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Pre-admission CHADS2 and CHA2DS2-VASc scores predict long-term outcomes after first spontaneous intracranial hemorrhage

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Abstract

Background: Spontaneous intracranial hemorrhage (ICH) results in significant morbidity and mortality. Approximately 50% patients die within the first 30 days of the index hemorrhage, and of those who survive, only a minority is expected to be functionally independent. The ability to predict long-term functional outcomes may facilitate decision making in early management of ICH. This study aim to evaluate for the first time whether CHADS 2 score and CHA 2 DS 2 -VASc developed to stratify the risk of ischemic stroke among patients with AF is useful in predicting the functional outcomes among patients surviving their first spontaneous ICH. Methods: This single-centered observational registry was carried out between 1996 and 2010 and included 691 consecutive patients with the first spontaneous ICH. Results: Amongst these, 427 patients (60.1 ± 15.2 years, male: 62.5%) surviving the 30 days after the first ICH fulfilling the inclusion criteria were studied. At 1 year and 2 years, 52.9% and 54.8% patients had unfavorable outcome as defined as modified Rankin score of ≥3. In both univariate and multivariate analysis, increasing age, a higher pre-admission CHADS 2 and CHA 2 DS 2 -VASc scores surgical intervention for the ICH were associated with unfavorable outcomes. The c statistic of the CHADS 2 score as a predictor of favorable outcome was 0.59 (95% CI: 0.54-0.64, p <0.0001) with the optimal cutoff to predict favorable outcome at CHADS 2 ³1 with sensitivity of 73.9% and specificity of 39.4%. On the other hand, the C statistic of the CHA 2 DS 2 -VASc score to predict favorable outcome was similar to that of the CHADS 2 score (C-statistic: 0.58, 95% CI: 0.53-0.63, p =0.003) with the optimal cutoff at CHA 2 DS 2 -VASc ³3. The sensitivity and specificity were 67.7% and 46.3% respectively. Conclusion: The outcome of ICH patients surviving the first 30 days was poor. CHADS 2 and CHA 2 DS 2 -VASc appeared to be a reasonable score to predict long-term ICH outcomes.

Background

Spontaneous intracranial hemorrhage (ICH) accounts for 10 to 15% of all strokes in Caucasians[1-3] and up to 35% in Chinese,[4-6] and results in significant morbidity and mortality. Approximately 50% of patients with ICH die within 30 days of the index hemorrhage, and of those who survive, only a minority is expected to be functionally independent.[7] Early prognostication may allow risk stratification for early mortality as well as long-term functional outcomes, thus possibly improving individual treatment and allocation of hospital resources. In fact, various clinical parameters have been identified to be of prognostic significance regarding early mortality. Much less is known for long-term functional outcomes for ICH survivors.

The $CHADS_2$ (Congestive heart failure, Hypertension, Age≥75 years, Diabetes, previous Stroke) score and more recently the CHA_2DS_2-VASc (CHA_2DS_2-Vascular disease, Age 65-74 years, Sex category) score are validated risk stratification schemes used to estimate ischemic stroke in patients with atrial fibrillation (AF). In addition to the stroke prediction in patients with AF, $CHADS_2$ score has been demonstrated to be related to the occurrence of ischemic stroke even in patients without pre-existing AF,[8] the severity and short-term outcome,[9] and long-term mortality in patients with ischemic stroke.[10] Its prognostic performance in ICH in regard to long-term functional outcomes has not been previously evaluated.

Therefore, we hypothesize that the long-term functional outcomes of patients surviving an ICH may also been captured by the $CHADS_2$ and CHA_2DS_2-VASc scores. The objective of this study was to determine whether specific patient characteristics or risk factors, including the $CHADS_2$ and CHA_2DS_2-VASc scores, were predictive of long-term functional outcomes in patients surviving their first ICH.

Methods

Study Population

From May 1996 to February 2010, 691 consecutive patients (62.1 ± 0.6 years, male: 60.1%) with first episode of spontaneous ICH admitted to our neurosurgical unit were recruited. Patients were excluded if they were under 18 years of age, had ICH secondary to arteriovenous malformation, aneurysm, cavernoma, other vascular malformations, tumor, trauma, hemorrhagic transformation of cerebral infarctions, and/or had an incomplete data. 427 patients were included in the final analysis.

