volume (table 1⇓). The main factor driving the variation in volume of severe sepsis admissions was the number of beds in the critical care unit (table 2⇓), and this was also associated with university status. Half of the admissions with severe sepsis met four systemic inflammatory response syndrome criteria, and most had more than one organ dysfunction (table 1⇓).

Depending on the volume grouping, the number of units, admissions, and median volume differed (table 2⇓). In grouping by quarters of units, the groups had roughly equal number of units and increasing number of admissions in the higher volume groups. In grouping by quarters of admission, the groups had roughly similar number of admissions with decreasing number of units. The median volume was consistently lower in the unit quarter groups than in the admission quarter groups.

Admissions with severe sepsis were slightly older and had a higher level of acute severity of illness compared with all admissions to units to critical care units in the case mix programme database (mean age 60 years, median ICNARC physiology score 16) (table 3⇓). Most admissions had no previous severe comorbidities and, before admission, were able to carry out activities of daily living without assistance. Admissions were predominantly from the hospital ward, and more than half were mechanically ventilated in the first 24 hours after admission to the unit. Admissions were resource intensive, with long lengths of unit and hospital stay and high unit and acute hospital mortality (table 3⇓).

Admissions in the highest volume quarter had the lowest ICNARC physiology score but were more likely to have had a previous illness (table 3⇓). Crude unit mortality and ultimate acute hospital mortality were lowest for admissions in the highest quarter. Grouping volume by quarters of admissions, instead of by quarters of critical care units, did not substantially change any of the baseline variables across the quarters.

The multivariable analysis showed that, after adjustment for confounders, although the volume-outcome relation was significantly non-linear (P<0.001 for fractional polynomial degree 2 compared with linear), no significant overall relation existed between volume and acute hospital mortality (P=0.65) (fig 2⇓). However, the 95% confidence intervals around the estimated odds ratios do not rule out a magnitude of effect that may be considered clinically important. We also found no significant interaction between volume and acute severity of illness (P=0.46) (fig 3⇓) or receipt of mechanical ventilation (P=0.42) (fig 4⇓).

Secondary analyses grouping volume by quarters of critical care units supported the finding of no association between volume and outcome after adjustment for confounders (supplementary table B). Grouping volume by quarters of admissions, instead of critical care units, did not change the association. We also found no significant interaction between volume and acute severity of illness, when both volume and ICNARC physiology score were grouped by quarters (supplementary table C). When we grouped volume by quarters of critical care units, we found a significant interaction between volume and receipt of mechanical ventilation, with higher adjusted odds of mortality in the lowest quarter of volume for the mechanically ventilated admissions (table 4⇓). However, this interaction did not remain when we grouped volume by quarters of admissions. We also saw a similar magnitude of odds ratios in the highest severity of illness quarter, although we had less power to detect an interaction with severity of illness owing the smaller sample sizes per group.

Discussion

This study found no relation between volume and outcome for all admissions with severe sepsis to adult general critical care units in the UK. Subgroup analyses found no significant interaction between volume and severity of illness or receipt of mechanical ventilation.

Strengths and weaknesses of study

The study has several strengths: the completeness, coverage, and representativeness of the data analysed; the application of an objective, standardised method to determine an admission as having severe sepsis; the ability to adjust extensively for case mix; and the adjustment for clustering of patients' outcomes. Failure to adjust for clustering of outcomes in volume-outcome studies has been previously shown to lead to bias through an overestimation of the effect estimates.[19]

Several limitations are also worth noting. Firstly, bias may have arisen from misclassification of cases of severe sepsis. We used physiological and diagnostic data from the first 24 hours of

admission to the critical care unit to identify admissions with severe sepsis. As a result, patients with severe sepsis whose primary or secondary reasons for admission were misclassified as non-infectious could have been missed. Additionally, admissions with diseases other than severe sepsis that fulfil the systemic inflammatory response syndrome criteria (such as acute pancreatitis) may have been misclassified. Despite the potential for bias, we based identification of severe sepsis on raw physiological and diagnostic data using objective, standardised criteria across units. Secondly, as for any observational study, the possibility of residual confounding exists. Given that the major confounder is units' case mix, and adjustment was carried out using the validated ICNARC physiology score from the ICNARC model plus other known confounders, residual confounding is unlikely to be a major source of bias. The final limitation is the use of hospital mortality instead of mortality at a specific time point as the main study outcome. Use of data on location after discharge from acute hospital, however, goes some way towards minimising the limitation associated with an event based, rather than a time based, measure (for example, 30 day mortality).

