Predicting Early Mortality of Acute Ischemic Stroke
Score-Based Approach

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Background and Purpose—Several risk factors are known to increase mid- and long-term mortality of ischemic stroke patients. Information on predictors of early stroke mortality is scarce but often requested in clinical practice. We therefore aimed to develop a rapidly applicable tool for predicting early mortality at the stroke unit.

Methods—We used data from the nationwide Austrian Stroke Unit Registry and multivariate regularized logistic regression analysis to identify demographic and clinical variables associated with early (≤7 days poststroke) mortality of patients admitted with ischemic stroke. These variables were then used to develop the Predicting Early Mortality of Ischemic Stroke score that was validated both by bootstrapping and temporal validation.

Results—In total, 77 653 ischemic stroke patients were included in the analysis (median age: 74 years, 47% women). The mortality rate at the stroke unit was 2% and median stay of deceased patients was 3 days. Age, stroke severity measured by the National Institutes of Health Stroke Scale, prestroke functional disability (modified Rankin Scale >0), preexisting heart disease, diabetes mellitus, posterior circulation stroke syndrome, and nonlacunar stroke cause were associated with mortality and served to build the Predicting Early Mortality of Ischemic Stroke score ranging from 0 to 12 points. The area under the curve of the score was 0.879 (95% CI, 0.871–0.886) in the derivation cohort and 0.884 (95% CI, 0.863–0.905) in the validation sample. Patients with a score ≥10 had a 35% (95% CI, 28%–43%) risk to die within the first days at the stroke unit.

Conclusions—We developed a simple score to estimate early mortality of ischemic stroke patients treated at a stroke unit. This score could help clinicians in short-term prognostication for management decisions and counseling. **(*Stroke*. 2019;50:349-356. DOI: 10.1161/STROKEAHA.118.022863.)**

Key Words: brain ischemia ■ heart diseases ■ mortality ■ risk factors ■ stroke

Stroke is the major cause of long-term disability in adults, and the second leading cause of death worldwide.[1] Thirty-day mortality rate of ischemic stroke has been estimated at around 15% in high-income countries[2–4] and several factors are known to increase stroke mortality.[3,5–11] Predictors of early mortality, however, have been less intensively addressed thus far. This is unfortunate, as more refined prognostication of poor outcome including death is especially needed in the first days after the acute event. Such knowledge would impact on management decisions, which can range from recognizing the need for intensified monitoring to withdrawal from maximal therapy. It would be also most helpful in the communication with partners and family members about the possible fate of the stroke victim.

To provide such insights and a clinically useful tool we set out to develop a simple scoring instrument for Predicting Early Mortality of Ischemic Stroke (PREMISE) based on data of the nationwide Austrian stroke unit network.

Methods

Data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Setting and Patients

Starting in 2003, a growing network of currently 38 stroke units prospectively collects a comprehensive set of data on demographic and clinical characteristics of adult stroke patients across Austria. The tight network of stroke units in Austria allows to care for about two-thirds of all acute strokes admitted to a hospital with their data

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Table 1. Demographic and Clinical Characteristics of Deceased Versus Nondeceased Ischemic Stroke Patients

