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Development and external validation of new nomograms including electrocardiogram changes to predict the 6-month prognosis of patients with subarachnoid haemorrhage in the emergency department

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ABSTRACT

Objectives: To develop a new nomogram including electrocardiogram changes that can predict prognosis in patients with subarachnoid haemorrhage (SAH) using our preliminary research results and to perform external validation of a new nomogram.

Design: Retrospective, observational study

Setting: Emergency department (ED) of a university affiliated tertiary hospital between January 2009 and March 2015

Participants: Adult patients with SAH were enrolled. Exclusion criteria were: age<19 years; administration of a cardiovascular drug with no baseline ECG; cardiac arrest on arrival; traumatic SAH; referral from other hospitals because initial ECG could not be obtained; and referral to other hospitals from the ED as their prognosis could not be evaluated.

Primary outcome measures: The 6-month prognosis was assessed using the Glasgow Outcome Scale (GOS). We defined a poor outcome as a GOS score of 1, 2, or 3.

Results: A total of 202 patients were included for analysis. From the preliminary study, age, electrocardiogram changes (ST depression or tall T wave), and scoring systems were selected to predict prognosis in patients with SAH using multivariate logistic regression. We developed simplified nomograms using these variables. Discrimination of the developed nomograms including the World Federation of Neurosurgical Societies (WFNS) scale, Hunt and Hess (HH) system, and Fisher scale was superior to those of WFNS scale, HH system, and Fisher scale (0.912 vs. 0.813; p<0.001, 0.913 vs. 0.826; p<0.001, and 0.885 vs. 0.746; p<0.001, respectively). The calibration plots showed excellent agreement. In the external validation, the discrimination of the newly developed nomograms incorporating the three scoring systems was also good, with an AUC value of 0.809, 0.812, and 0.772, respectively.

Conclusions: We developed and externally validated new nomograms using only three independent variables. Our new nomograms were superior to the WFNS scale, HH systems, and Fisher scale in predicting prognosis and are readily available.

Keywords

Subarachnoid haemorrhage, electrocardiogram, prognosis, nomogram, emergency department

ARTICLE SUMMARY

Strengths and limitations of this study

- Our nomogram is the first to combine electrocardiogram changes and other prognostic factors in patients with subarachnoid haemorrhage.
- Our nomogram is solely based on electrocardiogram changes, age, and conventional scoring systems, which are easily and readily obtainable during the patient's course in the ED.
- Because this study is a retrospective, observational study, the predictive probability could be overestimated more than in a prospective study.
- Self-fulfilling prophecy regarding prognosis may have affected the results.

INTRODUCTION

Subarachnoid haemorrhage (SAH) is defined as a haemorrhage in the subarachnoid space and the reported incidence is 9-11 per 100,000 person years in worldwide.[1] SAH accounts for 4% of all cerebrovascular disease and develops at a relatively young age, with approximately 50% of patients experiencing disability or death.[2] Because of the high mortality and low recovery rate, predicting prognosis in patients with SAH is crucial.[1-3] Botterell et al. presented the first grading system for SAH in 1956,[4] and different systems have since been developed. The Hunt and Hess (HH) system, the World Federation of Neurosurgical Societies (WFNS) scale, and the Fisher scale have been widely used globally.[5-7] The above three systems are simple, but do not include clinically important factors, such as comorbidity, age, and vital signs on admission, and differences between the grades for each system are ambiguous. A range of scoring scales have been developed to overcome the limitations of the existing scoring scales.[5-10]

Factors such as age, past medical history (hypertension, diabetes mellitus, history of brain disease), blood pressure and initial level of consciousness on admission, and cerebral aneurysm size have been reported to be independently associated with prognosis of patients with SAH.[8 11] Electrocardiogram (ECG) abnormalities have also been studied as a prognostic factor. ECG abnormalities are observed in 40 - 90% of patients with SAH [12-14] and have been associated with hyperactivity of the sympathetic nervous system due to autonomic nervous system dysregulation.[15]Since the hyperactivity of the sympathetic nerve reflects the degree of cerebral haemorrhage, ECG changes may be associated with patient prognosis. The most common reported abnormalities are QT prolongation, ST segment changes and T wave abnormalities.[15 16] A number of studies have investigated the prognostic value of ECG abnormalities.[17 18] However, the role of an abnormal ECG as a prognostic predictor remains debatable. QTc changes and ST segment changes have been reported as the parameters most significantly associated with prognosis,[17 19] although further studies reported no significant association between ECG change and outcome.[12 14 19] Because of this uncertainty, the existing system for predicting the prognosis of patients with SAH does not include ECG changes as a prognostic variable. However, ECG is an inexpensive test which is readily available in an emergency setting. Because accelerated sympathetic activity reaches its climax in the first 24 hours after the onset of SAH, ECG abnormalities develop during the early stage of disease,

disappearing over time.[13 15 16] Therefore, it is important to consider ECG changes as an initial prognostic factor. We conducted preliminary research to investigate the association between the abovementioned prognostic factors, including ECG changes, and prognosis of patients with SAH and found that age, ECG changes, and the three scoring systems were associated with patient prognosis.[20]

Among the computational models for predicting prognosis, the nomogram is very useful because it is a pictorial representation of a statistical predictive model that generates a numerical probability of a clinical event. It is more accurate than the conventional method using the odds ratio.[21] Therefore, the objective of this study was to develop a new nomogram that can predict prognosis of patients with SAH using the results of our preliminary research and to perform external validation of the new nomogram.

MATERIALS AND METHODS

1. Study design and populations

We performed a retrospective, observational study to develop a new nomogram that can predict prognosis of patients with SAH. We enrolled patients with SAH diagnosed by brain computed tomography (CT) scans or xanthochromia of cerebrospinal fluid in the emergency department (ED) between January 2009 and March 2015. Exclusion criteria were as follows: 1) age under 19 years; 2) administration of a cardiovascular drug, such as calcium channel blockers, with no baseline ECG; 3) cardiac arrest on arrival; 4) traumatic SAH. Additionally, patients were excluded if they were referred from other hospitals because initial ECG could not be obtained and patients were often treated with medication affecting the cardiovascular system. Patients referred to other hospitals from the ED were also excluded as their prognosis could not be evaluated. The study was reviewed and approved by the Institutional Review Board of Yonsei University College of Medicine, Severance Hospital [no. 4-2015-0345]. The requirement for informed consent was waived by the ethics committee because of the retrospective nature of the study.

2. Data collection

One investigator (J. Y. H) retrospectively collected the data through a review of the medical records. We collected demographic data, vital signs on admission, and past medical history, including a history of hypertension, diabetes mellitus, cardiovascular and cerebrovascular diseases. The Glasgow Coma Scale (GCS), HH, and WFNS scores were obtained from assessing the neurological abnormality and the level of consciousness. The amount of blood, the location and size of cerebral aneurysm, and the presence or absence of intraventricular haemorrhage (IVH) and intracerebral haemorrhage (ICH) were determined based on CT scans reported by board-certified radiologist. ECG findings were assessed by one emergency physician blinded to patient prognosis using the Marquette Universal System of Electrocardiography® (MUSE, GE healthcare, Milwaukee, USA). Abnormal ECG findings were classified into four groups: ST elevation, ST depression, T wave inversion, and tall T wave. ST elevation was defined as ≥0.1 mV elevation in at least 2 contiguous leads other than leads V2-V3. For leads V2-V3, the following cut-off points applied: ≥0.2 mV in men ≥40 years, ≥0.25 mV in men <40

years, or ≥0.15 mV in women. ST depression was defined as ≥0.05 mV depression in all leads. An inverted T wave was defined as less than 0.1 mV from the baseline, and a tall T wave was defined as greater than 1 mV in depth. [19] QTc was redefined and measured based on heart rate and was adjusted using Bazett's formula. The primary outcome of this study was assessed at 6 months after disease onset using the Glasgow Outcome Scale (GOS). We defined a poor outcome as a GOS score of 1, 2, or 3.

3. Data analysis

Statistical analysis was performed using SAS (version 9.2, SAS Inc., Cary, NC, USA) and R package (version 3.1.3, http://www.R-project.org). Categorical variables were described as frequencies (%), and continuous variables were described as mean ± standard deviation. We used the independent t-test for comparison of continuous variables and Fisher's exact test for categorical variables. From the preliminary study, age, ECG changes (ST depression or tall T wave) and scoring systems were selected to predict prognosis in patients with SAH using multivariate logistic regression. Each scoring system was entered individually into the multivariate logistic regression analysis with clinical variables, CT findings, and ECG abnormalities. Finally, we created three regression models including each scoring system and these models showed a significantly higher area under the receiver operating characteristic curve (AUC) values than those of the conventional scoring systems. In this study, we developed a simplified nomogram for the prediction of prognosis using age, ECG changes, and conventional scoring system. The performance of the nomograms in predicting outcomes was evaluated with respect to discrimination and calibration. Nomogram predictive accuracy (discrimination) is measured via a concordance index (c-index), analogous to the AUC, which quantifies the level of concordance between predicted probabilities and the actual chance of the event of interest occurring. A value of 0.5 indicates no predictive discrimination, and a value of 1.0 indicates perfect separation of patients with different outcomes. Calibration of the nomogram determines how far the predicted probabilities are from the observed outcome frequencies using graphic representations (calibration curve). A plot along the 45-degree line would indicate a perfect calibration model in which the predicted probabilities are identical to the actual outcomes. The predictive accuracy and calibration of the new nomogram was then externally validated with data derived from

another ED (validation set; n=141). The Delong method was used to compare the C-indexes of each model. P<0.05 was considered statistically significant.

RESULTS

1. Study population

A total of 665 patients with SAH were initially enrolled in the present study during the study period. Most patients (n=411; 61.8%) were excluded because they were referred from or to other hospitals. We also excluded 52 patients for the following reasons: age<19 years (n=12), no initial ECG (n=3), cardiac arrest on arrival (n=6), and SAH due to trauma (n=31). Finally, 202 patients were included in the primary analysis (Fig 1). The baseline characteristics and ECG changes related to prognosis are summarised in Table 1. Of the 202 patients, 111 (54.9%) had a good outcome with a GOS of 4 or 5.

