Relationship between Annualized Case Volume and Mortality in Sepsis

A Dose–Response Meta-analysis

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ABSTRACT

Background: The relationship between annualized case volume and mortality in patients with sepsis is not fully understood. The authors performed a dose–response meta-analysis to assess the effect of annualized case volume on mortality among patients with sepsis in the intensive care unit, emergency department, or hospital, hypothesizing that higher annualized case volume may lead to lower mortality.

Methods: The authors searched PubMed and Embase through July 2015 to identify observational studies that examined the relationship between annualized case volume and mortality in sepsis. The predefined outcome was mortality. Odds ratios with 95% CIs were pooled using a random-effects model.

Results: Ten studies involving 3,495,921 participants and 834,009 deaths were included. The pooled estimate suggested that annualized case volume was inversely associated with mortality (odds ratio, 0.76; 95% CI, 0.65 to 0.89; $P = 0.001$), with high heterogeneity ($I^2 = 96.6\%$). The relationship was consistent in most subgroup analyses and robust in sensitivity analysis. Dose–response analysis identified a nonlinear relationship between annualized case volume and mortality (P for nonlinearity less than 0.001).

Conclusions: This meta-analysis confirmed the study hypothesis and provided strong evidence for an inverse and a nonlinear dose–response relationship between annualized case volume and mortality in patients with sepsis. Variations in cutoff values of category for annualized case volume across studies may mainly result in the overall heterogeneity. Future studies should uncover the mechanism of volume–mortality relationship and standardize the cutoff values of category for annualized case volume in patients with sepsis. **(Anesthesiology 2016; 125:168-79)**

IN the past few decades, a number of studies have evaluated the relationship between hospital volume and patient outcomes in varieties of medical and surgical conditions.[1–4] Several studies have also evaluated the volume–outcome relationship in critically ill patients.[5–7] Sepsis is a leading cause of death among critically ill patients in the United States, which puts an enormous strain on the healthcare system and is becoming a pressing public health crisis.[8] In the past decades, the incidence of sepsis has rapidly increased worldwide,[9–12] while the mortality from sepsis has steadily decreased over time despite the absence of novel therapeutics.[13,14] Early recognition, treatment, and advances in processes of care mainly contribute to the declining mortality.[15] The number of septic patients treated in a hospital (*i.e.*, annualized case volume or hospital volume), reflecting experience, may also partly be associated with this decline. However, the relationship between annualized case volume and mortality in patients with sepsis has not been fully understood.

What We Already Know about This Topic

- Much evidence suggests that hospitals with higher volumes of septic patients have better outcomes in sepsis.

What This Article Tells Us That Is New

- A dose–response meta-analysis (10 studies, 3.4 million patients, 0.83 million deaths) demonstrated a consistent dose–response relationship with lower mortality in higher volume hospitals with up to 400 cases (intensive care unit, emergency department) per year; above this level, the outcomes plateaued. The findings were consistent across subgroups and may help plan optimal centralization of care.

Previous studies have evaluated the relationship between annualized case volume and mortality in patients with sepsis but have shown inconsistent results.[16–25] Therefore, we performed this meta-analysis with the following objectives: (1) to examine the relationship between annualized case

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 Anesthesiology 2016; 125:168-79

<zdoi;10.1097/ALN.0000000000001133>

volume and mortality in patients with sepsis, hypothesizing that higher annualized case volume may lead to lower mortality; and (2) to investigate the dose–response relationship between annualized case volume and mortality in sepsis.

Materials and Methods

This meta-analysis was conducted and reported according to the Meta-analysis of Observational Studies in Epidemiology checklist.[26]

Data Sources and Search Strategy

We searched PubMed and Embase from inception to July 1, 2015, without any restrictions. Search terms included those related to volume, sepsis, and their variants. Details of the search strategy are available in appendix 1. We also manually searched reference lists of all the included studies as well as relevant review articles. Additionally, we also reviewed conference abstracts for unpublished work but failed to identify any eligible studies for inclusion.

Study Selection and Eligibility Criteria

Two authors (W.-J.G. and X.-D.W.) independently undertook the searches. After the removal of duplicates, we screened the titles and abstracts for relevance and accessed full text to identify eligibility of studies for inclusion in this meta-analysis. We included any observational studies (such as cohort study, case–control study, or cross-sectional study) that examined the relationship between annualized case volume and mortality among adults with sepsis, severe sepsis, or septic shock in the intensive care unit (ICU), emergency department, or hospital.

Data Extraction

Data extraction was performed by W.-J.G. and was confirmed independently by two other authors (J.Z. and F.W.). The following information was extracted from each included study: first author, year of publication, country where the study was done, sepsis identification, clinical setting, number of sepsis cases, overall mortality rate, volume grouping (*i.e.*, tertiles, quartiles, quintiles, or other groupings), volume category (*i.e.*, the category according to the various cutoff values of annualized case volume), multivariate adjusted risk estimates for each category, study design, and covariates in the fully adjusted model. Extracted data were entered into a predefined standardized Excel (Microsoft Corporation, USA) file. The supplementary files of included studies were also examined for data extraction.

Quality Assessment

Quality assessment was evaluated by using the Newcastle–Ottawa Scale,[27] which is a validated scale for assessing the quality of nonrandomized studies in meta-analyses. This scale awards a maximum of nine stars to each study: four stars for selection of participants and measurement of exposure, two stars for comparability, and three stars for assessment of outcomes and adequacy of follow-up. We assigned scores of 0 to 3, 4 to 6, and 7 to 9 for low, moderate, and high quality of studies, respectively.