Variables	Stroke Unit Mortality n=1 567	Stroke Unit Survival n=76 086	*P* Value
Age, y, median (Q1, Q3)	81.9 (74.9, 87.3)	73.8 (63.7, 82)	<0.001
18–59, n (%)	65 (4.1)	14 483 (19)	
60–69, n (%)	147 (9.4)	15 349 (20.2)	
70–79, n (%)	456 (29.1)	22 726 (29.9)	
80–89, n (%)	675 (43.1)	19 992 (26.3)	
≥90, n (%)	224 (14.3)	3536 (4.6)	
Female sex, n (%)	936 (59.7)	35 640 (46.8)	<0.001
Prestroke functional status, n (%)			<0.001
mRS score 0	678 (43.3)	52 613 (69.1)	
mRS score 1	227 (14.5)	8656 (11.4)	
mRS score 2	181 (11.6)	5104 (6.7)	
mRS score 3	253 (16.1)	5566 (7.3)	
mRS score 4	182 (11.6)	3645 (4.8)	
mRS score 5	46 (2.9)	502 (0.7)	
Admission NIHSS, median (Q1, Q3)	19 (13, 24)	3 (1, 7)	<0.001
0–4, n (%)	101 (6.4)	46 447 (61)	
5–11, n (%)	230 (14.7)	18 339 (24.1)	
12–23, n (%)	807 (51.5)	9933 (13.1)	
≥24, n (%)	429 (27.4)	1367 (1.8)	
Stroke onset-door time, min, median (Q1, Q3)	79 (53, 141)	118 (60, 265)	<0.001
Clinical stroke syndrome at admission, n (%)			<0.001
POCS	211 (13.5)	11 948 (15.7)	
TACS	825 (52.6)	8134 (10.7)	
PACS	390 (24.9)	29 105 (38.3)	
LACS	105 (6.7)	23 901 (31.4)	
Other	36 (2.3)	2998 (3.9)	
IV thrombolysis, n (%)	448 (28.6)	12 374 (16.3)	<0.001
Onset-thrombolysis time, min, median (Q1, Q3)	120 (94, 165)	125 (94, 170)	0.407
Endovascular therapy, n (%)	79 (5)	705 (0.9)	<0.001
Onset-angiography time (min.), median (Q1, Q3)	193 (147, 255)	185 (140, 249.8)	0.518
Vascular risk factors and diseases, n (%)			
Hypertension	1311 (83.7)	60 774 (79.9)	<0.001
Diabetes mellitus	438 (28)	18 639 (24.5)	0.002
Hyperlipidemia	619 (39.5)	42 378 (55.7)	<0.001
Smoking	140 (8.9)	13 583 (17.9)	<0.001
Atrial fibrillation	781 (49.8)	19 318 (25.4)	<0.001
Previous stroke	408 (26)	17 444 (22.9)	<0.001
Heart disease	637 (40.7)	19 437 (25.5)	<0.001
Coronary artery disease	248 (15.8)	6808 (8.9)	<0.001
Other cardiac diseases*	520 (33.2)	16 060 (21.1)	<0.001
Peripheral artery disease	160 (10.2)	5056 (6.6)	<0.001
Stroke cause, n (%)			<0.001
Cardiogenic-embolism	768 (49)	19 422 (25.5)	
Macroangiopathy	208 (13.3)	9366 (12.3)	
Microangiopathy (lacunar stroke)	154 (9.8)	20 443 (26.9)	
Unknown	418 (26.7)	25 270 (33.2)	
Other	19 (1.2)	1585 (2.1)	
Stroke unit stay, d, median (Q1, Q3)	3 (1, 4)	2 (1, 4)	0.07

All these explanatory variables were included in the multivariate model for the target variable early stroke unit mortality. For the model following variables were grouped together: (1) mRS categories 1–5 (= preexisting functional impairment), (2) TACS, PACS, and LACS (= nonposterior circulation stroke syndromes), (3) cardiogenic-embolism, macroangiopathy, unknown and other stroke causes (= nonlacunar stroke causes). IV indicates intavenous; 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; and TACS, total anterior circulation stroke syndrome.

*Heart failure, cardiomyopathy, or valve disease.

therefore entered into the present registry.[12] There is no formal triage and it is recommended by the Austrian health authorities that all patients with a suspected acute stroke should be admitted to a stroke unit. However, because of limited resources, that is, stroke unit beds, patients with more subacute strokes, milder symptoms, lower risk situations, a prevailing cardiac or general medical disorder or old/multimorbid patients are also admitted to general neurological wards or internal medicine and the data of those patients are therefore not captured in the Austrian Stroke Unit Registry.

Data collection and clinical ratings are performed by experienced stroke neurologists using standardized definitions of variables and scores. To ensure high data quality, immediate electronic data entry is obligatory. The web-based database includes online plausibility checks and help. Biannual educational meetings serve to guarantee uniform data documentation and discuss and develop clinical guidelines and standard operating procedures, which are published in the official journal of the Austrian Neurological Society and freely available on the webpage of the Austrian Stroke Society (www.ögsf.at). Clinical stroke syndrome is classified according to the Oxfordshire Stroke Classification Project Criteria,[13] and cause is determined according to the Trial of ORG 10172 in Acute Stroke Treatment criteria.[14]

More details on the Austrian stroke unit registry and the definition of variables and ratings have been described previously.[15]

The Austrian stroke unit registry is part of a governmental quality assessment program for nationwide stroke care and is financed by the Federal Ministry of Health. All data are anonymized and centrally administered by the Gesundheit Österreich GmbH—the national research and planning institute for health care, a competence and funding center of health promotion. All scientific analyses included in this

study were approved and supervised by a national academic review board.[16] No informed consent was obtained.

For this study, we used data of all patients aged ≥18 years who were registered with the final diagnosis of acute ischemic stroke (excluding patients with a transient ischemic attack) between January 1, 2006, and December 31, 2017, and had a complete data set.

