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Cerebrospinal Fluid Production Rate and Functional Outcome After Aneurysmal Subarachnoid Haemorrhage

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Abstract

Introduction

Cerebrospinal fluid (CSF) physiology may be altered after aneurysmal subarachnoid haemorrhage (aSAH), but the relationship between CSF production rate (PRcsf) and clinical outcome is poorly understood.

Methods

In this prospective observational cohort study, PRcsf was measured in 70 patients with aSAH using pressure-controlled LiqueGuard7® drainage at 0 mmHg. Measurements were obtained on three consecutive days and averaged for analysis. The primary outcome was six-month functional status, dichotomised as favourable (modified Rankin Scale [mRS] 0–2) or poor (mRS 3–6). A WFNS-only prognostic model was compared with WFNS plus continuous PRcsf.

Results

Fifty-three patients (75.7%) had a favourable six-month outcome and 17 (24.3%) a poor outcome. PRcsf was substantially lower in patients with poor outcome (median 36.20 vs 149.56 mL/h; $p < 0.001$) and correlated inversely with six-month mRS ($\rho = -0.568$, $p < 0.001$). Each 10 mL/h increase in PRcsf was associated with lower odds of poor outcome after adjustment for WFNS (OR 0.772, 95% CI 0.671–0.887; $p < 0.001$). Adding PRcsf increased model discrimination from AUC 0.730 to 0.848. The association remained consistent across focused sensitivity analyses. Lower PRcsf was also associated with delayed cerebral ischaemia. In 12 participants reassessed approximately four weeks later, repeat PRcsf measurements showed close agreement with the initial measurements (ICC=0.9997).

Conclusions

Higher net CSF replenishment after aSAH was associated with more favourable six-month functional outcome, with the association persisting after adjustment for admission WFNS grade.

Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) is characterised not only by the abrupt release of arterial blood into the subarachnoid space, but by a complex secondary disturbance of cerebrospinal fluid (CSF) physiology. Blood products disseminate through the subarachnoid space, often the ventricular and parenchymal compartments, where erythrocyte lysis, extracellular haemoglobin, haem and inflammatory mediators contribute to secondary brain injury⁽¹⁾. CSF haemoglobin has been associated with subsequent neurological injury after aSAH, while endogenous intrathecal haemoglobin-scavenging mechanisms may become saturated following haemorrhage^(1, 2). These observations suggest that the CSF compartment is an important determinant of the biochemical environment to which the injured brain is exposed, rather than simply a passive reservoir for extravasated blood⁽³⁾.

The response of the CSF system to intracranial haemorrhage may also involve active changes in fluid production and transport. The choroid plexus is increasingly recognised as an immunologically responsive interface capable of modifying CSF secretion in response to inflammatory signalling. Experimental work has demonstrated that intraventricular blood can activate Toll-like receptor 4–SPAK–NKCC1 signalling within the choroid plexus, producing inflammation-dependent CSF hypersecretion, while more recent work has identified the choroid plexus as a critical link between innate immune activation and pathological CSF dysregulation^(4, 5). Water transport pathways may also be altered after SAH. Increased AQP1 and AQP4 expression has been demonstrated in human brain tissue following SAH, and experimental disruption of AQP4 impairs interstitial fluid clearance and aggravates cerebral oedema^(6, 7, 8, 9). Collectively, these findings raise the possibility that CSF dynamics after haemorrhage represent an active component of the physiological response to injury.

This possibility has important clinical implications. Established outcome models in aSAH are dominated by markers of the severity of the initial insult, including neurological grade, age and radiological haemorrhage burden^(10, 11). These variables are powerful predictors of outcome but provide limited information about the subsequent physiological response of the CSF system. In particular, CSF production rate (PRcsf) has received little attention in aSAH despite the direct exposure of the choroid plexus and CSF pathways to blood and inflammatory mediators. Whether PRcsf is associated with six-month functional outcome after aSAH, beyond established measures of initial haemorrhage severity, remains uncertain.

This prospective study examined the association between PRcsf and six-month functional outcome after aSAH and assessed whether PRcsf provided additional outcome-related information beyond admission WFNS grade. We hypothesised that the association between PRcsf and functional outcome would not be explained solely by initial haemorrhage severity or intracranial morphology.

Study design and Methods

Participants

This prospective observational study included consecutive adult patients with aSAH treated at the National Hospital for Neurology and Neurosurgery between October 2022 and July 2025, undergoing CSF drainage as part of their clinical management.

A total of 70 participants were included in the primary cohort. Patients were included irrespective of the presence of intraventricular or intracerebral extension of haemorrhage, which were recorded separately as markers of SAH severity. Patients were excluded where PRcsf measurement could not be performed safely, the CSF drainage catheter was considered non-functional, or valid measurements could not be obtained, such as when a patient suddenly changed position.

Written informed consent was obtained from the patient or, where capacity was impaired, from an appropriate legal representative in accordance with the approved study procedure. The study was conducted in accordance with the Declaration of Helsinki.

Study size

No formal a priori sample-size calculation was performed. This was a prospective observational study in which the study size was determined by the number of eligible patients in whom PRcsf could be prospectively measured during the predefined recruitment period. Given the limited prior human data on PRcsf after aSAH, there was insufficient evidence on which to specify a reliable expected effect size for an a priori power calculation. The study was therefore considered exploratory and hypothesis-generating, with emphasis placed on effect estimates, 95% confidence intervals and sensitivity analyses rather than post-hoc estimation of statistical power.

Measurement of cerebrospinal fluid production rate

PRcsf was measured using the LiquoGuard7® pressure-controlled CSF drainage system (Möller Medical GmbH, Fulda, Germany) through an external ventricular drain (EVD) or lumbar drain (LD) that had been inserted for routine clinical management and deemed safe for CSF measurement. The pressure-controlled measurement technique was developed and previously described by our group, Tariq et al., and the same standardised protocol was used in the present study⁽¹²⁾.

Patients were positioned completely supine, and the LiquoGuard's external pressure transducer was aligned at the level of the external auditory meatus, which served as the hydrostatic reference point. The LiquoGuard system was connected to the existing CSF drainage catheter and set to maintain a reference pressure of 0 mmHg. Under these conditions CSF was actively removed as pressure rose above the set threshold.

A 20-minute stabilisation period was observed to allow equilibration of the intracranial CSF compartment to the imposed pressure condition. CSF removed during this period was excluded from the PRcsf measurement.

Following stabilisation, CSF output was measured for 30 minutes while the patient remained supine and the reference pressure was maintained at 0 mmHg. The mean drainage rate displayed by the LiquoGuard during this interval was recorded in mL/h and represented the PRcsf value for that study day. Continuous LiquoGuard flow traces were reviewed during the measurement period to confirm stability of the recorded output.

Each participant underwent three separate PRcsf measurements on three consecutive days. For all participant-level statistical analyses, PRcsf was defined as the arithmetic mean of the three daily measurements:

$$PRcsf_{participant} = \frac{PRcsf_{day1} + PRcsf_{day2} + PRcsf_{day3}}{3}$$

The cumulative CSF volume corresponding to each 30-minute measurement period was calculated as:

$$V_{30} = PRcsf \times 0.5$$

where V_{30} represents the calculated volume over 30 minutes in mL and PRcsf is expressed in mL/h.

Operational definition of PRcsf and relation to Davson's equation

For the purposes of this study, PRcsf was operationally defined as the net CSF replenishment rate into the drainable CSF compartment during controlled low-pressure drainage. It should therefore not be interpreted as a direct measurement of isolated choroid plexus epithelial secretion.

This distinction is important when considering Davson's equation, which describes the steady-state relationship between intracranial pressure, sagittal sinus pressure, resistance to CSF outflow and CSF formation:

$$ICP = (I_f \times R_{out}) + P_{ss}$$

Where P_{ss} represents sagittal sinus pressure, I_f CSF formation rate and R_{out} resistance to CSF outflow. Davson's formulation describes CSF formation and absorption under an intact hydrodynamic equilibrium and has been validated in human CSF hydrodynamic studies using infusion-testing paradigms⁽¹³⁾. In contrast, the present pressure-controlled drainage technique deliberately alters this equilibrium by lowering CSF pressure and providing an external drainage pathway.

Under these conditions, the physiological pressure gradient governing CSF absorption is altered and fluid entering the CSF compartment can preferentially leave through the drainage catheter. Accordingly, the flow recorded by LiquoGuard cannot be interpreted simply as I_f derived from Davson's equation. Rather, it represents the net rate of CSF entering and replenishing the drainable CSF compartment under the defined pressure-controlled conditions.

The term PRcsf is therefore used here to describe net CSF replenishment rather than isolated choroid plexus secretion. The measured value may incorporate choroid plexus secretion together with fluid exchange and redistribution between ventricular, subarachnoid, interstitial and other intracranial fluid compartments. Historical constant-pressure and infusion studies have similarly demonstrated that estimates of CSF formation or net CSF flow obtained under experimentally altered hydrodynamic conditions can substantially exceed conventional resting physiological estimates⁽¹⁴⁾.

Safety monitoring during measurement

Particular attention was paid to the safety of pressure-controlled drainage at 0 mmHg, especially in participants exhibiting high measured PRcsf values. A theoretical concern with

sustained drainage rates approaching 150 mL/h is that rapid removal of a finite static CSF volume could result in intracranial hypotension and associated neurological symptoms.

Participants were monitored throughout the 20-minute stabilisation period, the 30-minute measurement period and for at least 30 minutes following completion of measurement. Clinical monitoring specifically included the development of headache, dizziness, nausea or vomiting, altered level of consciousness, new cranial nerve disturbance, including diplopia, facial weakness or dysarthria, or any other new neurological symptom potentially attributable to intracranial hypotension or excessive CSF drainage.