Statistical Analysis

Multivariate odds ratios (ORs) and corresponding 95% CIs between extreme levels of annualized case volume (highest *vs.* lowest) were pooled using a random-effects model, accounting for clinical heterogeneity. Heterogeneity across studies was assessed by using the Q statistic with its P value and I^2 statistic.[28,29] The I^2 statistic is used to quantify the proportion of total variation in the effect estimation that is due to between-study variation. An I^2 value greater than 50% indicates significant heterogeneity. Distribution between annualized case volume and mortality in each category was described using a scatter plot. The analysis requires data on the median or mean level of annualized case volume in each category (X-axis) and the corresponding mortality rate of that category (Y-axis). After excluding two studies because of no available data,[18,20] 8 of 10 studies were included for the analysis.[16,17,19,21–25] Publication bias was assessed by visually inspecting a funnel plot and also evaluated by using the Egger test.[30]

Subgroup Analyses and Sensitivity Analysis

To explore the possible sources of heterogeneity among studies, we carried out the following subgroup analyses: study design (cohort *vs.* cross-sectional), sepsis identification (administrative coding *vs.* clinical screening), quality of the risk adjustment (administrative risk adjustment *vs.* case-mix adjustment),[31] clinical setting (ICU *vs.* emergency department *vs.* hospital), annualized case volume grouping (quintiles *vs.* quartiles *vs.* tertiles), sepsis with malignancies (yes *vs.* no), adjusted hospital region and/or teaching status (yes *vs.* no), sample size (greater than 50,000 *vs.* less than 50,000), and study quality (high *vs.* moderate). To test the robustness of the relationship, we also conducted a sensitivity analysis, which was investigated by omitting one study at each turn and examining the influence of each individual study on the overall risk estimate (the "leave one out" approach). A two-sided P value less than 0.05 was considered statistically significant. All analyses were performed using Stata statistical software version 13.0 (StataCorp, USA).

Dose–Response Analysis

We used the methods proposed by Greenland and Longnecker[32] and Orsini *et al.*[33] for the dose–response analysis. We computed study-specific ORs and 95% CIs from the natural logarithms of the ORs and CIs across categories of annualized case volume. The method requires that the amount of annualized case volume, distributions of cases and noncases, and ORs with 95% CIs are known for

at least three quantitative categories of annualized case volume. We excluded three studies from trend estimation because of less than three quantitative categories[16] or no available data.[18,24] The median or mean level of annualized case volume in each category was assigned to the corresponding OR for each study. If the median or mean level was not provided and reported in ranges, we estimated the midpoint in each category by calculating the average of the lower and upper boundaries of that category. If the highest category was open ended, the midpoint of the category was set at 1.5 times the lower boundary of that category. If the lowest category was open ended, the midpoint of the category was set at 0.5 times the upper boundary of that category. All analyses were performed using R software (http://www.R-project.org; accessed April 5, 2016).

Results

Literature Search

Figure 1 shows the study selection process. Our initial search yielded 148 records. After exclusion of duplicates and screening the titles and abstracts, we obtained 16 full-text articles. After reviewing the full text, 10 studies met the inclusion criteria and were included in the qualitative synthesis.[16–25] We included nine studies in the quantitative meta-analysis.[16–23,25] One study that did not report available data for analysis was excluded from the quantitative meta-analysis.[24]

Study Characteristics

The characteristics of the included studies are shown in table 1. Eight of 10 were retrospective cohort studies,[16,19–25] and 2 of 10 were cross-sectional studies.[17,18] These studies were published between 2007 and 2015. The number of participants in the studies ranged from 3,437 to 1,213,219. The meta-analysis consisted of 3,495,921 participants and 834,009 deaths. Grouping and category of annualized case volume showed wide variability, but adjusted estimates could be determined for all studies even though the adjusted factors were slightly different. Details of the quality assessment of included studies are outlined in table 2. The average score was 6.7, and the score for each study was 5 or above, suggesting that all the studies were of moderate or high quality.

Annualized Case Volume and Risk of Mortality

Nine studies that provided available data were included for quantitative meta-analysis.[16–23,25] Annualized case volume was inversely associated with mortality; that is, higher annualized case volume was associated with lower mortality (OR, 0.76; 95% CI, 0.65 to 0.89; P = 0.001; fig. 2), with significant heterogeneity (I^2 = 96.6%). Figure 3 shows a scatter plot describing the distribution between annualized case