Table 1. Clinical characteristics of study populations

	Good outcome (n=111)	Poor outcome (n=91)	Total (n=202)	p values
Age (year)	53.7±12.3	61.1±13.7	57.0±13.4	<0.001
Sex, male	36(32.4%)	36(39.6%)	72(35.6%)	0.305
Vital signs				
Systolic blood pressure (mmHg)	154.5±29.3	169.6±41.0	154.5±35.7	0.003
Heart rate(/min)	80.5±17.5	84.7±22.1	82.4±19.8	0.137
Respiratory rate(/min)	15.5±2.2	16.7±6.0	16±4.3	0.072
Body temperature (℃)	36.4±0.5	36.3±0.7	36.4±0.6	0.123
Chronic comorbidities				
Hypertension	32(28.8%)	43(47.3%)	75(37.1%)	0.007
Diabetes mellitus	7(6.3%)	9(9.9%)	16(7.9%)	0.435
Cerebrovascular accident	5(4.5%)	3(3.3%)	8(4.0%)	0.516
CT findings				
Aneurysmal SAH	87(88.4%)	61(67.0%)	148(73.3%)	0.227
Posterior circulation aneurysm	23(20.7%)	18(19.8%)	41(20.3%)	0.178
Aneurysm sizes(mm)	4.0±3.2	4.6±4.9	4.3±4.0	0.258
Intracerebral haemorrhage	7(6.3%)	26(28.6%)	33(16.3%)	<0.001
Intraventricular haemorrhage	17(15.3%)	41(45.1%)	58(28.7%)	<0.001
ECG changes				
ST elevation	6 (5.4%)	11 (12.1%)	17 (8.4%)	0.125

	ST depression	2 (1.8%)	29 (31.9%)	31 (15.3%)	<0.001
	T wave inversion	11(9.9%)	10(11%)	21 (10.4%)	0.821
	Tall T wave	1 (1%)	9 (9.9%)	10 (5.0%)	0.006
	QTc (msec)	458.1±39.1	479.1±53.0	467.6±46.9	0.002
Scoring systems					
	WFNS scales	1.2±0.7	3.1±1.6	2.0±1.5	<0.001
	HH system	2.1±0.6	3.4±1.1	2.6±1.1	<0.001
	Fisher grade	2.9±0.8	3.1±0.5	3.2±0.8	<0.001

CT, computed tomography; SAH, subarachnoid haemorrhage; ECG, electrocardiogram; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

2. ECG changes of patients with SAH

Of 202 patients, 79 (39.1%) had ECG changes, which included ST elevation in 17 (8.4%), ST depression in 31 (15.3%), T wave inversion in 21 (10.4%), and tall T wave in 10 (5.0%) patients. ST depression and tall T waves were detected more often in patients with a poor outcome than in those with a good outcome (29 patients (31.9%) vs. 2 patients (1.8%); p<0.001 and 9 patients (9.9%) vs. 1 patient (0.9%); p=0.006, respectively). The QTc of patients with a poor outcome was significantly longer than that of patients with a good outcome (479.1±53.0 sec vs. 458.1±39.14 sec; p=0.002).

3. Nomograms for the prediction of prognosis

From the preliminary study, we created three models including age, ECG changes (ST depression or tall T wave), and each scoring system by backward Wald logistic regression analysis. Since ST depression and tall T wave formation do not occur simultaneously, they were considered as one variable. In this study, we established three nomograms incorporating each scoring system (Fig 2). By calculating the total number of points and locating it on the total point scale, we were easily able to draw a straight line down to estimate the predicted prognosis. For example, if a 50-year-old patient had ST depression on the initial ECG with a WFNS score of 3, a final score of 160 could be attained as the sum of each corresponding score (39 points for age, 50 points for WFNS 3, and 71 points for ST depression) and the predicted probability of poor prognosis was 95.9%.

The Harrell's C-index for the new nomogram including the WFNS scale to predict prognosis of patients with SAH (0.912; 95% CI, 0.871 to 0.954) was significantly higher than that of the WFNS scale (0.813; 95% CI, 0.758 to 0.868; p<0.001). Also, the C-indexes of the two nomograms including the HH system and Fisher scale were greater than those of the HH system and Fisher scale (0.913 (0.872-0.955) vs. 0.826(0.772-0.879); p<0.001 and 0.885(0.839-0.931) vs. 0.746(0.687-0.805); p<0.001, respectively). There was no significant difference in the predictive accuracy of the three newly established models (p=0.350). The calibration plots presented an excellent agreement between predicted and observed probabilities of the 6-month prognosis, and exhibited a close approximation between the probabilities (Fig 3).

4. External validation of the nomograms

The new nomograms were externally validated using the independent dataset listed in Table 2. The C-indexes of nomograms including the WFNS scale, HH systems, and Fisher scale were 0.809 (0.735-0.884), 0.812 (0.737-0.886) and 0.772 (0.691-0.852), respectively. The calibration plots presented an acceptable agreement in the external validation cohort between the nomogram prediction and actual observation (Fig 4).

Table 2. Clinical characteristics of the external validation group

	Good outcome (n=77)	Poor outcome (n=64)	Total (n=141)	p-value
Age (year)	53.2±11.1	59.6±14.5	56.2±13.2	0.04
ECG changes				
STD or Tall T	13 (16.9%)	33 (51.6%)	46 (32.6%)	<0.001
Scoring systems				
WFNS scales	1.4±0.9	2.9±1.6	2.1±1.5	<0.001
HH system	2.3±0.7	3.2±1.0	2.7±1.0	<0.001
Fisher grade	3.1±0.5	3.5±0.6	3.3±0.6	<0.001

ECG, electrocardiogram; STD, ST depression; WFNS, World Federation of Neurosurgical Societies;

HH, Hunt and Hess.

DISCUSSION

In this study, we developed and externally validated new nomograms using three independent variables to determine the 6-month prognosis in patients with SAH admitted to the ED. The three independent variables were age, ECG changes, including ST depression or tall T wave formation, and conventional scoring systems, such as the WFNS scale, HH systems, and Fisher scale. The new nomograms demonstrated a significantly higher predictive accuracy than conventional scoring systems.

The association between ECG changes and prognosis has been previously studied, yet the association between abnormal ECG and prognosis prediction remains controversial. We previously investigated whether the ECG could be used as to evaluate patient prognosis. The most frequent ECG change associated with SAH is QTc prolongation.[12 17 20 22] In 2012, Huang et al. investigated whether early ECG abnormalities recorded in the ED were associated with in-hospital mortality among patients with SAH. QTc prolongation was found to be independently associated with in-hospital mortality. [17] A further study also demonstrated the association between in-hospital mortality and QTc prolongation. [22] However, the underlying mechanism for this finding remains unclear. In our previous study, QTc prolongation was associated with poor prognosis and mortality (survivor vs. non-survivor; 464.9±46.4 msec vs. 486.0±47.5 msec, p=0.04) However, multivariate logistic analysis revealed that QTc prolongation was not independently associated with poor prognosis in patients with SAH.[20] Other ECG changes associated with poor prognosis in patients with SAH are ST depression and non-specific ST segment changes (NSSTC).[17] Sudden increased intracranial pressure compresses the brain triggering a sympathetic discharge. This creates a relative ischaemic state of the myocardium and causes ischaemic changes on the ECG. ST depression and NSSTC were found to be significantly associated with mortality or poor neurologic outcome.[17 22] Furthermore, the combination of tall T waves, tall P waves, large U waves, and prolonged QT has been associated with increased mortality. [23] In our study, ST depression or tall T waves were also independently associated with poor prognosis.

In addition to ECG changes, reports have suggested that other factors may be associated with prognosis among patients with SAH.[8 11 24-26] In our study, patient age was significantly associated with prognosis. Age was found to be a major independent prognostic factor in many studies.[24-26] This could

be explained by the fact that the aged brain may have less ability to recover from initial bleeding. Increased initial bleeding among aged patients also explains the poor outcomes.[24]

Classification and scoring systems to predict the prognosis of patients with SAH have been developed since 1956. The most broadly used systems are the HH system and WFNS scale.[7] The HH system, divides disease status into five grades based on patient symptoms and level of consciousness. [10] Although this system is a good reflection of patient prognosis, the demarcation between each grade is ambiguous because of less clearly defined scales of consciousness.[7] To overcome this shortcoming, the WFNS scale uses the GCS as the prognostic predictor and the neurologic deficit was added to differentiation between WFNS grade 2 and 3. However, there was occasional overlap between grades II and grade III and the predicted outcomes may not differ substantially.[27 28] To reduce the ambiguity between WFNS grade 2 and 3, a modified WFNS scale was developed.[9] However, the modified WFNS scale failed to show any significant prognostic differences between grade 3 and 4.[23]

The association between radiological findings and patient outcome has been previously reported. [7] In 1980, Fisher et al. developed a scale assigning a grade according to the pattern of blood demonstrated on the initial CT scan for the prediction of cerebral vasospasm after SAH. [6] Although it was designed to predict vasospasm, the predictive value of patient outcome has also been reported. However, the Fisher scale was designed when radiological technology resolution was only 10% of current resolution. In the clinical context, it is uncommon for blood clots less than 1 mm in true thickness to occur in the subarachnoid space and to have no blood visible on the initial CT scan. Therefore, Fisher grades 1 and 2 were uncommon.[7]

Several advances, including the refinement of neurosurgical techniques, have taken place in SAH management since these scales were developed. Furthermore, reports found that the demarcation of the grades using these scales was ambiguous. To overcome these issues, we developed simple models by adding age or ECG changes to the existing models. The nomogram can generate an individual probability of a clinical event, such as mortality, by integrating prognostic variables. [21] With this advantage, a nomogram is being utilised to predict disease prognosis in different fields. Our nomogram used only three prognostic factors, such as existing scoring systems, age, and ECG changes. The existing scoring systems are widely used. Age and ECG changes are easily and readily

obtainable during the patient's admission at the ED. Our nomogram was the first approach to combine ECG changes and other prognostic factors in patients with SAH. This combination approach had more accurate predictive power than those of conventional scoring system alone and there was excellent agreement between predicted and observed probabilities of 6-month prognosis.

Our study has several limitations. First, this study was a retrospective analysis; therefore, it is possible that the results could differ from those of other centres, and the predictive probability could be overestimated more than in a prospective study. Second, we excluded patients referred from or to other hospitals and this raises the possibility of selection bias. However, the patients were excluded because initial ECG could not be obtained or patients' prognosis could not be evaluated. Third, interval from the onset of symptoms to arrival at the ED differs for each patient. ECG changes may not have been visible when patients presented late to the ED. Finally, the self-fulfilling prophecy regarding prognosis is an important issue: poor initial clinical status could be associated with the delivery of less invasive care. This bias is common to the vast majority of prognostication studies and we could not evaluate the prognostic factors in a strictly masked manner.

