External Validation of the PREMISE Score in the Athens Stroke Registry

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Background: A simple score was proposed recently for Predicting Early Mortality from Ischemic Stroke (PREMISE) derived from the Austrian Stroke Unit Registry. This score could be useful in clinical practice and research. However, its generalizability is uncertain, as it was validated internally only. *Aims*: We aimed to validate the PREMISE score externally. *Methods*: The analysis was performed in the Athens Stroke Registry. The PREMISE score was calculated as described in the original publication. The outcome was death within 7 days after stroke. Logistic regression analysis was used to estimate the relative death risk in different strata of the PREMISE score using the lowest values of the score (ie, 0-4) as the reference category. We assessed the score's calibration by the Hosmer-Lemeshow goodness-of-fit test and its discriminatory power by calculating the area under the receiver operating characteristics curve (AUC). *Results*: In 2608 consecutive patients (median age 71 years, 38.8% women) with acute ischemic stroke treated in the stroke unit, mortality increased with increasing PREMISE score from .1% (95% confidence intervals [95% CI]: 0%-.2%) in patients with a score of 0-4 to 28.2% (95% CI: 14.1%-42.3%) in patients with a score of ≥10. The risk for death was more than 6 times higher in patients with a PREMISE score of ≥10 compared to patients with 0-4 points (odds ratio [OR]:6.21, 95% CI:4.13-8.29). The PREMISE score showed excellent calibration (Hosmer-Lemeshow χ^2: .01, *P*= .99) and good discriminatory power (AUC .873, 95% CI: .844-.901). *Conclusions*: The present study confirms the prognostic accuracy of the PREMISE score in an independent cohort of patients with acute ischemic stroke treated in the stroke unit.

Key Words: PREMISE score—ischemic stroke—death—mortality—stroke unit

Introduction

A simple score was proposed recently for Predicting Early Mortality from Ischemic Stroke (PREMISE) based on the Austrian Stroke Unit Registry. The PREMISE score was shown to provide a reliable estimate of early (within 7 days) mortality after acute ischemic stroke in patients treated in the stroke unit. It comprises of 6 readily assessed clinical features: age, preexisting disability, stroke severity, vascular diseases, posterior circulation stroke syndrome, and nonlacunar stroke mechanism. Patients with a high PREMISE score (ie, ≥10 points) had a high mortality risk of 35%, whereas patients with a low score (ie, 0-3 points) had <1% risk of early death. This score could be useful in the clinical setting as well as in research. However, its generalizability is uncertain, as it was validated only internally, but not externally.[1]

The aim of the present study was to validate the PREMISE score externally and assess its prognostic accuracy in an independent cohort of patients with acute ischemic stroke treated in the stroke unit.

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Methods

Data from this work not provided in this article will be shared after reasonable request of any other investigator for purposes of replicating procedures and results. The scientific use of the data was approved by the local ethics committees.

The analysis was performed in the Athens Stroke Registry, a prospective registry of consecutive patients with acute ischemic stroke admitted in the Stroke Unit of Alexandra Hospital (Athens, Greece) between 1992 and 2012. The design of the Athens Stroke Registry was described previously.[2]

Stroke severity was assessed with the National Institutes of Health Stroke Scale score (NIHSS) at admission.[3] The PREMISE score was calculated as described in the original publication.[1] Briefly, patients' scores were calculated based on their age (1 point if 60-69 years; 2 points if ≥70 years), preexisting disability (1 point if modified Rankin Scale score 1-5), stroke severity (2 points if NIHSS 5-11; 4 points if NIHSS 12-23; 5 points if NIHSS ≥ 24), vascular diseases (1 point for diabetes mellitus; 1 point for heart disease defined as coronary artery disease, heart failure, cardiomyopathy, or valve disease), clinical stroke syndrome (1 point for posterior circulation syndromes), and stroke mechanism (1 point for nonlacunar stroke). The outcome assessed was death within 7 days after acute ischemic stroke.

