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ABSTRACT

BACKGROUND AND PURPOSE: Early brain injury is a major determinant of clinical outcome in poor-grade (World Federation of Neurosurgical Societies [WFNS] IV–V) aneurysmal SAH and is radiologically defined by global cerebral edema. Little is known, though, about the effect of global intracranial hemorrhage volume on early brain injury development and clinical outcome.

MATERIALS AND METHODS: Data from the multicentric prospective Poor-Grade Aneurysmal Subarachnoid Hemorrhage (POGASH) Registry of consecutive patients with poor-grade aneurysmal SAH admitted from January 1, 2015, to August 31, 2022, was retrospectively evaluated. Poor grade was defined according to the worst-pretreatment WFNS grade. Global intracranial hemorrhage volume as well as the volumes of intracerebral hemorrhage, intraventricular hemorrhage, and SAH were calculated by means of analytic software in a semiautomated setting. Outcomes included severe global cerebral edema (defined by Subarachnoid Hemorrhage Early Brain Edema Score grades 3–4), in-hospital mortality (mRS 6), and functional independence (mRS 0–2) at follow-up.

RESULTS: Among 400 patients (median global intracranial hemorrhage volume of 91 mL; interquartile range, 59–128), severe global cerebral edema was detected in 218/400 (54.5%) patients. One hundred twenty-three (30.8%) patients died during the acute phase of hospitalization. One hundred fifty-five (38.8%) patients achieved mRS 0–2 at a median of 13 (interquartile range, 3–26) months of follow-up. Multivariable analyses showed global intracranial hemorrhage volume as independently associated with severe global cerebral edema (adjusted OR, 1.009; 95% CI, 1.004–1.014; $P < .001$), mortality (adjusted OR, 1.006; 95% CI, 1.001–1.01; $P = .018$) and worse clinical outcome (adjusted OR, 0.992; 95% CI, 0.98–0.996; $P < .010$). The effect of global intracranial hemorrhage volume on clinical-radiologic outcomes changed significantly according to different age groups (younger than 50, 50–70, older than 70 year of age). Volumes of intracerebral hemorrhage, intraventricular hemorrhage, and SAH affected the 3 predefined outcomes differently. Intracerebral hemorrhage volume independently predicted global cerebral edema and long-term outcome, intraventricular hemorrhage volume predicted mortality and long-term outcome, and SAH volume predicted long-term clinical outcome.

CONCLUSIONS: Global intracranial hemorrhage volume plays a pivotal role in global cerebral edema development and emerged as an independent predictor of both mortality and long-term clinical outcome. Aging emerged as a reducing predictor in the relationship between global intracranial hemorrhage volume and global cerebral edema.

ABBREVIATIONS: aSAH = aneurysmal SAH; aOR = adjusted OR; DCI = delayed cerebral ischemia; EBI = early brain injury; EVD = external ventricular drain; GCE = global cerebral edema; GHV = global intracranial hemorrhage volume; ICH = intracerebral hemorrhage; ICP = intracranial pressure; IQR = interquartile range; IVH = intraventricular hemorrhage; LOC = loss of consciousness; POGASH = Poor-Grade Aneurysmal Subarachnoid Hemorrhage; SEBES = Subarachnoid Hemorrhage Early Brain Edema Score; WFNS = World Federation of Neurosurgical Societies; V = volume

Aneurysmal rupture, microcirculation compromise, and elevated intracranial pressure (ICP) contribute to the development of early brain injury (EBI), which plays a pivotal role in determining disability and mortality in patients with aneurysmal SAH (aSAH).[1,2]

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EBI, which translates clinically in the severe neurologic deficits (World Federation of Neurosurgical Societies [WFNS] IV–V) on admission as well as in loss of consciousness (LOC) for the effect of transient cerebral ischemia,[3] has emerged as a leading cause of mortality in the past decades, outnumbering the proportion of patients dying from either rebleeding or delayed cerebral ischemia (DCI) related brain swelling.[4,5] Poor aSAH grades and ictal LOC have been shown to be clinical predictors of global cerebral edema (GCE) which is, in turn, the only radiologic marker of EBI, evaluated on a 4-grade scale, Subarachnoid Hemorrhage Early Brain Edema Score (SEBES).[6,7] The modified Fisher grade, a commonly used and accepted scale grading the amount of intracranial bleeding, has not been shown to be predictive of GCE.[6] In this study we sought to evaluate the effects of the primary hemorrhage volume, calculated on the first admission CT examination after aneurysmal rupture, on EBI and clinical outcome in a national prospective multicentric registry on patients with poor-grade aSAH.