CONCLUSIONS

We developed new nomograms using only three independent variables: ECG changes including ST depression or tall T wave formation, age, and widely used conventional scoring systems, such as the WFNS scale, HH systems, and Fisher scale. Our new nomograms are valuable in predicting the 6-month prognosis of patients with SAH at an early stage after ED admission. Our new models are superior to the WFNS scale, HH systems, and Fisher scale in predicting prognosis and are readily available.

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COMPETING INTERESTS

The authors declare that they have no competing interest.

CONTRIBUTORSHIP STATEMENT

YSP designed this study with JYH, IP, and SPC. JYH, JSY, and MJK contributed to the data acquisition. HSL and YSP performed the data analysis. JYH and YSP drafted this manuscript, and all other authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board of our hospital [no. 4-2015-0345]. Written informed consent was waived by the ethics committee.

DATA SHARING

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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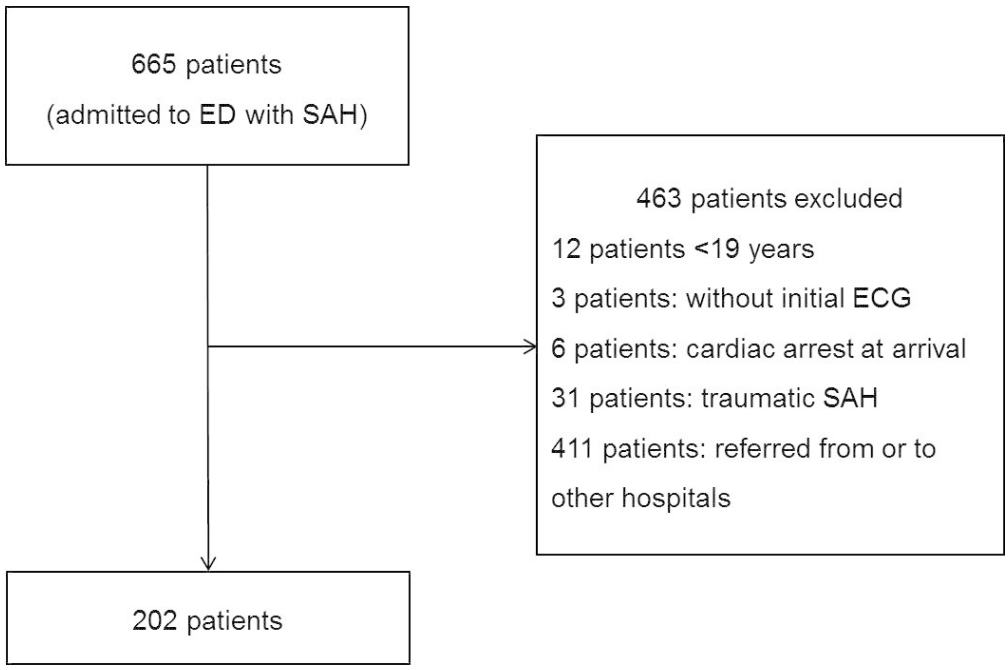
FIGURE LEGENDS

Figure 1. Flow diagram of the study subjects. ED, emergency department; ECG, electrocardiogram

Figure 2. The newly developed nomograms. Nomograms for predicting 6-month prognosis among patients with subarachnoid haemorrhage incorporating World Federation of Neurosurgical Societies scale (A), the Hunt and Hess system (B) and Fisher scale (C). STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

Figure 3. Calibration curves of the nomograms incorporating the World Federation of Neurosurgical Societies scale (A), Hunt and Hess system (B), and Fisher scale (C). All calibration plots (dotted lines) show close approximation to the logistic calibration (solid lines), indicating excellent agreement between the predicted and observed probabilities of the 6-month prognosis. STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

Figure 4. External validation of the nomograms incorporating World Federation of Neurosurgical Societies scale (A), the Hunt and Hess system (B) and Fisher scale (C). Receiver operating characteristic (ROC) curves of the nomograms are on the top line. The discrimination ability of newly developed nomograms was good, with an AUC value of 0.809 (95% CI, 0.735-0.884), 0.812 (95% CI, 0.737-0.886), and 0.772 (95% CI. 0.691-0.852), respectively. The calibration curves are on the bottom line. The calibration plots presented good agreement between the nomogram prediction and actual observation. STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess; AUC, area under the curve; CI, confidence interval.



Flow diagram of the study subjects/ ED, emergency department; ECG, electrocardiogram

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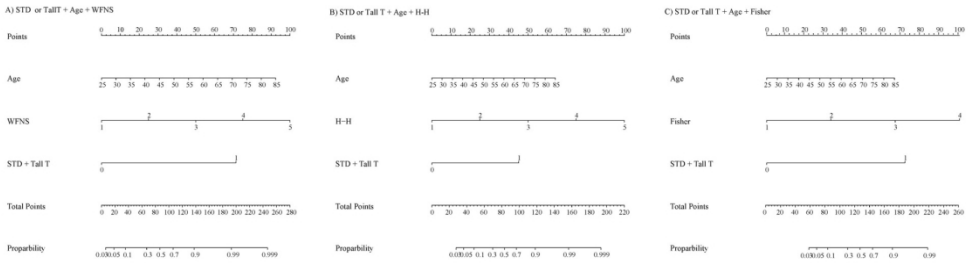

The newly developed nomograms/Nomograms for predicting 6-month prognosis among patients with subarachnoid haemorrhage incorporating World Federation of Neurosurgical Societies scale (A), the Hunt and Hess system (B) and Fisher scale (C). STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

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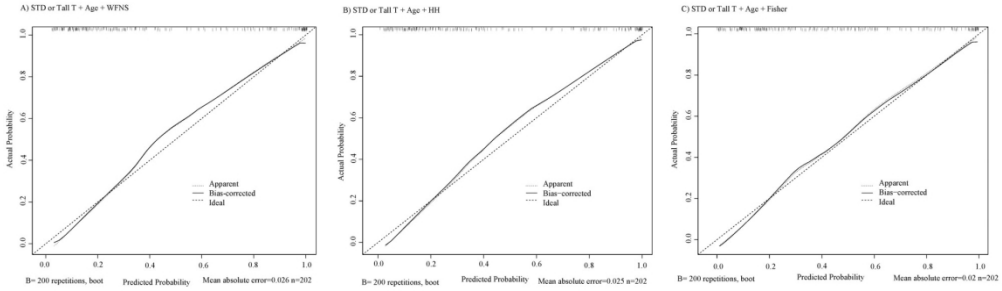

Calibration curves of the nomograms incorporating the World Federation of Neurosurgical Societies scale (A), Hunt and Hess system (B), and Fisher scale (C). All calibration plots (dotted lines) show close approximation to the logistic calibration (solid lines), indicating excellent agreement between the predicted and observed probabilities of the 6-month prognosis. STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

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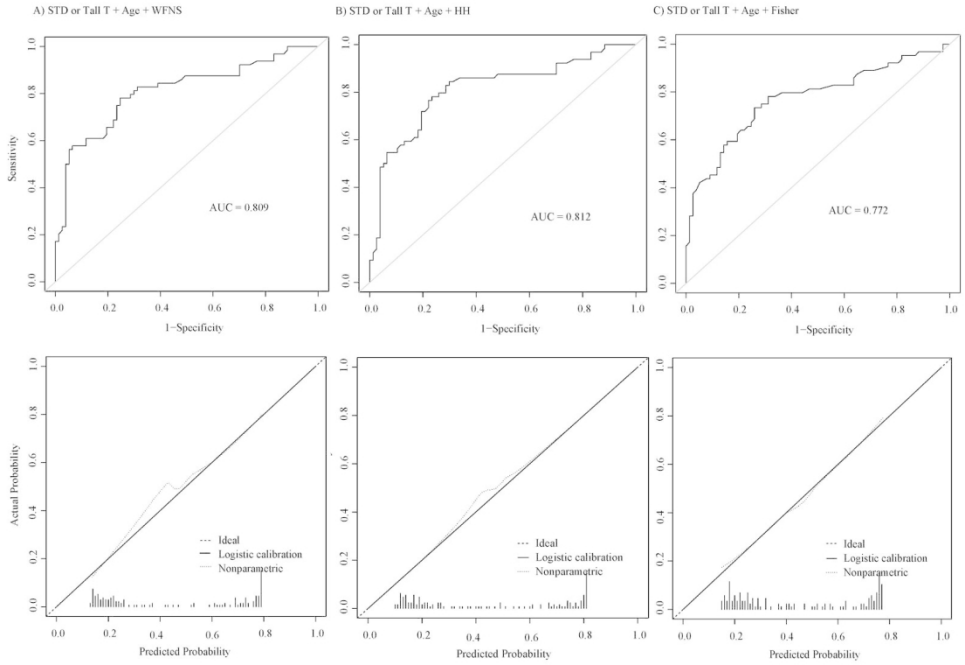

External validation of the nomograms incorporating World Federation of Neurosurgical Societies scale (A), the Hunt and Hess system (B) and Fisher scale (C)./ Receiver operating characteristic (ROC) curves of the nomograms are on the top line. The discrimination ability of newly developed nomograms was good, with an AUC value of 0.809 (95% CI, 0.735-0.884), 0.812 (95% CI, 0.737-0.886), and 0.772 (95% CI. 0.691-0.852), respectively. The calibration curves are on the bottom line. The calibration plots presented good agreement between the nomogram prediction and actual observation. STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess; AUC, area under the curve; CI, confidence interval.

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Reporting checklist for prediction model development and validation study.

Based on the TRIPOD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the TRIPOD reporting guidelines, and cite them as:

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		Reporting Item	Page Number
	#1	Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	
	#2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	
	#3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	
	#3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	
Source of data	#4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	

	#4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.
Participants	#5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.
	#5b	Describe eligibility criteria for participants.
	#5c	Give details of treatments received, if relevant
Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.
	#6b	Report any actions to blind assessment of the outcome to be predicted.
Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured
	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.
Sample size	#8	Explain how the study size was arrived at.
Missing data	#9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.
Statistical analysis methods	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.
	#10b	If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.
	#10c	If you are validating a prediction model, describe how the predictions were calculated.
	#10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.
	#10e	If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done

Risk groups	#11	Provide details on how risk groups were created, if done.
Development vs. validation	#12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.
Participants	#13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.
	#13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.
	#13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).
Model development	#14a	If developing a model, specify the number of participants and outcome events in each analysis.
	#14b	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.
Model specification	#15a	If developing a model, present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).
	#15b	If developing a prediction model, explain how to the use it.
Model performance	#16	Report performance measures (with CIs) for the prediction model.
Model-updating	#17	If validating a model, report the results from any model updating, if done (i.e., model specification, model performance).
Limitations	#18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).
Interpretation	#19a	For validation, discuss the results with reference to

		performance in the development data, and any other validation data
	#19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.
Implications	#20	Discuss the potential clinical use of the model and implications for future research
Supplementary information	#21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.
Funding	#22	Give the source of funding and the role of the funders for the present study.

