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Research Paper

Impact of Anion Gap on Outcome in Patients with Subarachnoid Hemorrhage

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Abstract
Introduction
Spontaneous or non-traumatic subarachnoid hemorrhage is sudden bleeding in the subarachnoid space not due to external cause. It accounts for 5–10% of all strokes.
There is need for a non-invasive means of investigation for prognostication and treatment. The Anion Gap has been found to be useful in this regard.
Literature Review
Patients with spontaneous SAH tend to be younger than patients with other stroke subtypes, thus leading to an enormous burden of premature mortality.[4,5]
Even with optimal management in the ICU, non-traumatic SAH still has high in-hospital mortality rates. Epidemiological investigations have shown high rates of non-traumatic SAH and in-hospital mortality rates of up to 40%.[7]
Half of surviving SAH patients experience long-term neuropsychological complications and lower quality of life.[9]
Therefore, interventions for such underlying diseases and stabilization of homeostasis play extremely important roles in ICH.[10]
Non-invasive and inexpensive tests are needed to identify those at greater risk of death and prevent mortalities.[11]
Anion gap (AG) predicts the long-term neurological and cognitive outcomes of spontaneous intracerebral hemorrhage. AG predicts recovery of ICH patients.
Materials and Methods
It is a prospective study. Fifty patients were studied. Neurological and cognitive functions were assessed using Glasgow coma scale (GCS)
Demographic data and clinical features were collected for all patients, including age, sex, socioeconomic status, history of diseases and medications, midline shift, and intraventricular hemorrhage (IVH). All the patients had neurological examination, and Glasgow coma scale (GCS) assessed at admission.
Blood samples were taken and the AG was calculated with the formula: AG=[Na+(mmol/L)+K+(mmol/L)]−[Cl− (mmol/L)+HCO3 − (mmol/L)]
Results
For all the patients, a correlation between Anion Gap and Outcome of the all the patients showed that mortality was associated with increasing anion gap, p=0.020, which is statistically significant.
For patients with AG<=16mmol/L
The association between GCS and AG and showed that as AG increased GCS reduced, p=0.132.
For patients with AG >=16mmol/L
The association between the Anion Gap and Outcome showed Mortality was associated with increasing AG, p=0.565.
Discussion
A correlation between Anion Gap and Outcome of the all the patients showed that the mortality associated with increasing anion gap was p=0.020, which is statistically significant.
This corresponds with the study done by Changli Zhong et al in which patients with higher AG levels had higher in-hospital (p = 0.006) and ICU mortality (p = 0.003).[17]
This also corresponds with J Shen et al. who stated that depending on the variable tested, there was an association between higher serum AG levels and hospital all-cause mortality in different subgroups.[18]

Conclusion
There is need for an accurate non-invasive technique for measuring hemodynamic changes and prognostication in patients with spontaneous SAH. Several studies have found the importance of using a simple arithmetically derivable formula to get the AG which can serve the above functions. This study has also confirmed the importance of using the AG to monitor critical patients.

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I. Introduction

Spontaneous or non-traumatic subarachnoid hemorrhage is sudden bleeding in the subarachnoid space not due to external cause. It accounts for 5–10% of all strokes. [1]Another study found it in 2–7% of all strokes[2].

It is a potentially devastating disease caused primarily by ruptured intracranial aneurysms. However, the disease-specific burden of non-traumatic SAH is unusually heavy and may be underestimated.[3]

There is need for a non-invasive means of investigation for prognostication and treatment. The Anion Gap has been found to be useful in this regard.

II. Literature Review

Patients with spontaneous SAH tend to be younger than patients with other stroke subtypes, thus leading to an enormous burden of premature mortality.[4,5]

Half of the patients with non-traumatic SAH are reported to be younger than 60 years, of which one-third are reported to expire before arrival at the hospital, while others required Intensive Care Unit (ICU) treatment .[6]

Even with optimal management in the ICU, non-traumatic SAH still has high in-hospital mortality rates. Epidemiological investigations have shown high rates of non-traumatic SAH and in-hospital mortality rates of up to 40%.[7]

However, many patients have a history of underlying diseases such as hypertension, diabetes, hyperlipidemia, and respiratory diseases. These diseases influence the pathogenesis of ICH and impact the recovery status.[8]

Half of surviving SAH patients experience long-term neuropsychological complications and lower quality of life.[9]

Therefore, interventions for such underlying diseases and stabilization of homeostasis play extremely important roles in ICH.[10]

Non-invasive and inexpensive tests are needed to identify those at greater risk of death and prevent mortalities.[11]

The clinical diagnosis of spontaneous intracerebral hemorrhage (sICH) mainly depends on the neuroimage evidence, such as computed tomography (CT) and magnetic resonance image (MRI). These tests provide a rapid recognition of sICH and differential diagnosis from other cerebrovascular diseases, such as ischemic stroke (IS) and subarachnoid hemorrhage (SAH), with high specificity and sensitivity. However, the neuroimages can neither distinguish the microenvironments of body fluid nor have predictive values for the neurological complications of the patients. [12]

Neuroimaging indications, which are provided by CT and MRI scans, have been widely applied clinically and could provide rapid diagnosis of ICH. However, neuroimaging technology also has some limitations in clinical practice. First, only 50% of patients with progressive bleeding would be positively detected by imageological findings. Second, these technologies hardly offer a predictive value for the prognosis of patients. Therefore, researchers currently focus on the molecule-based study in stroke, which provides important clinical clues for not only precise diagnosis and outcome prediction of the disease, but also pathogenesis investigations on ICH. Elevated serum AG level results from the production of increased organic acid or decreased anions.[13]

Numerous studies have focused on exploring novel biomarkers for predicting the outcomes in ICH. Several serum or plasma molecules have been considered to be significantly correlated with the neurological and/or cognitive impairments after ICH onset. However, most of these molecule-based studies have only been proof-of-concept so far, and have not been introduced in routine clinical practice. Hence, it is imperative to develop a clinical routine-based model to predict patient outcome in ICH.[14]

