CHEST

The Volume-Outcome Relationship in Critical Care

A Systematic Review and Meta-analysis

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OBJECTIVE: The purpose of this study was to systematically review the research on volume and outcome relationships in critical care.

METHODS: From January 1, 2001, to April 30, 2014, MEDLINE and EMBASE were searched for studies assessing the relationship between admission volume and clinical outcomes in critical illness. Bibliographies were reviewed to identify other articles of interest, and experts were contacted about missing or unpublished studies. Of 127 studies reviewed, 46 met inclusion criteria, covering seven clinical conditions. Two investigators independently reviewed each article using a standardized form to abstract information on key study characteristics and results.

RESULTS: Overall, 29 of the studies (63%) reported a statistically significant association between higher admission volume and improved outcomes. The magnitude of the association (mortality OR between the lowest vs highest stratum of volume centers), as well as the thresholds used to characterize high volume, varied across clinical conditions. Critically ill patients with cardiovascular (n = 7, OR = 1.49 [1.11-2.00]), respiratory (n = 12, OR = 1.20 [1.04-1.38]), severe sepsis (n = 4, OR = 1.17 [1.03-1.33]), hepato-GI (n = 3, OR = 1.30 [1.08-1.78]), neurologic (n = 3, OR = 1.38 [1.22-1.57]), and postoperative admission diagnoses (n = 3, OR = 2.95 [1.05-8.30]) were more likely to benefit from admission to higher-volume centers compared with lower-volume centers. Studies that controlled for ICU or hospital organizational factors were less likely to find a significant volume-outcome relationship than studies that did not control for these factors.

CONCLUSIONS: Critically ill patients generally benefit from care in high-volume centers, with more substantial benefits in selected high-risk conditions. This relationship may in part be mediated by specific ICU and hospital organizational factors. CHEST 2015; 148(1):79-92

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Volume-outcome relationships are well established in many surgical conditions and high-risk procedures in health care.[1] Under these relationships, higher numbers of procedures are thought to lead to better patient outcomes through the development of procedural skill.[2] Such observations lend conceptual support to the development of regionalized systems of surgical care, in which patients are selectively referred to high-volume providers.[3] Selective referral has substantially improved the quality of care for patients in need of these planned high-risk procedures, with improved outcomes over time due in large part to concentration of care.[2]

Given the current shortage of ICU physicians and the overall complexity of critical illness, critical care is also an attractive target for regionalization. However, unlike in many surgical conditions, the volume-outcome relationship in critical illness is still incompletely characterized.[4] In the absence of a well-defined volume-outcome relationship, regionalization of critical care may increase costs while delaying definitive therapy for extremely sick patients in need of rapid diagnosis and treatment. Moreover, regionalization is only one potential strategy for region-wide organization of critical care.[5] Without a greater understanding of the mechanism of the volume-outcome relationship, which may in part be determined by organizational factors that are correlated with volume, we may miss out on opportunities to improve outcomes for small-volume providers without large-scale reorganization of care.

The goal of this study was to perform a systematic review of literature to assess the volume-outcome relationship among critically ill adult patients. In addition to providing summary information, we sought to understand organizational factors that may be potential mechanisms for this effect by analyzing the differences between positive and negative studies.

Materials and Methods

We performed a systematic review of research studies examining the volume-outcome relationship in critical care. The complete review protocol was submitted to the PROSPERO registry of systematic reviews (CRD42011001265) prior to beginning the study search, study review, data extraction, and analyses.

Study Selection Criteria

Eligible studies were observational studies that assessed the association between critically ill admissions volume (at either the level of the hospital, ICU, ED, or physician) and patient mortality (within the ICU, hospital, or a fixed time period after admission). All observational studies including registries and retrospective observational analyses of existing clinical or administrative databases were eligible. We excluded studies on volume and outcome in trauma, neonatal critical care, and pediatric critical care as these service lines are already extensively regionalized. We also excluded studies when we either could not determine the proportion of patients who were admitted to an ICU or the proportion of patients in the ICU was $<$ 50%.

Search Methods

To identify candidate studies we searched MEDLINE and EMBASE for English-language articles published between January 1, 2001, and April 30, 2014. Our search algorithm included medical subject heading terms and text words for both critical illness and clinical conditions that are likely to result in critical illness (e-Appendix 1, e-Table 1). All searches were combined in a reference manager database (Resyweb). When articles separately analyzed distinct clinical conditions, we analyzed the data of each condition separately, treating the data as separate studies. We excluded studies published before 2001 because the practice of critical care and critical care outcomes has changed considerably since that time.[6,7] We also searched several other sources: we reviewed the reference lists of selected studies, we contacted experts in the field to identify missed or unpublished studies, and we performed a manual examination of abstracts books from the main international meetings of critical care medicine (International Symposium on Intensive Care and Emergency Medicine, European Society Intensive Care Medicine Meeting, Society of Critical Care Medicine) between 2007 and 2014 to locate additional relevant titles. For studies published in abstract form, the primary author was contacted to identify manuscripts in progress.

Study Selection, Data Collection, and Analyses

Identifying Studies: All retrieved records and reports were assessed independently by two authors. First, titles and abstracts were screened to identify obvious exclusions (ie, records that were found by our electronic searches but were clearly irrelevant to this review). Second, full-text reports were retrieved to determine whether they met the selection criteria. Any disagreements were resolved through discussion.

