

The role of imaging in predicting 3-month prognosis of primary intracerebral hemorrhage: a single-center, prospective observational study in tertiary care hospital

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Background: Due to the high morbidity and mortality of primary intracerebral hemorrhage (ICH), several non-contrast computed tomography (NCCT) imaging markers were proposed to determine the prognosis of affected patients. We prospectively evaluated the predictive accuracy of certain imaging features and established a predictive model composed of highly relevant imaging and clinical features to identify the 3-month functional outcome in primary ICH patients

Methods: Patients admitted for primary ICH to a tertiary care center (Al-Zahra Hospital, Isfahan, Iran) were prospectively included from September 2021 to October 2023. Inclusion criteria were defined as: Patients aged ≥ 18 years with primary or spontaneous ICH confirmed on NCCT at the time of admission. The baseline NCCT was conducted in the early stage of ICH (within 6 hours from symptom onset). The initial NCCT images were obtained within 6 hours from symptom onset. After 3 months, functional outcome of patients was assessed using the modified Rankin Scale (mRS); with mRS ≥ 3 as poor prognosis and mRS ≤ 2 as favorable prognosis. The Chi-squared and Logistic regression tests were used for determining the association between clinical and imaging features in differentiating patients' prognosis. Machine learning algorithm [support vector machine (SVM)] was also used to determine the importance rate of each relevant imaging sign in predicting prognosis.

Results: A total of 203 primary ICH patients were included, among which 119 patients (58.6%) had unfavorable prognosis at 3 months. Age, diastolic blood pressure, and Glasgow Coma Scale (GCS) score at admission were significantly associated with prognosis. Among imaging features, hemorrhage volume [95% confidence interval (CI): 0.972–0.991, $P < 0.001$], the presence of midline shift (95% CI: 2.038–7.911, $P < 0.001$), blend sign (95% CI: 1.081–3.760, $P = 0.026$), satellite sign (95% CI: 1.451–4.764, $P = 0.001$), and black hole sign (95% CI: 2.262–12.714, $P < 0.001$) were significantly different among 2 groups. SVM algorithm showed hemorrhage volume the most important prognostic imaging feature (importance rate: 100%), along with black hole (63.1%), midline shift (54%), satellite (20.4%), and blend sign (15.6%); with decreasing order of importance.

Conclusions: Using certain radiological and clinical features, we established a model with considerable prognostication in management of patients with primary ICH in emergency departments.

Keywords: Intracerebral hemorrhage (ICH); neuroimaging; machine learning; prognosis; imaging features

Submitted Jun 26, 2024. Accepted for publication Mar 26, 2025. Published online Jun 03, 2025.

doi: 10.21037/qims-24-1299

View this article at: <https://dx.doi.org/10.21037/qims-24-1299>

Introduction

Spontaneous or primary intracerebral hemorrhage (ICH), accounting for 85% of all cases of hemorrhagic strokes, is characterized by non-traumatic bleeding within the brain parenchyma, typically caused by small-vessel disease due to amyloid angiopathy or chronic, uncontrolled hypertension (1,2).

Although ICH accounts for approximately 10–20% of all stroke cases worldwide, it remains the most lethal stroke type, with a 30-day mortality rate of up to 40% and 1-year mortality rate of up to 50%. Despite recent advances in the interventional management of ischemic stroke patients, the beneficial effects of medical and interventional treatment on the survival and long-term prognosis of patients with ICH have lagged in recent clinical trials (3,4). Consequently, early accurate stratification of ICH outcomes in the emergency department is strongly desired and would facilitate the implementation of appropriate therapeutic options for affected patients (5). As a result, several prognostic tools encompassing different combinations of imaging markers were introduced to manage patients with primary ICH. Most notably, imaging markers of hemorrhage expansion held great promise in predicting prognosis in patients with ICH. These imaging signs include the spot sign, the spot-tail sign in computed tomography (CT) angiography, along with the island sign, blend sign, satellite sign (SS), black hole sign, and swirl sign in non-contrast computed tomography (NCCT). These imaging features are clinically important, as their presence elaborates the need for the initiation of anti-hematoma expansion treatments in the acute phase of ICH (6). The volume of the hemorrhage is another important prognostic indicator for 30-day mortality in primary ICH (7).

NCCT of the brain remains the imaging modality of choice in the acute setting (8). In addition to differentiating ICH from Ischemic stroke, NCCT provides detailed information about probable hemorrhage etiology and quantitative imaging features such as hemorrhage location and volume, midline structure shift, presence of intraventricular hemorrhage (IVH), and markers for early hematoma expansion including the black hole sign (BHS), the SS, and the blend sign (9,10). Baseline hematoma volume was found to be a well-known predictor of hematoma expansion and poor functional outcome in ICH (7,11,12). In addition, markers for early hematoma expansion were related to unfavorable clinical outcomes within 90 days in patients with ICH (13). Early, accurate

identification of NCCT markers suggestive of hematoma expansion is crucial, as the implementation of anti-hematoma expansion therapies will be translated into more favorable clinical outcomes in ICH patients (14). In addition to radiological parameters, several clinical indicators were shown to be predictive of poor outcome in ICH, including advanced age, increased systolic blood pressure, and lower Glasgow Coma Scale (GCS) score at presentation (7,15,16). For instance, lower GCS at presentation, previous ischemic stroke, and history of smoking were correlated with ICH expansion and indicated poor prognosis (16). Therefore, it is imperative to note certain clinical and laboratory markers in the initial encounter of primary ICH patients to improve prognostication and medical decision-making in affected patients.

