Paper

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CLINICAL

Comparison of predictive scores of symptomatic intracerebral haemorrhage after stroke thrombolysis in a single centre

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ABSTRACT Symptomatic intracerebral haemorrhage following thrombolysis for ischaemic stroke causes significant morbidity and mortality. This study assessed which of four risk scores (SEDAN, HAT, GRASPS and SITS) best predicts symptomatic intracerebral haemorrhage.
Methods: Data from 431 patients treated at Aberdeen Royal Infirmary (2003–2013) were extracted from a thrombolysis database. Score performance was compared using area under the curve.
Results: Any intracerebral haemorrhage occurred in 12% of patients (53/413); 11% fulfilling the SITS-MOST symptomatic intracerebral haemorrhage definition (6/53), 34% the ECASS II definition (18/53), and 43% the National Institute of Neurological Disorder and Stroke definition (23/53). Stroke severity, as defined by the National Institutes of Health Stroke Scale, significantly improved after 24 hours in patients without intracerebral haemorrhage, but not in those with. Significant symptomatic intracerebral haemorrhage predictors were age, glucose, stroke severity, hyperdense middle cerebral artery on CT scan, ASPECTS score and anti-platelet therapy. The haemorrhage after thrombolysis score performed best at predicting symptomatic intracerebral haemorrhage (area under the curve 0.67–0.78, $p < 0.001$).
Conclusion: The haemorrhage after thrombolysis score uses the least variables and has the best predictive value for symptomatic intracerebral haemorrhage. Using predictive scores for clinical decision making depends on estimation of overall benefits as well as risk.

KEYWORDS outcome prediction, predictive risk scores, stroke thrombolysis, symptomatic intracerebral haemorrhage

DECLARATION OF INTERESTS No conflict of interest declared.

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INTRODUCTION

Stroke is the third most common cause of death in Scotland and accounts for approximately 5% of total UK NHS costs.[1] Thrombolytic therapy using intravenous alteplase is currently the only licensed therapy for acute ischaemic stroke (AIS). The most recent meta-analysis of thrombolysis for AIS demonstrates a 9.0% decrease in death and 4.2% decrease in dependency (defined as a modified Rankin Score of 3 to 6[2]) three months after stroke, when thrombolysis is given in the first three or six hours of symptom onset compared to control.[3] However, the leading complication of thrombolysis is the development of symptomatic intracerebral haemorrhage (SICH), which carries significant morbidity and mortality. Of those thrombolysed, 7.7% developed SICH, compared to 1.8% in control groups, with SICH accounting for most of the early deaths in the thrombolysed groups.[3]

This complication could be minimised if physicians could reliably predict which AIS patients might develop SICH after thrombolysis. Several studies have developed risk scores to try and estimate which patients are most at risk of SICH post-thrombolysis to inform thrombolysis decision making (e.g. the SEDAN, HAT, GRASPS and SITS scores[4-7]). The aim of the current study was to test the performance of these scores and to see which was most valid in a population treated by a single stroke centre.

METHODS

Study population

Patients admitted to Aberdeen Royal Infirmary with a diagnosis of acute ischaemic stroke who were thrombolysed between 2003 and 2013 (majority enrolled from 2009 onwards) were entered in the Safe Implementation of Treatment in Stroke (SITS) database

(n=431). This is a European-wide database for monitoring the safety of thrombolysis use in ischaemic stroke patients.[8] Patients are entered as part of clinical audit and information collected includes age, gender, pre-stroke functional status (modified Rankin score), comorbidity, glucose, blood pressure and stroke severity (National Institutes of Health Stroke Scale – NIHSS[9]) at 0 hours, 2 hours, 24 hours and 7 days post-thrombolysis, plus findings from the initial and 24 hour post-thrombolysis CT scan. The latter includes presence of intracerebral haemorrhage (ICH) as previously described.[7] This anonymised audit was approved by our local ethics committee.

