Effect of Comorbidities on the Outcome of Patients with Aneurysmal Subarachnoid Hemorrhage: A Prospective Observational Study

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Abstract

Background The pathophysiological changes following aneurysmal subarachnoid hemorrhage (aSAH) lead to a varied degree of neurological deficit and cognitive decline. The presence of comorbidities can contribute to the progression and course of the disease resulting in high morbidity and mortality.

Methods A total of 140 patients with aSAH, scheduled for surgical clipping or endovascular coiling were included. The patients' comorbidities were recorded. The postoperative outcome was evaluated using Glasgow Outcome Scale at 1 month following discharge. Multiple logistic regression analysis was performed to identify variables predicting poor outcome, taking into consideration those variables which were significant in univariate analysis.

Results Sixty-six percent of these patients with aSAH had associated comorbidities. In our patient cohort, we found that smoking and hypertension were associated with worse outcome (odds ratio [OR] = 4.63 [confidence interval [CI] = 1.83–11.7] and OR = 2.92 [CI = 1.41–6.01], respectively). Hypothyroidism, diabetes mellitus, coronary artery disease, and asthma did not influence the neurological outcome because of their small number.

Conclusion Presence of comorbidities like smoking and hypertension significantly worsen the outcome of these patients with aSAH.

Keywords
► aneurysmal subarachnoid hemorrhage
► comorbidities
► hypertension
► smoking
► Glasgow Outcome Scale

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating cerebrovascular condition distinguished by the extrava-sation of blood into the subarachnoid space in the setting of a ruptured cerebral aneurysm. It had an annual incidence of 6.1 per 100,000 population in 2010 and has continued to decline annually by 1.7%.[1] Although the incidence of aSAH in

India remains largely unknown, nonetheless, an autopsy study had documented the mean incidence of aneurysms in the Indian population to be 1%.[2]

The presence of comorbidities can have a direct or indirect contribution to the formation, progression, and course of the disease. Diseases such as hypertension (HTN), smoking, and diabetes mellitus (DM) may disrupt the balance between local hemodynamic stress and the strength of cerebral vessels at a molecular level and can contribute to its formation or rupture. The impact of comorbidities on the neurological outcome has shown variable and contradictory results. Avdagic et al, in their prospective observational study on 50 patients with aSAH, demonstrated a higher frequency of negative neurological outcome (Glasgow Outcome Scale [GOS] 1–3) in patients with HTN.[3] Smoking is associated with decreased odds of poor outcomes.[4] However, the relationship of type 2 DM with aSAH still remains uncertain.[5]

With the background of existing literature, we hypothesized that the presence of comorbidities in a patient with aSAH will influence the course of the disease and thereby the neurological outcome of patients. Hence, the present study was conducted to observe the impact of comorbidities on perioperative complications and neurological outcome of patients who were managed surgically or by endovascular coiling after aSAH.

Materials and Methods

This prospective observational study was performed in a tertiary care institute in India from November 2016 to October 2017 in adult patients (20–65 years of age) of both sexes scheduled for surgical clipping or endovascular coiling of cerebral aneurysm within 3 days of ictus. Patients with preexisting clinical and/or radiological evidence of hydrocephalus or vasospasm and those with preexisting intellectual disability were excluded from the study. Ethical clearance was received from the Institute Ethics Committee and written informed consent was taken from all the patients or their relatives.

The demographic, clinical, and radiological data of the patients were noted. It included the age, gender, Glasgow Coma Scale (GCS) at admission, Hunt and Hess scale (H and H), World Federation of Neurological Surgeons (WFNS) grade, Fisher grade, the size, and site of the aneurysm. Various comorbid illnesses reported were also recorded.

All the patients received either balanced inhalational or total intravenous anesthesia as per institutional protocol. In addition, all patients received 0.5 to 1 g/kg mannitol at the time of skin incision. Intraoperative complications such as hypotension, HTN, arrhythmias, and brain bulge were recorded. Temporary clipping time, intraoperative rupture, and blood loss were also recorded. Hypotension was defined as a fall in the mean arterial pressure (MAP) > 30% of the baseline preoperative value, sustained for > 5 minutes. This was managed with administration of crystalloid and/or blood based on blood loss assessment and arterial blood gas analysis; followed by noradrenaline infusion, if the blood

pressure was unresponsive to fluid administration/blood transfusion. HTN was defined as MAP > 30% of baseline preoperative value sustained for > 5 minutes and was managed with increasing the depth of anesthesia and analgesia, and/or by administration of a β-blocker.