Statistical Analysis

Continuous covariates are summarized as median value and interquartile range (IQR). Associations are presented as odds ratios (OR) with their corresponding 95% confidence intervals (95% CI). Logistic regression analysis was performed to estimate the relative death risk in different strata of the PREMISE score using the group of patients with PREMISE score of 0-4 as the reference category. To validate the PREMISE score, we assessed 2 parameters: calibration (ie, the agreement between the actual and predicted rates of outcome) and discrimination (ie, the degree to which the score enables the discrimination between patients who had the outcome and those who did not). The former was assessed by the Hosmer-Lemeshow goodness-of-fit test for logistic regression. The latter was assessed by calculating the area under the receiver operating characteristics curve (AUC) and the 95% CI. The level of significance was set at 5%. Statistical analyses were performed with STATA version 11.1 (StataCorp, College Station, TX). All reported tests are 2-sided.

Results

The dataset comprised of 2608 patients with acute ischemic stroke who were hospitalized in the acute stroke unit of Alexandra Hospital, Athens, Greece between 1992 and 2012. The baseline characteristics of patients are summarized in Table 1. The median age was 71 years (IQR: 63-79 years) and 1012 patients (38.8%) were females, which is comparable to the derivation cohort as published by Gattringer et al (74 years and 47%, respectively).[1] Approximately 3.8% of patients were treated with intravenous thrombolysis, and no patient was treated with endovascular thrombectomy.

Mortality increased with increasing PREMISE score ranging from .1% (95% CI: 0%-.2%) in patients with a PREMISE score of 0-4 to 28.2% (95% CI: 14.1%-42.3%) in patients with a score of ≥10 (Fig 1). The risk for mortality was more than 6 times higher in patients with a PREMISE score of ≥10 compared to patients with 0-4 points (OR: 6.21, 95% CI: 4.13-8.29; Fig 2).

The PREMISE score showed excellent calibration (Hosmer-Lemeshow χ^2: .01, P = .99) and good discriminatory power (AUC .873, 95% CI: .844-.90, supplemental file).

Discussion

The present study confirms the prognostic accuracy of the PREMISE score to predict early death in an independent cohort of patients with acute ischemic stroke treated in the stroke unit: the score showed excellent calibration and good discriminatory power with an AUC of .873 (similar to the AUC of the original publication, ie, .879). We also confirmed the high mortality risk in patients with high PREMISE score (10% in patients with a score of ≥8, and 35% in patients with a score of ≥10) and the very low mortality risk in patients with low PREMISE score (.1% in patients with a score of 0-4). These data support its use in clinical practice and research, especially to identify patients with high probability of early death (eg, >10% probability in the 17% of patients of the overall cohort who had a score of ≥8). Potentially, it may be used to assist management decisions, for example, closer monitoring of the patients' vital signs and clinical status, or withdrawal from maximal therapy. In addition, it could be helpful for counselling patients and families.[1]

The strengths of this study are the large sample of consecutive patients and the use of 2 statistical methods (discrimination and calibration) to validate the prognostic accuracy of the score. On the contrary, the limitations of the study include the fact that the dataset was derived from a single center, which was located in Europe like the dataset that was used for the derivation of the score. Therefore, validation in non-European populations is needed. Also, we do not have available related data to explore the role of early "do-not-resuscitate" or other withdrawal-of-care orders on outcome, since there is always the risk of self-fulfilling prophecies. Moreover, the statistical power of our cohort to support a meaningful analysis of the score's performance in the subgroup of patients who were treated with intravenous thrombolysis or endovascular thrombectomy, as is the