MATERIALS AND METHODS

Data Availability

All data and materials can be accessed on reasonable request addressed to the Principal Investigator of the Registry, Pietro Panni, MD.

Standard Protocol Approvals, Registrations, and Patient Consents

The local ethics committees approved both the inclusion and use of patient data in the Poor-Grade Aneurysmal Subarachnoid Hemorrhage (POGASH) Registry (NCT04945603). Patients' data were managed according to the Declaration of Helsinki. Informed consent for the scientific use of clinical-radiologic anonymized data was signed by patients' relatives or proxies.

Study Population and Variable Description

POGASH (NCT04945603) is an ongoing prospective multicentric registry pooling anonymized data from prospectively collected and maintained institutional databases at 9 academic institutions/tertiary referral centers on a national level. All consecutive poor grade aSAH patients admitted to the emergency department of each participating center from June 2016 to August 2022 to provide at least 6 months of follow-up for patients surviving the acute phase of hospitalization were included for the present study.

Inclusion criteria for the present study were as follows:

- Patients consecutively admitted to the emergency department because of WFNS IV–V aSAH, regardless from treatment indication/abstention
- Available clinical follow-up
- Available anonymized DICOM files of the admission CT scan.

Exclusion criteria were as follows:

- Patients younger than 18 years of age
- aSAH due to trauma or vascular malformations other than cerebral aneurysms.

A detailed description of the entire variable list is provided as Online Supplemental Data.

Variables were grouped according to baseline and demographic features as well as the 4 different phases of the clinical course of the disease: EBI, intensive care unit, hospitalization, follow-up. Considering the EBI phase, poor grade was defined according to the worst pretreatment clinical grade, ie, at nadir.[8,9] LOC was recorded only in cases of at least >60-minute length, for this has been shown to be peculiar to early brain injury in the most severe forms of aSAH, regardless of subsequent recovery or direct intubation.[3] Time-metrics variables (time to external ventricular drain [EVD] placement and time to treatment of the culprit aneurysm) were derived by directly examining the documents of the ambulance service. Time of the ambulance call was considered as a proxy for aSAH onset. DCI was defined according to a previously reported definition.[10] Clinical outcome was scored according to the mRS assessed by qualified personnel in each center according to a predefined follow-up schedule.

Neuroradiologic Evaluation of the Admission CT Scan

CT axial slices obtained for the selected patients on admission were retrieved from each institution's digital archive system, stored as DICOM files, and sent, anonymized, to the promoting center core imaging lab (Neuroradiology Department, San Raffaele University Hospital in Milan) for a re-evaluation blinded to the results of treatment or clinical follow-up. Each CT scan was evaluated for the presence of acute hydrocephalus, modified Fisher grade,[11] the presence of acute subdural hematoma, intraventricular hemorrhage (IVH), intracerebral hemorrhage (ICH), and GCE.

The presence of GCE was scored according to the presence, at the first admission CT scan, of complete or near-complete effacement of the hemispheric sulci and basal cisterns and/or bilateral and extensive disruption of the hemispheric gray-white matter junction.[6] This evaluation has been performed on 2 admission CT slices, the first one at the level of basal ganglia/subinsular region and the second, more cranial, at the level of the centrum semiovale.[7] GCE was dichotomized and considered to be present for SEBES grades 3–4 (clear and extensive bihemispheric involvement).

