

Predictors of Mortality in Spontaneous Intracerebral Hemorrhage Cases

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ABSTRACT

Aim and objectives: This study was done with the aim of finding clinical and radiological correlation of patients with spontaneous intracerebral hemorrhage (SICH) and its correlation with 90-day mortality. The primary objective was to study the clinical, laboratory and radiological predictors of mortality in patients of intracerebral hemorrhage. The secondary objective was to compare 90-day mortality in patients with spontaneous intracerebral hemorrhage with that to coagulopathy related intracerebral hemorrhage.

Methods: This was a longitudinal, observational study carried out from June 2020 to June 2022 at Govt hospital situated in North India. The relevant history and clinical examination was done according to pre designed and pretested protocol. All patients underwent non-contrast computerized tomography imaging, their Glasgow coma scale score and intracerebral hemorrhage score were noted. For the sake of coagulopathy related intracerebral hemorrhage, the patients were classified as taking single antiplatelet, dual antiplatelet agents and oral anti-coagulant drugs. These patients were followed up daily during the hospital stay and regularly thereafter until 90 days. Functional outcome of patients was determined by modified Rankin's scale at 30 days and 90 days. The statistical analysis was done using SPSS software.

Results: A total of 235 cases were studied. 202 patients were detected to have hypertension, out of which 25 (12.37%) deaths were recorded within 48hrs of admission, 77 (38.1%) and 85 (42%) of patients with hypertension had died at 30 days and 90 days respectively. Similarly, out of 40 diabetics in this cohort, 15 (37.5%) and 18 (45%) deaths occurred at 30 and 90 days. 97 out of 235 cases who consumed alcohol, 56 (57.7%) and 61 (62.9%) died at 30 and 90 days. Among 52 smokers in this study, 21 (40.4%) and 24 (46.2%) died at 30 and 90 days. Death at 30 and 90 days was significantly more among subjects with intracerebral hemorrhage score of 3 or more with P value of 0.001 and also in patients with GCS score less than 8. Higher mortality rates were seen among subjects with modified Rankin's scale (mRS) score 6 with P value of 0.001 at 30 days. Total number of coagulopathy related intracerebral hemorrhage cases were 99/235. On radiological correlation between spontaneous intracerebral hemorrhage and coagulopathy related intracerebral hemorrhage, this study did not find any strong correlation. The P value was 0.913 at 30 days and 0.961 at 90 days.

Conclusion: This study found that comorbidities like hypertension and type 2 Diabetes mellitus were significant predictors of mortality in spontaneous intracerebral hemorrhage cases. The significant correlation was also found between consumption of alcohol and smoking with mortality in intracerebral hemorrhage cases. The 30 and 90-day mortality was significantly among subjects with ICH score 3 or more and also in patients with GCS score less than 8. Similarly, higher mortality is seen with higher modified Rankin score at 30 days. On radiological examination, the Intra cerebral bleed volume greater than 30 ml was greatest predictor of death. This study did not find coagulopathy as a strong predictor of mortality when compared with spontaneous modified Rankin score. Similarly, the location of intra cerebral bleed was not associated with higher mortality in this study.

Keywords: Glasgow Coma Scale score (GCS), spontaneous intra cerebral hemorrhage (SICH), intracerebral hemorrhage score (ICH), modified Rankin score (mRS), cerebro-vascular accidents (CVA). Dual antiplatelet (DAPT), oral anticoagulant (OAC). Activities for daily living (ADL).