The patients were followed up in the postoperative period in neurosurgical intensive care unit (NICU). Various postoperative complications including delayed cerebral ischemia, cerebral infarction, hydrocephalus, rebleed, pneumonia, and renal dysfunction were noted. Delayed cerebral ischemia was defined as the occurrence of fresh neurological deficit or a decrease of at least two points on the GCS which persisted for at least 1 hour, not apparent immediately after aneurysm occlusion, and could not be attributed to other causes including pharmacological sedation, hydrocephalus, seizures, and dislodgement of permanent clip. Hydrocephalus was diagnosed based on ventricular dilatation on noncontrast computer tomography (CT) of the head. Rebleeding was diagnosed based on the acute deterioration of neurological status accompanied by the appearance of new hemorrhage on head CT. Patients with a higher WFNS grade of subarachnoid hemorrhage (SAH), prolonged clipping time (more than 10 minutes), intraoperative aneurysm rupture with hemodynamic instability, grade 3 and 4 brain bulge, or massive blood loss, were electively ventilated postoperatively.[6] The total duration of postoperative ventilation, NICU stay and hospital stay, and the incidence of in-hospital mortality were recorded.

Following discharge, the patients were followed up telephonically a month later for assessment of the neurological outcome using the GOS.[7] Outcome was defined as a dichotomous variable (i.e., favorable outcome: GOS = 4–5, unfavorable outcome: GOS = 1–3).

Statistical Analysis

Quantitative data such as age, GCS, GOS, H and H, and WFNS grades are presented in descriptive form as either mean (±standard deviation), or median (±interquartile range [IQR]) if customarily distributed and skewed variables, respectively. The normalcy of quantitative data was checked using the Kolmogorov–Smirnov test. For normally distributed quantitative data, means were compared using unpaired Student's "t" test for two groups. For skewed data, Mann–Whitney test was applied. A paired t-test or Wilcoxon signed-rank test, whichever appropriate, was applied to compare the follow-up means or median, respectively. Qualitative or categorical variables such as sex, Fisher grade, comorbidities, type of procedure, and mortality causes were described as frequencies and proportions. Proportions were compared using chi-square or Fisher's exact test, whichever applicable. Univariate analysis followed by multiple logistic regression analysis was performed to identify variables predicting poor outcome, taking into consideration those variables which were significant in univariate analysis. These variables were selected based on clinical impression and previous research.[3,8] The number of patients who underwent coiling was much lesser than the patients who underwent clipping.
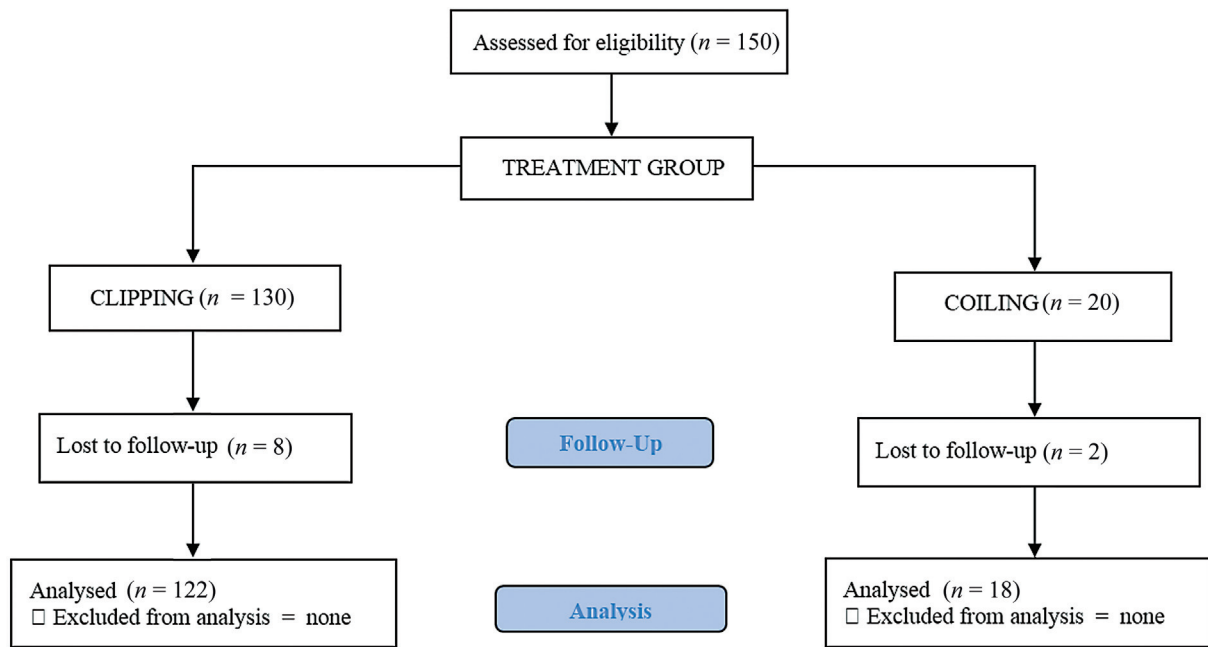
Fig. 1 CONSORT diagram.

