Predicting Functional Outcome and Symptomatic Intracranial Hemorrhage in Patients With Acute Ischemic Stroke

A Glimpse Into the Crystal Ball?

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When encountering a patient with ischemic stroke, a stroke physician needs to make an outcome prediction for several reasons. First, a prediction may help patients and families have more realistic expectations about the patient's future and plan their long-term living arrangements.[1] Second, outcome prediction may be useful in making treatment decisions: for example, avoidance or de-escalation of aggressive treatment measures in patients who would achieve an excellent outcome regardless of such therapy or in those who would experience a poor and unacceptable outcome despite that treatment. Third, outcome prediction could aid in stroke research to control for case-mix variation in nonrandomized studies and to refine selection criteria in randomized, controlled acute stroke trials.

An ideal stroke prognostic score system should include a limited number of readily available and relevant parameters, be easily and quickly applicable in the clinical setting (eg, without the need of complex mathematical formulas or nonconventional time-consuming additional investigations), be accurate with low intra- and inter-rater disagreement, be validated externally in large independent and preferably multiple populations, and be proven reliably useful in guiding treatment decisions.

Extensive research has been performed during the recent years on prognostic scores for the prediction of stroke outcome and risk of symptomatic intracranial hemorrhage (sICH).[2–4] This review summarizes current prognostic scores, discusses the scientific background behind the scores' main components, acknowledges their strengths and limitations, and highlights the areas which warrant further research. Because of the space limitations, scores which were initially developed for one outcome (eg, functional outcome) and were later validated also for other outcomes (eg, post-thrombolytic sICH) will be discussed only for the initially validated outcome. Furthermore, scores for strictly selected populations and scores for patients treated with endovascular procedures are not included in this review.

Scores for Prediction of Functional Outcome in the Overall Ischemic Stroke Population

Several prognostic scores (Table 1; Figure 1) have been introduced to aid in the prediction of outcome in patients with ischemic stroke.[5–14]

Pathophysiologic Insights Into Scores' Constituents and Stroke Outcome

Among the individual components, the most common is stroke severity (except for Stroke-Thrombolytic Predictive Instrument [TPI] for favorable outcome) evaluated mainly by the use of the National Institutes of Health Stroke Scale Score (NIHSS). NIHSS is the most widely used scale of stroke severity and has been implemented both in randomized controlled acute stroke trials[15] and in observational studies.[16] Strengths of the NIHSS scale include its simplicity, the short time needed to assess it, the extensive assessment of its inter-rater reliability[17] which further increases with the use of available videotape training,[18] and the ability to extract the scale using medical records.[17] NIHSS score has already been shown to predict stroke outcome.[19] However, the NIHSS has been criticized for its complexity and the underweighting for posterior circulation strokes, a shared problem by all stroke scales.[20] A few prognostic scores implement the Canadian Neurological Scale (CNS),[21] which has shown good inter-rater reliability[22] and can be converted to the NIHSS score with the use of a validated conversion mathematical formula.[23] None of the scores used Scandinavian Stroke Scale.

Numerous studies identified a strong association between increasing age and unfavorable stroke outcome, which is independent of stroke severity, characteristics, or complications.[24,25] Age is a frequent and heavily weighted scores' covariate (except for Wang et al's[11] and TPI for favorable outcome), either as continuous or as categorical (Table 1).

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Table 1. Prognostic Scores Developed for Predicting Outcome in the Overall Ischemic Stroke Population

