



# The course of cerebrospinal fluid parameters $\leq 20$ days after aneurysmal subarachnoid hemorrhage

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## ABSTRACT

**Background:** Aneurysmal subarachnoid hemorrhage (aSAH) patients have an inflammatory response in the cerebrospinal fluid (CSF). We determined CSF cell counts, erythrocyte/leukocyte ratio, and glucose- and protein concentrations in patients  $\leq 20$  days after aSAH without bacterial meningitis. Such knowledge may help to interpret CSF parameters in patients with an external drain if nosocomial bacterial meningitis or ventriculitis is suspected.

**Methods:** Patients with aSAH admitted between 2010 and 2017 with at least one CSF sample  $\leq 20$  days after ictus were included from a prospectively collected database. CSF samples were excluded if the patient used antibiotics or if the CSF culture was positive. We calculated estimated marginal means with 95% confidence intervals (CIs) with linear mixed models for CSF cell counts, glucose- and protein concentrations.

**Results:** We included 209 patients with 306 CSF samples. Highest estimated median leukocyte count was 305 (95%CI:225–412)  $\times 10^6/L$ , and the lowest estimated median erythrocyte/leukocyte ratio was 109 (95%CI:73–163). Estimated mean glucose concentrations remained within the normal range. The estimated median protein concentration decreased from 3.3 g/L (95%CI:2.5–4.2) on day 0 to 1.0 g/L (95%CI:0.8–1.2) on day 14.

**Conclusion:** The limits we found for the inflammatory reaction in aSAH patients may help physicians to interpret CSF parameters in aSAH patients with an external CSF drain. Future studies are needed to compare CSF parameters in aSAH patients with and without bacterial meningitis or ventriculitis.

## 1. Introduction

In patients with aneurysmal subarachnoid hemorrhage (aSAH) the presence of blood in the subarachnoid space results in a local sterile inflammatory response [1–3]. Although many studies found elevated cerebrospinal fluid (CSF) concentrations of inflammatory parameters such as interleukins after aSAH [1–5], the course of CSF cell counts, erythrocyte/leukocyte ratio and glucose- and protein concentrations in the CSF after aSAH remains unclear. Such knowledge may help to interpret CSF parameters in patients with an external drain if nosocomial bacterial meningitis or ventriculitis is suspected. In clinical practice it can be difficult to discriminate an infection from an inflammatory reaction. In aSAH patients fever may occur in the absence of an infection [6], and patients may have nuchal rigidity. We investigated the course of CSF cell counts, erythrocyte/leukocyte ratio, and glucose- and protein concentrations in aSAH patients without bacterial meningitis or

ventriculitis during the initial 3 weeks after ictus.

## 2. Methods

### 2.1. Study design and population

We performed retrospective analyses of data collected prospectively for aSAH patients admitted to the University Medical Center Utrecht (UMCU) between January 1, 2010 and June 30, 2017. Our cohort included aSAH patients with at least one CSF sample obtained by lumbar puncture or by sampling from an external lumbar drain (ELD) or an external ventricular drain (EVD) during the first 20 days after ictus. The day of ictus was defined as day 0. A CSF sample was included if the erythrocyte counts, leukocyte counts, and cell culture results were available. If only the cell culture was unavailable, we did include samples if there was no clinical suspicion of bacterial meningitis or