Study Design

This was a single-center registry based on the clinical outcomes of Chinese patients with first spontaneous ICH.[11, 12] After admission, data pertaining to the index ICH, demographics, cardiovascular risk factors, previous use of anti-thrombotic medication (aspirin, clopidogrel, or warfarin), were retrieved from the Clinical Management System Database of the hospital. ICHs were classified into intra-cerebral hemorrhage, subarachnoid hemorrhage, and subdural hemorrhage. The location of intra-cerebral hemorrhage was classified as lobar (gray matter and the underlying subcortical white matter) and deep cerebral (periventricular white matter, caudate, globus pallidus, putamen, internal capsule, thalamus, cerebellar, and brainstem).[13] For cases designated as pure intra-ventricular hemorrhage after review of all available films, they were categorized as deep intra-cerebral hemorrhage. After discharge, all patients were followed-up in our outpatient clinic. Clinical data concerning the subsequent use of anti-thrombotic therapy, recurrent ICH, and death during the follow-up period were retrieved from medical records and discharge summaries from all local hospitals. Patients who were lost to follow-up were contacted by phone. Survival data were also obtained from the Births and Deaths General Register Office.

End-point and Definitions

The major clinical end-points were functional dependence at 1 year and 2 years. The 1-year and 2-year functional dependence were assessed using the modified Rankin Score (mRS) (Table 1). Favorable functional status was defined as mRS 0-2, while unfavorable functional status was mRS 3-6.[12, 14, 15] The secondary outcome was death at 1 year.

Statistical Analysis

Continuous variables were expressed as mean ± standard derivation while discrete variables were reported in percentages. Statistical comparisons of the baseline clinical characteristics were made using

Student's *t* test, one-way ANOVA or Fisher's exact test as appropriate. Event rates were calculated as the number of events divided by patient-years. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using uni-variate and multi-variate Cox proportional hazards regression models. Multivariate analyses were performed with an enter regression model in which each variable with a *p*-value of < 0.1 (based on univariate analysis) was entered into the model. For descriptive purposes, patients were classified into strata according to the $CHADS_2$ score ($CHADS_2$=0, $CHADS_2$=1, $CHADS_2$=2, and $CHADS_2$=3-6) and the CHA_2DS_2-VASc score (CHA_2DS_2-VASc=0, CHA_2DS_2-VASc=1, CHA_2DS_2-VASc=2, CHA_2DS_2-VASc=3, and CHA_2DS_2-VASc=4-9). The prognostic performance of the $CHADS_2$ and CHA_2DS_2-VASc scores regarding functional status at 1 year and 2 years were assessed using the C-statistic. Calculations were performed using SPSS software (version 19.0) and MedCalc software. All tests are two-sided, and *p*-values were considered significant if < 0.05. Area under the curve (C-statistic) for receiver operating characteristic (ROC) curve was calculated using Analyze-It for Excel with Delong-Delong comparison for C-statistic. The C-statistic integrates measures of sensitivity and specificity of the range of a variable. Ideal prediction yields a c-statistic of 1.00 whereas prediction no better than chance is associated with a c-statistic of 0.5.

Results

Table 2 summarizes the clinical characteristic of the study cohort. A total of 427 patients surviving the 30 days after the first ICH were recruited. The mean age was 60.1 ± 15.2 years with a male predominance of 62.5 %. Intra-cerebral hemorrhage accounted for the majority (93.7%, lobar hemorrhage: 32.3%, and deep hemorrhage: 61.4%) of all ICHs, with subarachnoid hemorrhage (5.2%) and subdural hemorrhage (1.2%) making up the remainder. Surgical evacuation of the hematoma was performed in 203 patients (47.5%). Among these patients,

The mean $CHADS_2$ and CHA_2DS_2-VASc scores were 1.2 ± 1.2 and 3.1 ± 1.4 respectively. $CHADS_2$ score of 0, 1, 2, 3, and 3-6 were present in 32.1%, 35.8%, 19.7%, and 12.4% of patients respectively. For CHA_2DS_2-VASc score, score of 0, 1, 2, 3, and 4-9 were present in 8.4%, 30.4%, 30.0%, 15.9%, and 15.2% respectively (Table 2).