ASTRAL[7]	BOAS[6]	GWTG[10]	iScore[9] (1-year/30-day prediction)	PLAN[8]	TPI[13] (for mRS≤1)	TPI[13] (for mRS≥5)	SSV[5]	Wang et al[11]	Weimar et al.[4]
Age 1 pt per 5 y	Age 1 pt if ≥78 y	Age 0 pts if <60 y 1 pt if 60–70 y 5 pts if 70–80 y 9 pts if ≥80 y	Age 1 pt per 1 y for both predictions	Age 1 pt per 10 y (maximum 10 pts)	Male sex Not reported	Age Not reported	Age Not reported	Consciousness 5 pts if impaired	Age Not reported
NIHSS 1 pt per 1 pt in NIHSS	NIHSS 1 pt if NIHSS≥10	NIHSS NIHSS=0–2; 0 pts NIHSS=3–5; 10 pts NIHSS=6–10; 21 pts NIHSS=11–15; 37 pts NIHSS=16–20; 48 pts NIHSS=21–25 ; 56 pts NIHSS>25; 65 pts	CNS CNS=0; 70/105 pts CNS=1–4; 40/65 pts CNS=5–7; 25/40 pts CNS≥8; 0/0 pts	Neurological deficit Arm weakness; 2 pts Leg weakness; 2 pts Neglect or aphasia; 1 pt	Admission SBP Not reported	NIHSS Not reported	Living alone before stroke Not reported	Dysphagia 3 pts	NIHSS Not reported
Onset-to-admission time 2 pts if >180 min	Persistent upper limb paralysis* 1 pt	Mode of arrival Private=0 pts Not via ED=1 6 pts Ambulance= 12 pts	Stroke subtype Lacunar; 0/0 pts Non-lacunar; 15/30 pts Undetermined; 20/30 pts	Reduced level of consciousness 5 pts	Previous stroke Not reported	Glucose on admission Not reported	OHS score ≤2 before stroke Not reported	Urinary incontinence 4 pts	
Visual field defect 2 pts if present	Need for O_2 administration† 1 pt	Female sex 3 pts	Male sex 5/10 pts	Preadmission medical comorbidities Dependence; 1.5 pts Cancer; 1.5 pts CHF; 1.0 pts AF; 1.0 pts	Onset-to-treatment time Not reported	ASPECTS score Not reported	Normal GCS verbal score Not reported	Body temperature 2 pts if >36.5°C	
Glucose on admission 1 pt if <3.7 or >7.3 mmol/L	Need for urinary catheter‡ 1 pt	CVD risk factors AF; 5 pts No previous stroke or TIA; 2 pts CAD; 5 pts DM; 2 pts No history of dyslipidemia; 2 pts	CVD risk factors§ AF; 5/10 pts CHF; 10/10 pts MI; 5 pts/NA smoking; 5 pts/NA		IV thrombolysis Not reported		Able to lift both arms to horizontal level Not reported	Hyperglycemia without DM history 2 pts	
Decreased level of consciousness 3 pts if present			Comorbid conditions Cancer; 15/10 pts Renal dialysis; 40/35 pts Patient-dependent preadmission 20/15 pts Glucose on admission ≥7.5 mmol/L; 10/15 pts				Able to walk alone or with stick/frame Not reported		

AF indicates atrial fibrillation; ASPECTS, Alberta Stroke Program Early CT Score; ASTRAL, age, severity of stroke measured by admission NIH Stroke Scale score, stroke onset to admission time, range of visual fields, acute glucose, and level of consciousness; BOAS, Bologna Outcome Algorithm for Stroke; CAD, coronary artery disease; CHF, congestive heart failure; CNS, Canadian Neurological Scale; CVD, cardiovascular disease; DM, diabetes mellitus; ED, emergency department; GCS, Glasgow Coma Scale; GWTG, Get With The Guidelines; IV, intravenous; MI, myocardial infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; pt(s), point(s); OHS, Oxford Handicap Scale; PLAN, preadmission comorbidities, level of consciousness, age, neurologic deficit; SBP, systolic blood pressure; SSV, six simple variables; TIA, transient ischemic attack; and TPI, Stroke-Thrombolytic Predictive Instrument.

*Inability to keep the arm raised, still present at discharge from stroke unit, ie, on average 5 days after admission.

†Administered when the saturation was ≤92%.

‡Only cases of confirmed urinary retention or incontinence have been taken into account.

§CVD risk factors refer to the patient's history except for smoking where current status is used.