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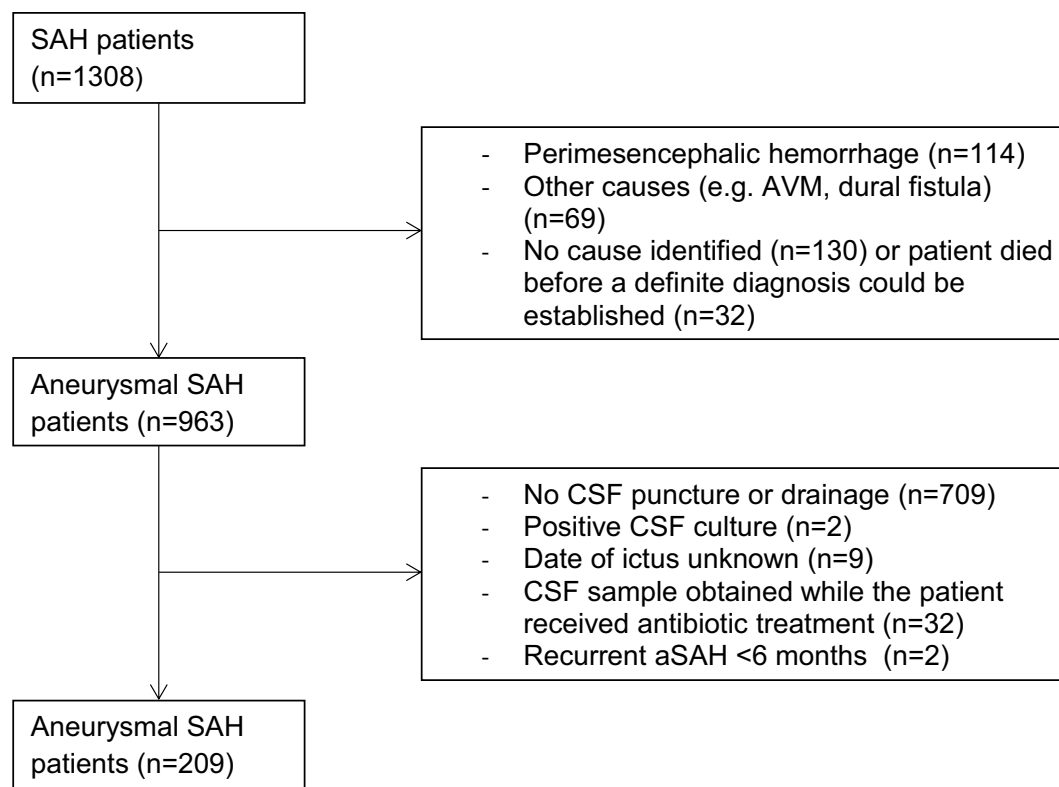


Fig. 1. Patient flowchart.

SAH = subarachnoid hemorrhage; aSAH = aneurysmal subarachnoid hemorrhage; AVM = arteriovenous malformation; CSF = cerebrospinal fluid.

**Table 1**  
Patient characteristics.

	All patients N = 209 (%)
Female sex (%)	140 (67)
Mean age [SD]	60 [13]
PAASH score <sup>a</sup>	
1 (GCS 15)	29 (14)
2 (GCS 11-14)	79 (38)
3 (GCS 8-10)	37 (18)
4 (GCS 4-7)	33 (16)
5 (GCS 3)	25 (12)
Aneurysm in anterior circulation (%)	162 (78)
Median Hijdra sum score [IQR]	24 [18-30]
Infection < 20 days after ictus	66 (32)

<sup>a</sup> PAASH score could not be determined in six intubated patients. SD = standard deviation; PAASH = Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage score; GCS = Glasgow Coma Score; IQR = interquartile range.

ventriculitis and if CSF was obtained by lumbar puncture or at the day of drain placement. Exclusion criteria were: 1) unknown date of ictus; 2) CSF sample obtained while the patient was receiving antibiotic treatment other than selective decontamination of the digestive tract (SDD) or selective oropharyngeal decontamination (SOD); 3) antibiotic treatment (except for SDD/SOD) stopped < 48 h prior to CSF sampling; 4) positive CSF culture; and 5) previous aSAH < 6 months.

## 2.2. Local treatment protocol

In our hospital, CSF sampling is performed in case of a hydrocephalus or a clinical suspicion of bacterial meningitis or ventriculitis. First line treatment of a hydrocephalus is a lumbar puncture if not contra-indicated by hemocephalus or a large intracerebral hematoma.

