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ORIGINAL ARTICLE

Radiological Estimation of Intracranial Blood Volume and Occurrence of Hydrocephalus Determines Stress-Induced Hyperglycemia After Aneurysmal Subarachnoid Hemorrhage

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Abstract

Acute phase after aneurysmal subarachnoid hemorrhage (aSAH) is associated with several metabolic derangements including stress-induced hyperglycemia (SIH). The present study is designed to identify objective radiological determinants for SIH to better understand its contributory role in clinical outcomes after aSAH. A computer-aided detection tool was used to segment admission computed tomography (CT) images of aSAH patients to estimate intracranial blood and cerebrospinal fluid volumes. Modified Graeb score (mGS) was used as a semi-quantitative measure to estimate degree of hydrocephalus. The relationship between glycemic gap (GG) determined SIH, mGS, and estimated intracranial blood and cerebrospinal fluid volumes were evaluated using linear regression. Ninety-four [94/187 (50.3%)] among the study cohort had SIH (defined as GG > 26.7 mg/dl). Patients with SIH had 14.3 ml/1000 ml more intracranial blood volume as compared to those without SIH [39.6 ml (95% confidence interval, CI, 33.6 to 45.5) vs. 25.3 ml (95% CI 20.6 to 29.9), $p = 0.0002$]. Linear regression analysis of mGS with GG showed each unit increase in mGS resulted in 1.2 mg/dl increase in GG [$p = 0.002$]. Patients with SIH had higher mGS [median 4.0, interquartile range, IQR 2.0–7.0] as compared to those without SIH [median 2.0, IQR 0.0–6.0], $p = 0.002$. Patients with third ventricular blood on admission CT scan were more likely to develop SIH [67/118 (56.8%) vs. 27/69 (39.1%), $p = 0.023$]. Hence, the present study, using unbiased SIH definition and objective CT scan parameters, reports "dose-dependent" radiological features resulting in SIH. Such findings allude to a brain injury-stress response-neuroendocrine axis in etiopathogenesis of SIH.

Keywords Hemorrhagic stroke · Hyperglycemia · Hydrocephalus · Delayed cerebral ischemia · Shunt

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Abbreviations

ANOVA	Analysis of variance
AG	Admission glucose
aSAH	Aneurysmal subarachnoid hemorrhage
AUROC	Area under receiver operator characteristic
BCI	Bicaudate index
CAD	Computer-aided detection
CI	Confidence interval
CSF	Cerebrospinal fluid
CT	Computed tomography
DCI	Delayed cerebral ischemia
EVD	External ventricular drain
GG	Glycemic gap
GUI	Graphic user interface
HbA1c	Glycated hemoglobin
H&H	Hunt and Hess
HU	Hounsfield unit

IQR	Interquartile range
mFS	Modified Fisher score
mGS	Modified Graeb score
NSICU	Neurosciences intensive care unit
ROC	Receiver operating characteristic
SAH	Subarachnoid hemorrhage
SIH	Stress-induced hyperglycemia
TH	Threshold Hounsfield
VPS	Ventriculoperitoneal shunt
WFNS	World Federation of Neurological Surgeons

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a form of hemorrhagic stroke that affects middle-aged individuals and is associated with high morbidity and mortality. Early intervention to secure ruptured aneurysm is now an accepted and recommended clinical practice. Such treatment algorithm has decreased early mortality secondary to aneurysmal re-rupture. Management of post-operative complications like hydrocephalus, delayed cerebral ischemia (DCI), and metabolic derangements (including cerebral salt wasting and stress-induced hyperglycemia, SIH) are routine practice in neurocritical care units. Occurrence of such metabolic derangements can also exacerbate DCI resulting in secondary brain injury and associated morbidity [1–3]. Hence, identifying contributors and understanding etiopathogenesis of such metabolic derangements (e.g., SIH) is an essential step to develop necessary therapies to mitigate secondary brain damage after aSAH. However, hyperglycemic thresholds used to define SIH in critical illnesses are varied until recently [4–7]. Glycemic gap (GG) is an accepted index to assess SIH that is solely dependent on degree of admission hyperglycemia relative to patient's own preadmission glycemic control (described below under "Materials and Methods").

Incidence of SIH after aSAH is variable and frequently reported to be dependent on presenting acuity [7]. In our 5-year retrospective aSAH cohort, we observed strong association of SIH with both standard admission clinical and radiological aSAH scales. However, most commonly used radiological scales, Fisher scale and modified Fisher scale (mFS), are subjective and estimate amount of cisternal blood and presence/absence of intraventricular hemorrhage on admission computed tomography (CT) image and observer dependent. These scales neither account for quantitative amount of intracranial blood nor presence and/or severity of hydrocephalus. Both of these factors are reported to have "dose-dependent" positive correlation with DCI, the most commonly studied complication in aSAH survivors, during the post-operative period [8, 9]. None of these radiological features are systematically and quantitatively investigated for occurrence of SIH.

Hence, in this exploratory study, we estimated volume of intracranial blood and cerebrospinal fluid (CSF) using image segmentation software and hydrocephalus using modified Graeb score (mGS). We first validated the study methodology to occurrence of DCI in our cohort. Subsequently, we investigated if SIH has any relationship to the amount of intracranial blood and/or acute hydrocephalus after aSAH. Knowledge from this study is aimed to provide objective information regarding radiological basis for occurrence of SIH and potentially aid in developing automated prognostic tools in management aSAH.

Materials and Methods

Patients

The institutional review board at the University of Oklahoma Health Sciences Center approved the study. Patient consent was waived due the retrospective nature of the study as it involved chart review and image analysis (in a de-identified manner) with no risk to the patients. The cohort of patients investigated in the present study is the same as previously reported [7] and included patients admitted with aSAH between January 1, 2011 and December 31, 2015, to the neurosciences intensive care unit (NSICU) at Oklahoma University Medical Center, Oklahoma City. Cohort characteristics are detailed in Table 1. Inclusion criteria for the study were similar to our previous study on SIH [7] that included patients presenting within 3 days of symptom onset, admission serum glucose and glycosylated hemoglobin (HbA1c), as well as CT scans prior to external ventricular drain (EVD) placement. The CT scan was processed and studied using image segmentation software as detailed below. The patients included in the study are represented in Fig. 1.