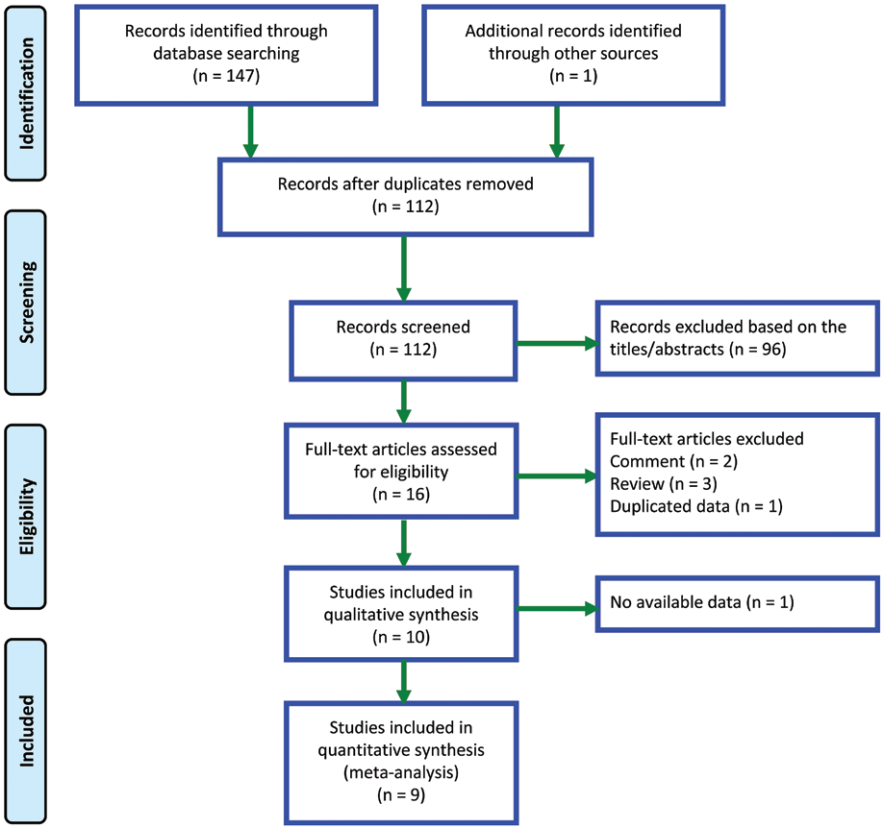

Fig. 1. Flow diagram of the study selection process.

Table 1. Characteristics of the Included Studies

Study	Country	Population	Sepsis Identification	Clinical Setting	Number of Participants	Mortality, %	Endpoints	Volume Grouping	Volume Category, Cases/Year	Multivariate OR (95% CI)	Study Design	Covariates in Fully Adjusted Model
Peelen *et al.*[16]	The Netherlands	Adults with severe sepsis	Clinical screening	ICU	4,605	34.7	In-hospital mortality	NR	72.8 ± 44.0*	0.97 (0.943–0.997)	Retrospective cohort	Age, sex, SAPS II score, and number of dysfunctioning organ systems
Powell *et al.*[17]	United States	Adults with severe sepsis	Administrative coding	ED	87,166	18	In-hospital mortality	Quartiles	25–145 146–248 249–371 > 371	1 (reference) 0.90 (0.82–0.99) 0.83 (0.74–0.93) 0.73 (0.64–0.83)	Cross-sectional	Age, sex, comorbid conditions, payer status, income, hospital bed size, and teaching status
Banta *et al.*[18]	United States	Adults with severe sepsis	Administrative coding	Hospital	1,213,219	17.8	In-hospital mortality	Quartiles	0–8,626 8,627–14,676 14,677–19,574 19,575–48,225	1 (reference) 0.80 (0.71–0.90) 0.90 (0.80–1.00) 0.90 (0.81–1.00)	Cross-sectional	Age, sex, ethnicity, payer status, transfer status, Charlson score, hospital region, hospital location, and teaching status
Shahin *et al.*[19]	United Kingdom	Adults with severe sepsis	Clinical screening	ICU	30,727	29.5	In-hospital mortality	Quartiles	70 (59–75)† 98 (95–103)† 130 (121–138)† 190 (168–206)†	1 (reference) 0.94 (0.80–1.10) 0.89 (0.77–1.04) 0.92 (0.78–1.08)	Retrospective cohort	Age, sex, acute severity of illness, comorbid conditions, location before admission, and teaching status
Zuber *et al.*[20]	France	Adults with septic shock and malignancies	Clinical screening	ICU	3,437	59	ICU mortality	Tertiles	19.6 ± 13.7* 37.7 ± 17.7* 76.9 ± 27.2*	1 (reference) 0.82 (0.59–1.14) 0.63 (0.46–0.87)	Retrospective cohort	Age, sex, SAPS II score, Charlson score, type of ICU admission, admission category, type of malignancy, neutropenia, bone marrow transplantation, and organ failures

(*Continued*)

Table 1. (Continued)

Study	Country	Population	Sepsis Identification	Clinical Setting	Number of Participants	Mortality, %	Endpoints	Volume Grouping	Volume Category, Cases/Year	Multivariate OR (95% CI)	Study Design	Covariates in Fully Adjusted Model
Gaieski *et al.*[21]	United States	Adults with severe sepsis	Administrative coding	ICU	914,200	28.1	In-hospital mortality	Quintiles	< 50 50–99 100–249 250–499 > 499	1 (reference) 0.85 (0.80–0.90) 0.75 (0.71–0.79) 0.72 (0.68–0.76) 0.64 (0.60–0.69)	Retrospective cohort	Age, sex, race, comorbid conditions, payer status, discharge year, hospital region, hospital location, teaching status, specific organ dysfunction information, and APR-DRG risk of mortality
Kocher *et al.*[22]	United States	Adults with severe sepsis	Administrative coding	ED	528,767	17.8	In-hospital mortality	Quintiles	30–141 142–240 241–346 347–524 > 524	1 (reference) 0.83 (0.79–0.87) 0.80 (0.76–0.85) 0.74 (0.69–0.78) 0.62 (0.58–0.67)	Retrospective cohort	Age, sex, race, insurance, income, comorbid conditions, hospital bed size, hospital region, hospital location, teaching status, APR-DRG severity, and APR-DRG risk of mortality
Shahul *et al.*[23]	United States	Adults with severe sepsis	Administrative coding	ICU	646,988	34.3	In-hospital mortality	Tertiles	< 11 11–60 > 60	1.188 (1.074–1.315) 1.090 (1.031–1.152) NR	Retrospective cohort	Age, sex, race, income, Charlson score, hospital region, and teaching status
Walkey and Wiener[24]	United States	Adults with severe sepsis	Clinical screening	ICU	56,997	25.6	In-hospital mortality	Quartiles	30–317 318–437 438–603 604–977		Retrospective cohort	Age, sex, race, hospital bed size, hospital region, and proportion of severe sepsis cases transferred to long-term acute care hospitals