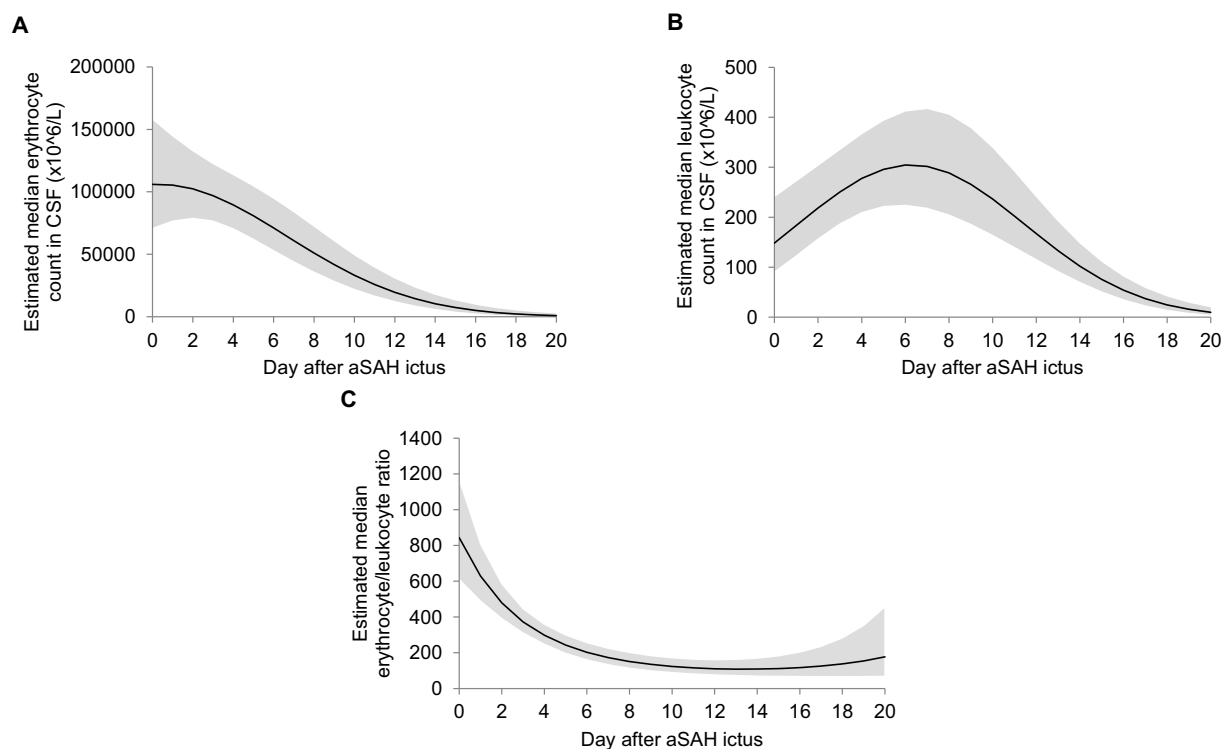
Patients on the intensive care unit (ICU) received SDD and/or SOD if the expected stay at the ICU was > 48 h. In addition, cooling was administered to ICU patients if the body temperature was > 40 °C. No prophylactic antibiotics were given at the neurology and neurosurgery medium care units or wards.

