Prognostic value of premorbid hypertension and neurological status in aneurysmal subarachnoid hemorrhage: pooled analyses of individual patient data in the SAHIT repository

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OBJECT The literature has conflicting reports about the prognostic value of premorbid hypertension and neurological status in aneurysmal subarachnoid hemorrhage (SAH). The aim of this study was to investigate the prognostic value of premorbid hypertension and neurological status in the SAH International Trialists repository.

METHODS Patient-level meta-analyses were conducted to investigate univariate associations between premorbid hypertension (6 studies; n = 7249), admission neurological status measured on the World Federation of Neurosurgical Societies (WFNS) scale (10 studies; n = 10,869), and 3-month Glasgow Outcome Scale (GOS) score. Multivariable analyses were performed to sequentially adjust for the effects of age, CT clot burden, aneurysm location, aneurysm size, and modality of aneurysm repair. Prognostic associations were estimated across the ordered categories of the GOS using proportional odds models. Nagelkerke’s $R^2$ statistic was used to quantify the added prognostic value of hypertension and neurological status beyond those of the adjustment factors.

RESULTS Premorbid hypertension was independently associated with poor outcome, with an unadjusted pooled odds ratio (OR) of 1.73 (95% confidence interval [CI] 1.50–2.00) and an adjusted OR of 1.38 (95% CI 1.25–1.53). Patients with a premorbid history of hypertension had higher rates of cardiovascular and renal comorbidities, poorer neurological status ($p < 0.001$), and higher odds of neurological complications including cerebral infarctions, hydrocephalus, rebleeding, and delayed ischemic neurological deficits. Worsening neurological status was strongly independently associated with poor outcome, including WFNS Grades II (OR 1.85, 95% CI 1.68–2.03), III (OR 3.85, 95% CI 3.32–4.47), IV (OR 5.58, 95% CI 4.91–6.35), and V (OR 14.18, 95% CI 12.20–16.49). Neurological status had substantial added predictive value greater than the combined value of other prognostic factors ($R^2$ increase > 10%), while the added predictive value of hypertension was marginal ($R^2$ increase < 0.5%).

CONCLUSIONS This study confirmed the strong prognostic effect of neurological status as measured on the WFNS scale and the independent but weak prognostic effect of premorbid hypertension. The effect of premorbid hypertension could involve multifactorial mechanisms, including an increase in the severity of initial bleeding, the rate of comorbid events, and neurological complications.

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KEYWORDS subarachnoid hemorrhage; prognostic factors; hypertension; neurological status; meta-analysis; outcomes; vascular disorders

ABBREVIATIONS C-1 = CONSCIOUS I trial; CHF = congestive heart failure; CI = confidence interval; D-SAT = University of Washington database of subarachnoid treatment; DIND = delayed ischemic neurological deficit; GOS = Glasgow Outcome Scale; HHU = Heinrich Heine University Concomitant Intraventricular Fibrinolysis and Low-Frequency Rotation after Severe Subarachnoid Hemorrhage Trial; IHAST = Intraoperative Hypothermia for Aneurysm Surgery Trial; IMASH = Intravenous MASH; ISAT = International Subarachnoid Aneurysm Trial; IVH = intraventricular hemorrhage; MASH = Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage; OR = odds ratio; RCT = randomized controlled trial; SAH = subarachnoid hemorrhage; SAHIT = SAH International Trialists; SHOP = Subarachnoid Hemorrhage Outcomes Project; WFNS = World Federation of Neurosurgical Societies.