Anion gap (AG) predicts the long-term neurological and cognitive outcomes of spontaneous intracerebral hemorrhage. AG predicts recovery of ICH patients. AG is an algorithmic parameter that calculates the difference between serum cation and anion concentrations, and is based on the following equation: $AG=[Na+(mmol/L)+K+(mmol/L)]-[Cl-(mmol/L)+HCO3-(mmol/L)]$. AG reflects the acid-base equilibrium in body fluids and plays a pivotal role in metabolic acidosis and ischemic anoxic encephalopathy.[15]

Early identification and appropriate treatment regimens can improve the overall survival of patients with SAH. Thus, a robust and easily accessible clinical indicator for determining prognosis is needed for patients with SAH. [16]

III. Materials and Methods

It is a prospective study. Fifty patients were studied. Neurological and cognitive functions were assessed using Glasgow coma scale (GCS)

The number of patients in the ≥16 mmol/L group was 30(60%) 20 (40%) was in the <=16mmol/L group. All patients had correction of AG imbalance.

Exclusion criteria were patients with traumatic brain injury, patients without imaging. None of our patients had cancer.

Demographic data and clinical features were collected for all patients, including age, sex, socioeconomic status, history of diseases and medications, midline shift, and intraventricular hemorrhage (IVH). All the patients had neurological examination, and Glasgow coma scale (GCS) assessed at admission. Recovery outcomes were assessed by Glasgow Coma scale (GOS) at discharge. Scoring evaluations were conducted by experienced doctors: consultants, senior registrars and registrars. Sera were drawn by dorsum of the hand, forearm venipuncture or femoral tap into plain tubes from each patient at different times after admission and sent to the lab.

The AG was calculated with the formula: AG=[Na+(mmol/L)+K+(mmol/L)]−[Cl− (mmol/L)+HCO3 − (mmol/L)]

The AG of the entire population was done. Then the group was divided into two, those with AG <=16mmol/L, and those with AG>=16mmol/L. Statistical analysis was done with SPSS. The GCS, AG, and outcomes were were analysed for each of those groups.

Treatments were intravenous crystalloids, broadspectrum antibiotics, diuretics Mannitol and frusemide, antihypertensives, insulin for sugar control, analgesics. DVT prophylaxis was TED stockings.

IV. Results

Statistics

		GCS	Outcome	AG
N	Valid	50	50	50
	Missing	0	0	0
Mean		9.0800	1.4600	17.8240
Median		9.0000	1.0000	17.6500
Mode		7.00[a]	1.00	13.60[a]
Std. Deviation		3.71341	.50346	6.08285
Minimum		3.00	1.00	5.00
Maximum		15.00	2.00	35.00

a. Multiple modes exist. The smallest value is shown

Table 1, statistics of the study population.

AG

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	-10.00	1	2.0	2.0	2.0
	7.40	1	2.0	2.0	4.0
	7.50	1	2.0	2.0	6.0
	8.00	1	2.0	2.0	8.0
	9.70	1	2.0	2.0	10.0
	9.90	1	2.0	2.0	12.0
	11.30	1	2.0	2.0	14.0
	11.80	1	2.0	2.0	16.0
	12.50	1	2.0	2.0	18.0
	12.60	1	2.0	2.0	20.0
	13.20	1	2.0	2.0	22.0
	13.60	2	4.0	4.0	26.0
	14.00	1	2.0	2.0	28.0
	14.20	1	2.0	2.0	30.0
	14.80	1	2.0	2.0	32.0
	15.10	1	2.0	2.0	34.0
	15.70	1	2.0	2.0	36.0
	15.80	2	4.0	4.0	40.0

	16.30	1	2.0	2.0	42.0
	17.30	1	2.0	2.0	44.0
	17.40	1	2.0	2.0	46.0
	17.50	2	4.0	4.0	50.0
	17.80	1	2.0	2.0	52.0
	17.90	2	4.0	4.0	56.0
	18.10	1	2.0	2.0	58.0
	18.70	1	2.0	2.0	60.0
	19.00	1	2.0	2.0	62.0
	19.70	1	2.0	2.0	64.0
	20.00	1	2.0	2.0	66.0
	21.00	1	2.0	2.0	68.0
	21.10	1	2.0	2.0	70.0
	21.40	1	2.0	2.0	72.0
	21.60	1	2.0	2.0	74.0
	22.00	1	2.0	2.0	76.0
	22.60	1	2.0	2.0	78.0
	23.00	2	4.0	4.0	82.0
	23.20	1	2.0	2.0	84.0
	23.60	1	2.0	2.0	86.0
	24.00	2	4.0	4.0	90.0
	24.70	1	2.0	2.0	92.0
	26.50	1	2.0	2.0	94.0
	28.40	1	2.0	2.0	96.0
	29.50	1	2.0	2.0	98.0
	35.00	1	2.0	2.0	100.0
	Total	50	100.0	100.0	

Table 2, the frequency of the Anion Gap for the study population.

Outcome

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Survival	27	54.0	54.0	54.0
	Died	23	46.0	46.0	100.0
	Total	50	100.0	100.0	

Table 3, the total Outome.