Consequently, considering the high morbidity and mortality of primary ICH and the importance of determining early prognosis using predictive models and the lack of similar studies in our country, this study aimed to establish a predictive model using relevant neuroimaging features and clinical parameters in determining the 90-day functional outcome in patients with primary ICH. This study provides an easy-to-employ prognostication model for clinicians in the emergency department and would improve medical decision-making in the management of patients with primary ICH. In our current study, we also employed a machine learning algorithm [support vector machine (SVM)] to evaluate the predictive role of certain imaging features for differentiating ICH patients with poor and good prognosis. We present this article in accordance with the TRIPOD+AI reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-24-1299/rc>).

Methods

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institutional Ethics Committee of Isfahan University of Medical Sciences (approval date: 8/1/2021, protocol code IR.MUI.MED.REC.1400.446) and the National Research Ethics Board (approval number IR.MUI.MED.REC.1400.446). Written and verbal informed consent were obtained from participants after a complete explanation of the study. For patients with impaired consciousness, we obtained informed consent from their families. For such patients, according to our national medical ethical committee guidelines, we initially approached their first-degree male

relative (if applicable) and patients' spouses were approached for obtaining informed consent in other cases. For rare instances when neither a male relative nor a spouse were available, we obtained informed consent from the patients' older children.

Patient selection and study design

In this prospective study, we recruited and analyzed imaging and clinical markers of 203 patients with primary ICH between September 2021 and October 2023 who were referred to and hospitalized at our university hospital (Al-Zahra General Hospital, Isfahan University of Medical Sciences, Iran), which is a large tertiary stroke center. Inclusion criteria were defined as: Patients aged ≥ 18 years with primary or spontaneous ICH confirmed on NCCT at the time of admission. The baseline NCCT was conducted in the early stage of ICH (within 6 hours from symptom onset). Patients were excluded from our study if they had any of the following: (I) traumatic brain injury, (II) secondary ICH due to hemorrhagic transformation following ischemic infarction, hemorrhage associated with brain tumor, arteriovenous malformation, cerebral cavernous malformation, dural arteriovenous fistula, intracranial venous thrombosis, or rupture of intracranial aneurysms, (III) presence of primary IVH, (IV) neurosurgical hematoma evacuation or external ventricular drainage prior to obtaining brain imaging, (V) CT images with severe artifact, and (VI) previous or current history of consumption of anticoagulant medications. Patients' baseline demographic characteristics (age, gender), underlying comorbidities (history of hypertension, diabetes mellitus, central nervous system diseases such as ischemic stroke, cardiovascular diseases, and renal diseases), baseline GCS score, and smoking history were also collected using a defined paper research template at admission. Data regarding imaging features were also collected in our devised paper research templates and were transferred onto Excel sheets for analytical purposes.

Image data and evaluation

All images were acquired using the same scanning protocol in the 64-slice spiral CT scanner (Siemens). The protocol consisted of 120 KV, 280 mA, axial layer thickness 5 mm, and CTDIvol >40 mGy. For more consensus, all baseline NCCT images were simultaneously examined by an experienced radiologist (S.H.), who had 10 years

of experience in neuroradiology and a radiology resident (T.J.) with 1 year of neuroimaging diagnosis experience and the following imaging features were evaluated using standardized definitions (17):

(I) Hemorrhage location: deep (basal ganglia, thalamus, internal capsule, corona radiata, or corpus callosum), brain hemisphere, cerebellum, brainstem, and others.

(II) Hemorrhage volume quantification: using the ABC/2 method (also known as Tada formula) for parenchymal ICH without IVH. In this method, A corresponds to the largest hematoma diameter on axial image, B corresponds to the largest perpendicular diameter to A on the same image slice, and C corresponds to the number of slices in which the hematoma was observed multiplied by the slice thickness (*Figure 1*) (18). For ICH with an intraventricular component, only the parenchymal component was assessed using this formula. All the lengths were measured in cm and volumes in mL.

(III) Presence of midline shift: The midline of the brain was determined by drawing a line connecting the anterior and posterior borders of the falx cerebri. The maximum vertical distances from the center of the midbrain, septum pellucida, pineal calcification, and the falx cerebri to the brain midline were measured and recorded as the midline shifts in mm. If different midline shift values were present in multiple slices, we chose the maximum value from all recorded midline shift values. As previous studies have reported different thresholds for midline shift (13,16,19), in this study we have also selected 3 mm as the cutoff value for further analyzing its association with the prognosis of primary ICH, where (yes/no; yes defined as a midline shift greater than 3 mm). We also evaluated whether different midline shift values were correlated with prognosis.