Table 1. *Baseline characteristics of patients*

	Early death (within 7 days)		
	No n = 2,525	Yes n = 83	*P* Value
Age (y), mean (SD)	69.7 (12.1)	77.04 (9.14)	<.001
Sex (male), n (%)	1562 (61.86)	34 (40.96)	.0001
Hypertension, n (%)	1778 (70.42)	65 (78.31)	.12
Diabetes mellitus, n (%)	684 (27.09)	27 (32.53)	.273
Current smoking, n (%)	818 (32.40)	14 (16.87)	.0028
Dyslipidemia, n (%)	936 (37.07)	21 (25.30)	.029
Peripheral arterial disease, n (%)	110 (4.36)	2 (2.41)	.389
Atrial fibrillation, n (%)	845 (33.47)	51 (61.45)	<.001
Coronary artery disease, n (%)	653 (25.86)	25 (30.12)	.384
TOAST, n (%)			<.001
Lacunar	620 (24.55)	1 (1.20)	
Large vessels	482 (19.1)	6 (7.23)	
Cardioembolic	886 (35.1)	52 (62.65)	
Cryptogenic	470 (18.6	24 (28.92)	
Other	67 (2.65)	–	
Clinical syndrome, n (%)			<.001
LACS	604 (23.92)	1 (1.20)	
TACS	696 (27.56)	67 (80.7)	
PACS	690 (27.33)	4 (4.82)	
POCS	167 (6.61)	11 (13.25)	
Other	368 (14.57)	–	<.001
NIHSS, median (IQR)	5 (12)	24 (5)	<.001
Intravenous thrombolysis, n(%)	98 (3.88)	1 (1.20)	.209
MRS>0, n (%)	198 (7.84)	13 (15.66)	.01

Abbreviations: LACS, lacunar stroke syndrome; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PACS, partial anterior circulation stroke syndrome; POCS, posterior circulation stroke syndrome; TACS, total anterior circulation stroke syndrome.

P values are derived from independent samples Student's test or Mann-Whitney test for continuous variables and chi-squared test for nominal variables.

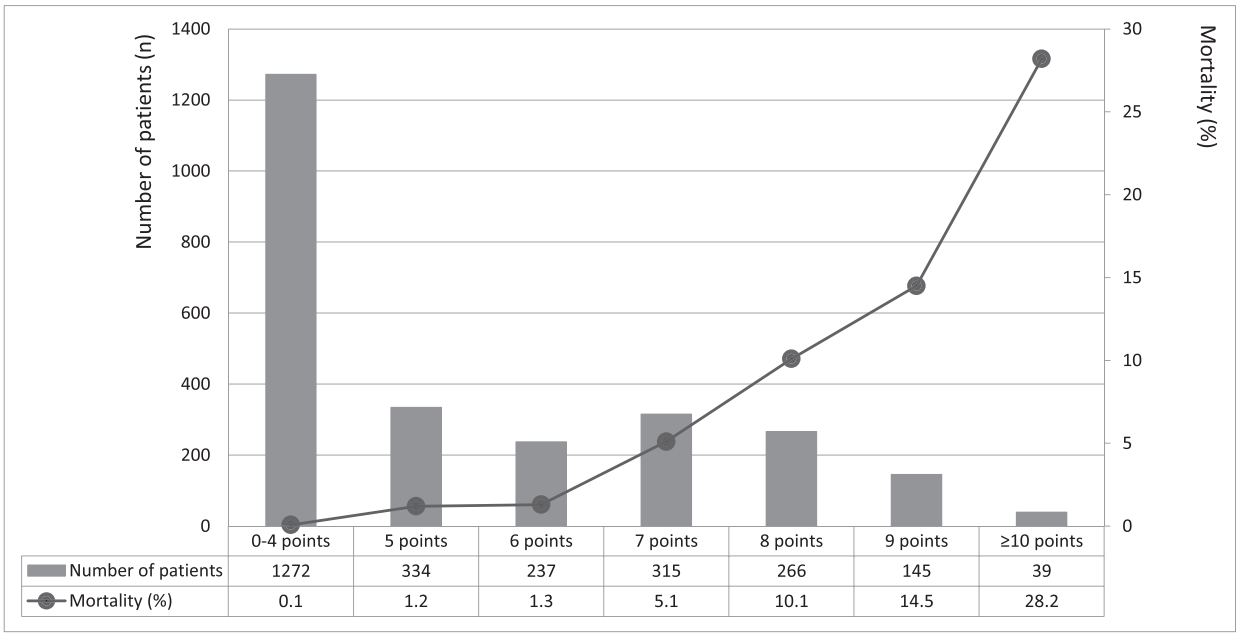

Figure 1. *Frequency distribution and death rates in the Athens Stroke Registry according to the PREMISE score.*