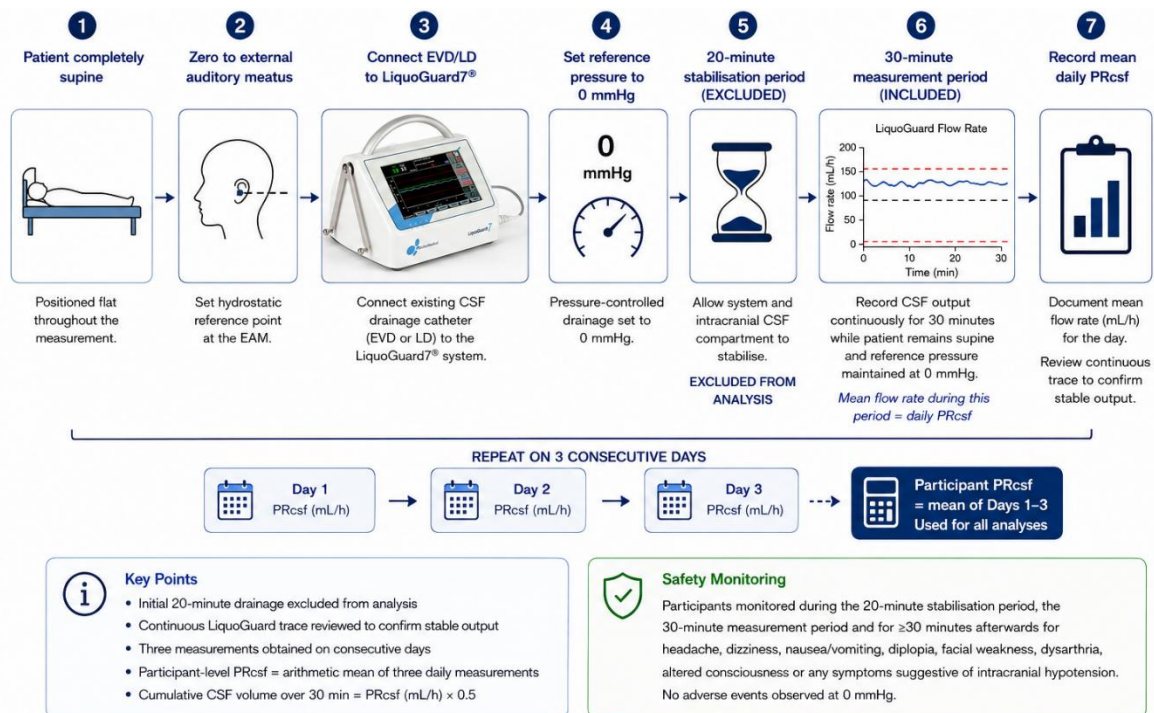


Figure 1. Standardised protocol for measurement of cerebrospinal fluid production rate (PRcsf).

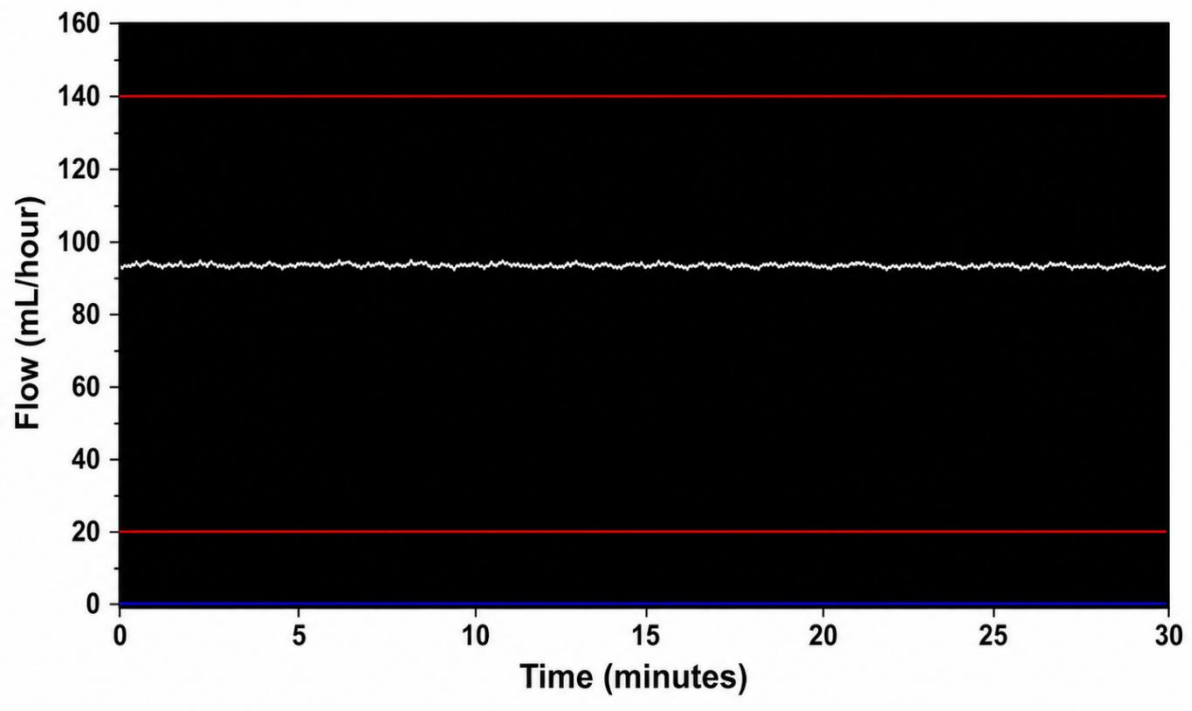


Figure 2. Representative reconstruction of a LigoGuard flow trace illustrating stable CSF output over the 30-minute measurement period, with only minor fluctuations around a consistent mean flow rate.

Catheter patency and intracranial pressure monitoring

Catheter function was assessed before each PRcsf measurement. Documented catheter obstruction was recorded as a potential source of measurement artefact.

As an additional assessment of catheter patency, intracranial pressure as displayed by the LigoGuard was monitored before, throughout and after each study measurement. A blocked or poorly communicating catheter would be expected to produce an abnormal, non-physiological or inconsistent pressure response and was therefore considered alongside the clinical assessment of catheter function. Measurements were accepted only where the drainage system remained clinically patent and the observed pressure behaviour was compatible with a functioning catheter.

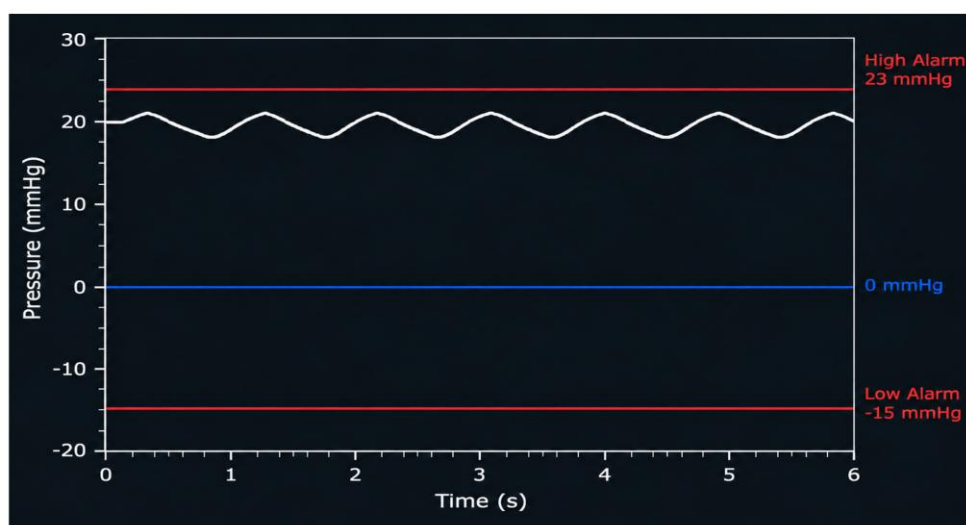


Figure 3. Representative reconstruction of a LiquoGuard pressure trace illustrating intracranial pressure stability.

The site of measurement was recorded as EVD or LD, and the presence of any additional CSF diversion devices was documented.

Clinical data collection

Baseline demographic and clinical variables included age, sex, relevant co-morbidities, regular medication, Glasgow Coma Scale (GCS) score at presentation, GCS at discharge, hospital length of stay, intensive care unit length of stay, aneurysm location and treatment modality.

Neurological severity at presentation was graded using the World Federation of Neurosurgical Societies (WFNS) scale. Haemorrhage burden was assessed using the modified Fisher scale. Premorbid functional status was recorded using the modified Rankin Scale (mRS).

Definitive aneurysm treatment was classified as either endovascular coiling or surgical clipping.

Secondary neurological complications were extracted from the patients' electronic health records and included hydrocephalus, cerebral vasospasm, delayed cerebral ischaemia, cerebral infarction, haemorrhagic transformation, rebleeding and central nervous system infection where present.

Intracranial pressure (ICP) was assessed alongside PRcsf as an additional physiological variable. For each study day, mean daily ICP was derived from the available continuous ICP recording. Where monitoring was performed through LiquoGuard, its continuous pressure trace was reviewed to derive both mean daily ICP and mean ICP during the 30-minute PRcsf measurement period. Where separate intraparenchymal ICP monitoring was available, the corresponding continuous trace was also reviewed for the relevant study day and measurement period.

Participant-level resting ICP was defined as the arithmetic mean of the three daily pre-measurement ICP values.