(IV) The presence or absence of markers of hematoma expansion; including the blend sign, the SS, and the BHS. The criteria for each of the relevant imaging signs were as follows (20):

- ❖ Blend sign: uneven densities with an attenuation difference of at least 18 Hounsfield units (HU) between the areas with different densities (*Figure 2A*).
- ❖ SS: any small hematoma completely isolated from the main hematoma observed at least in one image slice. The shortest distance between

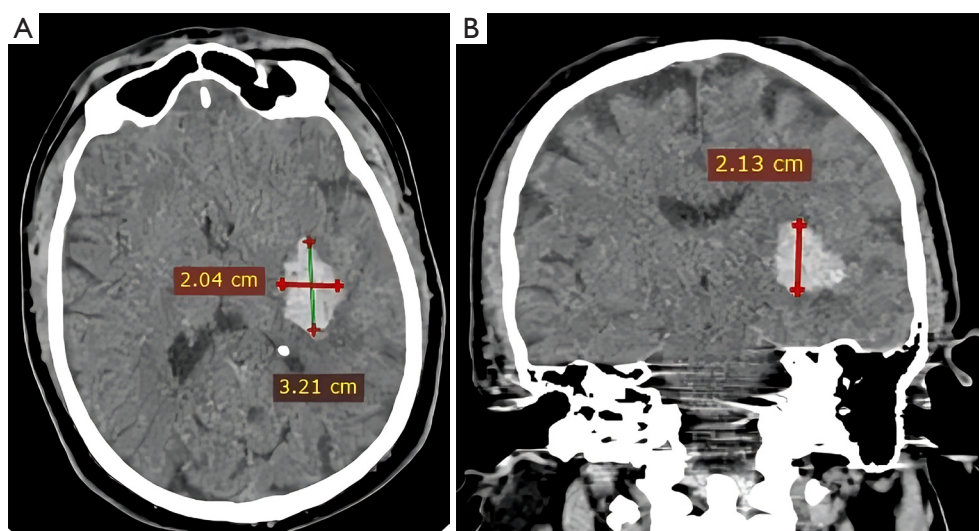


Figure 1 A 78-year-old male with primary ICH in the right temporal lobe. NCCT axial (A) and coronal images (B) show how to calculate ICH with ABC/2 formula. In this patient, it is approximately 6.7 cc. ABC/2, ellipsoid volume equation in which A represents the maximum length in cm, B represents width perpendicular to A on the same slice, and C represents the number of slices multiplied by the slice thickness. ICH, intracerebral hemorrhage; NCCT, non-contrast computed tomography.

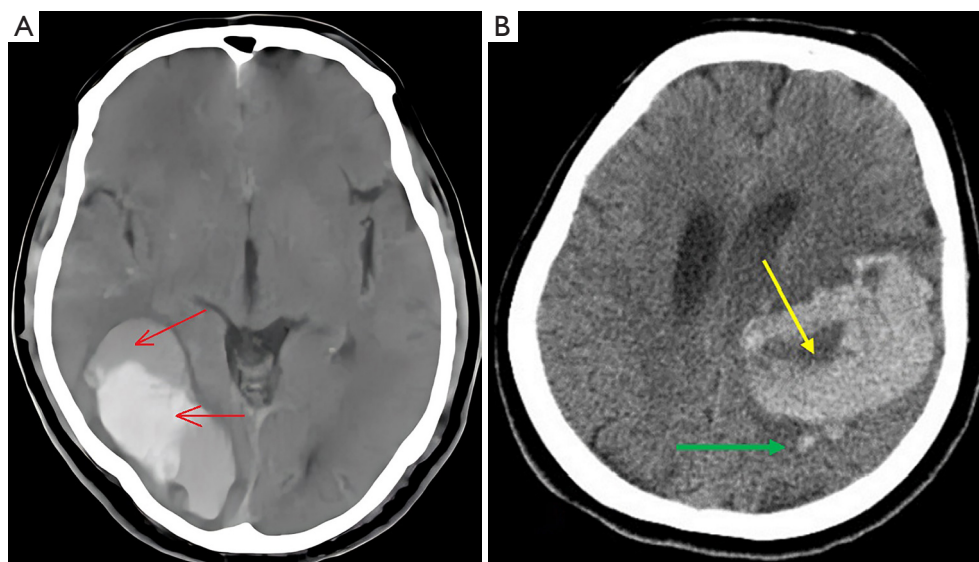


Figure 2 NCCT axial images. (A) Right occipital ICH with two different densities (blend sign, red arrows). (B) Left parietal ICH. The hypodense area within the hematoma (black hole sign, yellow arrow) and two small hematomas seen separately in the posterior aspect of the largest one (satellite sign, green arrow). ICH, intracerebral hemorrhage; NCCT, non-contrast computed tomography.

this small hematoma and the main hematoma was 1–10 mm (*Figure 2B*).