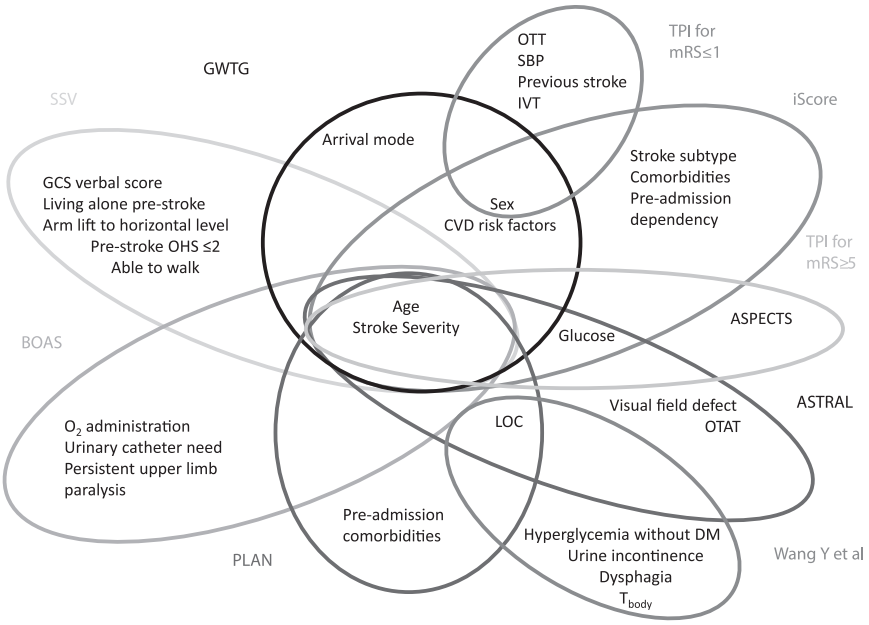

Figure 1. Illustration of scores for prediction of functional outcome in the overall ischemic stroke population. Please note that (**A**) age and stroke severity are the only variables in the score by Weimar et al., and (**B**) PLAN and iScore share a common variable: comorbidities. ASPECTS indicates Alberta Stroke Program Early CT Score; ASTRAL, age, severity of stroke measured by admission NIH Stroke Scale score, stroke onset to admission time, range of visual fields, acute glucose, and level of consciousness; BOAS, Bologna Outcome Algorithm for Stroke; CVD, cerebrovascular disease; DM, diabetes mellitus; GCS, Glasgow Coma Scale; GWTG, Get With The Guidelines; IVT, intravenous thrombolysis; LOC, level of consciousness; mRS, modified Rankin Scale; OTAT, onset-to-admission time; OTT, onset-to-treatment time; PLAN, preadmission comorbidities, level of consciousness, age, neurologic deficit; SBP, systolic blood pressure; SSV, six simple variables; Tbody, body temperature; and TPI, Stroke-Thrombolytic Predictive Instrument.

Hypoglycemia or hyperglycemia at admission is among the constituents of several prognostic scores (4 scores).[7,9] The cutoff values used in the age, severity of stroke measured by admission NIH Stroke Scale score, stroke onset to admission time, range of visual fields, acute glucose, and level of consciousness (ASTRAL) score to define hypo- and hyperglycemia were derived from the results of a previous observational study based on the Acute Stroke Registry and Analysis of Lausanne (ASTRAL)[26]; the IScore uses a threshold of 7.5 mmol/L.[9] In humans, hyperglycemia upregulates the production of thrombin-antithrombin complexes,[27] stimulates the tissue factor production,[28] and decreases the activity of the recombinant tissue plasminogen activator,[29] which impair recanalization.[30] In addition, hyperglycemia reduces cerebral blood flow by inhibiting vasodilation[31] and is also associated with oxidative stress and reperfusion injury.[32] Moreover, hyperglycemia attenuates the inflammatory response (increased production of proinflammatory cytokines such as tumor necrosis factor and nuclear factor κB)[33] and upregulates lipoxygenase and cyclooxygenase pathways, which promote vasoconstriction (increased production of eicosanoids[34] and thromboxane A2).[35] Regarding hypoglycemia, data are scarce. Animal studies suggest that hypoglycemia in large middle cerebral artery strokes is associated with higher acute mortality and, in some cases, larger infarct volumes than normoglycemia.[36,37] In humans, studies result in rather conflicting evidence for the effect of hypoglycemia on acute stroke outcome.[38]

Of interest, time delay between stroke onset and admission (ASTRAL score only) is also a score component (Table 1). This finding may be associated with more frequent use of recanalization procedures (ie, intravenous thrombolysis and endovascular treatment) in patients arriving early at the hospital, earlier control of physiological parameters like blood pressure (BP), glycemia and temperature, timely assessment of dysphagia, and early implementation of strategies to prevent complications (eg, venous thromboembolism) and recurrence. Most importantly, time delay reflects progression of ischemic brain injury. Of note, the significance of the time interval between stroke onset and score assessment was not addressed before; this parameter could potentially influence which parameters were identified as components of the scores (eg, certain parameters may be important for a score being assessed at admission, whereas other parameters may be important for scores assessed at 24 hours after stroke onset), the accuracy of the score (eg, the longer one waits to make a prediction regarding outcome, the less there is to predict and therefore the more accurate the prediction), and its role in clinical practice and research (a score assessed at baseline may be useful for acute stroke treatment trials, whereas a score assessed at 24 hours after stroke onset will obviously not).

