Journal of Neurology (2019) 266:2620–2628
https://doi.org/10.1007/s00415-019-09454-2

ORIGINAL COMMUNICATION

Selection of anterior circulation acute stroke patients for mechanical thrombectomy

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Received: 5 February 2019 / Revised: 7 June 2019 / Accepted: 27 June 2019 / Published online: 3 July 2019

Abstract

Background The use of mechanical thrombectomy (MT) for acute ischemic stroke (AIS) patients has increased with a parallel burden in procedural costs. We tested whether a new prognostic score could identify patients who are unlikely to benefit from MT.

Methods Patients from our endovascular stroke registry were assessed for imaging and clinical outcome measures and randomly divided into two subsets for derivation and validation. We created a new prognostic score based on clinical and radiological prognostic factors of poor outcome (mRS score ≥ 3) from the derivation cohort. Receiver operating characteristics curve analysis was used to assess the discrimination ability of the score. The score was then validated and compared to the MR PREDICTS score.

Results The derivation/validation included 270/116 patients, respectively. After multivariate logistic regression analysis, pre stroke mRS, age, admission glycaemia, admission NIHSS, collateral flow, Clot Burden Score, Alberta Stroke Program Early CT score were used to create a new prognostic scoring system called Tor Vergata Stroke Score (TVSS). TVSS revealed a good prognostic accuracy with an AUC of 0.825 [95% CI 0.77–0.88] in the derivation cohort and an AUC of 0.820 [95% CI 0.74–0.90] in the validation cohort. When compared to the MR PREDICTS in the validation cohort, TVSS demonstrated higher prediction ability which was, however, not statistically significant (0.80 vs 0.78; $P = 0.26$).

Conclusions TVSS is a reliable tool for selection of AIS candidates for MT and optimization of transfer to comprehensive stroke centers.

Keywords Acute ischemic stroke · Mechanical thrombectomy · Prognosis · Score

Introduction

Mechanical thrombectomy (MT) has become a milestone in the treatment of an increasing number of acute ischemic stroke (AIS) patients [1–3]. Systematic reviews showed that MT, while associated with high financial cost, provides a large advantage in terms of clinical outcome. MT is considered cost-effective when a threshold of $50,000 per quality-adjusted life year gained is adopted [4]. A major concern is the risk of futile reperfusion which occurs when successful reperfusion fails to improve functional outcome. According to recent endovascular stroke trials futile reperfusion occurs in 19–43% of treated patients [1–3]. Transfer from non-MT sites to tertiary stroke centers may result in wasted resources if eligibility to MT does not apply. Thus, caution in the selection of MT candidates should be mandatory. Elderly subjects are perceived to be at higher risk of poor

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-019-09454-2) contains supplementary material, which is available to authorized users.

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outcome despite MT due to ageing and comorbidities. Still, some authors suggest that age should not be considered as an exclusion criterion for recanalization treatments. The Third International Stroke Trial (IST-3) showed the benefit of intravenous thrombolysis (IVT) irrespective of age [5]. A recent metanalysis concluded that patients older than 80 years benefit from MT as much as other age groups [6]. Along with age, clinical severity, the Alberta Stroke Program Early CT score (ASPECTS) and collateral flow are other prognostic factors assessed before treatment decision-making [5, 7, 8]. To provide physicians with an easy-to-use tool, we aimed to create a novel prognostic score, based on clinical and imaging pre-treatment data, able to predict outcome in AIS patients with large vessel occlusion (LVO) of anterior circulation and potential indication for MT.

Materials and methods

Patients

Four hundred-forty patients with AIS, prospectively assessed and included in our endovascular stroke registry (between August 2012 and June 2017), were considered. Inclusion criteria for patient selection were: (1) occlusion of middle cerebral artery or terminal internal carotid artery, alone or in combination, or proximal internal carotid artery in combination with an intracranial vessel, on computed tomography-angiography (CTA) and confirmed on conventional angiography; (2) groin puncture within 6 h of symptom onset; (3) NIH Stroke Scale (NIHSS) ≥ 10. 42 were posterior circulation stroke and 12 did not fulfill inclusion criteria leaving 386 patients suitable for analysis.

