The Volume-Outcome Relationship in Critical Care

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The volume-outcome relationship in critical care:

a systematic review and meta-analysis

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Abbreviations list: volume, outcome, systematic review, critical care

Purpose: To systematically review the research on volume and outcome relationships in critical care.

Data sources: MEDLINE and EMBASE from January 1st 2001 to April 30th 2014 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 Bibliographies were reviewed to identify other articles of interest and experts were contacted about missing or unpublished studies.

Study selections: Of 127 studies reviewed, 46 met inclusion criteria, covering 7 clinical conditions.

Data extraction: Two investigators independently reviewed each article using a standardized form to abstract information on key study characteristics and results.

Data synthesis: Overall, 29 (63%) of studies reported a statistically significant association between higher admission volume and improved outcomes. The magnitude of the association (mortality odds ratio (OR) between lowest versus 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-gastro-intestinal (n=3, OR=1.30 [1.08-1.78]), neurological (n=3, OR=1.38 [1.22-1.57]) and post-operative admission diagnoses (n=3, OR=2.95 [1.05-8.30]) were more likely to benefit from admission to a higher volume centers compared to lower volume centers. Studies that controlled for ICU or hospital organizational factors were less likely to find a significant volume-outcome relationship then 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.

Clinical trial registration: PROSPERO registry of systematic reviews (registration number: CRD42011001265)

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 (4).

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 (5). 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 (6). 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.

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 which assessed the association between critically ill admissions volume (at either the level of the hospital, intensive care unit (ICU), emergency department (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 ICU patients was less than 50%.

Search methods

To identify candidate studies we searched MEDLINE and EMBASE for English-language articles published between January 1st, 2001 and April 30th 2014. Our search algorithm included medical subject heading (MeSH) terms and text words for both critical illness and clinical conditions that are likely to result in critical illness (see supplementary material). 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 have changed considerably since that time (7-8). 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 (i.e. records that were found by our electronic searches but were clearly irrelevant to this review). Second, full-text reports were retrieved to determine if they met the selection criteria. Any disagreements were resolved through discussion.

Data extraction

Data extraction was performed independently by two authors using a pre-specified data extraction form. Information extracted included: 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); 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

endpoint and the type of statistical analysis. i.e., 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 endpoint (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 (9). 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 in order 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 odds ratio of death in patients treated in a low-volume center compared to patients treated in a high-volume center, so that an OR greater than 1 would indicate increased risk in low-volume compared to 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 odds ratios based on the multivariate model used in each study.

Separate meta-analyses were performed to combine the study estimates for each of presenting problems in critical illness (respiratory, cardiovascular, neurological, hepato-gastrointestinal or renal diagnosis, sepsis, post-operative conditions or any indications). Studies which 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 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: 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 attributable 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 (10). 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 (11), ICU size, ICU level , intensivist physician staffing (12), nurse to bed ratio (13) and intensivist to bed ratio. At the hospital level, these might include geographical position, hospital size, teaching status (14), technology capacity, trauma center designation (15), 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 to 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 (Figure 1). One study reported three different patient subsets and was analyzed as three distinct studies (16). One study reported two different patient subsets and was analyzed as two distinct studies (17). One study reported the volume-outcome relationship in two different health care systems; we analyzed the data as two different studies (18). We did not retrieve any reference from abstracts 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. 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 (17, 19-20). Seven clinical conditions were covered: respiratory diagnoses including mechanical ventilation, acute respiratory failure and pneumonia (13 studies) (16-17, 21-31) cardiovascular diagnoses including cardiac arrest and cardiogenic shock (8 studies) (32-39) sepsis (6 studies) (40-45) ; neurological diagnoses (3 studies) (16, 46-47) ; hepatogastrointestinal diagnoses (3 studies) (16, 48-49); renal diagnoses (3 studies) (50-51); and post-operative conditions including pancreatectomy, hepatectomy, esophagectomy, major vascular surgery (7 studies) (52-58). 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 and high volume institutions varied greatly within and across clinical conditions. For 38 studies

(83%) the primary outcome was hospital mortality, followed by 30 days mortality (n=4, 9%), ICU mortality (n=4, 8%), survival to admission from the ED (n=2, 4%), peri-operative 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 odds ratios comparing the lowest volume group with the highest volume group in 7 conditions, separately. Eight studies could not be included in the final analyses because they had insufficient data to calculate odds ratio (22, 42, 45, 53, 55-56, 58-59) . The results of these studies are presented in Table 3. 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 post-operative diagnosis (n=3), found a positive association between volume and outcome. In studies looking at the subset of patients with respiratory diagnosis (n=7), with cardio-vascular diagnosis (n=4), with hepato-gastro-intestinal diagnosis (n=2), with neurological diagnosis (n=2), there was on average a positive association between higher volume and better outcomes. However, there was substantial heterogeneity, especially in subsets of patients respiratory, cardio-vascular, sepsis and with post-operative 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 (29).