Introduction

Intracerebral hemorrhage (ICH) means bleeding occurring in the brain parenchyma. It may be primary, spontaneous, or non-traumatic. It is the usually fatal, where 30-day mortality is up to 40% and severe disability in remaining survivors¹. Elderly, hypertension, and patients on oral anticoagulant treatment (OAT) are important risk factors for this disease.^{2, 3, 4}. ICH is an important problem in India, with annual incidence of 10–30/100,000 population^{5,6,7}. It accounts for 15 million strokes per year in the world out of which, 35–50% of patients die in 30 days.^{8,9,10} In Asia incidence of ICH is twice as high as in Western countries.¹¹

The common clinical presentation of ICH are focal neurological deficits, severe headache, nausea, vomiting, vertigo, systolic blood pressure greater than 220 mmHg, and sudden onset decreased consciousness. The common causes of ICH are hypertensive (spontaneous) ICH, ruptured saccular aneurysm, vascular malformations or hemorrhages associated with bleeding disorders.

Computerized tomogram (CT) scan and magnetic resonance imaging (MRI) have facilitated in locating and assessing the extent of ICH and also aids in prognosis. Even after numerous randomized therapeutic trials for ICH it is not clear whether surgical or medical treatments is conclusively beneficial to these patients.^{12,13} In a recent study, early surgical intervention has shown significant improvement in clinical outcome¹⁴.

There is 18 % rise in hospital admissions for ICH, mainly due to increases in elderly population, inadequate blood pressure (BP) control, and rise in use of anticoagulants, and antiplatelet agents.^{15,16} on the other hand there are other studies where decrease in incidence have been recorded primarily due to improved access to medical care and BP control^{17, 18, 19}. Thus, this study was conceived with aim to study, the clinical and radiological profile of patients with ICH.

Aim & Objectives

The aim of this study was to study the clinical and radiological correlation of patients with spontaneous ICH and its correlation with 90-day morbidity. The primary objective was to study the clinical characteristics, laboratory and radiological profile in patients of ICH with the secondary objective of studying the morbidity profile of ICH patients at 90 days from onset and to compare 30-day morbidity in patients with spontaneous ICH with coagulopathy related ICH.

Materials and Methods

This study was conducted at tertiary care Govt hospital situated in north India. This was a longitudinal, observational study carried out from June 2020 to June 2022. All patients of ICH aged more than 18 years, reported to hospital during the study period were enrolled. The exclusion criteria were aneurysmal or sub-Arachnoid Hemorrhage, Extradural Hemorrhage, Intracranial tumors, Head Trauma or patients unwilling for study. IEC clearance obtained vide letter no 154/2020 dated 04/12/2020. The sample size of 40 was calculated based on previous study²⁰. All patients presenting with and fulfilling the inclusion criterion were included in this study after obtaining informed consents. Detailed relevant history and clinical examination was done according to predesigned and pretested protocol. All patients underwent non contrast computed tomography (NCCT) imaging, Glasgow Coma Scale (GCS) score and ICH score were noted for each patient. They were investigated with hematological and biochemical parameters, and chest X-ray, electrocardiogram (ECG), urine examination was done. CT scan features of hematoma in volume and location were recorded. Other parameters in the CT scan included were the presence of ventricular extension, presence of midline shift and inferences correlated with prognosis. The volume of hematoma was calculated by using formula $(A \times B \times C / 2 = \text{length} \times \text{width} \times \text{thickness} / 2 \text{ in cm}^3)$. The other investigations as and when required like CT Angiography and MR Angiography were done according to requirement and whenever possible. The patients were managed during the hospital stay with adequate control of hypertension as target BP 160/90 mm Hg, treatment of raised intracranial pressure, maintenance of fluid and electrolyte balance, maintenance of airway, and general supportive measures were provided and noted. The treatment of inter current infections and associated complications were also treated as per requirements. All the patients were followed up daily during the hospital stay and regularly thereafter until 90 days. Functional outcome of patients was determined by modified Rankin's scale (mRS) at 30 days and 90 days. The statistical analysis was done using SPSS software. The level of statistical significance was set at p value <0.05.