Data Extraction: Data extraction was performed independently by two authors using a prespecified data extraction form. Information extracted included the following: study characteristics (study design, period, and setting); patient characteristics (inclusion and exclusion criteria); definition of volume (unit of measurement, continuous or categorical variable and, if categorical, thresholds); outcomes (mortality in the ED, ICU, hospital, or at a fixed time point, ICU, and hospital lengths of stay); statistical methods (multivariable modeling technique, adjustment for cluster effect, and list of adjustment variables); and structural characteristics of the ICU, hospital, and health system. We collected the effect size quantifying the strength of the association between volume and mortality. We collected all available estimates, regardless of the unit of measurement for volume, the method of operationalizing volume, the end point, and the type of statistical analysis, that is, according to the measurement unit of volume (at the hospital, unit, or care provider level), to the definition of the volume variable (continuous or categorical), to the end point (intensive care, in-hospital, or 30-day mortality), and according to the analysis (raw or adjusted estimates). For each study, two authors evaluated independently the risk of bias using a modification of a previously published approach to effectiveness reviews.[8] This scale included attributes of risk adjustment, adjustment for correlated data, and adjustment for temporal trends.

Data Analysis

First, among selected studies, we checked the data used to exclude in the final analysis results from subpopulation of studies already included. For the synthesis, we initially planned to primarily focus on the volume treated as a continuous variable. However, the most frequently reported measure of the volume-outcome effect was the OR of death in patients treated in a low-volume center compared with patients treated in a high-volume center, so that an OR $>$ 1 would indicate increased risk in low-volume compared with high-volume center. Because of considerable variability in the numbers of categories used (defined according to tertiles, quartiles, or quintiles) and in the thresholds used to define these categories, we focused on the effect comparing the lowest volume group with the highest volume group. For the synthesis, we used the adjusted ORs based on the multivariate model used in each study.

Separate meta-analyses were performed to combine the study estimates for each of the presenting problems in critical illness (respiratory, cardiovascular, neurologic, hepato-GI or renal diagnosis, sepsis, postoperative conditions, or any indications). Studies that lacked sufficient data to calculate an OR were excluded from the meta-analyses. Their results were analyzed qualitatively and are reported separately. Because some studies published in 2001 and later contained data from earlier time periods, we performed a sensitivity analysis in which we excluded all studies containing data earlier than 2001.

Higgins' I^2 statistics and between-study variance τ^2 were calculated to assess the amount of heterogeneity across studies. The effect sizes were combined using a random-effects meta-analysis model because we expected a substantial heterogeneity due to diversity of design across studies. All reported *P* values were two-sided. Analyses were performed using Stata statistical software release 11 (StataCorp LP).

To assess potential mechanisms underlying the volume-outcome effect, we used a conceptual framework in which the ICU volume-outcome relationship could be attributed to three factors: acquisition of clinical skill at high-volume centers ("practice-makes-perfect"), selective referral to high-volume centers, and the presence of specific organizational factors that are associated with outcome and may be more common at high-volume centers.[9] This last category includes structural factors that might be associated with high volume and high quality. At the ICU level, these might include ICU type,[10] ICU size, ICU level, intensivist physician staffing,[11] nurse-to-bed ratio,[12] and intensivist-to-bed ratio. At the hospital level, these might include geographic position, hospital size, teaching status,[13] technology capacity, trauma center designation,[14] hospital, and ED level. This third factor is analogous to unmeasured confounding, since to the degree that these factors mediate the volume-outcome relationship, controlling for them would attenuate the observed effect. Therefore, to determine the role of organizational factors as a mechanism for the volume-outcome relationship, we qualitatively compared studies that did and did not control for these factors. To the degree that the results of volume-outcome studies depend on controlling for these factors, the volume-outcome relationship may be due to correlation between high-volume and ICU organizational best practices. To the degree that the results of volume-outcome studies do not depend on controlling for these factors, the volume-outcome relationship may be due to clinical skill and selective referral.

Results

Of 6,037 potentially relevant references, we reviewed 127 publications fulfilling our search criteria, of which 42 references (33%) met all criteria for inclusion (Fig 1).

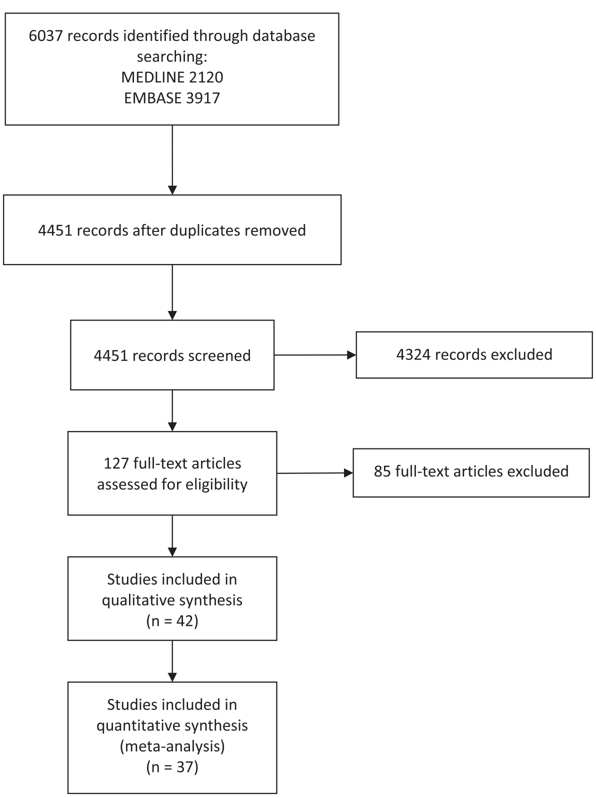

Figure 1 – *Flow diagram of study selection. The main reasons for exclusion of full-text articles were absence of details regarding ICU or hospital mortality or majority of population not including critically ill patients.*

One study reported three different patient subsets and was analyzed as three distinct studies.[15] One study reported two different patient subsets and was analyzed as two distinct studies.[16] One study reported the volume-outcome relationship in two different health-care systems; we analyzed the data as two different studies.[17] We did not retrieve any reference from abstract books of the main international meetings of critical care medicine. This resulted in 46 distinct studies for analysis.