Radiological assessment

The CT brain examination obtained at presentation was reviewed to characterise initial haemorrhage severity and intracranial morphology. This was also the closest CT examination preceding the first PRcsf measurement.

Radiological variables included modified Fisher grade, intraventricular haemorrhage (IVH), intracerebral haemorrhagic extension, hydrocephalus, Evans index (EI), Subarachnoid Haemorrhage Early Brain Oedema Score (SEBES), global cerebral oedema and midline shift.

Where severe ventricular compression prevented reliable identification of the frontal horns, the Evans index was recorded as non-measurable.

SEBES was formally scored using the predefined axial levels of the scale. Global cerebral oedema was additionally characterised according to the extent of diffuse sulcal effacement, ventricular compression and preservation of grey-white differentiation.

A marked 'tight-brain' phenotype was defined by severe diffuse sulcal effacement accompanied by marked ventricular compression or non-visualisation of the frontal horns.

Sylvian fissure haemorrhage was additionally recorded as a radiological variable as a secondary exploratory radiological analysis. Blood was considered present where Sylvian fissure or

adjacent cortical subarachnoid blood was identified on CT. This variable was examined because human tracer studies demonstrate prominent CSF transport adjacent to large arterial trunks, including around the Sylvian fissures and middle cerebral arteries, making this region relevant to periarterial/lymphatic fluid exchange⁽¹⁵⁾.

These imaging variables were included to examine whether differences in measured PRcsf could be explained by haemorrhage burden, hydrocephalus, cerebral swelling, ventricular compression or altered intracranial compliance.

Reproducibility cohort

Measurement reproducibility was assessed in a subset of 12 participants from the primary cohort who underwent repeat PRcsf assessment approximately four weeks after their initial measurement. These repeat measurements were analysed separately and did not constitute additional observations in the primary outcome analyses.

Seven participants underwent repeat assessment through the same CSF drainage route, while five underwent repeat measurement through a different drainage route, permitting comparison between ventricular and lumbar measurements.

At each assessment, PRcsf was again measured on three consecutive days, and the arithmetic mean of the three daily measurements was used as the participant-level value for comparison between the two assessment periods.

Agreement between the two measurements was assessed using the intraclass correlation coefficient with absolute agreement, Bland-Altman analysis, absolute paired differences and percentage differences. Reproducibility was examined for the complete 12-participant cohort and separately for same-site and different-site measurements.

Outcomes

The primary clinical outcome was functional status at six months measured using the modified Rankin Scale.

Six-month mRS scores were retrieved from the patients' electronic health records. Functional outcome had been assessed by a clinician directly involved in the participant's clinical care who was blinded to the PRcsf measurement.

For the principal prognostic analysis, poor functional outcome was defined as mRS 3–6, with mRS 0–2 classified as favourable functional outcome.

Secondary outcomes included GCS at discharge, six-month mortality, total hospital length of stay, intensive care unit length of stay and subsequent requirement for permanent CSF diversion.

Statistical analysis

PRcsf was analysed primarily as a continuous variable using the participant-level mean of the three consecutive daily measurements.

For secondary descriptive and exploratory analyses, participants were additionally classified using historical physiological estimates of CSF production. Ekstedt's human CSF hydrodynamic studies provided an important historical reference for normal CSF formation⁽¹⁶⁾ and the

conventional physiological estimate of 18–24 mL/h, also described in our previous study⁽¹²⁾, which was used to define the category boundaries:

- low PRcsf: <18 mL/h, representing values below the lower boundary of the conventional physiological range.
- standard PRcsf: 18–24 mL/h, representing values within the historically accepted range and providing the physiological reference category.
- high PRcsf: >24 mL/h, representing values above the upper boundary of the conventional physiological range.

These categories were chosen to examine clinical outcomes in relation to PRcsf below, within and above conventional physiological expectations, rather than to establish aSAH-specific prognostic thresholds.

Categorical analyses were regarded as supportive and exploratory, while principal inferential analyses were based on continuous PRcsf.

Distributional assumptions were assessed using visual inspection and the Shapiro-Wilk test. Continuous variables were reported as mean with standard deviation or median with interquartile range according to their distribution, while categorical variables were reported as number and percentage.

Associations between continuous PRcsf and ordinal variables were assessed using Spearman rank correlation. Comparisons of PRcsf between two groups were undertaken using the Mann-Whitney U test, and comparisons involving more than two groups used the Kruskal-Wallis test with appropriate post-hoc testing where required.

The principal prognostic analysis examined poor six-month functional outcome, defined as mRS 3–6, using logistic regression. A baseline model containing WFNS grade was compared with a second model containing WFNS grade and continuous PRcsf. Associations were reported as odds ratios with 95% confidence intervals.

Model discrimination was assessed using the area under the receiver operating characteristic curve with 95% confidence intervals. The incremental contribution of PRcsf was evaluated using comparison of model AUCs and a likelihood-ratio test between nested models.

Additional exploratory and sensitivity analyses examined whether the relationship between PRcsf and functional outcome was attenuated after accounting for established or plausible clinical and hydrodynamic confounders, including age, modified Fisher grade, EI, SEBES, global cerebral oedema, tight-brain phenotype, hydrocephalus and drainage route.

Given the cohort size multivariable modelling was deliberately parsimonious to reduce overfitting. Potential confounders were therefore examined in focused sensitivity models rather than incorporated simultaneously into a single large multivariable model.

The relationship between PRcsf and six-month mortality was considered exploratory. Associations with aneurysm location were also considered exploratory.

For categorical analyses with small expected cell counts, Fisher's exact test was used in preference to Pearson's χ^2 test.

The association between participant-level PRcsf and resting ICP was assessed using Spearman rank correlation. PRcsf was compared according to DCI, vasospasm, treatment modality,

hydrocephalus, drainage route, Sylvian fissure haemorrhage and permanent CSF diversion using Mann–Whitney U tests, with rank-biserial correlation reported as an effect size for key comparisons.

Differences in PRcsf across aneurysm locations were assessed using the Kruskal–Wallis test. Pairwise comparisons were corrected for multiple testing using the Holm method. An exploratory rank-based regression model was used to examine the relationship between aneurysm location and discharge neurological status before and after inclusion of continuous PRcsf.

Reproducibility was assessed using a two-way mixed-effects intraclass correlation coefficient for absolute agreement of a single assessment-level PRcsf value [ICC(A,1)], with participants treated as random effects and assessment occasion as a fixed effect. For this analysis, each assessment-level value represented the arithmetic mean of the three daily PRcsf measurements obtained within that assessment period. The ICC was reported with a 95% confidence interval calculated using the McGraw–Wong F-distribution approximation. Agreement was additionally evaluated using Bland–Altman analysis and absolute and percentage paired differences. ICC estimates and their confidence intervals were independently recalculated in Python using NumPy and SciPy.

AUC confidence intervals were estimated using non-parametric bootstrap resampling.

All statistical tests were two-sided, with statistical significance defined as $p < 0.05$. Statistical analyses were performed using R version 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Analysis domain	Variable / outcome	Statistical approach	Purpose
Primary exposure	PRcsf	Continuous participant-level PRcsf, calculated as the mean of measurements obtained on three consecutive days	Primary exposure for inferential analyses
Primary clinical outcome	Six-month functional outcome: favourable mRS 0–2 vs poor mRS 3–6	Binary logistic regression	Assess the association between PRcsf and six-month functional outcome
Baseline prognostic model	WFNS + poor six-month outcome	Logistic regression	Quantify discrimination using established admission neurological severity
Incremental prognostic model	WFNS + continuous PRcsf + poor six-month outcome	Logistic regression; likelihood-ratio test comparing nested models	Determine whether PRcsf provides additional prognostic information beyond WFNS
Model discrimination	WFNS model vs WFNS + PRcsf model	Receiver operating characteristic analysis; AUC with 95% CI; comparison of AUCs	Quantify incremental model discrimination associated with PRcsf
Haemorrhage severity	Modified Fisher grade	Spearman rank correlation and focused sensitivity modelling	Examine whether PRcsf is associated with radiological haemorrhage burden
Ventricular morphology	Evans index	Spearman rank correlation and sensitivity modelling	Assess whether ventricular size is associated with PRcsf measurement
Early cerebral oedema	SEBES	Spearman rank correlation and sensitivity modelling	Assess whether cerebral oedema severity is associated with PRcsf
Severe cerebral swelling	Global cerebral oedema / tight-brain phenotype	Mann–Whitney U test and focused sensitivity modelling	Test whether cerebral swelling or ventricular compression is associated with PRcsf measurement
Hydrocephalus	Present vs absent	Mann–Whitney U test	Assess whether hydrocephalus is associated with PRcsf
Drainage route	EVD vs LD	Mann–Whitney U test	Determine whether measurement route is associated with PRcsf
Sylvian fissure haemorrhage	Blood present vs absent	Mann–Whitney U test	Assess whether the anatomical distribution of subarachnoid blood is associated with PRcsf
Catheter function	Documented obstruction and ICP behaviour	Descriptive assessment	Evaluate catheter-related measurement artefact
Neurological status at discharge	GCS at discharge	Spearman rank correlation	Explore the relationship between PRcsf and neurological status at discharge
Mortality	Six-month survival	Mann–Whitney U test and exploratory logistic regression where appropriate	Explore the relationship between PRcsf and six-month mortality
Hospital stay	Total hospital length of stay	Spearman rank correlation	Explore the relationship between PRcsf and duration of hospitalisation
ICU stay	ICU length of stay	Spearman rank correlation	Explore the relationship between PRcsf and duration of intensive care
Permanent CSF diversion	VP shunt required vs not required	Mann–Whitney U test	Explore the relationship between PRcsf and subsequent requirement for permanent CSF diversion
Aneurysm location	Anatomical aneurysm location	Kruskal–Wallis test with post-hoc comparison where appropriate	Exploratory assessment of anatomical variation in PRcsf
PRcsf categories	Low <18 mL/h; standard 18–24 mL/h; high >24 mL/h	Descriptive statistics; Kruskal–Wallis test or Fisher’s exact test where appropriate	Secondary descriptive and exploratory assessment of PRcsf according to conventional physiological ranges
Sparse categorical data	Categorical comparisons with small expected cell counts	Fisher’s exact test	Avoid unreliable χ^2 approximation where cell counts are sparse
Four-week reproducibility	Initial vs repeat PRcsf in 12 participants	ICC with absolute agreement; Bland–Altman analysis; absolute and percentage paired differences	Assess temporal reproducibility of PRcsf
Cross-route reproducibility	Repeat measurement through same vs different CSF drainage route	ICC, Bland–Altman analysis and paired differences	Assess whether PRcsf remains reproducible across EVD and LD measurement routes
Statistical threshold	Principal hypothesis test	Two-sided $p < .05$; effect estimates with 95% CIs	Statistical inference
Multiplicity	Secondary and exploratory analyses	Analyses designated exploratory and interpreted principally using effect estimates and 95% CIs rather than isolated p -values	Reduce the risk of overinterpretation arising from multiple testing

