Caseload as a factor for outcome in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis

A systematic review

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Object. Increasing evidence exists that treatment of complex medical conditions in high-volume centers is found to improve outcome. Patients with subarachnoid hemorrhage (SAH), a complex disease, probably also benefit from treatment at a high-volume center. The authors aimed to determine, based on published literature, whether a higher hospital caseload is associated with improved outcomes of patients undergoing treatment after aneurysmal subarachnoid hemorrhage.

Methods. The authors identified studies from MEDLINE, Embase, and the Cochrane Library up to September 28, 2012, that evaluated outcome in high-volume versus low-volume centers in patients with SAH who were treated by either clipping or endovascular coiling. No language restrictions were set. The compared outcome measure was in-hospital mortality. Mortality in studies was pooled in a random effects meta-analysis. Study quality was reported according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria.

Results. Four articles were included in this analysis, representing 36,600 patients. The quality of studies was graded low in 3 and very low in 1. Meta-analysis using a random effects model showed a decrease in hospital mortality (OR 0.77 [95% CI 0.60–0.97]; $p = 0.00$; $I^2 = 91\%$) in high-volume hospitals treating SAH patients. Sensitivity analysis revealed the relative weight of the 1 low-quality study. Removal of the study with very low quality increased the effect size of the meta-analysis to an OR of 0.68 (95% CI 0.56–0.84; $p = 0.00$; $I^2 = 86\%$). The definition of hospital volume differed among studies. Cutoffs and dichotomizations were used as well as division in quartiles. In 1 study, low volume was defined as 9 or fewer patients yearly, whereas in another it was defined as fewer than 30 patients yearly. Similarly, 1 study defined high volume as more than 20 patients annually, and another defined it as more than 50 patients a year. For comparability between studies, recalculation was done with dichotomized data if available. Cross et al., 2003 (low volume ≤ 18 , high volume ≥ 19) and Johnston, 2000 (low volume ≤ 31 , high volume ≥ 32) provided core data for recalculation. The overall results of this analysis revealed an OR of 0.85 (95% CI 0.72–0.99; $p = 0.00$; $I^2 = 87\%$).

Conclusions. Despite the shortcomings of this study, the mortality rate was lower in hospitals with a larger caseload. Limitations of the meta-analysis are the not uniform cutoff values and uncertainty about case mix. (<http://thejns.org/doi/abs/10.3171/2013.9.JNS13640>)

KEY WORDS • meta-analysis • subarachnoid hemorrhage •
intracranial aneurysm • caseload • hospital volume • vascular disorders

CASELOAD in relation to outcome has been a topic of an increasing number of publications in the medical literature. Hospital volume and outcome are generally more strongly associated for medical conditions that require more complex management.^{15,35} Regulations for centralization of specialized care are emerging from the medical field, government, and health insurance companies. For treatment of patients with ruptured cerebral

aneurysms, a complex disease, several studies with contrasting results have appeared.^{6,7,16} The purpose of this study was to perform a meta-analysis to investigate the relationship between caseload and outcome in series of patients undergoing treatment of aneurysms after subarachnoid hemorrhage (SAH). The treatment modality could be either clipping or coiling. Hospital mortality was chosen as the outcome measure.

Abbreviations used in this paper: GRADE = Grading of Recommendations Assessment, Development and Evaluation; SAH = subarachnoid hemorrhage.

Methods

The meta-analysis was constructed according to the

MOOSE (meta-analysis of observational studies in epidemiology) guidelines.³⁷ An independent experienced librarian searched the literature published in MEDLINE, Embase, and the Cochrane Library through September 28, 2012, using the following key words: SAH, case load, outcome, aneurysm. No language restrictions were used. For a detailed search string please see Table 1. Studies were eligible for inclusion if they met the following criteria: 1) evaluated in-hospital mortality after open and/or endovascular treatment in patients with ruptured intracranial aneurysms, 2) compared low-volume with high-volume hospitals, and 3) provided an odds ratio or core data to calculate an odds ratio. If the same data were used in more than one article, the most recent or largest data set was included. Duplicate papers were removed. Conference abstracts, reviews, editorials, meta-analyses, and animal studies were also excluded. Studies were excluded if they did not provide postoperative mortality rates in patients treated for ruptured aneurysms with endovascular coiling or surgical clipping in relation to volume. Two researchers (M.v.A. and H.D.B.) independently reviewed the titles and abstracts of the articles. In the case of disagreement during this process, a third reviewer (J.d.V.) was asked. From the remaining articles, full-text versions were obtained and were independently evaluated by the same researchers. From the full-text versions, reference screening was performed to evaluate other possible studies. A data