BMJ Open

Development and external validation of new nomograms by adding electrocardiogram changes (ST depression or tall T wave) and age to conventional scoring systems to improve the predictive capacity in patients with subarachnoid haemorrhage

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Development and external validation of new nomograms by adding electrocardiogram changes (ST depression or tall T wave) and age to conventional scoring systems to improve the predictive capacity in patients with subarachnoid haemorrhage

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ABSTRACT

Objectives: To develop new nomograms by adding electrocardiogram changes (ST depression or tall T wave) and age to three conventional scoring systems, namely, World Federation of Neurosurgical Societies (WFNS) scale, Hunt and Hess (HH) system, and Fisher scale, that can predict prognosis in patients with subarachnoid haemorrhage (SAH) using our preliminary research results and to perform external validation of the three new nomograms.

Design: Retrospective, observational study

Setting: Emergency departments (ED) of two universities affiliated tertiary hospital between January 2009 and March 2015

Participants: Adult patients with SAH were enrolled. Exclusion criteria were age <19 years; no baseline electrocardiogram; cardiac arrest on arrival; traumatic SAH; referral from other hospital and referral to other hospitals from the ED.

Primary outcome measures: The 6-month prognosis was assessed using the Glasgow Outcome Scale (GOS). We defined a poor outcome as a GOS score of 1, 2, or 3.

Results: A total of 202 patients were included for analysis. From the preliminary study, age, electrocardiogram changes (ST depression or tall T wave), and three conventional scoring systems were selected to predict prognosis in patients with SAH using multivariable logistic regression. We developed simplified nomograms using these variables. Discrimination of the developed nomograms including WFNS scale, HH system, and Fisher scale was superior to those of WFNS scale, HH system, and Fisher scale (0.912 vs. 0.813; p<0.001, 0.913 vs. 0.826; p<0.001, and 0.885 vs. 0.746; p<0.001, respectively). The calibration plots showed excellent agreement. In the external validation, the discrimination of the newly developed nomograms incorporating the three scoring systems was also good, with an AUC value of 0.809, 0.812, and 0.772, respectively.

Conclusions: We developed and externally validated new nomograms using only three independent variables. Our new nomograms were superior to the WFNS scale, HH systems, and Fisher scale in predicting prognosis and are readily available.

Keywords

Subarachnoid haemorrhage, electrocardiogram, prognosis, nomogram, emergency department

ARTICLE SUMMARY

Strengths and limitations of this study

- Our nomograms are the first to combine electrocardiogram changes and other prognostic factors in patients with subarachnoid haemorrhage.
- Our nomograms are solely based on electrocardiogram changes, age, and conventional scoring systems, which are easily and readily obtainable during the patient's course in the ED.
- Because this study is a retrospective, observational study, the predictive probability could be overestimated more than in a prospective study.

INTRODUCTION

Subarachnoid haemorrhage (SAH) is defined as haemorrhage in the subarachnoid space, and the reported incidence is 9-11 per 100,000 person years in worldwide.[1] SAH accounts for 4% of all cerebrovascular disease and develops at a relatively young age, with approximately 50% of patients experiencing disability or death.[2] Because of the high mortality and low recovery rate, predicting prognosis in patients with SAH is crucial.[1-3] Botterell et al. presented the first grading system for SAH in 1956,[4] and different systems have since been developed. The Hunt and Hess (HH) system, the World Federation of Neurosurgical Societies (WFNS) scale, and the Fisher scale have been widely used globally.[5-7] The above three systems are simple, but do not include clinically important factors, such as comorbidity, age, and vital signs on admission, and differences between the grades for each system are ambiguous. A range of scoring scales has been developed to overcome the limitations of the existing scoring scales.[5-10]

Factors such as age, past medical history (hypertension, diabetes mellitus, history of brain disease), blood pressure and initial level of consciousness on admission, and cerebral aneurysm size have been reported to be independently associated with prognosis of patients with SAH.[8 11] Electrocardiogram (ECG) abnormalities have also been studied as a prognostic factor. ECG abnormalities are observed in 40-90% of patients with SAH[12-14] and have been associated with hyperactivity of the sympathetic nervous system due to autonomic nervous system dysregulation.[15] Since the hyperactivity of the sympathetic nerve reflects the degree of cerebral haemorrhage, ECG changes may be associated with patient prognosis. The most common reported abnormalities are QT prolongation, ST segment changes, and T wave abnormalities.[15 16] A number of studies have investigated the prognostic value of ECG abnormalities.[17 18] However, the role of an abnormal ECG as a prognostic predictor remains debatable. QTc changes and ST segment changes have been reported as the parameters most significantly associated with prognosis,[17 19] although further studies reported no significant association between ECG change and outcome.[12 14 19] Because of this uncertainty, the existing system for predicting the prognosis of patients with SAH does not include ECG changes as a prognostic variable. However, ECG is an inexpensive test which is readily available in an emergency setting. Because accelerated sympathetic activity reaches its climax in the first 24 hours after the onset of SAH, ECG abnormalities develop during the early stage of disease, disappearing over time.[13]

[15] [16] Therefore, it is important to consider ECG changes as an initial prognostic factor. We conducted preliminary research to investigate the association between the abovementioned prognostic factors, including ECG changes, and prognosis of patients with SAH and found that age, ECG changes, and the three scoring systems were associated with patient prognosis.[20]

Among the computational models for predicting prognosis, the nomogram is very useful because it is a pictorial representation of a statistical predictive model that generates a numerical probability of a clinical event. It is more accurate than the conventional method using the odds ratio.[21] Therefore, the objective of this study was to develop new nomograms that can predict prognosis of patients with SAH using the results of our preliminary research and to perform external validation of the new nomograms.

MATERIALS AND METHODS

1. Study design and populations

We performed a retrospective, observational study to develop new nomograms that can predict prognosis of patients with SAH and to perform external validation of the new nomograms. This study was conducted on two independent cohorts of patients with SAH from two hospitals. We enrolled patients with SAH diagnosed by brain computed tomography (CT) scans or xanthochromia of cerebrospinal fluid in the emergency department (ED) of Severance Hospital between January 2009 and March 2015 as primary cohort. Exclusion criteria were as follows: 1) age under 19 years; 2) administration of a cardiovascular drug, such as calcium-channel blockers, with no baseline ECG; 3) cardiac arrest on arrival; and 4) traumatic SAH. Additionally, patients were excluded if they were referred from other hospitals because initial ECG could not be obtained and patients were often treated with medication affecting the cardiovascular system. Patients referred to other hospitals from the ED were also excluded as their prognosis could not be evaluated. For model external validation, 141 patients with SAH were enrolled in another ED of Gangnam Severance Hospital between January 2011 and December 2014 according to the inclusion and exclusion criteria. We collected sufficient data to score all variables in the established nomogram. The study was reviewed and approved by the Institutional Review Board of Yonsei University College of Medicine, Severance Hospital [no. 4-2015-0345]. The requirement for informed consent was waived by the ethics committee because of the retrospective nature of the study.

2. Patient and public involvement

Patients and public were not involved in the development of the research questions or in the design of the study because of its retrospective nature.

3. Data collection

One investigator (J. Y. H.) retrospectively collected the data through a review of the medical records. We

collected demographic data, vital signs on admission, and past medical history, including a history of hypertension, diabetes mellitus, and cardiovascular and cerebrovascular diseases. The Glasgow Coma Scale (GCS), HH, and WFNS scores were obtained from assessing the neurological abnormality and the level of consciousness. Patient outcome was assessed using the Glasgow Outcome Scale (GOS) and blinded to the ECG findings. The amount of blood, the location and size of cerebral aneurysm, and the presence or absence of intraventricular haemorrhage (IVH) and intracerebral haemorrhage (ICH) were determined based on CT scans reported by board-certified radiologist. ECG findings were assessed by another emergency physician blinded to patient prognosis using the Marquette Universal System of Electrocardiography® (MUSE, GE healthcare, Milwaukee, USA). Abnormal ECG findings were classified into four groups: ST elevation, ST depression, T wave inversion, and tall T wave. ST elevation was defined as ≥0.1 mV elevation in at least 2 contiguous leads other than leads V2-V3. For leads V2-V3, the following cut-off points were applied: ≥0.2 mV in men ≥40 years, ≥0.25 mV in men <40 years, or ≥0.15 mV in women. ST depression was defined as ≥0.05 mV depression in all leads. An inverted T wave was defined as less than 0.1 mV from the baseline, and a tall T wave was defined as greater than 1 mV in depth. [19] QTc was redefined and measured based on heart rate and was adjusted using Bazett's formula. The primary outcome of this study was assessed at 6 months after disease onset using GOS. We defined a poor outcome as a GOS score of 1, 2, or 3.

4. Data analysis

Statistical analysis was performed using SAS (version 9.2, SAS Inc., Cary, NC, USA) and R package (version 3.1.3, http://www.R-project.org). The sample size was calculated on the basis of the area under the receiver operating characteristic curve (AUC) of the nomogram. A difference of 0.1 between the conventional scoring system with an AUC of 0.78 and new nomogram with an AUC of 0.88 was selected as the minimum clinically significant value. We assumed that the allocation ratio of good and poor outcome group was 4.5 to 5.5. The correlation between the two predictive models was assumed to be 0.5. We estimated that a sample size of 183 patients would be sufficient to evaluate the primary outcome at a significance level of 0.05 (two-sided) with 80% power. Validation cohort was 70% of the primary cohort.