As we specifically aimed to address early stroke unit mortality within the first week, we primarily excluded patients who stayed longer than 7 days at the stroke unit. In secondary sensitivity analysis, we also considered the total cohort of ischemic stroke patients without a restriction of stroke unit stay (see the online-only Data Supplement).

Statistical Analysis and Score Development

All data were processed using the statistical environment R (version 3.3.2) by an experienced statistician (Dr Posekany). The χ^2 test was used for univariate comparisons between categorical variables. Group comparisons of quantitative or ordinal variables were performed using the Wilcoxon rank sum or Kruskal-Wallis tests as appropriate. Regression coefficients were tested using a *t* test. To account for multiple testing, the significance level was set at $P<0.001$, which corresponds to the Bonferroni correction with correction factor of 50.

Multivariate analysis was used to determine independent predictors for early stroke mortality. Candidate explanatory variables were identified as follows: variables (1) with a clinically plausible link to ischemic stroke mortality based on literature review, (2) available in the Austrian stroke unit registry, and (3) assessed within the first day of stroke, serving our aim to develop an early mortality risk score applicable almost immediately after stroke onset. For this reason, we also did not consider stroke-related complications as they occur at variable and often later time points. All variables that were included in the multivariate model are listed in Table 1.

For multivariate analysis, a regularized logistic regression model with the Least Absolute Shrinkage and Selection Operator method was fitted by using the R package glmnet.[17] In brief, regularized regression penalizes coefficients close to 0 leading to shrinking the coefficients toward 0, that is, coefficients are smaller and will not be different from 0 unless the variable is actually relevant. Thus, Least Absolute Shrinkage and Selection Operator regression allows for a selection of relevant influential variables in an alternative way to model selection via Akaike or Bayesian information criterions. To determine the relevance of explanatory variables for a score, this approach for model selection has advantages over alternative methods.[18] The relevant variables for our model were determined by an intermediate model where shrinkage still takes place, whereas the full model gives the best summand to use in the mortality score.

The PREMISE score was developed based on variables that were independently associated with stroke unit mortality in multivariate analysis. Score points were defined heuristically according to the effect size of the β -coefficients by rounding to the next positive integer value and it was intended that the overall risk score could be calculated by summing up all components of the score. The area under the receiver-operating characteristics curve (area under the curve [AUC], also known as C statistics) and respective 95% CIs were calculated to measure the discrimination of the score about early ischemic stroke mortality. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Table 2. Multivariate Logistic Regression Model Including Variables Associated With Early Ischemic Stroke Mortality

Variable	β Coefficient	SE	Z Value	OR	95% CI
(Intercept)	–7.38	0.18	–41.54	0	0
Age 60–69	0.61	0.16	3.95	1.85	1.36–2.50
Age 70–79	1.07	0.14	7.69	2.93	2.23–3.85
Age 80–89	1.11	0.14	7.91	3.04	2.31–4.0
Age ≥90	1.35	0.16	8.69	3.86	2.85–5.23
NIHSS 5–11	1.60	0.12	13.13	4.97	3.91–6.32
NIHSS 12–23	3.33	0.11	29.96	27.92	22.45–34.71
NIHSS ≥24	4.53	0.12	37.76	92.33	73.0–116.77
Prestroke functional disability, mRS score >0	0.11	0.06	1.77	1.11	1.0–1.25
Heart disease*	0.34	0.06	5.86	1.40	1.25–1.56
Diabetes mellitus	0.20	0.06	3.17	1.22	1.08–1.38
Posterior circulation stroke syndrome	0.42	0.08	5.12	1.52	1.30–1.79
Nonlacunar stroke cause	0.51	0.09	5.48	1.66	1.38–1.99
Hyperlipidemia	–0.41	0.06	–7.11	0.67	0.60–0.75

mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

*Defined as cardiomyopathy, heart insufficiency, valve disease, coronary heart disease (excluding atrial fibrillation).

Score Validation

The PREMISE score was developed by using the data of patients with acute ischemic stroke who had been registered between January 1, 2006, and December 31, 2016. Validation was attempted in 2 directions. First and as previously recommended,[19] we used bootstrapping (random sampling with replacement) for internal score validation. Hereby, the AUC was calculated based on bootstrapping 2000× from the original data. In the bootstrapping process, data samples of the same size as the original data were drawn randomly from the original data set resulting in 2000 artificial new data sets for which the score was tested again about its predictive quality. Based on these 2000 results, the AUC and its 95% confidence region were estimated. Second, we also looked for temporal validation[19] by applying the PREMISE score to data from ischemic stroke patients recorded in the Austrian stroke unit registry from January 1 to December 31, 2017.

