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Validation of the Premise Score after Addition of Recurrent Stroke Variable to Predicting Early Mortality in Acute Ischemic Stroke Patients

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Abstract

BACKGROUND: Predicting Early Mortality of Acute Ischemic Stroke (PREMISE) score is a recent scoring derived from the Austrian Stroke Unit Registry. Internal validation assigned by Haji Adam Malik General Hospital Medan in 2020 stated that the performance of its discrimination was not strong enough and leads to a further necessity for an improvement by an addition of another variable.

AIM: This study aims to assess the calibration and discrimination performance of the PREMISE score after addition of recurrent stroke variable to predicting early mortality in acute ischemic stroke patients.

METHODS: Retrospective cohort study was performed in a population of ischemic stroke patients admitted to Haji Adam Malik General Hospital Medan from January to December 2019. The score's calibration was calculated by the Hosmer–Lemeshow goodness-of-fit test and its discriminatory power by calculating the area under curve (AUC) after adding the recurrent stroke variable.

RESULTS: In total, 223 ischemic stroke patients were included in the analysis, there were 69 patients with recurrent stroke (30.9%). The PREMISE score showed good calibration (Hosmer–Lemeshow p = 0.331) and a strong enough discrimination power with an AUC value of 0.783. The addition of the recurrent stroke variable to the PREMISE score showed an increase score's calibration with Hosmer–Lemeshow p = 0.575 and discrimination power with an AUC value of 0.806.

CONCLUSION: The PREMISE score after the addition of the recurrent stroke variable showed an increase calibration and discrimination performance to predicting early mortality in acute ischemic stroke patients.

Background

Stroke is still a major concern of world's health issues and a leading cause of death and disability worldwide [1]. According to the data from the World Health Organization, in 2005, there were around 5.8 million deaths due to stroke, increased to 6.5 million in 2015 and are expected to increase to 7.8 million in 2030 [2].

In Indonesia, based on national data, stroke shows the highest mortality rate, namely, 15.4% as a cause of death. Age <45 years was 12.9% and over 65 years was 35.8%. From these data, it was suspected that an increase in the incidence of stroke correlated with older age [3]. Research by Rambe *et al*. (2012), 562 stroke patients from 25 hospitals in North Sumatra, the mean age was 59 years. The results of computed tomography (CT) head scan in this study showed cerebral infarction in 53.7% of patients, hemorrhagic in 27% of patients, and hemorrhagic infarction in 2.1% of patients [4]. Sihotang (2015) explained that the profile of patients with ischemic stroke was found that 32.9% of the patients were hospitalized when they died [5].

The mortality rate within 30 days after ischemic stroke is estimated to be around 15% in developed countries and several factors are known to increase the stroke mortality rate. However, predictors of early death have not been studied intensively. A better prognostic associated with a poor outcome including death is urgently needed in the 1st day after an acute attack. Several investigators attempted to establish clinical scores for predictors of early death in acute ischemic stroke patients, including Saposnik *et al*. with IScore, O'Donnell *et al*. with the PLAN score, and Papavasileiou *et al*. with ASTRAL score. However, IScore, PLAN score, and ASTRAL score only predict mortality in 30 days and 1 year after the onset of ischemic stroke so they cannot be used as predictors of early death (≤7 days after stroke onset) in acute ischemic stroke patients [6], [7], [8].

Gattringer *et al*. (2019) developed a clinical score to predict premature death in acute ischemic stroke patients. This clinical score was developed from the Austrian National Stroke Archives. Age, stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS), pre-stroke functional

disability (modified Rankin Scale > 0), pre-existing diabetes and heart disease, posterior circulation stroke syndrome, and non-toxic causes of stroke were associated with underlying mortality. Predicting Early Mortality of Acute Ischemic Stroke (PREMISE) score had a maximum score of 12 points. The PREMISE score showed good discrimination (AUC 0,873, 95% CI: 0,844-0,90). Patients with a score ≥10 have a 35% risk (95% CI, 28–43%) of dying within the first few days of hospitalization in the stroke unit [9]. Ntaios *et al*. (2019) conducted external validation of the PREMISE score in Athens, Greece. In this study, mortality increased with increasing PREMISE score. The risk of death for acute stroke patients was 6 times higher in patients with a PREMISE score >10 compared with patients with a score of 0–4 points (OR: 6.21, 95% CI: 4.13–8.29) [10].