Categorical variables were described as frequencies (%). Parametric data are presented as mean (SD), and non-parametric data are presented as the median and interquartile range (IQR). We used the independent t-test for comparison of two groups distributed normally, whereas the Mann–Whitney U test was used for the comparison of two groups that were not distributed normally. Fisher's exact test was used for categorical variables. From the preliminary study, age, ECG changes (ST depression or tall T wave) and three conventional scoring systems such as WFNS scale, HH system, and Fisher scale were selected to predict prognosis in patients with SAH on the basis of the results of multivariable logistic regression using backward Wald selection. As ST depression and tall T wave formation do not occur simultaneously, they were considered one variable. The scoring systems were entered individually as continuous variables into the model with clinical variables, CT findings, and ECG abnormalities. In this study, we developed three simplified nomograms including age, ECG changes, and each scoring system and compared the predictive performance of new nomograms with those of the WFNS scale, HH system, and Fisher scale. The performance of the nomograms in predicting outcomes was validated with respect to discrimination and calibration. Nomogram predictive accuracy (discrimination) is measured via a concordance index (c-index), analogous to AUC, which quantifies the level of concordance between predicted probabilities and the actual chance of the event of interest occurring. A value of 0.5 indicates no predictive discrimination, and a value of 1.0 indicates perfect separation of patients with different outcomes. The Delong method was used to compare the C-indexes of each model. Calibration of the nomogram determines how far the predicted probabilities are from the observed outcome frequencies using graphic representations (calibration curve). A plot along the 45-degree line would indicate a perfect calibration model in which the predicted probabilities are identical to the actual outcomes. The calibration curves are presented as apparent and bias-corrected calibration plots using the bootstrapping methods with 200 resamples. The predictive accuracy and calibration of the new nomograms was then externally validated with data derived from another ED (validation set; n=141). $P<0.05$ was considered statistically significant.

RESULTS

1. Study population

A total of 665 patients with SAH were initially enrolled in the present study during the study period. Most patients (n=411; 61.8%) were excluded because they were referred from or to other hospitals. We also excluded 52 patients for the following reasons: age<19 years (n=12), no initial ECG (n=3), cardiac arrest on arrival (n=6), and SAH due to trauma (n=31). Finally, 202 patients were included in the primary analysis (Fig 1). The baseline characteristics and ECG changes related to prognosis are summarised in Table 1. Of the 202 patients, 111 (54.9%) had a good outcome with a GOS of 4 or 5.

Table 1. Clinical characteristics of study populations

	Good outcome (n=111)	Poor outcome (n=91)	Total (n=202)	p values
Age (year)	53.7 (12.3)	61.1 (13.7)	57.0 (13.4)	<0.001
Sex, male	36 (32.4%)	36 (39.6%)	72 (35.6%)	0.305
Vital signs				
Systolic blood pressure (mmHg)	154.5 (29.3)	169.6 (41.0)	154.5 (35.7)	0.003
Heart rate (/min)	80.5 (17.5)	84.7 (22.1)	82.4 (19.8)	0.137
Respiratory rate (/min)	15.5 (2.2)	16.7 (6.0)	16 (4.3)	0.072
Body temperature (℃)	36.4 (0.5)	36.3 (0.7)	36.4 (0.6)	0.123
Chronic comorbidities				
Hypertension	32 (28.8%)	43 (47.3%)	75 (37.1%)	0.007
Diabetes mellitus	7 (6.3%)	9 (9.9%)	16 (7.9%)	0.435
Cerebrovascular accident	5 (4.5%)	3 (3.3%)	8 (4.0%)	0.516
CT findings				
Aneurysmal SAH	87 (88.4%)	61 (67.0%)	148 (73.3%)	0.227
Posterior circulation aneurysm	23 (20.7%)	18 (19.8%)	41 (20.3%)	0.178
Aneurysm sizes (mm)	4.0 (3.2)	4.6 (4.9)	4.3 (4.0)	0.258
Intracerebral haemorrhage	7 (6.3%)	26 (28.6%)	33 (16.3%)	<0.001
Intraventricular haemorrhage	17 (15.3%)	41 (45.1%)	58 (28.7%)	<0.001

ECG changes					
	ST elevation	6 (5.4%)	11 (12.1%)	17 (8.4%)	0.125
	ST depression	2 (1.8%)	29 (31.9%)	31 (15.3%)	<0.001
	T wave inversion	11(9.9%)	10(11%)	21 (10.4%)	0.821
	Tall T wave	1 (1%)	9 (9.9%)	10 (5.0%)	0.006
	QTc (msec)	458.1 (39.1)	479.1 (53.0)	467.6 (46.9)	0.002
Scoring systems					
	WFNS scales	1 (1~1)	4 (2~5)	2 (1~4)	<0.001
	HH system	2 (2~2)	4 (3~5)	3 (2~4)	<0.001
	Fisher grade	3 (3~3)	4 (3~4)	3 (3~4)	<0.001

CT, computed tomography; ECG, electrocardiogram; HH, Hunt and Hess; SAH, subarachnoid haemorrhage; WFNS, World Federation of Neurosurgical Societies

2. ECG changes of patients with SAH

Of 202 patients, 79 (39.1%) had ECG changes, which included ST elevation in 17 (8.4%), ST depression in 31 (15.3%), T wave inversion in 21 (10.4%), and tall T wave in 10 (5.0%) patients. ST depression and tall T waves were detected more often in patients with a poor outcome than in those with a good outcome (29 patients (31.9%) vs. 2 patients (1.8%); p<0.001 and 9 patients (9.9%) vs. 1 patient (0.9%); p=0.006, respectively). The QTc of patients with a poor outcome was significantly longer than that of patients with a good outcome (479.1 (53.0) sec vs. 458.1 (39.1) sec; p=0.002).

3. Nomograms for the prediction of prognosis

In this study, we established three nomograms incorporating each scoring system (Fig 2). The Harrell's C-index for the new nomogram including the WFNS scale to predict prognosis of patients with SAH (0.912; 95% CI, 0.871 to 0.954) was significantly higher than that of the WFNS scale (0.813; 95% CI, 0.758 to 0.868; p<0.001). Also, the C-indexes of the two nomograms including the HH system and Fisher scale were

greater than those of the HH system and Fisher scale (0.913 (0.872-0.955) vs. 0.826(0.772-0.879); p<0.001 and 0.885(0.839-0.931) vs. 0.746(0.687-0.805); p<0.001, respectively). There was no significant difference in the predictive accuracy of the three newly established models (p=0.350). The calibration plots presented an excellent agreement between predicted and observed probabilities of the 6-month prognosis and exhibited a close approximation between the probabilities (Fig 3).

4. External validation of the nomograms

The new nomograms were externally validated using the independent dataset (Fig 1) listed in Table 2. The C-indexes of nomograms including the WFNS scale, HH systems, and Fisher scale were 0.809 (0.735-0.884), 0.812 (0.737-0.886), and 0.772 (0.691-0.852), respectively. The calibration plots presented an acceptable agreement in the external validation cohort between the nomogram prediction and actual observation (Fig 4).

Table 2. Clinical characteristics of the external validation group

	Good outcome (n=77)	Poor outcome (n=64)	Total (n=141)	p-value
Age (year)	53.2 (11.1)	59.6 (14.5)	56.2 (13.2)	0.04
ECG changes				
STD or Tall T	13 (16.9%)	33 (51.6%)	46 (32.6%)	<0.001
Scoring systems				
WFNS scales	1 (1~1)	3 (1~4)	1 (1~4)	<0.001
HH system	2 (2~2)	3 (2~4)	2 (1~4)	<0.001
Fisher grade	3 (3~3)	4 (3~4)	3 (3~4)	<0.001

ECG, electrocardiogram; STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

DISCUSSION

In this study, we developed and externally validated new nomograms using three independent variables to determine the 6-month prognosis in patients with SAH admitted to the ED. The three independent variables were age, ECG changes, including ST depression or tall T wave formation, and conventional scoring systems, such as the WFNS scale, HH systems, and Fisher scale. The new nomograms demonstrated a significantly higher predictive accuracy than conventional scoring systems.

The association between ECG changes and prognosis has been previously studied, yet the association between abnormal ECG and prognosis prediction remains controversial. We previously investigated whether the ECG could be used as to evaluate patient prognosis. The most frequent ECG change associated with SAH is QTc prolongation.[12 17 20 22] In 2012, Huang et al. investigated whether early ECG abnormalities recorded in the ED were associated with in-hospital mortality among patients with SAH. QTc prolongation was found to be independently associated with in-hospital mortality. [17] A further study also demonstrated the association between in-hospital mortality and QTc prolongation. [22] However, the underlying mechanism for this finding remains unclear. In our previous study, QTc prolongation was associated with poor prognosis and mortality (survivor vs. non-survivor; 464.9±46.4 msec vs. 486.0±47.5 msec, p=0.04). However, multivariable logistic analysis revealed that QTc prolongation was not independently associated with poor prognosis in patients with SAH.[20] Other ECG changes associated with poor prognosis in patients with SAH are ST depression and non-specific ST segment changes (NSSTC).[17] Sudden increased intracranial pressure compresses the brain triggering a sympathetic discharge. This creates a relative ischaemic state of the myocardium and causes ischaemic changes on the ECG. ST depression and NSSTC were found to be significantly associated with mortality or poor neurologic outcome.[17 22] Furthermore, the combination of tall T waves, tall P waves, large U waves, and prolonged QT has been associated with increased mortality. [23] In our study, ST depression or tall T waves were also independently associated with poor prognosis.

In addition to ECG changes, reports have suggested that other factors may be associated with prognosis among patients with SAH.[8 11 24-26] In our study, patient age was significantly associated with prognosis. Age was found to be a major independent prognostic factor in many studies.[24-26] This could be explained by the

fact that the aged brain may have less ability to recover from initial bleeding. Increased initial bleeding among aged patients also explains the poor outcomes.[24]

Classification and scoring systems to predict the prognosis of patients with SAH have been developed since 1956. The most broadly used systems are the HH system and WFNS scale.[7] The HH system, divides disease status into five grades based on patient symptoms and level of consciousness.[10] Although this system is a good reflection of patient prognosis, the demarcation between each grade is ambiguous because of less clearly defined scales of consciousness.[7] To overcome this shortcoming, the WFNS scale uses the GCS as the prognostic predictor and the neurologic deficit was added to differentiation between WFNS grades 2 and 3. However, there was occasional overlap between grades 2 and grade 3 and the predicted outcomes may not differ substantially.[27 28] To reduce the ambiguity between WFNS grades 2 and 3, a modified WFNS scale was developed.[9] However, the modified WFNS scale failed to show any significant prognostic differences between grades 3 and 4.[23]

The association between radiological findings and patient outcome has been previously reported.[7] In 1980, Fisher et al. developed a scale assigning a grade according to the pattern of blood demonstrated on the initial CT scan for the prediction of cerebral vasospasm after SAH.[6] Although it was designed to predict vasospasm, the predictive value of patient outcome has also been reported. However, the Fisher scale was designed when radiological technology resolution was only 10% of the current resolution. In the clinical context, it is uncommon for blood clots less than 1 mm in true thickness to occur in the subarachnoid space and to have no blood visible on the initial CT scan. Therefore, Fisher grades 1 and 2 were uncommon.[7]

Several advances, including the refinement of neurosurgical techniques, have taken place in SAH management since these scales were developed. Furthermore, reports found that the demarcation of the grades using these scales was ambiguous. To overcome these issues, we developed simple models by adding age and ECG changes to the existing models. The nomogram can generate an individual probability of a clinical event, such as mortality, by integrating prognostic variables.[21] With this advantage, a nomogram is being utilised to predict disease prognosis in different fields. Our nomograms used only three prognostic factors, such as existing scoring systems, age, and ECG changes. The existing scoring systems are widely

used. Age and ECG changes are easily and readily obtainable during the patient's admission at the ED.

