Original Article

Spontaneous Intracerebral Hemorrhage among Hypertensive Patients in Saudi Arabia: Study from a Tertiary Center

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Abstract

Background: Spontaneous intracerebral hemorrhage (ICH) is the second most common cause of stroke, yet there is paucity of evidence regarding the same from Saudi Arabia.

Objectives: To describe the clinical characteristics of spontaneous ICH as well as determine the role of gender in ICH and the usefulness of the ICH scoring system for assessing the 30-day mortality risk.

Patients and Methods: This retrospective study included all patients diagnosed with spontaneous ICH at King Fahd Hospital of the University, Al Khobar, Saudi Arabia, between April 01, 2014, and April 30, 2019. Data regarding clinical characteristics, risk factors, and radiological features of ICH were extracted. Further, gender-related differences were determined. The 30-day mortality rates were assessed using the ICH score.

Results: A total of 148 patients were diagnosed with spontaneous ICH during the study period. Of these, 100 (67.5%) were male and the overall mean age was 60 ± 15 years. About 48% of the male patients were aged ≤50 years compared to 27% of the female patients ($P = 0.016$). Impaired renal function (35.8%) and diabetes (33.7%) were the most frequent risk factors; hemiparesis (51%) and language impairment (42%) were the most common presenting symptoms; and basal ganglia (40.5%) was the most common location. The 30-day mortality rate was 30%. The mean ICH score at presentation was significantly high in those who died within 30 days of presentation (2.2 ± 1.6; $P < 0.0001$). Each increase in the ICH score was associated with an increase in mortality rate ($P < 0.001$ for trend).

Conclusion: Patients with spontaneous ICH were found to have a high prevalence of vascular risk factors and mortality rate. The ICH scoring system was shown to be a useful clinical tool for evaluating the 30-day mortality risk.

Keywords: Basal ganglia, gender, hypertension, intracerebral hemorrhage, Saudi Arabia, stroke

INTRODUCTION

Intracerebral hemorrhage (ICH) accounts for 10–20% of all strokes, with a higher incidence in Asians compared with other ethnicities.[1,2] In developing countries, the incidence of ICH was found to have increased; however, in developed countries, its incidence has decreased. This decrease was

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due to adequate control of modifiable risk factors, mainly hypertension (HTN).[3,4] In the Middle East, the rates of ICH have been variably reported to account for 6.5% to 30.7% of the stroke patients.[5]

Spontaneous ICH occurs more frequently secondary to HTN or cerebral amyloid angiopathy (CAA).[6] Pathologic studies have suggested that microscopic "pseudoaneurysms" are relatively common in patients with spontaneous ICH.[6,7] Hypertensive vasculopathy appears to be multistep process involving intimal hyperplasia and hyalinosis in the vessel wall. Uncontrolled HTN or sudden increase in blood pressure (BP) may promote vascular rupture.[7] Increased evidence suggests that subcortical brain structures are mostly affected by HTN-related ICH, although lobar (cortical) hemorrhages have been also reported.[6,7] Other factors that contribute to ICH through their effect on cerebral small vessels disease and microaneurysms formations include smoking, alcohol intake,[2,8] diabetes,[9] and prior antiplatelet use.[10] Low low-density lipoprotein (LDL) level has a protective effect against ischemic stroke, but increases the risk for hemorrhagic strokes.[11] This is because low cholesterol level may promote endothelium smoothing and necrosis, making cerebral vessels prone to microaneurysms, which are the main pathological findings in ICH.[11]

Data on the influence of gender on ICH characters and outcome remain limited and with varying results. However, ICH has been found to be more prevalent in males compared with females in the general population.[12] This may be because estrogen has been shown to confer protection against cerebrovascular disease, as it enhances healthy vascular endothelial function and promotes vascular remodeling.[13] Females are also more likely to have better outcome than males, likely because sex hormones could work as anti-inflammatory and anti-apoptotic factors in neuronal oxidative metabolic process of ICH.[13] However, as the level of estrogen decreases in postmenopausal women, the risk of ICH increases.[12]