Volumetric Analysis of Global Intracranial Hemorrhage Volume

The volumetric analysis method has been previously described.[12] Software-based semiautomatic segmentation and volumetric quantification were performed using OsiriX MD (https://www.osirix-viewer.com/). The determination of blood volume according to the ROI methodology was based on a tissue-specific threshold interval between 45 and 90 HU, to avoid bone-related artifacts in anatomically challenging regions like the skull base and the parenchyma-skull interface at the convexity and the manual outline of areas of blood on each CT section. The pixels with a similar attenuation in the neighboring areas were automatically connected by the software. Hemorrhage volumes were calculated in milliliters obtained by multiplying section thickness by the hemorrhage area in cases of volumetric scans. For nonvolumetric scans (eg, posterior fossa imagined with 2.5-mm slices and supratentorial space with 5-mm slices), 2 separate volumes were derived, one for posterior fossa and one for supratentorial space, and their sum was calculated. An example of global hemorrhage

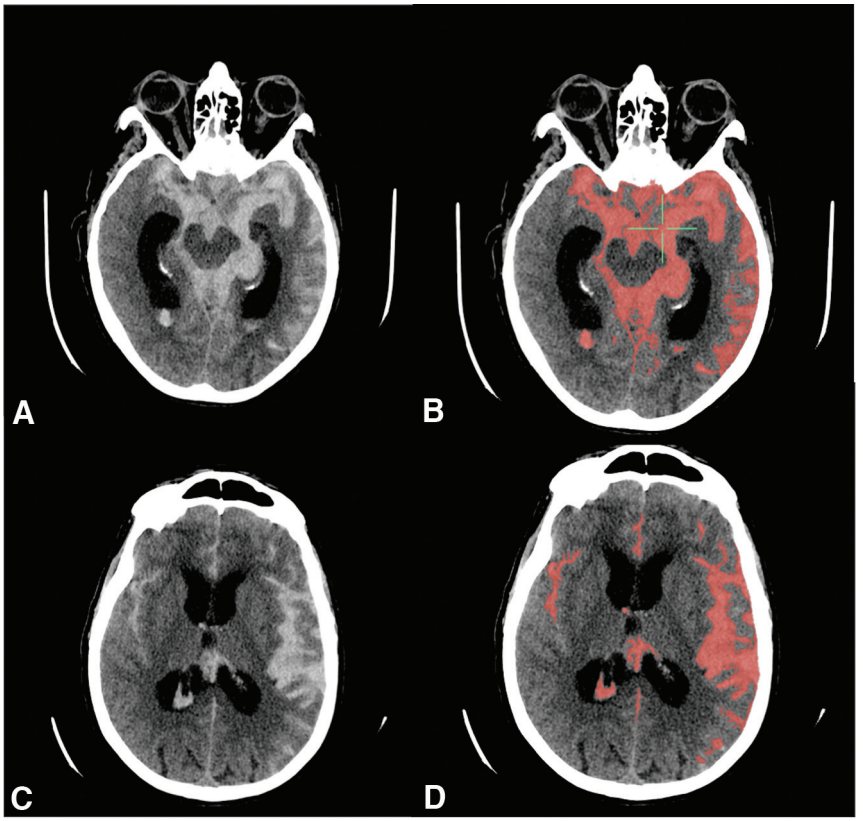


FIG 1. Example of GHV semiautomatic segmentation with the neighboring method. The threshold was set between 45 and 90 HU. *A* and *C*, Basal hyperdensitites. *B* and *D*, The results of the semiautomatic segmentation of hemorrhage with a threshold set between 45 and 90 HU.

volume (GHV) segmentation is provided in Fig 1. The same process was applied to derive volumes for GHV distributions, namely the volume of ICH (ICH-V), volume of IVH (IVH-V) and volume of SAH (SAH-V).

Statistical Analysis

Quantitative variables are expressed as means (SD), and categoric variables are expressed as numbers (percentage). To evaluate interobserver agreement for GHV, 2 independent neuroradiologists, with >10 years of experience, blinded to treatment choice, clinical evolution, and outcome, evaluated a random sample made up of the first 80 consecutive CT scans included in the Registry (20% of the studied population), chosen regardless of center provenience, and calculated the GHV. A Bland-Altman graph was constructed and inspected to assess value distribution, and it is reported as Online Supplemental Data. Age stratification was based on its median value and interquartile range (IQR) distribution in the studied population. The aim of the present study was to ascertain the role of GHV on the development of EBI (SEBES grades 3–4 GCE as a radiologic proxy for EBI) and clinical outcome: in-hospital mortality (mRS 6 vs 0–5) and long-term clinical outcome (mRS 0–2 vs 3–6 at follow-up). Bivariate comparison and multivariable binary logistic regression analyses were performed for the 3 predefined outcomes, determining unadjusted and adjusted ORs (aORs) along with corresponding 95% CIs and *P* values for significance.