(*Continued*)

Table 1. (Continued)

Study	Country	Population	Sepsis Identification	Clinical Setting	Number of Participants	Mortality, %	Endpoints	Volume Grouping	Volume Category, Cases/Year	Multivariate OR (95% CI)	Study Design	Covariates in Fully Adjusted Model
Goodwin *et al.*[25]	United States	Adults with severe sepsis or septic shock	Administrative coding	ICU	9,815	29.2	In-hospital mortality	Tertiles	1–74 75–299 > 299	1.56 (1.25–1.94) 0.99 (0.90–1.09) 1 (reference)	Retrospective cohort	Age, sex, race, insurance, Charlson score, need for mechanical ventilation, probability of mortality as determined by the sepsis mortality prediction score, and hospital region

*Mean ± SD. †Median (interquartile range).
APR-DRG = All Patient Refined Diagnosis Related Groups; ED = emergency department; ICU = intensive care unit; NR = not reported; OR = odds ratio; SAPS = Simplified Acute Physiology Score.

volume according to the median or mean level of annualized case volume in each category from one of the eight studies and the corresponding mortality rate of that category.

Subgroup Analyses and Sensitivity Analysis

To explore the potential source of heterogeneity across studies, we carried out several subgroup analyses, as shown in table 3. Variations in cutoff values of category for annualized case volume across studies may be the main reason for the overall heterogeneity. The relationship between annualized case volume and mortality was consistent in all subgroups except for sepsis identification by clinical screening, unadjusted hospital region and/or teaching status, and moderate study quality. To further confirm the robustness of the results, we conducted a sensitivity analysis. Exclusion of any individual study from our meta-analysis in figure 2 did not meaningfully change the magnitude or direction of the summary effect for the relationship between annualized case volume and mortality (appendix 2).

Dose–Response Analysis

Seven studies were included in the dose–response analysis.[16–21,23] We observed a nonlinear dose–response relationship between annualized case volume and mortality (P for nonlinearity less than 0.001). Figure 4 shows the effect of annualized case volume as a continuous variable on mortality in patients with sepsis. Reduction in mortality is seen throughout the distribution, as annualized case volume increases from the lower extreme to the higher extreme; however, the mortality benefit of a higher annualized case volume tapers off around 400 cases, which is clearly evident in figure 4.

Publication Bias

Although the Egger test suggests that there was no evidence of publication bias ($P = 0.08$), it is hard to rule out the existence of publication bias by visual inspection of the funnel plot (fig. 5) since only nine studies were included in the quantitative meta-analysis.

Discussion

Main Findings

To the best of our knowledge, this meta-analysis is a more comprehensive update that systematically and quantitatively evaluates the relationship between annualized case volume and mortality in patients with sepsis. This meta-analysis supports the hypothesis that higher annualized case volume is associated with a lower mortality. This relationship seems to be robust and consistent in subgroup analyses. Furthermore, we identified a nonlinear dose–response relationship between annualized case volume and mortality in sepsis.

Comparison with Other Studies

Two previous reviews investigated the relationship between ICU volume and outcome and found an inverse

Table 2. Methodological Quality Assessment of Included Studies by Newcastle–Ottawa Scales

	Selection					Outcome			
Study	Exposed Cohort	Nonexposed Cohort	Ascertainment of Exposure	Outcome of Interest	Comparability	Assessment of Outcome	Length of Follow-up	Adequacy of Follow-up	Total Score
Peelen *et al.*[16]	*	*	*	*	**	*	—	—	7
Powell *et al.*[17]	*	*	*	*	**	*	—	—	7
Banta *et al.*[18]	*	*	*	*	**	*	—	—	7
Shahin *et al.*[19]	—	*	*	*	*	*	—	—	5
Zuber *et al.*[20]	*	*	*	*	**	*	—	—	7
Gaieski *et al.*[21]	*	*	*	*	**	*	*	—	8
Kocher *et al.*[22]	*	*	*	*	*	*	—	—	6
Shahul *et al.*[23]	*	*	*	*	**	*	*	—	8
Walkey and Wiener[24]	*	*	*	*	*	*	—	—	6
Goodwin *et al.*[25]	*	*	*	*	**	*	—	—	7

Single asterisk indicates 1 score, double asterisk indicates 2 scores, and dash indicates 0 scores.

