ORIGINAL ARTICLE

Predictors of Early Neurological Deterioration in Patients with Spontaneous Intracerebral Hemorrhage.

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ABSTRACT

Background: Intracerebral hemorrhage (ICH) is the second most common cause of stroke, following ischemic stroke and has been described to be associated with high morbidity and mortality.

Aim: We investigated the association between the clinical, laboratory and radiographic factors on one hand and early neurological deterioration (END) after first ever intracerebral hemorrhage (ICH) on the other hand.

Patients and methods: We identified forty consecutive patients with ICH who were admitted to the stroke or intensive care units of the Neurology Department Zagazig University Hospitals within the first 24 hours of onset. Mean age was 58.125±11.37 years ranging from 30 to 83 years with median of age 60 years. Males were 31 (77.5%) and 9 (22.5%) were females. Glasgow Coma Scale (GCS) score, National Institute of Health Stroke Scale (NIHSS) score, laboratory investigations, and radiological investigations to assess the site and size of the intracerebral hematoma were recorded on admission. The study endpoint was the occurrence of END within 7 days after ICH.

Results: We found that males were 31 (77.5%) and 9 (22.5%) were females. six of our patients (15%) presented END. Lower GCS score, higher NIHSS score, lobar hematoma, and larger hematoma volume were independent predictors for END after ICH.

Conclusion: There are different early predictors of spontaneous intracerebral hemorrhage (sICH) outcome which can be classified into clinical predictors, laboratory predictors and radiological predictors which can help in the risk categorization of patients.

Keywords: intracerebral hemorrhage, predictors, early neurological deterioration, outcome.

INTRODUCTION

Spontaneous intracerebral haemorrhage (sICH) accounts for about 10% to 15% of all strokes subtypes and affects over 1 million people per year globally. It is characterized by high rates of mortality and residual disability amongst survivors, with no therapeutic strategies of definitive benefit currently [1]. Neurological deterioration (ND) is common after ICH and it is associated with increased length of in-hospital stay, poor functional recovery and death [2]; although, reliable and easy-to-use predictors allowing the early recognition of unstable at-risk patients are not well confirmed.

PATIENTS AND METHODS

We included in this prospective cohort study 40 patients diagnosed with sICH, with mean age 58.125±11.37 years ranging from 30 to 83 years with median of age 60 years. Males were 31 (77.5%) and 9 (22.5%) were females. Patients were above 18 years old with first ever sICH diagnosed with Computerized Tomography (CT) scan of the brain and admitted within the first 24 hours of onset to stroke and intensive care units of Neurology Department Zagazig University Hospitals.

We excluded those who suffered from isolated intraventricular hemorrhage, hemorrhage secondary to brain tumor, dural venous sinus thrombosis or ruptured arteriovenous malformation or aneurysm, patients on anticoagulants, patients receiving

immunomodulatory treatment (e.g. corticosteroids, azathioprine, methotrexate, other cytostatic and biologicals agents as monoclonal antibodies), patients with head injury and surgery within 4 weeks preceding the event, patients with pre-existing infections like tuberculosis and hemorrhagic diseases or blood malignancies and patients with severe degree of hepatic or renal disease.

A written informed consent was obtained and signed by the patient himself or the patient's first degree relatives when the patient's consciousness is impaired and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University (ZU-IRB#:4384/19-3-2018). The work had been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Full medical and neurological history was taken, stressing on vascular risk factors including hypertension, diabetes mellitus, dyslipidemia, and smoking.

General and neurological examination was done with assessment of neurological function on admission using Glasgow Coma Score (GCS) and classifying our patients into three categories; those with score of 3-7, 8-13 and more than 13 [3] and using the National institutes of Health Stroke Scale (NIHSS), an 11-item neurologic examination stroke scale that provides a quantitative measure of stroke-related neurologic deficit. The maximum possible score is 42, with the minimum score being a 0, each of score items given between a 0 and 4. The severity of the stroke can be categorized according to the points of the score into: No stroke symptoms (0), minor (1-4), moderate (5-15), moderate to severe (16-20) and severe (21- 42) [4].

