Subarachnoid Hemorrhage Early Brain Edema Score (SEBES) as a radiographic marker of clinically relevant intracranial hypertension and unfavorable outcome after subarachnoid hemorrhage

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Abstract

Background and purpose: The severity of early brain edema (EBE) after aneurysm rupture was reported to be strongly associated with the risk of poor outcome after aneurysmal subarachnoid hemorrhage (SAH). Using the recently developed Subarachnoid Hemorrhage Early Brain Edema Score (SEBES), we analyzed the predictors of EBE and its impact on complications related to intracranial pressure (ICP) increase after SAH and on poor outcome.

Methods: All consecutive SAH cases treated between January 2003 and June 2016 with assessable SEBES were included (n = 745). Data on demographic characteristics, medical history, initial severity of SAH, need for conservative ICP treatment and decompressive craniectomy, occurrence of cerebral infarctions and unfavorable outcome at 6 months (modified Rankin scale score > 2) were collected. Univariable and multivariable analyses were performed.

Results: Younger age (<55 years; adjusted odds ratio [aOR] 3.16, 95% confidence interval [CI] 2.28–4.38), female sex (aOR 1.64, 95% CI 1.16–2.31), poor initial clinical condition (World Federation of Neurosurgical Societies score 4–5; aOR 1.74, 95% CI 1.23–2.46), presence of intracerebral hemorrhage (aOR 1.63, 95% CI 1.12–2.36), hypothyroidism (aOR 0.60, 95% CI 0.37–0.98) and renal comorbidity (aOR 0.29, 95% CI 0.11–0.78) were independently associated with SEBES (scores 3–4). There was an independent association between SEBES 3–4 and the need for conservative ICP treatment (aOR 2.43, 95% CI 1.73–3.42), decompressive craniectomy (aOR 2.68, 95% CI 1.84–3.89), development of cerebral infarcts (aOR 2.24, 95% CI 1.53–3.29) and unfavorable outcome (aOR 1.48, 95% CI 1.0–2.17).

Conclusions: SEBES is a reliable predictor of ICP-related complications and poor outcome of SAH. Our findings highlight the need for further research of the impact of patients’ demographic characteristics and comorbidities on the severity of EBE after SAH.
INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating type of stroke with high morbidity and mortality [1]. Common complications after the initial bleed include early brain injury (EBI), symptomatic vasospasm, and brain edema [2]. Consequently, brain swelling results in increased intracranial pressure (ICP), which increases the risk of cerebral ischemia due to a reduction of cerebral perfusion pressure [3,4]. When pathologically elevated, ICP is not manageable with conservative therapeutic options, and a decompressive craniectomy (DC) may be necessary.

For proper conservative and surgical ICP management after SAH, identification of early markers of cerebral edema is of paramount clinical importance. Treatment timing in particular has been shown to be essential for outcome of patients selected for DC [5,6]. Previously, the Subarachnoid Hemorrhage Early Brain Edema Score (SEBES) was introduced as a radiological biomarker of delayed cerebral ischemia and predictor of death or severe disability [7]. Another study supported the clinical relevance of SEBES as a prognostic tool for delayed resolution of cerebral edema associated with poor outcome after SAH [8]. However, whether SEBES can be used to predict the development of intracranial hypertension necessitating conservative and/or surgical ICP treatment is currently unknown. In addition, demographic and clinical characteristics impacting the severity of early brain edema (EBE) after SAH have thus far been poorly investigated. To date, an association between patient age and SEBES has been reported [9].

The aim of the present study was to investigate the predictive value of SEBES with regard to SAH course, with a special emphasis on the complications related to ICP increase. Moreover, we analyzed the association between the baseline characteristics of SAH patients and the severity of the condition based on the SEBES to identify the risk factors for EBE after SAH.

MATERIALS AND METHODS

Patient population

This retrospective analysis was based on an institutional observational cohort and contains all eligible consecutive cases with SAH treated at the University Hospital of Essen between January 2003 and June 2016. We included all patients with available pretreatment native computed tomography (CT) imaging (<72 h after ictus), enabling SEBES assessment (n = 745). The study was approved by the institutional ethics committee (Ethik-Kommission, Medizinische Fakultät der Universität Duisburg-Essen; registration number:15-6331-BO) and registered in the German clinical trial register (DRKS; unique identifier: DRKS00008749).