Results

From January 1, 2006, to December 31, 2017, 87 673 ischemic stroke patients with a stay of ≤7 days were registered at an Austrian stroke unit. Complete data were available in 86 794 individuals (99%), of whom 77 653 were treated between 2006 and 2016 and served as the score development cohort (Figure I in the online-only Data Supplement). The median age of these patients was 74 years and 47% were women. All patients underwent acute brain imaging (computed tomography or magnetic resonance imaging) and ECG. Examination of brain-supplying vessels (either sonography, computed tomography, or magnetic resonance angiography) was performed in 87% of patients. Seventeen percent of patients received intravenous thrombolysis. Mortality rate within the first week after admission to the stroke unit was 2% (n=1567). There were no significant mortality time trends across the study period (years 2006–2017; $P=0.17$).

Univariate Analysis

Deceased patients were ≈8 years older, more often women, had more preexisting functional disability (according to the modified Rankin Scale [mRS]) and more severe strokes as reflected by the National Institutes of Health Stroke Scale (NIHSS; Table 1). In general, vascular risk factors and cardiovascular

diseases were more frequently observed in patients with early death. Stroke unit mortality was also remarkably higher in patients who had a cardioembolic stroke cause (49% in deceased versus 25.5% in patients who survived, $P<0.001$). Inversely, rates of hyperlipidemia and smoking were lower in deceased patients (Table 1).

Multivariate Analysis

In a multivariate logistic regression analysis (Table 2), higher age, higher admission NIHSS, prestroke mRS score >0, heart disease (defined as coronary artery disease, heart failure, cardiomyopathy, or valve disease), diabetes mellitus, posterior circulation stroke syndrome (compared with anterior circulation stroke syndromes), and nonlacunar stroke cause remained independently associated with a higher risk of early stroke unit mortality. The rate of hyperlipidemia remained lower in deceased patients.

Mortality Risk Score

All variables positively associated with early stroke mortality in the multivariate model were subsequently used to develop the PREMISE score, which is shown in Table 3.

The AUC of the PREMISE score was 0.879 (95% CI, 0.871–0.886) as displayed in Figure 1, and did not change after bootstrapping. There was also no evidence for poor calibration (Hosmer-Lemeshow X^2 test p=0.2).

Figure 2 indicates the probability of stroke unit mortality according to points on the risk score. Because of limited observations, score points 10, 11, and 12 were grouped together and formed the highest score category of ≥10. Patients with maximal score points had a risk of 35% (95% CI, 28%–43%) to die within the first 7 days at the stroke unit.

Additionally, we also performed temporal validation by testing the score in the population of ischemic stroke patients that were admitted to Austrian stroke units in the year 2017 (n=9141). Score discrimination for this sample was comparable with an AUC of 0.884 (95% CI, 0.863–0.905; Figure 3). Again, bootstrapping did not identify differences in score discrimination.

Table 3. Predicting Early Mortality of Ischemic Stroke (PREMISE) Score

Risk Factors for Stroke Unit Mortality	Points
Age	
60–69, y	+1
≥70, y	+2
Preexisting disability	
Modified Rankin Scale scores 1–5	+1
Stroke severity	
NIHSS 5–11	+2
NIHSS 12–23	+4
NIHSS ≥24	+5
Vascular diseases	
Diabetes mellitus	+1
Heart disease*	+1
Clinical stroke syndrome	
Posterior circulation stroke syndrome	+1
Stroke cause	
Nonlacunar	+1
Maximal score points	=12

NIHSS indicates National Institutes of Health Stroke Scale.

*Defined as coronary artery disease, heart failure, cardiomyopathy, or valve disease.

Secondary Analysis

For sensitivity analysis, we also tested the PREMISE score in the total cohort of ischemic stroke patients without restricting their stay at the stroke unit (n=85 331, of which 1 846 had died). Baseline characteristics of these patients and results from multivariate regression analysis are provided in the online-only Data Supplement. In this cohort, the PREMISE score showed a comparable high discrimination capacity with an AUC of 0.867 (95% CI, 0.860–0.874) in the derivation and 0.873 (95% CI, 0.850–0.895) in the validation cohort (see the online-only Data Supplement).