## 2.3. Data collection

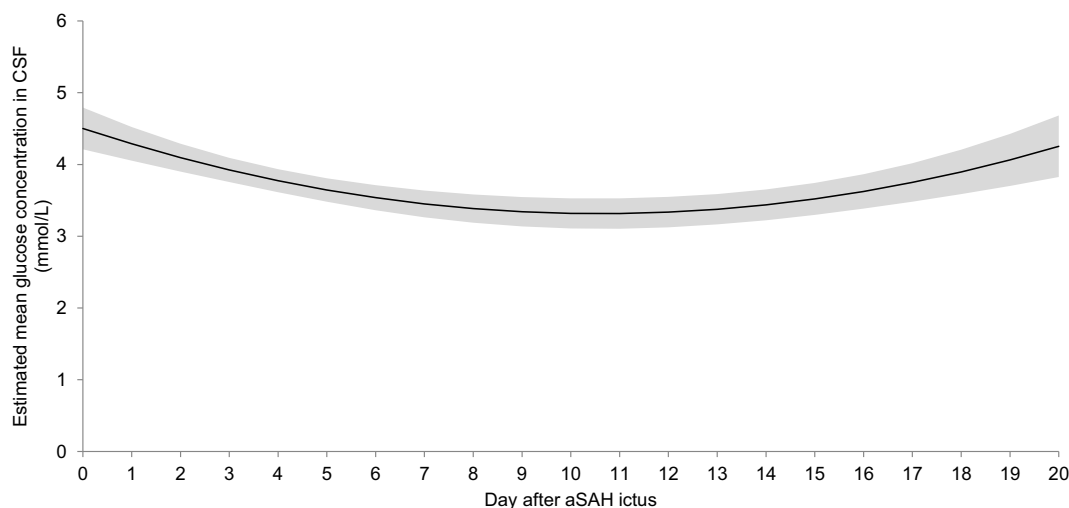
The following characteristics were retrieved: age, sex, date of ictus, Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage (PAASH) score [7], Hijdra sum score for the amount of extravasated blood on the initial head computed tomography[8], location of the ruptured aneurysm, and the presence of an infection. We defined infections according to the criteria from the Center for Disease Control [9], except for the diagnosis of nosocomial bacterial meningitis and ventriculitis which we defined as ‘a positive CSF culture’ because symptoms such as fever, nuchal rigidity and drowsiness can be present in aSAH patients without there being an infection [6]. We also documented date of CSF sampling, CSF cell counts, glucose- and protein concentrations, cell culture results, and location of CSF sample collection.

## 2.4. Statistical analysis

To investigate the course of CSF parameters within 20 days after ictus, we used linear mixed models for continuous outcomes [10]. We incorporated a random intercept and a random effect for time (i.e. the days after ictus) in all models except for the leukocyte count, erythrocyte/leukocyte ratio, and glucose models. A random effect for time was excluded in the leukocyte and glucose models, since the corresponding variance component was near zero. A random intercept was excluded for the erythrocyte/leukocyte ratio to achieve model convergence. Time squared was included in all models to accommodate a non-linear progression. We constructed two models for each variable, one without covariable adjustment and one with covariable adjustment



**Fig. 2.** Estimated median erythrocyte (a); leukocyte count (b); and erythrocyte/leukocyte ratio (c) in CSF  $\leq 20$  days after aSAH ictus. aSAH = aneurysmal subarachnoid hemorrhage; CSF = cerebrospinal fluid. Shaded area indicates the 95% confidence interval.



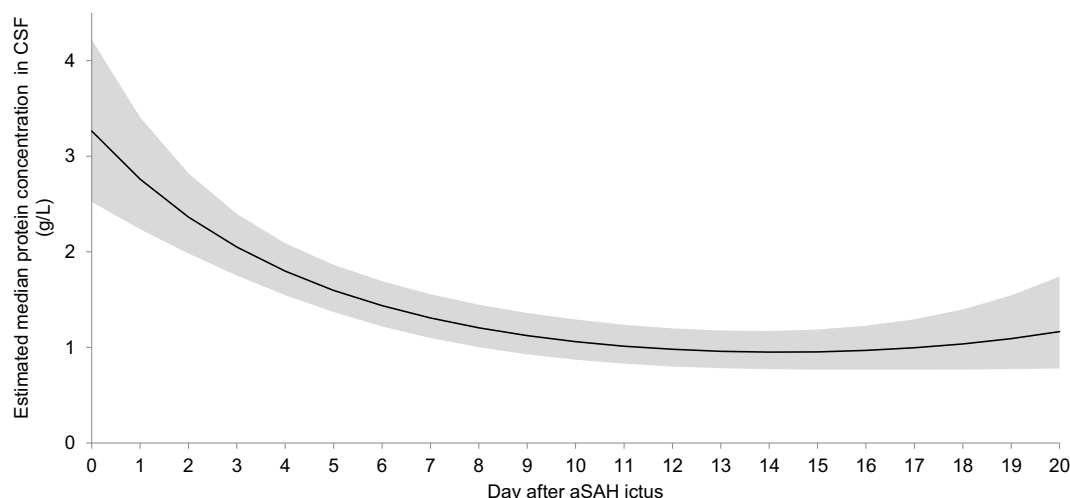
**Fig. 3.** Estimated mean glucose concentration in CSF  $\leq 20$  days after aSAH ictus. aSAH = aneurysmal subarachnoid hemorrhage; CSF = cerebrospinal fluid. Shaded area indicates the 95% confidence interval.