Functional outcomes at 1 year and 2 years

Of these 427 patients, only 47.1% and 45.2% patients achieved favorable outcome (mRS score 0–2) at 1 year and 2 year. Table 3 summarize the baseline characteristics of patients dichotomized by favorable and unfavorable outcome at 1 year and 2 years respectively. Patients with unfavorable outcome at 1 year and 2 year were older (65.0 ± 13.4 years *vs.* 54.7 ± 15.2 years and 64.7 ± 13.6 *vs.* 54.6 ± 15.2 years, both *p*<0.01), had a higher pre-admission $CHADS_2$ (1.37 ± 1.25 *vs.* 1.01 ± 1.07 and 1.38 ± 1.24 *vs.* 0.98 ± 1.06, both *p*<0.01) and CHA_2DS_2-VASc scores (3.25 ± 1.37 *vs.* 2.86 ± 1.30, 3.25 ± 1.37 *vs.* 2.85 ± 1.30, both *p*<0.01), and were also more likely to have undergone surgical intervention for the ICH (62.8% *vs.* 30.3%, *p*<0.001 and 63.2% *vs.* 45.2%, *p*<0.01) compared with patients with favorable outcomes. The relationships between the $CHADS_2$ and CHA_2DS_2-VASc scores on admission and the modified Rankin

score at 1 year and 2 years were shown in Figures 1 and 2 respectively. Among patients of different strata of the $CHADS_2$ and CHA_2DS_2-VASc scores, patients with higher $CHADS_2$ and/or CHA_2DS_2-VASc scores had a lower rate of favorable outcomes. In multivariate analysis, in addition to age and surgical procedure, high baseline $CHADS_2$ and CHA_2DS_2-VASc scores were associated with unfavorable outcomes.

In order to compare the prognostic performance of the $CHADS_2$ and CHA_2DS_2-VASc scores in predicting favorable outcome, the sensitivity, specificity and C-statistic for $CHADS_2$ score as well as the CHA_2DS_2-VASc score in relation to favorable outcomes at 2 years were determined (Table 4). The C statistic of the $CHADS_2$ score as a predictor of favorable outcome was 0.59 (95% CI: 0.54-0.64, $p<0.0001$) with the optimal cutoff to predict favorable outcome at $CHADS_2$ ³1 with sensitivity of 73.9% and specificity of 39.4%. On the other hand, the C statistic of the CHA_2DS_2-VASc score to predict favorable outcome was similar to that of the $CHADS_2$ score (C-statistic: 0.58, 95% CI: 0.53-0.63, $p=0.003$) with the optimal cutoff at CHA_2DS_2-VASc ³3. The sensitivity and specificity were 67.7% and 46.3% respectively.

Discussion

In this study, we have evaluated for the first time whether $CHADS_2$ score and CHA_2DS_2-VASc developed to stratify the risk of ischemic stroke among patients with AF is useful in predicting the functional outcomes among patients surviving their first spontaneous ICH. We show in a cohort of 427 patients surviving the 30 days after the first ICH that less than a half of them achieved favorable outcome as defined as modified Rankin score 0-2 at 1 year and 2 years. Multivariate analysis reveals that pre-admission $CHADS_2$ score and CHA_2DS_2-VASc score, age, and surgical procedure were associated with unfavorable outcomes at 1 year and 2 years.

ICH is the most devastating and the least treatable form of stroke in clinical practice. Nearly 50% of patients died within the first 30 days after the index ICH. For those surviving the acute phase, only a minority of patients is expected to be functionally independent; majority of patients suffer significant residual disability.[7] In contrast to Caucasians, the burden of ICH appears to be higher in Asians, particular Chinese.[4-6] For instance, the incidence of ICH amongst Chinese is three-fold higher than that of Caucasian population.[1-6] It has been suggested that the higher incidence of ICH may be related to a higher prevalence of hypertension in the Chinese population, a lower blood pressure threshold to ICH,[16] or a low awareness of hypertension in Chinese.[17] In fact, as in the present cohort, more than 50% of patients had pre-existing hypertension prior to the index ICH.