In 2020, researchers have conducted external validation of the PREMISE score in predicting the early death of acute ischemic stroke patients at RSUP H Adam Malik Medan. The data source used came from secondary data in the form of medical records of patients treated with acute ischemic stroke in 2019. From this study, the PREMISE score had a good calibration performance with a value of p = 0. 331 in the Hosmer–Lemeshow test and a strong enough discrimination performance in predicting premature death in acute ischemic stroke patients with an AUC value of 0.783. The strong discrimination performance with AUC < 0.8 is due to the fact that there are two components of the PREMISE score that do not significantly affect the early mortality of acute ischemic stroke patients, namely, the pre-existing disability component and posterior circulation stroke syndrome which can statistically affect the AUC value. On this basis, the researchers felt the need to modify the score by adding predicted variables for early death that could improve the discrimination performance of the PREMISE score.

The aim of the study was to assess the discriminative performance of the PREMISE score after the addition of recurrent stroke variable to predict an early death in acute ischemic stroke patients.

Methods

This study was an observational analytic study with a retrospective cohort study design where the data source was secondary data form medical records of all acute ischemic stroke patients who underwent treatment at the Stroke Corner, High Dependency Unit, High Care Unit, and Intensive Care Unit of Haji Adam Malik General Hospital Medan in a period of time from January 1, to December 31, 2019. The inclusion criteria were all acute ischemic stroke patients who were enforced based on history, physical examination, and head CT scan and had complete PREMISE score model component data. Patients with acute ischemic stroke with symptoms of systemic inflammatory response syndrome or sepsis on admission and acute ischemic stroke patients who went home for outpatient treatment or went home at their own request before 7 days of stroke onset were excluded from the study.

The PREMISE score is a clinical score that is assessed when a stroke patient is admitted to the hospital (in the acute phase), which consists of six assessment components, namely, age, stroke severity as measured by NIHSS, pre-stroke functional disability (modified Rankin Scale > 0), heart disease and pre-existing diabetes, posterior circulation stroke syndrome, and non-lacunar causes of stroke with a maximum total of 12 points and used to predict premature death in acute ischemic stroke patients. Recurrent stroke is defined as a stroke that occurs after previously having a history of either a bleeding stroke or a blockage stroke with or without clinical improvement. Early mortality in acute ischemic stroke patients was death in <7 days after stroke onset in acute ischemic stroke patients assessed based on integrated patient progress records in medical records.

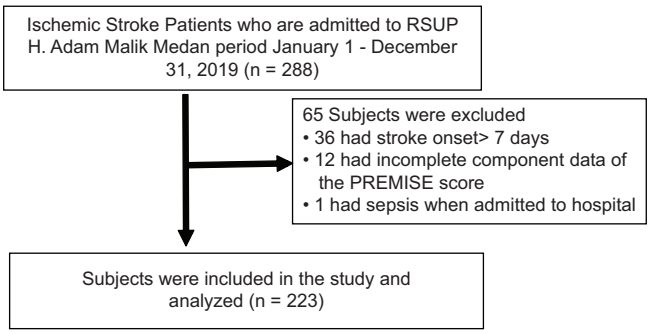

Figure 1: Research subject recruitment flow

This research is a continuation of the PREMISE score validation study where the research has been approved and passed the ethical review from the Health Research Ethics Committee of the Faculty of Medicine, University of North Sumatra with number 106/KEP/USU/2020 which was issued on June 30, 2020. After making preparations by creating a proposal and a research permit, the researchers looked for patient data in the register book or computer in the Stroke Corner, HDU, HCU, and ICU RSUP HAM. Based on the medical record number obtained in the register book or computer, a patient's medical record was searched in the Medical Record Installation Room RSUP HAM to collect data on the basic characteristics and components of the PREMISE score and recurrent stroke variables. Then, the total PREMISE score was calculated and the tracking of patient progress records was integrated to see the outcome of acute ischemic stroke patients. The results obtained are recorded on the data collection sheet. After that, data processing and analysis are carried out.

Univariate analysis was carried out to analyze the characteristics of one variable by conducting descriptive tests and the performance of the scoring system in this study was assessed for calibration and discrimination. Discrimination performance is calculated by assessing the AUC on the Receiver Operating Characteristic (ROC) curve.

Results

During the tracing of medical records in that time frame, 288 patients were obtained, 65 patients were excluded, which 36 patients were excluded because the stroke onset was more than 7 days, 12 patients had incomplete data component of the PREMISE score, 11 patients suffered from sepsis when admitted to hospital, and six patients went home before the 7th day of stroke onset. Then, the total number of patients included was 223 patients (Figure 1).

Based on the demographic characteristics of 223 research subjects (Table 1), it was found that the average age of all study subjects was 60.48 ± 12.12 years, where the most age was <60 years as many as 102 people (45.7%) and the least aged >70 years as many as 51 people (22.9%). The majority of the gender were male, namely, 118 people (52.9%). The highest level of education is elementary school with 73 people (32.7%) and most of them do not work as many as 69 people (30.9%).