Data selection

Poor 3-month functional outcome was defined as a modified Rankin Scale (mRS) ≥ 3. Successful reperfusion was defined as a Thrombolysis in Cerebral Infarction (TICI) score ≥ 2b [9]. All clinical and imaging characteristics expected to predict outcome based on recent literature and evaluated by stroke physicians between admission to emergency department and the beginning of MT were included in the analysis. They were: age, gender, NIHSS, site of occlusion, history of hypertension, diabetes, smoking, atrial fibrillation, admission glycemia, admission systolic blood pressure, Alberta Stroke Program Early CT score (ASPECTS) on non-contrast CT, collaterals adequacy and Clot Burden Score (CBS) on pre-treatment CTA, intravenous thrombolysis (IVT) [7, 8, 10–12]. For assessment of collaterals on CTA we adopted a scale from 0 to 3 derived from the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial [13]. Collateral score was dichotomized in poor (0–1) and good (2–3). The validity of dichotomization has been already established [8]. For all patients an already existing score, called MR PREDICTS score, was then calculated (https://mrpredicts.shinyapps.io/RRRR_1/) to predict probability of a poor 3-month functional outcome [14]. MR PREDICTS score was assessed as a benchmark in terms of prediction ability. The study was approved by Tor Vergata Hospital ethics committee. Informed consent was obtained from all patients or their relatives.

Statistical analysis

To ensure generalizability of our result, as a first step we divided our full sample in a derivation cohort ($n = 270$) and a validation cohort ($n = 116$) using random sampling until the two cohorts were matched in terms of all predictor and outcome variables (Fisher Exact test for categorical variables the Mann–Whitney U test for continuous data). All analyses leading to the creation of our prognostic score were retrospectively performed on data prospectively included in the registry, on the derivation cohort only. Performance evaluation was carried out on the 'unseen' validation cohort only. As mentioned previously, we employed a single dichotomous outcome variable: "good outcome" (mRS ≤ 2) and "poor outcome" (mRS ≥ 3). We employed univariate analysis on all variables (Fisher Exact test for categorical variables the Mann–Whitney U test for continuous data). For variables which showed significant ($P < 0.05$) differences between outcome groups at univariate analysis, we fitted a univariate binary logistic regression with model (dependent variable: outcome) to build a receiver operating characteristic (ROC) curve, from which the optimal operating point (i.e., cutoff) was determined by maximizing the Youden index ($J = \text{sensitivity} + \text{specificity} - 1$). All these variables were dichotomized according to their respective cutoff, and this derived set of binary predictors was included in a multivariate logistic regression model (dependent variable: outcome). We then designed a risk stratification score calculated by adding n points (defined as the odds ratio associated with each variable in multivariate logistic regression, rounded to the nearest integer) for each independent variable significantly associated with poor outcome. This yielded a single, per-patient score which was derived using the derivation cohort only. Successively, the discrimination ability of this score was evaluated through ROC curve analysis in the validation cohort. The ability to predict 90-day mortality as well as particularly unfavorable outcome (90-day mR = 5 and 6) was also evaluated. Additionally, the performance of our score was also compared to that of the MR PREDICTS score [15]. Statistical analyses were performed using IBM

SPSS version 23 software (IBM SPSS Statistics, Armonk, NY).

Results

Baseline characteristics of the two cohorts (derivation and validation) along with the result of statistical testing are shown in Table 1. As mentioned above, the cohorts were sampled at random until no statistical difference in any variable was found.

Results of univariate analysis showing variables associated to functional outcome in the derivation cohort are reported in Table 2.

According to the results of univariate analysis, multivariate logistic regression included age, glycaemia, ASPECTS, CBS, NIHSS at onset, pre stroke mRS, active smoking, site of arterial occlusion, collateral flow. Also, univariate ROC analysis yielded the following thresholds for continuous variables: age > 80 years (AUC 0.608), ASPECTS ≤ 8 (AUC 0.674), NIHSS at onset > 17 (AUC 0.690), CBS ≤ 5 (AUC 0.663), glycaemia > 111 mg/dL (AUC 0.666). Seven predictors were identified: age, baseline glycaemia, ASPECTS, CBS, NIHSS score at onset,

Table 1 Clinical, imaging and procedural characteristics in the derivation and validation cohort