The 30-day mortality rates in ICH patients range from 30% to 50%.[1,2] The ICH score[14] was designed as a clinical scale to help standardize ICH research and clinical management protocol. It has been validated to be a good tool for evaluating the degree of ICH severity and estimating the 30-day mortality rates: ICH score of >2 was shown to have high sensitivity (85.7%) but low specificity (65.2%).[15]

Despite the burden and high mortality rates with HTN-related ICH, there is a significant paucity of studies in this field from Saudi Arabia. The aims of the current study were to describe the features of ICH in hypertensive patients, and determine if gender contributes to the clinical characteristics, etiological risk factors, and radiological features of ICH in those patients. Finally, the study would also evaluate the use of ICH scoring system as a clinical grading scale to assess the 30-day mortality risk.

PATIENTS AND METHODS

This retrospective study included all patients diagnosed with spontaneous ICH at King Fahd Hospital of the University (KFHU), Al Khobar, Saudi Arabia, between April 01, 2014, and April 30, 2019. KFHU is a tertiary care teaching hospital that provides comprehensive stroke services to patients of all nationalities presenting from across the region. The study was approved by the Institutional Review Board of Imam Abdulrahman Bin Faisal University, Dammam.

Inclusion and exclusion criteria
The diagnosis of ICH was based on the International Classification of Diseases, 10th Revision code I61. All patients had confirmed ICH on head CT. Primary ICH was defined according to the World Health Organization definition of stroke.[16] Patients were identified as having HTN if they had a history of HTN, were taking anti-HTN medications, or had BP >140/90 mmHg that persisted for at least 14 days after the onset of ICH and the diagnosis of HTN was confirmed during follow-up.[17] Exclusion criteria were as follows: (1) Patients with subdural/epidural hematoma or traumatic ICH;[2] (2) presence of subarachnoid hemorrhage or vascular malformation; (3) hemorrhages due to tumors; (4) hemorrhagic transformation of ischemic stroke; (5) ICH due to cerebral venous thrombosis, coagulopathy, moyamoya disease, or vasculitis; and 6) anticoagulant- or thrombolytic-related ICH.[2]

Variables
Demographic characteristics, vascular risk factors, and laboratory parameters
The demographic characteristics included were age, gender, and nationality. In addition, the prevalence of the following risk factors were determined: (1) diabetes;[9] (2) current smoking status; (3) use of alcohol; (4) ischemic heart disease; (5) low LDL levels (<70mg/dl);[11] (6) impaired renal function, defined as glomerular filtration rate (GFR) <60 ml/min/1.73m² (creatinine clearance [CrCl] was calculated as an estimate of GFR, according to the Chronic Kidney Disease Epidemiology Collaboration CKD-EPI equation);[18] and (7) prior use of antiplatelet[10] and anti-hypertensive medications.[7-11]

The mean values of the following laboratory investigations were collected: serum fasting blood sugar (FBS), LDL,

hemoglobin A1c, and CrCl. All samples were collected by venipuncture. Considering the neuroprotective effect of sex hormones,[13] patients were categorized into two groups: ≤50 years and >50 years.

Clinical and radiological data

The following clinical and radiological data were collected: systolic, diastolic, and mean arterial blood pressure (SBP, DBP, and MAP) at admission and SBP after 24 hours; Glasgow coma scale (GCS) score; seizures, and need for mechanical ventilation. Presenting symptoms included hemiparesis or hemiplegia, headache, hemianesthesia, vomiting, language impairment, and imbalance. Level of consciousness was assessed based on the recorded GCS score at presentation as follows: lucid, GCS 13–15; altered sensorium, GCS 8–12; Coma, GCS <8. Acute hypertensive response was defined as SBP ≥140 mmHg on two recordings taken 5 minutes apart within 24 hours of the onset of symptoms.[19] Baseline SBP was classified as mild if the readings were between 140 and 180 mmHg, and severe if >180 mmHg.