Table 1: Distribution of research subject demographic characteristics

Demographic Characteristics	n = 223	%
Age (years), mean ± SD	60.48 ± 12.12	
Age Group		
<60 years	102	45.7
60–69 years	70	31.4
≥70 years	51	22.9
Gender		
Male	118	52.9
Women	105	47.1
Education		
No school	10	4.5
Elementary school	73	32.7
Junior High	41	18.4
High school	59	26.5
Bachelor	40	17.9
Profession		
Government employees	34	15.2
Entrepreneur	65	29.1
Housewife	55	24.7
Does not work	69	30.9

Based on the characteristics of the medical conditions of the 223 research subjects (Table 2), it was found that the most of the study subjects had pre-existing disabilities, namely, 201 people (90.1%). For the level of stroke severity, the NIHSS mean value was 14.76 ± 6.97 with the highest NIHSS value that is between 12–23 as many as 115 people (51.6%). Hypertension risk factors were found in more than 50%

Table 2: Distribution of the characteristics of the subject's medical conditions

Characteristics of Medical Conditions	n = 223	%
Pre-existing defects		
Yes	201	90.1
No	22	9.9
Stroke severity (NIHSS), mean ± SD	14.76 ± 6.97	
NIHSS 0–4	8	3.6
NIHSS 5–11	72	32.3
NIHSS 12–23	115	51.6
NIHSS≥24	28	12.6
Risk factor		
Hypertension	143	64.1
Heart disease	103	46.2
Diabetes mellitus	98	43.9
Smoke	97	43.5
Dyslipidemia	86	38.6
Posterior circulation stroke syndrome		
Yes	19	8.5
No	204	91.5
Non-lacunar stroke		
Yes	133	59.6
No	90	40.4
Recurrent stroke		
Yes	69	30.9
No	154	69.1
PREMISE score, mean ± SD	6.60 ± 2.38	
PREMISE score 0–4	33	14.8
PREMISE score 5–9	163	73.1
PREMISE score≥10	27	12.1

of the subjects, namely, 143 people (64.1%). The study subjects with posterior circulation stroke syndrome were only found in 19 people (8.5%) and 133 people (59.6%) were found with non-lacunar causes of stroke. Research subjects with recurrent stroke were only 69 people (30.9%). The mean PREMISE score of the research subjects was 6.60 ± 2.38 where the highest PREMISE score is between 5–9 as many as 163 people (73.1%).

The clinical outcome of research subjects from a total of 223 study subjects (Table 3) was found that 22 people (9.9%) had premature death (≤7 days of stroke onset) while 46 people (20.6%) died.

The discrimination performance of the PREMISE score based on the AUC value on the ROC curve (Figure 2) in this study obtained an AUC value of 0.783 (95% CI 0.676–0.889).

Table 3: Frequency distribution of clinical outcomes of research subjects

Clinical Outcomes	n = 223	%
Early Death (≤7 days of stroke onset)		
Yes	22	9.9
No	201	90.1
Output (state when going home)		
Died	46	20.6
Life	177	79.4

The discrimination performance of the PREMISE score after adding the recurrent stroke variable based on the AUC value on the ROC curve (Figure 3) in this study obtained an AUC value of 0.806 (95% CI 0.766–0.845).

The calibration performance of the PREMISE score after adding the recurrent stroke variable based on the Hosmer–Lemeshow goodness-of-fit test showed excellent calibration (Increase score's calibration with Hosmer–Lemeshow from p = 0.331 top = 0.575).