Study Characteristics

General study characteristics are shown in Table 1.[18-56] The majority of included studies were from North America (n = 25, 54%) and included data after 2001 (n = 35, 76%). Three studies included all ICU admissions.[16,18,19] Seven clinical conditions were covered: respiratory diagnoses including mechanical ventilation, acute respiratory failure, and pneumonia (13 studies)[15,16,20-30]; cardiovascular diagnoses including cardiac arrest and cardiogenic shock (eight studies)[31-38]; sepsis (six studies)[39-44]; neurologic diagnoses (three studies)[15,45,46]; hepato-GI diagnoses (three studies)[15,47,48]; renal diagnoses (three studies)[17,49]; and postoperative conditions including pancreatectomy, hepatectomy, esophagectomy, major vascular surgery (seven studies).[50-56] The majority of studies (n = 24, 52%) used clinical databases rather than administrative databases. The most common unit of analysis used was hospital volume (n = 25, 54%), followed by ICU volume (n = 14, 30%), ED volume (n = 4, 9%), and then intensivist volume (n = 1, 2%). The threshold used to differentiate low-volume and

TABLE 1] General Characteristics of Included Studies

Study/Year	Population	Country	Study Period	Type of Database	Unit of Analysis	Centers	Patients	Outcomes
Ananthakrishnan et al[48]/2008	Medical (acute liver failure) and surgical (liver transplant)	USA	2001-2004	Administrative	Hospital	Unknown	25,907	In-hospital mortality
Callaway et al[31]/2010	Medical (cardiac arrest)	USA and Canada	2005-2007	Clinical	Hospital	254	4,087	In-hospital mortality
Carr et al[32]/2009	Medical (cardiac arrest)	USA	2002-2005	Clinical	Hospital	39	4,674	In-hospital mortality
Chen et al[33]/2003	Medical (intraaortic balloon pump)	USA	1994-1998	Clinical	Hospital	750	12,730	In-hospital mortality
Cha et al[34]/2012	Medical (cardiac arrest)	South Korea	2006-2008	Administrative	ED	679	27,662	In-hospital mortality
Cooke et al[20]/2012	Medical (mechanical ventilation)	USA	2009	Administrative	Hospital	119	5,131	30-d mortality
Cross et al[45]/2003	Medical and surgical (subarachnoid hemorrhage)	USA	1998-2000	Administrative	Hospital	1,546	16,399	In-hospital mortality
Cudnik et al[35]/2012	Medical (cardiac arrest)	USA	2009	Clinical	Hospital	155	4,125	In-hospital mortality
Darmon et al[21]/2011	Medical (mechanical ventilation)	France	2004-2005	Administrative	Hospital	294	179,197	In-hospital mortality
Dimick et al[51]/2002	Surgical (hepatic resection)	USA	1994-1998	Clinical	Hospital	52	569	In-hospital mortality
Dimick et al[50]/2003	Surgical (esophageal resection)	USA	1994-1998	Administrative	Hospital and surgeon	35	366	In-hospital mortality
Durairaj et al[15]/2005	Medical (respiratory)	USA	1991-1997	Clinical	Hospital	29	16,949	In-hospital mortality
Durairaj et al[15]/2005	Medical (neurologic)	USA	1991-1997	Clinical	Hospital	29	13,805	In-hospital mortality
Durairaj et al[15]/2005	Medical (GI)	USA	1991-1997	Clinical	Hospital	29	12,881	In-hospital mortality
Giles et al[52]/2009	Surgical (ruptured aortic abdominal aneurysm)	USA	2000-2005	Administrative	Hospital	Unknown	28,429	In-hospital mortality
Glance et al[18]/2006	Medical and surgical	USA	2001-2003	Clinical	ICU	92	70,757	In-hospital mortality

(Continued)

TABLE 1] *(continued)*

Study/Year	Population	Country	Study Period	Type of Database	Unit of Analysis	Centers	Patients	Outcomes
Gopal et al[22]/2011	Medical (mechanical ventilation)	England	1996-2006	Clinical	Hospital	12	17,132	ICU mortality
Joseph et al[53]/2009	Surgical (pancreatic resection)	USA	2005	Administrative	Hospital	434	Unknown	Perioperative death
Kahn et al[23]/2006	Medical (mechanical ventilation)	USA	2002-2003	Clinical	Hospital	37	20,241	In-hospital mortality/ ICU mortality
Kahn et al[24]/2009	Medical (mechanical ventilation)	USA	2004-2006	Administrative	Hospital	169	30,677	30-d mortality
Knipp et al[54]/2007	Surgical (aortic dissection)	USA	1995-2003	Administrative	Hospital	Unknown	3,013	In-hospital mortality
Kuo et al[55]/2001	Surgical (esophageal resection)	USA	1992-1999	Administrative	Hospital	64	1,193	In-hospital mortality
Lecuyer et al[25]/2008	Medical (acute respiratory failure)	France	1997-2004	Clinical	ICU	28	1,753	ICU mortality
Lin et al[26]/2008	Medical (pneumonia)	Taiwan	2002-2004	Administrative	Physician	Unknown	87,479	30-d mortality
Macomber et al[56]/2012	Liver transplantation	USA	2009-2010	Administrative	Hospital	63	5,130	In-hospital mortality
Metnitz et al[19]/2009	Medical and surgical	Austria	1998-2005	Clinical	ICU	40	83,259	In-hospital mortality
Moran et al[28]/2008	Medical and surgical (mechanical ventilation)	Australia and New Zealand	1995-2009	Clinical	ICU	136	208,810	In-hospital mortality
Needham et al[27]/2006	Medical and surgical (mechanical ventilation)	Canada	1998-2000	Administrative	Hospital	95 (surgical); 126 (medical)	20,219	30-d mortality
Nguyen et al[17]/2011	Medical (renal failure)	France	1997-2004	Clinical	ICU	32	9,449	In-hospital mortality
Nguyen et al[17]/2011	Medical (renal failure)	USA	1997-2004	Clinical	ICU	76	3,498	In-hospital mortality