Results:

In this study, a total of 235 cases were studied from 01 July 2020 to 30 April 2020. Out of these 150 (63.82%) cases were males. The average age in cohort aged above 60 years was 70 and aged below 60 years was 48 years. The total number of cases which were more than 60

years of age were 49.36%. Number of deaths when age greater than 60 years were 44 (37.9%), and 50 (43.1%), at 30 and 90 days respectively. 202 patients were detected to have hypertension, out of which 25 (12.37%) deaths recorded within 48hrs of admission, 77 (38.1%) patients had died at 30 days and 85 (42 %) at 90 days. Similarly, out of 40 diabetics in this cohort, 15 (37.5 %) deaths were recorded at 30 days and 18 (45 %) at 90 days. 03 of 235 patients had more than three

comorbidities. The common risk factors noted in this study were consumption of alcohol in 97 (41.27 %) and smoking history in 52 (22.12%) cases. 97 of 235 cases who consumed alcohol, 56 (57.7%) died at 30 days and 61 (62.9%) died at 90 days. Among 52 smokers in this study, 21 (40.4%) died at 30 days and 24 (46.2%) died at 90 days. The detailed distribution of these patients is described in table 1.

Table 1: The details of Baseline characters

Characteristic	No.	%
Age		
<60 Yrs	119	50.63
>60 Yrs	116	49.36
Sex		
Male	150	63.82
Female	85	36.17
Comorbidity		
HTN	141	60
HTN + DM	36	15.31
NIL	25	10.63
HTN+CAD	19	8.85
CAD	7	2.97
HTN+hypothyroidism	3	1.27
HTN+DM+CAD	2	.85
HTN+DM+CAD+ hypothyroidism	1	0.42
DM+CAD	1	.42
Risk Factors		
Alcohol	97	41.27
Smoking	52	22.12

The most common symptom in this study was hemiparesis which was seen in 207 (88.1%) cases. It was followed by facial deviation in 189 (80.4%) cases and speech abnormalities in 157 (66.8%) cases. The other symptoms were nausea and vomiting, loss of consciousness, headache, cranial nerve palsy, sensory loss, seizure, bowel involvement, gum bleed and chest pain. The commonest sign was High blood pressure, which was

seen in 197 (83.8%) cases. It was followed by speech abnormalities in 157 (66.8%) and loss of consciousness in 123 (52.3%) cases. The other clinical signs noted in this study were loss of motor power, cranial nerve palsies in 95 (40.4%), Cushing reflex in 58 (24.7%), papilledema in 33 (14 %), raised jugular venous pressure in 30 (12.8%), and ataxia in 14 (6%) cases. The details of these symptoms and signs are placed in table 2.

Table 2: The details of symptoms and signs noted in the study group

Symptoms	Frequency	Percent	Signs	Frequency	Percent
Hemiparesis	207	88.1%	BP >160	197	83.8%
Facial deviation	189	80.4%	Slurred speech	157	66.8%
Speech abnormality	157	66.8%	Loss of consciousness	123	52.3%
Nausea/ Vomiting	133	56.6%	Power < 3	101	43.0%
Loss of consciousness	123	52.3%	Cranial nerve palsy	95	40.4%
Headache	115	48.9%	Cushing reflex	58	24.7%
Cranial nerve	95	40.4%	Papilledema	33	14.0%
Sensory loss	18	7.7%	JVP	30	12.8%
Seizure	12	5.1%	AF	28	11.9%
Bowel/ bladder	4	1.7%	Ataxia	14	6.0%
Gum bleed	4	1.7%	Bruit	0	0.0%
Chest pain	1	0.4%	Murmur	0	0.0%

The average GCS score in cohort of 235 cases was 9.41. On correlation, we found higher rates of morbidity and mortality with GCS less than 8. For GCS less than 8 death at 30 days was seen in 66 (58.9%) patients while 44 (39.3) were dependent for ADL and independent for ADL were 2(1.8%). Similarly at 90 days the death was seen in 74 (60.2%) patients while 34(27.6%) were dependent for ADL and independent for ADL were 4 (3.3%) patients. For GCS greater than 8 at 30

days in this subset deaths were 19 (15.4%), dependent for ADL were 80 (65%) and independent for ADL were 24 (19.5%). The p value was 0.000. In same cohort at 90 days, death was seen in 20 (16.3%) patients, dependent for ADL were 77 (62.6%) and independent for ADL were 26 (21.1%) patients. The p value was 0.001. The details of mortality correlation with GCS was placed at table 3.