Discussion

In the present study, we used data from the nationwide Austrian stroke unit registry to identify risk factors for early stroke unit mortality after acute ischemic stroke. The proposed PREMISE risk model is a simple, quickly computable score explaining >85% of early stroke deaths, using only variables that are readily available shortly after the onset of ischemic stroke when admitted to the stroke unit. With its excellent diagnostic accuracy and practicability, this score may help stroke physicians to perform early bedside estimation of mortality risk in ischemic stroke patients. While early death was highly unlikely with score points 0 to 3 (<1%) it increased to 35% in the highest score category of ≥10 points.

Although a considerable number of studies on predictors of stroke mortality have already been published, they were conducted at a time when dedicated stroke unit management and specific stroke treatments were not yet widely available, have investigated heterogeneous stroke cohorts (ischemic and hemorrhagic strokes), treated in different systems of care (general ward versus stroke unit), and considered different time points of case fatality (inhospital to 1-year mortality). The vast majority of these studies focused on mid- and long-term mortality.[3,5–11,20,21] In contrast, information about the frequency and risk factors for early mortality in the first week is scarce, and only few studies have focused on inhospital mortality rates referring to a median hospital stay of 1 to 2 weeks. Depending on analyzed stroke subtypes (incorporation of intracerebral hemorrhage or not) or the system of care (stroke unit versus medical ward) inhospital case fatality rate was 5% to 15% with a rate of around 5% in patients that were initially treated at a stroke unit.[6,8,9,11,22]

Three dedicated risk scores on short- and mid-term ischemic stroke mortality have already been proposed.[3,5,6] Two of them were developed using data from the same Registry of the Canadian Stroke Network based on 11 regional stroke centers in Ontario and provided risk prediction on 30-day