(Continued)

TABLE 1] *(continued)*

Study/Year	Population	Country	Study Period	Type of Database	Unit of Analysis	Centers	Patients	Outcomes
Nuño et al[46]/2012	Medical and surgical (subarachnoid hemorrhage)	USA	2002-2007	Administrative	Hospital	Unknown	47,114	In-hospital mortality
Peelen et al[40]/2007	Medical (sepsis)	The Netherlands	2003-2005	Clinical	ICU	28	4,605	In-hospital mortality
Powell et al[39]/2010	Medical (sepsis)	USA	2007	Administrative	ED	551	87,166	In-hospital mortality and early hospital mortality
Shahin et al[41]/2012	Medical (sepsis)	UK	2008-2009	Clinical	ICU	170	30,727	In-hospital mortality
Shin et al[36]/2011	Medical (cardiac arrest)	South Korea	2006-2007	Clinical	ED	410	20,457	Survival to admission
Stub et al[37]/2011	Medical (cardiac arrest)	Australia	2003-2010	Clinical	Hospital	70	2,706	In-hospital mortality
Ro et al[38]/2012	Medical (cardiac arrest)	South Korea	2006-2008	Clinical	ED	410	10,425	Survival to admission and in-hospital mortality
Vaara et al[49]/2012	Medical (renal failure)	Finland	2007-2008	Administrative	ICU	23	1,558	In-hospital mortality
Zuber et al[42]/2012	Medical and surgical (sepsis)	France	1997-2008	Clinical	ICU	41	3,437	In-hospital mortality
Banta et al[43]/2012	Medical and surgical (sepsis)	USA	2005-2010	Administrative	Hospital	Unknown	1,213,219	In-hospital mortality
Shen et al[47]/2012	Medical (acute pancreatitis)	Taiwan	2000-2009	Administrative	Hospital	806	22,551	In-hospital mortality
Dres et al[29]/2013	Medical (acute respiratory failure)	France	1998-2001	Clinical	ICU	31	14,440	In-hospital mortality, ICU mortality

(Continued)

TABLE 1] *(continued)*

Study/Year	Population	Country	Study Period	Type of Database	Unit of Analysis	Centers	Patients	Outcomes
Fernández et al[16]/2013	Medical and surgical	Spain	2008	Clinical	ICU	29	4,001	In-hospital mortality
Fernández et al[16]/2013	Medical and surgical (mechanical ventilation)	Spain	2008	Clinical	ICU	29	1,923	In-hospital mortality
Shahin et al[30]/2014	Medical and surgical (mechanical ventilation)	UK	2008-2010	Administrative	ICU	193	104,844	In-hospital mortality
Walkey and Wiener[44]/2014	Medical and surgical (sepsis)	USA	2011	Clinical	ICU	124	56,997	Hospital mortality index

UK = United Kingdom; USA = United States of America.

high-volume institutions varied greatly within and across clinical conditions. For 38 studies (83%), the primary outcome was hospital mortality, followed by 30-day mortality (n = 4, 9%), ICU mortality (n = 4, 8%), survival to admission from the ED (n = 2, 4%), perioperative death (n = 1, 2%), and early hospital mortality (n = 1, 2%). Only 10 studies (21%) reported ICU or hospital lengths of stay as secondary outcomes.

Summary of Findings of Included Studies

Figure 2 shows the meta-analyses of adjusted ORs comparing the lowest-volume group with the highest-volume group in seven conditions separately. Eight studies could not be included in the final analyses because they had insufficient data to calculate OR.[19,21,41,44,51,53,54,56] The results of these studies are presented in Table 2. Among the remaining studies (n = 37), the consistency of the relationship varied considerably across diagnoses. All studies including patients with sepsis (n = 4) or patients with postoperative diagnosis (n = 3) found a positive association between volume and outcome. In studies looking at the subset of patients with respiratory (n = 7), cardiovascular (n = 4), hepato-GI (n = 2), and neurologic (n = 2) diagnoses, there was on average a positive association between higher volume and better outcomes. However, there was substantial heterogeneity, especially in subsets of patients with respiratory, cardiovascular, sepsis, and postoperative diagnoses (I^2 = 97.4%, 88.3%, 98%, 92.2% respectively). Conversely, in studies looking at a subset of patients with renal diagnosis (n = 3), the meta-analyses did not demonstrate a significant association and there was also considerable between-trial heterogeneity (I^2 = 50%). One study in patients with respiratory diagnoses documented a statistically significant association between higher volume and poorer outcomes.[28]

Between categories of medical conditions (respiratory, cardiovascular, neurologic, liver-GI, postoperative, and sepsis) high-volume to low-volume thresholds varied greatly. For respiratory diagnoses, the highest volume quartile > 699 showed a nonsignificant relationship between volume and outcome, whereas studies on cardiac arrest with 50 cases per year were more likely to show a significant relationship.