All variables emerging from bivariate comparison with $P < .2$ were included in the multivariable models. The results of multivariable modeling were expressed after adjustment for covariates and admission center, to eliminate potential biases due to center-related treatment variations. Bivariate comparison of baseline variables between the studied population and excluded patients was performed as a sensitivity analysis and is provided as Online Supplemental Data. To rule out the potentially confounding effect of hydrocephalus, it was forced into the 3 multivariable models. Bivariate and multivariable analyses for independent predictors of GCE were repeated in the subpopulation younger than 70 years of age, to rule out the potentially confounding effect of brain atrophy (Online Supplemental Data.). Scatterplots were constructed on the basis of multivariable-derived predicted probabilities of predefined outcomes. The Hosmer-Lemeshow test was performed to verify the appropriateness of each analysis. Collinearity among variables entered in the multivariable models was assessed by the variance inflation factor, with multicollinearity considered present for variance inflation factor values of any variable of at least 10. All statistical analyses were performed using SPSS, Version 20.0 (IBM) and in R environment (Version 4.1.3; http://www.r-project.org/).

RESULTS

Of 466 consecutive patients with poor-grade aSAH with available follow-up included in the Registry up to August 2022, data concerning 400 patients with available admission CT for volumetric quantification of GHV were included (flow chart included as Online Supplemental Data). Baseline characteristics and treatment-related hospitalization and follow-up of the population are reported in the Online Supplemental Data. LOC occurred more frequently in the excluded patients ($P = .017$).

Considering clinical-radiologic features of EBI, 257/400 (64.3%) patients were admitted in coma (WFNS V) and experienced prolonged LOC (74.7%). SEBES grades 3 and 4 were detected in 218/400 (54.5%) patients. The median GHV was 91 mL (IQR, 59–128 mL), median ICH-V was 14 (IQR, 4.5–32.5), median IVH-V was 12.5 (IQR, 4–26), and the median SAH-V was 73.6 (44–29). One hundred ten patients were treated surgically (27.5%), while 258 (64.5%) were treated endovascularly. Treatment abstention was chosen in 32 (8%) patients. Aneurysms were secured at a median of 5 hours (IQR 4–9 hours) since onset. One hundred twenty-three (30.8%) patients died during hospitalization. At a median follow-up of 24 months (IQR, 9–43 months), survivors had severe disabilities (median mRS, 4; IQR, 1–6), even though a nonnegligible proportion achieved functional independency (mRS 0–2; 155/400, 38.8%). The Online Supplemental Data report the