SICH risk prediction scores

Four prediction scores were used in this study – SEDAN (blood Sugar, Early ischaemic changes, hyperDense artery sign, Age, and NIH Stroke Scale score), haemorrhage after thrombolysis (HAT), GRASPS (Glucose at presentation, Race [Asian], Age, Sex [male], systolic blood Pressure at presentation, and Severity of stroke at presentation [NIHSS] score) and SITS. Table 1 lists the various components of each risk score.[4-7] With respect to the HAT score, it should be noted that to quantify the extent of early ischaemic change in the middle cerebral artery (MCA) territory, the Alberta Stroke Programme Early Computerised Tomography Score (ASPECTS) was utilised. This score evaluates ten anatomical sites within the MCA territory for signs of ischaemic change and produces a normal maximum score of 10 (no ischaemic changes), minus one point for each area with ischaemic changes.[10] In this study, it was assumed that an ASPECTS score of ≤ 7 denoted MCA territory hypodensity of > 1/3.

SICH definitions

SICH has numerous definitions. This study utilised only those definitions which are used by the respective SICH risk prediction scores. The SEDAN and HAT scores were developed using the European Cooperative Acute Stroke Study II (ECASS II) definition of SICH, i.e. ICH with worsening in the NIHSS score of ≥ 4.[5] The GRASPS score was developed using the National Institute of Neurological Disorder and Stroke (NINDS) definition: any ICH with a worsening in the NIHSS score of ≥ 1.[11] The SITS score uses the SITS-MOST definition, i.e. a local or remote parenchymal haemorrhage (PH2, a haemorrhage > 30% of the infarcted area with significant space-occupying effect)[12] and worsening of NIHSS ≥ 4.[11]

Predictor variables

The following variables were extracted from the SITS database to evaluate significant univariate predictors of SICH and any ICH: age; gender; weight; systolic and diastolic blood pressures; baseline NIHSS score; glucose; cholesterol; prior previous stroke or transient ischaemic attack; history of hypertension; diabetes mellitus; chronic heart failure; atrial fibrillation; use of anti-hypertensive, anti-platelet or statin medication; symptom onset to treatment time, presence of a hyperdense middle cerebral artery (HDMCA) on CT scan and ASPECTS score.

TABLE 1 Variables contributing to calculation of each risk score

Risk score (range of scores)	Variables comprising each score (points for score variable)
SEDAN (0–6)	• Admission blood glucose: ≥ 12mmol/L (2); 8.1–12mmol/L (1) • Presence of early infarct sign on CT scan (1) • HDMCA on CT scan (1) • Age ≥75 years (1) • NIHSS ≥10 (1)
HAT (0-5)	• Diabetes mellitus or admission blood glucose >200 mg/dL (1) • NIHSS: ≥20 (2); 15–19 (1) • Fraction of MCA territory hypodensity: >1/3 (2); 1/3 (1)
SITS (0–12)	• NIHSS: ≥13 (2); 7–12 (1) • Age ≥72 years (1) • Systolic Blood Pressure ≥146mmHg (1) • Weight ≥95 kilograms (1) • Blood glucose ≥10mmol/L (2) • Pre-stroke anti-coagulant therapy: aspirin and clopidogrel therapy (3); aspirin monotherapy (2) • Pre-stroke hypertension (1) • Onset-to-treatment time ≥180 minutes (1)
GRASPS (45–101)	• Age (years): >80 (17); 71–80 (15); 61–70 (11); ≤60 (8) • NIHSS: >20 (42); 16–20 (40); 11–15 (34); 6–10 (27); 0–5 (25) • Systolic blood pressure (mmHg): ≥180 (21); 150–179 (18); 120–149 (14); <120 (10) • Blood glucose (mg/dL): ≥150 (8); 100–149 (6); <100 (2) • Race: Asian (9); Non-Asian (0) • Gender: Male (4); Female (0)

HDMCA: hyperdense middle cerebral artery; CT: computerised tomography; NIHSS: National Institutes of Health Stroke Scale; MCA: middle cerebral artery.