for age, location of CSF sampling (ventricular or lumbar), and PAASH score. Models were estimated under restricted maximum likelihood and the validity of the model assumptions was assessed with an analysis of residuals. Since the distribution of CSF cell counts, erythrocyte/leukocyte ratio, and protein concentrations was skewed, these outcomes were log transformed to obtain near to normal distributions. From the analysis, we derived estimated marginal means over time with 95% confidence intervals (CIs). For ease of interpretation, we transformed log outcomes back to the original scale. For log transformed outcomes the exponential back transformation provides an estimate of the median (with 95% CI) on the original scale [11,12]. We subsequently constructed figures for the models with covariable adjustment to facilitate interpretation.

### 3. Results

We included 209 patients with 306 CSF samples (Fig. 1). Patient characteristics are shown in Table 1. CSF erythrocyte and leukocyte counts were available from all 306 samples, glucose concentrations were available from 287 samples, and protein concentrations from 292 samples. In total, 120 (39%) CSF samples were obtained by lumbar puncture or by sampling from an ELD, and 186 (61%) from an EVD. Details on the timing of CSF sampling are shown in Fig. S1. Crude values with 95% CI are shown in Table S1. We report the results of the covariable adjusted models (adjusted for age, location of CSF sampling, and PAASH score).

Median erythrocyte counts decreased over time, while median



**Fig. 4.** Estimated median protein concentration in CSF  $\leq 20$  days after aSAH ictus.

aSAH = aneurysmal subarachnoid hemorrhage; CSF = cerebrospinal fluid. Shaded area indicates the 95% confidence interval.

leukocyte counts increased to 305 (95%CI:225–412)  $10^6/L$  on day 6, after which leukocyte counts gradually decreased (Fig. 2a and b). The median erythrocyte/leukocyte ratio decreased from a ratio of 844 (95%CI:610–1168) on day 0 to 173 (95%CI:133–225) on day 7 and 109 (95%CI:73–163) on day 13 (Fig. 2c). Between days 14–20, the ratio increased to 178 (95%CI:69–457) on day 20.

The mean glucose concentration remained within the normal range with values between 3.5 and 4.5 mmol/L (Fig. 3). Median protein concentrations were elevated with a concentration of 3.3 (95%CI:2.5–4.2) g/L on day 0 and decreased to 1.3 (95%CI:1.1–1.6) g/L on day 7 and 1.0 (95%CI:0.8–1.2) g/L on day 14. Subsequently, protein concentrations slightly increased again to 1.2 g/L (95%CI:0.8–1.7) on day 20 (Fig. 4). Protein concentrations did not normalize  $\leq 20$  days after ictus.

#### 4. Discussion

The inflammatory response in the CSF in aSAH patients resulted in increasing leukocyte counts over time, while erythrocyte counts decreased. Accordingly, the erythrocyte/leukocyte ratio after aSAH decreased to a ratio of approximately 200 on day 7 and 100 on day 14, without normalization on day 20. Glucose concentrations remained within the normal range, while protein concentrations were elevated and decreased over time.