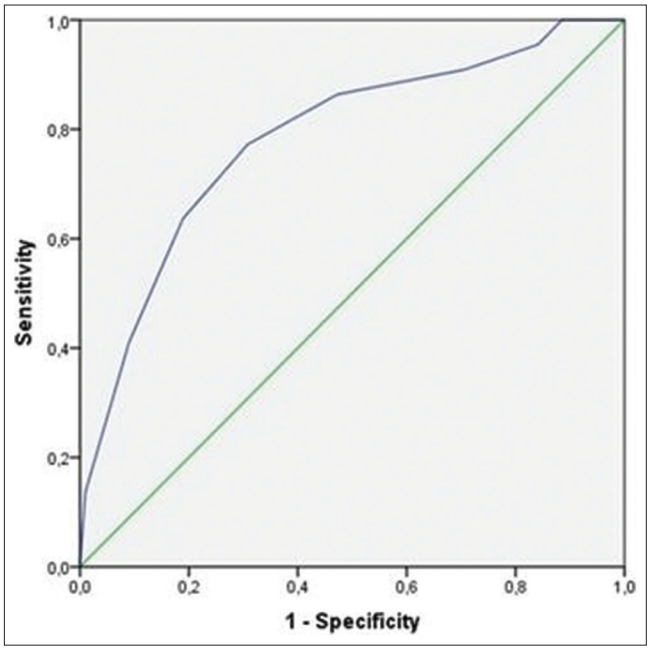

Figure 2: The PREMISE score ROC curve

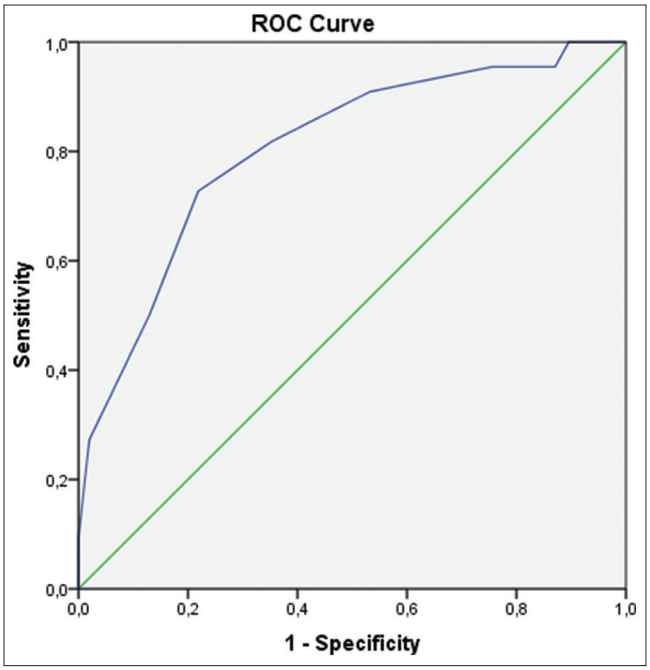

Figure 3: ROC curve of PREMISE score and value added of recurrent stroke

Discussion

Subjects in this study had a mean age of 60.48 years which is lower than the mean age of the study in the place of origin of the PREMISE score in Austria by Gattringer *et al*. (2019), namely, 73.80 years and also lower than the mean age in the external validation study of the PREMISE score in Greece by Ntaios *et al*. (2019), namely, 77.04 years. According to the researchers, this difference may be influenced by the degree of health and other risk factors that differ between people in Europe and people in Indonesia, especially in North Sumatra. The lower mean age indicates the low level of public health in the area which causes the morbidity rate is higher at a younger age [11].

In this study, the majority of research subjects were male, namely, 118 people (52.9%). This is in line with research at the place of origin of the PREMISE score in Austria by Gattringer *et al*. (2019), namely, 53% of the study subjects were male and in Greece where external validation of the PREMISE score by Ntaios *et al*. (2019) found that 62.8% of the subjects were male [9], [10].

The most of the research subjects were only graduated from elementary school as many as 73 people (32.7%) and the majority of research subjects did not work as many as 69 people (30.9%). This is in line with the Riskesdas (2013) data where the prevalence of stroke tends to be higher in people with low education and who do not work [12]. According to Sorensen *et al*. (2012), the low levels of education and employment affect health status. The level of education will be related to knowledge and access to health information, as well as work related to income and access to health services [13].

In this study, the most of the medical conditions of the study subjects were having pre-existing disabilities, namely, 201 people (90.1%) and the severity of stroke which assessed based on the NIHSS value, the NIHSS was obtained at the NIHSS value 12–23 as many as 115 people (51.6%). This is not in line with the research at the origin of the PREMISE score in Austria by Gattringer *et al*. (2019). From this study, it was found that the most of the medical conditions of the research subject had no previous disability or no symptoms, as much as 68.8% and 58.8% of them were having low NIHSS values, namely, NIHSS 0–4 or mild stroke symptoms. This difference has many influencing factors, one of which is from this study itself when tracing medical records. Researchers assessed pre-existing disabilities only through the history sheet from the medical records, because the previous disability assessments at the time that the patient was treated were never carried out in this study site, so that this subjective history may be recorded differently which can affect the researchers' assessment of the pre-existing disability score components. Similar to the pre-existing disability component, the assessment of the severity of stroke in this study used an existing NIHSS sheet that was medically recorded, this NIHSS sheet was assessed by several different residents who had never been equated or trained before both in knowledge and experience. It may also influence the assessment of stroke severity in this study [9], [10].