Our nomograms were the first approach to combine ECG changes and other prognostic factors in patients with SAH. This combination approach had more accurate predictive power than those of conventional scoring system alone, and there was excellent agreement between predicted and observed probabilities of 6-month prognosis.

Our study has several limitations. First, this study was a retrospective analysis; therefore, it is possible that the results could differ from those of other centres, and the predictive probability could be overestimated more than in a prospective study. Second, we excluded patients referred from or to other hospitals, and this raises the possibility of selection bias. However, the patients were excluded because initial ECG could not be obtained or patients' prognosis could not be evaluated. Finally, interval from the onset of symptoms to arrival at the ED differs for each patient. ECG changes may not have been visible when patients presented late to the ED. We need to assess the applicability of our new nomograms in future prospective studies and validate them in a multi-centre study.

CONCLUSIONS

We developed new nomograms using only three independent variables: ECG changes including ST depression or tall T wave formation, age, and widely used conventional scoring systems, such as the WFNS scale, HH systems, and Fisher scale. Our new nomograms are valuable in predicting the 6-month prognosis of patients with SAH at an early stage after ED admission. Our new models are superior to the WFNS scale, HH systems, and Fisher scale in predicting prognosis and are readily available.

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COMPETING INTERESTS

The authors declare that they have no competing interest.

CONTRIBUTORSHIP STATEMENT

YSP designed this study with JYH, IP, and SPC. JYH, JSY, and MJK contributed to the data acquisition. HSL and YSP performed the data analysis. JYH and YSP drafted this manuscript, and all other authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board of our hospital [no. 4-2015-0345]. Written informed consent was waived by the ethics committee.

DATA SHARING

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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FIGURE LEGENDS

Figure 1. Flow diagram of the study subjects. ED, emergency department; ECG, electrocardiogram

Figure 2. The newly developed nomograms. Nomograms for predicting 6-month prognosis among patients with subarachnoid haemorrhage incorporating World Federation of Neurosurgical Societies scale (A), Hunt and Hess system (B), and Fisher scale (C). The predicted probability (1/(1+exp(-A))) of each nomogram is as follows: predicted probability = 1/(1+exp(-A)), A) where A = -6.4930 + 0.0666 * age + 1.0802 * WFNS grade + 3.0820 * STD or tall T, B) where A = -8.4664 + 0.0671 * age + 1.5685 * HH grade + 2.8352 * STD or tall T, C) where A = -9.4180 + 0.0557 * age + 1.6794 * Fisher grade + 3.6150 * STD or tall T. By calculating the total number of points and locating it on the total point scale, we can easily draw a straight line down to estimate the predicted prognosis. For example, if a 50-year-old patient had ST depression on initial ECG with a WFNS score of 3, a final score of 160 could be attained as the sum of each corresponding score (39 points for age, 50 points for WFNS 3, and 71 points for ST depression) and the predicted probability of poor prognosis was 95.9%. STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

Figure 3. Performance of the nomograms incorporating the World Federation of Neurosurgical Societies scale (A), Hunt and Hess system (B), and Fisher scale (C).
Receiver operating characteristic (ROC) curves of the nomograms are on the top line. The discrimination ability of the newly developed nomograms was good, with an AUC value of 0.912 (95% CI, 0.871 to 0.954), 0.913 (95% CI, 0.872-0.955), and 0.885 (95% CI, 0.839-0.931), respectively. The calibration curves are on the bottom line. All calibration plots (dotted lines) show close approximation to the logistic calibration (solid lines), indicating excellent agreement between the predicted and observed probabilities of the 6-month prognosis. STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

Figure 4. External validation of the nomograms incorporating the World Federation of Neurosurgical

Societies scale (A), Hunt and Hess system (B), and Fisher scale (C). Receiver operating characteristic (ROC) curves of the nomograms are on the top line. The discrimination ability of newly developed nomograms was good, with an AUC value of 0.809 (95% CI, 0.735-0.884), 0.812 (95% CI, 0.737-0.886), and 0.772 (95% CI. 0.691-0.852), respectively. The calibration curves are on the bottom line. The calibration plots presented good agreement between the nomogram prediction and actual observation. STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess; AUC, area under the curve; CI, confidence interval.

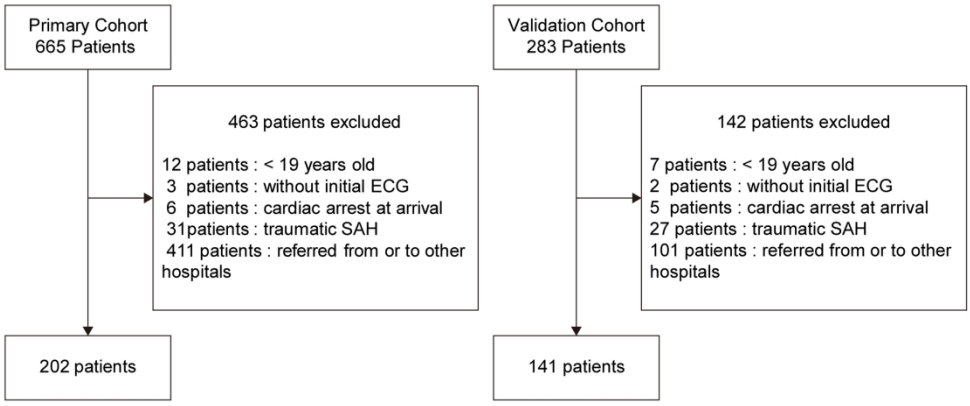

Figure 1. Flow diagram of the study subjects/ ED, emergency department; ECG, electrocardiogram

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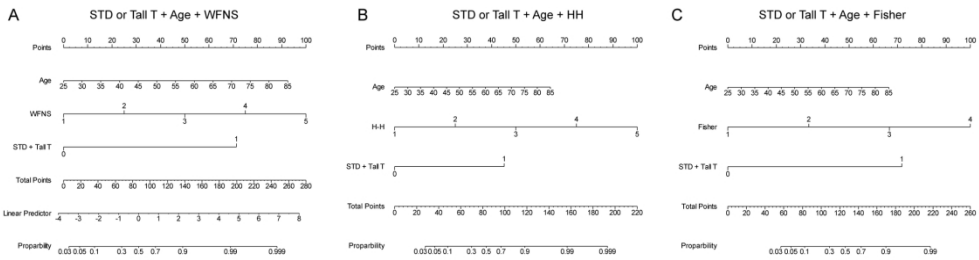

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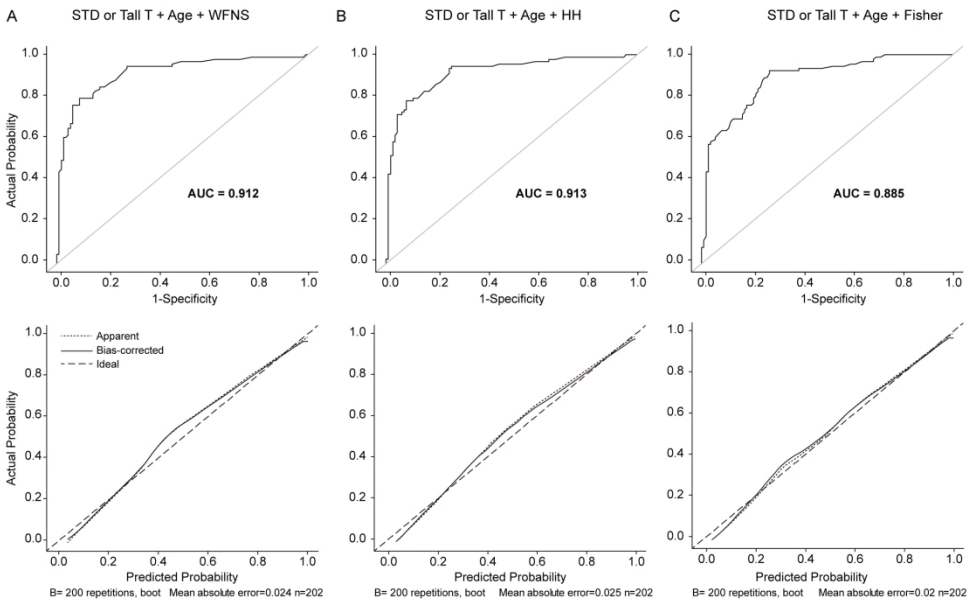

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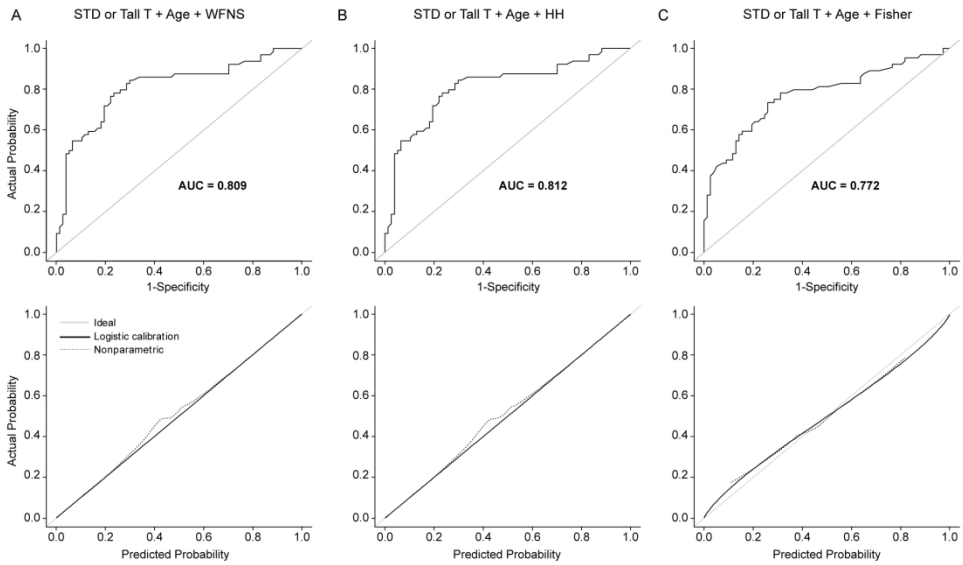

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209x125mm (300 x 300 DPI)

Reporting checklist for prediction model development and validation study.