Early identification of patients at high-risk of unfavorable outcomes including early death and significant disability may improve individual treatment and possibly allocation of hospital resources. In fact, poor prognostic indicators for early mortality and intermediate-term functional outcomes (6 months to 1 year) after spontaneous ICH have been investigated. These include clinical factors such as advanced age,[18-20] blood pressure,[21] hyperglycemia,[22] and hyperthermia;[23] as well as radiological parameters such

as hematoma size,[24, 25] intra-ventricular hemorrhage,[26] presence of hydrocephalus [27, 28] and significant midline shift.[28] However, clinical data concerning the long-term outcomes amongst those surviving the initial acute phase is relatively limited. Consistently with previous studies for study concerning intermediate-term outcomes, age is one of the most important predictors for long-term functional outcomes in our cohort. For instance, less than 50% of patients with age >65 years at the time of spontaneous ICH had favorable functional outcomes at 1 year and 2 years. This may be partly related to the functional status at older age, but also contributed by the poorer rehabilitation potential of the patients. As expected, the locations of the ICH impact also the functional outcomes of ICH survivors at 1 year and 2 years. However, individual clinical parameters such as prior stroke, diabetes mellitus, and hypertension *per se* did not really impact the subsequent functional outcomes. This may be partly related to the relative small effects of these individual risk factors on the subsequent functional outcomes, and/or the inadequacy of statistical power of the number of patients with these individual risk factors in our cohort. Nonetheless, one remarkable point of our study is that both $CHADS_2$ and CHA_2DS_2-VASc scores, summation of the impacts of individual risk factors, exhibit predictive power to long-term functional outcomes. Furthermore, $CHADS_2$ score appears to be comparable with or even superior than CHA_2DS_2-VASc scores in predicting long-term functional outcomes, despite the fact that latter consisting of 3 more parameters.

Our findings may have some clinical implications. As $CHADS_2$ and CHA_2DS_2-VASc scores exhibit predictive power to subsequent functional outcomes at 1 year and 2 years with different sensitivities and specificity, they may be used to guide the aggressiveness of acute management strategies. In addition, this may also be used to assist patients as well as patients' relatives to obtain a more realistic picture of the subsequent functional states and to formulate of long-term care plan.

Limitations

This study had several limitations. First**,** it was limited by the relatively small sample size and a single-centered observational design. Second, this was a hospital-based study using single-hospital registry data and did not include patients with a milder form of ICH who did not require hospitalization. Third, quantitative analysis of the hematoma size had not been performed.

Conclusion

This study demonstrates that patients surviving ICH are at high risk of poor function outcomes. Prompt and timely prognostication and prediction of long-term outcome is especially important as this may allow more individualized acute care and risk stratification. $CHADS_2$ score and CHA_2DS_2-VASc developed to stratify the risk of ischemic stroke among patients with AF appears to be useful in predicting intermediate term functional outcomes amongst ICH survivors.

Abbreviations

AF: Atrial Fibrillation; CHADS2: Congestive heart failure, Hypertension, Age≥75 years, Diabetes, previous Stroke; CHA2DS2-VASc: Congestive heart failure, Hypertension, Age≥75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category; CI: Confidence Intervals; HR: Hazard Ratios; ICH: Intracranial Hemorrhage; mRS: modified Rankin Score; ROC: Receiver Operating Characteristic

Declarations

Ethics approval and consent to participate:

This study was approved by local Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB), and informed consent was not applicable since clinical data of participates were retrieved from the Clinical Management System Database of the hospital.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author only on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

Conceived and designed the project: DH, CWS. Performed the project: DH, MZ, KHC, WML, MLZ, AGL, WSY, LXY, KSP, KKL, CWS. Analyzed the data: DH CWS. Contributed materials/analysis tools: DH CWS. Wrote the paper: DH, MZ, KHC, WML, MLZ, AGL, WSY, LXY, KSP, KKL, CWS. All authors read and approved the final manuscript.

