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# Assessment of Sustained Systemic Inflammatory Response Syndrome and CSF Markers as Predictive Values Associated with Shunt-Dependent Hydrocephalus after Aneurysmal Subarachnoid Hemorrhage

Ahmed Elghity[1]*, Walid El Halaby[2], Wleed Raafat[2], Omar Sorour[2], Ahmed Atallah[2]

*[1]Department of Neurosurgery, Al-Sahel Teaching Hospital, Cairo, Egypt; [2]Department of Neurosurgery, Faculty of Medicine, Cairo University, Giza, Egypt*

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***Correspondence:** Ahmed Elghity, Neurosurgery Specialist, Al-Sahel Teaching Hospital, Cairo, Egypt. E-mail: ahmedelghaity@gmail.com
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## Abstract

**AIM:** This study was conducted to detect incidence and risk factors of shunt-dependent hydrocephalus (SDH), including systemic inflammatory response syndrome (SIRS).

**PATIENTS AND METHODS:** After obtaining ethical approval from the research ethics committee of Cairo University, this study was conducted in two phases, Phase I in the form of follow-up study to detect the incidence of shunt-dependent hydrocephalus (HC) in patients with ruptured subarachnoid aneurysm then Phase II in the form of comparative one to detect the risk factors of acquisition of shunt-dependent HC and detect the predictive role of SIRS in SDH. The study included 90 patients with ruptured subarachnoid aneurysms followed up in the Department of Neurosurgery of Cairo University Hospital from April 2018 to April 2020.

**RESULTS:** The incidence of SDH was 28% among the studied patients with significant association with high-grade SIRS score [1.92 ± 1.2 vs. 1.2 ± 0.9, p = 0.004], Fisher score [3.4 ± 0.7 vs. 2.9 ± 0.9, p = 0.040], Hunt and Hess score [2.5 ± 1.3 vs. 1.8 ± 1.4, p = 0.033], and leukocytosis (the mean white blood cells [WBCs] were significantly higher in patients with HC at the 2$^{nd}$ [p = 0.005], 5$^{th}$ [p = 0.011], 6$^{th}$ [p = 0.010], and 7$^{th}$ days [p = 0.001]). The cerebrospinal fluid (CSF) WBCs and protein were significantly higher in the HC group. Furthermore, there was significant hypernatremia among the hydrocephalic group.

**CONCLUSION:** Despite the study's analytical design, we observed a link between high Fisher, SIRS, hypernatremia, and SDH in aneurysmal subarachnoid hemorrhage patients. Serum sodium, CSF WBCs, and protein may all be used to predict HC.

## Introduction

Hydrocephalus (HC) is a significant cause of morbidity after subarachnoid hemorrhage (SAH) caused by an aneurysm. Acute HC affects 6–87% of individuals, while chronic HC affects 6–64% of patients, necessitating permanent cerebrospinal fluid (CSF) diversion in the form of an implanted ventriculoperitoneal shunt or shunt another shunt [1].

Usually, HC caused by SAH makes impairment of CSF reabsorption by arachnoid granulation tissues, adhesions and/or obstruction of the ventricular system, and alteration of the dynamics of CSF [2]. Thrombin-induced TGF-b stimulation, nuclear factor [NF] kB activation, choroid plexus, and/or ependymal inflammation have all been related to HC [3].

Following a SAH, two-thirds of patients experience systemic inflammatory response syndrome (SIRS). Independent of infection, SIRS has been linked to a poor prognosis [4]. In aneurysmal SAH, few studies have addressed SIRS and shunt-dependent HC (SDH). The present study aimed to determine the relationship between persistent SIRS and the development of SDH in individuals with aneurysmal SAH as well as assessing the standardized scores of diagnosis of SDH that may be utilized as predictors for SDH in SAH patients.

## Patients and Methods

### *The type of study*

This study was conducted in two phases; Phase I in the form of follow-up of the patients admitted during the study period to detect the incidence of shunt-dependent HC in patients with ruptured subarachnoid aneurysm, then Phase II in the form of comparative one to detect the risk factors of acquisition of shunt-dependent HC and detect the predictive role of SIRS in patients with SAH who develop HC.

### Study site and time

This study took place in the Neurosurgery Department, Cairo University Hospital, over 2 years, from April 2018 to April 2020.

### Study population and inclusion criteria

The target population was adult patients [over 18 years] of both sexes who were admitted to the neurosurgery department during the study period with the following inclusion criteria; spontaneous SAH, diagnosed by computed tomography (CT) or xanthochromia on lumbar puncture [not traumatic], and having a verified cerebral aneurysm on CT angiography [CTA] or digital subtraction angiography [DSA].

### Exclusion criteria: Patients with the following criteria were excluded from the study

Those diagnosed with an infection during their first 7 days in the hospital. Patients with chronic renal failure, liver cirrhosis, chronic heart failure, a history of hematological disorders, mental or psychological disorders, and panic attacks, who are taking steroids and immunosuppressive drugs, acute status asthmatics with frequent beta-agonist administration, acute salicylate toxicity, acute alcohol intoxication, acute ketoacidosis [diabetic, starvation, and dehydration], acute ketoacidosis [diabetic, starvation, and dehydration].