The highest absolute hospital mortality differences between high-volume and low-volume institutions were found for hematologic patients with acute respiratory failure (36%), cardiac arrest (22%), cardiogenic shock and intraaortic balloon pump (14.8%), endovascular repair of ruptured abdominal aortic aneurysm (22%),

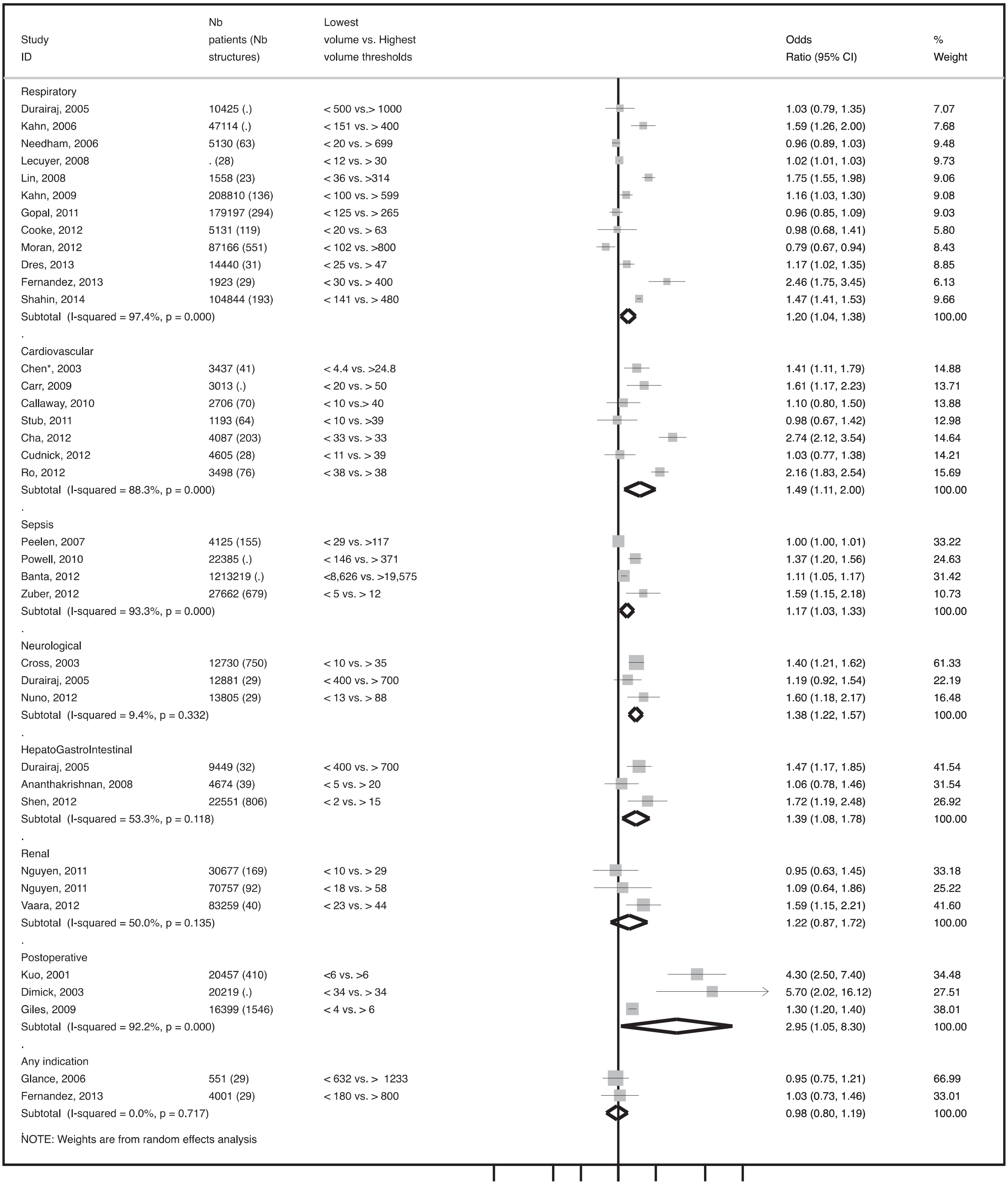

Figure 2 – *Forrest plots of comparisons between lowest and highest volume institutions for seven clinical conditions. Nb = number.*

and postesophagectomy (12.9%). These diagnoses shared the characteristic of being associated with the highest mortality rates within their diagnosis category.

Sensitivity Analysis

Figure 3 shows the meta-analyses of adjusted ORs comparing the lowest-volume group with the highest-volume group in seven conditions, after exclusion of

TABLE 2] Summary of Studies Not Included in the Meta-analysis

Clinical Condition	Positive Association	No Association
Respiratory	Darmon et al[21]/2011	...
Sepsis	Walkey and Wiener[44]/2014	Shahin et al[41]/2012
Neurologic	...	...
Hepato-GI	...	...
Renal	...	...
Postoperative	Dimick et al[51]/2002	Joseph et al[53]/2009
	Knipp et al[54]/2007	...
	Macomber et al[56]/2012	...
Any indication	Metnitz et al[19]/2009	...

eight studies with the majority of data from before 2001 (studies of Durairaj et al,[15] Needham et al,[27] Chen et al,[33] Cross et al,[45] Dimick et al,[50] Kuo et al[55]). The volume-outcome association remained unchanged after exclusion of these studies.