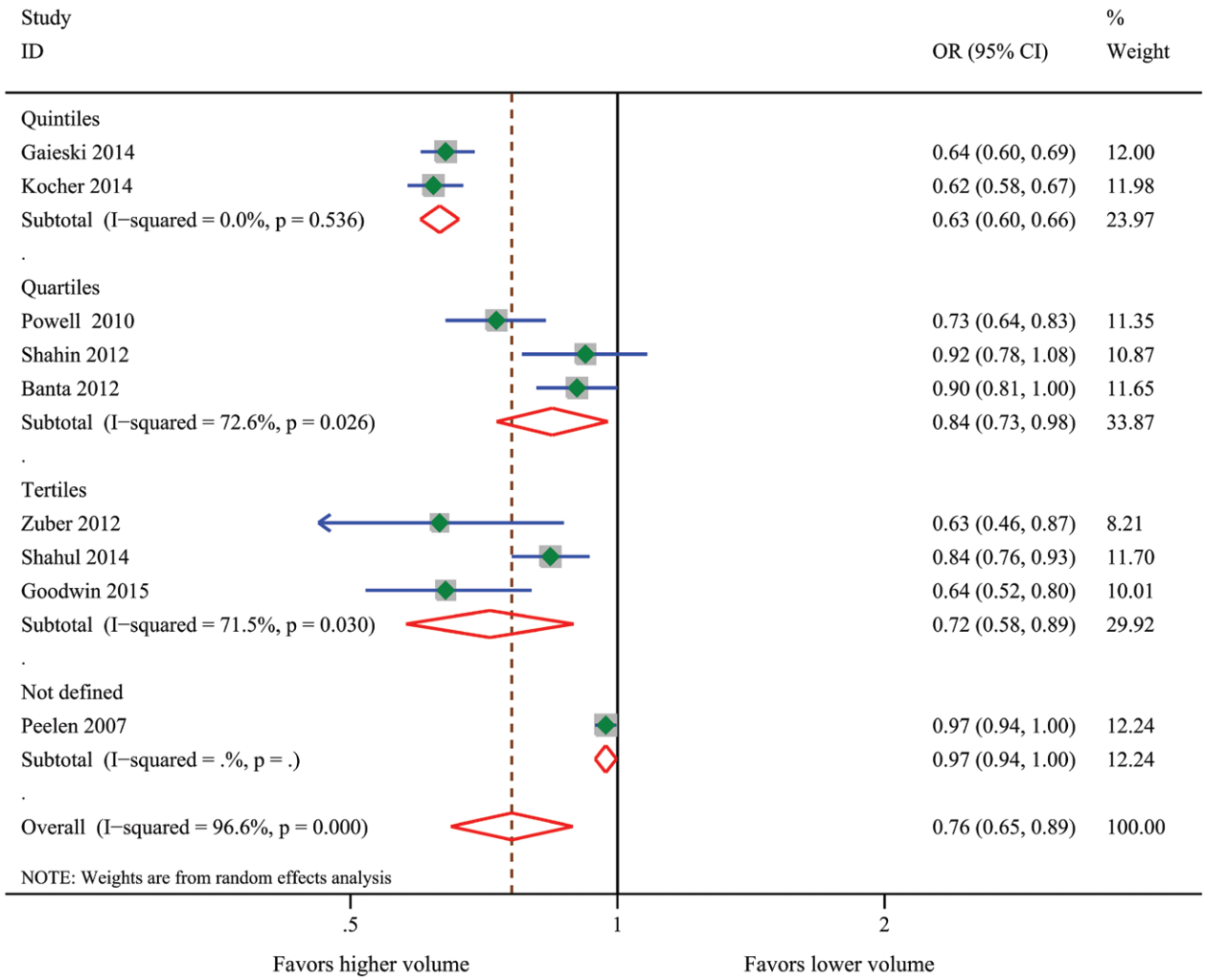

Fig. 2. Forest plot of the relationship between annualized case volume and mortality among patients with sepsis in the intensive care unit/emergency department/hospital according to volume grouping. OR = odds ratio.

volume–mortality relationship in critically ill adult patients.[34,35] The latest systematic review published by Nguyen *et al.*[36] was more recent and comprehensive than the two aforementioned meta-analyses.[34,35] However, the Nguyen systematic review recruited heterogeneous patient groups (*e.g.*, cardiovascular, respiratory, hepatogastrointestinal, sepsis, *etc.*) rather than just all critically ill patients and the other two included critically ill