Table 3: The correlation of mortality with GCS at presentation in the study group

GCS at admission	Outcome 30 Days			Outcome 90 Days		
	Death	Dependent	Independent	Death	Dependent	Independent
	=85 (36.17 %)	=124 (52.76 %)	=26 (11.06 %)	=94 (40 %)	=111 (47.23 %)	=30 (12.76 %)
Score >=8=123	19	80	24	20	77	26
	15.40%	65.00%	19.50%	16.30%	62.60%	21.10%
Score <=7=112	66	44	2	74	34	4
	58.90%	39.30%	1.80%	60.20%	27.60%	3.30%
Chi-square value	54.6601			63.43		
p-value	0.000**			0.001*		

In 235 cases, more than 30 ml volume of intracerebral bleed were detected in 126 cases. The mortality in these cases at 30 days was 82 (65.1%) and 91 (72.2%) at 90 days. In 109 cases where bleed was less than 30 ml, the 30-day mortality was 3 (2.8%) and 2.8 % at 90 days. The Intracerebral bleed volume greater than 30ml was strongly associated with death. The p value was 0.001. This study did not find any correlation between location of intracerebral bleed and

outcome at 30 days and 90 days. The P value been 0.213 at 30 days and 0.205 at 90 days. The details are placed in table no 4. This study also found significant mortality in cases where ICH was found with mass effect on NCCT Head at admission. The p value been 0.001 on radiological correlation between spontaneous and coagulopathy in cases of ICH, this study did not find any strong correlation. The P value been 0.913 at 30 days and 0.961 at 90 days.

Table 4: the correlation between volume of bleed and outcome at 30 & 90 days

Volume	Outcome at 30 days			Outcome at 90 days		
	Death	Dependent for ADL	Independent for ADL	Death	Dependent for ADL	Independent for ADL
< 30 ml	3	80	26	3	77	29
	2.8%	73.4%	23.9%	2.8%	70.6%	26.6%
> 30 ml	82	44	0	91	34	1
	65.1%	34.9%	0.0%	72.2%	27.0%	0.8%
Total	85	124	26	94	111	30
	36.2%	52.8%	11.1%	40.0%	47.2%	12.8%
p-value	0.001*			0.001*		

ICH bleed volume greater than or equal to 30 ml was significantly associated with death. The p value was 0.001

The average ICH score in this study was 2.29 at 30 days. Death at 30 and 90 days was significantly more among subjects with ICH score of 3 or more with P value of 0.001. Higher mortality rates were seen among subjects with mRS score 6 with P value of 0.001 at 30 days. The average mRS score at 30 days was 4.69 and at 90 days was

3.94. In 235 cases, outcome at 90 days for spontaneous ICH 136, resolved 81 (59.6%) and non-resolved 55 (40.4%) patients. Coagulopathy ICH 99 resolved 60 (60.6%) and non-resolved 39 (39.4%) patients. The details of correlation between ICH and mRS with mortality are placed in figure 1 & 2 respectively.