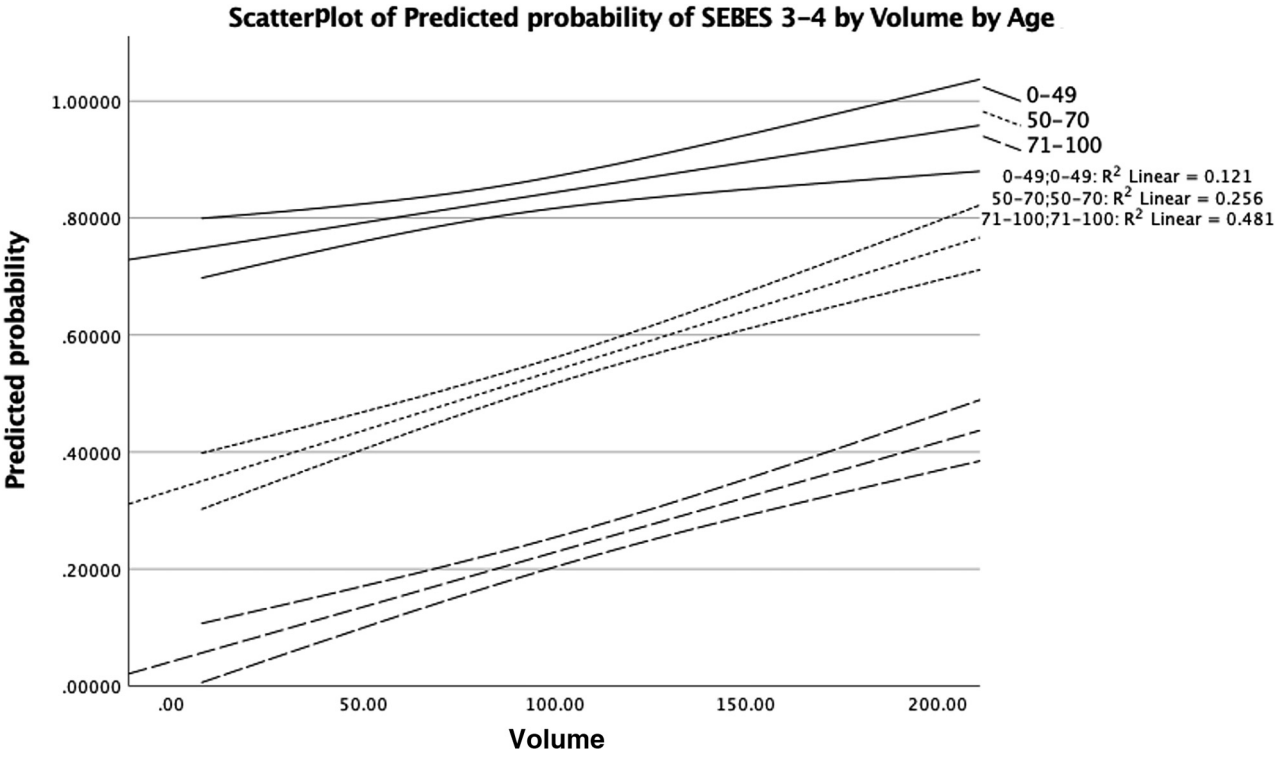


FIG 2. Scatterplot showing multivariable analysis–derived predicted probabilities of severe SEBES (SEBES grades 3–4) on the admission CT scan according to age (3 groups: younger than 50, 50–70, older than 70 years of age) and baseline GHV.

results of univariable analyses for factors associated with EBI development, in-hospital mortality, and long-term clinical outcome, respectively. The Online Supplemental Data show the results of multivariable analyses for independent predictors of severe GCE (SEBES 3–4) presence at the admission CT, in-hospital mortality, and long-term clinical outcome.

Worst pretreatment clinical grading (WFNS V at nadir), (aOR, 1.9; 95% CI, 1.2–3.2; $P = .002$) and GHV (aOR for every milliliter, 1.007; 95% CI, 1.002–1.012; $P = .007$) independently increased the chance of severe SEBES on the admission CT scan, while older age (aOR for every year, 0.90; 95% CI, 0.88–0.93; $P < .001$) independently reduced its chances. Considering in-hospital mortality, older age (aOR, 1.02; 95% CI, 1.00–1.04; $P = .014$), WFNS V (aOR, 3.7; 95% CI, 2–6.7; $P < .001$), rebleeding (aOR, 2.5; 95% CI, 1.3–4.5; $P = .003$), and GHV (aOR for every milliliter, 1.006; 95% CI, 1.001-1.01; $P = .018$) independently predicted in-hospital mortality, while EVD use (aOR, 0.48; 95% CI, 0.27–0.85; $P = .012$) was independently associated with reduced mortality.