Relationship Between Organizational Factors and Primary Study Results: Eighteen studies (39%) did not adjust their results to any ICU or hospital-level factor (Table 3). Studies that did not find a statistically significant association between higher patient volume and better outcomes were more likely to have adjusted their results for ICU-level factors (such as ICU type, ICU level, intensivist staffing model, nurse-to-bed ratio) and hospital-level factors (such as geographical position, teaching status, technological capacity, trauma center designation, or hospital level), compared with studies that did find a statistically significant association (Table 3).

All studies performed some risk adjustment (Table 4). Two studies (4%) used risk adjustment based on administrative data alone, 15 (33%) used risk adjustment based on a combination of administrative and some clinical data, and 30 (65%) used risk adjustment based on clinical models with historically good calibration and discrimination. Most adjusted for demographic characteristics such as age (n = 45, 98%) and sex (n = 36, 78%). Around one-half of studies (n = 22, 48%) adjusted for patient comorbidities; 34 studies (74%) adjusted for severity of illness using a physiologic measure. Eighteen (39%) adjusted for admission source. Thirteen (28%) adjusted for the diagnosis at admission. Other patient adjustments included insurance status (n = 5, 11%), race (n = 7, 15%), functional status (n = 2, 4%), ICU pre-length of stay (n = 3, 7%), life support measures (n = 6, 13%), the type of malignancy (n = 2, 4%), and the known prognostic for cardiac arrest (n = 6, 13%).

Discussion

We evaluated 40 studies on the volume-outcome relationship in broadly defined critically ill patients. The majority of studies found that patients admitted in high-volume structures had better outcomes, although the consistency and magnitude of the relationship, as well as the thresholds used to differentiate low-volume and high-volume centers, varied across clinical conditions. Studies showing no volume-outcome relationship were more likely to have adjusted their results for key ICU or hospital-level organizational factors.

Our results extend those of a prior systematic review in two ways.[4] First, we include many more studies (46 vs 13, several of which were published recently). Second, we specifically examine the characteristics of positive vs negative studies, providing new insight into the potential mechanism of the volume-outcome relationship not addressed in the prior review.

Within diagnosis categories, those with the highest risk of death are most likely to benefit from admission to a high-volume center. This variation of the volume-outcome relationship may be related to the complexity of diagnosis and management in these conditions. Durairaj et al[15] found that in comparison with a nonselected population of patients who were mechanically ventilated, only the most severe (ie, with an APACHE [Acute Physiology and Chronic Health Evaluation] III score > 57) benefited from high-volume hospitals. Glance et al[18] showed that only critically ill patients with a Simplified Acute Physiology Score (SAPS) 2 ≥ 30 benefited from a high-volume center. Darmon et al[21] found that in comparison with patients with ARDS who were mechanically ventilated, those with toxic coma did not benefit from mechanical ventilation admissions volume. Lecuyer et al[25] and Zuber et al[42] both looked at the subset of hematologic patients with acute respiratory failure or severe sepsis, finding large benefits from high-volume ICUs (OR = 0.63 [0.46-0.87]).

Only one study documented a statistically significant association between higher volume and worse outcomes.[28] The underlying reason for this result may be related to either the total workload or overall capacity strain in high-volume centers, which may be related to poor outcomes.[57] For one clinical condition category (patients undergoing renal support therapy), we were not able to find any association between volume and outcome.[17] Among the plausible explanations

