The incidence of SAH ranges from 6–21 cases per 100,000 people, depending on the population analyzed. Delayed cerebral vasospasm has been implicated as the primary complication-producing morbidity in patients with SAH. It usually occurs between 3 and 9 days after SAH onset and resolves over the next 10–14 days. Its etiology remains one of the most controversial topics in the neurosurgical literature.4,7,11 Because of DCV and other complications, the mortality associated with SAH remains at 30%–50% as a result of early and delayed ischemic processes and the elevation of intracranial pressure along with diminished cerebral perfusion.16 However, other mechanisms may influence a patient’s outcome given that only 54% of those with DCV and 16% of those without it have a poor outcome.22

Brain edema also occurs in SAH and may influence patient outcome, although it may not be detected by routine imaging methods.33,9 Astrocytic swelling has been implicated in the pathophysiology of this complication.1 To maintain cell volume, astrocytes take up or release organic osmolytes, such as taurine,1 which is present in the brain.19 Regarding SAH, some studies have shown no significant change in extracellular taurine levels,24 while others have found a trend toward increased taurine concentrations in CSF without any association with patient outcome.6 The results may vary according to the population analyzed. In fact, one study utilizing cerebral microdialysis revealed an increased extracellular taurine concentration in patients with SAH that was correlated with their outcome.18 However, that method is not as accessible or available as early as might be required. In addition, the effectiveness of the taurine concentration as a prognostic marker was not evaluated in detail in that study.

Previously described predictors of a poor outcome after SAH include patient age, Fisher grade, HH grade, and Glasgow Coma Scale score, among several other variables. The WFNS SAH scale is useful as a poor out-
come predictor for Grades IV and V, but patients with a mild neurological deficit may unexpectedly have a poor outcome. Up to 55% of patients with Fisher Grades 2 or 3 may have a poor outcome.

It is possible that the plasma taurine concentration may be elevated from the onset of SAH and may be associated with patient outcome, reflecting possible brain edema and explaining the unexpectedly poor outcome of patients with a mild neurological deficit after SAH.

**Methods**

**Study Participants**

In this prospective, blinded cohort study, approved by our institutional review board, we considered 211 consecutive patients who were admitted to the Emergency Department of our institute under the suspected diagnosis of a ruptured aneurysm (Fig. 1). Among these patients, only 41 fulfilled our study inclusion criteria: admission within the first 24 hours after SAH onset, HH Grade I–II, WFNS Grade I–II, 8 hours of fasting, not referred from another hospital, taking no medication during the previous 8 hours, and willingness to participate in the study and sign informed consent. One patient was excluded from the final analysis since taurine analysis was inconclusive. Data pertaining to demographic factors, comorbidities, Glasgow Coma Scale score, and HH grade were recorded on admission to the Emergency Department. Eighteen healthy volunteers were recruited as the control group.

Routine blood analyses were performed (complete blood count, glucose, electrolytes, partial thromboplastin time, international normalized ratio). All patients underwent a 4-vessel digital angiography and CT study for the diagnosis of a ruptured aneurysm.

**Sample Processing**

A 20-ml blood sample was taken from every patient upon admission to the Emergency Department. Samples were labeled with a serial number and taken to the laboratory, where taurine was measured. Blood samples were processed in a centrifuge at 3000 rpm. Plasma was collected and stored at -80°C until analysis. The samples were thawed, deproteinized with perchloric acid, neutralized with potassium carbonate, and processed in a centrifuge at 10,000 rpm for 10 minutes at 4°C. Supernatants were collected and analyzed using high-performance liquid chromatography. Personnel performing the biochemical analyses were blinded to any clinical information.

The samples were derivatized with o-phthalaldehyde/mercaptopethanol and injected into an Adsorbosphere OPA HS column (100 x 4.6 mm, 5-μm particle size, Alltech Associates) with a quaternary pump (1100 series, Agilent Technologies). The mobile phase consisted of an acetate buffer (AcO, 50 mmol/L, pH 5.9) with tetrahydrofuran and high-performance liquid chromatography–grade absolute methanol at a flow rate of 1.5 ml/min. The solvent program consisted of an isocratic elution (0–5 minutes) and a linear gradient (5–27 minutes) as follows: tetrahydrofuran 1.0%, 0–27 minutes; AcO 89%, 0–5 minutes, and 89%–77%, 5–27 minutes; absolute methanol 10%, 0–5 minutes, and 10%–22%, 5–27 minutes. The signals were recorded at 232-nm excitation and 455-nm emission wavelengths and analyzed with the ChemStation 10.02 software (Agilent Technologies). The results are expressed as the means ± standard error of the means or the median (25%–75%), according to the variable distributions.