Table 1. Summary of statistical analyses performed. PRcsf was analysed primarily as a continuous variable. The principal analysis examined the association between continuous PRcsf and poor six-month functional outcome (mRS 3–6), including comparison of a WFNS-only model with a WFNS-plus-PRcsf model. All other clinical, radiological and anatomical analyses were considered secondary or exploratory. Multivariable models were deliberately parsimonious because of the cohort size and number of outcome events.

Reporting guideline

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational cohort studies.

Ethical approval

The study was approved by the appropriate institutional research ethics committee and was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Informed consent was obtained from all participants with capacity prior to inclusion in the study. Where a participant lacked capacity, consent was obtained from their legally authorised representative in accordance with applicable ethical and legal requirements and, where possible, based on the participant's previously expressed wishes and values. REC number 144217.

Results

Cohort characteristics

Seventy participants with aSAH were included in the primary analysis. The mean age was 55.7 ± 14.7 years, and 48 participants (68.6%) were female. Clinical severity at presentation was broad with 5 participants (7.1%) WFNS grade 1, 25 (35.7%) grade 2, 1 (1.4%) grade 3, 20 (28.6%) grade 4 and 19 (27.1%) grade 5. Radiological haemorrhage burden was also substantial, with modified Fisher grade 1 in 11 participants (15.7%), grade 3 in 47 (67.1%) and grade 4 in 12 (17.1%).

Participant-level PRcsf was calculated as the mean of three measurements obtained on three consecutive days. The distribution was markedly non-normal (Shapiro–Wilk $W = 0.750$, $p < 0.001$), with a median PRcsf of 145.06 mL/h (IQR 85.93–150.72). Two participants (2.9%) had PRcsf < 18 mL/h, 5 (7.1%) were within the conventional 18–24 mL/h range, and 63 (90.0%) had values > 24 mL/h. Thus, elevated measured CSF replenishment was not confined to a small number of outliers but represented the dominant physiological pattern within the cohort.

For the primary analysis, PRcsf was measured through an EVD in 54 participants (77.1%) and through an LD in 16 (22.9%). No catheter obstruction was documented during the analysed measurements, and no participant developed clinically apparent symptoms attributable to low intracranial pressure or excessive CSF drainage during or immediately after measurement at 0 mmHg.

Characteristic	Value	Notes
Age, years	55.7 ± 14.7	Mean ± SD
Female sex	48 (68.6%)	n (%)
WFNS grade 1	5 (7.1%)	n (%)
WFNS grade 2	25 (35.7%)	n (%)
WFNS grade 3	1 (1.4%)	n (%)
WFNS grade 4	20 (28.6%)	n (%)
WFNS grade 5	19 (27.1%)	n (%)
Modified Fisher grade 1	11 (15.7%)	n (%)
Modified Fisher grade 3	47 (67.1%)	n (%)
Modified Fisher grade 4	12 (17.1%)	n (%)
PRcsf, mL/h	145.06 (85.93–150.72)	Median (IQR)
Low PRcsf (<18 mL/h)	2 (2.9%)	n (%)
Standard PRcsf (18–24 mL/h)	5 (7.1%)	n (%)
High PRcsf (>24 mL/h)	63 (90.0%)	n (%)
EVD measurement	54 (77.1%)	n (%)
LD measurement	16 (22.9%)	n (%)
Coiling	50 (71.4%)	n (%)
Clipping	17 (24.3%)	n (%)
Treatment not recorded	3 (4.3%)	n (%)
Hydrocephalus	35 (50.0%)	CT/clinical record
SEBES 0	61 (87.1%)	n (%)
SEBES 2	7 (10.0%)	n (%)
SEBES 4	2 (2.9%)	n (%)
Tight-brain phenotype	2 (2.9%)	n (%)
Hospital length of stay, days	25.5 (21.0–50.0)	Median (IQR)
ICU length of stay, days	17.0 (6.2–26.2)	Median (IQR)
Permanent CSF diversion	35 (50.0%)	VP shunt
Aneurysm location	n (%)	
ACom	33 (47.1%)	
MCA	16 (22.9%)	
PCom	9 (12.9%)	
ICA	5 (7.1%)	
Basilar	2 (2.9%)	
PICA	2 (2.9%)	
Other/unspecified	3 (4.3%)	

Table 2. Baseline clinical, radiological and measurement characteristics.

PRcsf and six-month functional outcome

At six months, 53 participants (75.7%) had a favourable functional outcome (mRS 0–2) and 17 (24.3%) had a poor outcome (mRS 3–6). Ten participants (14.3%) had died. The mRS distribution was strongly polarised, with 48 participants returning to mRS 0, while the adverse-outcome group was concentrated towards the severe disability and mortality end of the scale.

PRcsf showed a clear relationship with subsequent functional outcome. Higher PRcsf was associated with lower six-month mRS (Spearman $\rho = -0.568$, $p < 0.001$), indicating that increasing CSF replenishment was associated with less disability. This was also evident when outcome was dichotomised. Participants with poor six-month functional outcome had substantially lower PRcsf than those with favourable outcome (median 36.20 mL/h [IQR 20.38–122.46] vs 149.56 mL/h [IQR 128.84–150.81]; Mann–Whitney $U = 141$, $p < 0.001$, rank-biserial $r = -0.687$).

The descriptive PRcsf categories showed the same pattern. Both participants with PRcsf <18 mL/h died by six months, and all five participants with PRcsf between 18 and 24 mL/h had a poor outcome, including four deaths. In contrast, 53 of 63 participants with PRcsf >24 mL/h achieved mRS 0–2. Because the lower PRcsf groups were small, these categorical findings were considered supportive rather than primary. Importantly, the association remained clear when PRcsf was analysed continuously.