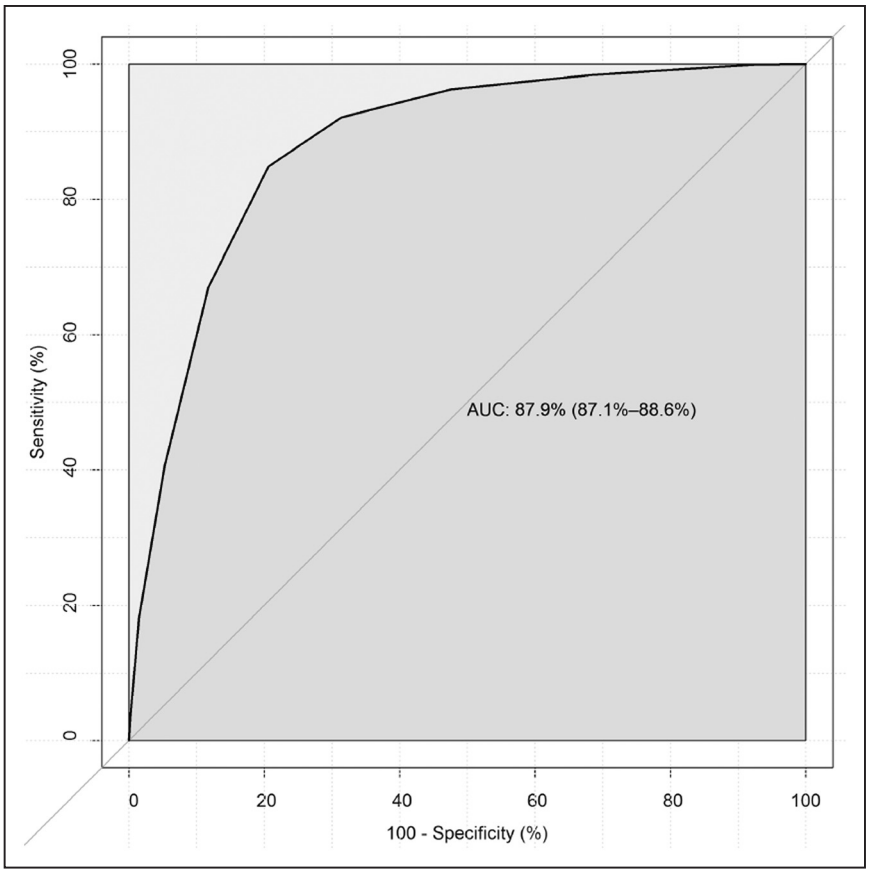


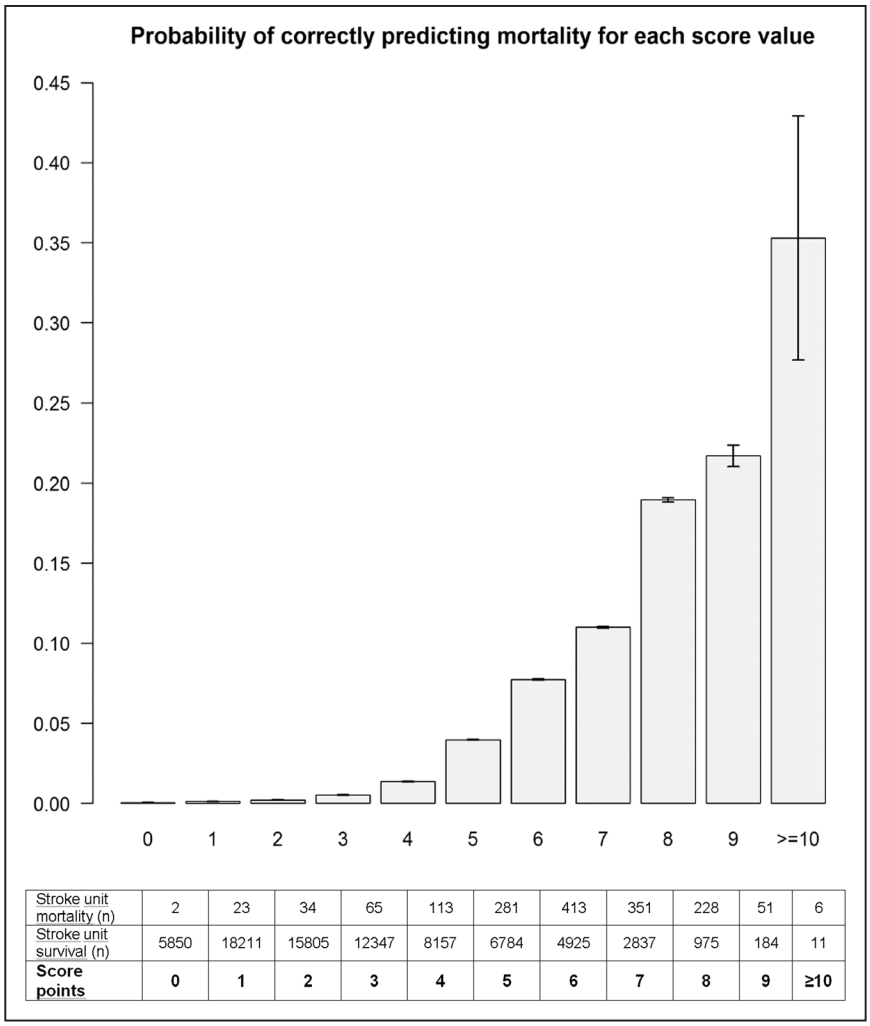
Figure 1. Area under the curve (AUC) of the Predicting Early Mortality of Ischemic Stroke (PREMISE) score in the derivation cohort.

mortality.[3,5] Only one score considered inhospital stroke mortality but no information on the duration of hospital stay was provided. For their study, Smith et al[6] used data from 274 988 stroke patients treated in 1 036 different volunteering hospitals within the American Get With The Guidelines Stroke Program (GWTG). The GWTG mortality score comprised the variables age, mode of hospital arrival as well as vascular risk factors and diseases. Discrimination of the model was fair with C statistics of 0.72, and patients with highest scores had a probability of death of around 25%. However, clinical practicability of this instrument might be limited because the score is difficult to calculate with points ranging from 0 to 204. In a second step, the authors also included the NIHSS into their risk model, which led to an improved C statistics of 0.85. However, the NIHSS was unfortunately only recorded in 40% of the GWTG cohort.[6]

Our study differs from this investigation in several ways. We used nationwide data from consecutive patients who were admitted to a stroke unit in Austria. Besides the comprehensive availability of stroke characteristics such as severity, syndrome, and cause, we were also able to control for prestroke functional disability. In prior studies, these important variables could often not be considered, as they were not available or incompletely documented.[5,6] Moreover, we aimed to develop a simple scoring tool, which can be calculated by the clinician at bedside. We specifically focused on acute mortality of ischemic stroke patients and consequently limited our analysis to a 7-day length of stay at the stroke unit. It is interesting that even within this short time period (deceased patients had a median stroke unit survival of 3 days), our score was able to achieve excellent diagnostic discrimination (with no evidence for poor calibration).