- ❖ BHS: hypodense area that is encapsulated within a hyperattenuating hematoma, with a

density difference of at least 28 HU between 2 areas of different densities (*Figure 2B*).

Images with poor quality or artifacts were excluded from our study.

Outcomes

After the initial NCCT of the brain was obtained and stored in the picture archiving and communication system (PACS) for future comparison, patients were followed at 90 days and their functional neurological outcome was evaluated using the modified Rankin Scale (mRS) (21,22) at 90 days post-discharge via telephone interview conducted by a trained medical staff (23). Our trained medical staff was blind to the patients' clinical and imaging data and performed the interview using a structured, Persian-translated version of mRS. This approach was employed to ensure adequate follow-up and reduce attrition. Based on mRS, a binary outcome was defined as a good prognosis (mRS ≤ 2) or a poor prognosis (mRS ≥ 3) (24).

Statistical analysis

The sample size was calculated 203 using logistic regression model and considering type one error rate of 5% and statistical power of 80% previous similar studies (25). Continuous and categorical data are reported as mean $\pm$ standard deviation (SD) for normally distributed data [median (range) for non-normally continuous variables] and frequency (percentages), respectively. The normality of continuous data was evaluated using the Kolmogorov-Smirnov test and Q-Q plot. Non-normally positive skewed data were subjected to logarithmic transformation for normalization. Continuous normally and non-normally distributed data were compared between two groups using independent samples *t*-test and non-parametric Mann-Whitney *U* test, respectively, while categorical variables by using the chi-squared test.

In this study, we tested the predictive value of various imaging features and clinical and demographic characteristics using chi-squared test and logistic regression. Those predictors that were significantly associated with dependent variable in univariate analysis were entered into multivariable logistic regression. Results of logistic regression were reported as odds ratio (OR) and 95% confidence interval (CI) for OR. During logistic regression modeling, we adjusted the predictive role of imaging features for potential confounding variables, such as age and gender. We also used machine learning algorithm SVM to evaluate the predictive role of imaging features for determining patient prognosis. Features we used in SVM were those predictors which we identified them as significant predictors of poor prognosis in univariate and

multivariable analyses. To ensure the generalizability and robustness of the models, the dataset is split into training and test sets, where the training set comprised 70% of samples is used to build the model, and remaining, i.e., 30% was considered as the test set, which was used for evaluating its performance. Moreover, the hyperparameters of the algorithms are tuned using 5-fold cross-validation within the training set, wherein the data is divided into five subsets, and the model is trained five times, each time using four subsets for training and one subset for validation. After finding the best values for hyperparameters, we use several metrics, including area under the receiver operator characteristic curve (AUC), sensitivity, specificity, and accuracy to determine the best performing model. All conventional statistical analyses were performed using SPSS version 26 (IBM Corp., SPSS Statistics for Windows, Version 26.0., Armonk, NY, USA) and SVM was run by using R free statistical software version 4.4 (R Core Team, 2023).

Results

Baseline characteristics

A total of 203 patients [female 78 (38.4%), male 125 (61.6%)] with primary ICH were identified during our study period, among whom 119 patients (58.6%) developed unfavorable prognosis in terms of functional neurological outcomes based on mRS. There was no statistically significant association between sex, history of hypertension, diabetes mellitus, cardiovascular diseases, renal diseases, previous ischemic stroke, elevated systolic blood pressure, and smoking ($P > 0.05$). However, for age, diastolic blood pressure, and GCS score at admission there were significant differences between the two groups ($P < 0.05$); indicating that advanced age (mean 68 ± 14.35), higher diastolic blood pressure (97.37 ± 24.67), and lower GCS score (mean 9.82 ± 4.92) at admission were associated with poor prognosis in primary ICH patients. The demographic and clinical characteristics of patients are shown in *Table 1*.

NCCT imaging markers and prognosis

Among NCCT imaging features obtained at baseline, the location of hemorrhage was not associated with different prognosis among patients (all $P > 0.05$). The volume of the hemorrhage was considerably associated with 90-day prognosis ($P = 0.001$), patients with larger hematoma

Table 1 Comparison of baseline clinical, demographic, and NCCT imaging features between primary ICH patients with favorable and poor prognosis