Definition of SIH

SIH was defined using previously reported terminology, GG as the difference between admission glucose (AG) and A1c-derived average glucose. The A1c-derived average glucose is, in turn, an estimate of the patient's preadmission glucose level obtained by applying to the admission HbA1c a conversion suggested by Nathan et al. [4] and Liao et al. [5]. The regression equation that produces the conversion is ($GG = AG - 28.7 \times HbA1c + 46.7$). As per our previous study on the same cohort, GG of > 26.7 mg/dl was determined to define SIH using receiver operating curve (ROC) analysis [7]. The same definition was retained for the present study. Of note, GG reported in the present study was estimated using admission serum glucose. All patients included in this study presented within 48 h of symptom onset.

Table 1 Baseline characteristics of the study cohort

Characteristics		Total (%) ($n = 187$)
Age (in years)	Mean ± SD	53.0 ± 13.2
	Median (IQR)	54.0 (45.0 - 61.0)
Intracranial blood volume (in ml per 1000 ml cranial volume)	Mean ± SD	32.5 ± 27.0
	Median (IQR)	26.1 (11.6–45.5)
Intracranial blood and CSF volume (in ml per 1000 ml cranial volume)	Mean ± SD	71.1 ± 35.1
	Median (IQR)	64.2 (46.5–93.9)
Sex	Male	63 (33.7%)
	Female	124 (66.3%)
Diabetes mellitus	No	172 (92.0%)
	Yes	14 (7.5%)
	Missing/unknown	1 (0.5%)
Hyperlipidemia	No	152 (81.3%)
	Yes	34 (18.2%)
	Missing/unknown	1 (0.5%)
Hypertension	No	65 (34.8%)
	Yes	121 (64.7%)
	Missing/unknown	1 (0.5%)
Smoker	No	61 (32.6%)
	Yes	116 (62.0%)
	Missing/unknown	10 (5.3%)
Delayed cerebral ischemia	Yes	56 (29.9%)
	No	114 (61.0%)
	Unknown	17 (9.1%)
WFNS	Grades 1–3	107 (57.2%)
	Grades 4–5	80 (42.8%)
Hunt and Hess	Grades I–III	130 (69.5%)
	Grades IV–V	57 (30.5%)
Modified Fisher	Grades 1–2	66 (35.3%)
	Grades 3–4	121 (64.7%)
Location of aneurysm	Anterior	145 (77.5%)
	Posterior	37 (19.8%)
	Unknown	5 (2.7%)
Aneurysm securing procedure	Clip ligation	57 (30.5%)
	Coil embolization	121 (64.7%)
	Unknown/none	9 (4.8%)
EVD placement	No	66 (35.3%)
	Yes	116 (62.0%)
	Unknown/ not offered	5 (2.7%)
VP shunt	No	133 (71.1%)
	Yes	23 (12.3%)
	Unknown/expired	31 (16.6%)
Admission hydrocephalus*	No	144 (77.0%)
	Yes	43 (23.0%)
Discharge disposition	Home/rehabilitation	118 (63.1%)
	LTAC/SNF	22 (11.8%)
	Death/hospice	47 (25.1%)

EVD external ventricular drain, *IQR* interquartile range, *LTAC* long-term acute care facility, *SD* standard deviation, *SNF* skilled nursing facility, *VP* ventricular peritoneal, *WFNS* World Federation of Neurological Surgeons Scale

*Hydrocephalus estimated using age-adjusted bicaudate index

Image Analysis

CT scans used for analyses were acquired within 48 h of symptom onset. The sensitivity of detecting blood after aSAH during this period, using modern CT scanner approaches ~ 100% [10]. An interactive computer-aided detection (CAD) tool was developed (by FA and BZ) and tested to automatically segment brain tissue and detect and quantify brain parenchymal/subarachnoid hemorrhage and ventricular/subarachnoid CSF on non-contrast brain CT images. Our CAD scheme included three main image processing steps or functions. First, the scheme asks users to create a seed point on brain tissue and apply a region growing algorithm to automatically segments brain regions by removing bony skull regions (Hounsfield unit, HU threshold, TH for skull was 96 HU). Due to the high intensity of the skull regions, a simple thresholding algorithm is used to differentiate skull regions from brain tissue. Second, our scheme segments brain region

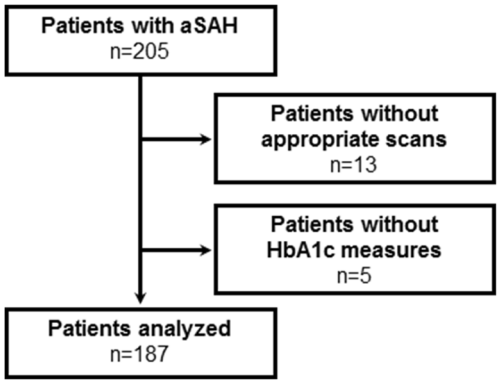

Fig. 1 Flowchart shows patient included and excluded in the present study

into three categories namely, brain tissue (light gray), hemorrhage (white, TH1 = 51 HU), and fluid (dark gray, TH2 = 16 HU) regions, respectively. The CAD scheme applied a multiple thresholding algorithm with two different values of (TH1>TH2) to detect desired regions. Pixels with CT number above TH1 are segmented as blood region while pixels with CT number smaller than TH2 are segmented as fluid region. Any pixels between TH1 and TH2 are classified as normal brain tissue. Next, the scheme provides a graphic user interface (GUI), which allows the user to visually inspect the initial segmentation result and select the corresponding function to correct the errors if applicable. Third, the scheme computes image features from the final segmented regions and saves the results into a database. Since this is an interactive and transparent CAD scheme, the entire image processing steps and the computed quantitative data can be visually examined in the GUI of the scheme as shown in Supplementary Figure 1. Supplementary Figure 2 provides a schematic overview of the entire interactive CAD segmentation workflow. Methodology for quantitative data acquisition is demonstrated in video file. Specifically, (1) volume of blood, CSF, and brain tissue (in ml) is estimated using this software program. (2) Intracranial volume is determined as a combined volume of the above three parameters. (3) Intracranial blood volume is expressed as a ratio of (blood volume to intracranial volume) × 1000. Such a ratio is used to obtain amount of intracranial bleeding in reference to respective individual's intracranial volume. Similarly, total of blood volume and CSF estimates fluid volume and is expressed as (blood volume + CSF to intracranial volume) × 1000 to provide quantitative estimation of hydrocephalus.