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**Methods**

**SAHIT Data**

The SAHIT repository contains prospectively collected, observational, and RCT data sets of patients with aneurysmal SAH who received treatment in the last 2 decades. Anonymized individual patient data were available on premorbid history of hypertension in 6 (n = 7249) of the 14 studies currently archived in the repository, and on patient neurological status measured on the World Federation of Neurosurgical Societies (WFNS) scale in 10 (n = 10,869) of these 14 studies. Included studies reflected, observational, and RCT data sets of patients with subarachnoid aneurysm affects predominately young adults and results in premature death in about 40% of patients. Survivors are largely left with prolonged functional impairments requiring their dependence on others to meet daily needs. It is now recognized that aneurysmal SAH is the end result of a chronic disorder of cerebral arteries and that the formation, growth, and eventual rupture of aneurysms is facilitated by preexisting hypertension. Hypertension has been identified as the most common comorbid disease, with reported prevalence estimates exceeding 40% in some studies. Despite a growing body of literature examining the relevance of hypertension to clinical outcomes after SAH, no clear evidence exists as to whether a premorbid history of hypertension is independently associated with outcome after SAH. While older studies focused on mortality outcomes and did not fully account for the influence of confounding factors such as patient age, more contemporary studies with better risk adjustment have also offered contradictory findings.

Patient neurological status is the single most important indicator of the severity of brain injury soon after SAH and is critical to treatment decisions and prediction of outcome. However, accurate estimation of the prognostic strength of neurological status has been challenging as investigators have usually focused on prognostic associations only in the context of patients who were enrolling as investigators have usually focused on preexisting hypertension. Hypertension has been identified as the most common comorbid disease, with reported prevalence estimates exceeding 40% in some studies. Despite a growing body of literature examining the relevance of hypertension to clinical outcomes after SAH, no clear evidence exists as to whether a premorbid history of hypertension is independently associated with outcome after SAH. While older studies focused on mortality outcomes and did not fully account for the influence of confounding factors such as patient age, more contemporary studies with better risk adjustment have also offered contradictory findings.

Patient neurological status is the single most important indicator of the severity of brain injury soon after SAH and is critical to treatment decisions and prediction of outcome. However, accurate estimation of the prognostic strength of neurological status has been challenging as investigators have usually focused on prognostic associations only in the context of patients who were enrolled into randomized clinical trials (RCTs) or single-hospital cohorts, with risk adjustment for a variable set of confounders. In this study, our aim was to investigate the role of premorbid history of hypertension and patient neurological status as prognostic factors in SAH, using individual patient data in the SAH International Trialists (SAHIT) repository (see Appendix for names of members in SAHIT collaboration).

**Statistical Analysis**

The distributions of variables were examined by frequency tables. Trends across ordered categorical variables were examined for significance using the Wilcoxon rank-sum test. Prognostic associations were investigated separately for history of premorbid hypertension and WFNS grade. Univariate association was estimated in patient-level meta-analyses. Meta-analyses were performed by fitting proportional odds logistic regression models to estimate prognostic associations across the ordinal categorical GOS for each study, and then pooling the derived effect-size estimates across studies by using a random effects model. A test of heterogeneity was performed to evaluate the likelihood of between-study variations in prognostic associations.

Multivariable analyses were thereafter performed to estimate the adjusted effect of premorbid hypertension or neurological status while accounting for other prognostic factors. This was achieved by fitting proportional odds logistic regression models to estimate prognostic associations across the ordered categories of the GOS. The models sequentially adjusted for core demographic, clinical, neuroimaging, and treatment factors that could confound the prognostic effect of premorbid hypertension or neurological status. The first model (Model A) adjusted for the fixed effect of study only. The second model (Model B) additionally adjusted for age and neurological status (age only in the case of neurological status as a predictor of interest). The third adjustment model (Model C) further adjusted for the effect of neuroimaging factors (Fisher CT clot burden, ruptured aneurysm location and size). The full model (Model D) further adjusted for the effect of modality of treatment (clipping vs coiling vs conservative treatment). To examine whether hypertension or neurological status added incremental predictive value above the combined value of other factors in the adjustment models, we computed and plotted differences in Nagelkerke’s R² values (partial R²) of the adjustment models when hypertension or neurological status is included and excluded from the models. These partial R² values provide a measure of the relative importance of a prognostic factor.