	Derivation cohort ($n=270$)	Validation cohort ($n=116$)	P
Age, (years), (mean ± SD)	72.3 ± 13.2	71.1 ± 13.5	0.44
Male, *n* (%)	113 (42)	46 (40)	0.27
Intravenous thrombolysis, *n* (%)	150 (56)	73 (63)	0.18
Pre stroke mRS > 0, *n* (%)	43 (16)	15 (13)	0.45
Atrial fibrillation, *n* (%)	100 (37)	37 (32)	0.33
Hypertension, *n* (%)	198 (73)	90 (78)	0.38
Smoking, *n* (%)	49 (18)	15 (13)	0.21
Diabetes, *n* (%)	52 (19)	16 (14)	0.20
Hypercholesterolemia, *n* (%)	78 (29)	29 (25)	0.43
Previous TIA/stroke, *n* (%)	34(13)	15 (13)	0.93
Coronary artery disease, *n* (%)	45 (17)	12 (10)	0.07
Glycaemia, (mg dL), (mean ± SD)	134.0 ± 51.6	127.0 ± 34.0	0.18
SBP[a], (mmHg), (mean ± SD)	147.6 ± 24.7	144.6 ± 26.0	0.075
Onset NIHSS[b], [median (IQR)]	18 (14–21)	18 (15–21)	0.79
Site of occlusion, *n* (%)			
MCA	178 (66)	76 (65.5)	0.57
Tandem	76 (28)	34 (29)	
t-ICA	8 (3)	1 (1)	
T-occlusion[c]	8 (3)	5 (4)	
Clot Burden Score, [median (IQR)]	6 (4–8)	6 (4–8)	0.91
ASPECT[d] score, [median (IQR)]	8 (7–10)	8 (7–10)	0.65
Onset to arterial puncture, (min), [median (IQR)]	225 (177–275)	220 (175–265)	0.60
Onset to recanalization, (min), [median (IQR)]	285 (232–336)	285 (240–330)	0.91
TICI[e] scale ≥ 2b, *n* (%)	206 (76)	84 (72)	0.47
ΔNIHSS[f], (mean ± SD)	− 3.12 ± 8.7	− 3.27 ± 8.1	0.66
Poor collateral flow, *n* (%)	89 (33)	39 (34)	0.90
mRS[g] > 2, *n* (%)	168 (62)	71 (62)	0.93
Mortality, *n* (%)	86 (32)	31 (27)	0.31

[a]Systolic blood pressure

[b]National Institutes of Health Stroke Scale

[c]Occlusion of the internal carotid artery, middle and anterior cerebral artery

[d]Alberta Stroke Program Early CT Score

[e]Thrombolysis in Cerebral Infarction scale

[f]Difference between onset and 24 h NIHSS

[g]Modified Rankin Scale

Table 2 Clinical, imaging and procedural characteristics in the good and poor outcome subgroups (derivation cohort)

	Good outcome mRS ≤ 2 ($n = 102$)	Poor outcome mRS > 2 ($n = 168$)	*P*
Age, (years), (mean ± SD)	69.0 ± 13.9	74.3 ± 12.4	0.001
Male, *n* (%)	38 (37)	75 (45)	0.23
Intravenous thrombolysis, *n* (%)	61 (60)	89 (53)	0.27
Pre stroke mRS[a] > 0, *n* (%)	9 (9)	34 (20)	0.013
Atrial fibrillation, *n* (%)	31 (30)	69 (41)	0.08
Hypertension, *n* (%)	70 (71)	126 (75)	0.43
Smoking, *n* (%)	20 (20)	29 (17)	0.63
Diabetes, *n* (%)	14 (14)	38 (23)	0.07
Hypercholesterolemia, *n* (%)	38 (37)	55 (33)	0.50
Previous TIA/stroke, *n* (%)	23 (22.5)	56 (33)	0.12
Coronary artery disease, *n* (%)	16 (16)	29 (17)	0.74
Glycaemia, (mg dL), (mean ± SD)	118.18 ± 35.0	143.67 ± 57.5	0.001
SBP[b], (mmHg), (mean ± SD)	146.9 ± 24.3	148.1 ± 25.8	0.57
Onset NIHSS[c], [median (IQR)]	16 (11–19)	19 (16–21)	< 0.001
Site of occlusion, *n* (%)			
MCA	79 (77.5)	99 (59)	0.007
Tandem	21 (21)	55 (33)	
t-ICA	0	8 (5)	
T-occlusion[d]	2 (2)	6 (4)	
Clot Burden Score, [median (IQR)]	7 (6–8)	6 (4–7)	< 0.001
ASPECT score[e], [median (IQR)]	9 (8–10)	8 (6–9)	< 0.001
Onset to arterial puncture, (min), (mean ± SD)	222.7 ± 70.9	230.7 ± 62.4	0.40
Onset to recanalization, (min), (mean ± SD)	264.6 ± 74.8	302.9 ± 89.9	< 0.001
TICI[f] scale ≥ 2b, *n* (%)	94 (92)	112 (61)	< 0.001
ΔNIHSS, [median (IQR)]	− 8.5 (− 12.7 to − 4.2)	0 (− 4.0 to 2 −)	< 0.001
Poor collateral flow, *n* (%)	12 (12)	77 (46)	< 0.001