For non-contrast CT scan examination, a 65-slice Siemens scanner (Siemens Healthcare, Forchheim, Germany) was used with the following parameter: 120 kV; 420 mAs; scan time, 6.82 s; thickness, 7 mm; pitch, 0.8 mm. For magnetic resonance imaging (MRI), 1.3 T and 3.0 T MRI scanners (GE Twinspeed, General Electric Medical Systems, Milwaukee, WI, USA; Philips Medical Systems, Eindhoven, The Netherlands) were used. Location of hemorrhage in CT scan or MRI was classified as: (1) supratentorial (basal ganglia, thalamus, and lobar); (2) infratentorial (brain stem and cerebellum); (3) multiple sites; or (4) primary intraventricular hemorrhage (IVH). Associated radiological features such as intraventricular extension (IVE), edema, and hydrocephalus were also studied. ICH volume was measured using the ABC/2 method, where A is wideness, B is length, and C is height (based on the section number found on CT),[20] and was further classified according to the size into ≤30 ml and >30 ml.

ICH scoring

The ICH score[14] was calculated as a summation of components' points. Parameters of this score included age >80 years (1 point); low GCS (3–4: 2 points; 5–12:1 point); IVH (1 point); infratentorial ICH (1 point), and ICH volume >30 ml (1 point).[14] Data on 30-day mortality in relation to ICH score were investigated.

Statistical analysis

The minimum required sample size was calculated to be 143, assuming that the prevalence of ICH account for 13.5% of all stroke patients,[21,22] with a precision of 5% and at alpha level of 0.05. Sample size was calculated through Epi Info 7.0. All analyses were performed using SPSS version 25 (SPSS Inc., Chicago, USA). Categorical variables are presented as frequencies and percentages. Quantitative variables were presented as mean and standard deviation. Independent sample t-test was used to compare the mean of continuous variables. P value <0.05 was considered statistically significant. The small number of ICH events did not allow performing multivariate analyses or logistic regression.

RESULTS

Demographics, risk factors, and laboratory parameters

A total of 148 of 775 stroke patients (19.1%) admitted to KFHU during the study period were diagnosed with spontaneous ICH. Of these, 100 were male (67.5%), and their age ranged from 30 to 103 years (mean: 60 ± 15 years). The mean age was similar between males and females (60 ± 15 years vs. 59 ± 13 years, respectively). In the ≤50-year age group, the ICH rate was significantly higher in males than females (male: 48/100 [48%]; females, 13/48 [27.3%]; P = 0.016) [Figure 1]. Regarding ethnicity, 70/148 (47.3%) were non-Saudi, of which 50 (71.4%) were Asians. There were more non-Saudi patients in the male group compared to females (P = 0.019). Impaired renal function and diabetes were the most frequent risk factors (35.8% and 33.7%, respectively) [Table 1]. The means of FBS, LDL, hemoglobin A1c, and CrCl were similar in both genders (P > 0.05) [Table 1].

Clinical presentations and radiological findings

Hemiparesis and language impairment were the most common presenting complaints (51% and 42%, respectively). Other presenting symptoms included headache (40%), hemi-anesthesia (25%),
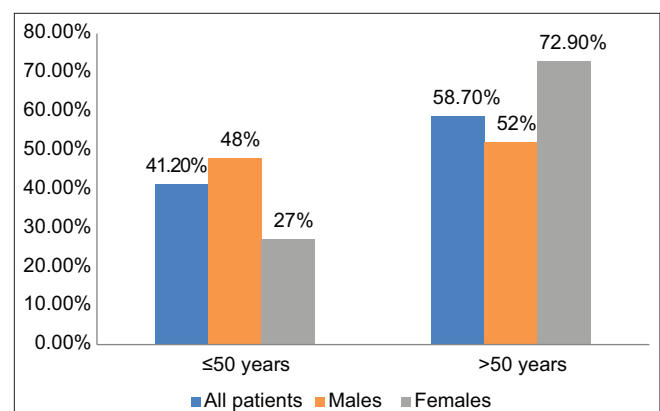
Figure 1: Age groups for patients with spontaneous intracerebral hemorrhage