**Grading Systems**

The radiological severity of SAH on admission was classified according to the Fisher grading system: Grade 1, no blood; Grade 2, < 1 mm of blood; Grade 3, > 1 mm of blood or cisternal blood; or Grade 4, presence of blood on the ventricular system. The clinical severity of SAH was classified according to the WFNS system: Grade I (headache only) to Grade V (deep coma or moribund). Outcome at discharge was classified according to the GOS, as previously reported: Score 1–2, poor outcome; Score 3–5, favorable outcome.

**Definition of Symptomatic DCV**

Symptomatic DCV was defined as clinical deterioration (new focal neurological deficit, decreased level of consciousness, or both) accompanied by a new infarct on
Taurine as predictor of outcome in SAH

CT scanning and severe vasospasm reported on TCD ultrasonography. Recordings were performed on the anterior circulation through a transtemporal window using a 2-MHz handheld probe. Delayed cerebral vasospasm was confirmed when the blood flow velocity was equal to or higher than 120 cm/second.

Clinical Management

In the first 24 hours after admission, TCD ultrasonography was performed to determine if there was DCV, and the procedure was repeated on Days 3, 5, and 7. All measurements were made using the same equipment and staff. The Lindegaard ratio was obtained and calculated bilaterally in accordance with its original description. A ratio ≥ 3 was used to define vasospasm.

All patients were called for diagnostic angiography within 24 hours of admission, and aneurysm obliteration was performed as soon as possible after admission (within 48 hours). Nimodipine (60 mg, enteral) was given every 4 hours, unless the systolic blood pressure fell below 120 mm Hg. All patients were treated with normal saline at a rate of 1 ml/kg/h and 500 ml of dextran-40 every 24 hours to maintain a central venous pressure between 12 and 14 mm Hg. An external ventricular drain was placed in all patients with symptomatic hydrocephalus. Transcranial Doppler ultrasonography was performed every 3rd day. Computed tomography scans were obtained on admission and at 48 hours after treatment of the aneurysm. The aneurysm was either clipped or coiled according to its characteristics, localization, and shape.

All patients underwent a second digital angiography study following proper treatment of the aneurysm. Follow-up and outcome was assessed using the GOS 3 weeks after discharge from the hospital. The physician performing the clinical evaluations was always blinded to the plasma taurine results.

Statistical Analyses

Fisher exact and chi-square tests were used to compare proportions. The associations between the taurine concentration and both the clinical scale scores and the laboratory examination results were analyzed using a multiple linear regression. The taurine concentration was compared among groups (that is, control, good outcome, and poor outcome groups) using a Kruskal-Wallis ANOVA followed by the Mann-Whitney U-test. A ROC curve was constructed to determine the cutoff point for the taurine concentration to differentiate between the groups. The Spearman correlation was used to evaluate the association between numeric variables. A logistic regression model was constructed to identify independent outcome predictors. All analyses were performed using SPSS 17 (SPSS, Inc.), and p < 0.05 was considered significant.

Results

The mean age of the patients with SAH, a group consisting of 22 women and 18 men, was 47.3 ± 2.0 years. The healthy volunteers had a mean age of 35.7 ± 2.9 years and included 6 women and 12 men. Aneurysm locations were as follows: ACoA (17 lesions), PCoA (14 lesions), choroid segment (2 lesions), A2 segment (1 lesion), M1 segment (4 lesions), hypophyseal artery (1 lesion), and posterior circulation (1 lesion). Admission Fisher grades were as follows: Grade 1, 2 patients; Grade 2, 5 patients; Grade 3, 16 patients; and Grade 4, 17 patients. All patients with SAH showed a mild neurological deficit on admission (HH Grade I–II, WFNS Grade I–II) and thus were predicted to have a favorable outcome. According to the GOS, 9 patients had a poor outcome, while 31 had a favorable one.

The sex distribution was not different between outcome groups (Table 1). The control group was younger (35.7 ± 2.9 years) than the patients with SAH in both the favorable (p = 0.032) and poor outcome groups (p = 0.013), but age was not different between the 2 SAH subgroups (favorable and poor outcome groups) and was not correlated with the taurine concentration in the entire sample (r² = 0.036, p = 0.167).

We analyzed the possible influence of aneurysm location on patient outcome. In the patients with aneurysms located in the PCoA and ACoA, which were the most frequent locations, the ratio of patients with a favorable or a poor outcome was not different (Table 1).

Regarding the Fisher scale, admitted patients showed every stage of the scale. For the most frequently observed stages (Grades 3 and 4), the Fisher scale was not associated with patient outcome (Table 1). Furthermore, neither the admission HH (I–II) nor the WFNS (I–II) grade was associated with patient outcome.