Characteristics	Favorable prognosis (N=84)	Poor prognosis (N=119)	P value
Gender			0.122
Female	27 (32.1%)	51 (42.9%)	
Male	57 (67.9%)	68 (57.1%)	
Age (years), mean $\pm$ SD	60.89 $\pm$ 14.56	68 $\pm$ 14.35	0.001
SBP at admission (mmHg), mean $\pm$ SD	161.74 $\pm$ 31.16	170.46 $\pm$ 34.9	0.064
DBP at admission (mmHg), mean $\pm$ SD	91.69 $\pm$ 15.47	97.37 $\pm$ 24.67	0.046
Baseline GCS score, mean $\pm$ SD	12.92 $\pm$ 3.46	9.82 $\pm$ 4.92	<0.001
Disease history			
DM			0.983
Yes	26 (41.3%)	37 (58.7%)	
No	58 (41.4%)	82 (58.6%)	
HTN			0.654
Yes	59 (40.4%)	87 (59.6%)	
No	25 (43.9%)	32 (56.1%)	
CNS disease			0.531
Yes	20 (37.7%)	33 (62.3%)	
No	64 (42.7%)	86 (57.3%)	
Cardiovascular disease			0.576
Yes	19 (38%)	31 (62%)	
No	65 (42.5%)	88 (57.5%)	
Renal disease			0.326
Yes	1 (20%)	4 (80%)	
No	83 (41.9%)	115 (58.1%)	
Smoking			0.176
Yes	13 (54.2%)	11 (45.8%)	
No	71 (39.7%)	108 (60.3%)	
Hematoma volume (mL)			
Mean $\pm$ SD	20.56 $\pm$ 29.34	45.54 $\pm$ 50.15	0.001
Median	9	30	
ICH location			
Brainstem			0.117
Yes	5 (25%)	15 (75%)	
No	79 (43.2%)	104 (56.8%)	

Table 1 (continued)

Table 1 (continued)

Characteristics	Favorable prognosis (N=84)	Poor prognosis (N=119)	P value
Cerebral hemispheres			0.760
Yes	30 (40%)	45 (60%)	
No	54 (42.2%)	74 (57.8%)	
Basal ganglia			0.065
Yes	30 (34.1%)	58 (65.9%)	
No	54 (47%)	61 (53%)	
Thalamus			0.342
Yes	19 (35.8%)	34 (64.2%)	
No	65 (43.3%)	85 (56.7%)	
Cerebellum			0.613
Yes	8 (36.4%)	14 (63.6%)	
No	76 (42%)	105 (58%)	
Midline shift >3 mm			<0.001
Yes	14 (20.9%)	53 (79.1%)	
No	70 (51.5%)	66 (48.5%)	
Midline shift (mm)			<0.001
Mean $\pm$ SD	1.07 $\pm$ 2.55	4.4 $\pm$ 5.62	
Median [range]	0 [0, 11]	0 [0, 22]	
CT imaging signs			
Black hole sign			<0.001
Yes	7 (15.2%)	39 (84.8%)	
No	77 (49%)	80 (51%)	
Satellite sign			0.001
Yes	24 (28.2%)	61 (71.8%)	
No	60 (50.8%)	58 (49.2%)	
Blend sign			0.026
Yes	20 (30.3%)	46 (69.7%)	
No	64 (46.7%)	73 (53.3%)	

Independent *t*-test, ANOVA test, and Chi-squared test were used for statistical analysis. ANOVA, analysis of variance; CNS, central nervous system; CT, computed tomography; DBP, diastolic blood pressure; DM, diabetes mellitus; GCS, Glasgow Coma Scale; HTN, hypertension; ICH, intracerebral hemorrhage; NCCT, non-contrast computed tomography; SBP, systolic blood pressure; SD, standard deviation.

volume at baseline (median 30 mL, 45.54 $\pm$ 50.15 mL) experiencing unfavorable outcomes at 90 days and those with smaller bleeding volume (median 9 mL, 20.56 $\pm$ 29.34 mL) developing favorable prognosis. Among 203 patients, 67

patients (33%) had midline shift >3 mm at initial NCCT imaging, of which 53 patients (79.1%) developed poor prognosis and 14 patients (20.9%) showed favorable prognosis and this association was shown to be statistically

Table 2 Association of NCCT imaging markers with 90-day prognosis using logistic regression analysis and machine learning SVM algorithm

Imaging marker	Odds ratio (95% CI)	P value	Importance rate with machine learning
Volume	0.981 (0.972–0.991)	<0.001	100%
Midline shift >3 mm			
Yes	4.015 (2.038–7.911)	<0.001	54%
No	1 (reference)		
Black hole sign			
Yes	5.362 (2.262–12.714)	<0.001	63.1%
No	1 (reference)		
Satellite sign			
Yes	2.629 (1.451–4.764)	<0.001	20.4%
No	1 (reference)		
Blend sign			
Yes	2.016 (1.081–3.760)	0.026	15.6%
No	1 (reference)		

CI, confidence interval; NCCT, non-contrast computed tomography; SVM, support vector machine.

significant ($P<0.001$). When evaluating the amount of midline shift in mm, we found that higher midline shift values (4.4 ± 5.62 mm) were inversely associated with prognosis at 3 months ($P<0.001$). Among CT imaging signs evaluated in this study, SS was the most frequently observed sign among patients (85, 41.9%), followed by the blend sign (66, 32.5%), and BHS (46, 22.7%). The presence of any of these imaging signs on initial NCCT was associated with worse outcome (all had $P<0.05$). Baseline imaging features of patients are demonstrated in *Table 1*.