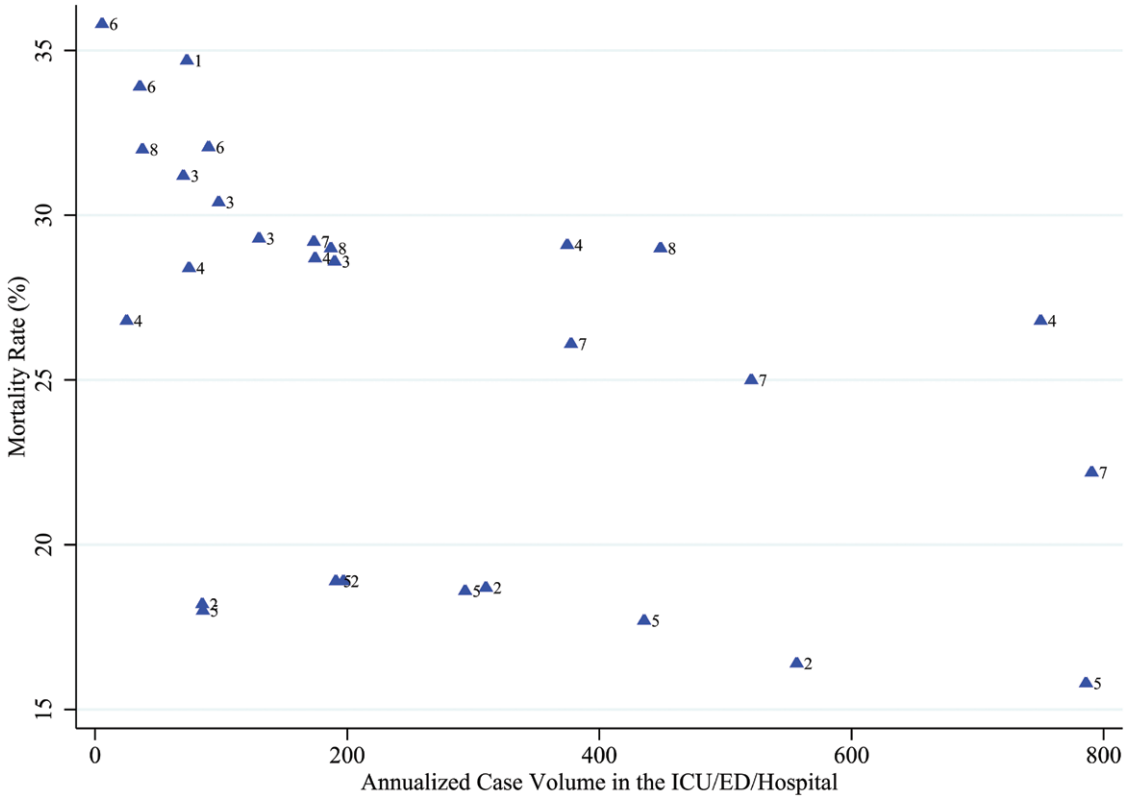

Fig. 3. Scatter plot describing the distribution between annualized case volume according to the median or mean level of annualized case volume in each category from one of the eight studies and the corresponding mortality rate of that category among patients with sepsis in the intensive care unit (ICU)/emergency department (ED)/hospital (study 1 = Peelen *et al.*,[16] study 2 = Powell *et al.*,[17] study 3 = Shahin *et al.*,[19] study 4 = Gaieski *et al.*,[21] study 5 = Kocher *et al.*,[22] study 6 = Shahul *et al.*,[23] study 7 = Walkey and Wiener,[24] and study 8 = Goodwin *et al.*[25]).

patients without highly selective conditions, which limited their applicability to patients with sepsis and made their findings even more difficult to put into perspective. To better specify the volume–mortality relationship in selected patients with sepsis, we performed a meta-analysis to assess the effect of annualized case volume on mortality in sepsis. Differences between our meta-analysis and the previous reviews should be noted. First, our meta-analysis paid attention to only patients with sepsis, which was highly homogeneous and selective. Second, we also unpacked the heterogeneity across studies by examining key subgroups based on study design and patient characteristics. Last, we found a nonlinear dose–response relationship between annualized case volume and mortality, which had not been investigated in previous reviews and may strengthen causal inference.

Possible Mechanisms for Findings

Although the volume–outcome relationship was first reported in 1979,[37] the underlying mechanism has not been fully understood and requires further exploration. There are three potential mechanisms of the volume–outcome relationship.[38–40] First is "practice makes perfect" (the increased frequency of encounters allows higher case volume centers to develop more experience and streamline processes to improve quality of care), which means that high volume leads to high quality. Second is "selective referral pattern" (patients disproportionately seek care at, and physicians refer to, hospitals known for high quality of care), which means that high quality leads to high volume. Third is "organizational structural factors" (high-volume hospitals possess other factors associated with improved outcome, such as high-intensity physician staffing, multidisciplinary care teams, and protocol use), which means that the volume–outcome relationship may not exist if we could properly control for these factors. In high-acuity emergent conditions, such as sepsis, the most likely mechanisms would be "practice makes perfect" and "organizational structural factors," as septic patients are acutely and severely ill and often do not have the luxury of choosing where they are treated.[17] Thus, "selective referral pattern" could play only a small role for better quality of care.

Implications for Clinical Practice

Sepsis, as a critically ill condition that heavily relies on quality of care, would certainly benefit more from high annualized case volume hospitals with sufficient supply

Table 3. Subgroup Analyses of Relationship between Annualized Case Volume and Mortality in Sepsis

Subgroup	No. Patients	No. Studies	Test of Relationship		Test of Heterogeneity	
			OR (95% CI)	*P* Value	I^2, %	*P* Value
Total[16–23,25]	3,438,924	9	0.76 (0.65–0.89)	0.001	96.6	< 0.0001
Study design						
Cohort studies[16,19–23,25]	2,138,539	7	0.74 (0.61–0.91)	0.003	97.4	< 0.0001
Cross-sectional studies[17,18]	1,300,385	2	0.81 (0.66–1.00)	0.048	83.4	0.014
Sepsis identification						
Administrative coding[17,18,21–23,25]	3,400,155	6	0.72 (0.63–0.83)	< 0.0001	90.5	< 0.0001
Clinical screening[16,19,20]	38,769	3	0.88 (0.75–1.04)	0.145	72.8	0.025
Quality of the risk adjustment						
Administrative risk adjustment[16–18,20–23]	3,398,382	7	0.76 (0.63–0.91)	0.003	97.4	< 0.0001
Case-mix adjustment[19,25]	40,542	2	0.77 (0.54–1.10)	0.155	85.6	0.008
Clinical setting						
ICU[16,19–21,23,25]	1,609,772	6	0.77 (0.63–0.94)	0.01	96.3	< 0.0001
ED[17,22]	615,933	2	0.67 (0.57–0.78)	< 0.0001	78.4	0.031
Hospital[18]	1,213,219	1	0.90 (0.81–1.00)	0.05	NA	NA
Volume grouping						
Tertiles[20,23,25]	660,240	3	0.72 (0.58–0.89)	0.003	71.5	0.03
Quartiles[17–19]	1,331,112	3	0.84 (0.73–0.98)	0.022	72.6	0.026
Quintiles[21,22]	1,442,967	2	0.63 (0.60–0.66)	< 0.0001	0	0.536
Sepsis with malignancies						
No[16–19,21–23,25]	3,435,487	8	0.77 (0.65–0.91)	0.002	97.0	< 0.0001
Yes[20]	3,437	1	0.63 (0.46–0.87)	0.004	NA	NA
Adjusted one or more following confounders (hospital region and/or teaching status)						
Yes[17–19,21–23,25]	3,430,882	7	0.75 (0.65–0.85)	< 0.0001	90.5	< 0.0001
No[16,20]	8,042	2	0.81 (0.53–1.22)	0.312	85.7	0.008
Sample size						
< 50,000[16,19,20,25]	48,584	4	0.80 (0.65–0.99)	0.037	85.8	< 0.0001
> 50,000[17,18,21–23]	3,390,340	5	0.74 (0.64–0.85)	< 0.0001	92.3	< 0.0001
Study quality						
High[16–18,20,21,23,25]	2,879,430	7	0.76 (0.65–0.90)	0.002	95.9	< 0.0001
Moderate[19,22]	559,494	2	0.75 (0.51–1.10)	0.145	94.7	< 0.0001