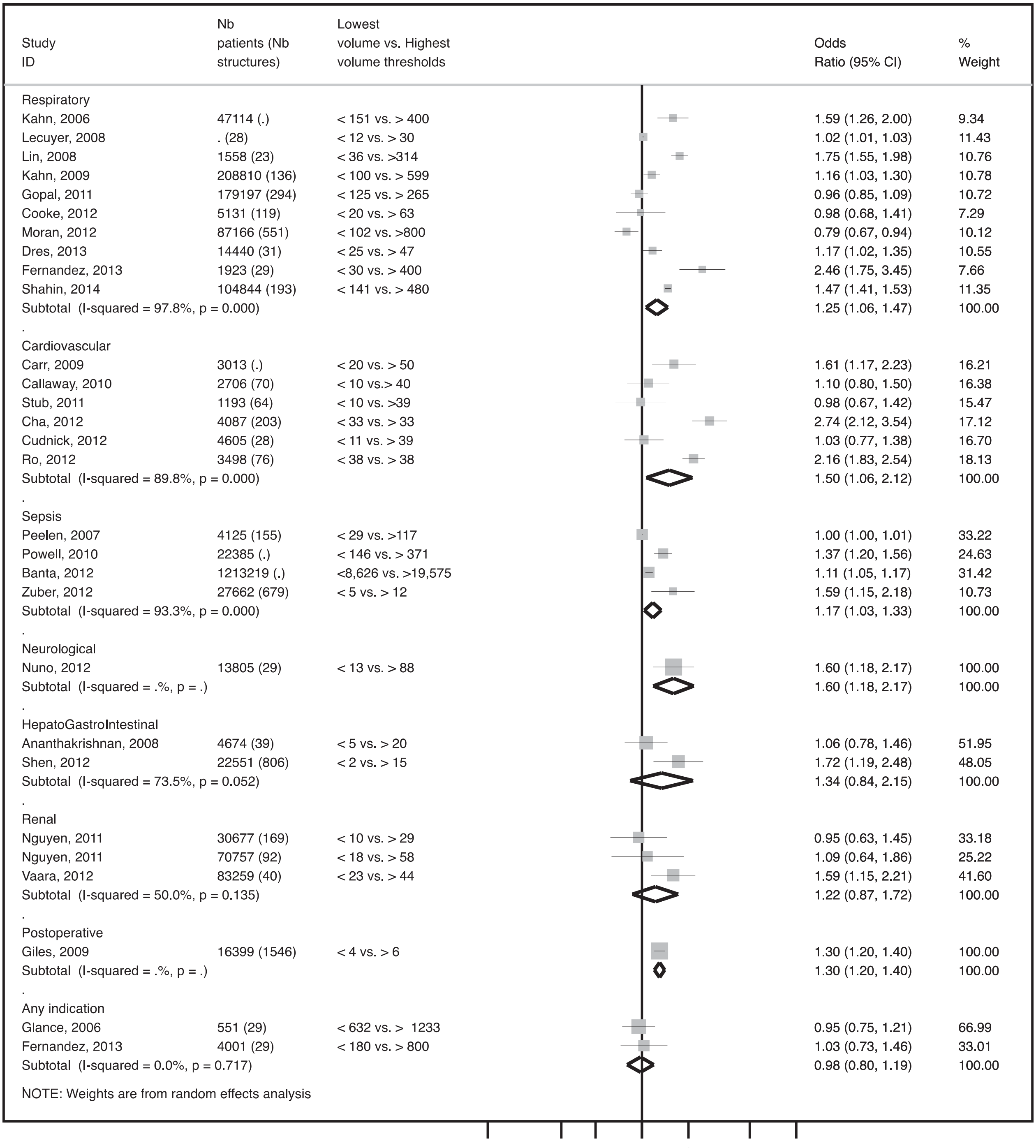

Figure 3 – *Sensitivity analysis: Forrest plots of comparisons between lowest and highest volume institutions for seven clinical conditions after exclusion of studies with data older than 2001. See Figure 2 legend for expansion of abbreviation.*

may be use of patients receiving dialysis as the unit of measurement (rather than the number of dialysis sessions performed, which may be more directly related to clinical experience) or the lack of inclusion of other relevant outcomes besides mortality (ie, renal function recovery). Additionally, renal support therapy is guided by an uncertain evidence base with regard to timing, the use continuous vs intermittent dialysis, and the dose of dialysis. Thus, clinical experience may not translate into higher outcomes for this condition.

We observed large differences among the thresholds used to differentiate low-volume and high-volume

TABLE 3] Relationship Between Methodologic Characteristics, ICU, and Hospital-Level Confounders and Primary Study Results

Study Characteristics	Positive Studies (n = 29, 63%)	Negative Studies (n = 17, 37%)
Unit of volume measure, No. (%)		
Hospital	15 (58)	11 (42)
ICU	8 (57)	6 (43)
ED	2 (100)	0 (0)
Intensivist	4 (100)	0 (0)
Sample size, No. (%)		
< 10,000	9 (53)	8 (47)
10,000-50,000	14 (70)	6 (30)
> 50,000	6 (75)	2 (25)
Unknown	...	1 (100)
Location, No. (%)		
North America	15 (58)	11 (42)
Europe	9 (69)	4 (31)
Other	5 (71)	2 (29)
Risk of adjustment		
Clinical	15 (52)	14 (48)
Administrative data with clinical adjustment	13 (87)	2 (13)
Administrative	1 (50)	1 (50)
ICU-level factors, No. (%)		
ICU type	1 (25)	3 (75)
ICU size	1 (100)	0 (0)
ICU level	0 (0)	1 (100)
Intensivist staffing model	2 (50)	2 (50)
Nurse-to-bed ratio	1 (50)	1 (50)
Intensivist-to-bed ratio	1 (100)	0 (0)
Hospital-level factors, No. (%)		
Hospital size	7 (88)	1 (12)
Teaching status	7 (47)	8 (53)
Technological capacity	2 (40)	3 (60)
Trauma center designation	0 (0)	2 (100)
Hospital level	0 (0)	1 (100)
ED level	2 (100)	0 (0)

ICU level (defined by the US Department of Veterans Affairs national bed control database): level 1 and 2 ICUs are where most subspecialty care and intervention are available. Level 3 and 4 ICUs provide more limited subspecialty care and intervention. Hospital level (defined in the Australian and New Zealand Intensive Care Society database): rural, metropolitan, tertiary, private. ED level (defined by the Korean government): level 1 and 2 are covered by emergency physicians 24/24; level 3 is basically equipped and usually served by general physicians.

centers between and within clinical condition categories. These differences mainly related to the prevalence of the diagnoses, and may be partly explained by variation in ICU bed availability across industrialized countries and the median size of acute care hospitals.[58] Countries with a large number of ICU beds are more likely to have a less restricted ICU admission policy and may admit less severe patients.[59] Our review highlights that the shape of the volume-outcome relationship varies within and across clinical condition categories. Consequently, our results do not support recommendations of minimal ICU volumes for diagnosis categories.