Strengths and weaknesses in relation to other studies

The results of this study are at odds with those of previous published studies. The two studies that looked at admissions with severe sepsis to critical care units both showed a reduction in hospital mortality in admissions treated in units with higher volumes. The study by Reinikainen et al was a retrospective analysis of 452 admissions with severe sepsis in 24 Finnish units.[12] After adjusting for severity of illness, they found an increased risk of death associated with treatment in smaller as compared with larger units. However, the study had two important limitations: the number of admissions and units enrolled was small, and the analysis did not take into account the clustering of patients' outcomes. The exposure variable for this study was a combination of size and teaching status of hospital/unit, rather than volume. Volume varied across the three exposure groups (median volumes from the four month study period were 10, 15, and 29); however, even allowing for the short study duration, these volumes are all towards the low end of the volume distribution in our study. The second study analysed 4605 admissions with severe sepsis treated in 28 Dutch units.[11] This study found a lower mortality for admissions treated in higher volume units. The authors accounted for clustering of outcomes by using generalised estimation equations. To overcome the potential bias of the small sample of units, they used a leverage analysis. Despite the leverage analysis showing that their results were not due to data from one specific unit, given the relatively small sample of units in the study, the possibility of a group of units biasing these results still exists. The volume of severe sepsis admissions in this study was lower on average than in our study but with similar variability across units (mean 73 (SD 44) *v* 119 (50)).

Our study confirms the results of two small volume-outcome studies done in the UK and based on all admissions to adult general critical care units.[20 21] After adjustment for case mix, no relation between volume and mortality was found. These studies were limited mainly by the lack of adjustment for clustering of data. Furthermore, the analysis was done on earlier, smaller samples of the same database as used for our study.

The possible finding of a threshold effect among mechanically ventilated patients admitted with severe sepsis would be in keeping with the literature on mechanically ventilated patients. Three studies, to date, have looked at the volume-outcome relation in all mechanically ventilated admissions admitted to a critical care unit.[22-24] Two of these studies showed a volume-outcome relation, but the third study failed to do so. The negative study did not adequately adjust for differences in case mix, which may explain the discrepant results.

Meaning of study

Several reasons might explain the lack of a volume-outcome relation in this study. Firstly, differences in outcomes between high and low volume units might become apparent only when the difference in volumes between groups is very large. Secondly, the units' patterns of practice may be altered by the information they receive from the case mix programme. The primary role of the case mix programme is to provide participating units with comparative data on their patients' outcomes. The units can then use the information to make changes to their services and programmes to improve their care. As the case mix programme has been in place for more than a decade, many units are likely to have made improvements, narrowing any existing gap in outcomes between high and low volume units. Thirdly, the wide dissemination of treatment guidelines (six hour resuscitation and 24 hour management bundles), through the surviving sepsis campaign, may have led to greater standardisation of practice across critical care units.[25]

The results of the subgroup analysis suggest a possibility that patients with greater severity of illness, receiving mechanical ventilation, or both may derive benefit from treatment in a higher volume unit. The discrepancy between the results from the two different volume groupings and from the fractional polynomial modelling may be explained by several mechanisms. The significant interaction result may be a false positive result that is an artefact of the arbitrary choice of thresholds for grouping units, supporting the use of continuous modelling over a categorical approach for the primary analysis. Alternatively, this may represent a genuine threshold effect—a functional form that fractional polynomials, and other continuous non-linear models, are not ideally placed to detect.[26] The analysis that grouped volume by quarters of units would have more power to detect such a threshold effect owing to the equal numbers of units in each group and the smaller median volumes in the lower quarters in the unit groupings. No gold standard exists for grouping volume, as shown by both the critical care literature and the general medical/surgical literature, which commonly use both methods.[3]

The results of this study have important implications for the organisation of critical care services. People have suggested that the treatment of critically ill patients should be centralised, with care carried out in specifically designated centres. The evidence supporting centralisation of critical care comes from successful analogous systems in trauma, paediatric, and neonatal care.[5 7 8] Despite the potential benefits of centralisation, many drawbacks exist. Potential harm to patients during transport, the loss of medical skills in the regional hospitals, and the separation of patients from family and familiar clinicians are some of the problems that have been raised.[6] These problems would be surmountable if a centralisation policy for critically ill patients saved lives. This study puts into question the risk:benefit ratio for centralisation, as we detected no benefit on mortality with treatment in high volume units for all admissions with severe sepsis.