ED = emergency department; ICU = intensive care unit; NA = not applicable; OR = odds ratio.

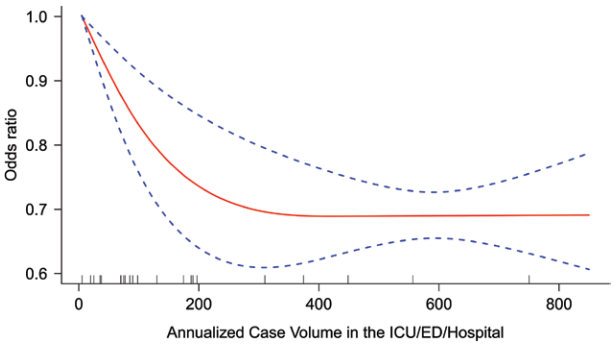

Fig. 4. Dose–response analysis of the relationship between annualized case volume and mortality among patients with sepsis in the intensive care unit (ICU)/emergency department (ED)/hospital.

of medical resources and experienced experts and nurses who deliver a high quality of care than from low case volume hospitals. Our meta-analysis demonstrated that there was an inverse and a nonlinear dose–response relationship between annualized case volume and mortality. These findings suggest that centralization of care units might help in patients with sepsis. However, fully implementing centralization of septic patients is impracticable and often has a high risk–benefit ratio, especially in the regional hospitals or rural areas. In addition, the existence of a volume–mortality relationship in patients with sepsis has prompted health systems to consider the regionalization of critical care through the creation of a tiered system. However, just as a coin has two sides, there are both advantages and disadvantages regarding regionalization. On the one hand, regionalization will improve patient outcomes and increase efficiency of care delivery[41]; on the other hand, regionalization is not without risks, and little is known about the cost and feasibility of regionalization. One recent study identified multiple barriers to the acceptance and implementation of regionalization strategy.[42] Thus, health systems should weigh the trade-off between the potential benefits and possible risks associated with regionalization when considering the strategy of regionalized critical care.

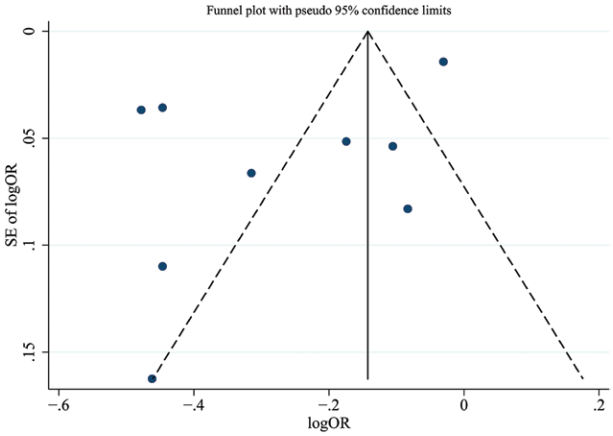

Fig. 5. Funnel plot for publication bias of the relationship between annualized case volume and mortality among patients with sepsis in the intensive care unit/emergency department/hospital. OR = odds ratio.

Call for Future Studies

Considering the current controversies and challenges, more studies on the volume–outcome relationship in patients with sepsis are still needed. First, further studies are required to uncover other potential mechanisms beyond "practice makes perfect" and "selective referral pattern," such as "organizational structural factors," including higher nurse-to-patient ratios, multidisciplinary care models, and protocols. Next, future guidelines are needed to standardize the cutoff values for annualized case volume in studies on the volume–outcome relationship in sepsis, which could overcome considerable heterogeneity and allow for assimilation of data, and then translate the evidence into clinical practice and policy implications. Finally, although there is a nonlinear dose–response relationship between annualized case volume and mortality in sepsis, the optimal volume threshold is essential for better outcomes. Two studies have shown worsening outcomes once the volume rose above a certain threshold.[43,44] One study suggested that mortality did not decrease further after a certain volume (n = 450 cases) was reached as volume increased.[43] This phenomenon was also observed in another study that found that after a volume threshold (n = 711 cases), there was no further mortality benefit.[44] Thus, it is important to maintain an optimal volume matched with the available resources.