GCS

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	3.00	3	6.0	6.0	6.0
	4.00	4	8.0	8.0	14.0
	5.00	2	4.0	4.0	18.0
	6.00	4	8.0	8.0	26.0
	7.00	6	12.0	12.0	38.0
	8.00	4	8.0	8.0	46.0
	9.00	6	12.0	12.0	58.0
	10.00	5	10.0	10.0	68.0
	11.00	2	4.0	4.0	72.0
	12.00	3	6.0	6.0	78.0
	13.00	1	2.0	2.0	80.0
	14.00	4	8.0	8.0	88.0
	15.00	6	12.0	12.0	100.0
	Total	50	100.0	100.0	

Table 4, the GCS of the study population

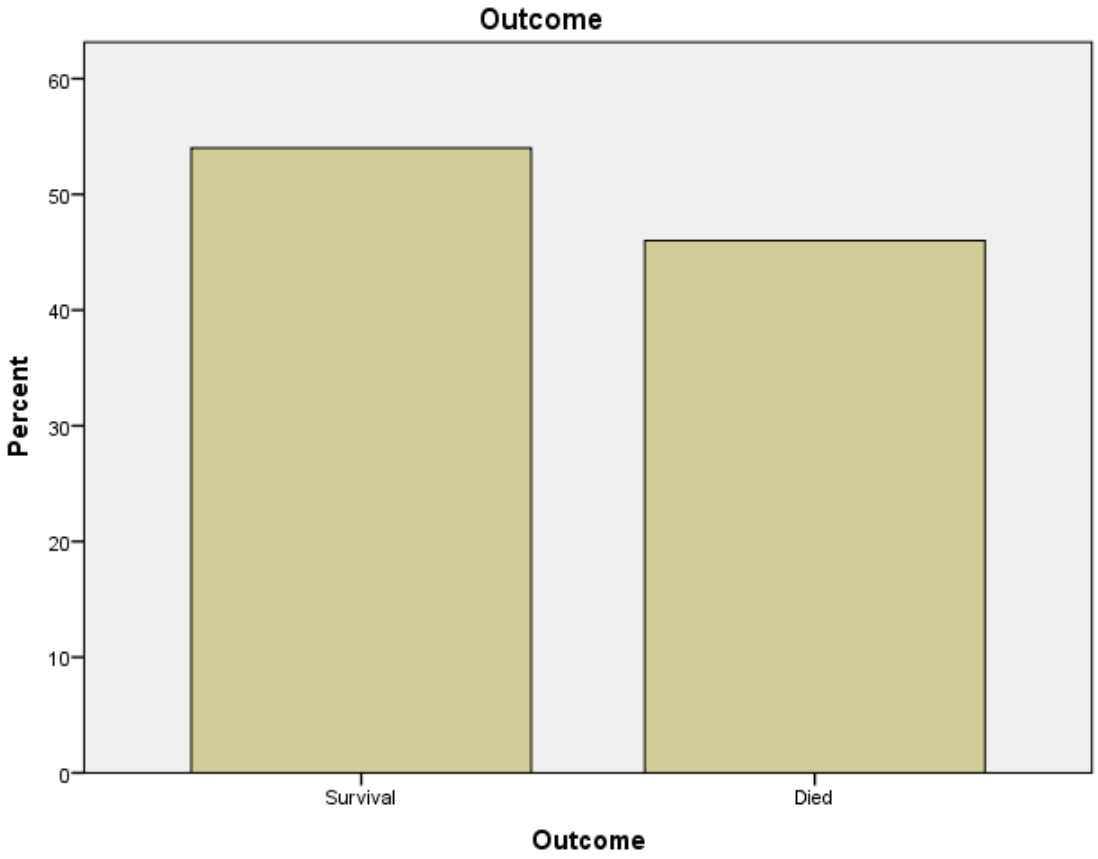

Figure 1, the outcome percent for all the patients.

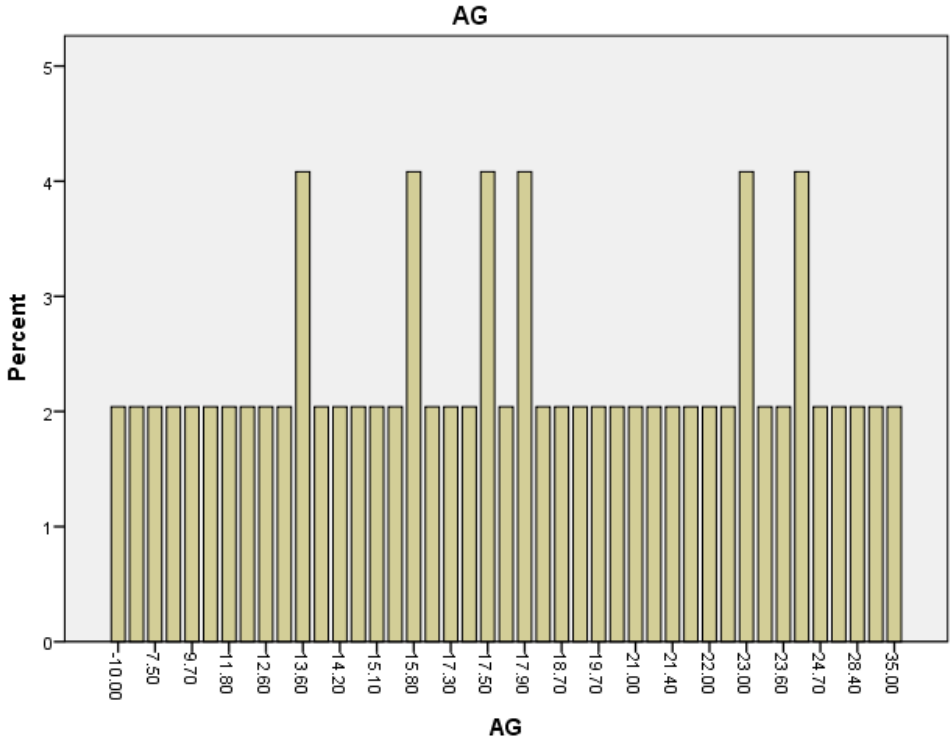

Figure 2, the Anion Gap percent for all the patients.