Statistical analysis

Data are presented as either means or percentages unless otherwise stated. Comparisons between groups were made using the Chi-square test and t-test where appropriate with significance defined as $p < 0.05$.

TABLE 2 Univariate analysis to determine possible factors predisposing to any intracerebral haemorrhage and SICH following thrombolysis

	All (n=431)	Any haemorrhage (n=54)	NINDS SICH Definition[1] (n=23)	ECASS II SICH Definition[2] (n=18)
Age (years) (SD)	70.1 (13.6)	76.2*** (10.4)	77.9 (9.3)	77.2** (9.8)
Male (%)	191 (44)	35 (65)	13 (57)	11 (61)
Weight (kg) (SD)	76.3 (16.6)	76.9 (18.3)	73.6 (17.3)	71.5 (17.1)
Systolic blood pressure (mmHg) (SD)	150.8 (21.9)	156.4 (19.1)	156.7 (16.5)	153.5* (16.1)
Diastolic blood pressure (mmHg) (SD)	80.7 (13.6)	83.4 (11.0)	82.4 (11.0)	80.9 (11.8)
Baseline NIHSS[3] (SD)	11.2 (6.7)	14.0* (6.0)	16.5**(6.1)	14.8*** (5.4)
24 hours NIHSS (SD)	8.9 (8.5)	15.1*** (10.3)	26.8*** (4.9)	27.5*** (5.3)
Onset to treatment time (min) (SD)	161.3 (57.7)	161 (61.4)	155.6 (71.1)	153.5 (71.4)
Glucose (mmol/L) (SD)	6.8 (2.2)	7.5(2.5)	7.7 (2.9)	7.9 (3.3)
Cholesterol (mmol/L) (SD)	4.5 (1.3)	4.2(1.0)	4.1 (1.3)	3.7 (0.6)
Previous stroke/TIA[4] (%)	72/367 (20)	16/49 (33)*	6/23 (26)	5/18 (28)
Hypertension (%)	200/369 (54)	29/49 (59)	13 (57)	10 (56)
Diabetes mellitus (%)	61/410 (15)	13/52 (25)*	8 (35)**	6 (33)*
Chronic heart failure (%)	22/369 (6)	5/49 (10)***	2 (9)	1 (6)
Current non-smoking status (%)	201/367 (55)	46/49 (94)**	19 (83)	14 (78)
Atrial fibrillation (%)	84/370 (24)	17/49 (35)*	6 (26)	5 (28)
Anti-hypertensive medication (%)	169/365 (46)	26/49 (53)	14 (61)	11 (61)
Anti-platelet medication (%)	132/348 (38)	30/48 (63)***	16 (70)*	14 (78)***
Statin medication (%)	93/365 (26)	14/49 (29)	6 (26)	5 (28)
HDMCA[5] (%)	114/430 (27)	19/53 (36)	10 (46)*	6 (35)
ASPECTS[6] (SD)	9.3 (1.2)	8.6*** (1.5)	7.7*** (2.6)	7.8*** (2.5)

Means are expressed with standard deviations. Percentages are expressed with numerator and denominator.
*p<0.05; **p<0.01; ***p<0.001
[1]Any haemorrhage with worsening of NIHSS ≥ 1; [2]Any haemorrhage with worsening of NIHSS ≥ 4; [3]National Institutes of Health Stroke Scale; [4]Transient ischaemic attack; [5]Hypodense middle cerebral artery; [6]Alberta Stroke Programme Early Computerised Tomography Score

