JNS

CLINICAL ARTICLE

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

Simone A. Dijkland, MD,[1] Blessing N. R. Jaja, MD, PhD,[2–4] Mathieu van der Jagt, MD, PhD,[5] Bob Roozenbeek, MD, PhD,[6,7] Mervyn D. I. Vergouwen, MD, PhD,[8] Jose I. Suarez, MD,[9] James C. Torner, PhD,[10] Michael M. Todd, MD,[11] Walter M. van den Bergh, MD, PhD,[12] Gustavo Saposnik, MD,[3,4,13] Daniel W. Zumofen, MD,[14,15] Michael D. Cusimano, MD, PhD,[2–4,16] Stephan A. Mayer, MD,[17] Benjamin W. Y. Lo, MD, PhD,[18] Ewout W. Steyerberg, PhD,[1,19] Diederik W. J. Dippel, MD, PhD,[6] Tom A. Schweizer, PhD,[2–4,16] R. Loch Macdonald, MD, PhD,[2–4,16] and Hester F. Lingsma, PhD,[1] on behalf of the SAHIT collaboration

Departments of [1]Public Health, [5]Intensive Care, [6]Neurology, and [7]Radiology and Nuclear Medicine, Erasmus MC–University Medical Center, Rotterdam; [12]Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen; [19]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden; [8]Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [2]Division of Neurosurgery and [3]Neuroscience Research Program, Li Ka Shing Knowledge Institute, and [13]Decision Neuroscience Unit, Division of Neurology, St. Michael's Hospital, University of Toronto; [4]Institute of Medical Science and [16]Department of Surgery, University of Toronto, Toronto, Ontario; [18]Departments of Neurology, Neurosurgery, and Critical Care, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada; [9]Departments of Anesthesiology and Critical Care Medicine, Neurology, and Neurosurgery, Johns Hopkins University, Baltimore, Maryland; [10]Department of Epidemiology, University of Iowa College of Public Health, Iowa City, Iowa; [11]Department of Anesthesiology, University of Minnesota Medical School, Minneapolis, Minnesota; [17]Department of Neurology, Henry Ford Health System, Detroit, Michigan; and [14]Department of Neurosurgery and [15]Section for Diagnostic and Interventional Neuroradiology, Department of Radiology, Basel University Hospital, University of Basel, Basel, Switzerland

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.

SUBMITTED February 21, 2019. **ACCEPTED** May 30, 2019.
INCLUDE WHEN CITING Published online August 23, 2019; DOI: 10.3171/2019.5.JNS19483.

©AANS 2019, except where prohibited by US copyright law

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.

https://thejns.org/doi/abs/10.3171/2019.5.JNS19483

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."[5,32] 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 observed 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-