Semi-quantitative data regarding ventricular enlargement was obtained using previously described mGS [11] to determine extent and location of hydrocephalus. Bicaudate index (BCI) to determine extent of hydrocephalus as described in previous studies [7, 12] was used to determine its predictive power in EVD and ventriculoperitoneal shunt (VPS) placement.

Statistical Analysis

Mean values were compared between SIH groups using a Student's *t* test. Linear regression was used to explore the associations between mGS, estimated intracranial blood and cerebrospinal fluid, and a continuous SIH measurement (defined by GG). Interaction terms were examined using the groups defined by measures of disease severity to see if the relationship between intracranial blood volume and SIH differed between these groups. To demonstrate the dose effect of clinical and radiological severity on SIH occurrence, H&H, mFS, intracranial blood, and intracranial blood + CSF were analyzed using correlation coefficient and their respective means compared using ANOVA. Univariate logistic regression was used to examine possible risk factors for SIH, DCI, EVD, and VPS placement. Factors with a p value < 0.10 were included in a multivariate logistic regression using the stepwise method.

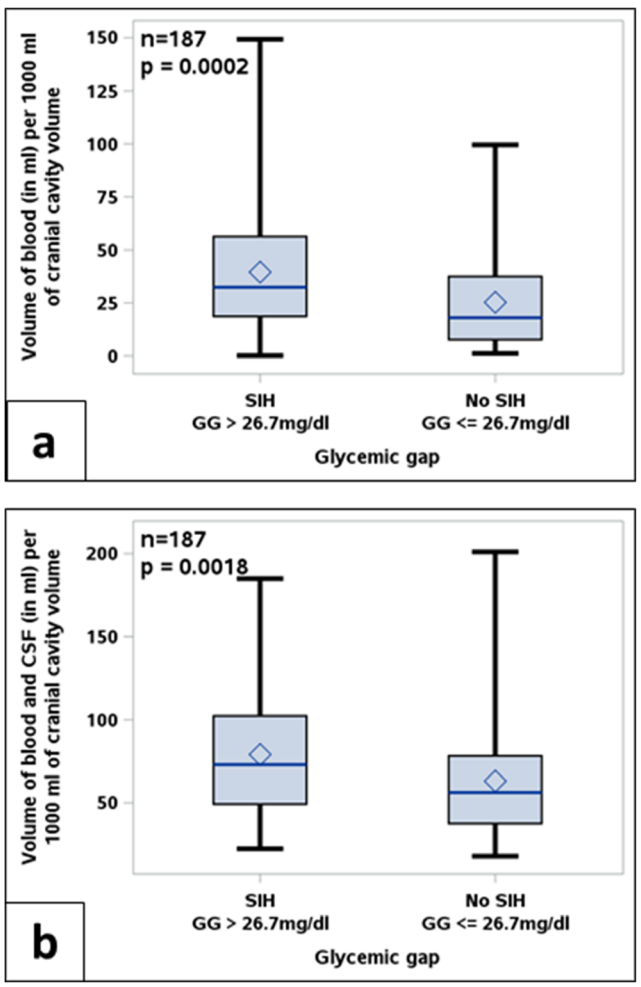

Fig. 2 Box plots show significant difference among patient developing stress-induced hyperglycemia in regard to their respective intracranial hemorrhage volume (**a**) and degree of hydrocephalus (**b**) using quantitative estimation

The relationship of standard clinical and radiological scales (H&H, WFNS, mFS) and quantitative estimated volumes (intracranial blood and CSF) with the primary endpoint (SIH) and a secondary endpoint (mortality) was compared using receiver operator characteristic (ROC) curves. The area under the ROC (AUROC) with 95% confidence intervals was calculated and compared for each radiological scale and estimated volume to assess for any differences between the AUROCs.

Results

One hundred eighty-seven patients over a 5-year period met the inclusion criteria for the study (Fig. 1). Baseline characteristics including patient demographics are enumerated in Table 1. Thirty-eight patients [38/187 (20.3%)] expired during hospitalization while 9/187 (4.8%) were discharged to an inpatient hospice facility. A GG of 26.7 mg/dl was considered as the optimum threshold for SIH as noted in our previous study on the same cohort. Ninety-four [94/187 (50.3%)] among the study cohort had SIH. Using this GG threshold, patients presenting with SIH had 14.3/1000 ml more intracranial blood volume as compared to those without SIH [39.6 ml (95% confidence interval, CI, 33.6 to 45.5) vs. 25.3 ml (95% CI 20.6 to 29.9), $p = 0.0002$] (Fig. 2a; Table 2). Similarly, those with SIH had, on an average, 16/1000 ml of more intracranial blood + CSF volumes as compared to those without SIH [79.1 ml (95% CI 71.9 to 86.2) vs. 63.1 ml (95% CI 56.2 to 70.1), $p = 0.027$] (Fig. 2b; Table 2). Linear regression analyses showed strong relationship between volume of intracranial blood and intracranial blood + CSF with mGS (Supplementary Figure 3). In the present cohort, each unit rise in mGS correlated with 2.44 and 2.58 ml per 1000 ml intracranial volume rise in blood volume and blood + CSF volume respectively. The AUROCs for each parameter in predicting mortality and SIH were not significantly different, although intracranial blood volume and blood + CSF volumes were associated with increased AUROC as compared to other parameters (Supplementary Figure 4).

Patients were segregated as per their disease presentation severity with grades of H&H I–III, WFNS 1–3, mFS 1–2 being categorized as good grades and H&H IV–V, WFNS 4–5, and mFS 3–4 as severe grades. A positive association was noted with GG and intracranial blood volume/combined intracranial blood and CSF volumes among those with lower grades. However, this interaction was not statistically significant between the respective severity categories (Fig. 3). However, average GG among patients with higher clinical/radiological grades was more as compared to those with lower grades (Table 3). Similarly, when segregated as per standard disease severity and quantitative radiological severity, GG showed a positive correlation (Fig. 4).