Unanswered questions and future research

Given that variation in outcome is seen across units, future research should potentially focus on other elements of service

delivery and organisation, beyond volume, used by units with good outcomes. If these elements can be better understood, then other units may be able to implement similar models of care.

Conclusions

This study found no relation between volume and ultimate acute hospital mortality in admissions with severe sepsis treated in critical care units in the UK.

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Ethical approval: The study had approval by the Ethics Committee at the London School of Hygiene and Tropical Medicine, and ICNARC has approval for the case mix programme database under section 251 of the NHS Act 2006 (approval No PIAG 2-10(f)/2005).

Data sharing: A technical appendix and the statistical code are available from the corresponding author at Jason.shahin@mcgill.ca.

1 Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med* 2002;137:511-20.
2 Kahn JM. Volume, outcome, and the organization of intensive care. *Crit Care* 2007;11:129.
3 Christian CK, Gustafson ML, Betensky RA, Daley J, Zinner MJ. The volume-outcome relationship: don't believe everything you see. *World J Surg* 2005;29:1241-4.
4 Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC case mix programme database. *Crit Care* 2006;10:R42.
5 Nathens AB, Jurkovich GJ, Maier RV, Grossman DC, MacKenzie EJ, Moore M, et al. Relationship between trauma center volume and outcomes. *JAMA* 2001;285:1164-71.
6 Kahn JM, Branas CC, Schwab CW, Asch DA. Regionalization of medical critical care: what can we learn from the trauma experience? *Crit Care Med* 2008;36:3085-8.
7 Tilford JM, Simpson PM, Green JW, Lensing S, Fiser DH. Volume-outcome relationships in pediatric intensive care units. *Pediatrics* 2000;106:289-94.
8 Ramnarayan P, Thiru K, Parslow RC, Harrison DA, Draper ES, Rowan KM. Effect of specialist retrieval teams on outcomes in children admitted to paediatric intensive care units in England and Wales: a retrospective cohort study. *Lancet* 2010;376:698-704.
9 London Trauma Office. London's trauma system. 2010. www.londontraumaoffice.nhs.uk/londons-trauma-system/about-the-london-trauma-system/.
10 Angus DC, Black N. Improving care of the critically ill: institutional and health-care system approaches. *Lancet* 2004;363:1314-20.
11 Peelen L, de Keizer NF, Peek N, Scheffer GJ, van der Voort PH, de Jonge E. The influence of volume and intensive care unit organization on hospital mortality in patients admitted with severe sepsis: a retrospective multicentre cohort study. *Crit Care* 2007;11:R40.
12 Reinikainen M, Karlsson S, Varpula T, Parviainen I, Ruokonen E, Varpula M, et al. Are small hospitals with small intensive care units able to treat patients with severe sepsis? *Intensive Care Med* 2010;36:673-9.
13 Parry G, Tucker J, Tarnow-Mordi W. Volume of procedures and outcome of treatment: NHS needs to understand relation more effectively. *BMJ* 2003;326:280.
14 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-29.
15 Harrison DA, Parry GJ, Carpenter JR, Short A, Rowan K. A new risk prediction model for critical care: the Intensive Care National Audit & Research Centre (ICNARC) model. *Crit Care Med* 2007;35:1091-8.
16 Harrison DA, Brady AR, Rowan K. Case mix, outcome and length of stay for admissions to adult, general critical care units in England, Wales and Northern Ireland: the Intensive Care National Audit & Research Centre case mix programme database. *Crit Care* 2004;8:R99-111.
17 The Information Centre. List of databases. 2010. www.icapp.nhs.uk/docdat/DatabaseList.aspx.
18 Royston P, Sauerbrei W. Multivariable model-building: a pragmatic approach to regression analysis based on fractional polynomials for modelling continous variables. John Wiley & Sons, 2008.
19 Panageas KS, Schrag D, Riedel E, Bach PB, Begg CB. The effect of clustering of outcomes on the association of procedure volume and surgical outcomes. *Ann Intern Med* 2003;139:658-65.
20 Jones J, Rowan K. Is there a relationship between the volume of work carried out in intensive care and its outcome? *Int J Technol Assess Health Care* 1995;11:762-9.
21 Goldfrad CK, Rowan K. Does "practice make perfect"? Volume of work and outcome in intensive care [abstract]. *J Epidemiol Community Health* 2000;54:779
22 Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. *N Engl J Med* 2006;355:41-50.
23 Kahn JM, Ten Have TR, Iwashyna TJ. The relationship between hospital volume and mortality in mechanical ventilation: an instrumental variable analysis. *Health Serv Res* 2009;44:862-79.
24 Needham DM, Bronskill SE, Rothwell DM, Sibbald WJ, Pronovost PJ, Laupacis A, et al. Hospital volume and mortality for mechanical ventilation of medical and surgical patients: a population-based analysis using administrative data. *Crit Care Med* 2006;34:2349-54.
25 Castellanos-Ortega A, Suberviola B, García-Astudillo LA, Holanda MS, Ortiz F, Llorca J, et al. Impact of the surviving sepsis campaign protocols on hospital length of stay and mortality in septic shock patients: results of a three-year follow-up quasi-experimental study. *Crit Care Med* 2010;38:1036-43.
26 May S, Bigelow C. Modeling nonlinear dose-response relationships in epidemiologic studies: statistical approaches and practical challenges. *Dose Response* 2005;3:474-90.