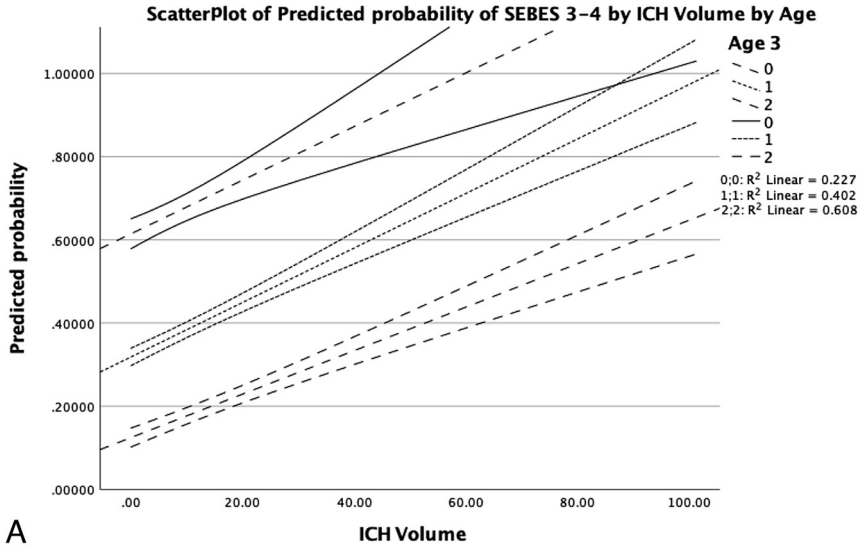
The independent predictors were retained by the multivariable analysis performed in the population younger than 70 years of age (Online Supplemental Data). Age (aOR for every year, 0.93; 95% CI, 0.91–0.96; $P < .001$), GHV (aOR for every milliliter, 0.992; 95% CI, 0.98–0.996; $P < .010$), cardiac arrest on admission (aOR, 0.12; 95% CI, 0.037–0.41; $P < .001$), WFNS V (aOR, 0.51; 95% CI, 0.28–0.9; $P = .029$), rebleeding (aOR, 0.42; 95% CI, 0.20–0.85; $P = .017$), the need for decompressive craniectomy (aOR, 0.18; 95% CI, 0.08–0.40; $P < .001$), and DCI (aOR, 0.24; 95% CI, 0.11–0.51; $P < .001$) independently predicted increased disability, while EVD use (aOR, 3.4; 95% CI, 1.6–7.4; $P = .002$) was independently associated with improved outcome. Only ICH-V, among bleeding distributions, was independently associated with SEBES 3–4, (aOR, 1.02; 95% CI, 1.01–1.04; $P < .001$). IVH-V and SAH-V emerged as independently associated with in-hospital mortality (aOR for IVH-V, 1.03; 95% CI, 1.01–1.05; $P < .001$; aOR for SAH-V, 1.015; 95% CI, 1.01–1.02; $P = .014$).

All 3 bleeding distributions emerged as independently associated with increased disability at long-term follow-up (Online Supplemental Data). Scatterplots showing multivariable analysis–derived predicted probabilities of severe SEBES on admission CT according to age and baseline GHV is reported in Fig 2, and according to age and different bleeding distributions in Fig 3. No collinearity was detected among independent predictors resulting from the multivariable models (variance inflation factor, <10). The Online Supplemental Data report number of patients along with their clinical outcome stratified per SEBES grades, age, and corresponding GHV volumes.

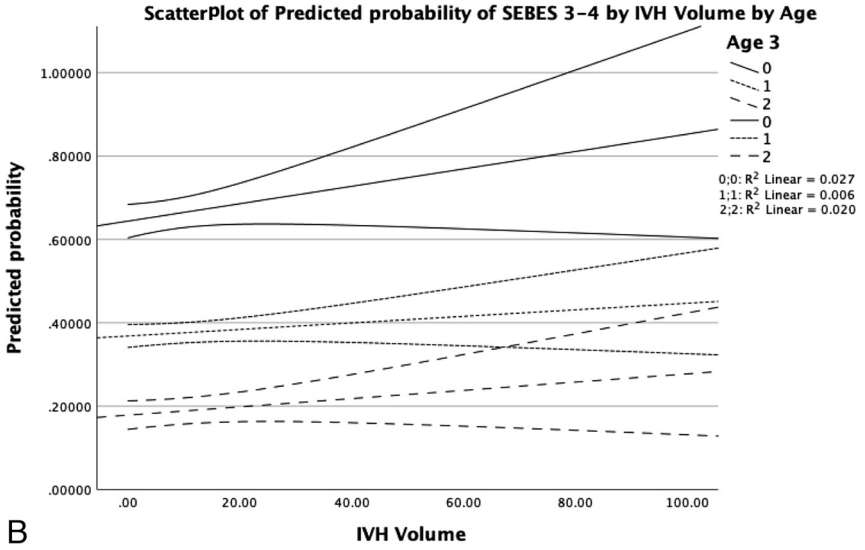
DISCUSSION

The volume of the primary bleed emerged as an independent predictor of both GCE and clinical outcome, and its clinical impact changed significantly throughout different age groups.