### Sample size calculation

It was done using G. power version 3.1 [5] to calculate the proportion of shunt-dependent HC among patients with SAH [one sample case] with effect size [g] 0.2, $\alpha$ error probability 0.05, power of study 95%, and constant proportion 50%. The total sample size to fulfill these criteria was 79 patients with SAH to be followed up and detect the incidence of SDH. The number increased to 90 patients to increase the power of the study.

### Clinical evaluation and outcome measures

All patients were examined on admission and again before aneurysm repair. A neurosurgeon not engaged in treating the patients during neurointensive care evaluated their Hunt and Hess grades.

### Radiological assessment

A neuroradiologist and neurosurgeons radiographically evaluate subarachnoid, ventricular, and ventricular blood. The modified Fisher score was used to assess SAH [6] using CT, CTA, DSA, and MRA.

### Data collection

Patients were assessed through a data collection form that included age, gender, history of smoking, history of alcohol consumption, comorbidities as diabetes, hypertension, heart, liver, or kidney diseases, previous brain surgery, and history of anticoagulants.

### Regarding the diagnosis of SIRS

SIRS was diagnosed when two or more of the following criteria were fulfilled [7] on any given day during the first 7 days of hospitalization: Temperature >38°C or <36°C, white blood cell (WBC) count >12,000 or <4000, heart rate >90 beats/min [tachycardia], and respiratory rate >20 breaths/min [tachypnea].

### CSF markers

It was assessed on admission and followed up during the 1$^{st}$ week of follow-up of SAH as WBCs, red blood cells (RBCs), protein, and glucose in CSF. WBCs, RBCs, protein, and glucose in CSF, as well as standard shunt predictors in patients with subarachnoid hemorrhage (the Fisher grade [6], WFNS grade [8], Hunt and Hess Score [9], and serum sodium) were assessed on admission and followed up during the first week of follow-up of subarachnoid hemorrhage.

### Statistical analysis

Data analysis was performed using SPSS v.25 [IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.]. The quantitative variables were described as mean ± standard deviation [SD]. Qualitative variables were expressed as numbers and percentages. The t-test was used to compare two groups on a normally distributed scale. The Mann–Whitney U-test was employed on non-normally distributed variables. Chi-squared test/Fisher exact was used to compare the two groups regarding categorical variables. Receiver operating curve was used to detect the optimal cutoff of different parameters in predicting shunt-related HC occurrence. Binary logistic regression analysis was done to determine various risk factors for developing HC. The findings were regarded as non-statistically significant when $p > 0.05$ was statistically significant when $p \leq 0.05$.

### Ethical consideration

All data were anonymous and confidential. The study was conducted according to the Declaration of Helsinki. The study protocol was approved by the research ethics committee of

Faculty of Medicine in Cairo University. Informed consent was obtained from all participants before enrolment in the study.

## Results

This study was conducted on 90 patients with a ruptured subarachnoid aneurysm to study the incidence of SDH and assess its different predictors. Out of the included ninety patients, 28% developed SDH during the follow-up period. The studied participants were 46 [51.1%] females and 44 [48.9%] males, with an average age of 57 ± 11 years old without a statistically significant difference between patients who developed and patients who did not develop HC regarding their age and sex [p > 0.05].

Of the 90 patients in the study, 37 [41.1%] of them were smokers, 12 [13.3%] reported alcohol intake, 13 [14.4%] of them had a history of previous brain surgery, and 42 [46.7%] of them were on anticoagulant medications. There were non-statistically significant differences between patients who developed and patients who did not develop HC regarding their smoking status, alcohol intake, previous brain surgery, and use of anticoagulants [p > 0.05]. Hypertensive disorders alone [52% vs. 32.3%, p = 0.006], or hypertensive disorders associated with diabetes [16% vs. 1.5%, p = 0.006], were more prevalent among SDH patients than patients who did not develop HC.

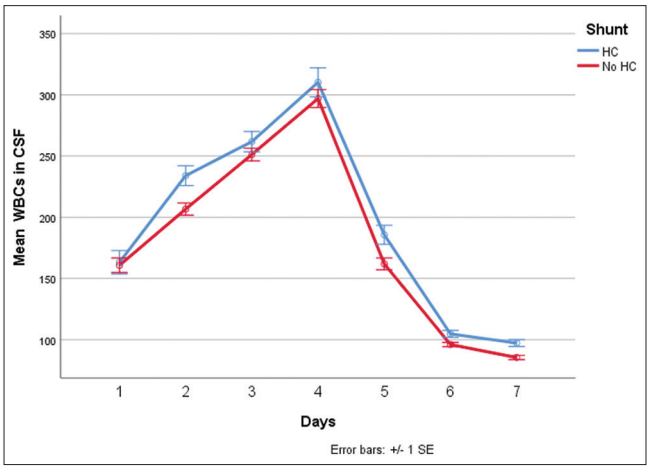


*Figure 1: Follow-up of the white blood cells in both groups*

The comparison between patients who developed shunt-dependent HC and patients who did not develop HC regarding SIRS parameters and SIRS score during the follow-up period demonstrates that, however, there was no statistically significant difference between SDH patients and patients who did not develop HC regarding suggesting temperature [9 (36%) vs. 18 (27.7%), p = 0.441], heart rate [16 (64%) vs. 30 (46.2%), p = 0.129] and respiratory rate [11 (44%) vs. 19 (29.2%), p = 0.183], the WBCs [11 (44%) vs. 12 (18.5%), 0.013], and the total SIRS score [1.92 ± 1.2 vs. 1.2 ± 0.9, p = 0.004] were significantly higher among SDH patients.