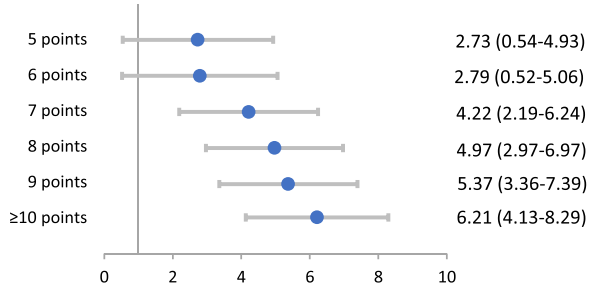

Figure 2. *Adjusted ORs and 95% CIs of the association between the PREMISE score and death within 7 days after acute ischemic stroke in the Athens Stroke Registry. Comparisons are made to patients with a score of 0-4.*

case with other scores[4,5]; given that these treatment modalities modify outcome, it may be possible that the performance is lower in these subgroups compared to the unselected population. In addition, further research is warranted to investigate whether this score makes a more accurate prediction of early mortality compared to the judgment of stroke physicians, as was assessed for other prognostic scores.[6,7] Moreover, it would be interesting to assess in future studies whether the addition of imaging parameters would increase the prognostic performance of the score. Similar attempts in the case of other prognostic scores were not successful.[8,9]

In conclusion, given the good prognostic accuracy assessed in both the derivation and the external validation cohorts, the PREMISE score may be used for the prediction of early death in patients with acute ischemic stroke treated in the stroke unit.

Author Contribution

George Ntaios: study concept, study design, statistical analysis and interpretation, preparation of manuscript, study supervision.

Georgios Georgiopoulos: statistical analysis and interpretation, critical revision of the manuscript.

Eleni Koroboki: data acquisition, critical revision of the manuscript.

Konstantinos Vemmos: data acquisition, critical revision of manuscript.

Disclosures

None related.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.04.023.

References

1. Appleton JP, Woodhouse LJ, Bereczki D, et al. Effect of glyceryl trinitrate on hemodynamics in acute stroke. Stroke 2019. STROKEAHA118023190.
2. Vemmos KN, Takis CE, Georgilis K, et al. The Athens stroke registry: results of a five-year hospital-based study. Cerebrovasc Dis 2000;10:133-141.
3. Brott T, Adams Jr HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-870.
4. Ntaios G, Papavasileiou V, Michel P, et al. Predicting functional outcome and symptomatic intracranial hemorrhage in patients with acute ischemic stroke: a glimpse into the crystal ball? Stroke 2015;46:899-908.
5. Vanacker P, Heldner MR, Seiffge D, et al. Astral-r score predicts non-recanalisation after intravenous thrombolysis in acute ischaemic stroke. Thromb Haemost 2015;113:1121-1126.
6. Ntaios G, Gioulekas F, Papavasileiou V, et al. Astral, dragon and sedan scores predict stroke outcome more accurately than physicians. Eur J Neurol 2016;23:1651-1657.
7. Saposnik G, Cote R, Mamdani M, et al. Jurassic: accuracy of clinician vs risk score prediction of ischemic stroke outcomes. Neurology 2013;81:448-455.
8. Ntaios G, Papavasileiou V, Faouzi M, et al. Acute imaging does not improve astral score's accuracy despite having a prognostic value. Int J Stroke 2014;9:926-931.
9. Ntaios G, Faouzi M, Ferrari J, et al. An integer-based score to predict functional outcome in acute ischemic stroke: the Astral score. Neurology 2012;78:1916-1922.