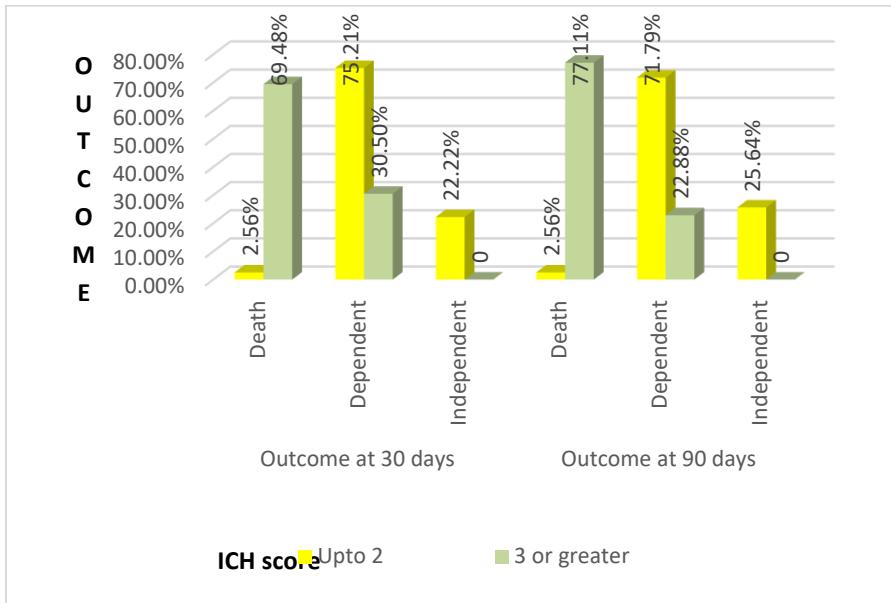


Fig 1: the details of ICH with mortality in study population at 30 & 90 days. Average ICH at 30 days was 2.28 and at 90 days was 2.28. The p value was 0.001.