Laboratory investigations included complete blood count, blood glucose level, liver and kidney function tests, coagulation profile, serum lipid profile, acute phase reactants especially CRP and erythrocyte sedimentation rate (ESR).

Computerized Tomography (CT) brain was done, for all patients, on admission with stress on identification of the site and the size of the hematoma. The size of the hematoma was measured by the formula (Equation A x B x C × 0.5) where A and B indicate the largest perpendicular diameters through the hyperdense area on the CT scan, and C indicates the thickness of the ICH (the number of slices containing hemorrhage) [5].

All patients were followed up to detect early neurological deterioration defined as a 4 point or greater increase in the NIHSS score or 2 point or greater decrease in the GCS or death from the time of admission to 7 days post-hemorrhage [6].

Statistical analyses: The data were coded and entered using the Statistical Package for the Social Sciences (SPSS version 22.0) software for analysis (IBM Corp.) [7].

RESULTS

We included in this prospective cohort study 40 adult patients with first ever acute ICH (31 males and 9 females with age ranged from 30 to 83 years).The mean age was 58.125±11.37.

Regarding to vascular risk factors, 87.5% of our patients were hypersensitive, 50% were dyslipidemic, 40% were current smokers, 27.5% were HCV positive and 15% were diabetics.

The most prevalent presentation in our patients was the right sided motor and sensory dysfunction followed by disturbed level of conscious then aphasia. No lateralization was observed in 2 patients (one was presented by headache and the other was presented by confusion) (Table 1).

The most prevalent NIHSS scores were moderate (5-15) in 40% then severe (16- 20) in 35%. Regarding GCS, the most prevalent score was (9-13) in 47.5% (Table 2).

Most of the included patients had left (65%) basal ganglia hematoma (52.5%) followed by lobar hematoma (30%) (Table (2).

The patients with END presented 15% while patients with non-END were 85% (Figure 1).

There was no statistically significant association between END and the risk factors among our patients (Table 3).

There was a statistically significant association between early neurological deterioration (END) and aphasia and seizures (Table 3).

END was highly statistically significantly associated with low GCS (3-7) and high NIHSS (> 21) (Table 4).

There was a statistically significant association between END and lobar location of intracerebral hematoma (p=0.034) and large hematoma volume (p=0.004) in our patients (Table 4).

There was a statistically highly significant association between END and elevated CRP and leukocytosis (Table 5).

Lower GCS score, higher NIHSS score, lobar hematoma, and larger hematoma volume were independent predictors for END (Table 6).

Table (1): clinical presentation, laboratory, and radiological investigations among studied group (N=40)

Systolic blood pressure	Mean± SD	175.5±23.19	
	Median (Range)	180.0 (130-230)	
Diastolic blood pressure	Mean± SD	100.25±8.61	
	Median (Range)	100.0 (80-120)	
Temperature	Mean± SD	37.04±0.25	
	Median (Range)	37.0 (36.7-38.5)	
Motor deficit	No	3	7.5
	Yes	37	92.5
Sensory deficit	No	3	7.5
	Yes	37	92.5
Aphasia	No	21	52.5
	Yes	19	47.5
Ataxia	No	38	95.0
	Yes	2	5.0
Disturbed level of consciousness	No	12	30.0
	Yes	28	70.0
Seizures	No	34	85.0
	Yes	6	15.0
Lateralization	No~	2	5.0
	Left	16	40.0
	Right	24	60.0
White blood cells	Mean± SD	11.09±5.06	
	Median (Range)	10.0 (3.3-27.5)	
C-reactive protein	Mean± SD	44.27±77.49	
	Median (Range)	12.29 (0.44-385.27)	
Hematoma volume	Mean± SD	32.18±39.6	
	Median (Range)	20.5 (2.25-200)	

SD; Standard Deviation.

Table (2): Glasgow Coma Scale, the National Institutes of Health Stroke Scale scores, and Hematoma Characters among studied group (N=40).