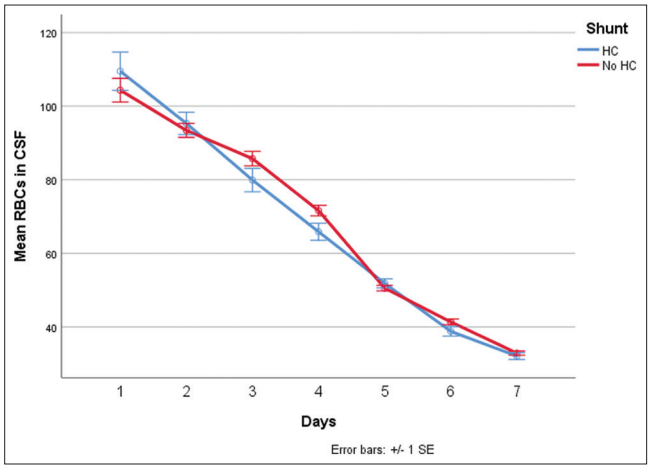


*Figure 2: Follow-up of the cerebrospinal fluid red blood cells in both groups*

There was a statistically significant increase of the mean Fisher's grade [3.4 ± 0.7 vs. 2.9 ± 0.9, p = 0.040], WFNS score [2.5 ± 1.3 vs. 1.8 ± 1.4, p = 0.033], and Hunt and Hess score [2.5 ± 1.3 vs. 1.8 ± 1.4, p = 0.033] in SDH patients than patients who did not develop HC.

Figure 1 demonstrates the changes of WBCs over time in SDH patients and patients who did not develop HC, the mean WBCs were significantly higher in patients with HC at the 2$^{nd}$ [p = 0.005], 5$^{th}$ [p = 0.011], 6$^{th}$ [p = 0.010], and 7$^{th}$ days [p = 0.001]. While regarding the decreasing of RBCs over time in SDH patients and patients who did not develop HC as demonstrated in Figure 2, the mean RBCs was significantly lower in SDH patients at the 4$^{th}$ day only [p = 0.039], which may be non-indicative for anything.

As shown in Figure 3, the mean CSF protein levels were significantly higher in SDH patients throughout the week of follow-up [p < 0.001]. The mean CSF protein level dropped significantly at the 4$^{th}$ [59.8 ± 9.9 vs. 52.2 ± 13, p = 0.009] day and increased significantly until the 7$^{th}$ day. There was no significant change in CSF glucose level over time in SDH patients and patients who did not develop HC. The mean CSF glucose level did not differ significantly in both groups [p > 0.05].

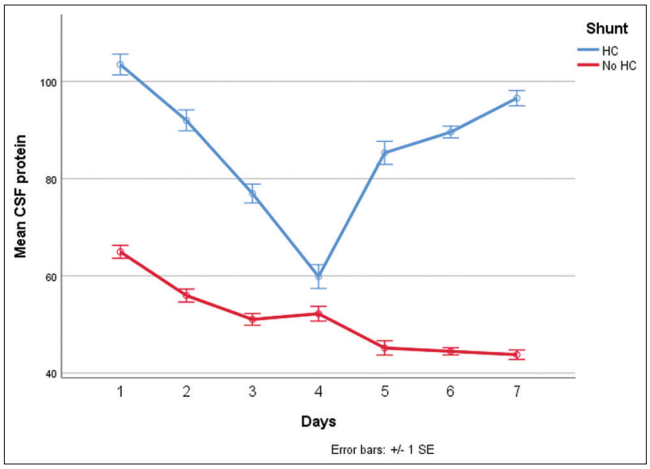


*Figure 3: Follow-up of the cerebrospinal fluid protein level in both groups*

As demonstrated in Figure 4, on the 1st day of follow-up, serum sodium was higher in patients who developed HC than patients who did not develop HC. Still, without a statistically significant difference, [146.2 ± 5.3 vs. 142.73.7, p = 0.066], there was a significant change in serum sodium level over time in patients who developed HC and those who did not develop HC. Still, the mean serum sodium level was significantly higher in patients with HC from the 2nd to 7th day of follow-up [p < 0.001].