We secondarily analyzed the relation between premorbid hypertension and selected comorbidities (medical and neurological complications) after SAH, to further ascertain the putative pathways by which premorbid hypertension influences the outcome of patients with SAH, if any. First, binary logistic regression models were fitted to evaluate the relation between premorbid hypertension and a history of myocardial infarction, atrial fibrillation, congestive heart failure (CHF), and renal disease, and the occurrence of hyperglycemia, renal failure, fever, and anemia during the inpatient course. We also evaluated the relation between premorbid hypertension and the occurrence of cerebral infarction, hydrocephalus, intraventricular complications, rebleeding, and delayed ischemic neurological deficit (DIND) during the inpatient course. Second, we adjusted the full model (Model D),...
examining the relation between premorbid hypertension and GOS outcome for the main effect of those comorbid factors and complications that were found to be related to premorbid hypertension, to examine how the prognostic strength of premorbid hypertension is impacted by further adjustment for comorbid factors and complications. Missing data were imputed using the technique of multiple imputations by chained equations. In all, we imputed 3% of total data points required for analysis of the effect of premorbid hypertension and 8.8% of total data points required for analysis of the effect of neurological status. The imputation models contained all covariates, GOS scores, and dummy variables for study. Twenty imputed datasets were generated for analyses. The significance level was set at $p < 0.05$. Meta-analysis was performed using Stata software (version 12.1, StataCorp), and other analyses were performed with the R software (version 2.15.3, R Foundation for Statistical Computation; http://www.r-project.org/) using the “rms” and “MICE” packages.

Results

The average age of the patients was 52.5 ± 13.4 years, and most were women (74.2%). The overall proportion of patients with a premorbid history of hypertension was 37.5% (range across studies 31%–48%). The distribution of neurological status was U-shaped across studies, except for the Intraoperative Hypothermia for Aneurysm Surgery study (IHAST, which excluded poor grade patients a priori); the ISAT; and data from Heinrich Heine University Concomitant Intraventricular Fibrinolysis and Low-Frequency Rotation after Severe Subarachnoid Hemorrhage Trial (HHU), which excluded good-grade patients a priori (Fig. 1). Patients with a premorbid history of hypertension were older and more likely to present with worse neurological status than patients without premorbid hypertension ($p \leq 0.001$). These patients experienced progressively worse crude outcome at 3 months (Table 1).

A premorbid history of hypertension was consistently associated with poorer outcome across studies (Fig. 2); the unadjusted odds ratio (OR) was 1.73 (95% confidence interval [CI] 1.50–2.00). There was no evidence of between-study heterogeneity in the estimates of the effect of premorbid hypertension ($I^2$ test of heterogeneity = 44.5%, $p = 0.108$).

Adjusting the effect of premorbid hypertension for age and neurological status resulted in a moderate decrease in the magnitude of the effect of premorbid hypertension (OR 1.37, 95% CI 1.24–1.52; Model B), suggesting that age and neurological status mediates part of the effect of premorbid hypertension on outcome. Further adjusting for CT clot burden, aneurysm size and location (Model C), and modality of treatment (Model D) had no further effect on the strength of the relation of hypertension with outcome (Table 2). In the secondary analysis, we found that patients with a premorbid history of hypertension had a significantly higher prevalence of preexisting cardiovascular events and renal disease, and higher rates of medical and neurological complications than patients without a premorbid history of hypertension (Table 3). In adjusted analyses, premorbid hypertension was independently associated with a history of myocardial infarction, a history of kidney disease, and higher odds of renal failure and fever, but not with higher odds of hyperglycemia, anemia, and pulmonary edema. Premorbid hypertension

![Fig. 1. Bar graph of the percentage distribution of neurological status (WFNS grade) in the included studies. Figure is available in color online only.](image-url)
was also independently associated with higher odds of neurological complications including cerebral infarction, hydrocephalus, intraventricular hemorrhage (IVH), rebleeding, and DINDs (Table 3). When we included rebleeding in the full adjustment model examining the relation of hypertension to GOS outcome (Model D), there was a slight reduction in the OR associated with the effect of premorbid hypertension, from 1.38 to 1.32, indicating rebleeding had a further explanatory effect on the relation between premorbid hypertension and outcome. Similar adjustment for history of myocardial infarction, history of kidney disease, renal failure, fever, cerebral infarction, hydrocephalus, IVH, and DINDs during admission had no effect on the prognostic strength of premorbid hypertension.