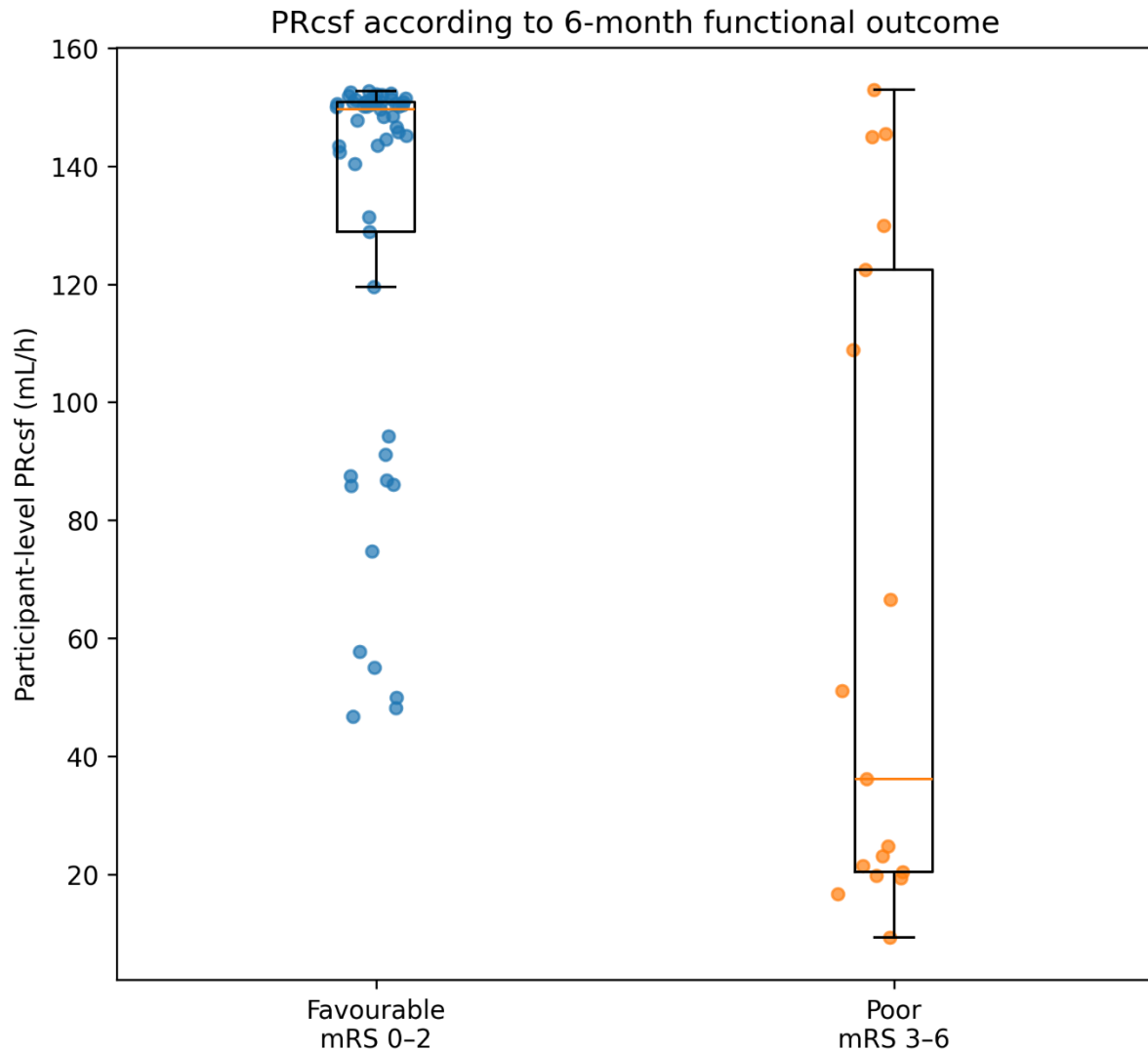


Figure 4. Cerebrospinal fluid production rate according to six-month functional outcome. Participant-level PRcsf was calculated as the mean of three measurements obtained on consecutive days. Participants with poor six-month functional outcome (mRS 3–6) demonstrated substantially lower PRcsf than those with favourable outcome (mRS 0–2).

Incremental information beyond admission WFNS grade

A central question was whether PRcsf merely reflected neurological severity at presentation or provided additional information about subsequent outcome.

In the baseline model, increasing WFNS grade was associated with poorer six-month outcome (OR 2.00 per grade increase, 95% CI 1.21–3.30, $p = 0.007$), with an AUC of 0.730. When continuous PRcsf was added, higher PRcsf remained strongly associated with a lower probability of poor outcome. Each 10 mL/h increase in PRcsf was associated with approximately 23% lower odds of mRS 3–6 (OR 0.772, 95% CI 0.671–0.887, $p < 0.001$).

Adding PRcsf improved model discrimination from an AUC of 0.730 to 0.848, an absolute increase of 0.118, and significantly improved model fit (likelihood-ratio $\chi^2 = 16.82$, $df = 1$, $p < 0.001$). The WFNS coefficient was attenuated after inclusion of PRcsf (OR 1.72, 95% CI 0.94–3.14, $p = 0.078$).

This pattern suggests that PRcsf is not simply duplicating WFNS. Rather, it appears to capture additional outcome-related information beyond the neurological condition at presentation.

Analysis	Estimate	95% CI	p value	AUC	Interpretation
Favourable outcome (mRS 0–2)	53/70 (75.7%)				
Poor outcome (mRS 3–6)	17/70 (24.3%)				
Six-month mortality	10/70 (14.3%)				
PRcsf in favourable outcome	149.56 mL/h	IQR 128.84–150.81	0.00002		
PRcsf in poor outcome	36.20 mL/h	IQR 20.38–122.46			
Continuous PRcsf vs 6-month mRS	Spearman $\rho = -0.568$		2.98e-07		Higher PRcsf associated with lower mRS
WFNS-only model: WFNS per grade	OR 2.00	1.21–3.30	0.0068	0.730 (0.591–0.851)	
WFNS + PRcsf model: WFNS per grade	OR 1.72	0.94–3.14	0.0782	0.848 (0.723–0.949)	
WFNS + PRcsf model: PRcsf per 10 mL/h	OR 0.772	0.671–0.887	0.00025	0.848 (0.723–0.949)	Lower odds of poor outcome with higher PRcsf
Incremental model comparison	Likelihood-ratio $\chi^2 = 16.82$ df = 1		0.00004	Δ AUC = 0.118	WFNS + PRcsf improved fit

Table 4. Six-month functional outcome and principal prognostic models.

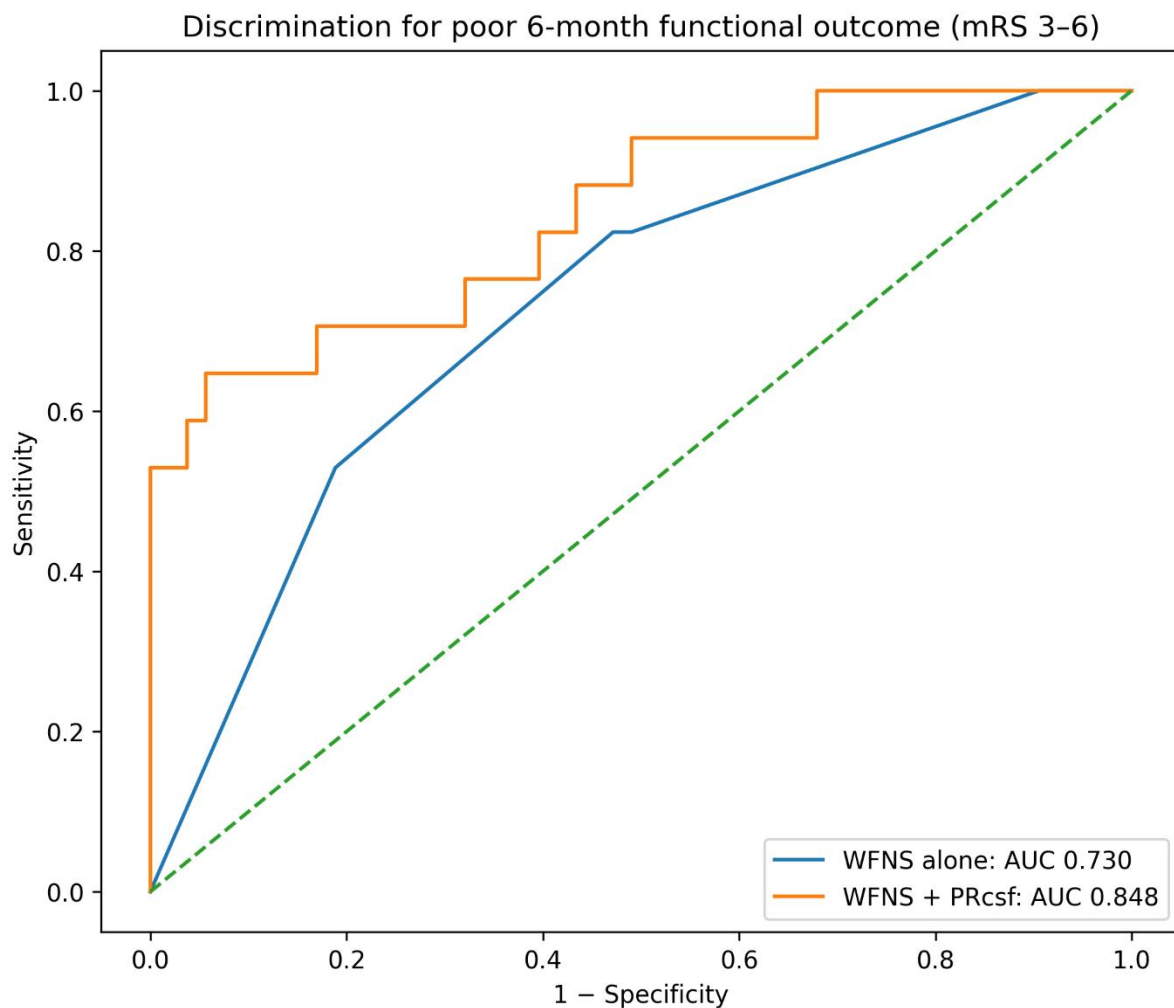


Figure 5. Discrimination for poor six-month functional outcome using WFNS alone and WFNS combined with PRcsf. Addition of continuous PRcsf to WFNS increased the area under the receiver operating characteristic curve from 0.730 to 0.848 and significantly improved model fit.

Relationship with initial disease severity

PRcsf demonstrated only a weak inverse association with WFNS grade at presentation ($\rho = -0.252$, $p = 0.035$). In contrast, there was no significant relationship between PRcsf and modified Fisher grade ($\rho = -0.101$, $p = 0.406$).

This distinction is important. PRcsf showed some relationship with initial clinical severity, but this association was modest and considerably weaker than its relationship with later functional outcome. At the same time, PRcsf was not related to radiological haemorrhage burden as measured by modified Fisher grade. Together, these findings suggest that PRcsf may reflect a physiological response occurring after the initial haemorrhage rather than simply serving as another measure of the severity of the presenting insult.

Intracranial pressure and PRcsf

Because PRcsf was measured under controlled drainage conditions, it was important to determine whether higher values simply reflected greater prevailing/baseline ICP driving passive CSF outflow.

Mean resting ICP was 20.87 ± 8.63 mmHg among the participants. There was no significant relationship between participant-level resting ICP and PRcsf (Spearman $\rho = -0.028$, $p = 0.889$). This finding argues against baseline pressure itself being the principal determinant of the measured flow rate.

In practical terms, participants with high PRcsf did not simply have higher ICP, and those with low PRcsf did not consistently have low ICP. This supports the interpretation that the LiquoGuard-derived measurement reflects more than passive pressure-driven drainage.

Ventricular morphology, cerebral oedema and the ‘tight-brain’ phenotype

A further concern was that PRcsf might predominantly reflect the size of the available ventricular CSF compartment or the degree of cerebral swelling.

There was essentially no association between Evans index and PRcsf ($\rho = -0.009$, $p = 0.943$; $n = 67$ with a measurable EI). This is particularly relevant because a measurement determined primarily by ventricular reservoir size would be expected to vary with ventricular calibre.