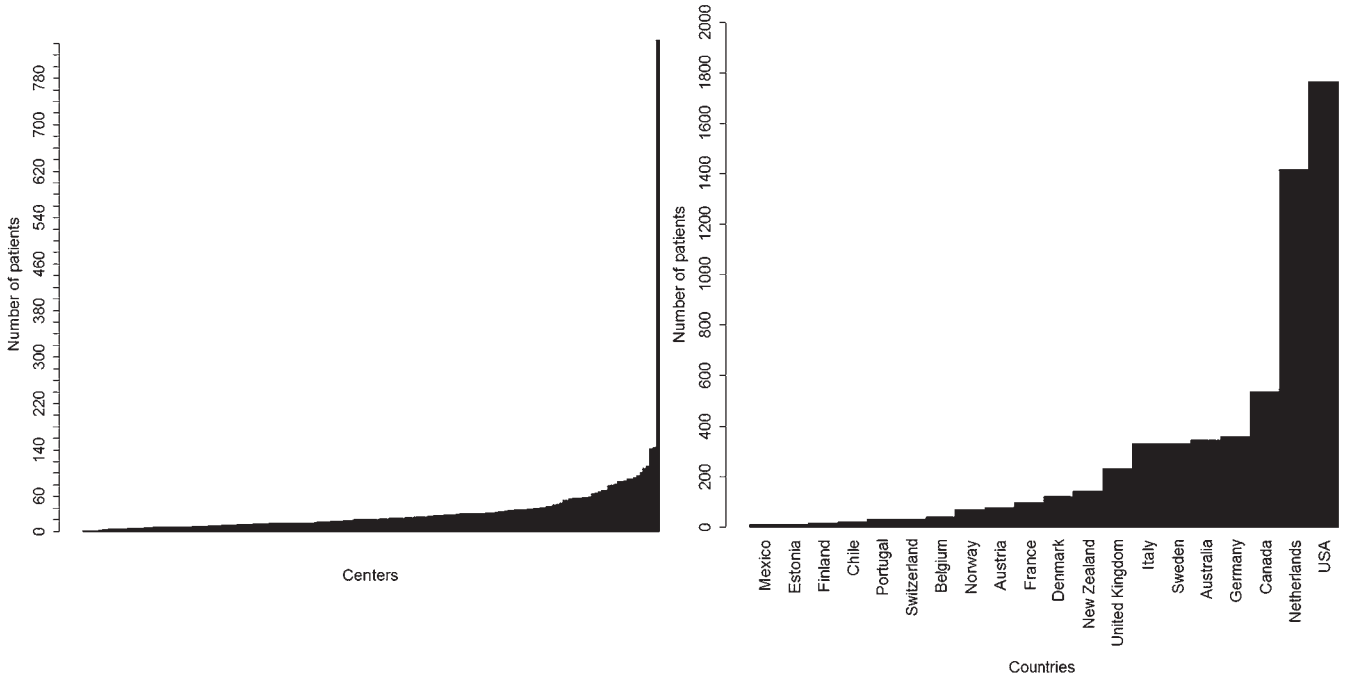

FIG. 1. Observed number of patients per center (**left**) in each of 179 centers, with numbers varying from 1 to 846 (median 20, IQR 11–37) and per country (**right**) in each of 20 countries, with numbers varying from 9 to 1765 (median 109, IQR 31–334).

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

		Unadjusted		Adjusted*	
	Unfavorable Outcome, n (%)	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.

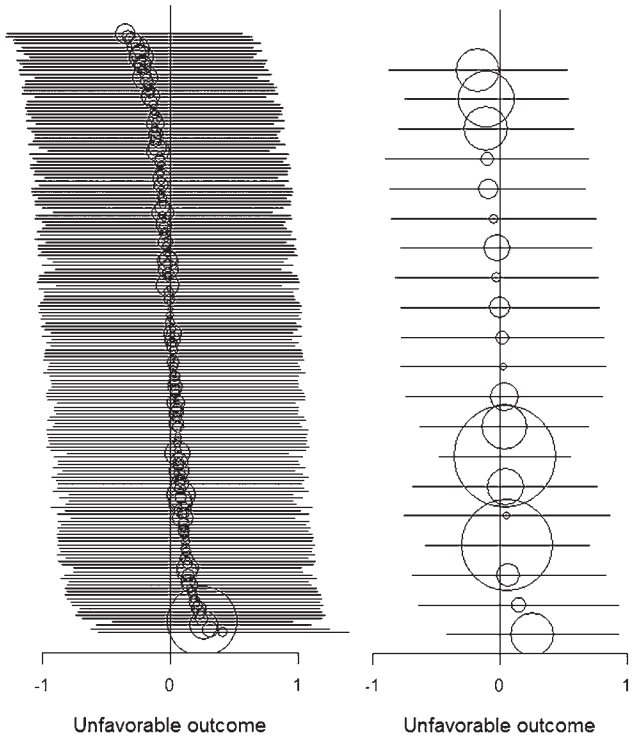

FIG. 2. Differences between centers (**left**) and countries (**right**) in unfavorable outcome, adjusted for age, history of hypertension, WFNS grade, Fisher grade, aneurysm location, aneurysm size, and time from aSAH to aneurysm treatment in a random effects model. The *circles* indicate the random 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