Adjustments for ICU or hospital-level factors seem to be a major determinant of the volume-outcome relationship. Within studies looking at the volume-outcome relationship among postoperative patients admitted in the ICU, those of Joseph et al[53] and Dimick et al[50] were not able to find any association. One explanation might be related to the adjustments of their results to managerial factors known to be associated with better outcomes (such as ICU staffing and the presence of a daily round by an intensivist) or to the technology capacity of their structures (such as the presence of an interventional radiology service). Similarly, the two studies on cardiac arrest that found negative results are those where the authors (Callaway et al[31] and Stub et al[37]) adjusted their results for organizational factors known to be associated with improved outcomes (ie, trauma center, cardiac center, 24-h cardiac interventional services). Again, these results emphasize the idea that the volume affected may be mediated in part by organizational factors that have a major impact on patient outcomes. To the degree that the volume outcome is in part mediated by organizational factors, increasing the size of low-volume centers or systematically transferring patients from low-volume to high-volume centers may not be the most efficient way to improve outcomes. Instead of conjunction, it may be beneficial to "export" organizational best practices to small-volume ICUs to improve their quality without systematically transferring patients.

Our study has several limitations. First, our systematic review may suffer from publication bias. Due to public health implications, studies showing no volume-outcome relationship might have more difficulties being published. Second, the majority of studies did not adjust their results to organizational factors and none directly adjusted for processes of care used. Thus, we had only a limited ability to assess for the mechanism of the volume-outcome relationship. Third, all studies used mortality as the primary outcome, though other patient outcomes

TABLE 4] Quality of Included Studies

Study/Year	Attributes of Risk Adjustment	Adjustment for Correlated Data	Adjustment for Temporal Trends[a]
Ananthakrishnan et al[48]/2008	Clinical	No	No
Callaway et al[31]/2010	Clinical	No	No
Carr et al[32]/2009	Clinical	Yes	No
Chen et al[33]/2003	Clinical	No	No
Cha et al[34]/2012	Administrative with clinical risk adjustment	Yes	No
Cooke et al[20]/2012	Administrative with clinical risk adjustment	Yes	...
Cross et al[45]/2003	Administrative with clinical risk adjustment	Yes	Yes
Cudnik et al[35]/2012	Clinical	Yes	...
Darmon et al[21]/2011	Clinical	No	No
Dimick et al[51]/2002	Clinical	Yes	No
Dimick et al[50]/2003	Clinical	No	No
Durairaj et al[15]/2005	Clinical	Yes	No
Durairaj et al[15]/2005	Clinical	Yes	No
Durairaj et al[15]/2005	Clinical	Yes	No
Giles et al[52]/2009	Administrative	No	Yes
Glance et al[18]/2006	Clinical	Yes	No
Gopal et al[22]/2011	Clinical	Yes	Yes
Joseph et al[53]/2009	Administrative	No	...
Kahn et al[23]/2006	Clinical	Yes	...
Kahn et al[24]/2009	Administrative with clinical risk adjustment	Yes	...
Knipp et al[54]/2007	Administrative with clinical risk adjustment	No	No
Kuo et al[55]/2001	Administrative with clinical risk adjustment	Yes	Yes
Lecuyer et al[25]/2008	Clinical	Yes	No
Lin et al[26]/2008	Administrative with clinical risk adjustment	Yes	No
Macomber et al[56]/2012	Administrative with clinical risk adjustment	Yes	Yes
Metnitz et al[19]/2009	Clinical	Yes	Yes
Moran et al[28]/2008	Clinical	Yes	Yes
Needham et al[27]/2006	Administrative with clinical risk adjustment	Yes	No
Nguyen et al[17]/2011	Clinical	Yes	No
Nguyen et al[17]/2011	Clinical	Yes	No
Nuño et al[46]/2012	Administrative with clinical risk adjustment	Yes	No
Peelen et al[40]/2007	Clinical	Yes	No
Powell et al[39]/2010	Administrative with clinical risk adjustment	Yes	...
Shahin et al[41]/2012	Clinical	...	...
Shin et al[36]/2011	Clinical	Yes	...
Stub et al[37]/2011	Clinical	No	No
Ro et al[38]/2012	Clinical	Yes	No
Vaara et al[49]/2012	Administrative with clinical risk adjustment	Yes	...
Zuber et al[42]/2012	Clinical	No	Yes
Banta et al[43]/2012	Administrative with clinical risk adjustment	Yes	Yes
Shen et al[47]/2012	Administrative with clinical risk adjustment	Yes	No
Dres et al[29]/2013	Clinical	Yes	Yes
Fernández et al[16]/2013	Clinical	Yes	...

(Continued)

TABLE 4] *(continued)*

Study/Year	Attributes of Risk Adjustment	Adjustment for Correlated Data	Adjustment for Temporal Trends[a]
Fernández et al[16]/2013	Clinical	Yes	...
Shahin et al[30]/2014	Administrative with clinical risk adjustment	Yes	...
Walkey and Wiener[44]/2014	Clinical	Yes	...

[a]For studies longer than 2 y.

such as discharge location, quality of life, and cognitive status are also patient-centered and outcomes of interest. Fourth, due to variation in the way that studies categorized volume and the lack of studies looking precisely at the volume-outcome relationship as a continuous variable, we could not directly assess for a "dose-response" effect. Fifth, our study may suffer from reporting bias. We may have excluded studies from critical care surgical literature that do not explicitly report ICU use.

In summary, critically ill patients appear to benefit from care in high-volume hospitals, though there is not complete consistency in this relationship. Variability may be partly explained by case mix, diagnosis complexity, and the type of adjustments. Our results highlight the major role of organizational factors on patient outcomes and that specific management and care practices may allow low-volume centers to provide a high quality of care.

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Additional information: The e-Appendix and e-Table can be found in the Supplemental Materials section of the online article.

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