Background
Intracerebral hemorrhage is the most devastating form of stroke. Location and baseline hematoma volume are strong predictors of mortality. Expansion of the initial hematoma is a further marker of poor prognosis. Several risk factors for hematoma expansion (HE) have to be identified.

Objectives
The objectives of this study were to detect the incidence of HE and to study its predictors.

Patients and methods
145 patients underwent this study by analyzing demographic factors and vascular risk factors such as hypertension, diabetes mellitus, and oral anticoagulant intake, as well as clinical factors using National Institutes of Health Stroke Scale (NIHSS) and radiological factors using computed tomography brain imaging.

Results
In this study, HE occurred in 55 (37.93%) patients. Expansion occurred in 45.45% of hypertensive patients, 55.56% of oral anticoagulant intake patients, 45.83% of low cholesterol level patients, 3.64% of diabetic patients, 85.71% of patients with high NIHSS, 35.71% of patients older than 60 years, 20% of patients with atrial fibrillation, and 22.2% of renal patients.

Conclusion
Warfarin intake, hypertension, low cholesterol, normal blood glucose, lack of blood disease, and high NIHSS are the main predictors of HE.

Keywords:
hematoma expansion, hemorrhagic stroke, spontaneous intracerebral hemorrhage

Introduction
Stroke is one of the most common, fatal, and debilitating neurologic diseases [1]. Spontaneous intracerebral hemorrhage (ICH) is a common disease that often leads to death or severe disability [2,3]. Spontaneous ICH is responsible for 6.3–13% of all strokes. The mortality rate from ICH is higher than cerebral infarctions [4], and approaches about 70% in certain patients [5].

Accurate prediction of the outcome in ICH patients is important for several reasons: a reliable prognosis must be given to patients and relatives as soon as possible, realistic rehabilitation goals should be set, and resources should be allocated in the most efficient way. Predicted outcome is also useful in deciding on possible interventions and comparing different treatments for ICH [6].

ICH is a complex pathological process with many of its effects on cerebral tissue as yet undefined. It is very unlikely that only one factor such as hematoma size would uniquely affect prognosis. Thus, the combination of prognostic factors is a logical approach toward outcome prediction. Historically, ICH was considered to be a monophasic event that stopped within minutes of onset. Recent studies reported that the occurrence of hematoma expansion (HE) for the first time was during the first 24 h after symptom onset [7]. HE is now considered one of the most important prognostic factors for mortality and outcome [8]. Several studies have identified clinical and radiological variables that are correlated with HE in ICH patients, such as warfarin intake, hypertension, cholesterol level, blood glucose level, blood diseases, initial hematoma volume, and National Institutes of Health Stroke Scale (NIHSS) [5,6,9].

This study has been conducted to evaluate the HE rate and its possible predictors in patients with spontaneous ICH in Benha, Egypt.

Patients and methods
This is a nested case–control study conducted from October 2015 to November 2016 in Benha University...
Hospitals. Study participants were informed of the possibility of using the data obtained for academic purposes. Confidentiality was assured to all participants and data used for this study were stripped of personally identifiable information.

**Patients**

Study participants were divided into two groups: HE patients \( (n=55) \) and control patients \( (n=90) \). They were selected by considering strict inclusion and exclusion criteria.

**Inclusion criteria**

The inclusion criteria were patients admitted to Benha University Hospitals Neuropsychiatry Department with computed tomography (CT) demonstrating spontaneous ICH, patients of both sexes, and age at least 16 years.

**Exclusion criteria**

Exclusion criteria were age of less than 16 years; patients with a history of head trauma; patients with underlying brain pathology; patients with subdural, subarachnoid, and extradural hemorrhage; and lack of informed consent.

**Methods**

All patients were subjected to the following: CT brain imaging to confirm the diagnosis of ICH, thorough medical history taking, full general and neurological examination, blood pressure monitoring, ECG, blood sugar level, liver function test, kidney function test, and lipid profile. Hematoma volume was calculated (on admission and 24 h after admission) using ABC/2 formula. Patients’ initial stroke severity was assessed by NIHSS scale (on admission and 24 h after admission).

**Statistical analysis**

The collected patients’ data were tabulated and analyzed using the SPSS version 16 software (SPSS Inc., Chicago, ILL company). Categorical data were expressed as number and % and analyzed using \( \chi^2 \) and Fisher’s exact tests. Continuous variables were presented as mean and SD and analyzed using ‘Student’s t-test’. The accepted level of significance in this work was 0.05 \( (P<0.05) \) was considered significant.