Adam Noble, PhD (King's College London, UK); Airton Leonardo de Oliveira Manoel, MD, PhD (Hospital Israelita Albert Einstein and Hospital Alemao Oswaldo Cruz, Brazil); Andreas Raabe, MD, PhD (University Hospital Bern, Switzerland); Andrew Molyneux, MD, PhD (Oxford University, UK); Audrey Quinn, MD (The General Infirmary, Leeds, UK); Bawarjan Schatlo, MD (University Hospital Göttingen, Germany); Benjamin W. Y. Lo, MD, PhD (Montreal Neurological Institute and Hospital, McGill University, Montreal, Canada); Blessing N. R. Jaja, MD, PhD (St. Michael's Hospital, University of Toronto, Canada); Charles C. Matouk, MD (Yale School of Medicine, New Haven, USA); Christian Fung, MD (University Hospital Bern, Switzerland); Daniel Hänggi, MD (University Hospital Mannheim, Mannheim, Germany); Daniel W. Zumofen, MD (Basel University Hospital, Switzerland); David Hasan, MD (University of Iowa, USA); Emanuela Keller, MD (University Hospital Zürich, Switzerland); Errol Gordon, MD (Mount Sinai Hospital, New York, USA); Gabriel J. E. Rinkel, MD, PhD (University Medical Center Utrecht, Utrecht, The Netherlands); George K. C. Wong, MD (Chinese University of Hong Kong, Hong Kong); Gustavo Saposnik, MD (St. Michael's Hospital, University of Toronto, Canada); Hitoshi Fukuda, MD, PhD (Kurashiki Central Hospital, Kyoto University, Okayama, Japan); James C. Torner, PhD (University of Iowa, USA); Jan-Karl Burkhardt, MD (University Hospital Zürich, Switzerland); Javier Fandino, MD (Kantonsspital Aarau, Switzerland); John D. Pickard, MD, PhD (University of Cambridge, UK); Jose I. Suarez, MD (Johns Hopkins University, Baltimore, MD, USA); Julian Spears, MD (St. Michael's Hospital, University of Toronto, Canada); Jürgen Beck, MD, PhD (University Hospital Bern, Switzerland); Karl Schaller, MD (University Hospital Zurich, Geneva, Switzerland); Kevin N. Sheth, MD (Massachusetts General Hospital, Boston, MA, USA); Kevin E. Thorpe, PhD (St. Michael's Hospital, University of Toronto, Canada); Luca Regli, MD, PhD (University Hospital Zürich, Neurosurgery, Switzerland); Martin Seule, MD (Kantonsspital St. Gallen, Switzerland); Martin N. Stienen, MD (University Hospital Zurich & Clinical Neuroscience Center, University of Zurich, Switzerland); Mervyn D. I. Vergouwen, MD, PhD (University Medical Center Utrecht, Utrecht, The Netherlands); Michael D. Cusimano, MD, PhD (St. Michael's Hospital, University of Toronto, Canada); Michael Reinert, MD (Ospedale Civico Lugano, Switzerland); Michael M. Todd, MD (University of Minnesota Medical School, Minnesota, USA); Michel Roethlisberger, MD (Basel University Hospital, Switzerland); Ming-Yuan Tseng, MD (Medicines and Healthcare Products Regulatory Agency, London, UK); Nima Etminan, MD (University Hospital Mannheim, Mannheim, Germany); Peter J. Kirkpatrick, MD (Addenbrooke's Hospital, University of Cambridge, UK); Peter D. Le Roux, MD (Lankenau Medical Center, Wynnewood, PA, USA); Philippe Bijlenga, MD (Hôpitaux Universitaire de Genève, Switzerland); R. Loch Macdonald, MD, PhD (St. Michael's Hospital, University of Toronto, Canada); Raphael Guzman, MD (Basel University Hospital, Switzerland); Roy T. Daniel, MD (University Hospital Lausanne, Switzerland); Rodolfo Maduri, MD (University Hospital Lausanne, Switzerland); S. Claiborne Johnston, MD, PhD (University of Texas, Austin, USA); Sen Yamagata, MD (Kurashiki Central Hospital, Kurashiki-city, Okayama, Japan); Serge Marbacher, MD, PhD (Kantonsspital Aarau, Switzerland); Stephan A. Mayer, MD (Henry Ford Health System, Detroit, MI, USA); Thomas Robert, MD (Ospedale Civico Lugano, Switzerland); Thomas Schenk, PhD (Friedrich-Alexander University, Erlangen, Germany); Tom A. Schweizer, PhD (St. Michael's Hospital, University of Toronto, Canada); Walter M. van den Bergh, MD, PhD (University Medical Center Groningen, The Netherlands); and Xinju Yang, MD, PhD (Tianjin Medical University General Hospital, Tianjin, China)