[a]Modified Rankin Scale

[b]Systolic blood pressure

[c]National Institutes of Health Stroke Scale

[d]Occlusion of the internal carotid artery, middle and anterior cerebral artery

[e]Alberta Stroke Program Early CT Score

[f]Thrombolysis in Cerebral Infarction scale

[g]Difference between onset and 24 h NIHSS

pre stroke mRS, collateral flow. TICI score was excluded from the subsequent analysis as it is not a pre-treatment phase variable. The results of multivariate binary logistic regression are shown in Table 3. Our prognostic score, called the Tor Vergata Stroke Score (TVSS), therefore ranged between 0 and 18. As successive univariate ROC analysis, our score showed a good discrimination ability in the validation cohort (AUC 0.820 [95% CI 0.74–0.90]) and higher (albeit not with a statistically significant difference) AUC when compared to the performance of the previously reported MR PREDICTS score (AUC 0.78. $P = 0.26$) in the same cohort (Fig. 1). Included variables and prediction ability of TVSS and MR PREDICTS scores are reported in Table 4. Concerning discrimination ability to predict 3-month mortality, a similar result was found with both scores (AUC 0.77 [95% CI 0.674–0.859] with TVSS and AUC 0.78 [95% CI 0.693–0.863] with MR PREDICTS score). Finally, to provide a coarse-grained idea of the stratification resulting from applying TVSS, the validation population was divided into three equally sized groups (low-, moderate-, and high-risk) on the basis of the overall distribution of TVSS (cutoffs: 33rd and 66th percentile, which corresponded to TVSS = 5 and TVSS = 11, respectively). Risks of poor outcome and mortality were respectively 30% and 7% in patients with low (0–5 points) risk, 75% and 30% in patients with moderate risk (6–11 points) score and 100% and 70% in patients with high (12–18 points) risk score (Table 5 and Fig. 2). In

Table 3 Multivariate binary logistic regression analysis including dichotomized variables (derivation cohort) predictive of poor outcome (90-day mRS ≥ 3)

	OR	95% CI	*P*	Score
Age > 80 years	2.22	1.1–4.4	0.025	2
Pre stroke mRS[a] > 0	3.39	1.3–8.5	0.010	3
ASPECTS[b] ≤ 8	2.02	1.1–3.8	0.028	2
Poor collateral flow	3.06	1.4–6.6	0.004	3
NIHSS[c] at onset > 17	2.26	1.2–4.2	0.010	2
Clot Burden Score ≤ 5	3.18	1.6–6.4	0.001	3
Baseline glycaemia > 111 mg/dL	2.90	1.6–5.3	0.001	3

[a]Modified Rankin Scale

[b]Alberta Stroke Program Early CT Score

[c]National Institutes of Health Stroke Scale

an additional sub analysis which dichotomized our population in extremely unfavourable outcome (mRS = 5 or 6) or not, we found a TVSS score cutoff of > 10 (AUC 0.783 [95% CI 0.70–0.87]) above which endovascular treatment is likely futile. Successful reperfusion was 74% in the validation cohort and not significantly different among different score groups (low risk 79%; moderate risk 67%; high risk 81%, $P = 0.32$).

