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Between-center and between-country differences in outcome after aneurysmal subarachnoid hemorrhage in the Subarachnoid Hemorrhage International Trialists (SAHIT) repository

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OBJECTIVE Differences in clinical outcomes between centers and countries may reflect variation in patient characteristics, diagnostic and therapeutic policies, or quality of care. The purpose of this study was to investigate the presence and magnitude of between-center and between-country differences in outcome after aneurysmal subarachnoid hemorrhage (aSAH).

METHODS The authors analyzed data from 5972 aSAH patients enrolled in randomized clinical trials of 3 different treatments from the Subarachnoid Hemorrhage International Trialists (SAHIT) repository, including data from 179 centers and 20 countries. They used random effects logistic regression adjusted for patient characteristics and timing of aneurysm treatment to estimate between-center and between-country differences in unfavorable outcome, defined as a Glasgow Outcome Scale score of 1–3 (severe disability, vegetative state, or death) or modified Rankin Scale score of 4–6 (moderately severe disability, severe disability, or death) at 3 months. Between-center and between-country differences were quantified with the median odds ratio (MOR), which can be interpreted as the ratio of odds of unfavorable outcome between a typical high-risk and a typical low-risk center or country.

RESULTS The proportion of patients with unfavorable outcome was 27% (n = 1599). The authors found substantial between-center differences (MOR 1.26, 95% CI 1.16–1.52), which could not be explained by patient characteristics and

ABBREVIATIONS aSAH = aneurysmal subarachnoid hemorrhage; CI = confidence interval; GOS = Glasgow Outcome Scale; IHAST = Intraoperative Hypothermia for Aneurysm Surgery Trial; IQR = interquartile range; MASH = Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage; MOR = median odds ratio; mRS = modified Rankin Scale; RCT = randomized clinical trial; SAHIT = Subarachnoid Hemorrhage International Trialists; TBI = traumatic brain injury; WFNS = World Federation of Neurosurgical Societies.

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timing of aneurysm treatment (adjusted MOR 1.21, 95% CI 1.11–1.44). They observed no between-country differences (adjusted MOR 1.13, 95% CI 1.00–1.40).

CONCLUSIONS Clinical outcomes after aSAH differ between centers. These differences could not be explained by patient characteristics or timing of aneurysm treatment. Further research is needed to confirm the presence of differences in outcome after aSAH between hospitals in more recent data and to investigate potential causes.

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KEYWORDS aneurysmal subarachnoid hemorrhage; center effects; quality of care; outcome; vascular disorders

DESPITE advances in treatment, functional outcome after aneurysmal subarachnoid hemorrhage (aSAH) remains poor.^{28,31} The combination of a relatively young age of onset and poor clinical outcomes makes aSAH a disease with major individual and economic impact.³⁰ The main evidence-based treatment recommendations in aSAH include endovascular coil embolization in patients with a ruptured aneurysm eligible for both endovascular coiling and neurosurgical clipping, administration of oral nimodipine and maintenance of euvolemia to prevent delayed cerebral ischemia (DCI), and drainage of cerebrospinal fluid in patients with hydrocephalus.⁵ However, many other interventions to prevent or treat complications in aSAH are less evidence-based.^{5,26} Also, discrepancies have been found between centers regarding clinical practice and adherence to guidelines for aSAH,^{4,11} suggesting differences in diagnostic and therapeutic policies between centers and countries that may contribute to variations in observed case-fatality rates across regions.²⁸

Between-center and between-country differences in outcome can be caused by random variation or by center-, country-, or patient-related factors (e.g., differences in country economic status or severity of aSAH), but they may also reflect differences in processes of care, including diagnostic and therapeutic policies and adherence to guidelines (quality of care). Insight into between-center or between-country differences in outcome may facilitate research evaluating the comparative effectiveness of structures and processes of care in aSAH (e.g., organizational structures, individual treatment interventions) and may consequently contribute to improvement in quality of care. We aimed to investigate the presence and magnitude of between-center and between-country differences in clinical outcome after aSAH.