Subarachnoid hemorrhage management

Initial treatment was performed in the neurosurgical intensive care unit. Ruptured aneurysms were generally identified by digital subtraction angiography, with further treatment allocation to either coiling or clipping. Treatment of a ruptured aneurysm was usually performed within 24 h after admission. Acute hydrocephalus was treated with an external ventricular drain, which also allowed continuous monitoring of ICP. Conservative management of cerebral vasospasm included oral nimodipine and maintenance of normovolemia. Endovascular vasospasm treatment was initiated in cases of refractory cerebral vasospasm.

In patients with a pathological ICP increase >20 mmHg, conservative ICP management was initiated consisting of forced cerebrospinal fluid drainage via external ventricular drain, deep sedation and relaxation, osmotic diuresis, and maintenance of normothermia. DC was performed either at admission (primary DC) based on the decision of the neurosurgeon on duty, or during the further course (secondary DC) due to persisting pathological ICP, defined as ICP >20 mmHg for more than 30 min despite maximal conservative treatment.

Patients with chronic hydrocephalus underwent ventriculoperitoneal shunt placement. In addition to the CT scan at admission, patients underwent additional CT scans within 24 h after aneurysm treatment, after any clinical deterioration, and prior to secondary decompression and/or shunt placement. There were no relevant changes in the management protocol for SAH during the reported years.

Data management

The first available pretreatment CT scan (<72 h after ictus) was reviewed by one of the authors (M.S.), blinded at that time to any clinical information. The SEBES values for all patients in the cohort were assessed as previously described [7] (Figure 1). The remaining data on demographic characteristics, medical history, laboratory values at admission, as well as baseline patient features, certain complications and outcome of SAH, were collected from the institutional prospective database. In particular, initial clinical and radiographic severity of SAH were recorded using the World Federation of Neurosurgical Societies (WFNS) [10] and the original Fisher scale [11] scores, respectively. Functional outcome was assessed at 6 months after SAH using the modified Rankin scale (mRS) [12]. Further SAH-related variables collected from the database were:
FIGURE 1 Two exemplary cases of subarachnoid hemorrhage with mild (case A, Subarachnoid Hemorrhage Early Brain Edema Score [SEBES] = 1) and severe (case B, SEBES = 4) brain edema on the admission CT scan. SEBES was based on a scale from 0 to 4 points. At two predetermined levels in each hemisphere, one point was assigned for the absence of visible sulci caused by effacement of sulci or absence of visible sulci with disruption of the gray–white matter junction, as determined by the authors of the original publication [7].

(i) Aneurysm location and size according to diagnostic digital subtraction angiography;
(ii) Presence of intracerebral (ICH) and intraventricular hemorrhage (IVH) on the admission CT scan;
(iii) Aneurysm rebleeding before treatment;
(iv) Treatment modality;
(v) Acute hydrocephalus (need for external ventricular drain);
(vi) Need for conservative or surgical (DC) ICP treatment;
(vii) Occurrence of any systemic infections during the intensive care unit stay based on common clinical, radiographic and laboratory criteria;
(viii) Persisting hydrocephalus requiring ventriculoperitoneal shunt placement;
(ix) Angiographic vasospasm requiring intra-arterial spasmolysis [13];
(x) Development of new cerebral infarctions on the follow-up CT scans up to 6 weeks after SAH.

For statistical evaluations, SEBES was assessed in a dichotomous manner after identification of a clinically relevant threshold based on the receiver-operating characteristic (ROC) curve. Patient age was dichotomized at 55 years according to the cohort’s median age. The WFNS and Fisher scales were dichotomized into low (WFNS score 1–3/Fisher score 1–2) and high (WFNS score 4–5/ Fisher score 3–4) grades. Occurrence of cerebral infarctions was evaluated in two ways: any infarction (vs. no infarctions), and multiple territorial infarctions (vs. single territorial infarctions). Finally, unfavorable outcome at 6 months after SAH was defined as an mRS score > 2.