References

1. Austin PC, Merlo J: Intermediate and advanced topics in multilevel logistic regression analysis. **Stat Med 36:**3257–3277, 2017
2. Bayman EO, Chaloner KM, Hindman BJ, Todd MM: Bayesian methods to determine performance differences and to quantify variability among centers in multi-center trials: the IHAST trial. **BMC Med Res Methodol 13:**5, 2013
3. Boogaarts HD, van Amerongen MJ, de Vries J, Westert GP, Verbeek AL, Grotenhuis JA, et al: Caseload as a factor for outcome in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. **J Neurosurg 120:**605–611, 2014
4. Citerio G, Gaini SM, Tomei G, Stocchetti N: Management of 350 aneurysmal subarachnoid hemorrhages in 22 Italian neurosurgical centers. **Intensive Care Med 33:**1580–1586, 2007
5. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al: Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. **Stroke 43:**1711–1737, 2012
6. Dijkland SA, Roozenbeek B, Brouwer PA, Lingsma HF, Dippel DW, Vergouw LJ, et al: Prediction of 60-day case fatality after aneurysmal subarachnoid hemorrhage: external validation of a prediction model. **Crit Care Med 44:**1523–1529, 2016
7. Dorhout Mees SM, Algra A, Vandertop WP, van Kooten F, Kuijsten HA, Boiten J, et al: Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. **Lancet 380:**44–49, 2012 (Errata in **Lancet 380:**28, 2012; **Lancet 380:**1994, 2012)
8. Egawa S, Hifumi T, Kawakita K, Okauchi M, Shindo A, Kawanishi M, et al: Impact of neurointensivist-managed intensive care unit implementation on patient outcomes after aneurysmal subarachnoid hemorrhage. **J Crit Care 32:**52–55, 2016
9. Fargen KM, Soriano-Baron HE, Rushing JT, Mack W, Mocco J, Albuquerque F, et al: A survey of intracranial aneurysm treatment practices among United States physicians. **J Neurointerv Surg 10:**44–49, 2018
10. Gray LJ, Sprigg N, Bath PM, Sørensen P, Lindenstrøm E, Boysen G, et al: Significant variation in mortality and functional outcome after acute ischaemic stroke between Western countries: data from the tinzaparin in acute ischaemic stroke