Methods

Study Population

The Subarachnoid Hemorrhage International Trialists (SAHIT) repository contains data on more than 15,000 SAH patients from 10 randomized clinical trials (RCTs) and 11 observational studies or registries. For the present study, we used data from multicenter studies of 3 different treatments: the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST), the Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage (MASH I and II) trials, and trials of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage (tirilazad trials),^{7,13,20,34,35} including a total of 6036 patients. The other studies in the SAHIT database could not contribute to the estimation of between-center and between-country differences, either

because they were single-center studies (and therefore no distinction could be made between study effect and center or country effect) or because no information on center or country was available in the SAHIT database. Details on the development of the SAHIT repository and the included studies have been reported previously.¹⁶ The SAHIT database was approved by the research ethics board at St. Michael's Hospital, Toronto, Canada. Patients previously consented to the use of their data for future related studies, and all data for the current study were anonymized. Therefore, neither approval from an institutional review board nor informed consent was required.

Primary Outcome Measure

The RCTs used either the Glasgow Outcome Scale (GOS)^{13,20,34} or modified Rankin Scale (mRS)^{7,35} score at 3 months for functional outcome. We therefore defined our primary outcome measure as functional outcome according to the GOS or mRS score at 3 months, combined into a composite endpoint by dichotomizing both outcomes into favorable (GOS score 4–5 or mRS score 0–3) versus unfavorable (GOS score 1–3 or mRS score 4–6).

Between-Center and Between-Country Differences

We used random effects (multilevel) logistic regression to estimate differences in functional outcome after aSAH between centers and countries in order to be able to account for random variation due to small sample sizes per center or country and for differences in patient characteristics and process measures. In a random effects model, fixed effects are estimated for patient and process characteristics, and random effects are estimated for the effect of center and country. The random effects model assumes a normal distribution of the random effects. The variance of the random effects (T^2) estimated in the random effects logistic regression model is a measure for the unexplained between-center or between-country differences, independent of both random variation (chance) and patient and process characteristics as included in the model. Since between-center and between-country differences may influence each other, we used one random effects logistic regression model with both center and country as random effects (Supplemental Text Box 1).

To facilitate interpretation of the between-center or between-country differences and allow for a direct comparison with the effect size (odds ratios) of patient characteristics, we calculated the median odds ratio (MOR) with 95% confidence interval (CI).^{21,27} For each pair of patients from different centers or countries, an odds ratio was computed between a patient from the center or country with the

highest risk for unfavorable outcome and a patient from the center or country with the lowest risk for unfavorable outcome. The MOR represents the median value of the distribution of these odds ratios for unfavorable outcome for all pairs of patients in our dataset. The MOR is calculated based on the T^2 estimated in the random effects model, using the following formula: $MOR = \exp(\sqrt{[2 \times T^2] \times \Phi^{-1}[0.75]})$, where Φ corresponds to the cumulative distribution function of the normal distribution with mean 0 and variance 1. Hence, $\Phi^{-1}(0.75)$ is the 75th percentile.^{21,27} If there are no unexplained between-center or between-country differences, $T^2 = 0$ and $MOR = 1$.

The random effects logistic regression model was considered for both unadjusted between-center and between-country differences and for between-center and between-country differences adjusted for differences in patient and process characteristics (fixed effects) between centers and countries. To enable comparison between the variance components of the unadjusted and adjusted models, we rescaled the variance of the adjusted models according to previously proposed methods.¹ The patient characteristics included in the model were age, history of hypertension, World Federation of Neurosurgical Societies (WFNS) grade, Fisher grade, aneurysm location (anterior cerebral artery aneurysms [including anterior communicating artery aneurysms], internal cerebral artery aneurysms [including posterior communicating artery aneurysms], middle cerebral artery aneurysms, or posterior circulation aneurysms [including vertebral and basilar artery aneurysms]), aneurysm size (≤ 12 mm, 13–24 mm, or ≥ 25 mm)¹⁹ and aneurysm treatment (clipping, coiling, or none). These variables are known predictors of poor outcome after aSAH.^{6,17–19} Because recommendations on the timing of aneurysm treatment differ between American and European guidelines, we additionally adjusted for the process measure “time from aSAH to aneurysm treatment.”^{25,32} All analyses were also adjusted for study as a fixed effect because the overall outcome may vary across studies. Centers that participated in multiple studies were given the same center code across studies. We performed sensitivity analyses in the centers that included more than 10 patients to evaluate the robustness of our results.