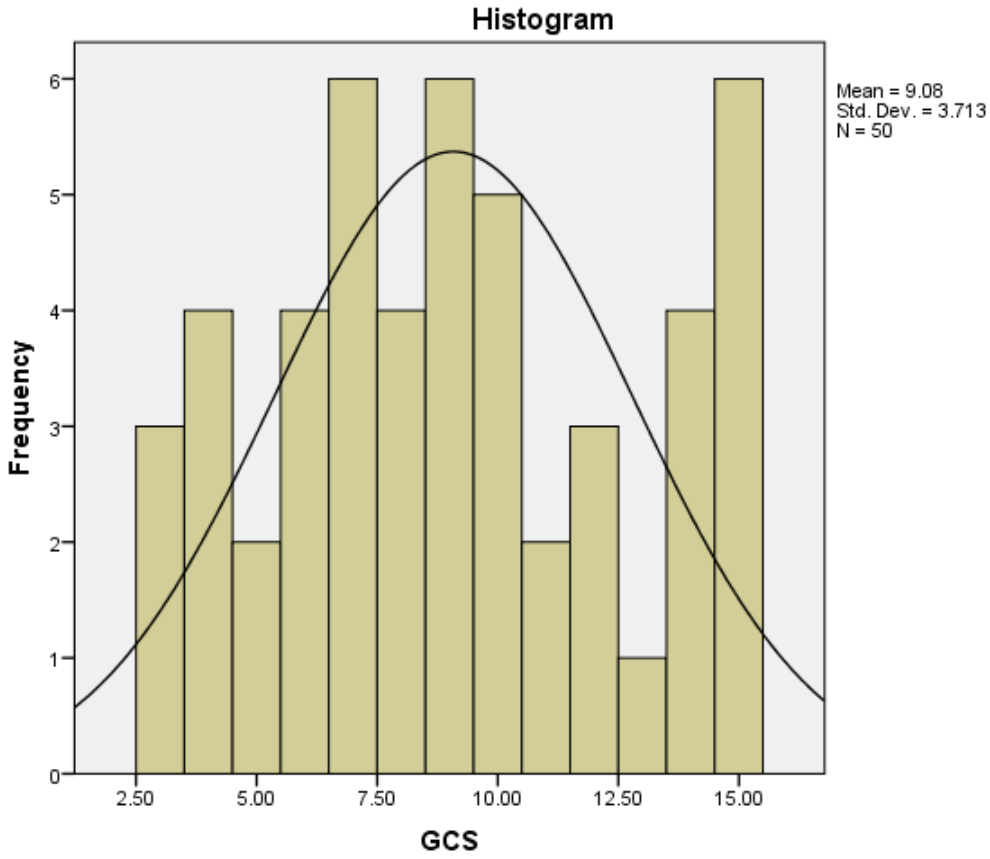

Figure 3 depicting the histogram of the GCS for all the patients.

A correlation between Anion Gap and Outcome of the all the patients showed that mortality was associated with increasing anion gap, p=0.020, which is statistically significant.

For Patients with Anion Gap <=16mmol/L

Statistics

		GCS	Outcome	AG
N	Valid	20	20	20
	Missing	0	0	0
Mean		10.1500	1.2000	11.3250
Median		10.0000	1.0000	12.9000
Mode		15.00	1.00	13.60[a]
Std. Deviation		3.57292	.41039	5.70576
Minimum		3.00	1.00	-10.00
Maximum		15.00	2.00	15.80

a. Multiple modes exist. The smallest value is shown

Table 5, the statistics of the Anion Gap for levels <16mmol/L

AG

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	-10.00	1	5.0	5.0	5.0
	7.40	1	5.0	5.0	10.0
	7.50	1	5.0	5.0	15.0
	8.00	1	5.0	5.0	20.0
	9.70	1	5.0	5.0	25.0
	9.90	1	5.0	5.0	30.0
	11.30	1	5.0	5.0	35.0
	11.80	1	5.0	5.0	40.0
	12.50	1	5.0	5.0	45.0
	12.60	1	5.0	5.0	50.0

	13.20	1	5.0	5.0	55.0
	13.60	2	10.0	10.0	65.0
	14.00	1	5.0	5.0	70.0
	14.20	1	5.0	5.0	75.0
	14.80	1	5.0	5.0	80.0
	15.10	1	5.0	5.0	85.0
	15.70	1	5.0	5.0	90.0
	15.80	2	10.0	10.0	100.0
	Total	20	100.0	100.0	

Table 6, the frequency of the Anion Gap for level <16mmols

Outcome

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Survived	16	80.0	80.0	80.0
	Died	4	20.0	20.0	100.0
	Total	20	100.0	100.0	

Table 7, the Outcome for patients with Anion Gap <16mmols

GCS

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	3.00	1	5.0	5.0	5.0
	5.00	1	5.0	5.0	10.0
	6.00	1	5.0	5.0	15.0
	7.00	2	10.0	10.0	25.0
	8.00	2	10.0	10.0	35.0
	9.00	1	5.0	5.0	40.0
	10.00	3	15.0	15.0	55.0
	11.00	2	10.0	10.0	65.0
	12.00	2	10.0	10.0	75.0
	14.00	1	5.0	5.0	80.0
	15.00	4	20.0	20.0	100.0
	Total	20	100.0	100.0	