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Tables

Table 1. Modified Rankin score[12, 14, 15, 29]

	Modified Rankin Score	Functional dependence
Favorable outcomes	0	No symptoms
	1	No significant disability. Able to carry out all usual activities, despite some symptoms
	2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
Unfavorable outcomes	3	Moderate disability. Requires some help, but able to walk unassisted
	4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
	5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
	6	Dead

Table 2. Baseline characteristics of patients with ICH surviving the first 30 days

Demographics	First-30-day survivors
Number	427
Male, n (%)	267 (62.5)
Age (years)	60.1 ± 15.2
Age ≥ 65 year, n (%)	183 (42.9)
Age ≥ 75 year, n (%)	129 (30.2)
Hypertension, n (%)	227 (53.2)
Diabetes, n (%)	69 (16.2)
Previous ischemic stroke, n (%)	31 (7.3)
Congestive heart failure, n (%)	11 (2.6)
Coronary artery disease, n (%)	29 (6.8)
Mean $CHADS_2$ score	1.2 ± 1.2
$CHADS_2$	
0, n (%)	137 (32.1)
1, n (%)	153 (35.8)
2, n (%)	84 (19.7)
3-6, n (%)	53 (12.4)
Mean CHA_2DS_2-VASc score	3.1 ± 1.4
CHA_2DS_2-VASc score	
0, n (%)	36 (8.4)
1, n (%)	130 (30.4)
2, n (%)	128 (30.0)
3, n (%)	68 (15.9)
4-9, n (%)	65 (15.2)
Types of intracranial hemorrhage	
Intracerebral hemorrhage, n (%)	400 (93.7)
Lobar, n (%)	138 (32.3)
Deep, n (%)	262 (61.4)
Subarachnoid hemorrhage, n (%)	22 (5.2)
Subdural hemorrhage, n (%)	5 (1.2)
Evacuation of hematoma, n (%)	203 (47.5)

Abbreviations: $CHADS_2$ score: Congestive heart failure, Hypertension, Age≥75 years, Diabetes, previous Stroke score; CHA_2DS_2-VASc score: CHA_2DS_2-Vascular disease, Age 65-74 years, Sex category score; ICH: intracranial hemorrhage.

Table 3. Baseline characteristics of 427 Post-ICH patients with favorable and unfavorable outcomes at 1 year and 2 year

Characteristics	mRS at 1 year			mRS at 2 year		
	Favorable outcomes	Unfavorable outcomes	p^a-value	Favorable outcomes	Unfavorable outcomes	p^b-value
Number	201	226		193	234	
Male, n (%)	134 (50.2)	133 (58.8)	0.10	130 (67.4)	137 (58.5)	0.06
Age (years)	54.7 ± 15.2	65.0 ± 13.4	<0.01	54.6 ± 15.2	64.7 ± 13.6	<0.01
Age 65 year, n (%)	61(30.3)	122 (54.0)	<0.01	57 (29.5)	126 (53.8)	<0.01
Age 75 year, n (%)	43 (33.3)	86 (38.1)	<0.01	39 (20.2)	90 (38.5)	<0.01
Hypertension, n (%)	103 (51.2)	124 (54.9)	0.45	98 (50.8)	129 (55.1)	0.37
Diabetes, n (%)	27 (13.4)	42 (18.6)	0.15	26 (13.5)	43 (18.4)	0.17
Previous ischemic stroke, n (%)	11 (5.5)	20 (8.8)	0.18	11 (5.7)	20 (8.5)	0.26
Congestive heart failure, n (%)	5 (2.5)	6 (2.7)	0.91	5 (2.6)	6 (2.6)	0.99
Coronary artery disease, n (%)	13 (6.5)	16 (7.1)	0.80	12 (6.2)	17 (7.3)	0.67
Mean $CHADS_2$ score	1.01 ± 1.07	1.37 ± 1.25	<0.01	0.98 ± 1.06	1.38 ± 1.24	<0.01
$CHADS_2$			<0.01			<0.01
0, n (%)	77 (38.3)	60 (26.5)		76 (39.4)	61 (26.1)	
1, n (%)	70 (34.8)	83 (36.7)		66 (34.2)	87 (37.2)	
2, n (%)	39 (19.4)	45 (19.9)		37 (19.2)	47 (20.1)	
3-6, n (%)	15 (7.5)	38 (16.8)		14 (7.3)	39 (16.7)	
Mean CHA_2DS_2-VASc score	2.86 ± 1.30	3.25 ± 1.37	<0.01	2.85 ± 1.30	3.25 ± 1.37	<0.01
CHA_2DS_2-VASc score			<0.01			<0.01
0, n (%)	25 (12.4)	11 (4.9)		24 (12.4)	12 (5.1)	
1, n (%)	68 (33.8)	62 (27.4)		66 (34.2)	64 (27.2)	
2, n (%)	51 (25.4)	77 (34.1)		49 (25.1)	79 (33.8)	
3, n (%)	33 (16.4)	35 (15.5)		32 (16.6)	36 (15.4)	
4-9, n (%)	24 (11.9)	41 (18.1)		22 (11.4)	43 (18.4)	
Types of intracranial hemorrhage						
Intracerebral hemorrhage, n (%)	185 (92.0)	215 (95.1)	0.19	177 (91.6)	223 (95.3)	0.13
Lobar, n (%)	82 (44.3)	56 (26.0)	<0.001	75 (38.8)	63 (26.9)	<0.01
Deep, n (%)	103 (55.7)	159 (74.0)	<0.001	102 (52.8)	160 (68.5)	
Subarachnoid hemorrhage, n (%)	12 (6.0)	10 (4.4)	0.47	12 (6.2)	10 (4.3)	
Subdural hemorrhage, n (%)	4 (2.0)	1 (0.4)	0.19	4 (2.2)	1 (0.4)	
Evacuation of hematoma, n (%)	61 (30.3)	142 (62.8)	<0.001	55 (45.2)	148 (63.2)	<0.01