For univariable analyses of the associations between SEBES and the study endpoints, the chi-squared test or Fisher’s exact test were used for categorical variables. Continuous variables

Study endpoints and statistical analyses

In the present study, we addressed the association of SEBES at admission with:

(i) Demographic characteristics and medical history of the patients, as well as the baseline SAH characteristics to identify the factors related to the severity of EBE;
(ii) ICP-related SAH complications (ICP increase requiring conservative treatment and/or DC);
(iii) Other SAH complications (aneurysm rebleeding, systemic infections, angiographic vasospasm and shunt dependency);
(iv) SAH outcome (new cerebral infarctions and unfavorable outcome at 6 months).
were analyzed with the Student’s t-test for normally distributed and the Mann–Whitney U-test for non-normally-distributed data. Statistically significant correlations with a p value of <0.1 were included in the multivariable binary logistic regression analysis. For the analysis of independent predictors of SAH complications and functional outcome, the multivariable analysis was adjusted for major baseline SAH characteristics: patient age; WFNS and Fisher grades; and presence of acute hydrocephalus. Data analysis was performed using SPSS statistical software (version 25, SPSS Inc., IBM). Differences with a p value of ≤0.05 were considered statistically significant.

RESULTS

Patient population

Between January 2003 and June 2016, a total of 994 patients with acute SAH were treated at our hospital. Of those, 745 patients with assessable SEBES values were included in the study. The baseline characteristics of the patients are presented in Supplementary Table S1.

SEBES and initial SAH severity

The proportion of patients with 0, 1, 2, 3 and 4 points on the SEBES was 11%, 14%, 23%, 17% and 35%, respectively. Based on the association with the primary SAH outcome endpoints on the ROC curves, SEBES was dichotomized into low (scores 0–2; n = 358 [48.1%]) and high (scores 3–4; n = 387 [51.9%]) grade.

Patients with SAH who had a high SEBES were more likely to present with higher WFNS (odds ratio [OR] 2.11, 95% confidence interval [CI] 1.57–2.83) and Fisher grades (OR 1.71, 95% CI 1.04–2.83), ICH (OR 1.99, 95% CI 1.46–2.71), and acute hydrocephalus (OR 1.40, 95% CI 0.99–1.96), and were more frequently selected for aneurysm clipping (OR 1.58, 95% CI 1.17–2.14). There was no difference with regard to aneurysm location and size, and presence of IVH between high and low SEBES (Supplementary Table S2). In the multivariate analysis, high WFNS grade (adjusted odds ratio [aOR] 1.74, 95% CI 1.23–2.46) and ICH presence (aOR 1.63, 95% CI 1.12–2.36) were independently associated with high SEBES (Table 1).

Patient characteristics as SEBES predictors

In the univariable analysis (Table S2), patients with high SEBES were more likely to be younger (<55 years; OR 3.12, 95% CI 2.31–4.20) and female (OR 1.33, 95% CI 0.98–1.81). In addition, patients with certain pre-existing morbidities (arterial hypertension [OR 0.59, 95% CI 0.43–0.80], hyperlipidemia [OR 0.61, 95% CI 0.36–1.02], hypothyroidism [OR 0.59, 95% CI 0.37–0.94], hyperuricemia [OR 0.12, 95% CI 0.03–0.51], diabetes mellitus [OR 0.50, 95% CI 0.26–0.98], cardiac [OR 0.47, 95% CI 0.29–0.75] and renal diseases [OR 0.25, 95% CI 0.10–0.62]) were less likely to have a high SEBES after SAH.

In the multivariable analysis (Table 1), we found younger age (<55 years; aOR 3.16, 95% CI 2.28–4.38), female sex (aOR 1.64, 95% CI 1.16–2.31), hypothyroidism (aOR 0.60, 95% CI 0.37–0.98) and renal disease (aOR 0.29, 95% CI 0.11–0.78) to be independently associated with SEBES 3–4. The exploratory analysis of the laboratory values at admission confirmed poorer renal function variables in individuals with low SEBES according to creatinine (median 0.99 vs. 0.89 mg/dl; p = 0.002), urea (median 14 vs. 13 mg/dl; p = 0.002) and glomerular filtration rate (87.76 vs. 90.71 ml/min/1.73 m²; p = 0.009 [Supplementary Table S2]).