Scales and hematoma characters			N	%
GCS	Severe	3-8	3	7.5
	Moderate	9-13	19	47.5
	Mild	>13	18	45.0
NIHSS	Mild	1-4	3	7.5
	Moderate	5-15	16	40.0
	Severe	16-20	14	35.0
	Extremely severe	21-42	7	17.5
Side of hematoma		Lt	26	65.0
		Rt	14	35.0
Site of hematoma		Basal ganglia	21	52.5
		Thalamic	4	10.0
		Lobar	12	30.0
		Cerebellar	2	5.0
		Brainstem	1	2.5
volume of hematoma (mm^3)		Mean± SD	32.18±39.6	
		Median (Range)	20.5 (2.25-200)	

GCS; Glasgow Coma Scale, NIHSS; National Institutes of Health Stroke Scale, SD; Standard Deviation.

Table (3): Association of early neurological deterioration (END) with basic demographic data, risk factors, and clinical presentation.

Basic demographic data, risk factors, and clinical presentation			END (N=6)	Non-END (N=34)	X^2	P
Age			63.5±18.63	57.17±9.69	1.266	0.213
SEX	FEMALE	N	3	6	3.06	0.08
		%	50.00%	17.60%		
	MALE	N	3	28		
		%	50.00%	82.40%		
Lateralization	NO	N	5	33	2.02	0.15
		%	83.30%	97.10%		
	YES	N	1	1		
		%	16.70%	2.90%		
Hypertension	NO	N	0	5	1.008	0.31
		%	0.0%	14.7%		
	YES	N	6	29		
		%	100.0%	85.3%		
Diabetes	NO	N	4	30	1.86	0.17
		%	66.7%	88.2%		
	YES	N	2	4		
		%	33.3%	11.8%		
Systolic blood pressure			180.0±21.9	174.7±23.6	0.51	0.613
Diastolic blood pressure			101.66±7.52	100.0±8.87	0.432	0.668
Aphasia	NO	N	0	21	7.8	0.005*
		%	0.00%	61.80%		
	YES	N	6	13		
		%	100.00%	38.20%		
Seizures	NO	N	3	31	6.78	0.009*
		%	50.00%	91.20%		
	YES	N	3	3		
		%	50.00%	8.80%		

X^2; Chi square test. P value was set at <0.05 for significant results & <0.001 for high significant result.

Table (4): Association of early neurological deterioration (END) with Glasgow Coma Scale, the National Institutes of Health Stroke Scale scores and hematoma characters.

Scales and hematoma characters			END (N=6)		Non-END (N=34)		Total (N-=40)		X^2	P
			N	%	N	%	N	%		
GCS	Severe	3-7	3	50	0	0	3	7.50	20.18	0.00**
	Moderate	8-13	3	50	16	47.1	19	47.50		
	Mild	>13	0	0	18	52.9	18	45.00		
NIHSS	Mild	1-4	0	0.00	3	8.8	3	7.50	13.1	0.004*
	Moderate	5-15	0	0.00	16	47.1	16	40.00		
	Severe	16-21	2	33.3	12	35.3	14	35.00		
	Extremely severe	>21	4	66.7	3	8.8	7	17.50		
Side of hematoma	LT		4	66.70	22	64.70	26	65.00	0.009	0.92
	RT		2	33.30	12	35.30	14	35.00		
Site of hematoma	Basal ganglia hematoma	No	4	66.70	15	44.10	19	47.50	1.04	0.308
		Yes	2	33.30	19	55.90	21	52.50		
	Thalamic hematoma	No	6	100.00	30	88.20	36	90.00	0.78	0.37
		Yes	0	0.00	4	11.80	4	10.00		
	Lobar hematoma	No	2	33.30	26	76.50	28	70.00	4.51	0.034*
		Yes	4	66.70	8	23.50	12	30.00		

Scales and hematoma characters			END (N=6)		Non-END (N=34)		Total (N-=40)		X^2	P
			N	%	N	%	N	%		
	Cerebellar hematoma	No	6	100.00	32	94.10	38	95.00	0.37	0.54
		Yes	0	0.00	2	5.90	2	5.00		
	Brainstem hematoma	No	6	100.00	33	97.10	39	97.50	0.18	0.67
		Yes	0	0.00	1	2.90	1	2.50		
Volume hematoma			73.83±64.25		24.83±19.54				3.081	0.004*

GCS; Glasgow Coma Scale, NIHSS; National Institutes of Health Stroke Scale, X^2; Chi square test.
P value was set at <0.05 for significant results & <0.001 for high significant result.