Oxygen administration (Bologna Outcome Algorithm for Stroke [BOAS] score) is another component (Table 1).[6] In view of the recent negative results of the Stroke Oxygen Study (SOS) trial,[39] this probably functions as a surrogate marker of other variables like comorbidities, rather than as an independent predictor. It would be interesting to see whether oxygen administration would still remain an independent covariate if a comorbidity index (eg, Charlson[40] or Elixhauser indexes[41]) was included in the model. This could possibly be also the case for other comorbidities included in some scores like cancer,[8,9] dementia,[9] renal dialysis,[9] atrial fibrillation,[8–10] coronary artery disease,[9,10,42] chronic heart failure,[8,9,42] diabetes mellitus,[9–12,42] hypertension,[42] smoking habit,[9] and dyslipidemia[10,43] or a more general approach of the prestroke functional status.[5,8,9]

In 3 scores,[9,10,13] sex is among their constituents. Several studies have reported on sex differences between stroke patients[44,45]; women seem to have more severe strokes at a higher age compared with men.[46] Also of interest, women are consistently less likely to receive thrombolytic treatment,[47] and the American Heart/Stroke Association highlighted the need for a female-specific stroke risk score.[48]

Table 2. Prognostic Scores Developed for Predicting Outcome After Intravenous Thrombolysis in Acute Ischemic Stroke

TPI for good outcome[13] (mRS≤1)	TPI for catastrophic outcome[13] (mRS≥5)	MOST[50]	DRAGON[49]
Male sex	Age	NIHSS	Age
Not reported	Not reported	NIHSS<10; 0 pt NIHSS=11–20; 1 pt NIHSS≥20; 2 pts	0 pt if <65 y 1 pt if 65–79 y 2 pts if ≥80 y
Admission SBP	NIHSS	ASPECTS score ≤7	Hyperdense cerebral artery sign or early infarct signs on CT
Not reported	Not reported	1 pt	Neither present; 0 pt Either present; 1 pt Both present; 2 pts
Previous stroke	Glucose on admission	Proximal occlusion present	Prestroke mRS
Not reported	Not reported	1 pt	1 pt if mRS>1
Onset-to-treatment time	ASPECTS score	SBP (time not defined)	Glucose on admission
Not reported	Not reported	1 pt if >150 mm Hg	1 pt if >8.0 mmol/L
IV thrombolysis		Recanalization <300 min	NIHSS
Not reported		Complete; 0 pt Partial; 1 pt None; 2 pts	NIHSS=0–4; 0 pt NIHSS=5–9; 1 pt NIHSS=10–15; 2 pts NIHSS>15; 3 pts
			Onset-to-treatment time
			1 pt if >90 min

ASPECTS indicates Alberta Stroke Program Early CT Score; DRAGON, (hyper)dense middle cerebral artery sign or early infarct signs on admission computed tomography (CT) head scan, prestroke modified Rankin Scale score 1, age, glucose level on admission, onset-to-treatment time, and NIHSS score; IV, intravenous; MOST, Multimodal Outcome Score for Stroke Thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; pt(s), point(s); SBP, systolic blood pressure; and TPI, Stroke-Thrombolytic Predictive Instrument.

Prediction Scores in Patients With Ischemic Stroke Treated With Intravenous Thrombolysis

The prognostic scores introduced for predicting functional outcome[13,49,50] or sICH[51–56] after intravenous thrombolysis in acute ischemic stroke are summarized in Tables 2 and 3, respectively (Figures 2 and 3).

Pathophysiologic Insights Into Scores' Constituents and Stroke Outcome

Stroke severity in the form of an established scale (NIHSS) is present in all scores, except for the TPI version for favorable outcome (modified Rankin Scale ≤1). It seems that stroke patients who gain most of thrombolysis are those with an NIHSS score between 4 and 25.[57] The cutoffs implemented do not reflect published ranges and might possibly be explained by the specific population used in each cohort (distribution of NIHSS), as well as the inclusion or not of posterior circulation strokes (severity of posterior circulation strokes is not so well correlated with the NIHSS score like the anterior circulation strokes). With regard to the risk of sICH in patients treated with thrombolysis, NIHSS has been associated with an increased risk of hemorrhage analyzed either as a dichotomous or as a continuous covariate.[58]

Given the importance of age in overall ischemic stroke patients (see Scores for Prediction of Functional Outcome in the Overall Ischemic Stroke Population), it is not surprising to find it also in most prognostic scores (except for hemorrhage after thrombolysis [HAT], Multimodal Outcome Score for Stroke Thrombolysis [MOST], and TPI for favorable outcome) in thrombolyzed patients (Table 2). Despite higher mortality risk and poorer functional outcome associated with increasing age in thrombolyzed patients,[59–61] age does not modify the relative response to thrombolysis. In fact, all large data sets[62–65] and trials (IST-3)[66] addressing this question show a similar response rate in elderly as in the younger population. Regarding the presence of age in the scores that predict sICH, it has been reported that there is a progressive risk of sICH at each decade of life between <60 and 80 years with no difference between 71- to 80- and 81- to 90-year age groups.[60] Moreover, a recent meta-analysis showed that age (either as a continuous or as a categorical variable) has been associated with an increased risk of hemorrhage in patients treated with thrombolysis.[58] Despite this added sICH risk, the benefits of early thrombolysis in the elderly are still present. The addition of age to HAT score, as stated in the original publication, did not improve the scale's predictive ability; this may be attributed to the different thresholds and cutoff points used or the various combinations of variables tested in the univariate analysis.[52]