Accordingly, we calculated the proportion of patients with low and high SEBES in different SAH subgroups depending on the number of independent predictors of low SEBES: older age (<55 years), male sex, presence of hypothyroidism and renal disease (Figure 2).

SEBES and SAH complications

Intracranial pressure-related complications

Pathologically elevated ICPs requiring conservative treatment were significantly more prevalent in patients with a SEBES of 3–4 (OR 3.06, 95% CI 2.26–4.13 and aOR 2.43, 95% CI 1.73–3.42, for

| Variable | aOR (95% CI) | p |
|----------|-------------|---|
| Pre-SAH characteristic | | |
| Age (<55 years) | 3.16 (2.28–4.38) | <0.0001 |
| Sex (female) | 1.64 (1.16–2.31) | 0.005 |
| Arterial hypertension | 0.83 (0.59–1.17) | 0.295 |
| Cardiac comorbidity | 0.86 (0.51–1.45) | 0.559 |
| Renal comorbidity | 0.29 (0.11–0.78) | 0.014 |
| Diabetes mellitus | 0.87 (0.42–1.80) | 0.700 |
| Hypercholesterinemia | 1.14 (0.62–2.09) | 0.673 |
| Hyperuricemia | 0.28 (0.06–1.38) | 0.118 |
| Hypothyroidism | 0.60 (0.37–0.98) | 0.043 |

| SAH characteristics | | |
| WFNS grade (4–5) | 1.74 (1.23–2.46) | 0.002 |
| Fischer grade (3–4) | 0.87 (0.49–1.55) | 0.643 |
| Presence of ICH | 1.63 (1.12–2.36) | 0.011 |
| Acute hydrocephalus | 1.30 (0.86–1.96) | 0.209 |
| Treatment modality (clipping) | 1.38 (0.99–1.93) | 0.056 |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICB, intracerebral hemorrhage; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurosurgical Societies Score. Bold values are used to highlight the significant p-values.
univariable [Supplementary Table S3] and multivariable [Table 2] analyses respectively, hereinafter). Furthermore, a high SEBES at admission was also predictive of general need for DC (OR 3.60, 95% CI 2.56–5.06 and aOR 2.68, CI 1.84–3.89). This association remained significant when analyzing separately the cases with primary DC (OR 3.19, 95% CI 2.18–4.67 and aOR 2.45, 95% CI 1.61–3.74) and secondary DC (OR 3.52, 95% CI 1.96–6.32 and aOR 2.38, 95% CI 1.26–4.48). The Kaplan–Meier survival plot (Figure 3) shows the impact of SEBES on the risk and timing of DC after SAH.

Other SAH complications

Univariate analysis showed a significant association between a high SEBES with angiographic vasospasm requiring intra-arterial spasmolysis (OR 1.69, 95% CI 1.19–2.40) and shunt-dependent hydrocephalus (OR 1.44, 95% CI 1.03–2.01), but not with aneurysm rebleeding (OR 1.44, 95% CI 0.76–2.61) and occurrence of systemic infections (OR 1.03, 95% CI 0.76–1.39). However, none of the non-ICP-related complications of SAH were independently associated with SEBES in the multivariable analysis (Table 3).