As a result, the analysis was performed grouping the patients undergoing clipping and coiling together. All tests were two-tailed with a 95% confidence interval (CI) and a level of significance of 5% ($p < 0.05$). Data were analyzed using SPSS Version 22 and Microsoft Excel 2010.

Results

A total of 150 patients with aSAH were enrolled in the study. However, 140 patients were analyzed (►**Fig. 1**).

Baseline Data
One hundred and twenty-two (87.1%) patients underwent surgical clipping and 18 (12.9%) endovascular coiling. The baseline demographic, radiological, and clinical characteristics of patients are described in ►**Table 1**. The median WFNS grade of the cohort was 2 with an IQR of 1 to 2, suggestive of good grade patients. The H & H grade and modified Fisher grade values are described in ►**Table 1**.

Out of the total 140 patients analyzed, 47 (33.6%) had no comorbidities while 93 (66.4%) had at least one comorbidity.

Table 1 Baseline demographic, radiological, and clinical characteristics

Parameter	Clipping n = 122	Coiling n = 18
Sex (male/female)	41/81	5/13
Age (y)	50.96 ± 11.8	50.17 ± 12.1
GCS at admission	15 (14–15)	14 (9–15)
H & H	2 (2–3)	2 (2–4)
WFNS	2 (1–2)	2 (1–4)
Modified Fisher grade	3 (3–4)	3 (2–4)
Size of aneurysm (small/large/giant)	115/7/0	16/0/2
Site (with single aneurysm) (ACOM/MCA/ICA/ACA/PCOM/DACA/PICA/Basilar)	39/33/11/8/6/5/2/1	5/4/5/0/0/0/0/1
Number of aneurysms (2/> 2)	11/8	1/0

Abbreviations: ACA, anterior cerebral artery; ACOM, anterior communicating artery; DACA, distal anterior cerebral artery; H & H, Hunt & Hess; GCS, Glasgow Coma Scale; ICA, internal carotid artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; PICA, posterior inferior cerebellar artery; WFNS, World Federation of Neurosurgeons.
Note: Data are presented as number or percentage, mean ± standard deviation or median (Interquartile range). N (%), number or percentage of patients.

Table 2 Distribution of comorbidities

Comorbidity	Total $n=140$	Clipping $n=122$	Coiling $n=18$
Hypertension	64 (45.7%)	57 (46.7%)	7 (38.8%)
Smoking	30 (21.4%)	26 (21.3%)	4 (22.2%)
Alcohol intake	21 (15%)	18 (14.7%)	3 (16.7%)
Diabetes mellitus	13 (9.3%)	10 (8.1%)	3 (16.7%)
Hypothyroidism	9 (6.4%)	8 (6.5%)	1 (5.6%)
Connective tissue disorders	5 (3.6%)	3 (2.4%)	2 (11.1%)
Coronary artery disease	5 (3.6%)	3 (2.4%)	2 (11.1%)
Asthma	3 (2.1%)	3 (2.4%)	0
Others	15 (10.7%)	12 (9.8%)	3 (16.7%)

Note: Data are represented as number or percentage. Some patients had more than one comorbid condition.