In our sample, 17 patients with SAH demonstrated symptomatic DCV, and 53% of them (9 patients) had a favorable outcome. Delayed cerebral vasospasm was more common in patients with a poor outcome than in those with a favorable outcome (Table 1). The taurine concentration remained nearly unchanged in patients with vasospasm (61.1 µmol/L [35.9–177.3 µmol/L]) compared with that in patients without this complication (50.8 µmol/L [43.6–83.0 µmol/L], p = 0.533; Fig. 2C).

The plasma taurine concentration was 28.5 µmol/L (21.0–34.3 µmol/L) in the control group and was elevated in all patients with SAH. The admission taurine concentration, compared with that in controls, was 2-fold higher in patients who had a favorable outcome (p < 0.001), while it was 6-fold higher in patients who were discharged with a poor outcome (p < 0.001). Furthermore, taurine increased in patients with a poor outcome as compared with the concentration in patients with a favorable outcome (p = 0.007; Fig. 2D and Table 1).

A ROC curve analysis was performed to determine the cutoff point to differentiate patients with SAH according to their outcome based on their admission taurine concentration. This analysis showed that a 102.5-µmol/L taurine concentration at admission identified patients who would have a poor outcome (area under the curve 0.792, p = 0.008) with 77% sensitivity and 97% specificity and positive and negative predictive values of 87% and 93%, respectively.

Because both taurine level and DCV were associated with patient outcome, these variables were included in a logistic regression to evaluate the contribution of each factor to our results. The analysis showed that both tau-
rine (p = 0.022) and DCV (p = 0.044) were independent predictors of a poor outcome (p = 0.901, Hosmer-Lemeshow goodness-of-fit test). Delayed cerebral vasospasm represented an OR of 27.9 (95% CI 1.090–714.9) to show a poor outcome at discharge, while taurine concentrations above 102.5 μmol/L represented a 105-fold higher risk (95% CI 8.3–1328.0, p < 0.001; Fig. 2A and B).

We sought other variables that might be associated with the taurine concentration using a multiple linear regression analysis. The BI, serum K⁺ levels, and platelet count were included in this analysis. Both the BI ($r^2 = 0.252, p = 0.001$) and K⁺ levels ($r^2 = 0.095, p = 0.021$) were inversely correlated with the plasma taurine concentration (Fig. 3).

### Discussion

It is well known that patients showing severe neurological deficits at SAH onset are likely to have a poor outcome. Surprisingly, patients with a mild deficit may also show a poor outcome.²⁰ It is likely that the cause of this unexpected result is difficult to prevent and remains to be determined. In our study, all patients with SAH had a good prognosis according to clinical scales (HH and WFNS); however, approximately 25% of the patients had a poor outcome.

It could be hypothesized that DCV was responsible for the patient outcomes. In fact, DCV was an independent predictor of a poor outcome (RR 27.7; Fig. 2A), but half of the patients (9 of 17) with this complication had a favorable outcome. Thus, in our sample, the probability of patients with DCV having a favorable or a poor outcome was nearly the same.

Because brain edema may occur at the onset of SAH and is accompanied by taurine release,¹³,¹⁸,⁹ we analyzed the plasma concentration of this amino acid, looking for an association with patient outcomes. Compared with levels in controls, admission taurine concentrations were increased (2-fold) in SAH patients with a favorable outcome, but they were further increased (6-fold) in SAH patients with a poor outcome at discharge (Fig. 2D). An increased taurine concentration at admission identified patients who would be discharged with a poor outcome, with sensitivity and specificity values of approximately 80% and 100%, respectively, and positive and negative predictive values of approximately 90%.

It could be further hypothesized that taurine level is a predictor of DCV, which could be the actual predictor of a poor outcome. However, logistic regression analysis showed that both factors are independent predictors of a poor outcome (Fig. 2A and B), suggesting that they each contribute to a poor outcome through independent mechanisms. Furthermore, DCV showed an OR of 27.7 for a poor outcome, while the OR for taurine was 105. Thus, the level of the sulfonic amino acid taurine was the main (and earliest) predictor in our study.

In support of its relationship with patient outcomes, taurine was correlated with a patient’s level of disability according to the BI (Fig. 3 left), indicating that patients

### Table 1: Results of bivariate and multivariate analyses of poor outcome predictors in aneurysmal SAH

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Poor Outcome</th>
<th>Favorable Outcome</th>
<th>Bivariate p Value</th>
<th>Multivariate p Value</th>
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<td>sex</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>5</td>
<td>13</td>
<td></td>
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<td></td>
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<tr>
<td>F</td>
<td>4</td>
<td>18</td>
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<td>mean age in yrs</td>
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<td>51.4 ± 3.3</td>
<td>46.1 ± 2.4</td>
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<td>ACoA</td>
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<td>Fisher scale</td>
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</tr>
<tr>
<td>3</td>
<td>3</td>
<td>13</td>
<td></td>
<td>0.500</td>
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<tr>
<td>4</td>
<td>4</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HH scale</td>
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<td>1</td>
<td>10</td>
<td></td>
<td>0.176</td>
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<td>symptomatic vasospasm</td>
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<td>0.002</td>
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<tr>
<td>present</td>
<td>8</td>
<td>9</td>
<td></td>
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<tr>
<td>median plasma taurine level in μmol/L (25%–75%)</td>
<td>173.1 (69.7–363.4)</td>
<td>49.7 (40.4–75.7)</td>
<td>0.007</td>
<td>0.022</td>
<td></td>
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</table>
Taurine as predictor of outcome in SAH