Abbreviations: $CHADS_2$ score: Congestive heart failure, Hypertension, Age≥75 years, Diabetes, previous Stroke score; CHA_2DS_2-VASc score: CHA_2DS_2-Vascular disease, Age 65-74 years, Sex category score; ICH: intracranial hemorrhage; mRS: modified Rankin score.

p^a: p value for 1 year.

p^b: p value for 2 year.

Table 4. Sensitivity, specificity, and predictive ability (C-statistics and the 95% confidence interval (CI)) for individual risk factors, $CHADS_2$ score and CHA_2DS_2VASc Score in relation to favorable prognosis at 2 years

	Sensitivity	Specificity	C-statistic (95% CI)	*p*-value
Favorable outcome				
$CHADS_2$			0.59 (0.54-0.64)	<0.0001
$CHADS_2$ □ 0	100.0	0.0		
$CHADS_2$ □1	73.9	39.4		
$CHADS_2$ □ 2	36.4	73.9		
CHA_2DS_2VASc			0.58 (0.53-0.63)	0.003
CHA_2DS_2VASc □1	100.0	0.0		
CHA_2DS_2VASc □2	95.1	12.4		
CHA_2DS_2VASc □3	67.7	46.3		

Abbreviations: $CHADS_2$ score: Congestive heart failure, Hypertension, Age≥75 years, Diabetes, previous Stroke score; CHA_2DS_2-VASc score: CHA_2DS_2-Vascular disease, Age 65-74 years, Sex category score.