Among these 93 patients, 49 (52.6%) had more than one comorbidity. The two most common comorbidities noted were HTN (64 [45.7%]) and smoking (30 [21.4%]). The frequency distribution of various other comorbidities is shown in ►**Table 2**.

Intraoperative Data

Five patients (3.57%) had HTN, whereas 17 patients (14%) suffered hypotension. Of the 17 patients with hypotension, none was from intraoperative aneurysm rupture, while 8 out of the 17 patients responded to boluses of crystalloid, 9 required blood transfusion, and none of them needed inotropes. The average temporary clipping time was 7.91 ± 8.25

minutes. Intraoperative rupture (IOR) of an aneurysm occurred in 53 (42.5%) patients during aneurysm clipping. However, there was no hemodynamic instability during and following IOR in any patient (►**Table 3**).

Postoperative Course

During the postoperative period 90 (64.3%) patients developed some complications until discharge to home. The most frequent complication encountered was delayed cerebral ischemia, which occurred in 72 (51.4%) patients, out of which 33 (45.8%) patients subsequently developed cerebral infarct. Other complications recorded have been described in ►**Table 3**. The median number of ventilation days, intensive care unit

Table 3 Intraoperative and postoperative events

Parameter	Clipping N (%)/median (IQR)	Coiling N (%)/median (IQR)
Hypertension	3 (2.5)	2 (11.1)
Hypotension	17 (14)	0
Intraoperative aneurysm rupture	53 (42.7)	–
Brain bulge	25 (20)	–
Temporary clipping time (min)	7.9 ± 8.25	–
Blood loss (mL)	305.4 ± 285	77.8 ± 37.3
Vasospasm	63 (51.6)	9 (50)
Cerebral infarction	33 (27)	0
Hydrocephalus	19 (15.6)	4 (22.2)
Rebleed	18 (14.8)	3 (16.7)
Pneumonia	14 (11.5)	1 (5.6)
Renal dysfunction	3 (2.5)	0
Tracheostomy	58 (47.55)	7 (38.89)
Mechanical ventilation (d)	4 (2–10)	1 (1–7)
Duration of ICU stay (d)	7 (5–15)	4 (4–10)
Duration of hospital stay (d)	15 (10–20)	10 (7–16)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.
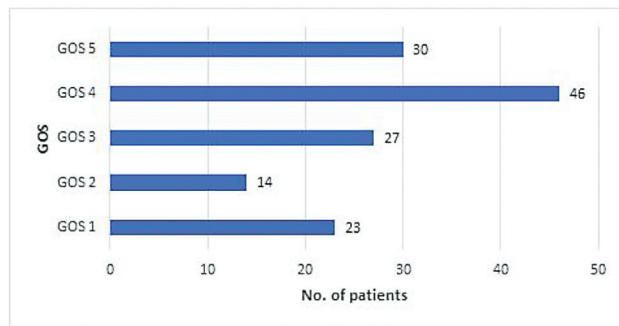Note: Data are presented as number (percentage) or median (interquartile range).

Fig. 2 Follow-up Glasgow Outcome Scale (GOS).

days, and duration of hospital stay were 4 (3.5–6), 7 (5–15), and 10 (8–14), respectively. In view of poor GCS and anticipated poor neurological outcome 65 (46.4%) patients required tracheostomy in the postoperative period (►Table 3). The overall in-hospital mortality was 13.5% (19) in our study population. The median duration of hospital stay for the survivors was 15 days, ranging from 5 to 44 days.

Follow-Up Outcome

The median GOS score was 4 with an IQR of 2 to 4. The overall frequencies of different GOS score is shown in ►Fig. 2. It was found that the majority of patients had a GOS score of 4/5 (32.8%/21.4%). The mortality at 30 days among those with any comorbidity was 18.3%, while it was 12.7% among the patients who did not have any comorbidity. Among the patients without comorbidity, complications in decreasing order of frequency were: vasospasm – 13 (27.7%), rebleed – 8 (17%), hydrocephalus – 4 (8.5%), cerebral infarct – 3 (6.4%), sepsis – 3 (6.4%), and renal dysfunction – 1 (2.1%).