SEBES showed a weak inverse relationship with PRcsf, but this did not reach statistical significance ($\rho = -0.205$, $p = 0.089$). The two participants with the most severe ‘tight-brain’ phenotype had numerically lower PRcsf than the rest of the cohort, but this comparison was not significant ($p = 0.537$) and is necessarily limited by the very small subgroup.

Hydrocephalus likewise had little influence on the measured PRcsf. Median PRcsf was 144.51 mL/h in those with hydrocephalus and 146.57 mL/h in those without ($p = 0.972$).

Overall, these analyses provide little evidence that ventricular size, hydrocephalus or global cerebral swelling alone explains the marked differences in PRcsf between participants.

Drainage route and catheter function

Median PRcsf was lower numerically in participants measured through an LD than through an EVD, but the difference was not statistically significant (98.17 mL/h vs 146.16 mL/h, $p = 0.124$).

No catheter obstruction was documented during any of the primary measurements. Catheter patency was also assessed by monitoring the LiquoGuard ICP signal before, during and after measurement, with no abnormal pressure behaviour suggesting occlusion.

These findings reduce the likelihood that the inter-participant differences in PRcsf were primarily caused by catheter location or mechanical obstruction.

Sylvian fissure haemorrhage

Sylvian fissure haemorrhage was present in 37 participants and absent in 33 according to the predefined radiological criteria. Median PRcsf was 148.42 mL/h in participants with Sylvian fissure blood and 143.40 mL/h in those without, with no significant difference between groups ($p = 0.251$).

The absence of an association is notable given the prominent periarterial CSF pathways surrounding the middle cerebral arteries within the Sylvian fissures and suggests that the aneurysm-location effect is unlikely to be explained simply by blood occupying this major glymphatic/perivascular pathway.

Aneurysm location and PRcsf

Aneurysm location showed a significant relationship with PRcsf in exploratory analysis. The principal anatomical groups comprised 33 ACom, 16 MCA, 9 PCom and 5 ICA aneurysms. Basilar and PICA aneurysms were represented by only two participants each and were therefore interpreted descriptively.

PRcsf differed substantially between the four larger anatomical groups. Median values were approximately 145 mL/h for ACom, 150 mL/h for MCA, 86 mL/h for PCom and 20 mL/h for ICA aneurysms, with a significant overall difference (Kruskal–Wallis $H = 14.384$, $df = 3$, $p = 0.0024$, $\varepsilon^2 \approx 0.20$).

The difference was driven predominantly by the ICA subgroup after correction for multiple pairwise comparisons. Post-hoc analysis demonstrated significantly lower PRcsf in ICA aneurysms compared with MCA (Holm-adjusted $p = 0.0006$), ACom ($p = 0.0012$) and PCom aneurysms ($p = 0.016$), while no significant differences were observed between ACom, MCA and PCom aneurysms after correction for multiple comparisons.

The small number of ICA cases means that this finding is worthy of further investigation.

Aneurysm location was associated with ranked discharge neurology in exploratory analysis ($p = 0.035$), accounting for approximately 13.5% of its variation. When continuous PRcsf was added to the model, the explained variance increased to approximately 30.7%. PRcsf remained strongly associated with discharge neurological status ($p < 0.001$), whereas the independent association with aneurysm location was no longer apparent ($p = 0.838$). This attenuation should not be interpreted as evidence of statistical mediation, but suggests that PRcsf may capture physiological information associated with the differences in neurological outcome observed between aneurysm locations.

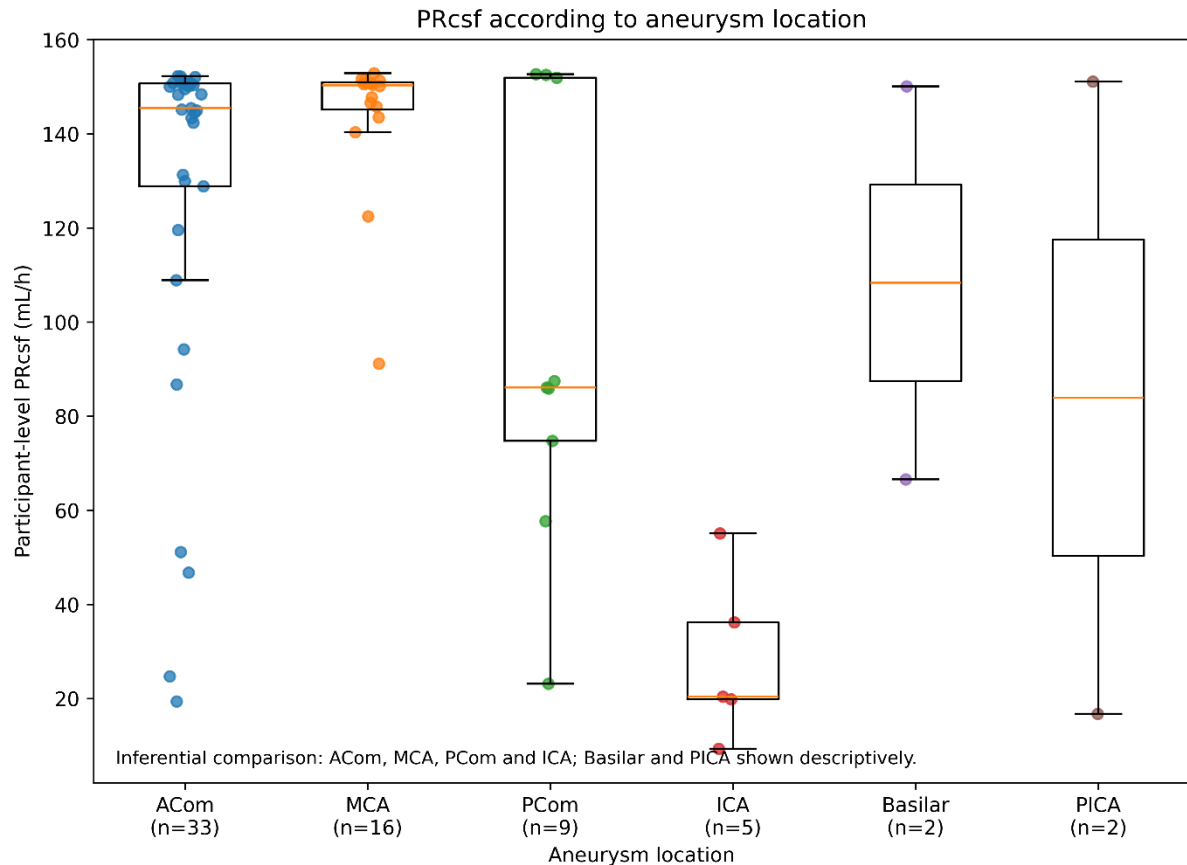


Figure 6. Distribution of PRcsf according to aneurysm location. Individual participant-level PRcsf values are shown according to aneurysm site. Inferential comparison was restricted to ACom, MCA, PCom and ICA groups because these contained at least five participants; basilar and PICA aneurysms are presented descriptively.

Delayed cerebral ischaemia and vasospasm

Secondary brain injury was examined because it may provide insight into whether PRcsf relates only to final functional status or also to clinically important events occurring during the post-haemorrhagic period.

Delayed cerebral ischaemia was documented in 25 participants. Participants who developed DCI had lower PRcsf than those who did not (median 108.88 mL/h vs 148.31 mL/h; Mann–Whitney $U = 388.5$, $p = 0.033$, rank-biserial $r = -0.309$).

This finding is notable because it extends the association beyond six-month disability as lower PRcsf is also observed in participants who subsequently developed a clinically consequential secondary cerebral injury. However, because DCI was a secondary exploratory endpoint and the study was not designed specifically to predict DCI, this result should be interpreted as hypothesis-generating rather than independent prediction.

Vasospasm was documented in 42 participants. In contrast, PRcsf did not differ significantly according to vasospasm status (median 144.22 mL/h vs 145.60 mL/h; Mann–Whitney $U = 525.5$, $p = 0.457$, rank-biserial $r = -0.106$).

The difference between these findings may be biologically relevant. Vasospasm does not invariably result in tissue ischaemia or clinical deterioration, whereas DCI represents a more consequential downstream cerebral injury. The present data therefore raise the possibility that

PRcsf relates more closely to the physiological state associated with secondary ischaemic injury than to vasospasm itself, although this requires confirmation in a larger cohort.

Treatment modality

PRcsf did not differ significantly according to definitive aneurysm treatment. Median PRcsf was similar in participants treated by coiling and clipping ($p = 0.579$), suggesting that the observed variation in PRcsf was not attributable to treatment modality.

Focused sensitivity analyses

Focused sensitivity analyses were undertaken to determine whether the association between PRcsf and six-month outcome was dependent on any single clinical or radiological characteristic.

The effect of PRcsf remained highly consistent after individual adjustment for age, modified Fisher grade, Evans index, SEBES, hydrocephalus, tight-brain phenotype, drainage route and Sylvian fissure haemorrhage. Across these models, the odds ratio for poor outcome remained approximately 0.75–0.78 per 10 mL/h increase in PRcsf, and the PRcsf association remained statistically significant throughout.

For example, after additional adjustment for Evans index, each 10 mL/h increase in PRcsf remained associated with lower odds of poor six-month outcome (OR 0.751, 95% CI 0.630–0.894, $p = 0.001$). Adjustment for modified Fisher grade (OR 0.771, 95% CI 0.671–0.886) and SEBES (OR 0.771, 95% CI 0.670–0.888) produced almost identical estimates.