Table 1: Demographic characteristics and vascular risk factors for spontaneous intracerebral hemorrhage (N=148)

| Characteristics	All patients	Male (n=100), n (%)	Female (n=48), n (%)	P
Age (years), mean±SD	60±15	60±16	59±13	0.863
Nationality, n (%)				
Saudi	78 (52.7)	46 (46.0)	32 (66.66)	0.019
Non-Saudi	70 (47.3%)	54 (54.0)	16 (33.33)	
Risk factors, n (%)				
Diabetes	50 (33.7)	36 (36.0)	14 (29.16)	0.411
Smoking	38 (25.6)	28 (28.0)	10 (20.8)	0.350
Ischemic heart disease	36 (24.3)	26 (26.0)	10 (20.8)	0.493
Prior history of ischemic stroke	41 (27.7)	28 (28)	13 (27.0)	0.907
Low LDL	42 (28.4)	25 (25.0)	17 (35.4)	0.188
Kidney impairment	53 (35.8)	33 (33.0)	20 (41.6)	0.303
Prior antiplatelet use	36 (24.3)	26 (26.0)	10 (20.8)	0.493
Alcohol intake	23 (15.5)	18 (18.0)	5 (10.4)	0.233
Prior history of HTN	93 (62.80)	12 (12)	17 (35.41)	0.62
Baseline antihypertensive	55 (37.1)	37 (37)	18 (36)	0.81
Baseline values for laboratory investigations (mean±SD)				
FBS (mg/dl)	165±69.1	163.5±73.1	161±61	0.833
LDL (mg/dL)	101.3±39.1	109.6±41.1	97.1±37.6	0.07
Hemoglobin A1c (%)	6.6±1.7	6.9±2	6.5±1.4	0.11
CrCl (ml/min/1.73 m^2)	75.7±31.5	72.6±33.6	81.7±26.2	0.07

FBS – Fasting blood sugar; LDL – Low density lipoprotein; CrCl – Creatinine clearance; SD – Standard deviation; HTN – Hypertension

vomiting (35%), and imbalance (8%). There were no gender-related differences in terms of GCS, seizures, intubation, BP level, and acute hypertensive response [Table 2].

All patients underwent non-contrast CT at initial evaluation within 24 hours of the onset of symptoms. Head MRI was performed in 20 patients (13.5%). ICH was mostly supratentorial (78.3%), and the most frequent location was basal ganglia (40.5%), followed by cerebral lobes (19.6%) and the thalamus (17.6%). Large hematoma volume was seen only in supratentorial ICH and was found in 30 patients (20.27%). No infratentorial hemorrhages had large hematoma volume. Radiological features in patients with ICH were similar in males and females, and the association was insignificant [Table 2].

Mortality

A total of 45 patients died (30%), with no difference in mortality rates by gender (males: 31%, females: 29.2%; $P = 0.907$). The ICH score ranged from 0 to 5 [Figure 2]. Of those who died, three had an ICH score of 0 and seven had a score of 1. The 30-day mortality rates for patients with ICH scores of 2, 3, and 4 were 36.3%, 63.15%, and 90%, respectively. All patients with an ICH score of 5 died. Each increase in the ICH score was associated with an increase in the 30-day mortality ($P < 0.001$ for trend). The mean ICH score at presentation was statistically high in cases with 30-day mortality (2.2 ± 1.6; $P < 0.0001$). Mortality was significantly associated with age ≥80, GCS <13, and CT location (infratentorial).
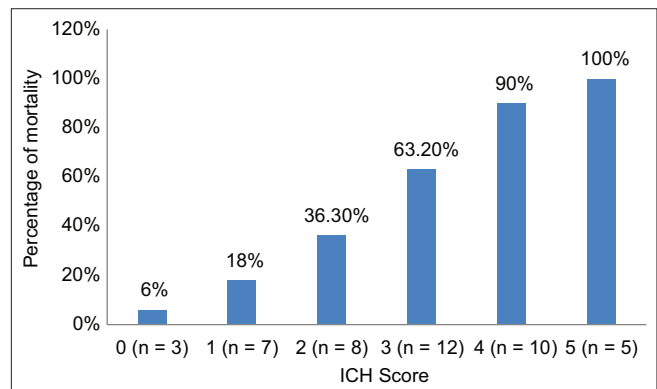
Figure 2: The ICH score and mortality