Table 8 shows GCS of patients with AG <=16

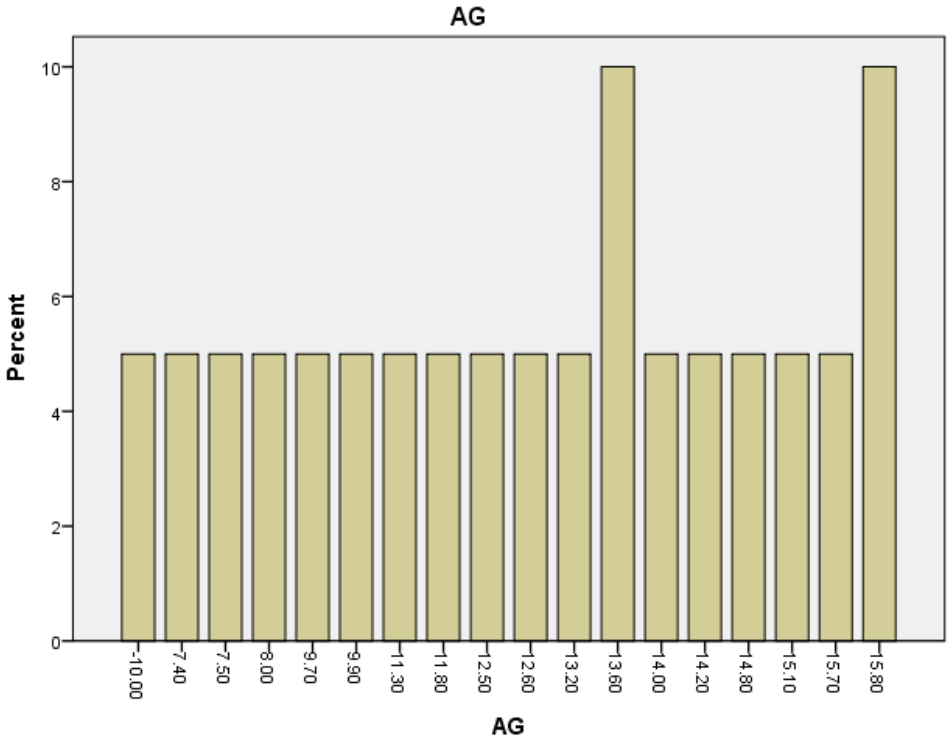

Figure 4, the bar chart Anion Gap <16mmol/L

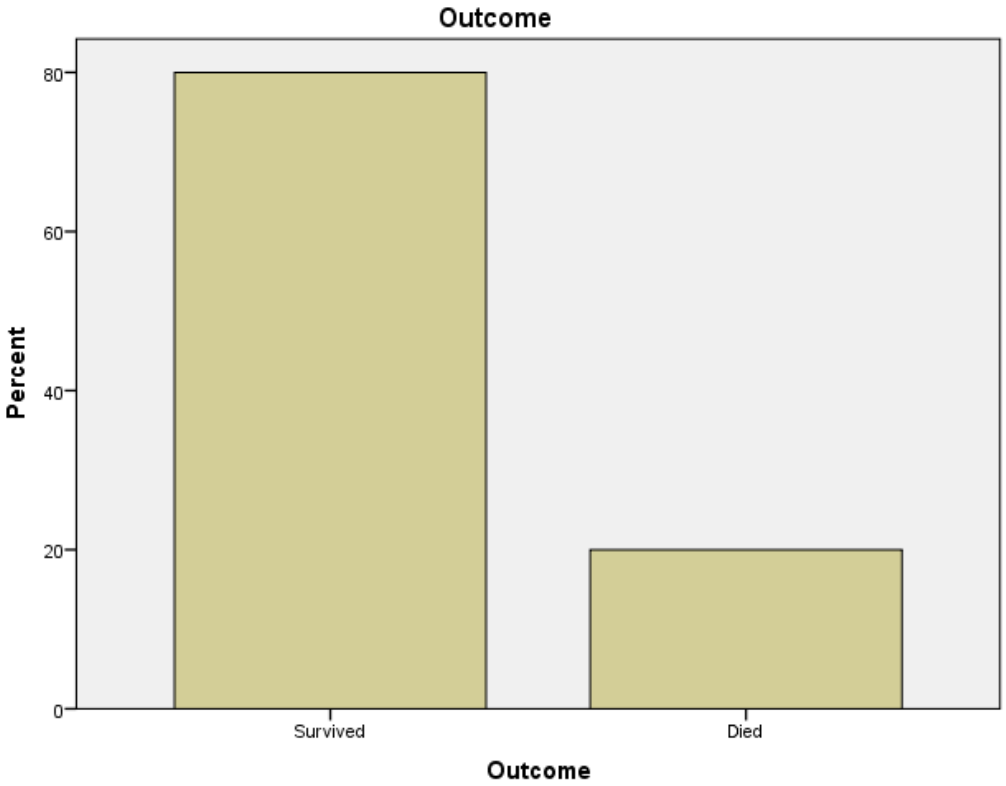

Figure 4, bar chart showing the outcome for <=16mmol/L

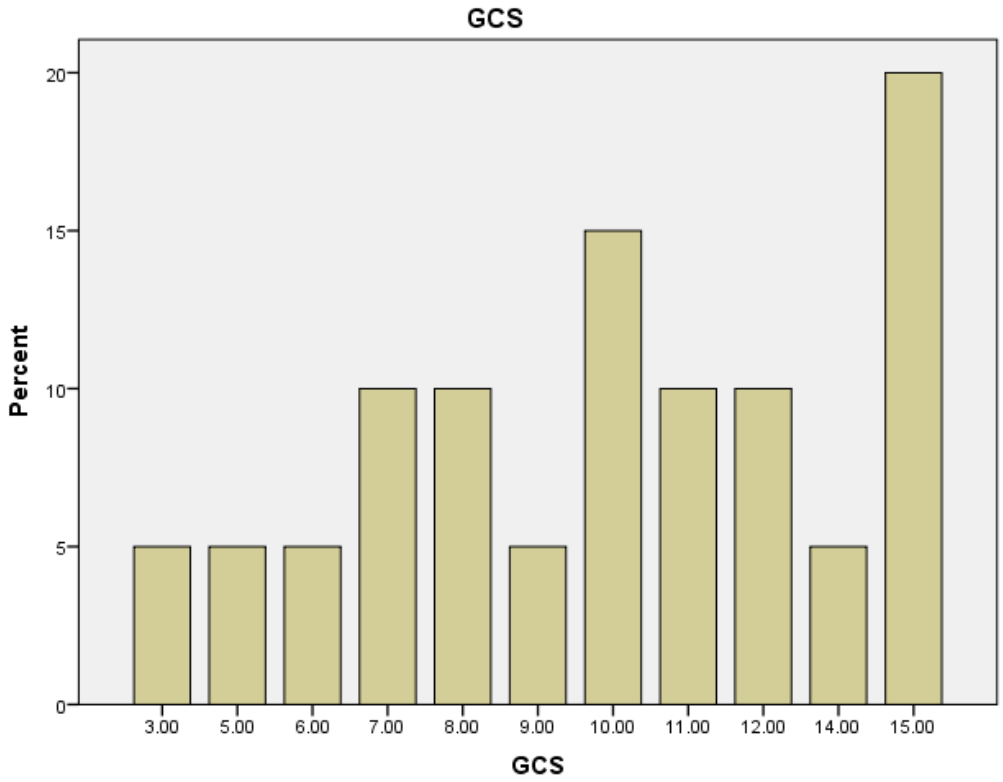

Figure 5, the bar chart of GCS for patients with AG <=16mmols/L

The association between GCS and Outcome showed that survival correlated with high GCS, p=0.010 which is statistically significant. The association between GCS and AG and showed that as AG increased GCS reduced, p=0.132.