Predictive accuracy of CT imaging features using logistic regression

The results of the logistic regression analysis (*Table 2*) for imaging characteristics shown to be statistically significant in prognosis determination, showed that higher volume of bleeding increases the risk for developing poor 90-day outcome (OR =0.981, 95% CI: 0.972–0.991, $P<0.001$). In addition, patients with midline shift greater than 3 mm were approximately 4 times more likely to experience unfavorable prognosis compared to patients without midline shift (OR =4.015, 95% CI: 2.038–7.911, $P<0.001$). Moreover, the presence of BHS was associated with a 5.3-fold increased risk of worse prognosis in primary ICH patients (OR =5.362, 95% CI: 2.262–12.714, $P<0.001$). SS

and blend sign also correlated with up to 2-fold increased risk of unfavorable prognosis (OR =2.629, 95% CI: 1.451–4.764, $P<0.001$ and OR =2.016, 95% CI: 1.081–3.760, $P=0.026$; respectively). The final fitted logistic regression model containing the aforementioned resulted 75% correct classification rate.

For determining the importance rate of each imaging sign in differentiating patients based on their 90-day mRS score, we used the SVM machine learning algorithm. Among the statistically significant imaging markers, hemorrhage volume was shown to have the highest importance rate in determining prognosis (importance rate: 100%). Other imaging signs in decreasing order of importance included, BHS (importance rate: 63.1%), midline shift greater than 3 mm (importance rate: 54%), SS (importance rate: 20.4%), and blend sign (importance rate: 15.6%) (*Table 2*).

We also utilized the SVM method using the above imaging features to establish the 90-day prediction model with the best performance. In the training set, the sensitivity and specificity were 47.3% and 76.2%, respectively, with the diagnostic accuracy rate of 64.7%. In the validation set, the sensitivity and specificity were 75% and 68.6%, respectively, and the diagnostic accuracy rate was 71.4%. The AUC of our model was calculated to be 0.737 ($P<0.001$) (*Figure 3*). All these results indicate relatively high correct

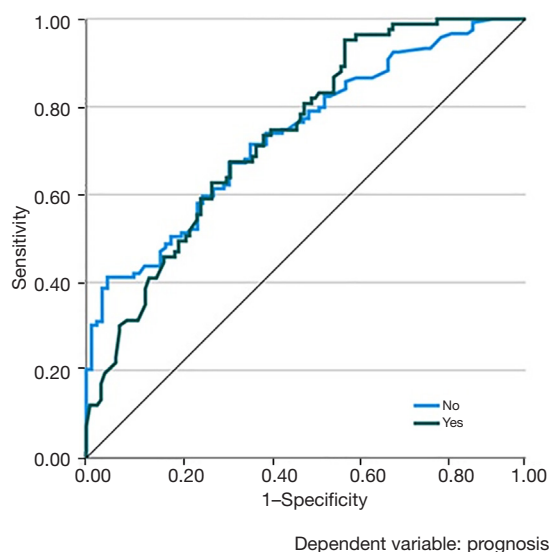


Figure 3 The ROC curve for NCCT imaging markers correlated with prognosis using machine learning algorithm (AUC =0.737, $P<0.001$). AUC, area under the ROC curve; NCCT, non-contrast computed tomography; ROC, receiver operator characteristics.

predictive ability of the fitted model.

Discussion

In this prospective study, we established a prognostication model for predicting the functional outcome of patients with primary ICH. The proposed model consisting of certain radiological features obtained from initial NCCT (hemorrhage volume, presence of midline shift, and the presence of markers of hematoma expansion such as blend sign, the BHS, and the SS) displayed considerable discriminative accuracy between unfavorable and favorable functional outcome of primary ICH based on mRS at 3 months. Machine learning-based analysis using the SVM algorithm also demonstrated classification performance and stability of these imaging parameters across all nested cross-validation runs, indicating sufficient generalizability of our results. The presence of certain clinical conditions was also associated with unfavorable prognosis, including higher diastolic blood pressure at presentation, advanced age, and lower GCS score at admission. Several predictive models encompassing radiological and clinical characteristics were proposed to determine the outcome of primary ICH patients at admission. There is growing interest in the early application of CT scan-based prognostication scoring

systems for evaluation of patients suspected of having ICH and it has shown acceptable discriminative ability equal to computed tomography angiography (CTA) for predicting neurological outcomes (16,26).