The deleterious effects of hyperglycemia (apart from Stroke Prognostication Using Age and NIH Stroke Scale [SPAN-100], MOST, and TPI for favorable outcome) on the outcome of thrombolyzed acute ischemic stroke patients, including the increased risk of intracranial hemorrhage, are well established.[67] It is still debatable whether hyperglycemia is only an epiphenomenon (ie, an acute stress response from activation of the hypothalamic-pituitary-adrenal axis causing a rise in cortisol and catecholamines or a result of brain damage in areas involved in glucose regulation) or cellular acidosis caused by anaerobic glycolysis, enhanced free radical production, increased blood–brain

Table 3. Prognostic Scores Developed for Predicting Intracerebral Hemorrhage After Intravenous Thrombolysis in Acute Ischemic Stroke

MSS[51]	HAT[52]	SITS[53]	GRASP (GWTG)[54]	SPAN-100[55]	SEDAN[56]
Age	Easily visible hypodensity on CT*	Age	Age	Age	Age
1 pt if >60 y	No; 0 pt <1/3 MCA territory; 1 pt ≥1/3 MCA territory; 2 pts	1 pt if ≥72 y	8 pts if <60 y 11 pts if 61–70 y 15 pts if 71–80 y 17 pts if >80 y	Years added to NIHSS; index positive of the sum is ≥100	1 pt if >75 y
NIHSS at baseline	NIHSS at baseline	NIHSS at baseline	NIHSS at baseline	NIHSS at baseline	NIHSS at baseline
NIHSS>10; 1 pt	NIHSS<15; 0 pt NIHSS=15–20; 1 pt NIHSS≥20; 2 pts	NIHSS<7; 0 pt NIHSS=7–12; 1 pt NIHSS≥13; 2 pts	NIHSS=0–5; 25 pts NIHSS=6–10; 27 pts NIHSS=11–15; 34 pts NIHSS=16–20; 40 pts NIHSS>20; 42 pts	NIHSS score added to age; index positive of the sum is ≥100	NIHSS≥10; 1 pt
Glucose on admission >8.325 mmol/L	Glucose on admission >11.1 mmol/L or history of DM	Glucose on admission >10.0 mmol/L	Glucose on admission		Glucose on admission
1 pt	1 pt	2 pts	2 pts if <100 mg/dL 6 pts if 100-149 mg/dL 8 pts if ≥150 mg/dL		0 pt if <8 mmol/L 1 pt if 8.1–12.0 mmol/L 2 pts if >12 mmol/L
PLTs $<1.5\times10^5/mm^3$		Antiplatelet treatment before stroke	SBP		Early infarct signs on CT*
1 pt		Aspirin only; 0 pt Aspirin and clopidogrel; 1 pts	10 pts if <120 mm Hg 14 pts if 120–149 mm Hg 18 pts if 150–179 mm Hg 21 pts if ≥180		1 pt if present
		SBP	Ethnicity		Dense or hyperdense cerebral artery sign on CT*
		1 pt if >146 mm Hg	9 pts if Asian 0 pts if non-Asian		1 pt if present
		Weight	Male sex		
		1 pt if >95 kg	4 pts		
		History of hypertension			
		1 pt if present			
		Onset-to-treatment time			
		1 pt if ≥180 min			

DM indicates diabetes mellitus; GRASP, Glucose Regulation in Acute Stroke Patients; GWTG, Get With The Guidelines; HAT, hemorrhage after thrombolysis; MCA, middle cerebral artery; MSS, Multicenter Stroke Survey; NIHSS, National Institutes of Health Stroke Scale; PLTs, platelets; pt(s), point(s); SBP, systolic blood pressure; SEDAN, blood sugar (glucose) on admission, early infarct signs and (hyper)dense cerebral artery sign on admission computed tomography (CT) head scan, age, and NIHSS; SITS, Safe Implementation of Treatments in Stroke; and SPAN-100, Stroke Prognostication Using Age and NIH Stroke Scale.