Discussion

Prediction of ischemic stroke outcome in the hyperacute setting could be very helpful. Compared to when IVT was the only existing therapy for AIS, we are now facing larger multidisciplinary stroke teams and increasing costs also due to technological requirements. In particular, LVO strokes present with more severe neurological deficits and are at high risk of poor outcome (with increased mid and long-term economic burden) and mortality [12, 14]. Currently, stroke physicians often face the dilemma of treating or not treating, especially for very elderly patients who may suffer from several comorbidities (beyond aging) such as pre stroke dementia and disability which potentially affect outcome [15, 16]. Properly balancing potential benefit of treatment with potentially futile reperfusion and costs requires information often unavailable at triage evaluation. Stroke prognostic models should aid stroke neurologists in treatment decision making [17–19]. Nevertheless, none of these models have been incorporated in clinical practice [20]. A recent study compared the accuracy of several stroke prognostic scales revealing that the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) score returned the best prognostic performance [19, 21]. However, the analyzed sample comprised only baseline clinical and demographic (not neuroimaging) data based models. In our study we developed a new score, called TVSS, based on a comprehensive clinical and neuroimaging pre-treatment data model which may able to predict mortality and poor outcome with good accuracy. This score ranges between 0 and 18. All seven included variables have to be

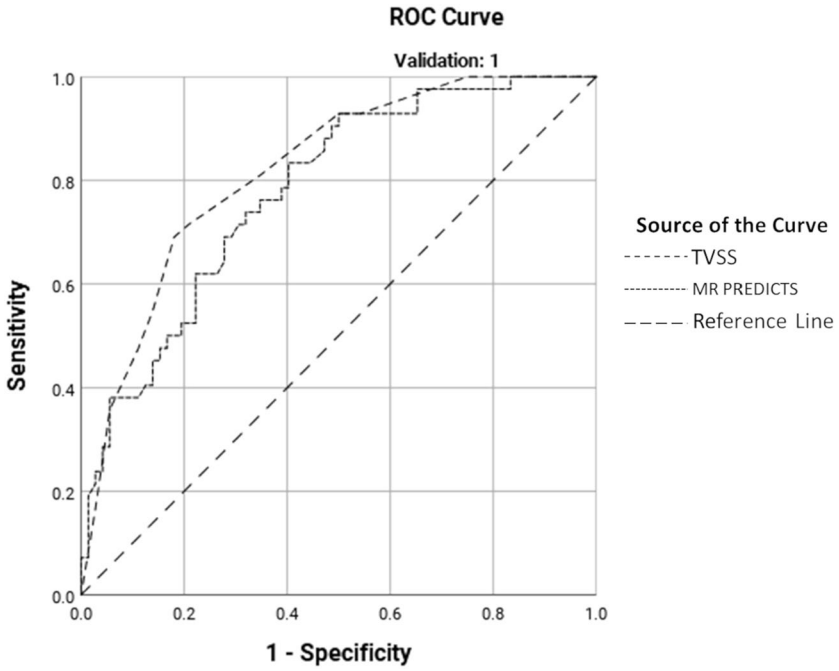

Fig. 1 Comparison of receiver operating characteristic (ROC) curves of the Tor Vergata Stroke Score (TVSS) and of the MR PREDICTS score. The TVSS ROC curve shows a trend toward better diagnostic predictiveness than MR PREDICTS score

Table 4 Comparison of included variables and prediction ability of TVSS and MR PREDICTS scores

	Included variables	Prediction
TVSS	Age > 80 years Pre stroke mRS > 0 ASPECTS[a] ≤ 8 Poor collateral flow NIHSS[b] at onset > 17 Clot Burden Score ≤ 5 Baseline glycaemia > 111 mg/dL	AUC 0.82 [95% CI 0.74–0.90]
MR PREDICTS	Age NIHSS Pre stroke mRS Previous stroke Diabetes mellitus Systolic blood pressure Intravenous tPA ASPECT score Location of occlusion (intracranial ICA[c], M1, M2) CTA[d] collateral flow (absent, poor, moderate, good) Estimated time from onset o groin puncture	AUC 0.78 [95% CI 0.69–0.86]

[a]Alberta Stroke Program Early Computed Tomography Score

[b]National Institutes of Health Stroke Scale

[c]Internal carotid artery

[d]Computed tomography angiography

evaluated in a dichotomous way (e.g., age > 80 = 2 points; age ≤ 80 = 0 points). The TVSS identifies three risk groups: low (0–5), moderate (6–11), high (12–18). Notably, 100% of patients in the higher quartile of the score presented a poor outcome with a 70% prevalence of death. This means that only 1 every 33.3 treated patients in this group is expected to have good outcome. Compared to the majority of previous prognostic scales, our score included critical neuroimaging variables such as ASPECTS and, above all, collateral flow and CBS. The main reason could be that previous scales were designed to screen all AIS patients irrespective of LVO diagnosis. On the other hand, our scale was conceived for AIS patients with LVO referring to a tertiary stroke center. Our results emphasize that multimodal neuroimaging (essentially non-contrast CT and CTA) and related scores, such as ASPECTS, collateral flow and CBS, are extremely useful in treatment decision making. CTA is usually performed soon after CT once a haemorrhagic lesion has been excluded. Nowadays it is often necessary since clinical or even CT derived information is not strictly associated to proximal intracranial artery occlusion. In this context, the MR PREDICTS also includes data derived from CTA (site of occlusion and collaterals).