Table (5): Relation of early neurological deterioration (END) with laboratory findings.

	END (N=6)	Non-END (N=34)	T/ Mann Whitney	P
White blood cells (Mean±SD)	17.1±6.88	10.03±3.62	3.604	0.001**
Alanine aminotransferase (Mean±SD)	27.28±22.1	21.33±12.91	0.874	0.388
Aspartate aminotransferase (Mean±SD)	44.61±19.9	29.7±18.4	1.513	0.139
Serum creatinine (Mean±SD)	0.823±0.18	1.19±0.57	-1.569	0.125
Erythrocyte sedimentation rate (Mean±SD)	15.5±5.85	20.08±13.2	-0.713	0.480
C-reactive protein (Mean±SD)	140.33±128.4	27.32±22.5	3.826	0.00**
International normalized ratio (Mean±SD)	1.17±0.29	1.13±0.22	0.356	0.724
Low-density lipoprotein cholesterol (Mean±SD)	103.63±25.49	114.92±28.74	-0.899	0.375

SD; Standard Deviation P value was set at <0.05 for significant results & <0.001 for high significant result.

Table (6): Multivariate logistic regression for independent predictors of early neurological deterioration (END).

Predictors	OR	95% CI		P
		Lower	Upper	
Aphasia	4.12	0.98	17.52	0.055
Seizures	2.147	0.87	5.214	0.124
GCS	6.254	1.24	11.254	0.002*
NIHSS	5.654	2.14	9.654	0.007*
Lobar hematoma	5.121	1.658	12.321	0.037*
Hematoma volume	8.541	2.14	17.524	0.00**
Temperature	2.587	0.547	12.321	0.354
White blood cells	3.254	0.87	18.21	0.087
C-reactive protein	3.547	0.874	19.654	0.065

CI; Confidence Interval, GCS; Glasgow Coma Scale, NIHSS; National Institutes of Health Stroke Scale, OR; Odds Ratio P value was set at <0.05 for significant results & <0.001 for high significant result.
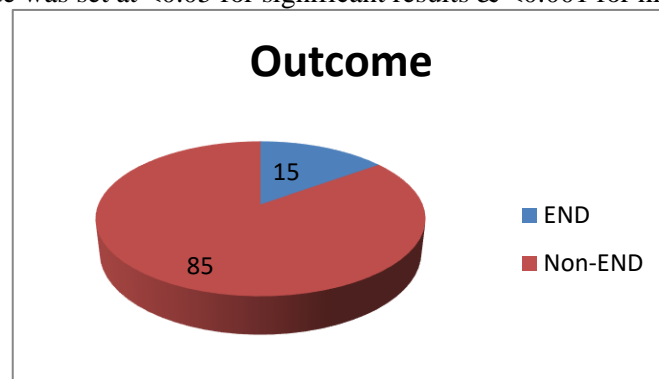

Figure 1. Pie chart describes early neurological outcome among studied group.

DISCUSSION

Spontaneous intracerebral hemorrhage (sICH) has been described to be the most fatal form of stroke accounting for nearly 10-15% of all strokes worldwide. The rate of mortality and disability after sICH reflects the pressing need to improve current therapy. Accurate identification of its outcome predictors may help ideal beginning time for immediate intervention and management. Earlier studies have investigated significant associations between clinical, laboratory and radiographic factors on one hand and outcomes in patients with sICH on the other hand [8].