It is a well-established paradigm that hemorrhage volume profoundly impacts functional clinical outcome for ICH patients (7). Several studies have proposed different cut-off values for hematoma volume for prognostication, with the majority reporting baseline volumes of 20–30 mL or greater suggestive of hematoma expansion and neurological deterioration, whereas baseline volumes of 10 mL or less were associated with more favorable clinical outcome and lower probability of hematoma expansion (11,27–29). In line with these findings, we found that patients with poor prognosis had a mean baseline ICH volume of 45.54 ± 50.15 mL. Machine learning-based assessment of predictive performance also showed the greatest predictive power for ICH volume, with OR =0.981, 95% CI: 0.972–0.991, $P<0.001$ and the importance rate of 100%; further indicating hemorrhage volume as the strongest indicator of 90-day outcome for primary ICH. When the bleeding sites were compared between patients with unfavorable and favorable prognosis within 3 months of the index ICH, we found no statistically significant association between hemorrhage location and functional outcome; discouraging the results of previous studies (29–33). The INTERACT2 study showed that hemorrhages originating from the thalamus, posterior limb of the internal capsule, and cerebellum were associated with poor functional outcome, specifically thalamic and internal capsule bleeding had the greatest association with major disability or death (31). In another study of Park *et al.* (29), bleeding within the posterior limb of internal capsule and thalamus were independent predictors of poor outcome in primary ICH. The proposed mechanisms for poor outcome associated with deep hemorrhages include functional coagulation differences, different anatomical structure injury, and higher hematoma expansion in deep bleeding (30,32). Contrary to this, results of The FAST trial showed that lobar ICH was associated with larger baseline hemorrhage volume, greater expansion of hemorrhage, and worse 90-day functional outcome in unadjusted analysis; however when adjusting for factors influencing outcome, patients with deep ICH paradoxically had worse outcome in 3 months (33). Despite the reported discrepancy and complex relationship between location of bleeding and 90-day functional outcome in the literature, our study showed no significant relationship between bleeding location and prognosis; although patients with hemorrhage

in the basal ganglia had worse outcome compared to other locations, this association was not statistically significant. The discrepancy observed in our study might be due to shorter follow-up period compared to previous studies.

Our study also demonstrated that the presence of midline shift correlated with poor outcome (OR =4.015, 95% CI: 2.038–7.911, $P<0.001$, and importance rate 54%), with the mean value of 4.4 ± 5.62 mm observed among patients with poor prognosis. Previous studies evaluating the association between midline shift value and clinical outcome in primary ICH patients reported different cut-off values ranging from 3.7 to 6 mm, to be a clinically significant threshold for worse outcome (34–36). In accordance with previous studies, our study found a low threshold for poor prognosis in terms of midline shift (34,35). In this study, NCCT-based markers of hematoma expansion; the blend sign, the BHS, and the SS were all significantly associated with poor outcome in primary ICH ($P<0.05$), with the BHS being the most important predictor on machine learning analysis (importance rate: 63.1%) followed by the SS (importance rate: 20.4%) and the blend sign (importance rate: 15.6%). This finding is in correlation with previous studies indicating that the BHS on initial NCCT is independently associated with poor outcome at 90 days with high specificity (37–39). The appearance of BHS on NCCT indicates that the presence of bleeding spots of varying age within the heterogeneous hematoma and risk for future hematoma growth. Additionally, Li *et al.* (40) found that blend sign may be identified on initial NCCT with high specificity (95.5%) for predicting hematoma expansion and poor outcome. The development of blend sign indicates an area of mixed hemorrhage with different bleeding times with possible re-bleeding and hematoma expansion (16). In another study in patients with primary ICH, the BHS and the blend sign were independent predictors of poor outcome, with the blend sign demonstrating higher accuracy (AUC for blend sign: 0.660 *vs.* BHS: 0.620) (39). Furthermore, the SS was an independent predictor of hematoma expansion and poor outcome in previous studies (41,42). Collectively, there is a wide heterogeneity in the reported predictive performance metrics of these NCCT imaging markers (17). It is important to consider that all these imaging markers represent different points of a continuum sharing a similar pathophysiological change and that these imaging-based markers should be used in combination with other important prognosis indicators, such as clinical variables to improve their predictive accuracy.

In this study, we also evaluated the influence of several clinical indicators in the prognosis of primary ICH patients. In line with previous studies (15,43), advanced age at presentation correlated with poor 90-day functional outcome, with the cut-off value of 68 years for differentiating between favorable and unfavorable prognosis. Gender was not a predictor of prognosis between the 2 groups in our study. Several studies have found that females was associated with higher ICH scores and worse prognosis, due to the more intense inflammatory responses generally present in females and various socioeconomic factors that may limit females' access to adequate medical care (44,45). This observed discrepancy might be attributable to variations in female study population, as the majority of female patients have equal access to healthcare services in our hometown. Additionally, in line with the results of our study, Amer *et al.* (15) conducted a study on 70 patients with primary ICH and evaluated the clinical and radiological parameters in determining prognosis. They found that gender was not a determining predictive indicator of worse functional outcome.

The association between hypertension and development of ICH was extensively investigated in the literature; and elevated systolic blood pressure at admission correlated with poor prognosis (46,47). Our study showed that patients with elevated diastolic blood pressure at presentation (97.37 ± 24.67 mmHg) had unfavorable 90-day outcome and high systolic blood pressure values and hypertension per se were not statistically different among the 2 groups. This may imply that the nominal value of blood pressure at admission is not the only indicator of outcome in affected patients, rather the dynamic changes in blood pressure during follow-up and hospitalization period may profoundly impact final prognosis (48). Additionally, the intensive blood pressure lowering during hospitalization might have lowered the risk of hematoma expansion and poor outcome among our study participants.