For patients with AG >=16mmol/L

Statistics

		GCS	Outcome	AG
N	Valid	30	30	30
	Missing	0	0	0
Mean		8.3667	1.6333	21.6567
Median		8.0000	2.0000	21.2500
Mode		9.00	2.00	17.50[a]
Std. Deviation		3.69047	.49013	4.22959
Minimum		3.00	1.00	16.30
Maximum		15.00	2.00	35.00

a. Multiple modes exist. The smallest value is shown

Table 9, the Statistics of the Anion Gap for levels >=16mmol/L

AG

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	16.30	1	3.3	3.3	3.3
	17.30	1	3.3	3.3	6.7
	17.40	1	3.3	3.3	10.0
	17.50	2	6.7	6.7	16.7
	17.80	1	3.3	3.3	20.0
	17.90	2	6.7	6.7	26.7
	18.10	1	3.3	3.3	30.0
	18.70	1	3.3	3.3	33.3
	19.00	1	3.3	3.3	36.7
	19.70	1	3.3	3.3	40.0
	20.00	1	3.3	3.3	43.3
	21.00	1	3.3	3.3	46.7
	21.10	1	3.3	3.3	50.0
	21.40	1	3.3	3.3	53.3
	21.60	1	3.3	3.3	56.7
	22.00	1	3.3	3.3	60.0
	22.60	1	3.3	3.3	63.3
	23.00	2	6.7	6.7	70.0
	23.20	1	3.3	3.3	73.3
	23.60	1	3.3	3.3	76.7
	24.00	2	6.7	6.7	83.3
	24.70	1	3.3	3.3	86.7
	26.50	1	3.3	3.3	90.0
	28.40	1	3.3	3.3	93.3
	29.50	1	3.3	3.3	96.7
	35.00	1	3.3	3.3	100.0
	Total	30	100.0	100.0	

Table 10, the frequency table for Anion Gap >= 16mmols/L

Outcome

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Survived	11	36.7	36.7	36.7
	Died	19	63.3	63.3	100.0
	Total	30	100.0	100.0	

Table 11, the Outcome for Anion Gap >=16mmols/L

GCS

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	3.00	2	6.7	6.7	6.7
	4.00	4	13.3	13.3	20.0
	5.00	1	3.3	3.3	23.3
	6.00	3	10.0	10.0	33.3
	7.00	4	13.3	13.3	46.7
	8.00	2	6.7	6.7	53.3
	9.00	5	16.7	16.7	70.0
	10.00	2	6.7	6.7	76.7
	12.00	1	3.3	3.3	80.0
	13.00	1	3.3	3.3	83.3
	14.00	3	10.0	10.0	93.3
	15.00	2	6.7	6.7	100.0
	Total	30	100.0	100.0	