trial (TAIST). **J Neurol Neurosurg Psychiatry 77:**327–333, 2006
11. Gritti P, Akeju O, Lorini FL, Lanterna LA, Brembilla C, Bilotta F: A narrative review of adherence to subarachnoid hemorrhage guidelines. **J Neurosurg Anesthesiol 30:**203–216, 2018
12. Guo G, Zhao H: Multilevel modeling for binary data. **Annu Rev Sociol 26:**441–462, 2000
13. Haley EC Jr, Kassell NF, Apperson-Hansen C, Maile MH, Alves WM: A randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in North America. **J Neurosurg 86:**467–474, 1997
14. Harrison DA, Prabhu G, Grieve R, Harvey SE, Sadique MZ, Gomes M, et al: Risk Adjustment In Neurocritical care (RAIN)—prospective validation of risk prediction models for adult patients with acute traumatic brain injury to use to evaluate the optimum location and comparative costs of neurocritical care: a cohort study. **Health Technol Assess 17:**vii–viii, 1–350, 2013
15. Hollingworth M, Chen PR, Goddard AJ, Coulthard A, Söderman M, Bulsara KR: Results of an international survey on the investigation and endovascular management of cerebral vasospasm and delayed cerebral ischemia. **World Neurosurg 83:**1120–1126, 1126.e1, 2015
16. Jaja BN, Attalla D, Macdonald RL, Schweizer TA, Cusimano MD, Etminan N, et al: The Subarachnoid Hemorrhage International Trialists (SAHIT) repository: advancing clinical research in subarachnoid hemorrhage. **Neurocrit Care 21:**551–559, 2014
17. Jaja BN, Cusimano MD, Etminan N, Hanggi D, Hasan D, Ilodigwe D, et al: Clinical prediction models for aneurysmal subarachnoid hemorrhage: a systematic review. **Neurocrit Care 18:**143–153, 2013
18. Jaja BN, Lingsma H, Schweizer TA, Thorpe KE, Steyerberg EW, Macdonald RL: Prognostic value of premorbid hypertension and neurological status in aneurysmal subarachnoid hemorrhage: pooled analyses of individual patient data in the SAHIT repository. **J Neurosurg 122:**644–652, 2015
19. Jaja BNR, Saposnik G, Lingsma HF, Macdonald E, Thorpe KE, Mamdani M, et al: Development and validation of outcome prediction models for aneurysmal subarachnoid haemorrhage: the SAHIT multinational cohort study. **BMJ 360:**j5745, 2018
20. Kassell NF, Haley EC Jr, Apperson-Hansen C, Alves WM: Randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in Europe, Australia, and New Zealand. **J Neurosurg 84:**221–228, 1996
21. Larsen K, Merlo J: Appropriate assessment of neighborhood effects on individual health: integrating random and fixed effects in multilevel logistic regression. **Am J Epidemiol 161:**81–88, 2005
22. Lingsma HF, Roozenbeek B, Li B, Lu J, Weir J, Butcher I, et al: Large between-center differences in outcome after moderate and severe traumatic brain injury in the international mission on prognosis and clinical trial design in traumatic brain injury (IMPACT) study. **Neurosurgery 68:**601–608, 2011
23. Lingsma HF, Steyerberg EW, Eijkemans MJ, Dippel DW, Scholte Op Reimer WJ, Van Houwelingen HC: Comparing and ranking hospitals based on outcome: results from The Netherlands Stroke Survey. **QJM 103:**99–108, 2010
24. Lipsman N, Tolentino J, Macdonald RL: Effect of country or continent of treatment on outcome after aneurysmal subarachnoid hemorrhage. Clinical article. **J Neurosurg 111:**67–74, 2009
25. Maas AI, Menon DK, Steyerberg EW, Citerio G, Lecky F, Manley GT, et al: Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. **Neurosurgery 76:**67–80, 2015
26. Macdonald RL: Delayed neurological deterioration after subarachnoid haemorrhage. **Nat Rev Neurol 10:**44–58, 2014
27. Merlo J, Chaix B, Ohlsson H, Beckman A, Johnell K, Hjerpe P, et al: A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. **J Epidemiol Community Health 60:**290–297, 2006
28. Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ: Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. **Lancet Neurol 8:**635–642, 2009
29. Pandey AS, Gemmete JJ, Wilson TJ, Chaudhary N, Thompson BG, Morgenstern LB, et al: High subarachnoid hemorrhage patient volume associated with lower mortality and better outcomes. **Neurosurgery 77:**462–470, 2015
30. Ridwan S, Urbach H, Greschus S, von Hagen J, Esche J, Boström A: Health care costs of spontaneous aneurysmal subarachnoid hemorrhage for rehabilitation, home care, and in-hospital treatment for the first year. **World Neurosurg 97:**495–500, 2017
31. Rinkel GJ, Algra A: Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. **Lancet Neurol 10:**349–356, 2011
32. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G: European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. **Cerebrovasc Dis 35:**93–112, 2013
33. Suarez JI, Zaidat OO, Suri MF, Feen ES, Lynch G, Hickman J, et al: Length of stay and mortality in neurocritically ill patients: impact of a specialized neurocritical care team. **Crit Care Med 32:**2311–2317, 2004
34. Todd MM, Hindman BJ, Clarke WR, Torner JC: Mild intraoperative hypothermia during surgery for intracranial aneurysm. **N Engl J Med 352:**135–145, 2005
35. van den Bergh WM, Algra A, van Kooten F, Dirven CM, van Gijn J, Vermeulen M, et al: Magnesium sulfate in aneurysmal subarachnoid hemorrhage: a randomized controlled trial. **Stroke 36:**1011–1015, 2005
36. van Essen TA, den Boogert HF, Cnossen MC, de Ruiter GCW, Haitsma I, Polinder S, et al: Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study. **Acta Neurochir (Wien) 161:**435–449, 2019
37. Velly LJ, Bilotta F, Fàbregas N, Soehle M, Bruder NJ, Nathanson MH: Anaesthetic and ICU management of aneurysmal subarachnoid haemorrhage: a survey of European practice. **Eur J Anaesthesiol 32:**168–176, 2015