*Imaging findings on the noncontrast head CT scan on admission.

barrier permeability, impaired mitochondrial function, influx of intracellular Ca^{++}, and cellular edema.[67] However, hyperglycemia is not included in all scores predicting functional outcome in tissue-type plasminogen activator–treated patients.

Early computed tomography (CT) changes in the middle cerebral artery territory, Alberta Stroke Program Early CT Score (ASPECTS) score, leukoaraiosis, and visible hypodensity have been correlated to intracranial hemorrhage after thrombolysis.[58,68] Each one of the above-mentioned variables correlates with the clot burden, time from symptom onset to CT, or damage of vessel walls in other areas of the brain. Indeed, all scores that aim to predict thrombolysis functional outcome, except for the TPI version for favorable outcome (modified Rankin Scale ≤1), include ≥1 imaging parameter. Of note, in MRI-DRAGON (magnetic resonance imaging-[hyper]dense middle cerebral artery sign or early infarct signs on admission CT head scan, prestroke modified Rankin Scale score 1, age, glucose level on admission, onset-to-treatment time, and NIHSS score), an adaptation of the original DRAGON score, the hyperdense middle cerebral artery sign and the early infarct signs on CT have been replaced by proximal middle cerebral artery occlusion in MRI and diffusion-weighted imaging ASPECTS ≤5, respectively.[69,70] In case of sICH prediction, imaging data were not used for the development of Multicenter Stroke Survey (MSS), Glucose Regulation in Acute Stroke Patients (GRASP), and SPAN-100 scores, whereas Safe Implementation of Treatments in Stroke (SITS) score used only infarct signs on CT/MRI variable in the univariate analysis. The rest of the scores include ≥1 imaging variable.

A meta-analysis of the randomized trials with intravenous alteplase in acute ischemic stroke has clearly shown that the increase in onset-to-treatment time significantly decreases the probability of a 3-month favorable outcome, increases

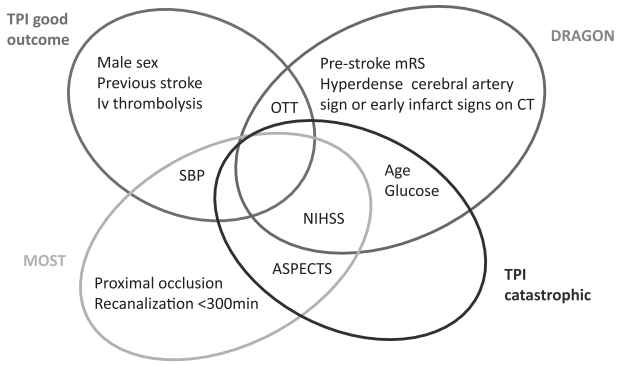

Figure 2. Illustration of prediction scores in patients with ischemic stroke treated with intravenous thrombolysis: functional outcome. ASPECTS indicates Alberta Stroke Program Early CT Score; DRAGON, (hyper)dense middle cerebral artery sign or early infarct signs on admission computed tomography (CT) head scan, prestroke modified Rankin Scale score 1, age, glucose level on admission, onset-to-treatment time, and NIHSS score; IV, intravenous; MOST, Multimodal Outcome Score for Stroke Thrombolysis; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment time; SBP, systolic blood pressure; and TPI, Stroke-Thrombolytic Predictive Instrument.

the odds of mortality, and has no effect on the presentation of large parenchymal hemorrhage.[64] Updated data from routine clinical practice for thousands of patients expand the beneficial effects of earlier IV recombinant tissue-type plasminogen activator administration in reduced in-hospital mortality, increased independent ambulation at discharge, and increased discharge to home.[71] Moreover, in the latter observational study, shorter onset-to-treatment time is also correlated with reduced sICH (odds ratio, 0.96; 95% confidence interval, 0.95–0.98). This conflicts with the earlier meta-analysis of randomized trials but also a systematic review of 55 thrombolysis studies which failed to identify onset-to-treatment time as a variable associated with sICH.[58] Onset-to-treatment time is present in 3 scores only.