**Results**

One hundred and forty-five patients with spontaneous ICH were included in this study; out of them, 90 (62.06%) were male and 55 (37.93%) were female, with a mean age of 55.72±9.93 years, ranging from 36 to 78 years. In all, 55.17% of the patients were smokers, whereas 44.83% were nonsmokers; 37.93% of the patients were diabetic and 75.86% were hypertensive. Patients’ mean BMI was 32.07±4.29, ranging from 25 to 45. In all, 10.34% patients had a history of blood diseases and 31.03% had a history of oral anticoagulant intake. Ninety (62.06%) patients achieved a good outcome, whereas 55 (37.93%) patients had HE. Patient characteristics, medical conditions with spontaneous ICH, and their relation with HE are shown in Table 1.

On admission, as regards the associated medical conditions, 100 (68.97%) patients had high mean arterial pressure, 55 (37.93%) patients had high blood glucose level, and 25 (17.24%) patients had atrial fibrillation (AF) on ECG. The mean NIHSS value at admission was 8.31±3.39, ranging from 3 to 16, whereas after 24 h it was 8.86±5.24, ranging from 3 to 20. High

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics and medical conditions, and their relation to hematoma expansion</th>
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<tbody>
<tr>
<td><strong>Total Expansion</strong></td>
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<tr>
<td>Age group ( (&lt;40) )</td>
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<td>40–50</td>
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<td>Obese Class II (severely obese) (35–40)</td>
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<td>Obese class III (very severely obese) (&gt;40)</td>
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<tr>
<td>Smoking</td>
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<td>Hypertension</td>
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<tr>
<td>Hx of HTN</td>
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<td>No Hx of HTN</td>
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<td>Diabetes mellitus</td>
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<td>Oral anticoagulants intake</td>
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DM, diabetes mellitus; HTN, hypertension; Hx, history.
mean arterial pressure, AF on ECG, and higher NIHSS were associated significantly with HE (Table 2).

Laboratory findings in patients with ICH showed disturbed kidney function tests in 31.03%. Disturbed liver function tests were noticed in 27.57% of patients. Low platelet count was noticed in 31.03% of patients. Low cholesterol level was found in 82.76% of patients. Disturbed kidney function tests and low cholesterol level were associated significantly with HE (Table 2).

Radiological findings in patients with spontaneous ICH showed that the main site of hematoma was deep (62.07%), with a mean volume of 31.16±30.24 cm³, followed by lobar hematoma (34.48%), with a mean volume of 24.67±24.28 cm³. At admission, intraventricular spread of blood was observed in 60 (41.38%) patients, whereas it became 62.76% after 24 h. In all, 13.79% of patients had hydrocephalus. Large hematoma (>50 cm³) and initial site of hematoma had a significant value on HE (Table 3).

### Discussion

Spontaneous ICH is a common disease that is responsible for 6.3–13% of all strokes, with a mortality rate higher than ischemic stroke [10]. Accurate prediction of the outcome in ICH patients is important for a reliable prognosis [11]. Studies show that up to 40% of acute ICH patients suffer significant HE, which is a vital prognostic factor of outcome prediction [12].

In the current study, the mean age of the studied sample was 55.72±9.933 years, with a significant increase of HE rate among older patients. This can be explained by increased incidence of amyloid angiopathy, especially at the cerebral microvascular level in old patients with symptomatic ICH that may lead to increased vessel shearing and lead to hematoma growth [13]. Camacho et al. [14] reported the same as our results, whereas in other studies age was of no significance [15].

In the current study, although there is a slight male preponderance for ICH, there was no significant difference regarding expansion among both genders because other risk factors are similar in both genders. Our study was in agreement with many other studies [16–18].

In all, 110 (75.86%) patients had a past history of hypertension. History of hypertension is associated more with HE, reaching a highly significant value because of impaired autoregulation mechanism in arterioles. Most of the studies agreed with ours [19,20]. However, Qi et al. [21] reported that the association between blood pressure and early HE remains controversial.

In addition, 100 (68.97%) patients had uncontrolled mean arterial blood pressure on admission. Uncontrolled blood pressure on admission is associated more with HE, also reaching a highly significant value. This is because new rupture of other, diseased arterioles may occur, giving rise to multiple, satellite hemorrhages. Our study is in agreement with those of Ovesen et al. [22] and Broderick et al. [10].

Regarding history of diabetes mellitus, we found that HE was significantly higher in those who did not have a history of diabetes rather than the ones who were
diabetic. The percentage of HE was 58.89% out of 90 nondiabetic patients. This may be because the brain edema effect by diabetes does not make sufficient space for hematoma to expand. Hesami et al. [23] and Chen et al. [24] also showed a significant inverse correlation with ICH expansion. In line with these latter studies, Qi et al. [21] found that history of diabetes mellitus was not associated with early HE.

However, also in our study, high blood glucose level on admission had no significance on incidence and rate of HE. Elevated admission blood glucose levels could be the consequence of a stronger metabolic response to stress caused by large hematomas or dense neurological deficits and may not be strongly relied on the study by Ovesen et al. [22]. Brouwers et al. [20] and Thorsten et al. [18] have the same results as ours.