Linear regression analysis exploring relationship of mGS with GG showed each additional unit increase in mGS resulted in 1.2 mg/dl increase in GG [$p = 0.002$] (Fig. 5a). Similarly, when dichotomized to those with and without SIH, patients with SIH had higher mGS [median 4.0, interquartile range, IQR 2.0–7.0] as compared to those without SIH [median 2.0, IQR 0.0–6.0] (Fig. 5b; Table 2). Although positive relationship of GG was noted in regard to admission H&H, WFNS, and mFS, the groups dichotomized as per disease severity (as mentioned above) were not different. However, patients with third ventricular blood at the time of admission were more likely to develop SIH [67/118 (56.8%) vs. 27/69 (39.1%), $p = 0.023$].

Of the 170 patients in whom DCI information was available, 56 (32.9%) developed DCI. The mean volume of intracranial blood was higher in those developing DCI as compared to those without [35.9 ml for DCI vs. 25.5 ml for those without DCI; mean difference 10.4 with 95% CI for difference 2.9 to 17.8; $p = 0.007$]. Combined intracranial blood and CSF volume although was more among those developing DCI but was not statistically significant [72.0 vs. 66.1 ml; $p = 0.27$]. However, median mGS score was higher in those developing DCI as compared to those who did not develop during hospital stay [4.0, IQR 2.0–6.5 vs. 2.0, IQR 0.0–6.0; $p = 0.004$].

Table 2 Radiological parameters determining occurrence of stress-induced hyperglycemia

Radiological feature	SIH (GG ≥ 26.7 mg/dl)	Mean/median (in ml)	95% CI/IQR	*p* value
Intracranial blood volume (in ml per 1000 ml cranial cavity)	Yes	39.6	33.6–45.5	0.0002
	No	25.3	20.6–29.9	
Intracranial blood and CSF volume (in ml per 1000 ml cranial cavity)	Yes	79.1	71.9–86.2	0.027
	No	63.1	56.2–70.1	
Modified Graeb score†	Yes	4.0	2.0–7.0	0.002
	No	2.0	0.0–6.0	

CI confidence interval, *CSF* cerebrospinal fluid, *GG* glycemic gap, *IQR* interquartile range

†Expressed in median

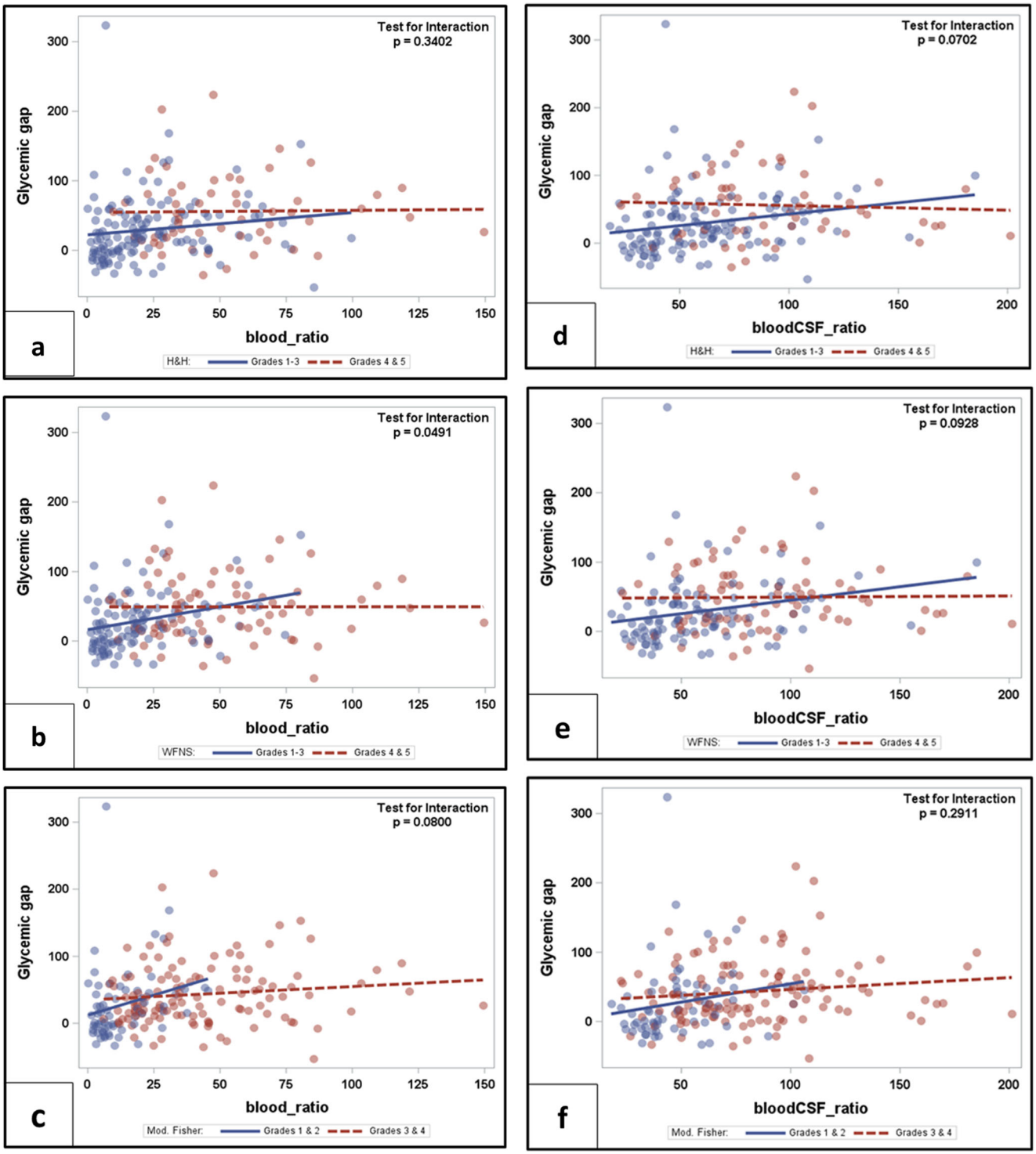

Fig. 3 Dose effect of glycemic gap in regard to intracranial blood volume (**a**–**c**) and degree of hydrocephalus (**d**–**f**) dependent on clinical (H&H Hunt and Hess, WFNS World Federation of Neurological Surgeons) and radiological (modified Fisher) scale