In the present study, following independent predictors for stroke unit mortality were identified: age, prestroke functional status (mRS score >0), stroke severity (NIHSS), diabetes mellitus, prior heart disease, posterior circulation stroke syndrome (compared with anterior circulation stroke syndromes), and nonlacunar stroke cause. In line with previous studies,[23] hyperlipidemia was associated with a lower risk of poststroke mortality (lipid paradox). However, we decided not to incorporate this variable in the proposed risk score as the definition of hyperlipidemia varies substantially in clinical practice and we had no information on prestroke statin use in our registry.

Not surprisingly,[24] initial stroke severity followed by age had the highest impact on early stroke mortality. To a lower extent, prestroke functional disability was also associated with early death. Interestingly, we did not observe much difference across prestroke mRS scores of 1 to 5 (compared with mRS score 0) and therefore combined these categories in the final risk model. We confirmed diabetes mellitus as an independent risk factor for early stroke mortality, which was also incorporated in the previously discussed GWTG inhospital mortality risk score.[6] Moreover, we identified preexisting heart disease (defined as coronary heart disease, heart failure, cardiomyopathy, or valve disease) as an important predictor for early mortality. Comparable to the GWTG score study,[6] we also found a single independent effect of coronary artery disease on mortality. An ischemic stroke usually leads to acute



Stroke unit mortality (n)	2	23	34	65	113	281	413	351	228	51	6
Stroke unit survival (n)	5850	18211	15805	12347	8157	6784	4925	2837	975	184	11
Score points	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**≥10**

Figure 2. Stroke unit mortality risk according to points on the Predicting Early Mortality of Ischemic Stroke (PREMISE) score.

stress response, catecholamine rush, vegetative disturbances including blood pressure elevation and thus could induce left ventricular decompensation or cardiac arrhythmias, which all together pose a serious, potentially fatal problem particularly in patients with structural cardiac disease and especially chronic heart failure.

Of note, atrial fibrillation—while clearly associated with mortality in univariate analysis—did not remain an independent predictor of stroke death after multivariate analysis. This could most likely be explained by a mediating effect of atrial fibrillation on stroke severity as it has been shown that atrial fibrillation causes the most severe strokes.[25]

Short-term mortality of patients with a posterior circulation stroke syndrome was also increased compared with anterior circulation stroke syndromes, which is most likely a consequence of brain stem damage or infratentorial mass effect usually leading to early and severe potentially lethal complications. It is known that the NIHSS does not adequately capture the spectrum of posterior circulation-related neurological deficits,[26] which could potentially also contribute to an independent effect of posterior circulation stroke syndrome on mortality.

Besides premorbid conditions, stroke-related complications are responsible for a substantial number of inhospital stroke deaths. We predefined not to include complications in our model as they occur at variable and mostly later time points in the course of stroke. This is consistent with an analysis from the Berlin stroke registry[8] comprising ischemic and hemorrhagic stroke patients. While the majority of early deaths in patients with a hospital stay of <7 days was attributable to nonmodifiable predictors with initial stroke severity, age, and prestroke disability having the largest impact, typical stroke-related complications played a bigger role in patients with a longer hospital stay. This fact also justifies not to aim at a complication-based model for predicting the risk of early mortality but to use only variables that are rapidly available soon after stroke onset and when the first prediction of the fate of the stroke patient is often requested. Along these lines, the PREMISE score could help in the identification of patients who need special clinical attention including adequate monitoring of vital functions during the acute phase of ischemic stroke. It could also assist in the decision process of stroke unit triage and inform counseling of patients and their relatives about the risk of early mortality.

A main strength of our study comes from the fact that it uses large prospectively collected multicenter data from consecutively admitted ischemic stroke patients mirroring real-world clinical practice of a tight nationwide stroke unit system. All Austrian stroke units are led by experienced