These results are notable because the population with poor-grade aSAH is the ideal one to study EBI, due to the high proportion of patients with severe neurologic deficit (WFNS IV–V), prolonged LOC, and the presence of GCE.[6,7] Blood extravasation occurring during aneurysmal rupture is known to cause an increase in ICP, a decrease in cerebral perfusion pressure, and transient ischemia (leading to LOC), part of EBI that,



A



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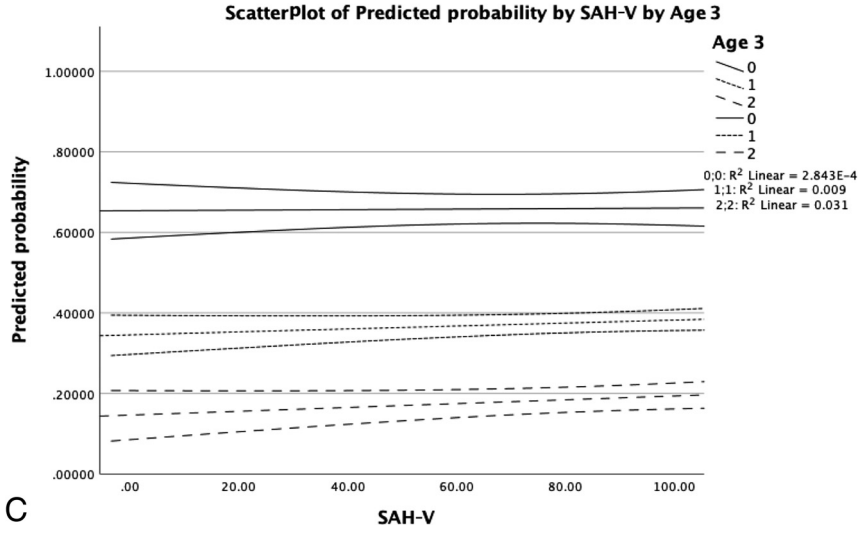

C

FIG 3. Scatterplot showing multivariable analysis–derived predicted probabilities of severe SEBES (SEBES grades 3–4) on the admission CT scan according to age (3 groups: younger than 50, 50–70, older than 70 years of age and baseline ICH-V (*A*), IVH-V (*B*), and SAH-V (*C*).

radiologically, is shown by the effacement of sulci and progressive disruption of the gray-white matter junction,[13] the so-called GCE.

The association between volumetric clot determination and outcome is not novel per se. Several articles have studied it, with most aiming at DCI prediction.[14-17] Nonetheless, the present work reports novel data concerning the largest multicentric poor-grade population available to date, which is the ideal one to study GCE, the radiologic proxy of early brain injury. In addition, the relatively long follow-up (median, 24 months) is ideal to better capture the true proportion of long-term independent survivors, strengthening the results concerning independent outcome predictors.[18]

Previous studies failed to detect an association between the modified Fisher scale and GCE.[6] This failure may likely be due to the greater granularity provided by the volumetric assessment of intracranial bleeding, which emerged as independently associated with GCE and predictive of clinical outcome. Of particular interest is the relationship between the volumetrically assessed primary bleed, age and the studied outcomes. Few data are available concerning the impact of age on EBI development;[6,13] the reported results add further insight into the pathophysiologic relationship between age and GHV (Fig 2), showing a significant variation of the effect of GHV on severe GCE development throughout different age groups. In the studied population, a given GHV can either be tolerated or associated with GCE, in-hospital death, and worse long-term clinical outcome according to the age of the patient (Fig 2, and Online Supplemental Data). This finding may suggest the presence of age-related thresholds of intracranial compliance, reminiscent of the Monro-Kellie doctrine and its subsequent modifications.[19,20] Even though we cannot completely exclude the effect of brain atrophy due to aging, the results were confirmed by sensitivity analysis in the population younger than 70 years of

age, reinforcing the hypothesis that the effect is likely due to surpassing the intracranial compliance impairment threshold.[21] It has been shown in animal models of pathologic ICP after severe ischemic or hemorrhagic stroke that besides the reduction of blood and CSF within the cranium, the brain parenchyma itself plays an active role in intracranial compliance, with evidence of neuronal somata and extracellular space shrinkage far from the lesion site.[20] GCE has recently been shown to be independently associated with ICP-related secondary events like the need for decompressive craniectomy for the treatment of refractory high ICP,[22] making it a radiologic marker of intracranial hypertension.