Our study included forty patients diagnosed with sICH, with mean age 58.125±11.37 years ranging from 30 to 83 years with median of age 60 years. Males were 31 (77.5%) and 9 (22.5%) were females. The overall mortality was 6 patients (85%).

Our results stated that the mean systolic blood pressure was 175.5±23.19 mmHg, the mean of diastolic blood pressure was 100.25±8.61 mmHg, and that blood pressure readings on admission had no statistically significant correlation to END (P=0.31). These results were in agreement with that of Specogna et al. (2014), who concluded that there is no correlation between mean blood pressure and END in acute ICH patients after random-effects analyses [9]. In contrast to our results, Chiquete et al. (2013) found that there was a significant relation between mortality following ICH and increased blood pressure on admission [10]. Fan et al. (2015) also concluded that blood pressure readings were significantly associated with END (p = 0.0004). This difference may be due to that they followed the patients up to 24 hours of emergency department arrival and we followed the patients up to 7 days post hemorrhage onset [11].

Fifteen percent of the studied patients had DM (6 out of 40 patients). Our results showed no significant relation between DM and END (P= 0.17). Compatible results were obtained by El-Tallawy et al. (2005), Fan et al. (2012), and Wang et al. (2015), and who reported non-significant relation between diabetes and mortality after ICH [12,13,14]. Different results were obtained by Arboix et al. (2000) who found that DM is an independent predictor of mortality after ICH [15]. Passero et al. (2003) determined that DM has statistical significant relation to 30 days mortality and Togha and Bakhtavar (2004) also stated that DM is an independent determinant of death in 122 patients with ICH [16,17].

In our study, we found that the most common clinical presentation in our patients was motor and sensory presentation (92.5% for both) mostly right sided hemiparesis and hemi hypoesthesia, followed by disturbed level of conscious and aphasia (70% and 47.5% respectively) then seizures (15%). Early neurological deterioration in our patients had a significant relation to seizures (P= 0.009) and aphasia (P= 0.005) but no significant relation between END and motor (p=0.15), sensory (P= 0.15) or incoordination (P= 0.54). This was compatible with the results of Attia et al. (2007), who found that among their 40 patients with sICH, motor symptoms represented about 92.5% and speech difficulties represented about 12.5%. But, seizures were higher than ours (17.5%) [18]. This was also matching with the results of Daverat et al. (1991), who estimated that one month mortality was significantly related to hemiparesis (P= 0.003), dysphasia (P= 0.001) and disturbed level of consciousness on admission (P= 0.001) [19]. In contrast to our results, Hu et al. (2013) found in a study including 266 Chinese patients that disturbed level of consciousness was more prevalent (44.0%), followed by focal neurological manifestations (43.2%) [20].

In our study, we found that 47.5% of the patients had GCS score 9- 13 on admission while 7.5% of patients were comatose on admission and there was a highly significant inverse relationship between GCS and patient's mortality (P= 0.000). The same results were obtained by Tuhrim et al. (1988) and El-Tallawy et al. (2005), who found that patient's outcome was significantly related to the level of consciousness as assessed by GCS [21,12]. Wang et al. (2014) and Zis et al. (2014) also determined that there is statistical significant relation of death after ICH with the admission GCS score (p< 0.001 and p= 0.01 respectively) [22,23].

Our results showed that the most prevalent NIHSS scores were moderate (5-15) in 40%, severe (16-20) in 35% and extremely severe (21-42) in 17.5% and there was a highly significant statistical relation between the seven day mortality and NIHSS (P= 0.004). In Hosomi et al. (2009) study, the NIHSS scores were mild in 22.9%, moderate in 22.4%, severe in 23.7% and extremely severe in 22.4% [24]. Essa et al. (2011) and Christensen et al. (2012) also found a statistically significant relationship between mortality following ICH and higher admission NIHSS (p= 0.001 and p< 0.001 respectively) [25,26]. Matched results were obtained by Mahdy et al. (2019) who found that admission NIHSS had a statistically significant relation with the 30 day mortality (P= 0.000) [27].