We found a strong prognostic effect of admission WFNS grade (Fig. 3, Table 2). Meta-analysis (Fig. 3) demonstrated each increase in neurological status on the WFNS grade resulted in an approximately doubling of the risk of poor outcome at 3 months. Between-study heterogeneity in the estimate of the effect of neurological status on the WFNS scale was not significant for all grades of WFNS, except for WFNS Grade V (poorest grade) patients: Grade II $I^2 = 17.3\%$, $p = 0.29$; Grade III $I^2 = 44.8\%$, $p = 0.05$; Grade IV $I^2 = 11.0\%$, $p = 0.35$; Grade V $I^2 = 78\%$, $p < 0.001$. Sequentially adjusting the effect of neurological status for age, neuroimaging covariates, and modality of treatment had only a slight effect on the magnitude of the effect of neurological status. In the full adjustment model (Model D), the ORs associated with the effect of neurological status were: WFNS Grade II, OR 1.85, 95% CI 1.68–2.03; WFNS Grade III, OR 3.85, 95% CI 3.32–4.47; WFNS Grade IV, OR 5.58, 95% CI 4.91–6.35; and WFNS Grade V, OR 14.18, 95% CI 12.20–16.49.

When we evaluated the prognostic strength of premorbid hypertension and neurological status in terms of added predictive value (Fig. 4), we found that premorbid hypertension added only marginal predictive value to adjustment models already containing prognostic factors. The partial $R^2$ in adjustment models was less than 0.5%. In contrast, admission neurological status had added incremental predictive value beyond those of other covariates in the adjustment models. The unadjusted $R^2$ was 22.7%. The partial $R^2$ in adjustment models was 14.0% (Model B), 14.2% (Model C), and 13.0% (Model D).

**Discussion**

This study addressed the inconsistencies in the literature regarding the role of premorbid history of hypertension as a prognostic factor in SAH. We found consistent evidence in support of a significant association between premorbid history of hypertension and poor outcome at 3 months. Although the association was weakened after adjusting for the effect of other prognostic factors, the effect of history of hypertension remained independent of these factors, suggesting that a premorbid history of hypertension is an independent prognostic factor for 3-month outcome after aneurysmal SAH. The study, however, demonstrated that premorbid hypertension added marginal prognostic information to models already containing other prognostic factors, such as age, neurological status, CT clot burden, aneurysm location and size, and method of treatment, suggesting that premorbid hypertension is a weak prognostic factor in SAH. Many studies have been published in the literature to support, refute, or an association between premorbid hypertension and outcome after SAH. The design of the present study enabled us to address a number of reasons that could have potentially contributed to the conflicting results of prior studies, including reasons such as variability in hypertension prevalence across studies, differences in case mix between centers, inadequate statistical power, lack of adjustment for important confounders, or differences in outcome measures due to dichotomization of the GOS to
evaluate the prognostic effect of hypertension for mortality or risk of unfavorable outcome.