In the context of a better health system cost control, acquisition of this information in peripheral hospitals could improve selection of patients who can benefit most from transfer to tertiary stroke centers.

In this regard CTA-based parameters (i.e., collateral flow and CBS) contributed in a greater extent to the total score (3 points each). This can be explained by the strong pathophysiological link between collaterals, perfusion status and sustenance to salvageable tissue [22]. Other variables which played an important role in the final score were pre stroke mRS and admission glycaemia. These findings are in line with the results of a recent work reporting that patients with pre-existing disability are older and have higher risk of unfavorable outcome despite MT [23]. Noteworthy, the cutoff value of pre stroke mRS was 0, suggesting that even slight disability may affect outcome, especially in elderly and that all efforts should be done to trace accurately and definitely pre stroke cognitive and physical condition (preferably in the pre-hospital setting) [15, 16, 23]. Compared to the MR PREDICTS score [14] IVT was not included in our score since no association with outcome was found (Table 4).

One of the issues commonly faced in clinical practice is the advanced age of the patient. While in the definition of MR PREDICTS no upper age limit was explicitly imposed, mean age was 65 ± 14 in the derivation cohort and 67 ± 12 in the validation cohort, i.e., noticeably lower than what is commonly encountered in daily clinical practice. In contrast, the ages of the populations employed in this paper were 72.3 ± 13.2 (derivation) and 71.1 ± 13.5 (validation). Moreover, with respect to MR PREDICTS we used a more comprehensive model in endovascular treated patients, to better define and capture the factors underlying the possible treatment benefit. For example, we included the clot burden score, which is considered an important factor able to influence reperfusion and clinical outcome. Conversely,

Table 5 Prediction chart for poor outcome and mortality (Tor Vergata Stroke Score)

Patient characteristics			Points
Age > 80 years			2
Pre stroke mRS[a] > 0			3
ASPECT[b] score ≤ 8			2
Poor collateral flow			3
NIHSS[c] at onset > 17			2
Clot Burden Score ≤ 5			3
Baseline glycaemia > 111 mg/dL			3
Score	Risk category	Poor outcome (%)	Mortality (%)
0–5	Low	30.2	7
6–11	Moderate	75.4	29.8
12–18	High	100	68.8

[a]Modified Rankin Scale

[b]Alberta Stroke Program Early CT Score

[c]National Institutes of Health Stroke Scale

MR PREDICTS includes the estimated time from onset to groin, which, however, is not commonly or easily available. Further, our score includes fewer variables (seven) with a good (and possibly better) prediction accuracy.

The identification of a cutoff value for pre stroke mRS (i.e. > 0) could represent a chance, compared to previous scales, to identify a subgroup of LVO stroke patients with poor response to MT. Our findings share some essential points with the MR PREDICTS study such as the weight of multimodal neuroimaging derived scores (i.e., collateral flow, site of occlusion), the idea of combining several variables to obtain a reliable prediction of outcome and the importance of individualizing treatment decision. Our work presents several limitations. First, the TVSS has been validated in a randomly selected cohort of patients derived from a single stroke center registry (albeit in a rigorous training-test split) and the performance of this score in additional, external populations should be assessed. Nevertheless, the single-center study design may have facilitated the standardization of our treatment algorithm. Second, the large time span over which data collection took place could have produced bias secondary to the introduction of new generation and more effective devices and to the increased skill of neurointerventionalists over the years. Two periods, before and after 2014, were compared and no differences were found in 3-month functional independence and successful reperfusion (Supplementary Table 1). Third, advanced neuroimaging variables are known to be better than clinical ones in the prediction of outcome [24]. However, while the analysis of a single variable has been deemed useful to understand the underlying mechanism of a pre-specified outcome, treatment benefit involves several factors simultaneously [25, 26]. Therefore, a multivariable model seems more suitable for personalization of treatment decision [25, 26]. Fourth, potential practical limitations may derive from time required to calculate the score. However (1) median door to CT time and stroke onset to groin puncture time from our "real world" data were 28 min (IQR 20–36) and