The stability of these effect estimates is important. It suggests that the association between PRcsf and outcome is not readily explained by a single marker of initial haemorrhage severity, ventricular morphology, cerebral swelling or measurement route.

Model	n	PRcsf OR per 10 mL/h	95% CI	p	Model AUC
WFNS + PRcsf (base model)	70	0.772	0.671–0.887	<0.001	0.848
+ age (per 10 years)	70	0.753	0.644–0.879	<0.001	0.858
+ modified Fisher grade	70	0.771	0.671–0.886	<0.001	0.853
+ Evans index	67	0.751	0.630–0.894	0.001	0.901
+ SEBES	70	0.771	0.670–0.888	<0.001	0.850
+ hydrocephalus	70	0.745	0.635–0.873	<0.001	0.878
+ tight-brain phenotype	70	0.774	0.674–0.890	<0.001	0.845
+ LD drainage route	70	0.775	0.675–0.891	<0.001	0.849
+ Sylvian fissure blood	70	0.763	0.661–0.882	<0.001	0.855

Table 5. Focused sensitivity models for the association between PRcsf and poor 6-month outcome.

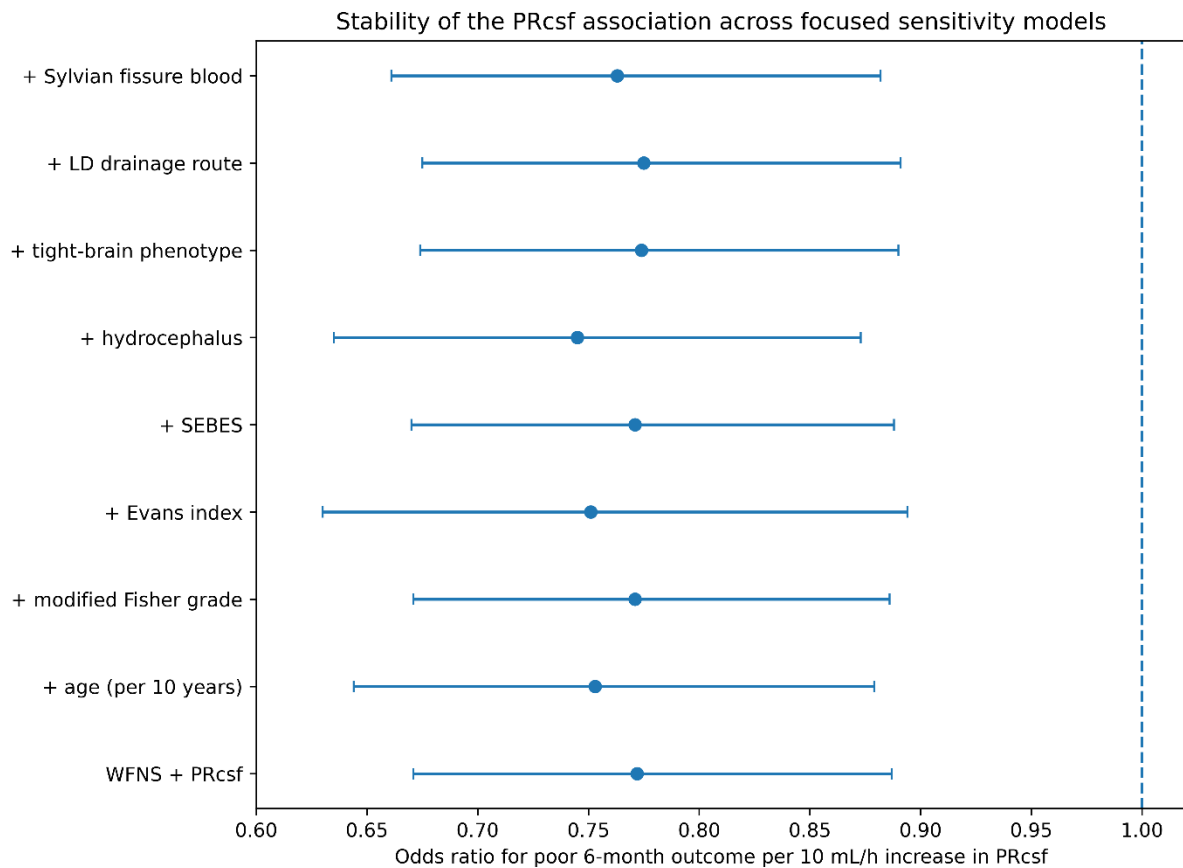


Figure 7. Stability of the association between PRcsf and poor six-month functional outcome across focused sensitivity models. Points represent odds ratios for poor outcome per 10 mL/h increase in PRcsf, with 95% confidence intervals, after adjustment for WFNS and the indicated additional covariate.

Secondary clinical outcomes

Higher PRcsf was associated with better neurological status at discharge ($p = 0.491$, $p < 0.001$). However, death inevitably influences discharge GCS and could therefore exaggerate this relationship. When participants who died were excluded, the association became much weaker and was no longer statistically significant ($p = 0.183$, $p = 0.162$).

This sensitivity analysis is important because it demonstrates why six-month mRS is the more robust endpoint for the study. The original association with discharge GCS appears to be partly driven by mortality rather than representing an independent relationship with neurological recovery among survivors.

The relationship with survival itself was pronounced. PRcsf was markedly lower among participants who died by six months than among survivors (median 21.76 mL/h [IQR 19.48–33.33] vs 148.02 mL/h [IQR 121.73–150.81]; Mann–Whitney $U = 13$, $p < 0.001$, rank-biserial $r = -0.957$). Because of the small cohort size this finding was treated as exploratory.

PRcsf was not significantly associated with hospital length of stay ($p = 0.097$, $p = 0.423$), ICU length of stay ($p = -0.133$, $p = 0.271$) or subsequent permanent CSF diversion. Median PRcsf was almost identical among participants who subsequently required a VP shunt and those who did not (144.97 vs 145.75 mL/h, $p = 0.597$).

This pattern suggests that PRcsf was more closely related to neurological outcome and survival than to duration of admission or subsequent dependency on permanent CSF diversion.

Four-week reproducibility of PRcsf

Twelve participants underwent repeat PRcsf assessment approximately four weeks after their initial measurement. Seven were reassessed through the same drainage route, while five underwent measurement through a different route, allowing both temporal and cross-route reproducibility to be examined.

The measurements were remarkably stable. Mean PRcsf was 104.28 mL/h initially and 103.63 mL/h four weeks later, giving a mean paired difference of only -0.65 mL/h. The median absolute difference was 1.01 mL/h, corresponding to approximately 1.1% of the initial value.

Absolute agreement between initial and repeat assessment-level PRcsf values was high [ICC(A,1) = 0.99973, 95% CI 0.99886–0.99993; $n = 12$], with Bland–Altman 95% limits of agreement of -2.80 to $+1.49$ mL/h. In the five participants assessed through different drainage routes, agreement was similarly high [ICC(A,1) = 0.99983, 95% CI 0.99875–0.99998].

This reproducibility is relevant to the interpretation of the wider cohort. The marked differences in PRcsf observed between individuals were far larger than the small within-individual differences seen four weeks apart, and measurements remained highly consistent even when the route changed from ventricular to lumbar or vice versa. This supports the view that PRcsf represents a reproducible individual physiological measurement rather than substantial random measurement variability.

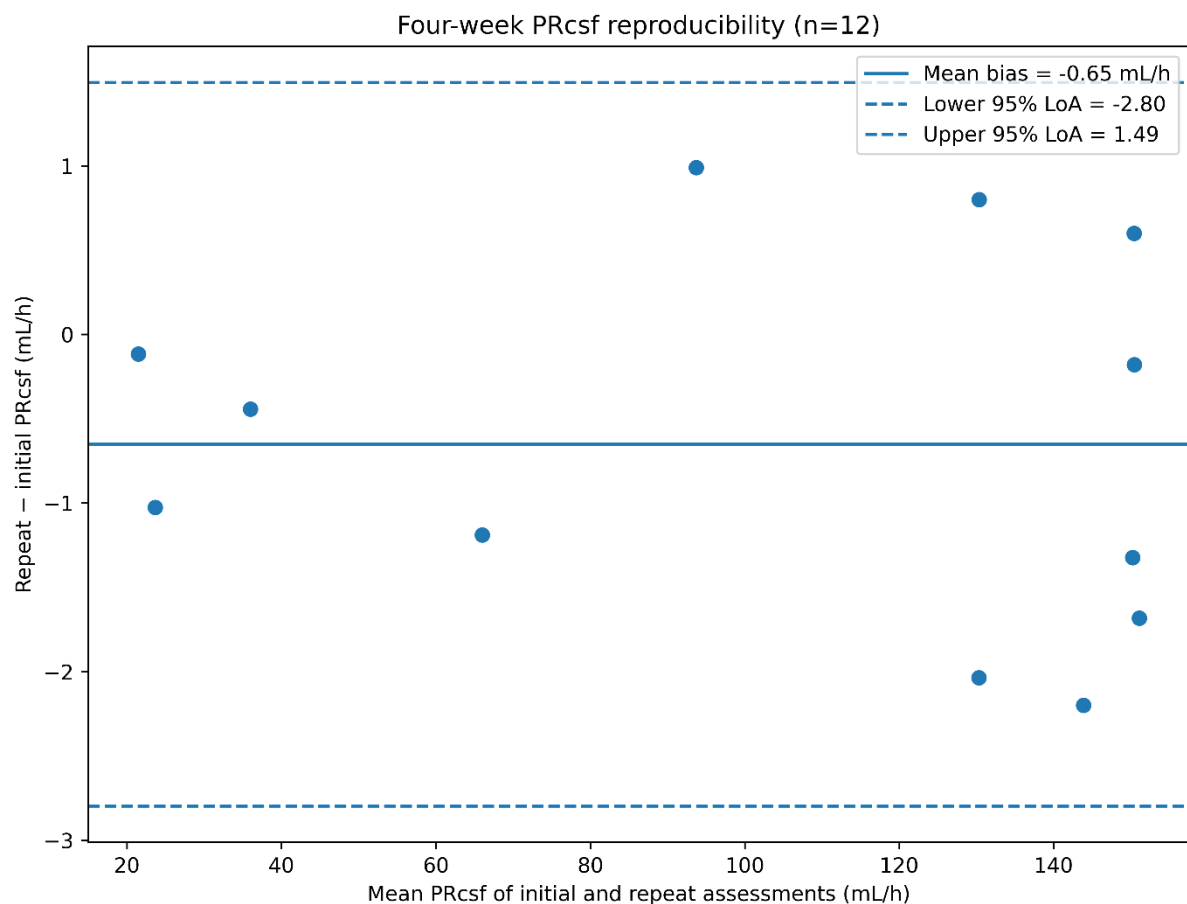


Figure 8. Bland–Altman analysis of PRcsf assessed approximately four weeks apart in 12 participants. Each assessment-level PRcsf value was calculated as the mean of three consecutive daily measurements. Each point represents one participant's paired difference (repeat minus initial assessment) plotted against the mean of the two