Figures

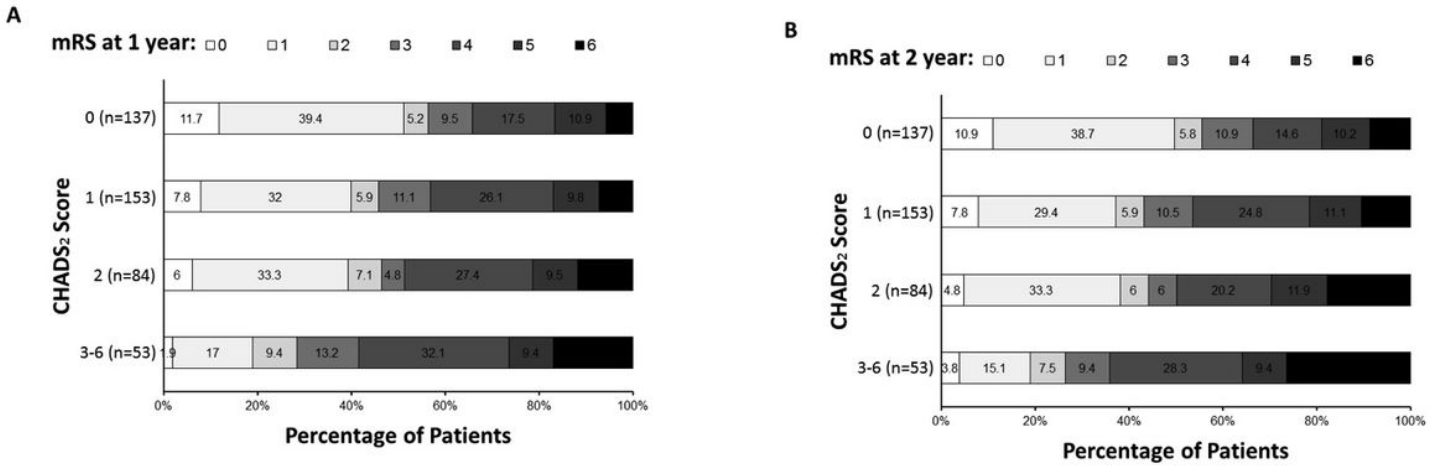

Figure 1

Modified Rankin scale (mRS) scores at 1 year and 2 years after the index ICH stratified according to CHADS2 scores. Abbreviations: CHADS2 score: Congestive heart failure, Hypertension, Age≥75 years, Diabetes, previous Stroke score; ICH: intracranial hemorrhage.

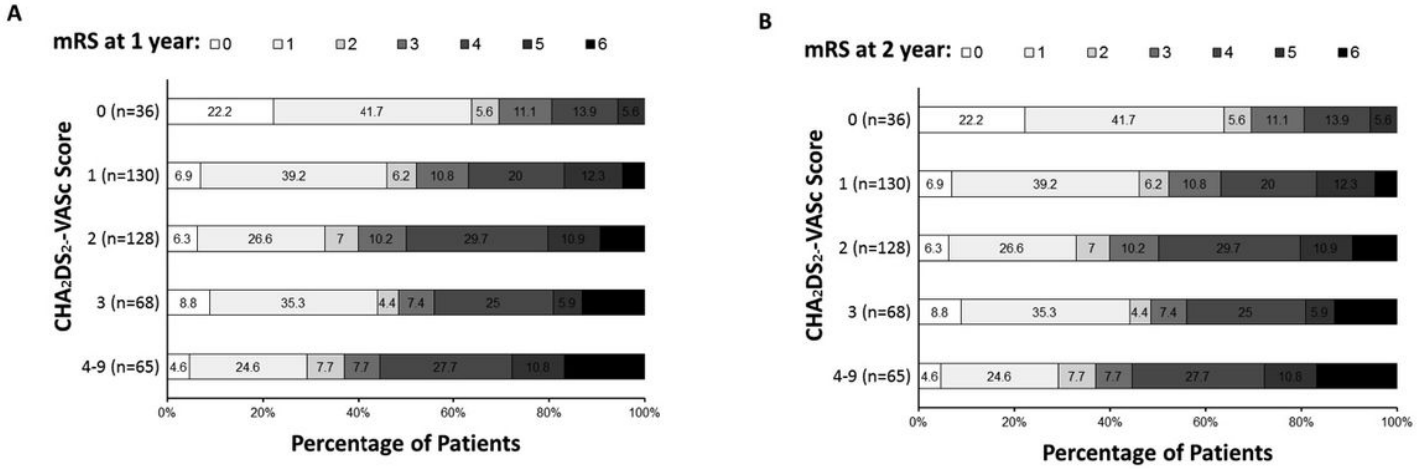

Figure 2

Modified Rankin scale (mRS) scores at 1 year and 2 years after the index ICH stratified according to CHA2DS2-VASs scores Abbreviations: CHA2DS2-VASc score: Congestive heart failure, Hypertension, Age≥75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category score; ICH: intracranial hemorrhage.