Disclosures

R.L.M. reports grants from the Brain Aneurysm Foundation, the Heart and Stroke Foundation of Canada, and Genome Canada outside the present workhaving a patent on a drug delivery system for treatment of cerebral vasospasm issued; and having been Chief Scientific Officer and an employee of Edge Therapeutics, Inc. J.I.S. reports grants from PCORI and support from BARD and Neurocritical Care Society outside the present work. S.A.M. reports personal fees from Idorsia Pharmaceuticals and Edge Therapeutics outside the present work. M.D.C. reports grants from Cancer Care Ontario, Canadian Institute for Military and Veteran Health Research, Mitacs Canada, Physicians' Services Inc. Foundation, and Academic Health Science Center Alternative Funding Plan outside the present work. G.S. is Associate Editor of the Emerging Therapies Section of *Stroke*.

Author Contributions

Conception and design: Steyerberg, Macdonald, Lingsma. Acqui-

sition of data: Jaja, Macdonald. Analysis and interpretation of data: Dijkland, Lingsma. Drafting the article: Dijkland. Critically revising the article: Jaja, van der Jagt, Roozenbeek, Vergouwen, Suarez, Torner, Todd, van den Bergh, Saposnik, Zumofen, Cusimano, Mayer, Lo, Steyerberg, Dippel, Schweizer, Macdonald, Lingsma. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Dijkland. Statistical analysis: Dijkland. Study supervision: Steyerberg, Macdonald, Lingsma.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Content. https://thejns.org/doi/suppl/10.3171/2019.5.JNS19483.

Previous Presentations

Portions of this work were presented in abstract form at the 4th European Stroke Organization Conference, Goteborg, Sweden, May 16–18, 2018, and in poster form at the 17th Biennial European Conference of the Society for Medical Decision Making, Leiden, The Netherlands, June 10–12, 2018.

Correspondence

Simone Dijkland: Erasmus MC–University Medical Center, Rotterdam, The Netherlands. s.dijkland@erasmusmc.nl.