As regards white blood cells (WBCs) count, it was between 3300 and 27,500 with median 10,000 per microliter. The elevated WBCs count was statistically significant related to END (P=0.001) suggesting that activation of the peripheral immune system aggravated brain damage after ICH. This

was correlated with the results of Mahdy et al. (2015) who found that the elevated WBCs count was statistically significant related to overall mortality (P= 0.010) [28]. This was also matched with the results of Sun et al. (2017) who found that admission leukocytosis is significantly related to poor outcome and END in patients with sICH [29]. Contrary to our results, El-Tallawy et al. (2005) and Behrouz et al. (2015) found that admission leukocytosis had no significant relation to poor outcome (P= 0.9) [12,30].

In the current study, our results showed a statistically significant relation between END and level of CRP measured on admission (P=0.00). This was in agreement with the results of Alexandrova and Danovska (2011) and Di Napoli et al. (2011) who found that the values of serum CRP levels on admission were significantly related fatal outcome (p = 0.003 and P= 0.004 respectively) [31,32]. Likewise, the risk of an adverse outcome increased 1.4 fold in the multivariable analysis for every 10-mg/L increase in CRP on admission according to the results that obtained by Löppönen et al. (2014) [33]. Our results were in disagreement with the results of Canova et al. (1999), who stated that CRP has no clinically beneficial prognostic value in patients with acute ICH. Their explanation was that the elevated CRP after hemorrhagic stroke is not attributable to the event itself, but rather indicates infection or inflammation somewhere else which ultimately necessitates further investigation [34].

In the present study, we found that serum level of LDL Cholesterol (LDL-C) of our patients on admission was 113.23±28.3mg/dL (mean±SD) and there was no significant relation (P=0.375) of patients` outcome and level of LDL-C. This was matching with the results of Ibrahim et al. (2018) who found that there was no significant relation (P=0.354) of patient's outcome and level of LDL-C [35]. Different results were found by Noda et al. (2009), who concluded that low level of LDL was significantly related to the mortality after ICH (P< 0.001) but these results were obtained from the study of 91219 persons during community-based cohort study [36]. Our results were also in disagreement with that of Rodriguez-Luna et al. (2011), who stated that there was significant relation of the low level of LDL-C with hematoma growth (P= 0.003) and END (P= 0.012) but the mean level of LDL-C in their patients was lesser than in our study [37].

In the current study, we found that the hematoma volume varied between our patients with mean volume 32.18±39.6 mm3 ranging from 2.25 to 200 mm3 (with median of volume 20.5 mm3) and there

was an extremely significant relation of END to the initial hematoma volume (P=0.004). Comparable results were also described by Daverat et al. (1991) and El-Tallawy et al. (2005) who found that there was significant relation of hematoma volume on admission with patient`s mortality [19,12].

In our study, we found that the most common site in CT findings was basal ganglia (52.5%) especially left sided (65%) followed by lobar and thalamic (30% and 10% respectively). We also found a statistically significant association between END and lobar location of intracerebral hematoma (P=0.034). Our results were matching with Daverat et al. (1991), Hu et al. (2013) and Lee et al. (2014) who reported that the most common site of ICH was the BG [19,20,38]. This was also matching with the results of Flemming et al. (1999) who found that 16 out of 61 (26%) patients with lobar hemorrhages deteriorated after admission [39]. On the other hand our results were in disagreement with the findings of Attia et al. (2007), who found that lobar hematoma was the most common (65%) then IVH (47.5%) followed by BG (15%) but this study included patients with younger mean of age [17].

In view of our results, we can conclude that lower GCS score, higher NIHSS score, lobar hematoma, and larger hematoma volume were independent predictors for END after ICH.

We recommend that neurologists and ICU specialists should consider adding site and size of the intracerebral hematoma into consideration when predicting neurological deterioration in patients with sICH, since lobar hematoma, and larger hematoma volume appear to be significantly correlated with END of patients with acute sICH.

We also recommend the routine use of GCS and NIHSS score in ICH patients during the initial and follow up evaluation as both can independently predict END of acute sICH.

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