assessment-level values. The solid line indicates the mean paired difference of -0.65 mL/h, and the dashed lines indicate the estimated 95% limits of agreement, from -2.80 to $+1.49$ mL/h. These findings indicate close agreement between assessment-level PRcsf values within this subgroup.

Discussion

The principal finding of this study is that PRcsf was strongly associated with six-month functional outcome after aSAH. Participants with favourable outcome had substantially higher PRcsf than those with poor outcome, and addition of continuous PRcsf to WFNS improved model discrimination from an AUC of 0.730 to 0.848. In contrast, PRcsf showed only a weak association with WFNS itself and no significant relationship with modified Fisher grade. This suggests that PRcsf is not simply a surrogate for the severity of the presenting haemorrhage, but may capture an aspect of the subsequent physiological response that is relevant to recovery.

Experimental work provides biological plausibility for altered CSF physiology following haemorrhage^(1, 2, 4, 5). Higher net CSF replenishment could therefore conceivably facilitate dilution, redistribution or clearance of injurious solutes.

The glymphatic system provides a complementary framework for these findings. Human tracer studies demonstrate widespread periarterial CSF transport, including prominent pathways around the Sylvian fissures, while recent human MRI data show that aSAH disrupts glymphatic CSF–interstitial fluid exchange^(15, 17). Experimental studies similarly implicate AQP4-dependent fluid transport in oedema and early brain injury after SAH^(7, 8, 9). Higher PRcsf may therefore identify patients in whom global CSF–interstitial fluid exchange remains comparatively preserved after haemorrhage, whereas reduced PRcsf may reflect impairment of this wider fluid-dynamic response.

Importantly, the observed variation in PRcsf was not readily explained by simple hydrodynamic factors. PRcsf was essentially unrelated to EI, hydrocephalus or resting ICP, while SEBES showed only a weak non-significant inverse association. The two severe tight-brain cases had numerically lower PRcsf, but this subgroup was too small for firm inference. There was also no significant difference between EVD and LD derived measurements, and no catheter obstruction was identified. Collectively, these findings provide little evidence that ventricular calibre, cerebral swelling, resting pressure or catheter route are major determinants of PRcsf across the cohort.

The Sylvian fissure analysis is relevant because these spaces contain major periarterial CSF pathways. Despite this, PRcsf did not differ according to the presence of Sylvian fissure haemorrhage. Thus, the association between aneurysm location and PRcsf is unlikely to be explained simply by blood occupying a major periarterial or glymphatic pathway. Blood distribution after aneurysm rupture is complex and overlapping between territories^(18, 19), which may partly explain why the presence of blood in one anatomical compartment was insufficient to determine global PRcsf.

Aneurysm location nevertheless showed an intriguing exploratory association. ICA aneurysms were associated with substantially lower PRcsf than ACom, MCA and PCom aneurysms, although only five ICA cases were available. Furthermore, when PRcsf was added to the exploratory model relating aneurysm location to discharge neurological status, PRcsf remained associated with outcome whereas the location effect was attenuated. This does not

demonstrate mediation, but raises the possibility that variation in CSF physiology contributes to some of the heterogeneity in recovery observed between aneurysm locations.

Lower PRcsf was also associated with DCI, whereas no significant association was observed with vasospasm. This distinction is potentially important because DCI is a multifactorial secondary brain injury and cannot be explained solely by large-vessel vasospasm^(20, 21). Impaired CSF or perivascular clearance of haemoglobin, inflammatory mediators and other vasoactive substances could plausibly contribute to the physiological environment in which DCI develops. However, whether reduced PRcsf precedes DCI or instead develops alongside secondary injury cannot be determined from the present study.

The measurement itself requires careful interpretation because some PRcsf values exceeded conventional estimates of resting CSF secretion⁽¹⁶⁾, a concern also raised in relation to our previous work⁽¹²⁾. Davson's equation describes CSF formation and absorption within a steady-state hydrodynamic framework, whereas the present protocol deliberately alters CSF pressure through an external drainage pathway⁽¹³⁾. Sagittal sinus pressure may also vary dynamically with CSF pressure during infusion and drainage rather than behaving as a fixed term⁽²²⁾. Recent lumped-parameter modelling further suggests that CSF formation may vary with capillary transmural pressure during manipulation of CSF pressure⁽²³⁾, while classical human hydrodynamic studies reported experimentally derived CSF formation rates substantially above conventional resting estimates, including values approaching 3 mL/min^(14, 24). These findings indicate that the components of Davson's relationship cannot necessarily be assumed to remain constant during pressure manipulation. Accordingly, LiquoGuard-derived PRcsf should be interpreted as net CSF compartment replenishment under controlled low-pressure drainage, rather than isolated choroid plexus secretion or a direct inversion of Davson's equation. This is also consistent with modelling suggesting that conventional infusion studies may misestimate CSF outflow resistance if changes in CSF formation are ignored⁽²⁵⁾.

The methodological observations support this interpretation. High-flow measurements remained stable during the 30-minute recording period without clinical evidence of intracranial hypotension, and PRcsf was highly reproducible when repeated approximately four weeks later. The mean paired difference was only -0.65 mL/h, with an ICC of 0.9997, and similarly high agreement was observed when the repeat measurement was obtained through a different drainage route. Reproducibility does not establish the biological source of the measured fluid, but it argues strongly against random measurement error or catheter location as the principal explanation for the marked differences observed between individuals.

The stability of PRcsf approximately four weeks apart raises the possibility that higher PRcsf reflects a pre-existing physiological characteristic associated with greater likelihood of survival and favourable recovery, rather than an increase induced by aSAH. However, both assessments were performed after haemorrhage, and a sustained post-haemorrhagic alteration could produce the same pattern. Without pre-ictus measurements, these explanations cannot be distinguished. Repeat assessment was also restricted to a subgroup of 12 participants, limiting generalisation of the observed stability to the entire cohort. These findings therefore support an association between post-aSAH PRcsf and outcome, but do not establish that aSAH increases PRcsf or that increasing PRcsf would improve recovery.

Strengths and limitations

Strengths include prospective measurement using a standardised protocol, three consecutive daily measurements per participant, blinded six-month functional assessment, detailed clinical and radiological phenotyping, focused sensitivity analyses and repeat-measurement assessment across both time and drainage route.

The study nevertheless has important limitations. It was single-centre, with a modest cohort and relatively few poor outcomes and deaths, limiting multivariable model complexity. No formal a priori power calculation was performed. Sample size was determined by prospective recruitment of eligible patients during the predefined study period. Although the principal associations were supported by substantial effect sizes, confidence intervals and consistent sensitivity analyses, smaller subgroup findings, particularly aneurysm location and severe cerebral oedema, remain exploratory and require validation in larger cohorts. The LiquoGuard measurement cannot distinguish the relative contributions of choroid plexus secretion, interstitial or vascular fluid exchange and redistribution between CSF compartments. Time from ictus to PRcsf measurement was also unavailable with sufficient precision for formal modelling. Finally, all observed relationships are associative and do not establish causality. External validation is required before PRcsf can be considered a prognostic biomarker for clinical use.

Conclusion

Higher net CSF replenishment after aSAH was associated with more favourable six-month functional outcome and provided information beyond WFNS grade. This relationship was not readily explained by haemorrhage burden, ICP, ventricular morphology, hydrocephalus, cerebral oedema, drainage route or Sylvian fissure haemorrhage. Together with its association with DCI and the high reproducibility of the measurement, these findings suggest that PRcsf may represent a candidate physiological biomarker of post-haemorrhagic CSF dynamics and recovery, potentially reflecting the capacity of the injured brain to maintain CSF–interstitial fluid exchange after haemorrhage.

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to this manuscript.

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Keywords

Aneurysmal subarachnoid haemorrhage; cerebrospinal fluid; cerebrospinal fluid production rate; functional outcome; WFNS; delayed cerebral ischaemia; glymphatic system; cerebrospinal fluid dynamics.

STROBE Statement

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies. The study design, setting, participant eligibility, PRCSF measurement protocol, clinical and radiological variables, outcome definitions, sample-size rationale, statistical methods, sensitivity analyses, missing-data handling, limitations and generalisability are reported in accordance with the STROBE recommendations.

A completed STROBE cohort checklist is provided as supplementary data.

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