Regarding BP, published data support that prethrombolysis levels do not correlate with 3-month unfavorable outcome.[72–76] However, SITS analysis shows an association between elevated diastolic BP and mortality at 3 months.[72] MOST and TPI for favorable outcome include systolic BP as a covariate. For the prediction of sICH, only 2 scores include BP (although systolic), despite data from the SITS and a large meta-analysis suggesting at least borderline correlation.[58,72,77]

According to the SITS data, males treated with alteplase have a higher risk of mortality (odds ratio, 1.19; 95% confidence interval, 1.10–1.29; $P<0.001$) and sICH (odds ratio, 1.25; 95% confidence interval, 1.04–1.51; $P=0.02$), but a similar functional outcome with females (odds ratio, 1.03; 95% confidence interval, 0.97–1.09; $P=0.39$).[78] These data come from the largest nonrandomized series (n=45 079) of thrombolysis and seem to answer the conflicting evidence of previous studies on the influence of sex in thrombolysis results.[79] Accordingly, the absence of sex in 2 of the 4 scores that predict functional outcome of thrombolyzed patients was expected. Regarding the sICH risk, sex is included in the GRASPS score (1 of the 6 scores); however, a recent meta-analysis did not recognize sex as a factor influencing sICH.[58]

Among the other variables which are only sporadically included in the scores, prior antiplatelet treatment does not appear in the scores that predict the outcome of thrombolysis because despite the increase in sICH, its impact on 3-month outcome is either neutral[80] or even borderline positive.[81] Regarding its presence in only 1 sICH score, it should be noted that even among the same study population, different sICH definitions and antiplatelet variables (eg, comparison of specific monotherapies or dual versus no therapy) lead to different results.[80] Last but not least, some scores do include information on prestroke disability and social environment (Tables 2 and 3).

Advantages and Limitations of the Prognostic Scores

Each prognostic score has different characteristics and properties, and consequently different strengths and limitations. The DRAGON score and the ASTRAL score are easy to evaluate without the need for mathematical formulas, calculators, or online tools. The ASTRAL score provides a color chart. The

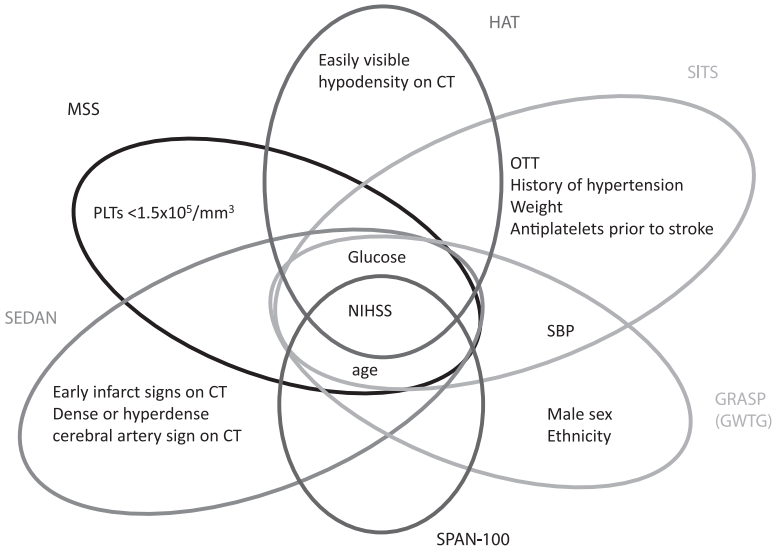

Figure 3. Illustration of prediction scores in patients with ischemic stroke treated with intravenous thrombolysis: symptomatic intracerebral hemorrhage. CT indicates computed tomography; GRASP, Glucose Regulation in Acute Stroke Patients; GWTG, Get With The Guidelines; HAT, hemorrhage after thrombolysis; MSS, Multicenter Stroke Survey; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment time; PLTs, platelets; SBP, systolic blood pressure; SEDAN, blood sugar (glucose) on admission, early infarct signs and (hyper)dense cerebral artery sign on admission computed tomography head scan, age, and NIHSS; and SPAN-100, Stroke Prognostication Using Age and NIH Stroke Scale.

iScore has a free Web application which simplifies the calculation of the score. The preadmission comorbidities, level of consciousness, age, neurologic deficit (PLAN) score does not include a stroke severity score like the NIHSS or the CNS as its constituent.[8] The ASTRAL score, the DRAGON score, the iScore, the Six Simple Variables score, and the Get With The Guidelines (GWTG) score have been extensively validated in external data sets and sometimes for the prediction of outcomes other than the ones for which they were originally developed.[69,70,82–95] These extended validations further increase the scores' reliability. The scores that are free of specialized laboratory tests or imaging techniques and include only simple parameters are more feasible for centers with limited resources.[5–12,43] However, we cannot underestimate the additional value of imaging and laboratory parameters. The prediction score cannot be simple just for the sake of simplicity if it does not serve its purpose. Dedicated stroke centers should be able to analyze noncontrast CT scans also during out-of-office hours. Other centers can use telemedicine/telestroke consultations.