Mortality was higher but statistically insignificant in cases with hematoma size >30 ml compared with ≤30 ml ($P = 0.064$) [Table 3].

DISCUSSION

Spontaneous ICH accounted for about one-fifth of all stroke patients in this study, which is a relatively higher rate compared with those reported from Western countries.[4] This discrepancy may be partially explained by the high prevalence of uncontrolled risk factors and due to Asians accounting for one-third of our study sample. The present study also found that males accounted for a significantly higher proportion of patients aged ≤50 years, which was in agreement with the findings of several studies.[12,21,22] This is likely because in women, estrogen confers neuroprotective effect on cerebral vasculature.[13] Another factor could be that in the ≤50-year-old age group, a significant proportion

Table 2: Clinical and radiological features of patients with spontaneous intracerebral hemorrhage (N=148)

Characteristics	All patients	Male (n=100), n (%)	Female (n=48), n (%)	P
Acute HTN response, n (%)				
Mild	53 (35.8)	33 (33.0)	20 (41.6)	0.303
Severe	95 (64.1)	67 (67.0)	28 (58.3)	
BP level (mean±SD mmHg)				
SBP	194.1±25.2	195.9±23.8	193.2±25.9	0.53
MAP	137.2±25.3	138.7±21.6	136.4±27	0.62
DBP	110.5±23.9	112.8±22.3	109.4±24.7	0.41
SBP at 24 h	155.4±12.9	158±11	158±9.66	0.93
Level of consciousness, n (%)				0.354
Lucid	96 (64.9)	62 (62.0)	34 (70.83)	
Altered sensorium	20 (13.5)	13 (13.0)	7 (14.5)	
Coma	32 (21.6)	25 (25.0)	7 (14.58)	
Intubation, n (%)	39 (26.35)	30 (30.0)	9 (18.75)	0.307
Supratentorial ICH, n (%)	115 (78.3)			0.333
Basal ganglia	60 (40.5)	39 (39.0)	21 (43.75)	
Thalamus	26 (17.6)	15 (15.0)	11 (22.9)	
Lobar	29 (19.6)	21 (21.0)	8 (16.66)	
Infratentorial ICH, n (%)	27 (18.2)			
Brainstem	16 (10.8)	10 (10.0)	6 (12.50)	
Cerebellum	11 (7.4)	9 (9.0)	2 (4.16)	
Multiple sites	6 (4.1)	6 (6.0)	0	
Primary IVH	1 (0.67)	1 (1.0)	0	
ICH volume >30 ml, n (%)	39 (26.35)	30 (30.0)	9 (18.75)	0.307
IVE, n (%)	43 (29.05)	32 (28.0)	11 (22.9)	0.350
Hydrocephalus, n (%)	9 (6.00)	6 (6.0)	3 (6.25)	0.887
Cerebral edema, n (%)	39 (26.35)	30 (30.0)	9 (18.75)	0.307

IVE – Intraventricular extension; IVH – Intraventricular hemorrhage; HTN – Hypertension; BP – Blood pressure; SBP – Systolic BP; DBP – Diastolic BP; MAP – Mean arterial blood pressure; ICH – Intracerebral hemorrhage; SD – Standard deviation

Table 3: Factors associated with 30-day mortality in patients with spontaneous intracerebral hemorrhage (N=148)