Of interest is the likely mechanism by which premorbid hypertension could increase the risk of poor outcome after SAH. Juvela alluded to the effect of chronic hypertension on arteriolar smooth muscle cells causing hypertrophy and premorbid narrowing of cerebral arteries, which could predispose to a higher risk of ischemic injuries after SAH. Other researchers have shown that cerebral infarction after SAH increases the likelihood of unfavorable outcome 5-fold and is significantly predicted by a history of hypertension. One study found that a higher risk of atherosclerosis independently predicted poor outcome in patients with SAH, which was unrelated to the occurrence of delayed cerebral ischemia, but was, in part, related to a marked decrease in rebleeding in patients with SAH who did not have or had minor degrees of atherosclerosis. A recent study found more severe initial bleeding, higher risk of rebleeding, and higher risk of in-hospital mortality in patients with premorbid hypertension relative to those without hypertension. Our own analysis corroborated the findings of previous studies. We demonstrated premorbid hypertension to be associated with more severe initial bleeding, cardiovascular and renal comorbidities, and a higher risk of medical and neurological complications. In particular, we found that accounting for the effects of age, neurological status and rebleeding decreased the magnitude of the effect of hy-

### Table 2. Relation of premorbid hypertension and neurological status to outcome in adjusted analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.82 (1.66–1.99)</td>
</tr>
<tr>
<td>WFNS grade</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2.02 (1.84–2.21)</td>
</tr>
<tr>
<td>III</td>
<td>6.62 (5.84–7.50)</td>
</tr>
<tr>
<td>IV</td>
<td>17.94 (15.54–20.70)</td>
</tr>
</tbody>
</table>

* Model A = predictor (hypertension or WFNS grade) + study; Model B = Model A + WFNS grade + age (age only in the analysis of the effect of neurological status); Model C = Model B + neuroimaging factors (Fisher grade + artery + ruptured aneurysm size); Model D = Model C + repair (clipping vs coiling vs conservative).

### Table 3. Relation of premorbid hypertension to comorbid conditions and complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (Event)*</th>
<th>Premorbid Hypertension</th>
<th>Adjusted OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>Yes (%)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6310 (145)</td>
<td>38 (1.0)</td>
<td>107 (4.5)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2421 (63)</td>
<td>21 (1.6)</td>
<td>42 (3.9)</td>
</tr>
<tr>
<td>CHF</td>
<td>2417 (28)</td>
<td>2 (0.2)</td>
<td>26 (2.4)</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>1422 (34)</td>
<td>8 (1.1)</td>
<td>26 (3.8)</td>
</tr>
<tr>
<td>Medical complications$§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1442 (730)</td>
<td>334 (44.9)</td>
<td>396 (56.7)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2440 (46)</td>
<td>9 (0.7)</td>
<td>37 (3.4)</td>
</tr>
<tr>
<td>Fever</td>
<td>5584 (2133)</td>
<td>1233 (35.6)</td>
<td>900 (42.4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1854 (518)</td>
<td>271 (26.3)</td>
<td>247 (30.0)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>4919 (553)</td>
<td>289 (9.4)</td>
<td>264 (14.3)</td>
</tr>
<tr>
<td>Neurological complications§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>7100 (1588)</td>
<td>928 (20.9)</td>
<td>660 (24.8)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>6758 (2718)</td>
<td>1557 (36.8)</td>
<td>1161 (46.0)</td>
</tr>
<tr>
<td>IVH</td>
<td>5809 (2729)</td>
<td>1566 (42.7)</td>
<td>1163 (54.2)</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>2089 (194)</td>
<td>88 (4.4)</td>
<td>106 (11.6)</td>
</tr>
<tr>
<td>DIND</td>
<td>7275 (1626)</td>
<td>979 (21.4)</td>
<td>647 (24.0)</td>
</tr>
</tbody>
</table>

* “N” indicates the total number of patients with known status on the variable, whereas “Event” is the number of patients who had the event.
† Interpretation of odds ratios: Patients with a history of hypertension had 3.26 times higher odds of a history of myocardial infarction compared with patients without a history of hypertension, after adjusting for age and the fixed effect of the study.
‡ Adjusted for fixed effect of study and age.
§ Adjusted for fixed effect of study and age, and WFNS grade.
hypertension, suggesting that these factors directly mediate, in part, the effect of premorbid hypertension on SAH outcome. Nonetheless, the effect of hypertension was still independent of the intermediary effect of age, neurological status, and rebleeding, suggesting other factors hitherto unknown to us may be involved as well. Although premorbid hypertension was shown to be a weak prognostic factor, the independent relation of premorbid hypertension to neurological complications in the present study and in previous studies suggests the need to consider a premorbid history of hypertension as a potential confounder in studies evaluating the effects of new therapies using neurological complications such as DIND or rebleeding as surrogate outcome measures.