Between categories of medical conditions (respiratory, cardio-vascular, neurological, liver-gastro-intestinal, post-operative, sepsis) high to low volume thresholds varied greatly. For respiratory

diagnoses, the highest volume quartile greater than 699 showed non-significant 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 and low volume institutions were found for hematological patients with acute respiratory failure (36%), cardiac arrest (22%), cardiogenic shock and IABP (14.8%), endovascular repair of ruptured abdominal aortic aneurysm (22%) and post-esophagectomy (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 odds ratios comparing the lowest volume group with the highest volume group in 7 conditions, after exclusion of 8 studies with majority of data from before 2001 (studies of Chen et al.; Cross et al.; Durairaj et al.; Kuo et al.; Needham et al.; Dimick et al.) (16, 28, 34, 46, 52, 57). The volume-outcome association remained unchanged after exclusion of these studies.

Relationship between organizational factors and primary study results

Eighteen (39%) studies did not adjust their results to any ICU or hospital level factor (Table 4). 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 to studies that did find a statistically significant association (Table 4).

All studies performed some risk-adjustment (Table 2). 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 gender (n=36, 78%). Around half of studies (n=22, 48%) adjusted for patient co-morbidities, 34 studies (74%) adjusted for severity of illness using a physiological 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 LOS (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 forty 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 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 (5). 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. found that in comparison to a non-selected population of mechanically ventilated patients, only the most severe

(i.e. with an APACHE III score>57) benefited from high volume hospitals (16). Glance et al. showed that only critically ill patients with a SAPS 2 equal or greater than 30 benefited from a high volume center (19). Darmon et al. found, that in comparison to mechanically ventilated patients with from acute respiratory distress syndrome, those with toxic coma did not benefit from mechanical ventilation admissions volume (22). Lecuyer et al. and Zuber et al. both looked at the subset of haematological patients with acute respiratory failure or severe sepsis, finding large benefits from high volume ICUs (OR= 0.63 [0.46-0.87]) (26, 43).

Only one study documented a statistically significant association between higher volume and worse outcomes (29). 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 (60). For one clinical condition category (patients undergoing renal support therapy), we were not able to find any association between volume and outcome (18, 50). Among the plausible explanations 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 (i.e. renal function recovery). Additionally, renal support therapy is guided by an uncertain evidence base with regard to timing, the use continuous versus 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 and high volume centers between and within clinical condition categories. These differences mainly related to the prevalence of the diagnoses, may be partly explained by variation in ICU bed availability across industrialized countries and the median size of acute care hospitals (61). 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 (62). 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 post-operative patients admitted in the ICU, those of Joseph et al. and Dimick were not able to find any association (52, 56). 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 (Stub et al. and Callaway et al.) adjusted their results for organizational factors known to be associated with improved outcomes (i.e. trauma center, cardiac center, 24h cardiac interventional services) (32, 38). Again, these results emphasize the idea that the volume effected 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 to high volume centers may not be the most efficient way to improve outcomes. Instead conjunction, it may be beneficial to “export” organizational best-practices to small volume ICUs in order 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 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 high quality of care.

Authors's contributions:

Drafting the manuscript: YLN, DJW

Statistical analyses: YLN, DJW, YY, LT, JB

Critical revision of the manuscript for important intellectual content: YLN, DJW, YY, LT, DCA, PR, JMK, BG

All Authors read and approved the final manuscript

BG is the guarantor of the entire manuscript.

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Table 1: General characteristics of included studies

Table 2: Quality of included studies

Table 3: Summary of studies not included in the meta-analysis

Table 4: Relationship between methodological characteristics, intensive care unit and hospital-level confounders and primary study results

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.

Figure 2: Forrest plots of comparisons between lowest and highest volume institutions for 7 clinical conditions

Figure 3: Sensitivity analysis: Forrest plots of comparisons between lowest and highest volume institutions for 7 clinical conditions after exclusion of studies with data older than 2001