Because the MOR is an overall measure for between-center and between-country differences, we also compared the effect estimates for the individual centers and countries to identify the hospitals or countries with the highest and lowest risk of unfavorable outcome. The estimated random effects (betas) for unfavorable outcome of the individual centers and countries were presented graphically by plotting them with a 95% CI.

Statistical analyses were performed with R software version 3.3.1 (R Foundation for Statistical Computing). Missing data were statistically imputed using single imputation (mice package R). The CIs around the MOR were computed with the `confint.merMod` function (lme4 package R).

Results

Study Population

We analyzed data from 5972 aSAH patients from 179

centers in 20 different countries, after excluding patients with missing data on functional outcome ($n = 54$) or unknown center ($n = 10$). Missing data on history of hypertension (22%), Fisher grade (22%), aneurysm location (18%), aneurysm size (23%), and timing of aneurysm treatment (8%) were imputed. Unfavorable outcome at 3 months occurred in 1599 patients (27%), and 872 patients (15%) died. The patients' median age was 53 years (interquartile range [IQR] 44–62). A total of 1132 patients (19%) had a poor WFNS grade (4 or 5) at admission (Table 1). The number of included patients per center ranged from 1 to 846 (Fig. 1 left). The majority of patients were from the US ($n = 1765$, 30%) or from one of 14 countries in Europe ($n = 3155$, 53%). Other participating countries were Canada ($n = 536$), Australia ($n = 344$), New Zealand ($n = 142$), Chile ($n = 21$), and Mexico ($n = 9$) (Fig. 1 right). The centers located in the US participated in the IHAST and tirilazad studies. The United Kingdom was the only country that contributed to studies of all 3 treatments (Supplemental Fig. 1). Patient characteristics, such as age, history of hypertension and poor WFNS or Fisher grade at admission, were predictive of unfavorable outcome (Supplemental Table 1).

Between-Center Differences

We found between-center differences in functional outcome, both before and after adjustment for patient characteristics and time to aneurysm treatment (MOR 1.26, 95% CI 1.16–1.52, and adjusted MOR 1.21, 95% CI 1.11–1.44, respectively, Table 2). The MOR of 1.21 implies a median increase of 21% in odds of unfavorable outcome if a patient was treated in a hospital with higher risk of unfavorable outcome. This order of magnitude is comparable to the effect of hypertension or aneurysm size larger than 12 mm (Supplemental Table 1). While between-center differences were substantial in the tirilazad trials (adjusted MOR 1.22, 95% CI 1.10–1.46), we found no between-center differences beyond random variation, patient characteristics, and timing of aneurysm treatment in the IHAST (adjusted MOR 1.00, 95% CI 1.00–1.02) and MASH studies (adjusted MOR 1.00, 95% CI 1.00–1.50, Table 2).

The effect estimates for unfavorable outcome in individual centers were subject to substantial uncertainty (Fig. 2 left), making it difficult to identify individual centers that perform better or worse than others.

Between-Country Differences

No between-country differences were observed in the unadjusted (MOR 1.14, 95% CI 1.00–1.43) and adjusted (adjusted MOR 1.13, 95% CI 1.00–1.40) analyses (Table 2 and Fig. 2 right). Between-country differences beyond random variation, patient characteristics, and timing of treatment were absent in the IHAST (adjusted MOR 1.00, 95% CI 1.00–1.02) and the MASH studies (adjusted MOR 1.00, 95% CI 1.00–1.38) and nonsignificant in the tirilazad trials (adjusted MOR 1.14, 95% CI 1.00–1.46) (Table 2).