Using a stepwise selection to predict death/discharge to hospice, the intracranial blood volume and SIH defined by GG remained significant. The odds of dying were 3.5 times greater for patients who had SIH compared to those who did

Table 3 Stress-induced hyperglycemia distribution as per admission disease severity

Score	Grade	Mean ± SD	*p* value	Median (IQR)	*p* value
H&H	I–III	29.9 ± 46.8	0.001	19.8 (0.6–50.0)	0.004
	IV–V	55.8 ± 52.3		47.9 (19.2–82.4)	
WFNS	1–3	29.3 ± 20.1	0.006	19.7 (−0.7–48.6)	0.001
	4–5	49.2 ± 38.1		43.8 (14.6–75.9)	
Modified Fisher	1–2	27.4 ± 54.9	0.03	16.3 (−5.9–48.6)	0.001
	3–4	43.5 ± 46.2		32.9 (13.0–67.6)	

H&H Hunt and Hess, *IQR* interquartile range, *SD* standard deviation, *WFNS* World Federation of Neurological Surgeons Score

not ($p = 0.002$) when holding the intracranial blood volume constant. The odds of dying were 1.03 times greater for patients with higher intracranial blood volume ($p < 0.0001$) with SIH regarded as constant.

We also evaluated if various factors that determine hydrocephalus (e.g., BCI, mGS, intracranial blood volume, and SIH) could predict temporary or permanent CSF diversion in regard to EVD and VPS placement respectively. Of note, in 89 patients with SIH (GG > 26.7 mg/dl) at admission in whom treatment was offered, 23 underwent clipping and 65 underwent coiling and no securing procedure could be performed in one patient. VPS was placed by discharge in 4/15 (26.7%) for clipping group and 7/53 (13.2%) for coiling group, respectively, which are not significantly different

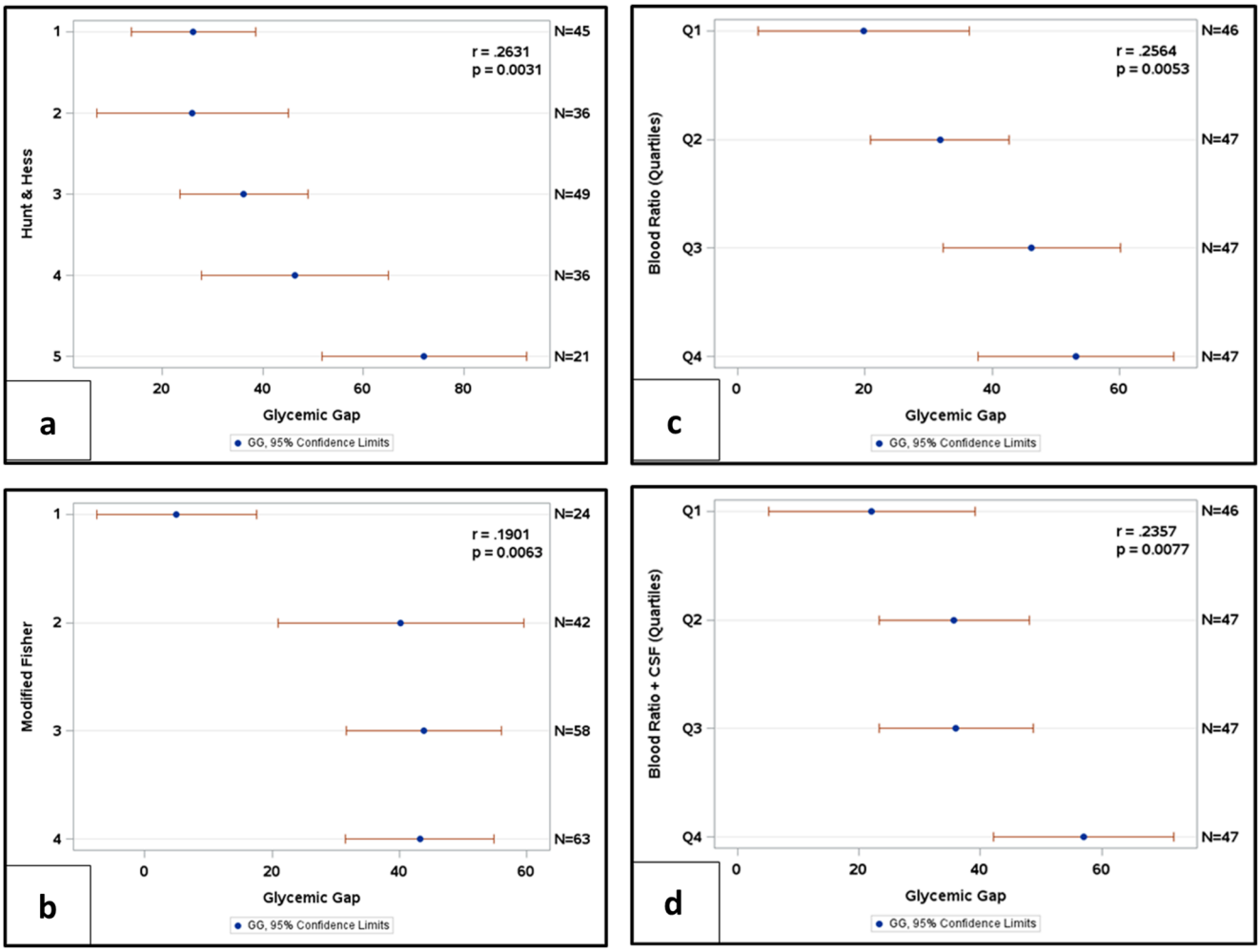

Fig. 4 Line diagram shows "dose effect" and progressive in glycemic gap with increasing clinical (**a**), radiological (**b**), and quantitative radiological grades (**c**, **d**)