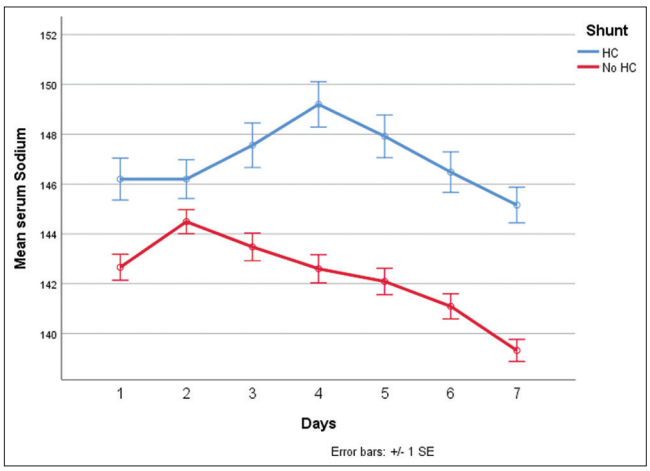


*Figure 4: Follow-up of the serum sodium level in both groups*

Table 1 shows a statistically significant role of CSF WBCs in predicting the occurrence of HC at the 2nd, 5th, 6th, and 7th days [p-values were 0.002, 0.003, 0.010, and 0.001]. On the 2nd day, the cutoff of CSF WBCs was 229 or more with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) which were 68%, 69.2%, 45.9%, and 84.9%, respectively. On the 5th day, the cutoff of CSF WBCs was 147 or more with sensitivity, specificity, PPV, and NPV which were 80%, 43.1%, 35.1%, and 84.8%, respectively. On the 6th day, the cutoff of CSF WBCs was 106 or more with sensitivity, specificity, PPV, and NPV which were 60%, 78.5%, 51.7%, and 83.6%, respectively. On the 7th day, the cutoff of CSF WBCs was 93 or more with sensitivity, specificity, PPV, and NPV which were 68%, 69.2%, 45.9%, and 84.9%, respectively.

There was a statistically significant role of CSF RBCs in the prediction of the occurrence of HC at the 4th day only [p = 0.030], the cutoff of CSF RBCs was ≤71 with sensitivity, specificity, PPV, and NPV which were 72%, 58.5%, 40%, and 84.5%, respectively.

There was no statistically significant role of CSF glucose in the prediction of the occurrence of HC during the week of follow-up [p > 0.05]. Table 2 and Figure 5 show that there was a statistically significant role of CSF protein in the prediction of the occurrence of HC at the 1st, 2nd, 3rd, 4th, 5th, 6th, and 7th days [p < 0.001]. On the 1st day, the optimal cutoff of CSF protein was 83 or more with sensitivity, specificity, PPV, and NPV which were 96%, 98.5%, 96%, and 98.5%, respectively. On the 2nd day, the optimal cutoff of CSF protein was 78 or more with sensitivity, specificity, PPV, and NPV which were 100%, 100%, 100%, and 100%, respectively. On the 3rd day, the optimal cutoff of CSF protein was 65 or more with sensitivity, specificity, PPV, and NPV which were 96%, 92.3%, 82.8%, and 98.4%, respectively. On the 4th day, the optimal cutoff of CSF protein was 49 or more with sensitivity, specificity, PPV, and NPV which were 84%, 47.4%, 38.2%, and 88.6%, respectively. On the 5th day, the optimal cutoff of CSF protein was 69 or more with sensitivity, specificity, PPV, and NPV which were 92%, 96.9%, 92%, and 96.9%, respectively. On the 6th day, the optimal cutoff of CSF protein was 66 or more with sensitivity, specificity, PPV, and NPV which were 96%, 100%, 100%, and 98.5%, respectively. On the 7th day, the optimal cutoff of CSF protein was 71 or more with sensitivity, specificity, PPV, and NPV which were 96%, 100%, 100%, and 98.5%, respectively.

Table 3 shows that there was a statistically significant role of serum sodium in the prediction of the occurrence of HC at the 1st, 3rd, 4th, 5th, 6th, and 7th days [p < 0.001%]. On the 1st day, the optimal cutoff of serum sodium was 142 or more with sensitivity, specificity, PPV, and NPV which were 64%, 43.1%,

**Table 1: Cutoff, area under curve, sensitivity, specificity, and positive and negative predictive values of sequential WBCs in CSF in the prediction of the occurrence of hydrocephalus**

| Items | 1st day | 2nd day | 3rd day | 4th day | 5th day | 6th day | 7th day |
|---|---|---|---|---|---|---|---|
| Cutoff | >120 | >229 | >224 | >290 | >147 | >106 | >93 |
| AUC | 0.529 | 0.691 | 0.559 | 0.570 | 0.680 | 0.671 | 0.713 |
| p-value | 0.657 | 0.002* | 0.422 | 0.318 | 0.003* | 0.010* | 0.001* |
| Sensitivity (95%CI%) | 84 (63.9–95.5) | 68 (46.5–85.1) | 72 (50.6–87.9) | 64 (42.5–82) | 80 (59.3–93.2) | 60 (38.7–78.9) | 68 (46.5–85.1) |
| Specificity (95%CI%) | 33.85 (22.6–46.6) | 69.2 (56.6–80.1) | 30.8 (19.9–43.4) | 49.2 (36.6–61.9) | 43.08 (30.8–56) | 78.5 (66.5–87.7) | 69.2 (56.6– 80.1) |
| PPV (95%CI%) | 32.8 (27.7–38.4) | 45.9 (35.1–57.2) | 28.6 (23–34.9) | 32.7 (24.9–41.5) | 35.1 (28.8–41.9) | 51.7 (37.9–65.3) | 45.9 (35.1–57.2) |
| NPV (95%CI%) | 84.6 (67.8–93.5) | 84.9 (75.6–91.1) | 74.1 (58–85.5) | 78 (66.6–86.4) | 84.8 (70.9–92.8) | 83.6 (75.6–89.3) | 84.9 (75.6–91.1) |

WBCs: White blood cells, AUC: Area under the curve, NPV: Negative predictive value, PPV: Positive predictive value, CSF: Cerebrospinal fluid.