The different effects of the GHV call for a better understanding of age-related pathologic responses. For example, cutoff values to start ICP-reducing therapies have varied historically according to different diseases (eg, diffuse traumatic brain injury versus focal mass effect due to ICH),[23] but there is no age-related cutoff of what can or should be considered pathologic. If confirmed by future studies, the critical role of GHV, a reproducible and measurable outcome predictor, could be of interest for practitioners directly involved in the emergency management of poor-grade aSAH and could help develop tailored, patient-specific treatments and timing in the EBI phase. Most interesting, even though GHV emerged as consistently and independently associated with the 3 predefined outcomes (GCE, in-hospital mortality, and long-term clinical outcome), its different distributions, namely ICH, IVH, and SAH, affected the predefined outcomes differently (Online Supplemental Data). ICH-V, a novel finding, emerged as independently associated with GCE development, likely due to the direct mass effect and swelling associated with large ICH and clinical outcome, but not with mortality. The impact on clinical outcome of the different bleeding distributions may be, at least partly, explained by the challenges inherent in their removal: Large space-occupying ICHs are usually removed during aneurysm clipping and associated with the use of decompressive craniectomy. This outcome may explain a reduced effect on mortality, while retaining a significant effect on disability. The removal of large IVH and SAH volumes still poses significant challenges and is less straightforward in clinical practice.[24,25]

Exemplar is the effect of EVD placement on clinical outcome, which is again modified by volume and varies (Online Supplemental Data) throughout different age groups. Besides, the choice to perform a primary decompressive craniectomy, currently investigated in one ad hoc randomized controlled trial,[26] could be influenced by the relationship between GHV and age. GHV could also be used for preclinical research, because the primary bleed precedes BBB disruption, GCE, neuroinflammation and oxidative cascades, which ultimately result in neuronal death.[27] In line with recent research,[4] all mortality predictors found by the reported multivariable model refer to the hyperacute phase of aSAH, with WFNS grade, rebleeding, and LOC confirmed as outcome predictors in aSAH.[3,9,28] The beneficial role of EVD has been previously reported.[29,30] Unlike prior results, we did not find treatment complications, IVH, or DCI as independent mortality predictors in the studied population, even though all were significantly associated with it in bivariate comparison.[31] The reason may be the disproportionate importance of EBI as a mortality predictor compared with the delayed effect of DCI, which has been shown, along with decompressive craniectomy and the presence of ICH, as a predictor of increased disability.[31]

The strength of this study lies in the largest sample to date of poor-grade aSAH prospectively included in the Registry, allowing a robust analysis of outcome predictors. Moreover, it shows the feasibility of GHV calculation with DICOM sources coming from different settings and acquired with different scanners.

We acknowledge, nonetheless, several limitations, particularly those inherent to its Registry status. The absence of guidelines for the management of poor-grade aSAH adds complexity to the search for outcome predictors, and the reported results, even though each multivariable analysis was corrected for participating centers, could have unavoidable intrinsic biases. We could not provide reliable and easy-to-be-implemented cutoff volumes to predict functional independence in the studied population because they are necessarily influenced by treatment strategies. Separate studies, addressing each GHV distribution, are going to be better informative.

The reported results, though, picture the real-life poor-grade aSAH management, which deserves further research to standardize the management of such a fragile patient population. We quantified GCE, which is only a radiologic surrogate of EBI, a much more complex pathophysiologic mechanism during the early stage of aSAH. The reported results are far from fully delineating all the causative mechanisms of it, and we hope that future studies are going to address this topic. Moreover, the present study does not report cerebral edema resolution and its predictors. We hope that the results are going to be considered by future research addressing this topic.

CONCLUSIONS

GHV after aneurysmal rupture emerged as both a radiologic marker of EBI and an outcome predictor. Its effects seem to be significantly modified by age. ICH-V, IVH-V, and SAH-V have different effects on clinical outcome. This finding may be of relevance for the design of future therapeutic studies. Moreover, the reported results could be of help for practitioners involved in the management of poor-grade aSAH, particularly in the EBI phase, as well as for caregivers and practitioners involved in the subacute management of these patients.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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