Admission neurological status reflects the severity of brain injury at the time of rupture. It is considered the single most important predictor of outcome in patients with SAH.6,37 Our analysis is consistent with this established finding. We further demonstrated that neurological status had substantially added predictive value above the combined value of other prognostic factors. The meta-analysis demonstrated that each increase in neurological grade resulted in an approximately doubling of the risk of poor outcome at 3 months. The CIs around the effect estimates in the present study, which are narrower than those of previous studies, indicate a more precise estimation of the prognostic strength of neurological status as measured on the WFNS scale. The high between-study heterogeneity noted among WFNS Grade V (poorest grade) patients could be indicative of the preferential exclusion of Grade V patients from RCTs.

The main strength of this study is the large size of the study population and the use of meta-analysis and multivariable analysis involving individual patient data to standardize analysis in each primary study, derive summary effect estimates directly from raw data, and adjust for a consistent set of adjustment factors, including repair modality. Considering the large sample size, case mix of patient populations, and practice settings reflected in the study, we have more precisely estimated the magnitude of the prognostic effect of premorbid hypertension and neurological status and most probably provided a level of evidence higher than prior studies in the literature on the prognostic value of these risk factors.

**FIG. 3.** Forest plot demonstrating consistency in the effect of neurological status (WFNS Grade I was the baseline category against which other categories of WFNS grade [Grade II, A; Grade III, B; Grade IV, C; Grade V, D] were compared).
However, the study has some limitations. How premorbid hypertension was precisely defined in all studies could not be ascertained, although the incidence is comparable across studies. The present study shares with previous studies the limitation of not investigating whether the prognostic effect of premorbid hypertension is related to the duration or severity of hypertension, or the adequacy or otherwise of blood pressure control. The limitations of using the WFNS scale for grading neurological status has been reviewed elsewhere. Although some other scales have shown relatively better interobserver agreement and a more graduated relationship to outcome than the WFNS scale, they were not better than the latter in the capacity to differentiate patients by outcome and are less popular than the WFNS scale. Some researchers have also argued about the optimal time point for assessing neurological status for purposes of prognostication, with different time points proposed in the literature, including clinical assessment soon after injury, and after neurological resuscitation. Third, because the study is not population based, there is the potential that we systematically underestimated the magnitude of prognostic associations, as patients who died prior to hospital admission were not accounted for. Furthermore, the data were weighted toward trial patients. However, our analysis showed that the effect of this skewed distribution may be relevant only with respect to the patients with the poorest grades. By imputing data, we made the assumption that missing data were missing at random, which may not necessarily be so, but there is no precise method to verify if data are truly missing at random. Nonetheless, the proportion of imputed data was sensible. Availability bias is possible, because the study included only a fraction of the potential number of previous RCTs and well-conducted prospective observational studies or hospital registries possible. The possibility of reporting (publication) bias was not examined because we considered a priori that the number of studies included in the meta-analyses was insufficient to reliably test for reporting bias; furthermore, the primary purpose of the analyzed studies was not to investigate prognostic associations. The GOS is a rather crude measure of functional status after SAH, but in the absence of better, refined outcome measures specific to SAH, the GOS continues to be widely used.

Conclusions

We have estimated the prognostic effect of neurological status and premorbid history of hypertension in larger cohorts than any prior studies, demonstrating their added incremental value beyond those of other prognostic factors. Our data may have implications for future interventional studies in SAH, in particular RCTs considering patient enrollment by prognostic targeting or stratification randomization on the basis of neurological status. Furthermore, this study may have settled a lingering question in the literature regarding the prognostic relevance of premorbid history of hypertension in SAH.

Appendix

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