Associated factors	Death (n=45), n (%)	Discharged (n=103), n (%)	P
Age (years)	9 (52.9)	8 (47.1)	0.048
≥80 (n=17, %)	36 (27.5)	95 (72.5)	
<80 (n=131, %)			
GCS	25 (48.1)	27 (51.9)	0.001
<13 (n=52, %)	20 (20.8)	76 (79.2)	
≥13 (n=96, %)			
CT location	16 (48.5)	17 (51.5)	0.01
Infratentorial (n=33, %)	29 (25.2)	86 (74.8)	
Supratentorial (n=115, %)			
Hematoma size (ml)	14 (43.8)	18 (56.2)	0.064
>30 (n=32, %)	31 (26.7)	85 (73.3)	
≤30 (n=116, %)			
IVE or IVH	37 (84.0)	7 (6.7)	0.003
Yes (n=44, %)			
ICH scores (Mean±SD)	2.2±1.6	1.05±1.3	<0.001

GCS – Glassgow coma scale; IVE – Intraventricular extension; IVH – Intraventricular hemorrhage; SD: Standard deviation; ICH – Intracerebral hemorrhage; CT – Computed tomography

of the patients were non-Saudi patients, which may be indicative of ethnicity having a role in the number of ICH cases from Saudi Arabia; however, further studies are required to confirm the same.

In almost all the patients in this study, ICH was HTN related and was a known pre-existing risk factor. Baseline impaired renal function has previously been reported to be a risk factor for ICH.[23] Similarly, in our study, the prevalence of impaired renal function was high among patients with ICH. This could be due to the higher percentage of patients having diabetes and HTN, which have been shown to be linked.[24] In addition, the diagnosis of HTN was confirmed in all patients unlike previous studies,[24-27] and this may be a possible explanation for higher frequency of diabetes in our study than reported elsewhere.[21,25,26,28] The current study had a high percentage of young males (41.2%), which may have contributed to the higher prevalence of smoking and alcohol intake reported here compared with that in previous studies from the Middle East.[21,25,26,28] The prevalence of other risk factors were similar between males and females, which may be because the proportion of premenopausal women in our study was low. The pattern of ICH was comparable with other studies from the Middle East and has been summarized in Table 4.

The renin–angiotensin–aldosterone system (RAAS) activity has been shown to increase in the acute phase of ICH, causing hypertensive response.[18] Considering that all patients in this study were hypertensive, and the fact that higher BP level has been reported more frequently in patients with chronic HTN than in non-hypertensive patients,[18] the level of BP in our patients was expected. Previous studies have suggested that sex hormones might influence the RAAS system, resulting in a lower BP level in females than in males.[29] However, the gender distribution in age groups might be related to similar blood pressure level in males and females.

The distribution of clinical symptoms in this study was similar with the current literature,[2] as hemiparesis, language impairment, headache, and seizure have been commonly reported in almost all studies,[2,21] including the Surgical Trial in Intracerebral Haemorrhage (STICH) study.[30] The high percentage of focal neurological symptoms such as hemiparesis and speech disturbances can be explained by the frequent involvement of deeper regions of the brain such as basal ganglia and brainstem, which in turn affect the motor tract system. Considering the radiological features in our patients, including the rate of thalamic and infratentorial location, IVE, and large hematoma volume, the frequencies of patients with low GCS and those requiring intubation were as expected.

The location of hemorrhages in the present study was similar to that reported in the INTERACT2 study,[7] except for the high frequencies in the lobar sites. The higher frequency of ICH in the lobar location in the present study as compared with previous studies[8,30] might be explained by

Table 4: Spontaneous intracerebral hemorrhage characteristics in our study compared with other studies from the Middle East