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What is already known on this topic

A relation between the volume of cases treated and patients' outcomes has been established for several surgical and medical conditions

Two small studies have suggested the presence of a volume-outcome relation for critically ill patients with severe sepsis

What this study adds

No relation was found between volume and acute hospital mortality for patients with severe sepsis admitted to adult general critical care units in the UK

No significant interaction was found between volume and either severity of illness or receipt of mechanical ventilation

Tables

Table 1| Inclusion criteria for 159 483 admissions to 170 adult general critical care units in 2008-09. Values are numbers (percentages) unless stated otherwise

Criteria	Quarter 1*	Quarter 2*	Quarter 3*	Quarter 4*
All admissions	**(n=22 842)**	**(n=34 566)**	**(n=42 728)**	**(n=59 347)**
Median (interquartile range) volume per year	320 (281-374)	432 (372-537)	573 (465-685)	829 (656-1022)
No of SIRS criteria met:				
0	716 (3.1)	829 (2.4)	792 (1.9)	969 (1.6)
1	2070 (9.1)	2853 (8.3)	2922 (6.8)	4291 (7.2)
2	5672 (24.8)	7986 (23.1)	9386 (22.0)	13 108 (22.1)
3	8675 (38.0)	13 150 (38.0)	16 690 (39.1)	23 224 (39.1)
4	5709 (25.0)	9748 (28.2)	12 938 (30.3)	17 755 (29.9)
Infection	6203 (27.2)	9655 (27.9)	12 497 (29.2)	16 843 (28.4)
No of organ dysfunctions:				
0	3883 (17.0)	4914 (14.2)	5904 (13.8)	8857 (14.9)
1	7129 (31.2)	10 457 (30.3)	12 714 (29.8)	18 491 (31.2)
2	6423 (28.1)	10 444 (30.2)	12 598 (29.5)	17 560 (29.6)
3	3480 (15.2)	5627 (16.3)	7402 (17.3)	9321 (15.7)
4-5	1927 (8.4)	3124 (9.0)	4110 (9.6)	5118 (8.6)
Admissions with severe sepsis	**(n=4348; 19.0%)**	**(n=7060; 20.4%)**	**(n=9390; 22.0%)**	**(n=12 740; 21.5%)**
SIRS criteria:				
Temperature	3156 (72.6)	5218 (73.9)	6910 (73.6)	9588 (75.3)
Heart rate	4146 (95.4)	6733 (95.4)	8972 (95.5)	12 142 (95.3)
Respiratory rate	4281 (98.5)	6991 (99.0)	9319 (99.2)	12 602 (98.9)
White blood cell count	3544 (81.5)	5766 (81.7)	7650 (81.5)	10 401 (81.6)
No of SIRS criteria met:				
3	2265 (52.1)	3532 (50.0)	4709 (50.1)	6227 (48.9)
4	2083 (47.9)	3528 (50.0)	4681 (49.9)	6513 (51.1)
Organ dysfunctions:				
Cardiovascular	3551 (81.7)	5810 (82.3)	7723 (82.2)	10 166 (79.8)
Respiratory	3292 (75.7)	5375 (76.1)	6966 (74.2)	9367 (73.5)
Metabolic	2036 (46.8)	3412 (48.3)	4781 (50.9)	6005 (47.1)
Renal	1048 (24.1)	1857 (26.3)	2435 (25.9)	3405 (26.7)
Haematological	546 (12.6)	928 (13.1)	1213 (12.9)	1753 (13.8)
No of organ dysfunctions:				
1	936 (21.5)	1395 (19.8)	1892 (20.1)	2842 (22.3)
2	1542 (35.5)	2527 (35.8)	3287 (35.0)	4491 (35.3)
3	1159 (26.7)	1871 (26.5)	2481 (26.4)	3171 (24.9)
4-5	711 (16.4)	1267 (17.9)	1730 (18.4)	2236 (17.6)