Fig. 2. Delayed cerebral vasospasm (A) and taurine concentration (B) were independent predictors of a poor outcome. Delayed cerebral vasospasm was more frequent in patients who had a poor outcome at discharge, although some patients with this complication had a favorable outcome. The taurine concentration was classified as either high or low according to a ROC curve (cutoff point 102.5 µmol/L). Only 1 patient with a high taurine level had a favorable outcome. The taurine concentration remained nearly unchanged in subjects with or without DCV (C) but was increased in patients with SAH, especially in those who had a poor outcome (D). Bars represent the percent cases for each group (A and B) or the median (20%–75%; C and D); *p < 0.05 versus control (D) or versus favorable outcome (A and B); +p < 0.05 versus favorable outcome.

Fig. 3. The BI (left) and serum K⁺ (right) were inversely correlated with taurine concentration, suggesting that the amino acid is associated with patient disability and perhaps with edema. *p < 0.05.
with high plasma taurine concentrations showed a reduced ability to perform daily activities. Those with the highest concentrations may have even died at discharge.

Because the increase in taurine was not related to DCV, we analyzed its possible relationship to brain edema. Several studies have shown that increased intracellular K+ concentrations cause edema, while K+ release. Thus, we chose serum K+ as a possible marker of edema. According to our results, the taurine and K+ concentrations were inversely correlated (Fig. 3 right).

It has been well documented in previous reports that brain edema occurs in patients with SAH. This dysfunction begins to develop immediately after ictus, but it may not be detected by routine imaging methods. After SAH, a global reduction in cerebral perfusion due to early vasoconstriction of the microvasculature and increased intracranial pressure due to the volume effect of extravascular blood are thought to result in cerebral ischemia and blood-brain barrier disruption with a consecutive increase in cerebral water content. This finding is important because brain edema is associated with a poor outcome in SAH; therefore, preventing this complication could improve patient recovery.

Severe cell swelling, characteristic of cytotoxic edema, can restrict the diffusion of substances in the interstitial fluid, leading to intracranial hypertension as the volume of the brain parenchyma increases to occupy a larger fraction of the cranial volume. The sulfonic amino acid taurine plays an important role in the regulation of cell volume in cultured neurons and glia. Taurine is widely distributed in different tissues and is involved in many physiological processes, such as osmoregulation, antioxidant defense, and the control of Ca++ homeostasis. Taurine efflux is accelerated by swelling, which is mediated by membrane channels capable of conducting anionic taurine and other amino acids. It is possible that an increased taurine concentration at admission is an early marker for edema; therefore, treating patients with high taurine plasma concentrations for brain edema may improve their outcome and prevent the death of SAH patients with mild neurological deficits.

It is speculative to conclude that brain edema is responsible for the poor outcome of some of our patients, because it was not directly measured in our study. The unexpected occurrence of poor outcomes in patients with mild deficits after SAH deserves additional preventative efforts. Our results suggest that increased taurine concentrations may reflect brain edema in these patients, which is probably responsible for at least part of their poor outcome.

We are aware of the limitations of this study. Further enrollment of patients with different grades of SAH and different treatments (endovascular vs surgical) should be evaluated, but this is the first report addressing taurine as a biological marker that may be used as a prognostic factor. Further studies are ongoing to test this hypothesis.

Conclusions

Our results indicate that in patients with a mild neurological deficit after aneurysmal SAH, clinical scales fail to predict a poor outcome. However, plasma taurine level at admission is a good predictor, showing some advantages over DCV, which is also associated with patient outcome. This suggests that taurine levels may alert the neurosurgeon to perform an intensive intervention to improve patient outcome.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Ríos, Barges-Coll, Pérez-Neri, Avendaño, Gomez-Amador. Acquisition of data: Barges-Coll, Pérez-Neri, Mendez-Rosito, Gomez-Amador. Analysis and interpretation of data: Ríos, Barges-Coll, Pérez-Neri, Avendaño, Mendez-Rosito. Drafting the article: Ríos, Barges-Coll, Pérez-Neri, Gomez-Amador. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ríos. Statistical analysis: Ríos, Barges-Coll, Pérez-Neri. Study supervision: Ríos.

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