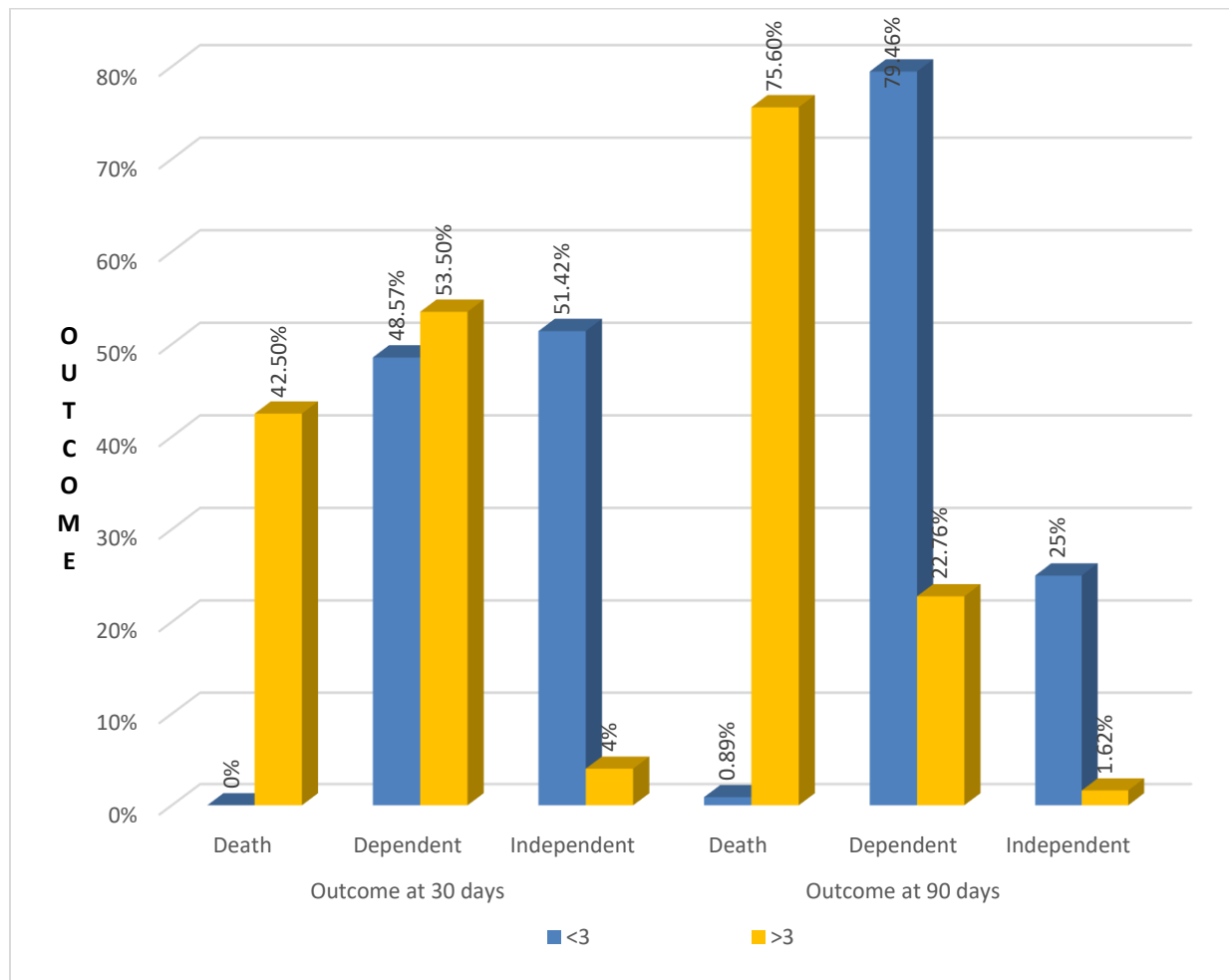


Fig 2: The details of mRS with mortality in study population at 30 & 90 days. Average mRS score at 30 days was 4.69 and at 90 days was 3.94 with p value of 0.001.

Discussion

Hemorrhagic stroke has devastating consequences. The need to identify potential risk factors, initiate corrective measures, and customize treatment cannot be overemphasized, especially in resources limited setting as in India. Spontaneous ICH is considered to be a disease of the elderly. In our study, average age was 70 years in a cohort of age group above 60 years. In similar study, the mean age was 66 years studied by *Hemphill et al.*²¹ *Hegde et al.*²² reported mean age was 58 years, which was much lower when compared to our study. In the Western world, however, the mean age of incident stroke was similar to our study i.e. 68 years in the USA and 71 years in Italy²³. On the contrary, other Indian studies found comparatively younger age of incidence.^{24,25,26,27}

This study reported 68 % male preponderance of disease. Similar male predominance was observed in other studies from Asia when compared with European and North American studies.^{28,29}

Hypertension was the most common risk factor in all the studies relating to SICH. *Feldmann et al.* have reported a relative risk of 3.9 for ICH in patients with hypertension.³⁰ *Hegde et al.*²² reported a definite history of hypertension among 57.8% patients, and nearly third of these patients were noncompliant hypertensive on irregular medication. In current study, 202 patients were detected to have hypertension, out of which 38.1% patients had died at 30 days and 42 % at 90 days. *Harthi et al.*²⁸ found higher rates of hypertension as the most prevalent risk factor (72.5%) followed by DM (54.4%) when compared with this study, *Itagi et al.*²⁹ reported hypertension in 38% cases followed by hypertension with diabetes mellitus in 23%. The other risk factors in descending order in their study were dyslipidemia, smoking, diabetes and alcohol excess. *Kay et al.* Hypertension was documented in 47.2% of the entire cohort of patients in study by *Kay et al.*³¹ and was the most common risk factor. The risk factors in descending order in their study were dyslipidemia, smoking, diabetes and alcohol excess.

Cigarette smoking is a known risk factor for ischemic stroke, increasing its relative risk three-fold. *Kay et al.*³¹ In a hospital based retrospective study done in Kolkata, reported approximately equal no of hemorrhagic (399) and ischemic stroke (393) in 792 patients of strokes who underwent CT scan. Hypertension was observed in 77.3% of ICH cases.²⁹

The second comorbidity seen in present study was T2DM. this study reported 40 cases of T2DM in a cohort of 235 SICH. Although, ischemic stroke is known to be independently associated with DM which increases its risk two to six times.