Parameters	Current study (N=148)	Awada et al.[26] (N=243)	Khan et al.[25] (N=53)	El Tallawy et al.[21] (N=64)	AlRajeh et al.[27] (N=107)	Celikbilek et al.[28] (N=106)	Almutawa et al.[32] (N=54)
Country	Saudi Arabia	Saudi Arabia	Qatar	Egypt	Saudi Arabia	Turkey	Bahrain
Mean age	60±15	56.9±18.2	57.1±13.3	62±12.65	60±18	62.5±14.91	66.3±12.9
Male to female ratio	2.1:1	2.74:1	3:1	1.6:1	2.2:1	1.3:1	1.8:1
Risk factors frequencies (%)							
HTN	62.8	64	79	81.2	62	73.5	87
Diabetes	33.7	23	26.4	23.4	16	23.6	42
Smoking	25.6	20	11.3	15.6	6	17.9	-
Ischemic heart disease	24.3	14	7.5	6.2	13	-	-
Alcohol intake	15.5	-	11.3	-	-	7.5	-
Prior history of ischemic stroke	24.3	-	16.9	4.7	1	-	-
Mortality (%)	30	19	30	-	23	34.9	37

HTN – Hypertension

the fact that CAA and HTN are both common conditions in the elderly,[6] and thus, may coexist and result in high frequency of lobar ICH. However, because radiological characters in different age group were not investigated, this hypothesis could not be confirmed. Lobar hemorrhages have been reported as the most common location of spontaneous ICH by Khan et al. and Celikbilek et al.[25,28]

There was no gender-related difference in the ICH mortality rate, which was in contrast to the findings of a meta-analysis[12] but similar to those of Khan et al.[25] Our findings can be partially explained by the lack of significant gender-related differences in ICH characteristics. Similar to findings in the literature, mortality was high in our study. This study also demonstrated the ICH score to be a reliable tool for determining the 30-day mortality rates, with a direct relationship between mortality and increase in the ICH score. The 30-day mortality rates for patients with ICH scores 0, 1, and 2 were relatively higher in comparison to that reported in the literature (0 point: 6% vs. 0%; 1 point: 18% vs 13%; 2 points: 36.3% vs 26.8%) but lower for scores of 3 and 4 (3 points: 63.3 vs 72%; 4 points 90 vs 97%).[14] Early assessment of patients with ICH scoring in this study could be related to these observations. Previous studies have suggested that delaying the use of ICH score might improve the 30-day mortality predictability compared with admission ICH scoring because some patients presenting with thalamic or infratentorial hemorrhages require early intubation, and thus would have a low GCS score and higher in ICH score.[15,31] Follow-up ICH and GCS score was not recorded in this study. Patients with an ICH score of 5 had an expected 30-day mortality rate. No patient in the current study had a score of 6, likely because no patient with infratentorial hemorrhage had large hematoma volume >30ml. As expected, all components of ICH were found to increase the risk of 30-day mortality, except large hematoma volume >30 ml – this could be because

brainstem or cerebellar hemorrhages were associated with worse outcome regardless of their size.[31,32]

Strengths and limitations

To the best of our knowledge, this was the first study from Saudi Arabia that assesses the 30-day mortality in patients with spontaneous ICH using the ICH score. However, the study has few limitations such as reporting data from only a single center. In addition, as this is a retrospective study, there may be incomplete data. The study also had a relatively small sample size, which could have contributed to no gender-related differences being reported and also limited the possibility of conducting multivariate analysis. Despite its limitations, ICH characters and risk factors in hypertensives have been highlighted in our study population.

CONCLUSION

Patients with spontaneous ICH were found to have a high prevalence of vascular risk factors and mortality rate. ICH scoring system was shown to be a valuable and easy clinical tool for evaluating the 30-day mortality risk, with the likeliness of mortality increasing with the score.

Ethical considerations

This study was approved by the Institutional Review Board (IRB) of Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia, on January 11, 2018 (Ref no.: IRB-2018-01-002). The need for informed consent was waived by the IRB owing to the study design. The study adhered to the principles of the Declaration of Helsinki, 2013.

Data availability statement

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Peer review

This article was peer-reviewed by five independent and anonymous reviewers.

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Conflicts of interest

There are no conflicts of interest.

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