recording form, developed for this purpose, was used by 2 authors (M.v.A. and R.B.) for independent data extraction from each study. After extraction, data were reviewed and were compared by the first author. Disagreement was solved by consensus. Assessment of the methodological quality of the studies included in the review was done according to the GRADE guidelines.¹⁴ The studies were independently assessed by the 2 researchers (R.B. and J.d.V.) for limitations, indirectness, inconsistency, imprecision, and publication bias. Overall in-hospital mortality after open surgical and/or endovascular treatment in patients with SAH was defined as the primary end point.

Statistical Analysis

To identify potential associations between hospital volume and mortality, a pooled odds ratio with 95% confidence intervals was constructed. The significance of the overall odds ratio was determined by the z-test. The Type I error was set at 0.05. The tests were 2-tailed. The random effects model was used as the preferable approach to manage potential between-study heterogeneity. Statistical heterogeneity across studies was quantified using the I^2 statistic. This statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance.¹⁹ The I^2 statistic was calculated from Q (the Cochran heterogeneity statistic) as follows: $I^2 = 100\% \times$

TABLE 1: Search strategy and results of MEDLINE, Embase, and Cochrane Library searches*

Step	Search	No. of Studies		
		PubMed	Cochrane	Embase
1	subarachnoid hemorrhage[MeSH:noexp]	14,980	375	26,035
2	subarachnoid haemorrhage[tiab] OR (subarachnoid[tiab] AND hemorrhage[tiab]) OR subarachnoid hemorrhage[tiab] OR subarachnoid haemorrhages[tiab] OR subarachnoid hemorrhages[tiab] OR SAH[tiab] OR SAHs[tiab] OR subarachnoid hematoma[tiab] OR subarachnoid bleeding[tiab]	17,916	930	22,474
3	Step 1 OR Step 2	22,212	1,214	31,404
4	intracranial aneurysm[MeSH]	19,901	333	23,962
5	(brain aneurysm[tiab] OR brain aneurysms[tiab] OR cerebral aneurysm[tiab] OR cerebral aneurysms[tiab])	4,006	372	5,034
6	Step 4 OR Step 5	20,790	492	30,331
7	rupture*[tiab]†	86,436	2,304	102,580
8	Step 6 AND Step 7	5,423	193	4,981
9	Step 3 OR Step 8	24,675	985	33,626
10	"neurosurgery/statistics and numerical data"[MeSH]‡	1,923	13	964
11	workload[MeSH]	13,778	487	24,873
12	high volume[tiab] OR high volumes[tiab] OR high-volume[tiab] OR higher volume[tiab] OR higher volumes[tiab] OR low volumes[tiab] OR lower volumes[tiab] OR low-volume[tiab] OR lower-volume[tiab] OR workload[tiab] OR (work[tiab] AND load[tiab]) OR caseload[tiab] OR caseloads[tiab] OR surgeon volume[tiab] OR workloads[tiab] OR surgical volume[tiab] OR operative volume[tiab] OR surgical volumes[tiab] OR operative volumes[tiab] OR (case[tiab] AND load[tiab]) OR case volume[tiab] OR case volumes[tiab] OR operation rate[tiab] OR operation rates[tiab] OR hospital volume[tiab] OR hospital volumes[tiab] OR highest-volume[tiab] OR highest-volumes[tiab]	42,833	24,767	56,421
13	Step 10 OR Step 11 OR Step 12	54,269	24,778	71,050
14	Step 9 AND Step 13	76	35	152

* MeSH = Medical Subject Headings; noexp = no explosion of MeSH heading; tiab = title/abstract.

† The asterisk in this field indicates that rupture was a major topic of these articles.

‡ Quotation marks indicate that the entire phrase was searched.

($Q - df$)/ Q . For sensitivity analysis, each study was removed in turn from the total, and the remaining studies were reanalyzed to identify the impact of each study on the overall result. Publication bias was graphically assessed using a funnel plot. In addition, Egger's test was used for quantitative assessment. Comprehensive Meta-Analysis software (version 2.2.046, BIOSTAT) was used for statistical analysis.