Sensitivity analyses with only centers that included 10 or more patients yielded similar between-center and between-country differences (Supplemental Table 2).

TABLE 1. Descriptive statistics of the studies in the SAHIT repository used for analysis of between-center and between-country differences

	IHASt	MASH I & II	Tirilazad
Study period	2000–2003	2000–2011	1991–1997
Original publication	Todd et al., 2005	Van den Bergh et al., 2005; Dorhout Mees et al., 2012	Kassell et al., 1996; Haley et al., 1997
Patients, n	1000	1484	3488
Centers, n	30	9	148
Countries, n	7	3	19
Continents	Europe, North America, Oceania	Europe, South America	Europe, North America, Oceania
Age in yrs, median (IQR)	52 (43–60)	56 (48–65)	51 (42–62)
History of hypertension, n (%) [*]	398 (40)	57 (4)	1124 (33)
Initial WFNS grade, n (%)			
1	660 (66)	728 (49)	1265 (36)
2	289 (29)	346 (23)	1028 (29)
3	51 (5)	64 (4)	408 (12)
4	0 (0)	218 (15)	346 (10)
5	0 (0)	127 (8)	441 (13)
Fisher grade, n (%) [†]			
1	54 (5)	1 (0)	330 (9)
2	342 (34)	22 (1)	451 (13)
3	474 (47)	43 (3)	2271 (66)
4	130 (13)	141 (10)	414 (12)
Aneurysm location, n (%) [‡]			
ACA/ACoA	391 (39)	190 (13)	1243 (36)
ICA/PCoA	318 (32)	117 (8)	1019 (29)
MCA	206 (21)	89 (6)	695 (20)
Pst circ (including BA & VA)	84 (8)	61 (4)	469 (13)
Aneurysm size, n (%) [§]			
≤12 mm	878 (88)	143 (10)	2549 (73)
13–24 mm	94 (9)	14 (1)	785 (23)
≥25 mm	24 (3)	2 (1)	126 (4)
Aneurysm treatment			
Clipping	1000 (100)	551 (37)	3151 (90)
Coiling	0 (0)	735 (50)	0 (0)
None	0 (0)	198 (13)	337 (10)
Time from aSAH to aneurysm treatment in days, median (IQR)	2.0 (1.0–4.0)	1.0 (1.0–2.0)	1.4 (1.0–1.8)
Outcome at 3 mos, n (%) [¶]			
Unfavorable	144 (14)	398 (27)	1057 (30)
Mortality	61 (6)	234 (16)	577 (17)

ACA = anterior cerebral artery; ACoA = anterior communicating artery; BA = basilar artery; circ = circulation; ICA = internal cerebral artery; MCA = middle cerebral artery; PCoA = posterior communicating artery; pst = posterior; VA = vertebral artery.

^{*} MASH: 1276 missing.

[†] MASH: 1277 missing. In the MASH trials, the Hijdra score was used to measure the amount of subarachnoid blood.

[‡] MASH: 1027 missing.

[§] MASH: 1325 missing.

[¶] Outcome was based on 3-month GOS scores for IHASt and the tirilazad studies and 3-month mRS scores for the MASH trials.

Discussion

We analyzed data from a large international repository of aSAH patients and observed substantial between-center differences in functional outcome that could not be explained by random variation, differences in patient characteristics, or timing of aneurysm treatment. We ob-

served no statistically significant between-country differences.