TABLE 2 Multivariable binary logistic regression analysis for subarachnoid hemorrhage complications

| Variable                  | aOR (95% CI) | p     | aOR (95% CI) | p     | aOR (95% CI) | p     |
|---------------------------|--------------|-------|--------------|-------|--------------|-------|
| Endpoint                  |              |       |              |       |              |       |
| SEBES (3–4)               | 0.92 (0.61–1.38) | 0.684 | 1.23 (0.83–1.81) | 0.301 | 2.43 (1.73–3.42) | <0.0001 |
| Age (<55 years)           | 2.78 (1.83–4.23) | <0.0001 | 0.97 (0.65–1.43) | 0.860 | 1.77 (1.24–2.52) | 0.002  |
| WFNS grade (4–5)          | 0.77 (0.52–1.14) | 0.188 | 1.67 (1.14–2.44) | 0.008 | 2.80 (1.98–3.97) | <0.0001 |
| Fischer grade (3–4)       | 3.26 (1.29–8.20) | 0.012 | 2.66 (1.06–6.70) | 0.038 | 2.18 (1.12–4.23) | 0.021  |
| Acute hydrocephalus       | 3.09 (1.72–5.56) | <0.0001 | 7.70 (3.88–15.30) | <0.0001 | 2.02 (1.32–3.08) | 0.001  |
| Endpoint: DC (any timepoint) |              |       |              |       |              |       |
| SEBES (3–4)               | 2.68 (1.84–3.89) | <0.0001 | 2.45 (1.61–3.74) | <0.0001 | 2.38 (1.26–4.48) | 0.007  |
| Age (<55 years)           | 1.88 (1.30–2.72) | 0.001 | 1.37 (0.92–2.04) | 0.126 | 3.23 (1.70–6.14) | <0.0001 |
| WFNS grade (4–5)          | 2.73 (1.87–3.99) | <0.0001 | 3.10 (2.01–4.76) | <0.0001 | 1.66 (0.91–3.03) | 0.102  |
| Fischer grade (3–4)       | 7.4 (2.51–21.47) | <0.0001 | 21.4 (2.85–160.66) | 0.003 | 2.03 (0.56–7.32) | 0.279  |
| Acute hydrocephalus       | 0.57 (0.37–0.90) | 0.015 | 0.33 (0.21–0.53) | <0.0001 | 3.11 (1.03–9.37) | 0.043  |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; DC, decompressive craniectomy; ICP, intracranial pressure; SEBES, Subarachnoid Hemorrhage Early Brain Edema Score; WFNS, World Federation of Neurosurgical Societies Score.
1.10–1.98; Supplementary Table S3) and multivariable (aOR 1.48, 95% CI 1.0–2.17; Table 3) analyses.

DISCUSSION

Early brain edema after aneurysm rupture influences the clinical course and outcome of SAH. In our large institutional cohort, we found SEBES to be a reliable marker of clinically relevant brain edema in SAH and identified baseline characteristics of patients associated with the severity of EBE and poor outcome after SAH.

Early brain edema after SAH: from causal background to clinical impact

Early brain edema is a widely used term in the literature summarizing the pathophysiological processes in the brain occurring directly after aneurysm rupture [8,14]. Extravasation of blood in the subarachnoid space causes a sudden increase in ICP with subsequent decrease in cerebral perfusion pressure, impairment of autoregulation and transient or persistent ischemia [8].

Early brain edema presents a substantial component of EBI. Endothelial damage and cell death results in the breakdown of the blood–brain barrier. This leads to increased permeability with subsequent diffuse vasogenic brain edema. The latter might further aggravate the severity of EBI by causing a vicious circle [15].

In general, the initial severity of SAH is a strong determinant of secondary complications and functional outcome after aneurysm rupture [16–19]. As to EBE, an independent association between its presence and the initial clinical condition of SAH patients could be demonstrated in the clinical context [20]. A relationship between EBE and further clinical course and functional outcome was reported for patients with traumatic brain injury [14] and SAH [21–23]. However, because there is still only a moderate level of clinical evidence and because of the absence of accepted quantification tools for EBE, there are no specific recommendations regarding the management of EBE in SAH guidelines [24].