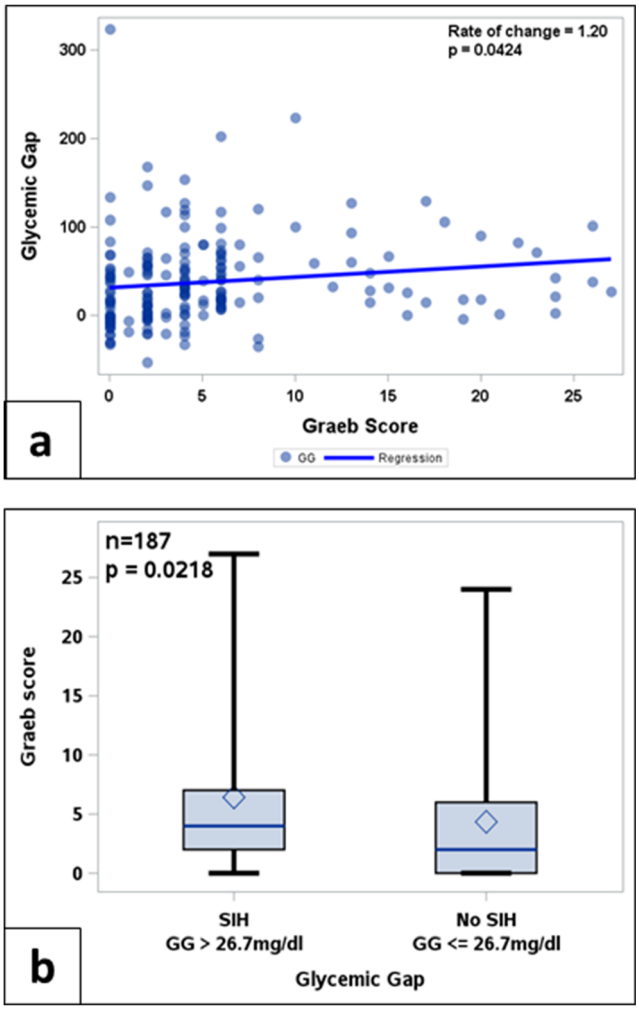

Fig. 5 **a** Linear and positive correlation noted between modified Graeb score and degree of stress-induced hyperglycemia (using glycemic gap). **b** Average modified Graeb score is higher among patient with stress-induced hyperglycemia defined by glycemic gap > 26.7 mg/dl

($p = 0.24$). Twenty patients expired during hospitalization and hence no information on need for VPS was available. In the univariate analysis, the following were statistically significant in predicting EVD placement: BCI [$p = 0.002$], SIH [$p = 0.008$], mGS [$p = 0.0005$], and intracranial blood volume [$p = 0.0011$]. However, in the multivariate model, only mGS [$p = 0.0004$] and intracranial blood volume [$p < 0.0001$] were significantly predictive of EVD placement. Elderly patients (age of 65 years and above) were more likely to have EVD placed than their younger counterparts [26/35 (83.9%) vs. 90/151 (59.6%), $p = 0.011$]. When examining VPS placement, BCI, mGS, and intracranial blood volume were significant. But in the multivariate model, only age-adjusted BCI criteria for hydrocephalus at the time of admission was predictive for VPS placement [odds ratio, OR 3.99 (95% CI 1.44 to 11.11), $p = 0.008$].

Discussion

In our study, we used a novel methodology to study SIH in aSAH patients. GG is an index that assesses degree of admission hyperglycemia in relation to patient's own premorbid glycemic control (i.e., HbA1c). Hence, the severity of hyperglycemia in our cohort is independent of pre-specified thresholds that are often used to study associative effects of dysglycemia and aSAH [13, 14]. We also used objective quantitative and semi-quantitative methods to assess hydrocephalus on admission CT scans of head while investigating their respective effect in causing SIH after aSAH. Such baseline data is necessary in aSAH patients as predictive models are developed in patient management and prognosis using machine-learning algorithms [15, 16].

We objectively demonstrate that both amount of intracranial blood and extent of hydrocephalus (i.e., mGS and quantitative intracranial blood + CSF volumes) are strongly associated with SIH. A positive correlation noted between admission GG and mGS alludes to a role of hydrocephalus in neurohumoral pathway resulting in SIH. Both admission SIH and intracranial blood volume independently predicted in-hospital mortality. Our results also confirm the associative role of intracranial blood volume in occurrence of DCI after aSAH [8]. The incidence of DCI in our cohort is comparable with existing literature [17–19]. We also demonstrate the effect of admission hydrocephalus and occurrence of DCI and dysglycemia that have not been reported previously. Multivariate models examining factors responsible for temporary and permanent CSF diversion (i.e., placement of EVD and VPS respectively) after aSAH are also comprehensively analyzed.

Role of Intracranial Blood Volume and Stress-Induced Hyperglycemia

Our study is first to report higher intracranial blood volume to be associated with SIH, using unbiased objective methodology, which is primarily dependent on patient's stress response to altered homeostasis after aSAH. A positive relationship was noted between intracranial blood volume and SIH among patients presenting with lower clinical and radiological grades as compared to those with higher grades. However, there was no statistically significant difference between their trends. Of note, higher-grade aSAH patients on an average had higher GG as compared to lower grade patients (Table 3). Hence, it is evident that while patients with low-grade presentation showed a dose-dependent response, higher-grade aSAH patients had an inherent neurohumoral response with resultant SIH that was independent of dose effect (Fig. 3). Patients with features of worse CT scan, e.g., hemorrhage

size, midline shift, and hydrocephalus oftentimes have resultant higher plasma glucose levels than those with milder findings on CT scan [20]. Mechanisms by which intracranial blood, after aSAH mounts a systemic response, like SIH is multifactorial, such factors involve development of hydrocephalus, release of cytokines, catecholamines, and other counter-regulatory hormones related to stress as noted previously in aSAH, intracerebral hemorrhage, and other critical illnesses [1, 2]. Systemic presence of such circulating humoral factors after aSAH is previously reported [2, 21]. Role of central sensors like hypothalamus in regulation of gluconeogenesis and glycogenolysis response in critical illness and after aSAH is also reported [22, 23]. Our study observed higher incidence of SIH in patients with third ventricular blood products on admission CT scan alluding to a direct effect of such blood products on hypothalamus, possibly facilitating hyperglycemic response. However, such association cannot be confirmed by our study, as corresponding humoral factors were not studied. In future, it would be interesting to study this effect and investigate how blood breakdown products might have a temporal response in aSAH patients during their post-ictal phase.