Results

Included Studies

The initial search revealed 263 studies (Table 1). After removing duplicate studies, abstracts from 211 studies, including one found by reference screening,³⁶ were evaluated. One hundred seventy-nine studies were excluded because they did not meet inclusion criteria. Thirty-two studies were considered for full-text evaluation.^{1-13,16-18,20-23,25-27,30-34,36,38-40} Twenty-eight studies were excluded for the following reasons: 2 were review studies,^{34,40} 5 had insufficient data,^{5,8,10,36,39} 3 included treatment of unruptured aneurysms,^{3,21,33} 8 contained single-center data,^{4,6,11-13,22,30,31} 3 had no caseload comparison,^{18,25,26} 2 did not have mortality as an outcome,^{1,20} 1 was an editorial,¹⁷ 3 had overlapping

source data,^{2,7,32} and 1 included only patients older than 65 years.³⁸ Therefore, 4 studies were included for final analysis (Fig. 1).^{9,16,23,27} The selected studies involved a total of 36,600 patients. Retrospective data from databases were used in 3 studies, and 1 evaluated data from a survey (Table 2). The treatment modality was clipping or endovascular coiling in 3 studies, and 1 study only evaluated open surgical results. Hospital volume definitions differed between studies. Cutoffs and dichotomizations were used as well as division in quartiles. Low volume was defined as 9 or fewer patients yearly in 1 study and as fewer than 30 in another. Similarly, high volume was defined as more than 20 patients annually in 1 study and as more than 50 patients annually in another. The definitions used in the articles were used for primary analysis. The methodological quality of 3 articles was graded as low and 1 as very low. Up-rating was not performed (Table 3).

Meta-Analysis

The overall meta-analysis suggested a significant relationship for in-hospital mortality for SAH patients in favor of high-volume hospitals (OR 0.77 [95% CI 0.60–0.97] random model) (Fig. 2A). The Q value for the test of heterogeneity was 33.2 ($p = 0.0001$), indicating heterogeneity and justifying the use of the random effects analysis. The

Fig. 1. Chart showing the results of the literature search.

TABLE 2: Characteristics of the studies

Authors & Year	Source, Years	Treatment modality	Definition of Vol	
			Low	High
Johnston, 2000	University Health Systems Consortium, 1994–1997	clipping & coiling	0–16 (1st quartile)	>45 (4th quartile)
Cross et al., 2003	database (California & Florida), 1998–2000	clipping & coiling	0–9 (1st quartile)	36–158 (4th quartile)
Hattori et al., 2007	Survey Japan, 2003	clipping	<30 (1st group)	≥50 (3rd group)
Leake et al., 2011	Nationwide Inpatient Sample (NIS) database, 2001–2008	clipping & coiling	≤20	>20

sensitivity analysis revealed a relative weight of the study by Hattori et al.¹⁶ Including this study and subsequently removing others by alternation lifted the point estimate slightly upward. The result was not statistically significant. However, removal of this study with very low quality (see Table 3) increased the effect size to an OR 0.68 (95% CI 0.56–84) (Fig. 2B).⁷ The funnel plot suggested publication bias; however, the Egger's test (intercept 1.21, $p = 0.86$ [2-tailed]) did not (Fig. 3). This result should be interpreted with great caution, because of the very limited number of studies. For comparability between studies, recalculation was done with dichotomized data if available (Table 4). Cross et al. (low volume ≤ 18 patients, high volume ≥ 19 patients) and Johnston (low volume ≤ 31 patients, high volume ≥ 32 patients) provided core data for recalculation.^{9,23} The overall results of this analysis of the 4 studies revealed an OR of 0.85 (95% CI 0.72–0.99).

Discussion

This meta-analysis demonstrates that treatment of patients with ruptured intracranial aneurysms in high-volume centers is associated with lower in-hospital mortality compared with low-volume centers. The positive correlation between a high-volume center and outcome could be attributed to several factors. First of all, high-volume centers more likely have a subspecialized team working in a multidisciplinary setting. A well-functioning and experienced team consisting of neurologists, neurosurgeons, neuroradiologists, neurointerventionalists, neurorehabilitation specialists, neurointensivists, and a dedicated nursing team will certainly contribute to a better outcome.^{5,8,24} A potential drawback of centralization would be the risk of rehemorrhage and death during transfer; however, as investigated by Bardach et al., the organization of SAH care in high-volume hospitals is justified not only for cost-effectiveness but also for patient outcome.¹