Based on the TRIPOD guidelines.

		Reporting Item	Page Number
Title	#1	Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	#2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction	#3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4
	#3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	5
Source of data	#4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	#4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6,7
Participants	#5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	#5b	Describe eligibility criteria for participants.	6
	#5c	Give details of treatments received, if relevant	N/A

		The aim of this study was to identify the relationship between initial status and final prognosis and did not consider intermediate treatment.	
Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7
	#6b	Report any actions to blind assessment of the outcome to be predicted.	7
Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured	7,8
	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	7
Sample size	#8	Explain how the study size was arrived at.	7
Missing data	#9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. We excluded patients referred from other hospitals because the initial ECG could not be obtained. We also excluded the patients without initial ECG. However, there were no missing data because all variables used were collected in usual practice.	9 Figure 1
Statistical analysis methods	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.	8
	#10b	If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	8
	#10c	If you are validating a prediction model, describe how the predictions were calculated.	8
	#10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8
	#10e	If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done	8,11

Risk groups	#11	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	#12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors	9,11
Participants	#13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	9 Figure1
	#13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	9 Table1
	#13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	11 Table2
Model development	#14a	If developing a model, specify the number of participants and outcome events in each analysis.	9
	#14b	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	10,11
Model specification	#15a	If developing a model, present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Figure 2 foot print
	#15b	If developing a prediction model, explain how to the use it.	Figure 2 foot print
Model performance	#16	Report performance measures (with CIs) for the prediction model.	11
Model-updating	#17	If validating a model, report the results from any model updating, if done (i.e., model specification, model performance).	N/A
Limitations	#18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	15

Interpretation	#19a	For validation, discuss the results with reference to performance in the development data, and any other validation data	Figure 1 table2
	#19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	13,14,15
Implications	#20	Discuss the potential clinical use of the model and implications for future research	15
Supplementary information	#21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	N/A
Funding	#22	Give the source of funding and the role of the funders for the present study.	N/A

BMJ Open

Development and external validation of new nomograms by adding electrocardiogram changes (ST depression or tall T wave) and age to conventional scoring systems to improve the predictive capacity in patients with subarachnoid haemorrhage: a retrospective, observational study in Korea

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Secondary Subject Heading:	Neurology
Keywords:	Subarachnoid haemorrhage, electrocardiogram, prognosis, nomogram, emergency department

Development and external validation of new nomograms by adding electrocardiogram changes (ST depression or tall T wave) and age to conventional scoring systems to improve the predictive capacity in patients with subarachnoid haemorrhage: a retrospective, observational study in Korea

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Word count: 5,116 words

ABSTRACT

Objectives: To develop new nomograms by adding electrocardiogram changes (ST depression or tall T wave) and age to three conventional scoring systems, namely, World Federation of Neurosurgical Societies (WFNS) scale, Hunt and Hess (HH) system, and Fisher scale, that can predict prognosis in patients with subarachnoid haemorrhage (SAH) using our preliminary research results and to perform external validation of the three new nomograms.

Design: Retrospective, observational study

Setting: Emergency departments (ED) of two universities affiliated tertiary hospital between January 2009 and March 2015

Participants: Adult patients with SAH were enrolled. Exclusion criteria were age<19 years, no baseline electrocardiogram, cardiac arrest on arrival, traumatic SAH, referral from other hospital and referral to other hospitals from the ED.

Primary outcome measures: The 6-month prognosis was assessed using the Glasgow Outcome Scale (GOS). We defined a poor outcome as a GOS score of 1, 2, or 3.

Results: A total of 202 patients were included for analysis. From the preliminary study, age, electrocardiogram changes (ST depression or tall T wave), and three conventional scoring systems were selected to predict prognosis in patients with SAH using multivariable logistic regression. We developed simplified nomograms using these variables. Discrimination of the developed nomograms including WFNS scale, HH system, and Fisher scale was superior to those of WFNS scale, HH system, and Fisher scale (0.912 vs. 0.813; p<0.001, 0.913 vs. 0.826; p<0.001, and 0.885 vs. 0.746; p<0.001, respectively). The calibration plots showed excellent agreement. In the external validation, the discrimination of the newly developed nomograms incorporating the three scoring systems was also good, with an AUC value of 0.809, 0.812, and 0.772, respectively.

Conclusions: We developed and externally validated new nomograms using only three independent variables. Our new nomograms were superior to the WFNS scale, HH systems, and Fisher scale in predicting prognosis and are readily available.

Keywords: electrocardiogram, emergency department, nomogram, prognosis, subarachnoid haemorrhage

ARTICLE SUMMARY

Strengths and limitations of this study

- Our nomograms are the first to combine electrocardiogram changes and other prognostic factors in patients with subarachnoid haemorrhage.
- Our nomogramsare solely based on electrocardiogram changes, age, and conventional scoring systems, which are easily and readily obtainable during the patient's course in the ED.
- Because this study is a retrospective, observational study, the predictive probability could be overestimated more than in a prospective study.

INTRODUCTION

Subarachnoid haemorrhage (SAH) is defined as haemorrhage in the subarachnoid space, and the reported incidence is 9-11 per 100,000 person years in worldwide.[1] SAH accounts for 4% of all cerebrovascular disease and develops at a relatively young age, with approximately 50% of patients experiencing disability or death.[2] Because of the high mortality and low recovery rate, predicting prognosis in patients with SAH is crucial.[1-3] Botterell et al. presented the first grading system for SAH in 1956,[4] and different systems have since been developed. The Hunt and Hess (HH) system, the World Federation of Neurosurgical Societies (WFNS) scale, and the Fisher scale have been widely used globally.[5-7] The above three systems are simple, but do not include clinically important factors, such as comorbidity, age, and vital signs on admission, and differences between the grades for each system are ambiguous. A range of scoring scales has been developed to overcome the limitations of the existing scoring scales.[5-10]

Factors such as age, past medical history (hypertension, diabetes mellitus, history of brain disease), blood pressure and initial level of consciousness on admission, and cerebral aneurysm size have been reported to be independently associated with prognosis of patients with SAH.[8 11] Electrocardiogram (ECG) abnormalities have also been studied as a prognostic factor. ECG abnormalities are observed in 40%-90% of patients with SAH[12-14] and have been associated with hyperactivity of the sympathetic nervous system due to autonomic nervous system dysregulation.[15] Since the hyperactivity of the sympathetic nerve reflects the degree of cerebral haemorrhage, ECG changes may be associated with patient prognosis. The most common reported abnormalities are QT prolongation, ST segment changes, and T wave abnormalities.[15 16] A number of studies have investigated the prognostic value of ECG abnormalities.[17 18] However, the role of an abnormal ECG as a prognostic predictor remains debatable. QTc changes and ST segment changes have been reported as the parameters most significantly associated with prognosis,[17 19] although further studies reported no significant association between ECG change and outcome.[12 14 19] Because of this uncertainty, the existing system for predicting the prognosis of patients with SAH does not include ECG changes as a prognostic variable. However, ECG is an inexpensive test which is readily available in an emergency setting. Because accelerated sympathetic activity reaches its climax in the first 24 hours after the onset of SAH, ECG abnormalities develop during the early stage of disease,

disappearing over time.[13 15 16] Therefore, it is important to consider ECG changes as an initial prognostic factor. We conducted preliminary research to investigate the association between the above mentioned prognostic factors, including ECG changes, and prognosis of patients with SAH and found that age, ECG changes, and the three scoring systems were associated with patient prognosis.[20]

Among the computational models for predicting prognosis, the nomogram is very useful because it is a pictorial representation of a statistical predictive model that generates a numerical probability of a clinical event. It is more accurate than the conventional method using odds ratio.[21] Therefore, the objective of this study was to develop new nomograms that can predict prognosis of patients with SAH using the results of our preliminary research and to perform external validation of the new nomograms.

MATERIALS AND METHODS

1. Study design and populations

We performed a retrospective, observational study to develop new nomograms that can predict prognosis of patients with SAH and to perform external validation of the new nomograms. This study was conducted on two independent cohorts of patients with SAH from two hospitals. We enrolled patients with SAH diagnosed by brain computed tomography (CT) or xanthochromia of the cerebrospinal fluid in the emergency department (ED) of Severance Hospital between January 2009 and March 2015 as primary cohort. Exclusion criteria were as follows: 1) age under 19 years; 2) administration of a cardiovascular drug, such as calcium-channel blockers, with no baseline ECG; 3) cardiac arrest on arrival; and 4) traumatic SAH. Additionally, patients were excluded if they were referred from other hospitals because initial ECG could not be obtained and patients were often treated with medication affecting the cardiovascular system. Patients referred to other hospitals from the ED were also excluded as their prognosis could not be evaluated. For model external validation, 141 patients with SAH were enrolled in another ED of Gangnam Severance Hospital between January 2011 and December 2014 according to the inclusion and exclusion criteria. We collected sufficient data to score all variables in the established nomogram. The study was reviewed and approved by the Institutional Review Board of Yonsei University College of Medicine, Severance Hospital [no. 4-2015-0345]. The requirement for informed consent was waived by the ethics committee because of the retrospective nature of the study.

2. Patient and public involvement

Patients and public were not involved in the development of the research questions or in the design of the study because of its retrospective nature.

3. Data collection

One investigator (J. Y. H.) retrospectively collected the data through a review of the medical records. We collected demographic data, vital signs on admission, and past medical history, including a history

of hypertension, diabetes mellitus, and cardiovascular and cerebrovascular diseases. The Glasgow Coma Scale (GCS), HH, and WFNS scores were obtained from assessing the neurological abnormality and the level of consciousness. Patient outcome was assessed using the Glasgow Outcome Scale (GOS) by one emergency physician blinded to the ECG findings. The amount of blood, the location and size of cerebral aneurysm, and the presence or absence of intraventricular haemorrhage (IVH) and intracerebral haemorrhage (ICH) were determined based on CT scans reported by board-certified radiologist. ECG findings were assessed by another emergency physician blinded to patient prognosis using the Marquette Universal System of Electrocardiography® (MUSE, GE Healthcare, Milwaukee, USA). Abnormal ECG findings were classified into four groups: ST elevation, ST depression, T wave inversion, and tall T wave. ST elevation was defined as ≥0.1 mV elevation in at least two contiguous leads other than leads V2-V3. For leads V2-V3, the following cut-off points were applied: ≥0.2 mV in men ≥40 years, ≥0.25 mV in men <40 years, or ≥0.15 mV in women. ST depression was defined as ≥0.05 mV depression in all leads. An inverted T wave was defined as less than 0.1 mV from the baseline, and a tall T wave was defined as greater than 1 mV in depth. [19] QTc was redefined and measured based on heart rate and was adjusted using Bazett's formula. There were no missing data except initial ECG because all variables used were collected in usual practice. The primary outcome of this study was assessed at 6 months after disease onset using GOS. We defined a poor outcome as a GOS score of 1, 2, or 3.