Previous studies have reported substantial between-center differences in other neurological diseases. Large between-center differences in outcome were found in a study in traumatic brain injury (TBI), based on more than 15,000 patients from both RCTs and observational stud-

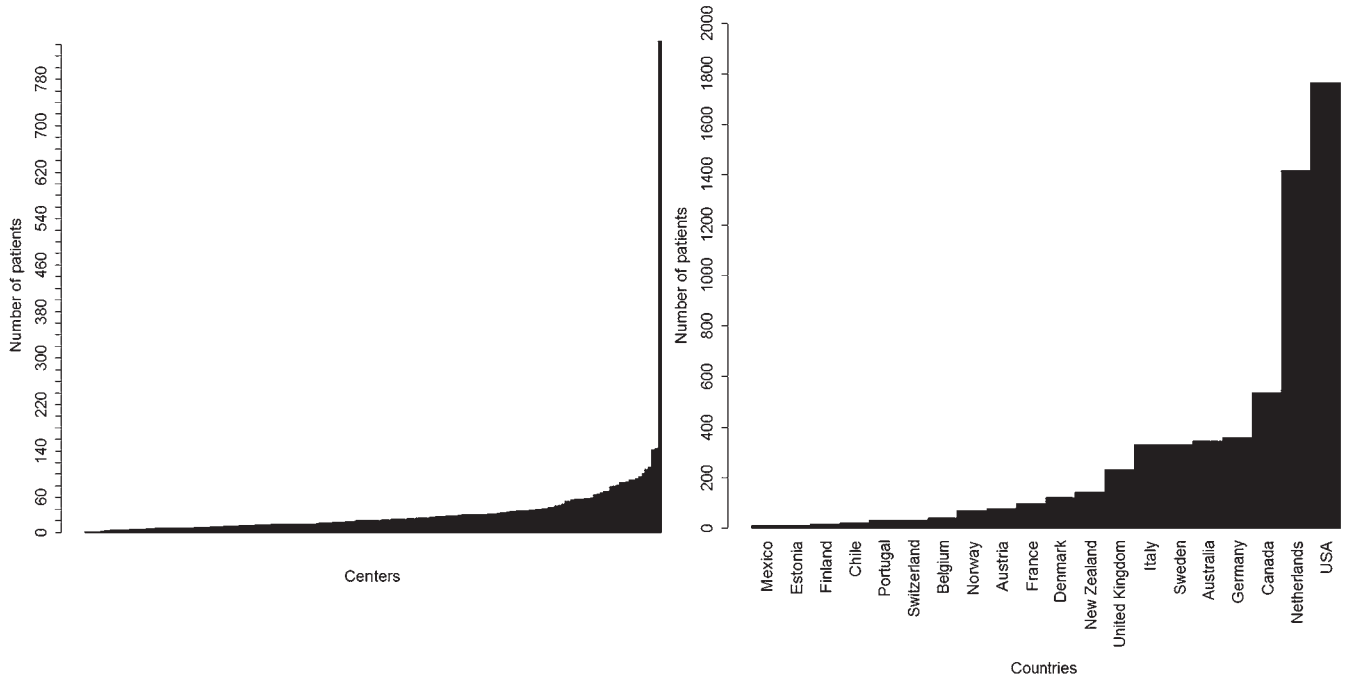


FIG. 1. Observed number of patients per center (**left**) in each of 179 centers, with numbers varying from 1 to 846 (median 20, IQR 11–37) and per country (**right**) in each of 20 countries, with numbers varying from 9 to 1765 (median 109, IQR 31–334).

ies.²² The between-center differences in our study were similar to those reported in TBI (comparable variances).²² Another example is the considerable between-center variability in functional outcome that was observed in patients enrolled in the Tinzaparin in Acute Ischemic Stroke Trial (TAIST).¹⁰ In aSAH, only a few studies have reported on between-center or between-country differences in outcome.^{2,24} Moreover, studies that evaluated between-center and between-country variability generally used fixed effect models, while random effects logistic regression is

preferred to better take into account clustering of patients, especially with a small number of patients per center or country.¹² The present study confirms the previously reported absence of between-center differences in outcome after aSAH within IHAST, but contradicts prior analyses by showing that between-center differences in outcome do exist within the tirilazad trials.^{2,24} Our results were based on a large repository, and we used advanced statistical methods accounting for differences due to random variation and patient or process characteristics.