Hypertension risk factors suffered by more than 50% of the study subjects, namely, as many as 143 people (64.1%), whereas other risk factors were suffered by <50% of study subjects. Hypertension is a major risk factor for stroke. From the research results from 28 hospitals, it was found that hypertension

contributed 73.9% as the main cause of ischemic stroke. Hypertension, diabetes mellitus, heart disease, dyslipidemia, and smoking were the main risk factors for ischemic stroke. However, in this study, the subjects who had diabetes mellitus, heart disease, dyslipidemia, and smoking are <50% of study subjects. This difference does not mean that diabetes mellitus, heart disease, dyslipidemia, and smoking are not at risk of causing a stroke. According to the researchers, this can occur due to many factors, such as incomplete data on medical records, no medical history was asked at the time of history taking, the patient did not admit to having these risk factors or the risk factors were indeed low in ischemic stroke patients who were admitted to the RSUP. H. Adam Malik Medan in 2019 [14].

The patient's condition was related to the cause of stroke, from 223 study subjects, it was found that the most common cause of stroke was the non-lacunar type of stroke, namely, 133 people (59.6%). This is in line with the study by Marti *et al*. (2011) where from the total ischemic stroke patients that treated, only 25% of the patients had a lacunar stroke type, while the remaining 75% were non-lacunar stroke types. Lacunar strokes are mostly asymptomatic and are often missed on head CT scans and about 20–28% of the population 65 years of age or older have lacunar infarcts on MRI images without clinical symptoms. Recurrent strokes were only affected 69 people (30.1%). This is influenced by the level of patient knowledge and access to health-care centers that make families feel that patients who had a stroke before do not need to be hospitalized [15].

From a total of 223 study subjects, 46 people (20.6%) died when returning from hospitalization and 22 people (9.9%) of the 46 people who died experienced premature death (≤7 days of stroke onset). Result in this study was higher than the study in the place of origin of the PREMISE score in Austria by Gattringer *et al*. (2019), in that study only 2% experienced premature death and in Greece where the external validation of the PREMISE score by Ntaios *et al*. (2019), the early mortality rate was only 3.2% [9], [10]. This difference has many influencing factors, one of which is based on the data of this study, it can be seen that the early mortality rate increases with increasing NIHSS score. In this study, the number of patients treated with a NIHSS score of 12–23 was 115 people (51, 6%). This suggests that more than 50% of the patients treated in this study were in moderate-to-severe clinical condition. Mittal and Goel (2017) said that NIHSS score of more than 15 was significantly associated with high mortality [16].

The discrimination performance in this study was obtained from the AUC value on the ROC curve which was 0.783 (95% CI 0.676–0.889). This value is lower than the research at the place of origin of the PREMISE score in Austria by Gattringer *et al*. (2019), where in this study, the AUC value on the ROC curve was 0.879 (95% CI 0.871– 0.886) and in Greece Ntaios *et al*. (2019). The AUC value on the ROC curve was 0.873 (95% CI 0.844–0.901). This difference can caused by many factors. One of them, according to the researchers, may be that in this study, there are several components of the PREMISE score that does not significantly affect the early mortality of acute ischemic stroke patients, namely, the pre-existing disability and posterior circulation stroke syndrome. This of course can statistically affect the AUC value [17]. After the addition of the recurrent stroke variable, the AUC value on the ROC curve increased by 0.806 (95% CI 0.766–0.845).

The calibration performance in this study was obtained from the Hosmer–Lemeshow value which was p = 0.331. This value is a good calibration and same than the research at the place of origin of the PREMISE score in Austria by Gattringer *et al*. (2019), where in this study with the Hosmer–Lemeshow p = 0.2 and in Greece Ntaios *et al*. (2019) with the Hosmer–Lemeshow p = 0.99 [17]. After the addition of the recurrent stroke variable, the Hosmer–Lemeshow value increased by p = 0.575.

Limitations

There are several limitations to this study. First, the assessment of the pre-existing disability component in acute ischemic stroke patients, all by assessing the patient's history on the history sheet on the medical record, this is different from the study in Austria which used the mRS sheet to assess pre-existing disability. In this study, the assessment was only from the history sheet. This subjective history may be recorded differently so that it will affect the researchers' assessment of the component of the score. Second, assessment of stroke severity based on the NIHSS value contained in medical records was assessed by several different residents who had never been equated or trained before both in knowledge and experience, this could also influence the assessment of the patient's stroke severity. Third, this study is a single-center study so that the PREMISE score in this study cannot be generalized. This is due to limited manpower, time, and cost. This could be the reason for another research in the future.

Conclusion

The PREMISE score after the addition of the recurrent stroke variable showed an increase the discrimination performance to predicting early mortality in acute ischemic stroke patients.

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