TABLE 3 Multivariable binary logistic regression analysis for SAH outcome

| Parameter                  | aOR (95% CI)       | p   | aOR (95% CI)       | p   | aOR (95% CI)       | p   |
|----------------------------|--------------------|-----|--------------------|-----|--------------------|-----|
| Endpoint:                  |                    |     |                    |     |                    |     |
| Cerebral infarct           | 2.24 (1.53–3.29)   | <0.0001 | 1.48 (1.02–2.14) | 0.037 | 1.48 (1.0–2.17)    | 0.047 |
| Multi-territorial infarct  |                    |     |                    |     |                    |     |
| Age (<55 years)            | 1.60 (1.08–2.36)   | 0.02 | 0.86 (0.60–1.24)   | 0.410 | 0.41 (0.28–0.60)   | <0.0001 |
| WFNS grade (4–5)           | 3.20 (2.15–4.77)   | <0.0001 | 2.38 (1.65–3.44)  | <0.0001 | 5.21 (3.62–7.49)  | <0.0001 |
| Fischer grade (3–4)        | 5.89 (1.97–17.56)  | 0.001 | 3.28 (1.13–9.51)   | 0.029 | 5.11 (1.94–13.48)  | 0.001 |
| Acute hydrocephalus        | 0.45 (0.28–0.74)   | 0.002 | 2.18 (1.31–3.63)   | 0.003 | 2.08 (1.33–3.25)   | 0.001 |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; SEBES, Subarachnoid Hemorrhage Early Brain Edema Score; WFNS, World Federation of Neurosurgical Societies Score.
SEBES: a reliable marker of EBE?

Various scores have been proposed for the assessment of radiographic presentation of SAH on the admission CT scan. The most commonly used radiographic scores include the original and modified Fisher scores [11,16], Hjdra sum score [25], Graeb score [26], Claassen score [27] and Barrow Neurological Institute (BNI) score [28]. Combinations of these scores have also been proposed to better predict the risk of delayed cerebral ischemia after SAH [29]. Complex grading scores, however, often fail to gain widespread use as compared to simpler scores such as the Fisher scale, probably for reasons of familiarity and time required to calculate them.

A radiographic scoring system specifically addressing EBE was lacking for a long time. Since the introduction of the SEBES by Ahn et al. in 2018 [7], several clinical studies assessing EBE using the SEBES have been performed. In particular, the SEBES has previously been proven accurately to predict delayed cerebral edema in SAH patients [7,8]. Recently, Elbach et al. [9] demonstrated that SEBES predicts outcome and delayed cerebral ischemia independently of vasospasm. The association between SEBES and functional outcome after SAH has also been shown in previous studies [8].

To understand the link between SEBES and SAH outcome, it is essential to clarify the relationship of the score to major clinical complications of SAH. In the present study, we confirmed the association between SEBES and risk of cerebral infarcts and poor outcome after SAH. We could also show independent associations with ICP-related secondary events such as ICP increase necessitating conservative and surgical management. Interestingly, other clinically relevant SAH complications, such as rebleeding, vasospasms and shunt dependency, were not significantly related to SEBES. This strong association between SEBES and ICP-related complications observed in our cohort underlies the clinical value of this score as a reliable radiographic marker of EBE after SAH, allowing its quantification in a simple manner. Treatment strategies for SAH patients based on SEBES values at admission might be helpful in the early identification and treatment of individuals at high risk of ICP-related secondary complications and poor outcome. Treatment timing is known to be crucial in the ICP management after traumatic brain injury, ischemic stroke and SAH [24]. Therefore, the quantification of EBE with SEBES and subsequent implementation in decision making might improve the prognosis of SAH patients.

Predictors of EBE and SEBES

Based on the observed associations between SEBES and the course and outcome of SAH, the identification of individuals who are prone to severe EBE after aneurysm rupture is of utmost clinical importance. Little previous research has been conducted with regard to predictors of SEBES. Only one previous study reported age as a predictor of EBE severity. Elbach et al. [9] described higher SEBES (3–4) in patients younger than 60 years in a cohort of 261 patients.

We have shown that a high SEBES was independently associated both with SAH-related features, including a high WFNS grade and the presence of ICH, and with demographic characteristics of the patients, such as younger age and female sex. In addition, presence of certain comorbidities such as hypothyroidism and renal diseases also independently influenced the risk of EBE development after SAH.