TABLE 2. Between-center and between-country differences in the total database (n = 5972) and within studies

	Unfavorable Outcome, n (%)	Unadjusted		Adjusted*	
		T ²	MOR (95% CI)	T ²	MOR (95% CI)
Between-center differences†					
Total‡ (n = 5972)	1599 (27)	0.062	1.26 (1.16–1.52)	0.045	1.21 (1.11–1.44)
IHAST (n = 1000)	144 (14)	0.000	1.00 (1.00–1.53)	0.000	1.00 (1.00–1.02)
MASH (n = 1484)	398 (27)	0.050	1.23 (1.00–1.85)	0.000	1.00 (1.00–1.50)
Tirilazad (n = 3488)	1057 (30)	0.074	1.28 (1.15–1.60)	0.047	1.22 (1.10–1.46)
Between-country differences§					
Total‡ (n = 5972)	1599 (27)	0.021	1.14 (1.00–1.43)	0.016	1.13 (1.00–1.40)
IHAST (n = 1000)	144 (14)	0.000	1.00 (1.00–1.69)	0.000	1.00 (1.00–1.02)
MASH (n = 1484)	398 (27)	0.000	1.00 (1.00–1.70)	0.000	1.00 (1.00–1.38)
Tirilazad (n = 3488)	1057 (30)	0.038	1.20 (1.05–1.58)	0.020	1.14 (1.00–1.46)

* Adjusted for age, hypertension, WFNS grade, Fisher grade, aneurysm location, aneurysm size, aneurysm treatment, and time from aSAH to aneurysm treatment.

† Adjusted for country as a random effect.

‡ Models in the total database were adjusted for study.

§ Adjusted for center as a random effect.

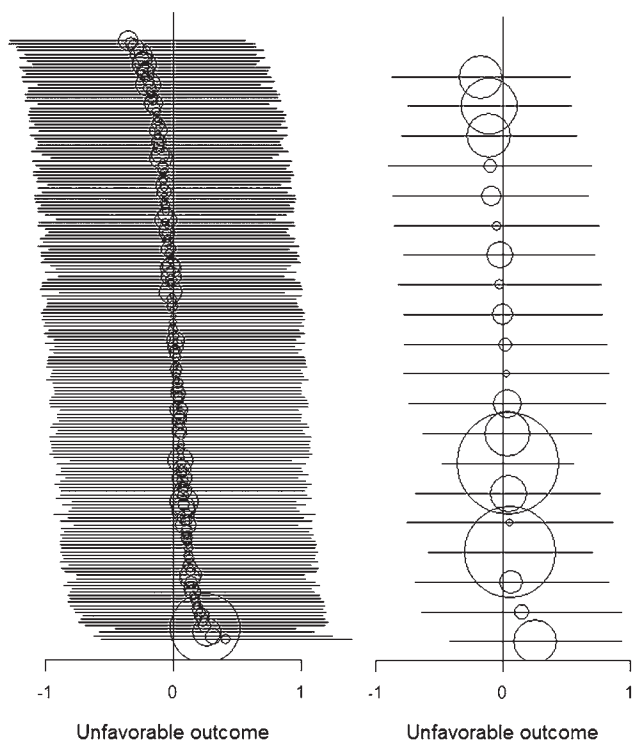


FIG. 2. Differences between centers (**left**) and countries (**right**) in unfavorable outcome, adjusted for age, history of hypertension, WFNS grade, Fisher grade, aneurysm location, aneurysm size, and time from aSAH to aneurysm treatment in a random effects model. The *circles* indicate the random effects for the individual centers (betas), and the size of the circle refers to the number of patients in each center. The *lines* reflect the 95% CIs.