Table 12, the GCS of the patients >=16mmols/L

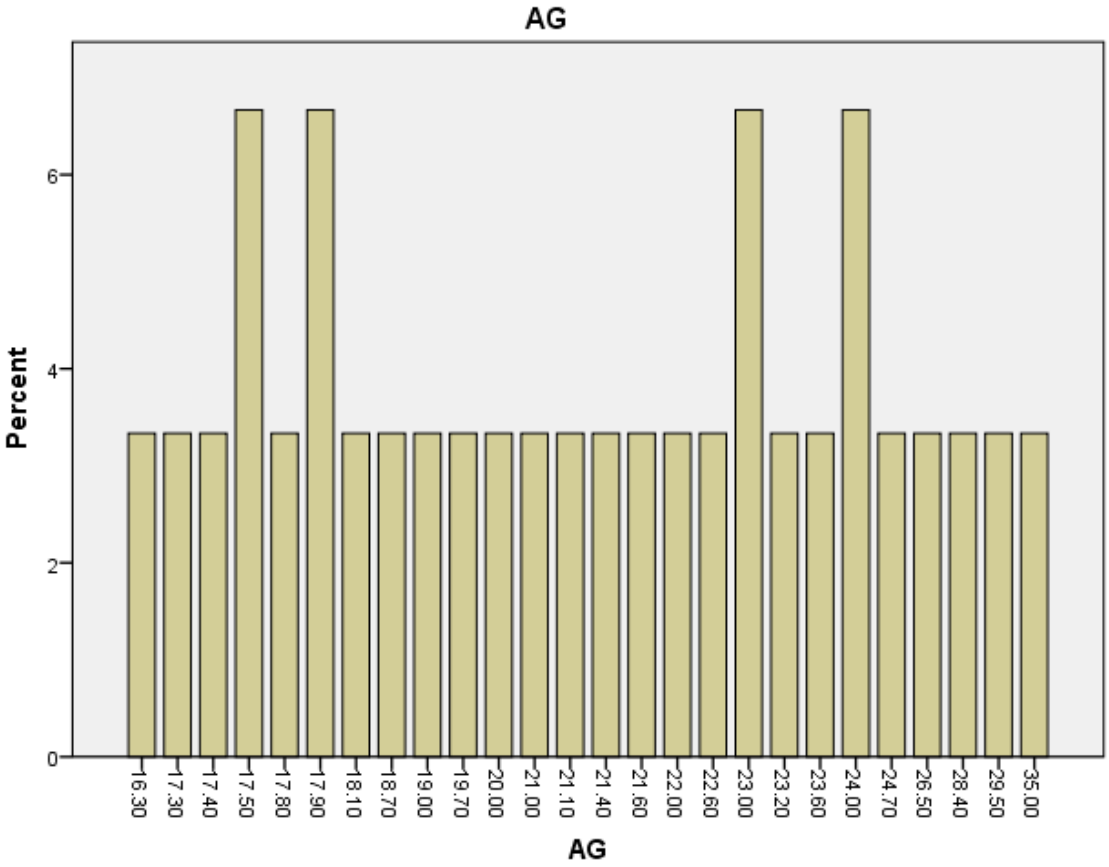

Figure 6, bar chart showing he anion Gap for level >=16mmols/L

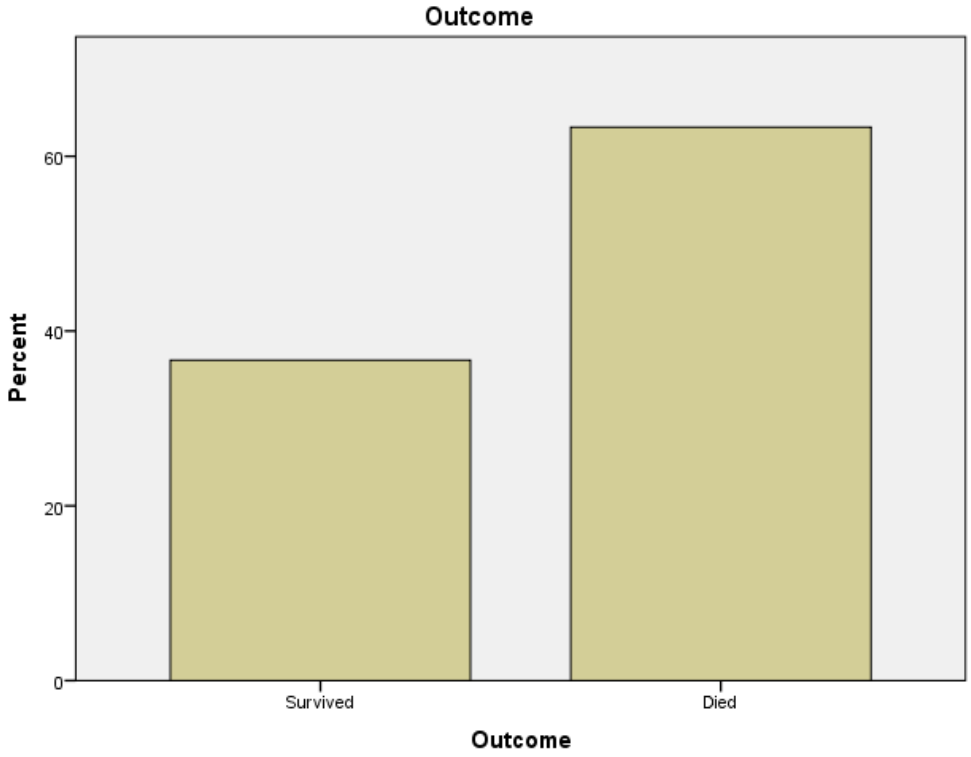

Figure 7, bar chart showing the outcome for levels >=16mmols/L

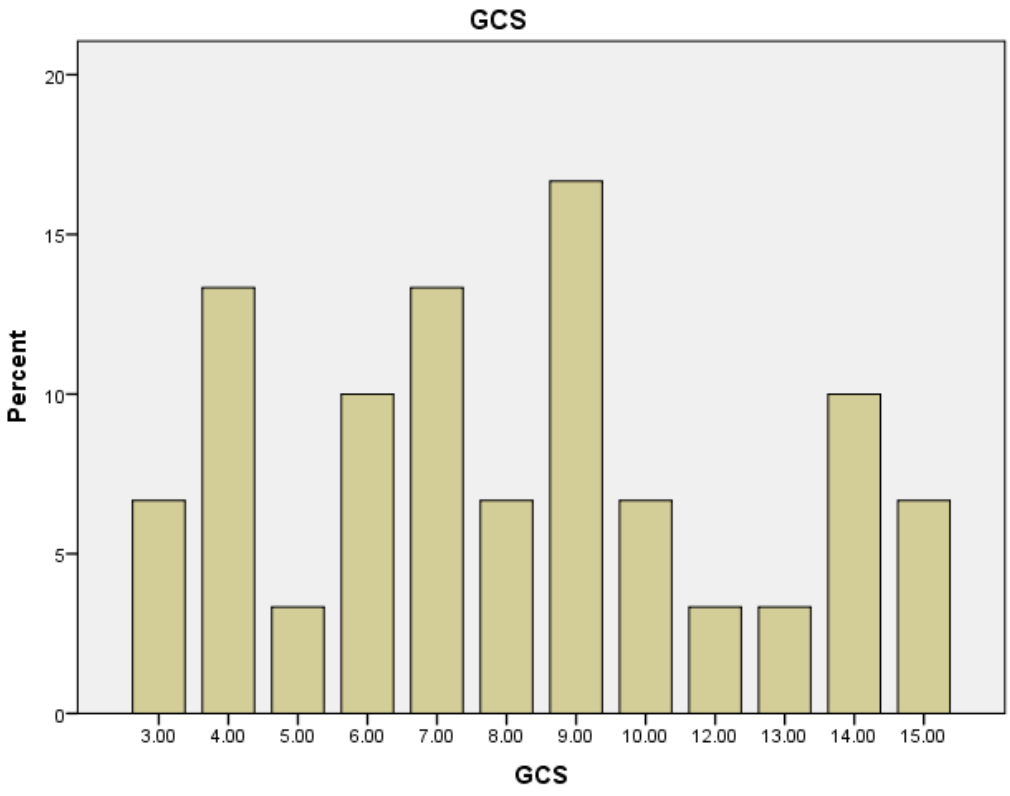

Figure 8, bar chart showing the GCS for patients with AG>=16mmols/L

The association between the Outcome and AG showed p=0.565

All patients
Fifty patients were studied. The mean for Anion Gap was 17.52, Standard Error of mean 0.994, Mean was 17.65, Mode 13.60, Standard Deviation was 7.3, the Minimum was -10, Maximum 35.