A possible explanation for the association between age and the severity of EBE may be physiological brain atrophy occurring in older age, providing a buffer for brain edema [8,30,31]. For comparison, a similar outcome can be found in non-SAH brain edema cohorts. A meta-analysis by Wu et al. [32] identified young age as a reliable early predictor for malignant brain edema after ischemic stroke.

Female sex is a well-known risk factor for incidence of SAH. However, it has not been connected to the occurrence of EBE. To our knowledge, the present study is the first to report a correlation between female sex and EBE in SAH patients. Of note, the association between sex and SEBES reached significance only after correction for other confounders in the multivariable analysis. In traumatic brain injury studies, young female patients were significantly more likely to experience cerebral edema after severe head injury and intracranial hypertension in comparison to male patients with similar injuries [33,34]. The association between sex and EBE might be related to Apolipoprotein E polymorphism. Sex-dependent impact of different Apolipoprotein E alleles was reported for certain neurological disorders, such as Alzheimer’s disease [35], primary progressive aphasia [36] and Huntington’s disease [37]. Furthermore, there are several clinical and experimental studies pointing out the role of Apolipoprotein E genotype in the development and severity of brain edema after acute brain injury [38-40]. Further research is mandatory to confirm and clarify the association between patient’s sex and EBE after SAH.

Interestingly, we found presence of hypothyroidism and renal disease (or disturbed renal function) to be associated with EBE after SAH. We hypothesize that, in renal disease, decreased renal clearance may lead to increased serum osmolality, which in turn may protect the brain from swelling in the presence of a defective blood-brain barrier and increased permeability [41-43]. Of note, increasing serum osmolality has been a commonly practised treatment modality of cerebral edema resulting from traumatic brain injury [44,45]. Furthermore, another interesting, although speculative, finding is the possible protective role of hypothyroidism in EBE severity. Unfortunately, no literature is available on hypothyroidism in relation to brain edema. As to the possible impact of thyroid-regulated metabolism on the processes in the brain after an acute injury, several studies found a better outcome after ischemic stroke in patients with hypothyroidism [46,47], whereas patients with hyperthyroidism were at higher risk of poor outcome after acute ischemic stroke [48,49]. Thyroid hormones might therefore act as modulators of pathophysiological processes in the development of brain swelling in the acutely injured brain.

In summary, further research is needed to validate these predictors, clarify the underlying pathophysiological pathways, especially...
with regard to hypothyroidism, and develop tools that might be helpful in influencing the severity and complications of EBE after SAH.

Study limitations

The major limitation of this study is its retrospective design. Therefore, some drawbacks must be taken into account. This was a single-center observational study with all the potential associated biases, therefore, its findings are subject to these limitations. To limit potential bias, examination of the CT scans was performed blinded to clinical information. SEBES was calculated by one author, because the inter-observer reliability of SEBES was high in the original publication by Ahn et al. [7]. Furthermore, SAH patients without an early CT scan, performed within 72 h after ictus, had to be excluded from the final analysis because no assessment of EBE was possible in these cases (Supplementary Table S4). Finally, all correlated variables were collected from a SAH database, which was generated from an electronic medical history database.

Conclusion

In conclusion, in the present study we demonstrated that SEBES was a reliable tool for the prognostication of ICP-related complications of EBE and poor outcome after SAH. Our findings highlight the need for further research on the impact of patients’ demographic characteristics and comorbidities on the severity of EBE after SAH.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Maryam Said: Investigation (lead); Project administration (lead); Resources (lead); Writing – original draft (lead). Meltem Guemues: Investigation (supporting). Annika Herten: Investigation (supporting). Thiemo Florian Dinger: Investigation (supporting). Mehdi Chihi: Investigation (supporting). Marvin Darkwah Oppong: Investigation (supporting). Cornelius Deusch: Writing – review and editing (supporting). Karsten H Wrede: Writing – review and editing (supporting). Christoph Kleinschnitz: Writing – review and editing (lead). Ulrich Sure: Writing – review and editing (lead). Ramazan Jabbarli: Conceptualization (lead); Data curation (equal); Formal analysis (lead); Methodology (lead); Resources (supporting); Supervision (lead); Visualization (lead); Writing – review and editing (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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