Overall, patients with comorbidities were more likely to have a poor outcome (GOS 1–3) with odds ratio (OR) of 3.2, in comparison with patients without any comorbidity.

Following univariate analysis of different comorbidities, clinical and radiological factors to assess the effect on the outcome in aSAH, it was observed that smoking, HTN, and coronary artery disease (CAD) were associated with poor outcome with an OR of 4.45 (1.81–10.9), 2.81 (1.41–5.59), and 14.14 (0.77–260.87), respectively (►Table 4). Further, multivariate regression analysis showed that smoking and HTN were independently associated with poor outcome with an adjusted OR of 4.63 (1.83–11.7) and 2.92 (1.41–6.01), respectively. In our study cohort, hypertensive patients were found to have higher odds of cerebral infarct with an OR of 2.2 (1–4.8). Smokers, on the other hand, had higher odds of a rebleed with an OR of 4.5 (1.68–12).

Discussion

A gamut of congenital and acquired illnesses and risk factors are commonly associated with SAH. Among the acquired ones, HTN and cigarette smoking have been identified as the most common modifiable risk factors.[9] HTN (45.7%), followed by smoking (21.4%) were most common associated comorbidities with aSAH patients in the present study.

Presence of comorbidities has been shown to influence the neurological outcome following aneurysmal clipping and after endovascular coiling. In the present study, it was observed that HTN increases the odds of a worse outcome at 1 month following discharge. Jaja et al too in a meta-analysis concluded that premorbid HTN is a weak, yet independent predictor of poor outcome.[10] Thus, our observations are in consonance with the findings of these various previous studies.

Table 4 Predictors of a poor outcome following aSAH

Variable	Univariate Odds ratio (95% CI)	p-Value	Multivariate Adjusted odds ratio (95% CI)
Age	0.50 (0.20–0.33)	0.629	–
Admission GCS	2.86 (0.53–1.96)	0.001[a]	–
H & H	7.24 (1.38–5.61)	0.001[a]	–
WFNS	5.91 (1.16–5.34)	0.002[a]	–
Fisher	8.26 (1.91–22.7)	0.021[a]	–
Smoking	4.45 (1.81–10.9)	0.001[a]	4.63 (1.83–11.7)
Hypertension	2.81 (1.41–5.59)	0.003[a]	2.92 (1.41–6.01)
Alcohol intake	2.16 (0.8–5.61)	0.106	–
Diabetes	1.01 (0.32–3.2)	0.973	–
Hypothyroidism	1.52 (0.39–5.93)	0.609	–
Connective tissue disease	0.78 (0.12–4.84)	0.794	–
Coronary artery disease	14.14 (0.77–260.87)	0.013[a]	–
Asthma	0.58 (0.052–6.63)	0.663	–

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; CI, confidence interval; GCS, Glasgow Coma Scale; H & H, Hunt & Hess; WFNS, World Federation of Neurosurgeons.
[a]p-Value < 0.05 was considered statistically significant.

Chronic HTN induces hypertrophy of arteriolar smooth muscle, leading to rightward shift of the cerebral autoregulation curve. The associated arterial narrowing renders these patients more vulnerable to cerebral ischemia/infarction after aSAH in the postoperative period. The same has been demonstrated in the present study and is consistent with the reports by Juvela et al and Jaja et al.[10–12] The higher odds of postoperative cerebral infarction may explain the worse neurological outcome among hypertensive patients. A recent retrospective cohort study which included 1,275 aSAH patients and conducted over a period of 13 years, also reported HTN as a significant predictor of stroke, myocardial infarction, and all-cause mortality.[13]

In contrast to the previous studies and the results of the present study, Hammer et al observed HTN as a predictor of good clinical outcome.[14] The variable effect of HTN in different ethnic groups could be due to the role of genetics, differences in dietary and cooking habits, environmental exposure, and type of initial treatment received.[15,16]

Rinkel et al found that patients on anticoagulant therapy following myocardial ischemia, CAD, atrial fibrillation, and valve prosthesis, etc. were associated with unfavorable outcomes following aSAH.[17] In our study, CAD was statistically significant upon univariate analysis. However, since the number of patients with CAD was less ($n = 3$), this could be an incidental finding. Therefore, greater number of patients with CAD could substantiate the above finding.