Several limitations of this study should be mentioned. First, the study data mainly rely on retrospective data based on hospital coding and can therefore be biased. Second, the patients within the studies were a selection of a population mainly from northern US databases. Infrastructural and geological characteristics might not be applicable to other countries. Third, the treatment modality might be associated with outcome and with hospital volume; centers also providing endovascular treatment have better results because of the lower associated morbidity and mortality rates as found in the International Subarachnoid Aneurysm Trial (ISAT) and recently the Barrow Ruptured Aneurysm Trial (BRAT).^{28,29} High-volume centers are more likely to have an endovascular treatment modality and thus will probably have better results.^{9,13} Fourth, we used unadjusted core data from the studies to attain comparability, since adjustment for case mix was not done or it was done in different ways. Hattori et al. corrected for initial clinical grade, but not for comorbidities and did not find a significant difference in the distribution of the World Federation of Neurosurgical Societies grade on admission between the different volume groups.¹⁶ Cross et al. corrected for comorbidities but not for initial grade.⁹ Leake et al. did not correct for comorbid conditions nor initial grade.²⁷ Johnston corrected for age but not for comorbidities or initial grade.²³ Fifth, the distinction between low volume and high volume is artificial. As shown, a uniform cutoff is not provided. At best, an approximate cutoff could be estimated. However, recalculation with dichotomized data revealed comparable results, centering the possible distinction between high volume and low volume around 20–30 patients yearly. Sixth, in-hospital mortality was chosen as the primary outcome measure; although commonly used as a measure of quality of care, it can be influenced by discharge policies. Better would be a more detailed outcome measure such as the modified Rankin Scale score; unfortunately, only the study by Hattori et al. provided these data.¹⁶ Finally, transfer of pa-

TABLE 3: GRADE evidence profile

Authors & Year	Study Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Magnitude of Effect	Quality
Johnston, 2000	observational	none	none	none	none	none	none	low
Cross et al., 2003	observational	none	none	none	none	none	none	low
Hattori et al., 2007	observational	serious	none	none	none	none	none	very low
Leake et al., 2011	observational	none	none	none	none	none	none	low

A

B

FIG. 2. Forest plots showing results of the meta-analysis of high versus low volume hospitals (**A**) and sensitivity analysis (**B**). The *squares* indicate the mean, the *whiskers* indicate the 95% CI, and the *diamonds* indicate the pooled estimate (the width of the *diamond* represents the 95% CI).

tients might cause bias. Patients who were likely to die were not transferred to a high-volume center for treatment; conversely, transferred patients tended to do better than patients in community hospitals.^{13,41}

This study does not answer the question of how much patients should be treated by a single surgeon or neurointerventionalist to obtain the best result.^{3,26,39} As previously stated, the results of treatment are not merely the merits of one specialist but the chain of care. In the scope of quality of care and the increasing demand for centralization, volume number alone is not sufficient as a parameter to guide these developments. Caseload should be seen as one of the cofactors related to outcome.

Conclusions

Despite shortcomings of the included studies but based on the best available data at this moment, mortality is lower in hospitals that treat a high volume of patients with SAH. Although a true cutoff value to distinguish between high- and low-volume centers could not be given, it probably can be centered between 20 and 30 patients annually. An explanation for the relationship between outcome and caseload could be a multidisciplinary approach resulting in a team dedicated to the care of patients with SAH. As such, the number of treated patients yearly cannot be used as a sole measure for quality of care.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

FIG. 3. Funnel plot. The *points* correspond to the treatment effects from individual studies, the *diagonal lines* show the expected 95% confidence intervals around the summary estimate. Odds ratios are plotted on a logarithmic scale.

TABLE 4: Study core data*

Authors & Year	High-Vol Hospitals				Low-Vol Hospitals			
	Total	Deaths	Alive	Mortality	Total	Deaths	Alive	Mortality
Johnston, 2000	4693 (7573)	1000 (1730)	3693 (5843)	21.3% (22.8%)	408 (1961)	115 (489)	293 (1472)	28.2% (24.9%)
Cross et al., 2003	2305 (4787)	622 (1387)	1683 (3400)	27.0% (29.0%)	2268 (4503)	877 (1652)	1391 (2851)	38.7% (36.7%)
Hattori et al., 2007	2522	257	2265	10.2%	2631	246	2385	9.4%
Leake et al., 2011	8247	1004	7243	10.6%	8556	1283	7273	14.2%

* Values are the number of patients unless specified otherwise. Numbers in parentheses indicate the number of patients if dichotomization was used (see text).

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