SIRS=systemic inflammatory response syndrome.

Table 1 (continued)

Criteria	Quarter 1*	Quarter 2*	Quarter 3*	Quarter 4*

*Volume of admissions with severe sepsis grouped by quarters of critical care units.

Table 2| Volume characteristics of 33 538 admissions with severe sepsis between 2008 and 2009 by critical care unit volume and admission volume

Characteristic	Quarter 1	Quarter 2	Quarter 3	Quarter 4
Distribution by critical care unit				
Total No of admissions	4348	7060	9390	12 740
Total No of units	43	42	43	42
Median (IQR) volume of admissions with severe sepsis per unit per year	70 (59-75)	98 (95-103)	130 (121-138)	190 (168-206)
No (%) hospital type: university or university affiliated	10 (23)	13 (31)	19 (44)	28 (67)
Median (IQR) No of beds in unit	6 (5-7)	8 (7-9)	10 (8-12)	14 (12-17)
Distribution by admission				
Total No of admissions	8544	8337	8435	8222
Total No of units	70	41	34	25
Median (IQR) volume of admissions with severe sepsis per unit per year	84 (68-95)	119 (105-126)	150 (141-166)	195 (191-212)
No (%) hospital type: university or university affiliated	21 (30)	9 (22)	24 (71)	16 (64)
Median (IQR) No of beds in unit	7 (6-8)	8 (7-10)	12 (10-15)	16 (13-18)

IQR=interquartile range.

Table 3| Baseline characteristics of 30 727 admissions with severe sepsis between 2008 and 2009 by volume. Values are numbers (percentages) unless stated otherwise