Role of Hydrocephalus in Determination of Stress-Induced Hyperglycemia

Occurrence of hydrocephalus after aSAH, temporary (requiring EVD placement) or permanent (requiring VPS placement), is frequent and multifactorial [24, 25]. In our previous study, the same cohort showed (using univariate analysis) SIH to be associated with EVD placement but neither SIH nor long-term premorbid hyperglycemic state (HbA1c) was associated with VPS placement [7]. In the present study, we further investigated the role of hydrocephalus and SIH using objective parameters. However, it is difficult to separate the cause and effect of SIH in relation to development of hydrocephalus after aSAH. The present study examining factors associated with hydrocephalus could not identify SIH to be an independent factor determining either EVD or VPS placement. This is contrary to previous study reporting admission hyperglycemia (defined as serum glucose ≥ 126 mg/dl) to be associated with VPS placement [13]. However, in that study, results were not segregated as per patient's premorbid diabetic status or determined SIH according to GG. Such an approach increases sensitivity but decreases specificity as demonstrated earlier [7]. Of note, occurrence and degree of hydrocephalus in our cohort is similar to intracerebral hemorrhage patients with intraventricular hemorrhage [26]. Such an association again alludes to activation of hypothalamic-pituitary-adrenal axis in resultant SIH.

Stress-Induced Hyperglycemia and Its Role in Clinical Outcome (Including DCI and Mortality)

Association of SIH with occurrence of DCI and in-hospital mortality was also evaluated in our study. Using AUROC analyses, it appears that both objective and subjective radiological features are more predictive of mortality in aSAH as compared to clinical (H&H and WFNS) and serological markers (GG) although not statistically significant (Supplementary Figure 4). Controlling for hemorrhage size-related effect, patients in our cohort had a 3.5 times higher mortality rate among SIH patients as compared to those without. Similarly, controlling for effects of SIH, the cohort had a 1.03 times higher mortality rate with higher intracranial blood volumes. It is well known that DM, high HbA1c, and even non-stress-related hyperglycemia are associated with in-hospital morbidity like higher infection rates, DCI, cerebral complications, and mortality [27–29]. Even our previous study reported increased mortality rate among those with SIH [7]. Similarly, hyperglycemia during hospitalization is reported to be also associated with long-term moderate to severe disabilities and higher 12-month mortality rates [30–32].

Study Limitations and Future Direction

We acknowledge limitations with our study that is inherent to any retrospective study, i.e., occasional unavailability of data points and presumption of accuracy of information recorded in the electronic medical record. Similarly, radiological portion of the study was limited by unavailability of proper scans in the system, error in software to recognize certain scans due to technical reasons. Segmentation software developed to estimate the blood and CSF volumes was based on predetermined HU-dependent pixel thresholds. Hence, estimation of volume may vary depending on software developed at other institutions or commercially available versions. However, all scans were analyzed using the same algorithm and hence intra-study validity of the results is maintained although values obtained in our study may not be comparable to other similar studies. There is a possibility that SIH observed in this study can reflect elevated intracranial pressure that cannot be verified due to retrospective nature and absence of documentation of opening pressure at the time of EVD insertion. Future studies need to be designed to verify principles of this study in a prospective cohort using predetermined inclusion and exclusion criteria. Similarly, apart from radiological determinants at the time of admission, simultaneous estimation of humoral factors (including temporal trend of glycemic control and infections) that determines SIH and VPS placement needs to be systematically and quantitatively investigated in future studies. Thus, our study provides baseline

data necessary to design any such future studies investigating SIH after aSAH.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Not applicable due to retrospective nature of the study design.