Caution is necessary when using stroke prognostic scores so that a prediction of grave outcome in a misclassified patient does not lead to withdrawal of patient care and consequently to a self-fulfilling prophecy.[2] Also, the evolution of acute stroke care and the potential launch of new evidence-based acute stroke treatments (eg, endovascular treatment, hypothermia) may reduce the prognostic accuracy of the scores in the future.[2] This may well be the case also for intravenous thrombolysis as it is not included as a parameter in these prognostic scores, and therefore, the prediction of outcome may be pessimistic and less accurate, as it was shown for the PLAN score.[8]

Future Areas of Research

Further external validation of the prognostic scores in different ethnicities, as well as in specific patient groups, would be desirable as it would further underline their reliability and allow for recalibration where necessary. Also, it would be interesting to investigate whether the addition of imaging or specialized laboratory tests (eg, copeptin),[96] biomarkers, or genetic profiles can increase their accuracy. In this context, recently the addition of multimodal imaging did not increase the prognostic accuracy of the ASTRAL score,[97] but it improved the accuracy of the MRI-DRAGON score.[69]

Moreover, further work is warranted to investigate whether prognostic stroke scores can be used as inclusion/exclusion criteria in randomized controlled trials of acute stroke treatment with the aim to assist in better selection of patients. Recruitment of patients with a nearly inevitable outcome (either favorable or unfavorable) reduces the statistical power of a trial and leads to a larger sample size as it only adds noise to the population that may show a treatment effect. Currently, trials elaborate certain parameters like the NIHSS and age as selection criteria; apart from these 2 parameters, most of the stroke prognostic scores combine several other parameters, and therefore, it may be possible that they provide a better selection of patients. Trials testing efficacy of agents aiming to reduce hemorrhagic complications of thrombolysis could possibly recruit only patients with high risk of sICH as judged by the scores; hence, reduce the number of study patients.

Many physicians would argue that prediction scores are not important and that physician-based prediction is more accurate, or perhaps that scores make a better prediction only compared with the less experienced stroke physicians.[98] However, we as clinicians base our predictions on the same clinical information that is included in the prediction scores. In this context, a stroke physician would need to have a significant experience to match the information provided by the large number of recorded parameters of hundreds or thousands of patients whose data were analyzed during the development of the prognostic scores. We need more comparative studies to judge this. For ischemic stroke, there is only one study, according to which the iScore was more accurate than stroke physicians.[99]

Further validation of stroke prognostic scores is necessary to render them reliable enough for decision making in individual patients. Regarding prediction of sICH, the most critical question is whether any score can guide an individualized decision to thrombolyze/not thrombolyze. In theory, this should be based on the predicted outcome in case the patient is not thrombolyzed, as well as on the predicted risk of sICH in case that patient is thrombolyzed. Such an attempt, based on 3 cutoff levels for the risk of sICH (<3%, 3% to 8%, >8%), was recently performed for controls and thrombolysis-treated patients in IST-3,[100] but there was no rationale behind these cutoff values. We think that the worst category cannot start from 8% if the overall percentage of sICH was 7% in the IST-3. But this is actually the principal question: What is the maximal acceptable and nonacceptable risk of sICH? There are no any generally accepted cutoffs for this scenario. In different setting, we would not refer a patient for carotid endarterectomy to a center with complication rates >5%.

In the long run, engineering prediction scores to include more elements, especially by incorporating imaging and biomarkers, may enhance their utility. Finally, perhaps the biggest challenge for these scores would be to convince stroke physicians to implement them in their daily clinical practice. As evidence for the reliability and practicability of such scores accumulates, their clinical and research use is likely to increase.

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and the International Journal of Stroke. He serves on the steering committee of the Basilar Artery International Cooperation Study (BASICS), the International Patent Foramen Ovale-Consortium, the Data and Safety Monitoring Board of Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE), and the intracranial hemorrhage-adjudication committee from Phase 3, Randomized, Placebo-Controlled, Double-Blinded Trial of the Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator (tPA) for Emergent Revascularization in Acute Ischemic Stroke (CLOTBUST-ER). Dr Tatlisumak was involved in the development of DRAGON and SEDAN scores and in the external validation of the Simple Variables Model. He has received through his institution research grants from Boehringer-Ingelheim, Sanofi-Aventis, H. Lundbeck A/S, Mitsubishi Pharma, PhotoThera, and BrainsGate, and speaker fees from Boehringer-Ingelheim, Bayer, and Professio Oy. Dr Strbian was involved in the development and/or external validation of the DRAGON, SEDAN, and Simple Variables Model.

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