**Table 2: Cutoff, area under curve, sensitivity, specificity, positive predictive value, and negative predictive value of sequential protein in CSF in the prediction of the occurrence of hydrocephalus**

| Items | 1st day | 2nd day | 3rd day | 4th day | 5th day | 6th day | 7th day |
|---|---|---|---|---|---|---|---|
| Cut off | >83 | >79 | >65 | >49 | >69 | >66 | >71 |
| AUC | 0.998 | 1.000 | 0.983 | 0.687 | 0.990 | 1.000 | 1.000 |
| p-value | <0.001** | <0.001** | <0.001** | <0.001** | <0.001** | <0.001** | <0.001** |
| Sensitivity (95%CI%) | 96 (79.6–99.9) | 96 (79.6–99.9) | 96 (79.6–99.9) | 84 (63.9–95.5) | 92 (74.0–99) | 96 (79.6–99.9) | 96 (79.6–99.9) |
| Specificity (95%CI%) | 98.5 (91.7–100) | 99.5 (94.5–100) | 92.3 (83–97.5) | 47.7 (35.1–60.5) | 96.92 (89.3–99.6) | 100 (94.5–100) | 100 (94.5–100) |
| PPV (95%CI%) | 96 (77.4–99.4) | 100 (85–100) | 82.8 (67.3–91.8) | 38.2 (31.6–45.2) | 92 (74.5–97.8) | 100 (85–100) | 100 (85–100) |
| NPV (95%CI%) | 98.5 (90.4–99.8) | 98.5 (90.5–99.8) | 98.4 (89.8–99.8) | 88.6 (75.3–95.2) | 96.9 (89.3–99.2) | 98.5 (90.5–99.8) | 98.5 (90.5–99.8) |

AUC: Area under the curve, NPV: Negative predictive value, PPV: Positive predictive value, CSF: Cerebrospinal fluid.

30.2%, and 75.7%, respectively. On the 3rd day, the optimal cutoff of serum sodium was 142 or more with sensitivity, specificity, PPV, and NPV which were 92%, 41.5%, 37.7%, and 93.1%, respectively. On the 4th day, the optimal cutoff of serum sodium was 144 or more with sensitivity, specificity, PPV, and NPV which were 80%, 63.1%, 45.5%, and 89.1%, respectively. On the 5th day, the optimal cutoff of serum sodium was 144 or more with sensitivity, specificity, PPV, and NPV which were 80%, 67.6%, 48.8%, and 89.8%, respectively. On the 6th day, the optimal cutoff of serum sodium was 145 or more with sensitivity, specificity, PPV, and NPV which were 60%, 92.3%, 75%, and 85.7%, respectively. On the 7th day, the optimal cutoff of serum sodium was 144 or more with sensitivity, specificity, PPV, and NPV which were 72%, 96.9%, 90%, and 90%, respectively.

There was a statistically significant role of different scores in the prediction of the occurrence of HC [$p < 0.05$%], as demonstrated in Table 4. Regarding SIRS score, the optimal grade for the prediction of the occurrence of HC was 2nd or more with sensitivity, specificity, PPV, and NPV which were 44%, 89.2%, 61.1%, and 75.7%, respectively. Regarding Fisher score, the optimal grade for the prediction of the occurrence of HC was 3rd or more with sensitivity, specificity, PPV, and NPV which were 52%, 69.2%, 39.4%, and 78.9%, respectively. Regarding Hunt score, the optimal grade for the prediction of the occurrence of HC was 2nd or more with sensitivity, specificity, PPV, and NPV which were 40%, 75.4%, 38.5%, and 76.6%, respectively. Regarding WFNs score, the optimal grade for the prediction of the occurrence of HC was 2nd or more with sensitivity, specificity, PPV, and NPV which were 40%, 75.4%, 38.5%, and 76.6%, respectively.

As shown in Table 5, the multivariable binary logistic regression analysis for the prediction of risk factors associated with the occurrence of HC [from baseline characteristics and scores %] showed that when sex [male%], age [more than 59 years%], hypertension, positive SIRS score, and positive Fisher and WFNS/Hunt scores were examined to predict the occurrence of HC, it was illustrated that the presence of positive SIRS score significantly increases the probability of HC occurrence 4.3 times [OR, 95%CI for OR was 1.13–16.4%]. Positive Fisher scores significantly increase the likelihood of HC occurrence 5.3 times [OR, 95%CI for OR was 1.01–27.8%].

## Discussion

During the present study period, 28% of individuals with ruptured SNA developed SDH. A broad range of HCP incidence in SAH patients from 6% to 67% has been described in the literature; most present studies show that this proportion is around 20–30% [9], [10], [11]. There was no statistically significant relationship between patients' age and SDH in the present study. In line with this, Aboul-Ela and his colleagues, who conducted a study on Egyptian populations to identify different predictors of shunt-related HC after ruptured SAH, showed no statistically significant association between age and HC [12]. International studies also found no statistically significant association between age and HC [13], [14] and [Rincon *et al*., 2010].