Abnormalities in ECG denoting AF in our study were recorded in 17.24% of our patients, and they had poor outcome in comparison with patients with normal ECG records. In agreement with our study, Dowlatshahi et al. [25] and Ovesen et al. [22] reported that ICH patients with AF on admission tend to have more HE than others.

In all, 45 (31.03%) patients had a history of oral anticoagulant intake, of whom 25 patients showed HE after 24 h. We found that history of oral anticoagulant intake is a highly significant strong predictor of HE. Warfarin use increases the risk of progressive bleeding and clinical deterioration, and doubles the risk of mortality [26]. In agreement with our study, Brouwers and colleagues and many others reported that the effect of anticoagulation with warfarin on ICH volume is probably the most striking finding of their studies [19,20,27].

We found that low platelet count in patients with symptomatic ICH during admission has no value in detecting HE. Only 31.03% of the patients had lab results of low platelet counts, with a small percentage of them having HE. This can occur because the platelets can still function properly despite the low platelet count. Ovesen et al. [22] disagree with our results, as they reported that during inpatient admission patients with low platelet counts—mostly due to anti-platelet therapy—had a higher risk of hematoma growth.

In this study, the cholesterol level was found to be significant to determine the outcome. There was no expansion with patients with dyslipidemia, whereas the expansion rate was highly significant with patients with low cholesterol levels. Similarly, Yingxu et al. [28] reported that there were no patients with primary ICH in their study on hypercholesterolemia. Explanations of why lower cholesterol levels could induce HE are weakening of the endothelial wall because of smooth muscle cell necrosis, reduction of platelet aggregability, and increase in the osmotic fragility of the erythrocyte cell membranes [29].

We found that 31.03% of the patients had primary impairment on admission. Larger hematoma volumes were observed among patients with renal impairment. Lai et al. [30] stated that raised serum creatinine and urea levels even within conventional reference intervals had a higher HE risk. Adults with kidney disease may develop a platelet defect that tends to parallel the patient’s increases in blood urea nitrogen and creatinine.

In addition, Yao et al. [31] showed that the incidence of enlargement significantly increased with severity of liver dysfunction. In our study, we found the opposite; only 27.57% of patients had a history of hepatic impairment with low incidence of HE, which was not significant enough to predict HE. This can be explained by the fact that liver dysfunction must be accompanied with increased consumption of alcohol or thrombocytopenia for HE to occur.

Initial site of hematoma is a very strong factor to predict hematoma enlargement. We found that HE was higher in deep hematomas, followed by lobar, and then other sites. We found that the site has a high significance value to predict HE. In agreement with our study, Inagawa et al. [32] and Brouwers et al. [20] reported that the determinants of hematoma volume differ by the location in ICH.

Patients who had larger baseline hematoma volumes showed higher HE rates in our study. Our results are in concordance with Chan et al. [33], who reported that hematoma volume of more than 60 cm³ was considered as a bad prognostic factor in a logistic regression model. The presence of a large hematoma at baseline CT scan may increase the effect of vessel shearing, cerebral edema, and high ICP leading to HE [21].

Other CT features, in particular intraventricular extension of the ICH, were not indicators of poor outcome; in our study, Silva et al. [34] and Yao and colleagues reported that intraventricular hemorrhage does not predict HE in patients with spontaneous ICH [35]. In disagreement with our study, other studies reported that intraventricular spread of blood is a strong indicator of HE and mortality [35,36].
In this study, the percentage of hydrocephalus related to HE has no significant value. In agreement with our study, others reported that SICH might lead to obstructive hydrocephalus that is probably not related to HE [37,38]. However, Qi et al. [21] reported that early HE had been observed in greater than one-third of patients with hydrocephalus after spontaneous ICH.

One of the most consistent and reliable clinical predictors of outcome and HE is the NIHSS on admission or in the first 24h after onset, in this study. We found that NIHSS score of 16 or more had an adverse impact on outcome and considered a highly significant predictor of HE. Other studies also revealed that NIHSS is particularly predictive of HE when NIHSS is 21 or more [25,39,40].

**Conclusion**

The present results revealed a highly significant increase in HE rate within spontaneous ICH patients. We have identified risk factors in this study that, if taken together, are highly predictive of HE after spontaneous ICH. A strong association was found between warfarin intake, hypertension, low cholesterol, normal blood glucose, lack of blood disease and high NIHSS, and HE. We also noticed that common risk factors such as age, AF, renal impairment, and initial site and size of hematoma were associated with HE but did not reach a highly significant prognostic value such as the factors mentioned before them.

**Recommendations**

Taking into account all the limitations of the study and the previous studies on the prevalence of hemorrhagic stroke, we recommend that patients with a history of warfarin intake or hypertension, lab results of low cholesterol, normal blood glucose, lack of blood disease and high NIHSS, and HE. We also noticed that common risk factors such as age, AF, renal impairment, and initial site and size of hematoma were associated with HE but did not reach a highly significant prognostic value such as the factors mentioned before them.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**