References

1. Kruyt ND, Musters A, Biessels GJ, Devries JH, Coert BA, Vergouwen MD, et al. Beta-cell dysfunction and insulin resistance after subarachnoid haemorrhage. Neuroendocrinology. 2011;93(2):126–32. https://doi.org/10.1159/000324097.
2. Kruyt ND, Biessels GJ, DeVries JH, Luitse MJ, Vermeulen M, Rinkel GJ, et al. Hyperglycemia in aneurysmal subarachnoid hemorrhage: a potentially modifiable risk factor for poor outcome. J Cereb Blood Flow Metab. 2010;30(9):1577–87. https://doi.org/10.1038/jcbfm.2010.102.
3. Kruyt ND, Roos YW, Dorhout Mees SM, van den Bergh WM, Algra A, Rinkel GJ, et al. High mean fasting glucose levels independently predict poor outcome and delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 2008;79(12):1382–5. https://doi.org/10.1136/jnnp.2007.142034.
4. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. Translating the A1C assay into estimated average glucose values. Diabetes Care. 2008;31(8):1473–8. https://doi.org/10.2337/dc08-0545.
5. Liao WI, Sheu WH, Chang WC, Hsu CW, Chen YL, Tsai SH. An elevated gap between admission and A1C-derived average glucose levels is associated with adverse outcomes in diabetic patients with pyogenic liver abscess. PLoS One. 2013;8(5):e64476. https://doi.org/10.1371/journal.pone.0064476.
6. Liao WI, Wang JC, Chang WC, Hsu CW, Chu CM, Tsai SH. Usefulness of glycemic gap to predict ICU mortality in critically ill patients with diabetes. Medicine (Baltimore). 2015;94(36):e1525. https://doi.org/10.1097/md.0000000000001525.
7. Ray B, Ludwig A, Yearout LK, Thompson DM, Bohnstedt BN. Stress-induced hyperglycemia after spontaneous subarachnoid hemorrhage and its role in predicting cerebrospinal fluid diversion. World neurosurgery. 2017;100:208–15. https://doi.org/10.1016/j.wneu.2017.01.008.
8. Ko SB, Choi HA, Carpenter AM, Helbok R, Schmidt JM, Badjatia N, et al. Quantitative analysis of hemorrhage volume for predicting delayed cerebral ischemia after subarachnoid hemorrhage. Stroke. 2011;42(3):669–74. https://doi.org/10.1161/strokeaha.110.600775.
9. Jimenez-Roldan L, Alen JF, Gomez PA, Lobato RD, Ramos A, Munarriz PM, et al. Volumetric analysis of subarachnoid hemorrhage: assessment of the reliability of two computerized methods and their comparison with other radiographic scales. J Neurosurg. 2013;118(1):84–93. https://doi.org/10.3171/2012.8.jns12100.
10. Cortnum S, Sorensen P, Jorgensen J. Determining the sensitivity of computed tomography scanning in early detection of subarachnoid hemorrhage. Neurosurgery. 2010;66(5):900–2; discussion 3. https://doi.org/10.1227/01.Neu.0000367722.66098.21.
11. Morgan TC, Dawson J, Spengler D, Lees KR, Aldrich C, Mishra NK et al. The Modified Graeb score. An enhanced tool for intraventricular hemorrhage measurement and prediction of functional outcome. 2013;44(3):635–641. doi:https://doi.org/10.1161/strokeaha.112.670653.
12. van Gijn J, Hijdra A, Wijdicks EF, Vermeulen M, van Crevel H. Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. J Neurosurg. 1985;63(3):355–62. https://doi.org/10.3171/jns.1985.63.3.0355.
13. Rincon F, Gordon E, Starke RM, Buitrago MM, Fernandez A, Schmidt JM, et al. Predictors of long-term shunt-dependent hydrocephalus after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2010;113(4):774–80. https://doi.org/10.3171/2010.2.JNS09376
14. Bian L, Liu L, Wang C, Hussain M, Yuan Y, Liu G, et al. Hyperglycemia within day 14 of aneurysmal subarachnoid hemorrhage predicts 1-year mortality. Clin Neurol Neurosurg. 2013;115(7):959–64. https://doi.org/10.1016/j.clineuro.2012.09.026.
15. Deo RC. Machine learning in medicine. Circulation. 2015;132(20):1920–30. https://doi.org/10.1161/circulationaha.115.001593.
16. Poulymenopoulou M, Malamateniou F, Vassilacopoulos G. Machine learning for knowledge Extraction from PHR big data. Stud Health Technol Inform. 2014;202:36–9.
17. Roos YB, de Haan RJ, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M. Complications and outcome in patients with aneurysmal subarachnoid haemorrhage: a prospective hospital based cohort study in the Netherlands. J Neurol Neurosurg Psychiatry. 2000;68(3):337–41.
18. Hijdra A, Van Gijn J, Stefanko S, Van Dongen KJ, Vermeulen M, Van Crevel H. Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: clinicoanatomic correlations. Neurology. 1986;36(3):329–33.
19. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke. 2010;41(10):2391–5. https://doi.org/10.1161/strokeaha.110.589275.
20. Alberti O, Becker R, Benes L, Wallenfang T, Bertalanffy H. Initial hyperglycemia as an indicator of severity of the ictus in poor-grade patients with spontaneous subarachnoid hemorrhage. Clin Neurol Neurosurg. 2000;102(2):78–83.
21. Vergouwen MD, van Geloven N, de Haan RJ, Kruyt ND, Vermeulen M, Roos YB. Increased cortisol levels are associated with delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2010;12(3):342–5. https://doi.org/10.1007/s12028-010-9331-8.
22. Schwartz MW, Porte D, Jr. Diabetes, obesity, and the brain. Science 2005;307(5708):375–379. doi:https://doi.org/10.1126/science.1104344.
23. Obici S, Zhang BB, Karkanias G, Rossetti L. Hypothalamic insulin signaling is required for inhibition of glucose production. Nat Med. 2002;8(12):1376–82. https://doi.org/10.1038/nm798.
24. Wang YM, Lin YJ, Chuang MJ, Lee TH, Tsai NW, Cheng BC, et al. Predictors and outcomes of shunt-dependent hydrocephalus in patients with aneurysmal sub-arachnoid hemorrhage. BMC Surg. 2012;12:12. https://doi.org/10.1186/1471-2482-12-12.

25. Lai L, Morgan MK. Predictors of in-hospital shunt-dependent hydrocephalus following rupture of cerebral aneurysms. J Clin Neurosci. 2013;20(8):1134–8. https://doi.org/10.1016/j.jocn.2012.09.033.
26. Appelboom G, Piazza MA, Hwang BY, Carpenter A, Bruce SS, Mayer S, et al. Severity of intraventricular extension correlates with level of admission glucose after intracerebral hemorrhage. Stroke. 2011;42(7):1883–8. https://doi.org/10.1161/strokeaha.110.608166.
27. Dumont T, Rughani A, Silver J, Tranmer BI. Diabetes mellitus increases risk of vasospasm following aneurysmal subarachnoid hemorrhage independent of glycemic control. Neurocrit Care. 2009;11(2):183–9. https://doi.org/10.1007/s12028-009-9232-x.
28. Ferguson S, Macdonald RL. Predictors of cerebral infarction in patients with aneurysmal subarachnoid hemorrhage. Neurosurgery. 2007;60(4):658–67; discussion 67. https://doi.org/10.1227/01.Neu.0000255396.23280.31.
29. de Rooij NK, Rinkel GJ, Dankbaar JW, Frijns CJ. Delayed cerebral ischemia after subarachnoid hemorrhage: a systematic review of clinical, laboratory, and radiological predictors. Stroke. 2013;44(1):43–54. https://doi.org/10.1161/strokeaha.112.674291.
30. Schlenk F, Vajkoczy P, Sarrafzadeh A. Inpatient hyperglycemia following aneurysmal subarachnoid hemorrhage: relation to cerebral metabolism and outcome. Neurocrit Care. 2009;11(1):56–63. https://doi.org/10.1007/s12028-009-9222-z.
31. Beseoglu K, Steiger HJ. Elevated glycated hemoglobin level and hyperglycemia after aneurysmal subarachnoid hemorrhage. Clin Neurol Neurosurg. 2017;163:128–32. https://doi.org/10.1016/j.clineuro.2017.10.037.
32. Juvela S, Siironen J, Kuhmonen J. Hyperglycemia, excess weight, and history of hypertension as risk factors for poor outcome and cerebral infarction after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2005;102(6):998–1003. https://doi.org/10.3171/jns.2005.102.6.0998.