Univariate analysis was performed to identify potential variables associated with SICH in our population. Multivariate analysis was not performed in view of the sample size, and because we wanted to test previously established risk scores rather than develop any new predictive models or scores. We conducted a post-hoc bootstrapping analysis of 1000 iterations to compare the predictive performances of the four SICH risk scores using the area under the receiver-operator curve (AUROC).[13] An AUROC=0.5 indicates the risk score performs no better than chance, whereas an AUROC of 1 indicates perfect discrimination. The best risk score was defined as the score with the largest statistically significant AUROC using analyses of variance.[14] Analyses were conducted using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Data on a total of 431 acute ischaemic stroke patients who received intravenous alteplase and were entered into the SITS database were analysed in this study. From comparison SITS data the baseline stroke severity and characteristics are similar to other patients receiving thrombolysis in the UK (mean age 70 vs 70 years, 78% free of disability pre-stroke [modified Rankin score <2] vs 86%, NIHSS 10 vs 12 and 40% total anterior circulation syndrome vs 46% respectively). Any ICH occurred in 12% (53/413) of patients; of these only 11% (6/53) fulfilled the SITS-MOST definition of SICH,[11] 34% (18/53) the ECASS II definition,[4] and 43% (23/53) the NINDS definition.[10] Mean NIHSS significantly improved in patients without ICH after 24 hours (10.8 [SD 6.6] to 8.0 [SD 7.8], p < 0.0001), whereas there was a non-

significantly increased NIHSS in patients who had any ICH (17.0 [SD 10.8] vs 14.0 [SD 6.1], p=0.08). Univariate analysis identified several significant predictors of SICH as defined by NINDS and ECASS II definitions following thrombolysis (Table 2); age, glucose, NIHSS, diabetes mellitus, HDMCA on CT scan, ASPECTS score and anti-platelet therapy prior to stroke onset.

Only six patients fulfilled the SITS-MOST definition of ICH (clinical data not shown in view of lack of statistical power). Additional univariate predictors for developing any ICH include previous cerebral ischaemic event, non-smoking status, congestive cardiac failure and atrial fibrillation. Onset to treatment time, gender, glucose levels and anti-hypertensive medication were not significant predictors.

The median values for the following scores are: SEDAN 2 (inter-quartile ratio [IQR] 1–2); HAT 1 (IQR 0–2); GRASPS 69 (IQR 62–75) and SITS 4 (IQR 3–6). The HAT score was the best predictor score regardless of definition of SICH (Table 3). The SITS score was the next best for an ECASS II definition of SICH whereas the GRASP score was the next best for the NINDS definition.

TABLE 3 Area under the receiver-operator curve values for the definitions of symptomatic intracerebral haemorrhage. Data expressed as mean (95% CI).

SICH risk prediction scores	AUROC of SICH Definitions		
	SITS-MOST (n=6)	ECASS II (n=8)	NINDS (n=23)
SEDAN	0.62 (0.61–0.63)	0.67 (0.65–0.69)	0.72 (0.71–0.73)
HAT	0.67 (0.65–0.69)	0.73 (0.71–0.75)	0.78 (0.75–0.81)
GRASPS	0.65 (0.63–0.67)	0.69 (0.66–0.70)	0.74 (0.72–0.76)
SITS	0.68 (0.66–0.69)	0.72 (0.70–0.74)	0.72 (0.70–0.73)

DISCUSSION

This study aimed to compare the accuracy of four different scoring systems to predict SICH in patients admitted to our hospital following thrombolysis. The HAT score is the simplest and best performing risk score regardless of SICH definition. This suggests that the variables used in this score (i.e. diabetes mellitus or glucose level, stroke severity and extent of early ischaemic change) are the strongest independent predictors of SICH. Higher NIHSS (i.e. stroke severity) likely correlates with the volume of ischaemic tissue at risk for haemorrhagic transformation.[15] The degree of visible hypodensity on the pre-treatment CT is thought to represent cytotoxic oedema and possible irreversible injury, which is associated with ICH after thrombolysis.[16] Experimental studies showed that diabetes mellitus and hyperglycaemia are associated with blood–brain barrier and microvascular impairments, as well as increased haemorrhagic infarct conversion after reperfusion.[17] A recent meta-analysis suggests that admission glucose but no prior diabetes predicts post-thrombolysis SICH.[18] However, admission glucose may be a surrogate marker of brain infarction severity (as a stress response) rather than a causal factor.