Two previous studies investigated the CSF erythrocyte and leukocyte counts and glucose and protein concentrations in patients with intraventricular hemorrhage (IVH) without macrovascular cause, thus excluding aSAH patients [13,14]. In both studies, a temporal pattern similar to our results was observed for the leukocyte count, glucose- and protein concentrations, although in one study the leukocyte increase occurred a few days earlier [14]. In contrast to our results, the erythrocyte count in IVH patients increased the first 3 days, possibly because of redistribution of blood into the ventricular system or insertion of the drain [14].

A strength of our study is that we investigated a cohort of consecutive patients with aSAH from a prospectively collected database, and hereby reduced selection bias. In addition, we incorporated age, location of CSF sampling, and clinical condition on admission score into our model to account for possible confounding. We specifically applied a mixed model with random coefficient to accommodate different time points of CSF sampling and repeated CSF sampling.

Several limitations need to be mentioned. First, we did not calculate the corrected leukocyte count or cell index, because data on blood erythrocyte counts at the time of CSF sampling was often lacking.

Although in one study the cell index allowed accurate diagnosis of ventriculitis in IVH patients [15], these results have not yet been validated. Second, data on the differential leukocyte count were unavailable for most patients. Therefore, we were unable to indicate if the pleocytosis was predominantly lymphocytic or neutrophilic and if the differential changed over time. Third, the CSF leukocyte count may have been affected by the use of SDD in ICU patients because of penetration of the antibiotic through the blood-brain barrier. Fourth, this study was embedded in clinical practice and thus CSF samples were obtained if there was an indication for a lumbar puncture or CSF drain resulting in a risk of bias by indication. For the first samples obtained from patients the risk of bias is low, since the indication for CSF sampling is drainage because of a hydrocephalus. For further samples, there is a risk of bias by indication, because these samples are obtained from patients who need long-term drain treatment due to disturbed CSF circulation. This might also explain why protein concentrations slightly increased from day 14 onwards. We aimed to diminish this bias as much as possible by excluding samples from patients with positive CSF cultures and patients who were treated with antibiotics. Moreover, the glucose levels in our study samples remained within limits for normal, which further strengthens our feeling that we have excluded CSF samples from patients with bacterial meningitis adequately. However, we cannot entirely exclude a risk of bias by indication. If this type of bias has played a role in our data, it will have resulted in higher leukocyte levels and thus lower erythrocyte/leukocyte ratios than in a genuine inflammatory CSF response after aSAH. Lastly, we included CSF samples from both lumbar punctures, ELDs, and EVDs to assure that the results resemble clinical practice as closely as possible. Unfortunately, the sample size of the subgroups was not large enough for subgroup analyses. It also was not possible to provide a comparison group of aSAH patients with culture-confirmed bacterial meningitis because there were only five CSF samples between 2010 and 2017 with a positive CSF culture. Since we have no comparator group, we were not able to assess the diagnostic performance of the limits we found. Therefore, our results may help physicians to interpret CSF parameters, but cannot be used to exclude bacterial meningitis or ventriculitis in aSAH patients with an external drain. Future studies are needed to compare CSF parameters in aSAH patients with and without bacterial meningitis or ventriculitis.

#### 5. Conclusion

Our study shows the course of basic CSF parameters during the inflammatory response in aSAH patients. The limits we found may help

physicians to interpret CSF parameters in aSAH patients with an external CSF drain.

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### Ethical approval and informed consent

Ethical approval and informed consent were waived for this study by the Institutional Review Board of the University Medical Center of Utrecht because it concerns a retrospective analysis of data obtained during routine clinical care.

### Author contributions

IK contributed to the data collection, data- and statistical analysis, interpretation of data, and drafting of the manuscript. NPAZ contributed to the data- and statistical analysis, interpretation of data, and manuscript revision. GJER contributed to interpretation of the data, and manuscript revision. MDIV contributed to the study concept/design, interpretation of data and manuscript revision, and provided study supervision.

### Declaration of Competing Interest

The authors declare that they have no competing interest.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jns.2020.116899>.

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