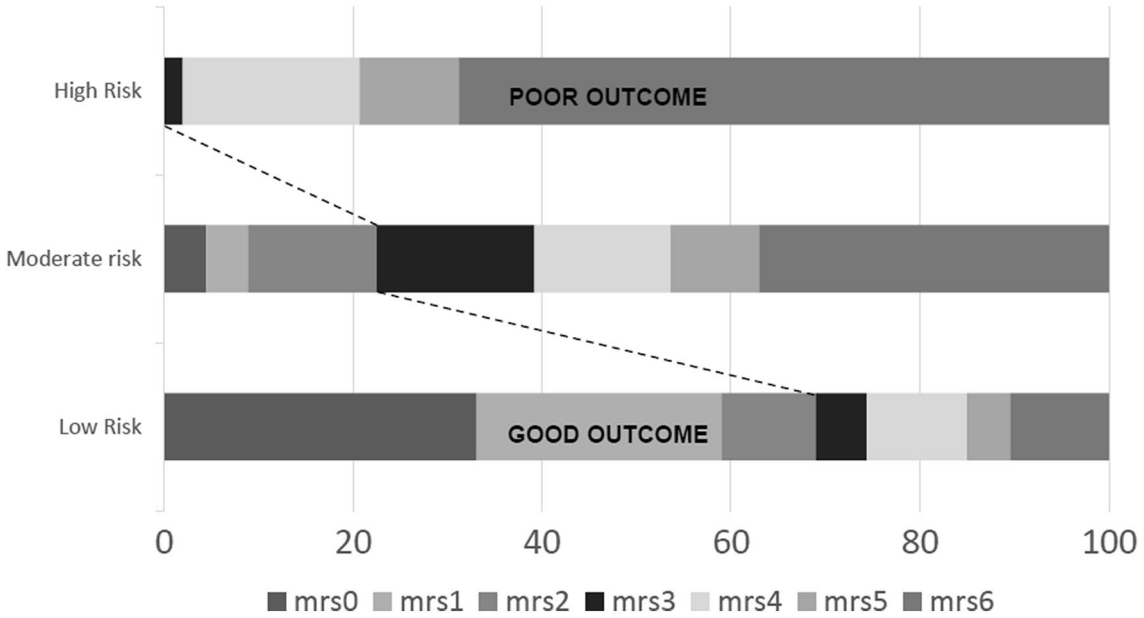

Fig. 2 Distribution of 3-month functional outcome in the three risk categories of the TVSS. Risk categories of the TVSS. Patients in the highest risk group have a predicted probability of poor outcome of 100%

220 min (IQR 175–267.5), respectively; (2) definite decision about treatment could be made only after acquisition of multimodal imaging, therefore about 40 min from admission to emergency department could be estimated to exhaustively calculate the score; (3) compared to our unselected cohort of patients, median door to CT time and stroke onset to groin puncture time in the MR CLEAN trial were longer [39 min (IQR 25–67) and 260 min (IQR 210–313), respectively] [1]. Given the potential widening of time-window based on multimodal neuroimaging, the above intervals could be reasonable, at least for difficult to diagnose and borderline cases. Further, one could hypothesize a future mentoring effect which could shorten time needed for score calculation. With its prognostic accuracy our seven-item score appears to be a reliable and promising tool for outcome prediction and accurate selection of candidates for endovascular stroke treatment but external validation is needed.

Acknowledgements This work was supported by the Italian Ministry of Health (RF-2013-02358679). We are grateful to Francesco Mori MD, Simone Napolitano, Domenico Samà MD, Barbara Rizzato MD, Vittoria Carla D'Agostino MD, Angela Giordano MD, Marta Panella MD for data collection.

Funding None in study design, collection, analysis and interpretation of data, writing and decision to submit the article for publication.

Compliance with ethical standards

Conflicts of interest None of the authors has conflict of interest to declare.

Ethical Standards The study was approved by Tor Vergata Hospital ethics committee.

Informed consent Informed consent was obtained from all patients or their relatives.

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