Table 1, statistics of the studied group. Table 2, the frequency of the Anion Gap for the whole group. The minimum Anion Gap was -10 (2%) and the Maximum was 35 (2%), Table 2. Table 3 showed the outcome.
27 (54%) patients survived, 23 patients (46%) died, Table 3.
Figure 1, overall outcome. Figure 2, bar chart showing the Anion Gap for all the patients.
Figure 3 depicting the histogram of the GCS for all the patients. Figure 4 bar chart showing the outcome
A correlation between Anion Gap and Outcome of all the patients showed that mortality was associated with increasing Anion gap, p=0.020, which is statistically significant.
The correlation between GCS and Outcome showed that mortality correlated with low GCS, p=0.001 which is statistically significant.
The correlation between the GCS and AG showed that the GCS reduced as the AG increased, p=0.022 which is statistically significant.

For Patients with Anion Gap <16mmol/L
Table 5,showed the statistics of the Anion Gap and Outome for patients with Anion Gap <16mmols/L. Table 6, the frequency of Anion Gap for patients with Anion Gap <16mmol/L. Table 7, the outcome for patients with Anion Gap <16mmol/L. Table 8, the GCS of patients with AG <=16mmols/L. Figure 5, bar chart of GCS for patients with AG <=16mmols/L. Figure 3, the outcome for patients with <16mmols/L.
The association between AG and outcome showed that mortality increased with increasing AG, p=0.361.
The correlation between the GCS and Outcome showed that mortality increased with reducing GCS, p=0.010 which is statistically significant.
The correlation between GCS and AG showed that as the AG increased the GCS decreased, p=0.132.

For patients with AG >=16mmols/L
Table 9 shows the statistics for Anion Gap and Outcome for patients with Anion Gap >16mmol/L. Table 10 shows the frequency of the Anion Gap. Table 11, shows the frequency the Outcome. Table 12, the GCS of the patients >=16mmols/L Figure 6, the bar chart for patients with AG >=16mmols/L. Figure 7 shows the Outcome for patients with AG >=16mmols/L.
Figure 8, bar chart showing the GCS for AG >=16mmols/L.
The association between the Anion Gap and Outcome showed Mortality was associated with increasing AG, p=0.565. The correlation between GCS and Outcome showed that mortality was associated with low GCS but p=0.081.The correlation between GCS and AG showed that the GCS reduced as the AG increased, but p=0.287

V. Discussion

Fifty patients were studied. Overall, the mean for Anion Gap was 17.52, Standard Error of mean 0.994, Mean was 17.65, Mode 13.60, Standard Deviation was 7.3, the Minimum was -10, Maximum 35. Table 1 shows the statistics of the studied group.
The minimum Anion Gap was -10 (2%) and the Maximum was 35 (2%), Table 2. 27 (54%) patients survived, 23 patients (46%) died, Table 3, Figure 1.
A correlation between Anion Gap and Outcome of the all the patients showed that the mortality associated with increasing anion gap was p=0.020, which is statistically significant.
This corresponds with the study done by Changli Zhong et al in which patients with higher AG levels had higher in-hospital (p = 0.006) and ICU mortality (p = 0.003).[17]
This also corresponds with J Shen et al. who stated that depending on the variable tested, there was an association between higher serum AG levels and hospital all-cause mortality in different subgroups.[18]
Survival correlated with higher GCS p=0.001 which is statistically significant.
There is a strong correlation between the GCS and AG level such that as the AG reduced the GCS improves p=0.02 which is statistically significant.

For Patients with Anion Gap <=16mmol/L
The association between AG and outcome showed that mortality increased with increasing AG, p=0.361. There is a strong correlation between GCS and outcome such that survival correlates with higher GCS p=0.010 which is statistically significant. The association between GCS and AG was 0.132

For patients with AG >=16mmol/L

The association between the Anion Gap and Outcome showed Mortality was associated with increasing AG, p=0.565. This corresponds with Changli Zhong et al who found that Multivariate analysis after adjusting for potential confounders indicated that high serum AG levels (≥16 mmol/L) were associated with increased risk of ICU and hospital all-cause mortality as compared to that with low serum AG levels (<16mmol/L). [19]

Also, our results corresponded with J. Shen et al, whose results indicated that the higher level of AG at admission predicted long-term poor outcomes in neurological and cognitive functions after ICH.[20]

Our findings agree with theirs when they stated that "in recent years, the age of onset of ICH has tended to be young. However, many patients have a history of underlying diseases such as hypertension, diabetes, hyperlipidemia, and respiratory diseases. These diseases influence the pathogenesis of ICH and impact the recovery status."[21] Because ICH usually leads to high rates of mortality and disability, accurate and timely diagnosis is the most important issue after the occurrence.[22]

Therefore, interventions for such underlying diseases and stabilization of homeostasis play extremely important roles in ICH. [23]

The impact of the hemorrhage may explain why the association between AG and Outcome was not significant in this study group compared with L. Shen et al. All patients recruited for their study received neurosurgical treatments for hematoma removal. Other adjuvant therapeutic treatments included drainage of CSF by lumbar puncture or lumbar cistern to reduce intracranial pressure[24]. In our own case, the patients were managed conservatively.

VI. Conclusion

There is need for an accurate non-invasive technique for measuring hemodynamic changes and prognostication in patients with spontaneous SAH. Several studies have found the importance of using a simple arithmetically derivable formula to get the AG which can serve the above functions. This study has also confirmed the importance of using the AG to monitor critical patients. It is not a substitute for surgical or other special life saving interventions like craniotomy, burrhole, EVD, lumbar puncture etc. neithr is it a substitute for neurological examinations like GCS, GOS, MMSE etc. Rather it is a useful adjunct to those procedures. We advocate its routine use in the Emergency, ICU or HDU as the case may be in assessing critical patients.

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