Strengths and Limitations

Our meta-analysis has several strengths. We conducted this meta-analysis by exhaustive search without any restrictions and reported it following the Meta-analysis of Observational Studies in Epidemiology guidelines. We used the estimates from the most fully adjusted models for each study to reduce the potential of confounding. We performed several subgroup analyses to explore the potential sources of heterogeneity and evaluate the robustness of the relationship. In addition, we investigated a nonlinear dose–response relationship between annualized case volume and mortality, which can help to quantify the relationship and to test the shape of this possible relationship.

Our meta-analysis has several caveats that affect the interpretation of the results. First, we found considerable heterogeneity across the studies in our meta-analysis. It was not surprising given the differences in the data source, study population, annualized case volume grouping and category, and study design. These factors could affect our results. Nevertheless, we used a random-effects model to pool multivariate estimates, which could reduce the bias to some extent. Furthermore, dose–response analysis supports our results. Second, the results still could have been biased since most studies were retrospective and therefore limited the ability to control for confounding. However, most studies in our meta-analysis fully adjusted the important confounders. Last, although we conducted a comprehensive search of literature, it is hard to rule out the existence of publication bias since only nine studies were identified, and current guidelines do not recommend testing for funnel plot asymmetry in analyses of fewer than 10 studies.[45]

Conclusions

In summary, the present meta-analysis confirmed our hypothesis and provided strong evidence for an inverse and a nonlinear dose–response relationship between annualized case volume and mortality in patients with sepsis. Variations in cutoff values of category for annualized case volume across studies may be the main reason for the overall heterogeneity. To clarify the volume–mortality relationship in patients with sepsis, future studies should uncover the mechanism of the volume–mortality relationship and standardize the cutoff values of category for annualized case volume.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

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Appendix 1. Search Strategy

Source: PubMed; Searched on: July 1, 2015; Results: 65

Search	Query	Results
1	"Sepsis"[Mesh]	95,929
2	"Shock, Septic"[Mesh]	18,862
3	"Systemic Inflammatory Response Syndrome"[Mesh]	99,035
4	Sepsis [tiab]	70,256
5	Septic [tiab]	40,355
6	Systemic Inflammatory Response Syndrome [tiab]	3,431
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	161,156
8	"Mortality"[Mesh]	294,223
9	Outcome[tiab]	682,024
10	Mortality[tiab]	521,826
11	Survival[tiab]	654,217
12	Death[tiab]	518,241
13	#8 OR #9 OR #10 OR #11 OR #12	2,054,531
14	Volume[ti]	441,020
15	Tidal[tiab]	23,382
16	Hemodialysis[tiab]	49,436
17	Stroke[tiab]	162,886
18	Lung[tiab]	462,499
19	Pressure[tiab]	649,816
20	Ventricule[tiab]	355
21	Gastric[tiab]	201,087
22	Platelet[tiab]	149,214
23	Blood[tiab]	1,557,858
24	Brain[tiab]	758,383
25	Hematoma[tiab]	30,418
26	Hemofiltration[tiab]	3,005
27	#14 NOT #15 NOT #16 NOT #17 NOT #18 NOT #19 NOT #20 NOT #21 NOT #22 NOT #23 NOT #24 NOT #25 NOT #26	33,060
28	#7 AND #13 AND #27	65

Source: Embase; Searched on: July 1, 2015; Results: 82

Search	Query	Results
1	Sepsis:ab,ti	101,715
2	Septic:ab,ti	56,467
3	Systemic inflammatory response syndrome:ab,ti	4,631
4	#1 OR #2 OR #3	140,951
5	Mortality:ab,ti	732,041
6	Outcome:ab,ti	921,088
7	Survival:ab,ti	907,398
8	Death:ab,ti	703,637
9	#5 OR #6 OR #7 OR #8	2,649,542
10	Volume:ti	75,406
11	Tidal:ab,ti	30,567
12	Hemodialysis:ab,ti	65,783
13	Stroke:ab,ti	241,845
14	Lung:ab,ti	627,768
15	Pressure:ab,ti	865,762
16	Ventricule:ab,ti	1,797
17	Gastric:ab,ti	281,245
18	Platelet:ab,ti	198,966
19	Blood:ab,ti	2,075,511

(*Continued*)

Appendix 1. (Continued)

Search	Query	Results
20	Brain:ab,ti	962,806
21	Hematoma:ab,ti	40,550
22	Hemofiltration:ab,ti	3,895
23	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	4,461,463
24	#10 NOT #23	41,447
25	#4 AND #9 AND #24	85
26	#4 AND #9 AND #24 AND ([embase]/lim OR [embase classic]/lim)	82

Appendix 2. Sensitivity Analysis

Study Omitted	OR	95% CI
Peelen *et al.*[16]	0.74	0.65–0.83
Powell *et al.*[17]	0.76	0.64–0.91
Banta *et al.*[18]	0.74	0.62–0.89
Shahin *et al.*[19]	0.74	0.62–0.88
Zuber *et al.*[20]	0.77	0.65–0.91
Gaieski *et al.*[21]	0.78	0.66–0.91
Kocher *et al.*[22]	0.78	0.67–0.91
Shahul *et al.*[23]	0.75	0.63–0.9
Goodwin *et al.*[25]	0.77	0.66–0.92
Combined[16–23,25]	0.76	0.65–0.89

OR = odds ratio.

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