However, with regards to ICH, the link with diabetes has not been consistent. *Zheng et al.*³² concluded that hyperglycemia was associated with poor functional outcome in patients with ICH. However, the pool of available evidence about blood glucose variability and ICH is still limited^{33,34} and random blood glucose has not been a predictor of mortality in the Indian ICH studies. In contrast to our study, the other Indian studies failed to demonstrate an association between blood glucose and poor outcome.^{22,24,25}

One of the most consistent predictors of poor outcome has been a Glasgow Coma Score of less than 8. *Bhatia et al.* and *Namaniet al.*^{24,26} reported a fatality of 72.9% and 100% respectively with poor GCS on admission.^{24,26} The average GCS score in cohort of 235 cases was 9.39. On correlation, we found higher rates of morbidity and mortality with GCS less than 8.

Volume of the clot is a crucial radiological predictor of outcome in ICH.³⁵ It has been reported that each mL increase in baseline clot volume is associated with a 1% increased risk of mortality.³⁶ It has also been shown that clinically significant hematoma growth occurs in up to 1/4 of ICH patients³⁷ and for each 10% increase in hematoma volume growth, the risk of death increases by 5%.³⁶ The mean volume of the clot in the mortality group was 32.45 ± 24.39 ml, and the mean volume amongst the survivors was 17.55 ± 15.59 ml. In this study, out of 235 cases of ICH, 126 were detected more than 30 ml volume of intracerebral bleed. This subgroup was having significant higher mortality at 30 days been 65.1% and 72.2 % at 90 days. A number of studies showed a direct relationship of hematoma volume with a clinical outcome in ICH.^{37,38}

The ICH score by *Hemphill* is good score for prognosticating SICH.³⁹ This study found the average ICH score in this study was 2.29 at 30 days. *Hegde et al.*²² and *Hemphill et al.*²¹ found ICH scores of less than 4 were having lesser mortality scores. *Bhatia et al.*²⁴ reported that mean ICH and ICHGS scores were significantly higher in patients who died.

The mRS score at 30 days was 4.69 and at 90 days was 3.94. In 235 cases, outcome at 90 days for spontaneous ICH 136, resolved 81 (59.6%) and non-resolved 55 (40.4%) patients. Coagulopathy ICH 99 resolved 60 (60.6%) and non-resolved 39 (39.4%) patients *Poon et al.*⁴⁰ reported that in spontaneous ICH, 1-year survival was 46.0%, the overall 30 days case fatality after ICH was 40 %¹. With a median mRS score of 4 at 90 days follow up our overall outcome too appears to be comparable to other reported Indian studies.

^{24,25}. In a recent analysis using National Hospital Discharge survey from USA, mortality rates of about 34%. Mortality was associated with race, female sex, age greater than 65 years, black women younger than 45 years, and middle-aged black men.⁴¹

Similar to this study, the predictors of outcome in early ICH found in other studies were age, ICH location, electrocardiographic abnormalities, and history of hypertension. The other studies also found lesion size, level of consciousness, midline shift, blood pressure or pulse pressure, kidney dysfunction, IVH and pupillary abnormality, as factors influencing outcome.

^{42,43,44,45}

Conclusion

This study found that comorbidities like HTN and T2DM were significant predictors of mortality in spontaneous ICH cases. The significant correlation was also found between consumption of alcohol and smoking with mortality in ICH cases. On correlation,

we found higher rates of morbidity and mortality at 30, 90 days with GCS less than 8 at admission with significant p value 0.000. The 30 and 90-day mortality was significantly among subjects with ICH score 3 or more. Similarly, higher mortality is seen with higher mRS score at 30-day. On radiological examination, the Intracerebral bleed volume greater than 30 ml was greatest predictor of death. This study also found higher mortality in ICH when presented with radiological evidence of mass effects at admission.

This study did not find coagulopathy as a strong predictor of mortality when compared with spontaneous ICH. Similarly, the location of intracerebral bleed was not with higher 90-day mortality in this study.

Limitation of studies: In this study period due to covid -19 pandemic it had been faced difficulty in follow-up such a large sample size of patients, with wearing of Personal Protective kit.

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