Characteristic	Quarter 1* (n=3977)	Quarter 2* (n=6490)	Quarter 3* (n=8619)	Quarter 4* (n=11 641)
Demographics				
Mean (SD) age	64.8 (16.2)	64.0 (16.4)	63.7 (16.7)	63.1 (16.7)
Male sex	2099 (52.8)	3454 (53.2)	4569 (53.0)	6371 (54.7)
White ethnicity	3734 (93.9)	5861 (90.3)	7781/8493 (91.6)	10 412 (89.4)
Acute severity of illness				
Median (IQR) APACHE II score†	19 (14-23) (n=3867)	19 (15-24) (n=6302)	19 (15-24) (n=8384)	19 (15-24) (n=11 374)]
Median (IQR) ICNARC physiology score	22 (17-29)	23 (17-30)	22 (16-29)	22 (16-28)
Medical history				
Severe comorbidities‡:	(n=3950)	(n=6450)	(n=8571)	(n=11 602)
Any previous illness	600 (15.2)	1060 (16.4)	1512 (17.6)	2333 (20.1)
Severe cardiovascular disease	87 (2.2)	76 (1.2)	141 (1.6)	164 (1.4)
Severe respiratory disease	148 (3.7)	245 (3.8)	303 (3.5)	373 (3.2)
Renal disease	21 (0.5)	81 (1.3)	131 (1.5)	291 (2.5)
Chronic liver disease	50 (1.3)	103 (1.6)	179 (2.1)	277 (2.4)
Haematological malignancy	136 (3.4)	216 (3.3)	281 (3.3)	491 (4.2)
Metastatic disease	76 (1.9)	111 (1.7)	164 (1.9)	251 (2.2)
Immunological dysfunction	230 (5.8)	422 (6.5)	595 (6.9)	984 (8.5)
Activities of daily living§:	(n=3948)	(n=6447)	(n=8480)	(n=11 602)
No assistance	2997 (75.9)	4615 (71.6)	6055 (71.4)	8319 (71.7)
Partial assistance	897 (22.7)	1763 (27.4)	2309 (27.2)	3158 (27.2)
Total assistance	54 (1.4)	69 (1.1)	116 (1.4)	125 (1.1)
Cardiac arrest¶	137 (3.4)	279 (4.3)	300 (3.5)	337 (2.9)
Admission variables				
Location before admission**:		(n=6489)		
Emergency/urgent surgery	810 (20.4)	1580 (24.4)	2170 (23.2)	2666 (22.9)
Elective/scheduled surgery	172 (4.3)	231 (3.6)	396 (4.6)	514 (4.4)
Hospital ward	1968 (49.5)	3119 (48.1)	4146 (48.1)	5825 (50.0)
High dependency unit	348 (8.8)	515 (7.9)	520 (6.0)	697 (6.0)
Emergency department	676 (17.0)	1042 (16.1)	1385 (16.1)	1933 (16.6)
Mechanical ventilation	2345/3975 (59.0)	4035/6488 (62.2)	5242/8618 (60.8)	6562/11 637 (56.4)
Length of stay:				
Median (IQR) days of unit stay	4.6 (1.9-10.7)	4.1 (1.8-9.4)	4.0 (1.8-9.1)	4.1 (1.9-9.3) (n=11 639)
Median (IQR) days of hospital stay	17 (8-33)	17 (8-34)	17 (8-35)	19 (9-37) (n=11 639)
Mortality:				
Unit mortality	1242 (31.2)	1973 (30.4)	2527 (29.3)	3326 (28.6)
Ultimate acute hospital mortality	1682/3940 (42.7)	2722/6396 (42.6)	3456/8563 (40.4)	4504/11 561 (39.0)
Hospital discharge location††:	(n=2063)	(n=3302)	(n=4662)	(n=6590)
Home, residential place of work/education, or non-health related institution	1849 (89.6)	2864 (86.7)	4057 (87.0)	5854 (88.8)
Nursing home or equivalent	62 (3.0)	108 (3.3)	168 (3.6)	196 (3.0)
Short term rehabilitation	105 (5.1)	231 (7.0)	333 (7.1)	323 (4.9)
Long term rehabilitation	24 (1.2)	49 (1.5)	64 (1.4)	131 (2.0)
Other health related institution	15 (0.7)	37 (1.1)	29 (0.6)	61 (0.9)
Hospice or equivalent	8 (0.4)	13 (0.4)	11 (0.2)	25 (0.4)

APACHE=acute physiological and chronic health evaluation; ICNARC=Intensive Care National Audit & Research Centre; IQR=interquartile range.

*Volume of admissions with severe sepsis grouped by quarters of critical care units.

†1327 admissions not eligible for calculation of APACHE II.[28]

Table 3 (continued)

Characteristic	Quarter 1* (n=3977)	Quarter 2* (n=6490)	Quarter 3* (n=8619)	Quarter 4* (n=11 641)

‡Severe cardiovascular disease was defined as New York Heart Association class IV angina; severe respiratory disease as shortness of breath with light activity due to a pulmonary disorder or chronic home ventilatory support; renal disease as receipt of chronic peritoneal dialysis or haemodialysis; chronic liver disease as portal hypertension or hepatic encephalopathy or biopsy proven cirrhosis; haematological malignancy as any evidence of acute or chronic myelogenous leukaemia, acute or chronic lymphocytic leukaemia, or lymphoma; metastatic disease as evidence of distant metastases to areas other than regional lymph nodes; and immunological dysfunction as congenital immunohumoral or cellular immune deficiency states or receipt of chemotherapy or prednisone. Excluding admissions with no evidence to assess past medical history.