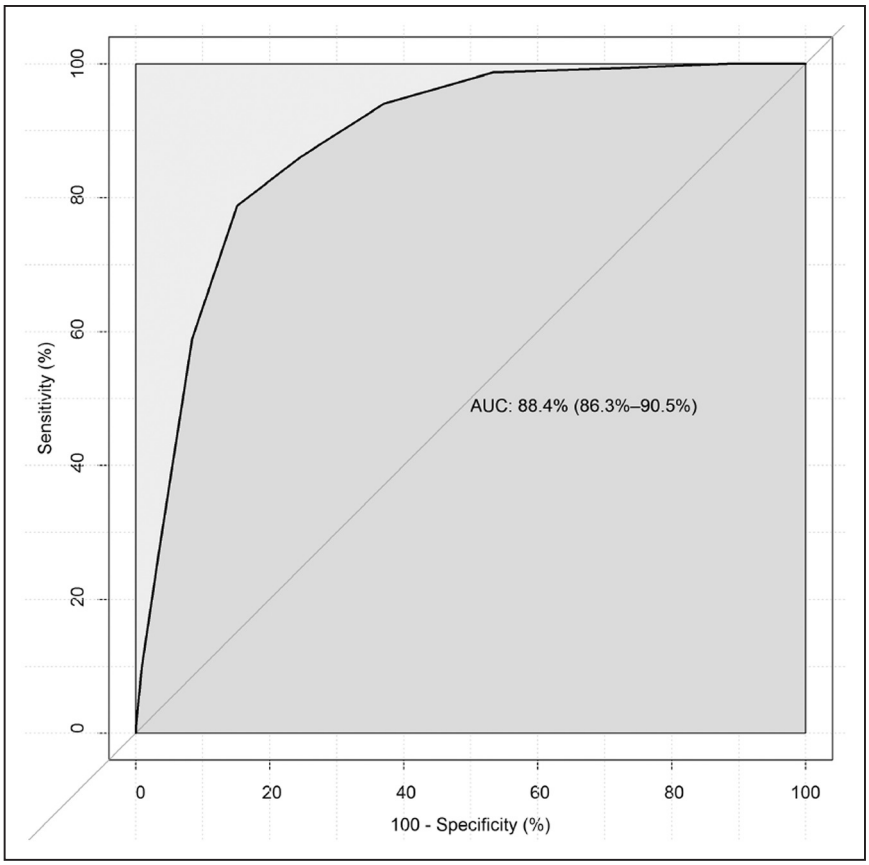


Figure 3. Discrimination of the Predicting Early Mortality of Ischemic Stroke (PREMISE) score in the temporal validation sample. AUC indicates area under the curve.

stroke neurologists, which improves reliability of clinical ratings and fosters sample homogeneity among acute ischemic stroke patients. However, the results of our study are potentially not transferable to the general population of ischemic stroke patients as we included only patients who were admitted to a dedicated acute stroke unit and patients with a very poor clinical baseline status or multimorbidity might have been admitted to a general or palliative care ward. The stroke unit setting allows a rapid and comprehensive stroke work-up and makes the variables used in the PREMISE score easily available, which may not be the case in other settings. On the other hand, stroke unit treatment is regarded as the gold standard of acute stroke care and has been consistently associated with lower mortality rates, irrespective of patient's age or clinical characteristics.[4,22,27–29] In this context, our score has additional value given that access to organized stroke unit care will hopefully become more widely available in the near future (as this is one specific priority aim of international stroke societies and healthcare organizations).[30] Likewise analyzed patients cannot be considered as fully representative of stroke patients overall but constitute those patients that were felt to still benefit from stroke unit treatment. This also explains the altogether low 7-day mortality rate of only 2% of our stroke unit cohort.

Another strength of our study is the application of 2 different score validations methods. After bootstrapping, which is one preferred internal validation method, the discrimination of the PREMISE score could also be confirmed by temporal validation. Nevertheless, generalizability of our score has to be tested in external cohorts.

Importantly (and similar to other published stroke risk scores), our cross-sectional study design did not allow accounting for dynamic and rapid changes of the admission stroke severity, which is especially relevant for patients who have received acute recanalization therapy. However, we did not observe an effect of intravenous thrombolysis and mechanical thrombectomy in our multivariate analysis. This seems surprising at first. However, patients amenable to recanalization therapy—particularly thrombectomy—are only a relatively small subgroup in our cohort. Furthermore, given the universally recommended use of these interventions, that is, without having a group from which these interventions were purposefully withheld, it is less surprising that we could not substantiate their impact on mortality. For the same reasons we decided not to incorporate other medical interventions (such as hemicraniectomy, use of antiplatelets or aggressive glucose lowering, etc) into our analysis. In addition, these interventions are initiated at variable time points that are not exactly captured in our registry.

The lack of information on clinical variables such as admission glucose or blood pressure levels, or other comorbidities that potentially increase the risk of early stroke death such as preexisting systemic diseases is another important limitation of our work. Since some variables of our risk score are known determinants of poor stroke outcome and thus might have favored treatment attitudes toward end of life care, we also have to acknowledge the potential of reverse causality. The specific cause of death would also have been of great interest but was not available in our and previously reported registry-based study settings. Finally, data were missing in a

few patients, which were primarily excluded from the analysis. While we cannot exclude that particularly patients with a poor a-priori prognosis might have been captured less stringently in our registry, the minor percentage of incomplete data should not have caused a major risk of bias.

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Disclosures

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