On the opposite side, as reported by Dorai *et al*., older age is associated with shunt-related HC [9]. The difference in the present study may be explained by the age range of patients with SDH [35–78 years] and non-SDH [39–78 years] was nearly similar. In this study, SDH was not associated with sex. Prior studies also argued the point [12], [13], [14]. In contrast, Dorai *et al*. reported that 23.8% of female patients had shunting operations compared to 15.9% of male patients [9]. Furthermore, according to Chan *et al*. study, 63.5% of

**Table 3: Cutoff, area under curve, sensitivity, specificity, positive predictive value, and negative predictive value of sequential serum sodium in the prediction of the occurrence of hydrocephalus**

| Items | 1st day | 2nd day | 3rd day | 4th day | 5th day | 6th day | 7th day |
|---|---|---|---|---|---|---|---|
| Cutoff | >142 | >144 | >142 | >144 | >144 | >145 | >144 |
| AUC | 0.673 | 0.616 | 0.719 | 0.846 | 0.827 | 0.807 | 0.838 |
| p-value | 0.009* | 0.069 | 0.001** | <0.001** | <0.001** | <0.001** | <0.001** |
| Sensitivity (95%CI%) | 64 (42.5–82) | 68 (46.5–85.1) | 92 (74–99) | 80 (59.3–93.2) | 80 (59.3–93.2) | 60 (38.7–78.9) | 72 (50.6–87.9) |
| Specificity (95%CI%) | 43.1 (30.8–56) | 44.6 (32.3–57.5) | 41.5 (29.4–54.4) | 63.1 (50.2–74.7) | 67.7 (54.9–78.8) | 92.3 (83–97.5) | 96.9 (89.3–99.6) |
| PPV (95%CI%) | 30.2 (23.1–38.3) | 32.1 (25–40) | 37.7 (32.4–43.4) | 45.5 (36.5–54.8) | 48.8 (38.9–58.8) | 75 (54.9–88.1) | 90 (69.2–97.3) |
| NPV (95%CI%) | 75.7 (63.2–84.9) | 78.4 (65.8–87.2) | 93.1 (77.6–98.1) | 89.1 (78.6–94.8) | 89.8 (79.8–95.2) | 85.7 (78.7–90.7) | 90 (82.7–94.4) |

AUC: Area under the curve, NPV: Negative predictive value, PPV: Positive predictive value.

**Table 4: Cutoff, area under curve, sensitivity, specificity, positive predictive value, and negative predictive value of different scores in the prediction of the occurrence of hydrocephalus:**

| Items | Fisher | Fisher's categories | Hunt | Hunt's categories | SIRS | SIRS categories | WFNS | WFNS categories |
|---|---|---|---|---|---|---|---|---|
| Cutoff | >3 | ---- | >2 | --- | >2 | ----- | >3 | --- |
| AUC | 0.636 | 0.583 | 0.626 | 0.577 | 0.657 | 0.666 | 0.626 | 0.577 |
| p-value | 0.032* | 0.193 | 0.049* | 0.265 | 0.021* | 0.016* | 0.049* | 0.265 |
| Sensitivity (95%CI%) | 52 (31.3–72.2) | 92 (74–99) | 40 (21.1–61.3) | 40 (21.1–61.3) | 44 (24.4–65.1) | 44 (24.4–65.1) | 32 (14.9–53.5) | 40 (21.1–61.3) |
| Specificity (95%CI%) | 69.2 (56.6–80.1) | 24.6 (14.8–36.9) | 75.4 (63.1–85.2) | 75.4 (63.1–85.2) | 89.2 (79.1–95.6) | 89.2 (79.1–95.6) | 78.5 (66.5–87.7) | 75.4 (63.1–85.2) |
| PPV (95%CI%) | 39.4 (27.8–52.3) | 31.9 (28.1–36) | 38.5 (24.8–54.3) | 38.5 (24.8–54.3) | 61.1 (40.7–78.2) | 61.1 (40.7–78.2) | 36.4 (21.5–54.4) | 38.5 (24.8–54.3) |
| NPV (95%CI%) | 78.9 (70.7–85.3) | 88.9 (66.5–97) | 76.6 (69.7–82.2) | 76.6 (69.7–82.2) | 80.6 (74.3–85.6) | 80.6 (74.3–85.6) | 75 (69.0–80.2) | 76.6 (69.7–82.2) |

AUC: Area under the curve, NPV: Negative predictive value, PPV: Positive predictive value.

patients who needed shunting after external ventricular drainage [EVD] weaning failed were female, whereas 34.5% were male [15].

**Table 5: Multivariable binary logistic regression analysis for the prediction of risk factors associated with the occurrence of hydrocephalus (from baseline characteristics and scores %)**

| Independent variables | p-value | OR | 95% C.I. for OR | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Age (more than 59 years%) | 0.135 | 0.428 | 0.141 | 1.300 |
| Gender (Males%) | 0.661 | 1.251 | 0.460 | 3.401 |
| Positive SIRS | 0.032* | 4.308 | 1.130 | 16.419 |
| Positive Fisher | 0.049* | 5.298 | 1.010 | 27.803 |
| Positive WFNS and Hunt scores | 0.720 | 0.790 | 0.218 | 2.864 |
| HTN | 0.055 | 0.353 | 0.122 | 1.021 |

SIRS: Systemic inflammatory response syndrome, HTN: Hypertension.

In the present study, patients who developed HC had higher total leukocytic count [significant in univariate analysis] and total SIRS score [significant in univariate and multivariate analysis]. The optimum SIRS score for predicting the incidence of HC was 2$^{nd}$ or more with sensitivity [44%], specificity [89.2%], PPV [61.1%], and NPV [75.7%]. In agreement with those results, according to Chang *et al*., leukocytosis is a strong predictor of SDH [14]. The significant relationship of leukocytosis in this research may be explained by inflammation linked to other cerebral injuries after SAH [16], [17], and [18], McMahon *et al*. also demonstrated that leukocytosis may predict imminent cerebral ischemia [16]. Acute SAH triggered inflammation of arachnoid villi. It prevented CSF absorption, resulting in adhesion and chronic blockage of arachnoid villi and ultimately SDH [14].