§Functional status was assessed by how much assistance was needed to carry out activities of daily living and defined as no assistance, partial assistance, or total assistance. Excluding admissions with no evidence to assess past medical history.

¶Defined as receipt of cardiopulmonary resuscitation in 24 hours before admission.

**Thirteen admissions direct from home not reported.

††Hospital survivors only. Excluding admissions transferred to another acute hospital.

Table 4| **Relation between volume of admissions with severe sepsis per year and mechanical ventilation status by different volume groupings**

Grouping and quarter	Strata specific odds ratio (95% CI)	P value*
Volume grouped by admissions		
No mechanical ventilation†:		P=0.48
1	1.0	
2	0.91 (0.77 to 1.06)	
3	0.94 (0.79 to 1.11)	
4	0.93 (0.78 to 1.11)	
Mechanically ventilation:		
1	1.0	
2	1.0 (0.87 to 1.15)	
3	0.92 (0.79 to 1.07)	
4	0.92 (0.79 to 1.08)	
Volume grouped by units†		
No mechanical ventilation:		P=0.005
1	1.0	
2	1.17 (0.96 to 1.42)	
3	0.96 (0.80 to 1.17)	
4	1.04 (0.86 to 1.25)	
Mechanically ventilation:		
1	1.0	
2	0.84 (0.71 to 0.99)	
3	0.86 (0.73 to 1.02)	
4	0.84 (0.71 to 0.99)	

*Calculated using likelihood ratio test comparing model with no interaction term to one with interaction term.

†Model adjusted for volume age, sex, ICNARC physiology score, comorbidities, activities of daily living, cardiac arrest, location before admission, and hospital type; an interaction term was placed between unit admission volume and mechanical ventilation.

Figures

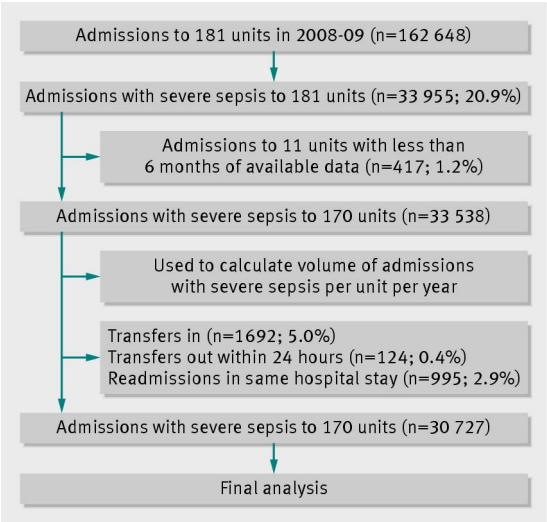

Fig 1 Flow chart of admissions and critical care units

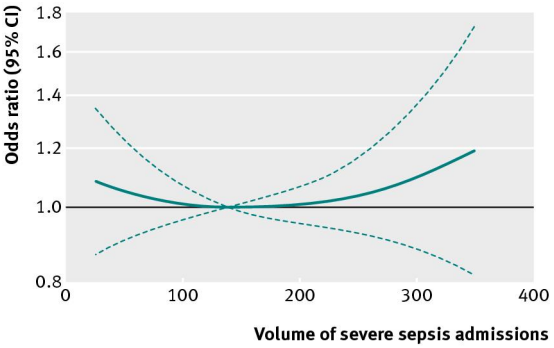

Fig 2 Odds ratio (95% CI) for effect of volume on acute hospital mortality. Volume modelled using fractional polynomials (degree 2) relative to mean volume of 138 admissions per year. Model adjusted for age (fraction polynomials degree 2), sex, ICNARC physiology score (fractional polynomials degree 2), mechanical ventilation, comorbidities, activities of daily living, cardiac arrest, location before admission, and hospital type