Between-center differences in clinical outcomes after aSAH persisted after adjustment for patient characteristics and timing of aneurysm treatment. Other factors that might explain between-center differences are residual confounding and registration bias. However, these factors are unlikely to account for our results. We adjusted for known prognostic factors for outcome after aSAH as well as for time from aSAH to aneurysm treatment. This reduced the risk for residual confounding, although we acknowledge that data on several other factors that might influence outcome (e.g., withdrawal of life-sustaining measures or severity of underlying systemic illness) were unavailable. Also, our analyses were performed on multiple RCTs with high-quality data. Altogether, differences in unfavorable outcome between centers might be best explained by differences in diagnostic and therapeutic policies or quality of care. We observed no statistically significant between-country differences, suggesting that hospitals with similar patient outcomes are not clustered within one country.

Differences in outcome after aSAH between centers due to different treatment policies or quality of care are undesirable. However, because of limited evidence regarding treatment strategies and differences in adherence to guidelines,^{5,11,26} it is expected that diagnostic and therapeutic policies for aSAH vary between centers and countries. This has been confirmed in previous studies.^{9,15,37} In our study, the causality between variation in treatment policies

or quality of care (other than timing of aneurysm treatment) and observed outcome differences could not be verified. We are therefore unable to present recommendations for current clinical practice. However, gaining insight into outcome differences between centers and countries is an important first step to evaluate practice variation and eventually improve clinical outcomes after aSAH. Our results provide the opportunity to perform comparative effectiveness research relating differences in structures and processes of care in aSAH between centers to differences in outcome. In TBI, such comparative effectiveness research is currently being conducted in a large prospective observational study.²⁵

Assessing the performance of individual hospitals and countries is challenging since the estimates for specific centers and countries are subject to substantial uncertainty. Because the effect of chance increases with a decrease in the number of treated patients or outcomes,²³ a recommendation for future comparative effectiveness research is to focus on sufficient numbers of patients per center or country.

We found that between-center differences were substantial in the tirilazad trials, but were absent in the more recent IHAST and MASH trials. The tirilazad trials included more centers than the IHAST and MASH trials (Supplemental Fig. 1), which increases the statistical power to identify differences in outcome. Moreover, progress has been made in diagnostic and therapeutic management since publication of the tirilazad trials and prognosis after aSAH may therefore have improved. For instance, the tirilazad studies and IHAST were (largely) conducted before publication of the International Subarachnoid Aneurysm Trial, so only 12% of the patients in our dataset underwent coil embolization. This and other factors related to the relatively old data limit the generalizability of our results to the contemporary aSAH population. Unfortunately, the more recent observational studies in the SAHIT repository could not contribute to the estimation of between-center and between-country differences, because they were conducted in a single center or information on center or country was not available in the SAHIT database.¹⁶ Given the evidence in aSAH and from related disease fields,^{4,22,36} we consider it unlikely that between-center differences in clinical outcomes after aSAH are no longer present in current clinical practice. Our results should however be confirmed in a multicenter prospective cohort study.

Some other limitations should be acknowledged. Our data are based on RCTs with strict inclusion criteria. This created a relatively homogeneous study population, which might have caused an underestimation of the between-center and between-country differences. Further, the varying inclusion criteria (e.g., neurological condition on admission, time from onset of aSAH to inclusion) across the studies^{13,20,34,35} made it impossible to assess the previously studied effect of center volume on outcome.^{3,29} Information on other center- and country-specific aspects could not be retrieved due to the historic nature of the data, and the current center- and country-specific characteristics would not be applicable to the time when the data were collected for these studies. For example, the presence of neurocritical

care teams has been associated with improved outcomes, and inclusion of this factor in future observational studies would be very important.^{8,14,33} Finally, we were unable to assess the effect of time on outcome differences, because the inclusion periods of the trials were relatively short, and only analyses on within-study time trends could be performed, since adjustment for study is required to distinguish between time effect and study effect.

Conclusions

Clinical outcomes after aSAH differ between centers. These differences could not be explained by random variation, patient characteristics, or timing of aneurysm treatment. Further research is needed to confirm the presence of differences between hospitals with respect to outcome after aSAH in more recent data and to investigate potential causes, such as variation in diagnostic and therapeutic policies or quality of care, in order to identify best practices and inform guidelines.

Appendix

Members of the SAHIT Collaboration

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