Regarding the SIRS, it was highly predictor for SDH [1.92 ± 1.2 in SDH vs. 1.2 ± 0.9 in the non-hydrocephalic group] with predominant higher grades in SDH patients in both multivariable and univariate analyses. This result was also concluded in Chang *et al*. study [14]. In univariate and multivariate analyses, Wessell and colleagues found SIRS in 35% of shunt-dependent patients versus 14% of non-shunt-dependent patients [p = 0.004] [19].

SIRS's predictive value for SDH acquisition after aneurysmal SAH is explained because SAH causes a non-infectious acute SIRS reaction marked by an increase in circulating cytokines and leukocytosis [Beseoglu *et al*., 2014]. Early CSF interleukin-6 [IL-6] rise has been shown to predict SDH [17]. In other studies, researchers attempted to explain the evidence of a link between SIRS and SDH as a localized inflammatory response after SAH [20], [21]. IL-6 levels in the CSF are elevated following SAH and have been linked to shunt dependency [22], [23].

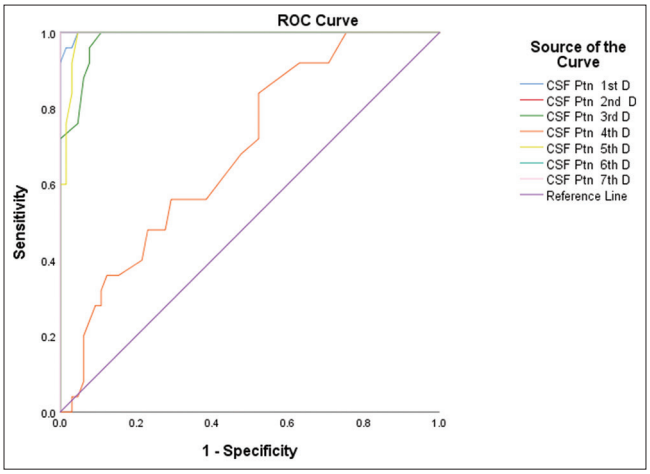


*Figure 5: Receiver operating characteristic curve for the prediction of the occurrence of hydrocephalus occurrence using cerebrospinal fluid protein level from the occurrence of rupture subarachnoid aneurysm till 1 week of follow-up*

There was a statistically significant increase of the mean Fisher's grade with a mean of 3.4 ± 0.7 in the hydrocephalic group versus 2.9 ± 0.9 in the non-hydrocephalic group [p = 0.040] in both univariate and multivariable analyses. There was a significant increase in WFNS score with a mean of 2.5 ± 1.3 in the hydrocephalic group versus 1.8 ± 1.4 in the non-hydrocephalic group [p = 0.033].

These results supported Wang *et al*. findings that SDH patients had higher mean Fisher SAH grade on presentation [13]. Moreover, various studies have shown that patients with high Hunt, Hess, and Fisher scores are more prone to shunt dependence [24], [25], [26]. Another study found that SDH patients had a higher mean Fisher SAH grade on presentation [27], [28]. On the contrary, the reported findings that baseline fisher grade have no significant effect of the acquisition of shunt-related hydrocephalus [29].

Regarding the Hunt and Hess scores, it was the same result of WFNS score, with a mean of 2.5 ± 1.3 in patients who developed SDH versus 1.8 ± 1.4 in patients who did not develop HC [p < 0.05]. According to Chang *et al*., patients with low Hunt and Hess grade were more prone to SDH [14].

Poor clinical Hunt and Hess grade is a significant independent predictor in the previous studies [30], [31]. Dorai *et al*. reported that 32% of patients with a poor Hunt and Hess grade [III, IV] needed a permanent V-P shunt [9]. Several previous studies omitted Hunt and Hess Grade V patients because they may die before

getting a V-P shunt [32], [33]. After accounting for a sustained SIRS, age, sex, Fisher, Hunt and Hess, and hypertension, only the higher SIRS score [OR, 95%CI for OR was 1.13–16.4] and Fisher score [OR, 95%CI for OR was 1.01 to 27.8] remained statistically significant regarding SDH as shown in the previous study conducted by Wessell and his colleagues [19]. They stated that the SIRS score and sex increased the probability of SDH on multivariable analysis [34]. However, in Wang *et al*., they studied the multivariable analysis on prediction of SDH accounted for age, sex, hypertension Fisher, and WFN. They found that only angler and WFN were affecting the acquisition SDH. Still, they did not examine the effect of SIRS as we did in the present study [13].

Regarding the serum sodium and CSF findings that can be used as laboratory predictors for the occurrence of SDH, there was a significant change in serum sodium level over time in patients who developed HC and patients who did not develop HC. However, the mean serum sodium level was still significantly higher in patients with SDH throughout the follow-up period [$p < 0.05$]. Hypernatremia was shown to be a clinical predictor of SDH in Chang and colleague's univariate analysis [14]. Hypernatremia is a poor prognostic factor following spontaneous SAH [17], [35]. Moreover, publications have reported early hypernatremia following SAH, which matches the present study [36]. On the opposite side, some studies show that hyponatremia is more common than hypernatremia following SAH [37], [38]. Because SAH patients frequently require therapeutic infusion of hyperosmolar fluids to help mitigate intracranial hypertension, the resultant hypernatremia is linked with poor outcomes in this patient population [17]. At present, normonatremia is considered the conservative, but safe management strategy for SAH patients.