Different studies on effect of smoking in aSAH patients have produced diverse results, ranging from good outcome to poor outcome/death.[4,14,18–20] Our study showed that smoking was associated with poor outcome in this patient population. Enhanced systemic coagulation, inflammation within the arterial wall, endothelial dysfunction, and elastin degradation, in smokers, might contribute to a poor outcome,[19] while neuroprotection secondary to anti-inflammatory and neurogenic vasodilatory effects mediated by nicotinic acetylcholine receptors on intracranial vessels could explain the above findings.[20] In contrast to the previous studies and the results of the present study, Hammer et al in the monoethnic German population reported an association of smoking with a good outcome.[14] Differences in the ethnicity of populations, presence of risk factors, environmental, socioeconomic differentiation, and cultural variations may also account for the heterogeneity in the results obtained.[21]

Chronic alcoholic intake too has been proven to be a risk factor for the development of aneurysm secondary to its effect on blood pressure, platelet function/clotting factors, and alterations in cerebral blood flow.[22–24] Worse outcome has been documented as a result of significant rebleeding and delayed ischemia in patients who had history of heavy alcohol intake.[25] However, probably our patients were not heavy consumers of alcohol, therefore history of alcohol intake was not associated with poor GOS at a 1-month follow-up. Similar findings were also noted by Sodhi et al.[8]

DM did not lead to worse outcome in our study as was also observed by Sodhi et al.[8] However, outcome following aSAH in a diabetic might depend upon duration and extent of control of DM. A previous meta-analysis of 17 studies which included 4,095 patients, showed that hyperglycemia was associated with higher odds of poor outcome (OR 3.1, 95% CI 2.3–4.3).[26] Hyperglycemia upholds secondary brain injury by promoting an oxidative state, enhancing matrix metalloproteinase activity, intravascular coagulation abnormalities, and metabolic dysfunction.[27–29] In addition, hyperglycemia aggravates brain edema, culminating in neuronal cell death, thus contributing to a worse neurological outcome.[30]

Avdagic et al too showed that nondiabetic patients have a better outcome than those with diabetes.[3] However, only 2% patients had DM in their study which makes interpretation difficult.

Hypothyroidism has been associated with vascular endothelial dysfunction due to impaired metabolism, abnormal mucopolysaccharide deposition in vessel walls, and aneurysm formation. Atchaneeyasakul et al suggested that hypothyroidism was independently associated with unruptured cerebral aneurysms.[31] However, its association with outcome is not yet studied. However, with very small number of hypothyroid patients in the present study, it will not be prudent to draw any conclusion from our study.

Different studies have demonstrated an association between connective tissue disorders like autosomal dominant polycystic kidney disease and Marfan's disease, with the risk of developing aneurysms. However, the association between connective tissue disorders with outcomes in aSAH patients has not been demonstrated.

Our study has several limitations. First, an intervention was performed in good-grade patients as is the standard of care in most neurosurgical centers. Thus limiting the generalization of results to all grades of aSAH. Second, there was a lack of a sufficient number of patients with specific comorbidities such as CAD, asthma, connective tissue disorders, and hypothyroidism. Third, recreational drug or ghutka abuse was not considered. Fourth, the inability to stratify the various comorbidities based on the severity and duration limits our ability to determine how the severity of the disease may affect the outcome. Similarly, the lack of quantification of smoking in terms of number of cigarettes smoked per day, and alcohol intake in terms of amount and years of consumption, could have influenced the results. Further studies with large number of patients with other comorbidities (connective tissue disease, hypothyroidism, and consumption of recreational drugs), are recommended.

Conclusions

The existence of comorbidities might influence the perioperative complications which can lead to a negative impact on the long-term neurological status despite successful surgical or endovascular intervention. Smoking and HTN are associated with poor neurological outcome in the current study.

Conflict of Interest
None declared.

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