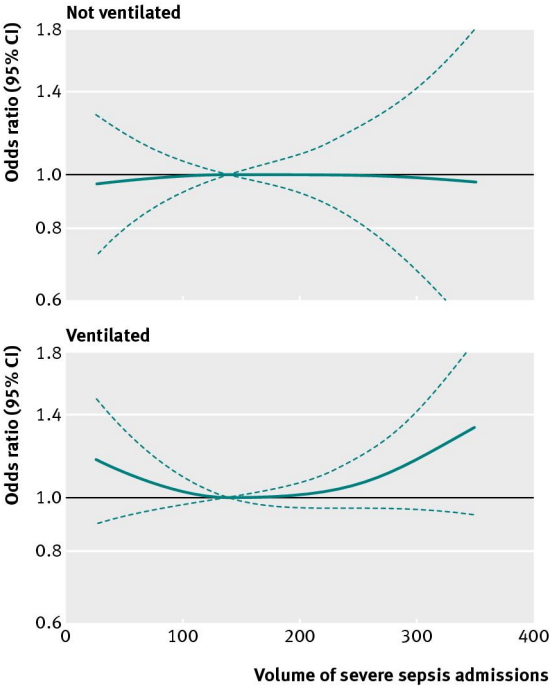

Fig 3 Odds ratio (95% CI) for interaction between effect of volume and mechanical ventilation on acute hospital mortality. Volume modelled using fractional polynomials (degree 2) relative to mean volume of 138 admissions per year. Model adjusted for age (fraction polynomials degree 2), sex, ICNARC physiology score (fractional polynomials degree 2), mechanical ventilation, comorbidities, activities of daily living, cardiac arrest, location before admission, and hospital type

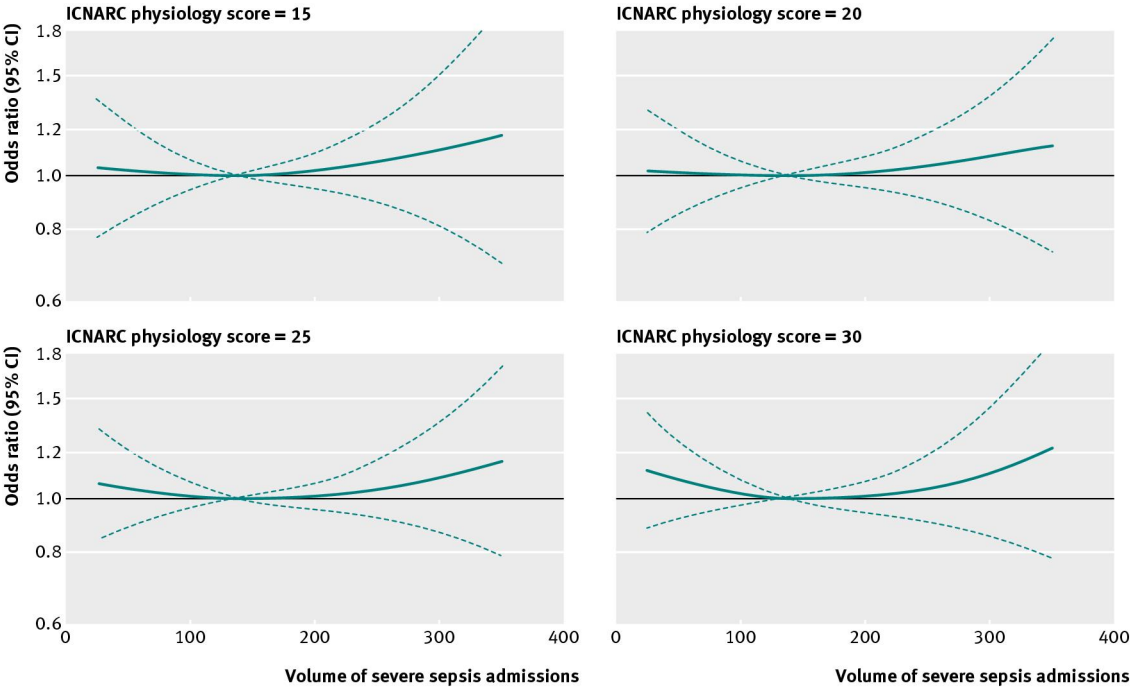

Fig 4 Odds ratio (95% CI) for interaction between effect of volume and Intensive Care National Audit & Research Centre (ICNARC) physiology score on acute hospital mortality. Volume modelled using fractional polynomials (degree 2) relative to mean volume of 138 admissions per year. Model adjusted for age (fraction polynomials degree 2), sex, ICNARC physiology score (fractional polynomials degree 2), mechanical ventilation, comorbidities, activities of daily living, cardiac arrest, location before admission, and hospital type