Our population variables, such as onset to treatment time, age, blood pressure or hypertension and gender add little predictive power. This is despite some of these variables being univariate predictors of any ICH in our population. Variables found to be significant predictors in univariate analysis may be associated with SICH, but may not be causally related. Multivariate analysis, as used in development of SICH predictor scores (e.g. HAT or SEDAN), identifies independent predictor variables. Many of these predictors (e.g. age, gender, non-smoking status and chronic heart failure) have been found in previous studies to be risk factors for ICH, although not necessarily SICH post-thrombolysis.[11] In particular, although blood pressure is a variable in the GRASPS and SITS scores, a recent meta-analysis of studies of SICH could not identify blood pressure even as a significant univariate predictor.[19] Onset to treatment time is a significant factor in estimating the benefit of thrombolysis with an approximate halving of benefit every 90 minutes. The risk of SICH appears mostly constant in the 0–6 hour time window, which may be one reason the SITS score performs less well than the HAT score.[3,19,20] The majority of patients (96%) in this series were treated with intravenous thrombolysis within the current accepted time window of within 4.5 hours of symptom onset. Systems should be optimised to maximise early delivery of stroke thrombolysis to maximise benefit. We did not find any difference in ASPECTS score with regard to onset to treatment time (data not shown), but the degree of appearance of early ischaemic change should be time-dependent, although other factors such as collateral circulation may affect ASPECTS score.

A meta-analysis by Whiteley et al.[19] showed that factors which may predict SICH following thrombolysis are those which also predict poor outcome following a stroke. The authors further concluded that predicting which patients will develop SICH may be difficult. Those patients predicted to have a high risk of SICH may not have a poor outcome following thrombolysis, and so clinical decision making is difficult.[19] A further recent analysis of patients from the third International Stroke Trial (IST-3) trial demonstrates that patients predicted to be at highest risk of developing SICH still achieve a net population benefit from receiving thrombolysis.[21] Similar

results to those found in this paper have been demonstrated by Strbian et al.,[22] who showed that the SEDAN scorehad the highest predictive power in 3012 patients with a 7.3% rate of SICH. They also concluded that none of the predictive scores they assessed, including HAT, SEDAN, GRASPS and SITS, had better than moderate performance when analysed using the area under the curve, similar to the findings from IST-3.[21]

This current study had some limitations. Patients admitted to a single stroke unit were studied and it is uncertain whether this study population is generalisable. Despite this the demographics and stroke severity of patients treated at our centre were similar to the average UK patient. Furthermore, this study may be underpowered for some of the analyses. The differing SICH definitions are a further limitation as this prevents precise comparison between SICH prediction scores. There is debate as to which SICH definition is the most relevant. The SITS-MOST definition seems a very narrow definition, being present in only 1.4% of the patients in this study, whereas the NINDS definition is too liberal as NIHSS can worsen by 1 point purely due to oedema after acute ischaemic stroke. The ECASS II definition is recognised as being the most pertinent in predicting poor and fatal outcomes.[23] Furthermore it is clear that minor haemorrhages (e.g. PH1), which can be excluded from some SICH definitions, may be associated with worse outcomes, and survivors of SICH tend to have poorer outcomes.[23]

In conclusion, this study demonstrates that age, glucose, stroke severity (as defined by the NIHSS score), diabetes mellitus, HDMCA on CT scan, ASPECTS and prior anti-platelet therapy are univariate predictors of developing SICH. The HAT score uses the simplest variables and appears to have the best predictive value for SICH in this population, regardless of definition. Despite this the HAT score does not assess overall benefit of thrombolytic therapy in addition to risk of harm. In particular it is notable that the increase in mortality at 7 days after thrombolysis, mostly due to SICH, appears to be negated by improved survival at six months in both the IST-3 trial[24] and the most recent systematic review of alteplase for ischaemic stroke. Further studies are required to determine whether SICH prediction scores should influence clinical decision-making in regard to the use of thrombolytic therapy for AIS. At a minimum, the HAT score could be used to estimate the risk of SICH in a given patient when discussing the risk and benefit of thrombolysis with stroke patients or their relatives.

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