The present study revealed that the optimal significant [$p < 0.01$] cutoff of the serum sodium in the prediction of SDH after SAH from the 1$^{st}$ day to the 7$^{th}$ day ranged from 142 to more than 144 with the area under the curve from 0.673 to 0.846 was supported in the previous studies done by Na and his colleagues [39].

The present study revealed a changing of CSF WBCs over time in patients who developed HC and those who did not develop HC. Still, the mean WBCs were significantly higher in patients with SDH almost all over the 1$^{st}$ week of follow-up [$p < 0.05$]. There was a statistically significant role of CSF WBCs in the prediction of the occurrence of HC at the 2$^{nd}$, 5$^{th}$, 6$^{th}$, and 7$^{th}$ days [p-value was 0.002, 0.003, 0.010, and 0.001].

Inflammation of arachnoid villi and a failure to absorb CSF due to aSAH that results in adhesion and chronic obstruction of arachnoid villi is sufficient to explain the ability of CSF WBCs to predict SDH in the immediate post-SAH period [14], [40], [41]. We found a decrease in RBCs over time in patients who developed HC and patients who did not develop HC. Still, the mean RBCs were significantly lower in patients with HC on the 4$^{th}$ day only [$p < 0.05$], which may be insignificant for anything. Only there was a statistically significant role of CSF RBCs in the prediction of the occurrence of HC on the 4$^{th}$ day [$p = 0.039$]. On the 4$^{th}$ day, the cutoff of CSF RBCs was ≤ or more with sensitivity, specificity, PPV, and NPV which were 72%, 58.5%, 40%, and 84.5%, respectively.

The poor role of CSF RBCs was supported by one previous study that reported a non-significant difference in CSF RBCs between individuals who developed SDH and those who did not [42]. However, many studies suggested an association between subarachnoid blood volume and shunt dependence [23], [43]. The study findings suggest that a sustained rise in RBC predicts chronic HC better than acute HC [1$^{st}$ week].

Regarding the CSF protein level, there was changing in its level over time in patients who developed HC and patients who did not develop HC. However, the mean CSF protein level was still significantly higher in patients with HC throughout the 1$^{st}$ week of follow-up [$p < 0.05$]. The mean CSF protein level dropped significantly on the 4$^{th}$ day then increased significantly till the 7$^{th}$ day. This finding was agreed with a study done by Esposito *et al*. who illustrated that patients' with SDH had higher CSF protein than patients without SDH after aneurysmal SAH [44]. Studies by Suzuki *et al.* [45], in addition to Wang *et al.* [12] were also in line with those results. This may be explained by increased CSF protein metabolite release from the injured brain, meninges, or CSF cells due to SAH, vasospasm, or acute HC [46].

There was a statistically significant role of CSF protein in the prediction of the occurrence of HC at the 1$^{st}$, 2$^{nd}$, 3$^{rd}$, 4$^{th}$, 5$^{th}$, 6$^{th}$, and 7$^{th}$ days [$p < 0.001$]. This finding was supported in a recent study conducted by Lenski *et al*. [42]. The present study was also supported by prior literature, which found significantly higher CSF TP levels on admission in patients with SDH compared to those with no shunt dependency, as described by Lewis *et al*., our study differs from that previous work in that we provided the time course of total protein levels, but they did not provide this information [47].

Another study found elevated mean TP levels in individuals with SDH at the start of an EVD challenge [76.5 mg/dL vs. 40.3 mg/dL; $p < 0.0001$] [15]. Overall, higher TP levels appear to help to predict shunt dependence in the 1$^{st}$ week following SAH. Still, more extensive studies are required to determine whether TP levels are changed on subsequent days.

There was no significant change in CSF glucose level over time in patients who developed HC and patients who did not develop HC. The mean CSF glucose level did not differ significantly in both groups [$p > 0.05$]. This result is supported by Wang *et al*. study [12]. Furthermore, a recent study done by Lenski *et al*. and reported the same poor role of CSF glucose level in predicting SDH after aSAH [42]. Based on those findings, we conclude

that monitoring CSF glucose levels is not diagnostically significant regarding shunt dependence following SAH.

## Conclusion

Despite the study's analytical design, we observed a link between high Fisher, SIRS, hypernatremia, and SDH in aneurysmal SAH patients. Serum sodium, CSF WBCs, and protein may all be used to predict SDH.

## Recommendations

We suggest carefully monitoring patients with high baseline Fisher and SIRS scores since they may need fast shunt intervention. Following up on those patients with serum sodium daily, CSF protein on admission, 4$^{th}$ day and at the end of the 1$^{st}$ week and CSF WBCs starting from the 5$^{th}$ day. There is no need to follow up on the CSF RBCs or glucose. Moreover, despite appropriate sodium levels, careful hydration control should be considered. We recommend a multicentric large size study to generalize the findings on SIRS score predictive value in the present study.

## Limitations

This study has some limitations as it is a single-center study.

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