While there may be a modest association between diabetes mellitus and the development of ICH and its prognosis (49), no correlation with the final outcome was reported in other studies (15,50). Our study also showed that diabetes mellitus was not correlated with unfavorable outcome. It is imperative to note that uncontrolled diabetes mellitus might profoundly facilitate atherosclerosis and cause worse prognosis in patients with primary ICH. However, patients in our study, had adequately controlled blood glucose levels at hospitalization and their prognosis was not inversely affected.

Despite the underlying detrimental alterations of the cerebrovascular system of patients with ICH, a history of cerebrovascular diseases was not correlated with prognosis in our study. In a study of Wong *et al.* (51), it was shown that stroke recurrence rate was high in patients with primary ICH (7.01%) during the 5-year follow-up period. Other studies have also found a hemorrhagic stroke recurrence rate between 7% and 12% (52,53). We assume that short follow-up period of our study participants hampered the detection of poor outcome in this patient population compared to previous studies. In our study, a significant inverse association was found between GCS score at admission and outcome, which is in line with previous studies showing that low GCS at admission was found to be independently associated with a worse short-term and long-term prognosis (54,55).

Contrary to previous studies, we found no correlation between underlying cardiovascular and renal diseases and 90-day functional outcome of primary ICH patients. Ghoshal *et al.* (56) found that chronic kidney disease increases the risk of ICH. Amer *et al.* also found that baseline elevated blood urea nitrogen levels inversely correlated with outcome (15). The existing discrepancy in our study could be explained in part by the medical condition of patients with underlying renal and cardiovascular diseases at admission. Patients with underlying kidney and cardiovascular diseases had well-controlled disease at hospitalization and their comorbidity was adequately controlled by medical therapy. As a result, this patient population did not experience worse outcome compared to other individuals without renal and cardiovascular disorders.

The impact of smoking on the functional outcome of primary ICH remains controversial. While some studies found a worse prognosis in tobacco users who develop ICH (57,58), other studies found no difference in functional outcome (59,60). Our study also showed no difference in the 90-day functional outcome of patients based on their smoking status.

We developed a predictive model for the first time for differentiating ICH patients with poor and good prognosis by using the SVM method. SVM is a model-free method and an efficient approach in classification problems without any assumption regarding the distribution and interdependency of the predictors. Due to its flexibility, it performs better than traditional statistical methods such as logistic regression, particularly in situations that

include multiple risk factors with interrelationships or multicollinearity, low sample size, and a limited knowledge of underlying biological relationships among risk factors. Despite remarkable aforementioned advantages and generalization capacity of the SVM, it has some weaknesses, such as feature selection challenges, algorithmic complexity that affects the training time of the classifier particularly in large data sets, development of optimal classifiers for categorical dependent variables with more than two categories and its unreliable performance in unbalanced data sets (61). In other words, high dimensional input vectors often reduce the computational efficiency and significantly slow down the classification process. Our study data set more benefits from the advantages of SVM instead of its weakness, however, if we used a larger sample size, we could develop a predictive model with more stable and reliable results, because we could able to train and test our model in subsets with larger sample size.

The major limitations of our current study were a short follow-up period of 3 months, functional outcome assessment being limited to the mRS, and a lack of laboratory markers assessment to establish a more comprehensive predictive model. We also did not evaluate other radiological markers of prognostication in ICH patients. Future studies are required to evaluate the predictive performance of all the relevant radiological and laboratory indicators in predicting prognosis of primary ICH in our patients particularly using machine learning-based image segmentation.

Conclusions

In summary, we evaluated the predictive performance of several NCCT imaging markers and clinical conditions in determining the 90-day prognosis of patients with primary ICH. This predictive model could be utilized by clinicians in the emergency department for prognostication purposes. Hemorrhage volume was associated with the most prognostication capability, followed by the BHS, midline shift, SS, and blend sign. Among clinical indicators, advanced age, elevated diastolic blood pressure, and low GCS score correlated with poor prognosis. On the other hand, hemorrhage location, females, history of diabetes mellitus, cardiovascular diseases, renal disease, and cerebrovascular accidents did not correlate with worse prognosis in our patients. Further study is required to evaluate the impact of other laboratory and imaging

indicators on prognosis of patients with primary ICH. Furthermore, future studies with larger sample size are suggested to evaluate the predictive performance of all the potentially relevant radiological and laboratory indicators in predicting prognosis of primary ICH particularly using machine learning-based image segmentation approaches.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD+AI reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-24-1299/rc>

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-24-1299/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments, and approved by the Institutional Ethics Committee of Isfahan University of Medical Sciences (approval date: 8/1/2021, protocol code IR.MUI.MED.REC.1400.446) and the National Research Ethics Board (approval number IR.MUI.MED.REC.1400.446). Informed consent was obtained from all subjects or patients' families involved in the study.

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Cite this article as: Hajiahmadi S, Jafari T, Naghavi S, Dashti F. The role of imaging in predicting 3-month prognosis of primary intracerebral hemorrhage: a single-center, prospective observational study in tertiary care hospital. *Quant Imaging Med Surg* 2025;15(6):5674-5688. doi: 10.21037/qims-24-1299