4. Data analysis

Statistical analysis was performed using SAS (version 9.2, SAS Inc., Cary, NC, USA) and R package (version 3.1.3, http://www.R-project.org). The sample size was calculated on the basis of the area under the receiver operating characteristic curve (AUC) of the nomogram. A difference of 0.1 between the conventional scoring system with an AUC of 0.78 and new nomogram with an AUC of 0.88 was selected as the minimum clinically significant value. We assumed that the allocation ratio of good and poor outcome group was 4.5 to 5.5. The correlation between the two predictive models was assumed to be 0.5. We estimated that a sample size of 183 patients would be sufficient to evaluate the primary outcome at a significance level of 0.05 (two-sided) with 80% power. The sample size of the external validation cohort was determined to be about 70% of the sample size of the primary cohort.

Categorical variables were described as frequencies (%). Parametric data are presented as mean (SD), and non-parametric data are presented as the median and interquartile range (IQR). We used the independent t-test for comparison of two groups distributed normally, whereas the Mann–Whitney U test was used for the comparison of two groups that were not distributed normally. Fisher's exact test was used for categorical variables. From the preliminary study, age, ECG changes (ST depression or tall T wave) and three conventional scoring systems such as WFNS scale, HH system, and Fisher scale were selected to predict prognosis in patients with SAH on the basis of the results of multivariable logistic regression using backward Wald selection. As ST depression and tall T wave formation do not occur simultaneously, they were considered one variable. The scoring systems were entered individually as continuous variables into the model with clinical variables, CT findings, and ECG abnormalities. In this study, we developed three simplified nomograms including age, ECG changes, and each scoring system and compared the predictive performance of new nomograms with those of the WFNS scale, HH system, and Fisher scale. The performance of the nomograms in predicting outcomes was validated with respect to discrimination and calibration. Nomogram predictive accuracy (discrimination) is measured via a concordance index (c-index), analogous to AUC, which quantifies the level of concordance between predicted probabilities and the actual chance of the event of interest occurring. A value of 0.5 indicates no predictive discrimination, and a value of 1.0 indicates perfect separation of patients with different outcomes. The Delong method was used to compare the C-indexes of each model. Calibration of the nomogram determines how far the predicted probabilities are from the observed outcome frequencies using graphic representations (calibration curve). A plot along the 45-degree line would indicate a perfect calibration model in which the predicted probabilities are identical to the actual outcomes. The calibration curves are presented as apparent and bias-corrected calibration plots using the bootstrapping methods with 200 resamples. The predictive accuracy and calibration of the new nomograms were then externally validated with data derived from another ED (validation set; n=141). $P<0.05$ was considered statistically significant.

RESULTS

1. Study population

A total of 665 patients with SAH were initially enrolled in the present study during the study period. Most patients (n=411; 61.8%) were excluded because they were referred from or to other hospitals. We also excluded 52 patients for the following reasons: age <19 years (n=12), no initial ECG (n=3), cardiac arrest on arrival (n=6), and SAH due to trauma (n=31). Finally, 202 patients were included in the primary analysis (Fig 1). The baseline characteristics and ECG changes related to prognosis are summarised in Table 1. Of the 202 patients, 111 (54.9%) had a good outcome with a GOS of 4 or 5.

Table 1. Clinical characteristics of study populations

	Good outcome (n=111)	Poor outcome (n=91)	Total (n=202)	p values
Age (year)	53.7 (12.3)	61.1 (13.7)	57.0 (13.4)	<0.001
Sex, male	36(32.4%)	36(39.6%)	72(35.6%)	0.305
Vital signs				
Systolic blood pressure (mmHg)	154.5 (29.3)	169.6 (41.0)	154.5 (35.7)	0.003
Heart rate(/min)	80.5 (17.5)	84.7 (22.1)	82.4 (19.8)	0.137
Respiratory rate(/min)	15.5 (2.2)	16.7 (6.0)	16 (4.3)	0.072
Body temperature (℃)	36.4 (0.5)	36.3 (0.7)	36.4 (0.6)	0.123
Chronic comorbidities				
Hypertension	32(28.8%)	43(47.3%)	75(37.1%)	0.007
Diabetes mellitus	7(6.3%)	9(9.9%)	16(7.9%)	0.435
Cerebrovascular accident	5(4.5%)	3(3.3%)	8(4.0%)	0.516
CT findings				
Aneurysmal SAH	87 (88.4%)	61(67.0%)	148(73.3%)	0.227
Posterior circulation aneurysm	23(20.7%)	18(19.8%)	41(20.3%)	0.178
Aneurysm sizes (mm)	4.0 (3.2)	4.6 (4.9)	4.3 (4.0)	0.258
Intracerebral haemorrhage	7(6.3%)	26(28.6%)	33(16.3%)	<0.001
Intraventricular haemorrhage	17(15.3%)	41(45.1%)	58(28.7%)	<0.001
ECG changes				
ST elevation	6 (5.4%)	11 (12.1%)	17 (8.4%)	0.125

ST depression	2 (1.8%)	29 (31.9%)	31 (15.3%)	<0.001
T wave inversion	11(9.9%)	10(11%)	21 (10.4%)	0.821
Tall T wave	1 (1%)	9 (9.9%)	10 (5.0%)	0.006
QTc (msec)	458.1 (39.1)	479.1 (53.0)	467.6 (46.9)	0.002
Scoring systems*				
WFNS scales	1 (1~1)	4 (2~5)	2 (1~4)	<0.001
HH system	2 (2~2)	4 (3~5)	3 (2~4)	<0.001
Fisher grade	3 (3~3)	4 (3~4)	3 (3~4)	<0.001

Data are presented as frequencies (%) or mean (standard deviation), unless otherwise indicated.

*median (interquartile range).

CT, computed tomography; ECG, electrocardiogram; HH, Hunt and Hess; SAH, subarachnoid haemorrhage; WFNS, World Federation of Neurosurgical Societies

2. ECG changes of patients with SAH

Of 202 patients, 79 (39.1%) had ECG changes, which included ST elevation in 17 (8.4%), ST depression in 31 (15.3%), T wave inversion in 21 (10.4%), and tall T wave in 10 (5.0%) patients. ST depression and tall T waves were detected more often in patients with a poor outcome than in those with a good outcome (29 patients (31.9%) vs. 2 patients (1.8%); p<0.001 and 9 patients (9.9%) vs. 1 patient (0.9%); p=0.006, respectively).The QTc of patients with a poor outcome was significantly longer than that of patients with a good outcome (479.1 (53.0) sec vs. 458.1 (39.1) sec; p=0.002).

3. Nomograms for the prediction of prognosis

In this study, we established three nomograms incorporating each scoring system (Fig 2).The Harrell's C-index for the new nomogram including the WFNS scale to predict prognosis of patients with SAH (0.912; 95% CI, 0.871 to 0.954) was significantly higher than that of the WFNS scale (0.813; 95% CI, 0.758 to 0.868; p<0.001). In addition, the C-indexes of the two nomograms including the HH system and Fisher scale were greater than those of the HH system and Fisher scale (0.913 (0.872-0.955) vs. 0.826(0.772-0.879); p<0.001 and 0.885(0.839-0.931) vs. 0.746(0.687-0.805); p<0.001,

respectively). There was no significant difference in the predictive accuracy of the three newly established models (p=0.350). The calibration plots presented an excellent agreement between predicted and observed probabilities of the 6-month prognosis and exhibited a close approximation between the probabilities (Fig 3).

4. External validation of the nomograms

The new nomograms were externally validated using the independent dataset (Fig 1) listed in Table 2. The C-indexes of nomograms including the WFNS scale, HH systems, and Fisher scale were 0.809 (0.735-0.884), 0.812 (0.737-0.886), and 0.772 (0.691-0.852), respectively. The calibration plots presented an acceptable agreement in the external validation cohort between the nomogram prediction and actual observation (Fig 4).

Table 2. Clinical characteristics of the external validation group

	Good outcome (n=77)	Poor outcome (n=64)	Total (n=141)	p-value
Age (year)	53.2 (11.1)	59.6 (14.5)	56.2 (13.2)	0.04
ECG changes				
STD or Tall T	13 (16.9%)	33 (51.6%)	46 (32.6%)	<0.001
Scoring systems*				
WFNS scales	1 (1~1)	3 (1~4)	1 (1~4)	<0.001
HH system	2 (2~2)	3 (2~4)	2 (1~4)	<0.001
Fisher grade	3 (3~3)	4 (3~4)	3 (3~4)	<0.001

Data are presented as frequencies (%) or mean (standard deviation), unless otherwise indicated.

*median (interquartile range).

ECG, electrocardiogram; STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

DISCUSSION

In this study, we developed and externally validated new nomograms using three independent variables to determine the 6-month prognosis in patients with SAH admitted to the ED. The three independent variables were age, ECG changes, including ST depression or tall T wave formation, and conventional scoring systems, such as the WFNS scale, HH systems, and Fisher scale. The new nomograms demonstrated a significantly higher predictive accuracy than conventional scoring systems.

The association between ECG changes and prognosis has been previously studied; however the association between abnormal ECG and prognosis prediction remains controversial. We previously investigated whether the ECG could be used to evaluate patient prognosis. The most frequent ECG change associated with SAH is QTc prolongation.[12 17 20 22] In 2012, Huang et al. investigated whether early ECG abnormalities recorded in the ED were associated with in-hospital mortality among patients with SAH. QTc prolongation was found to be independently associated with in-hospital mortality. [17] Another study also demonstrated the association between in-hospital mortality and QTc prolongation. [22] However, the underlying mechanism for this finding remains unclear. In our previous study, QTc prolongation was associated with poor prognosis and mortality (survivor vs. non-survivor; 464.9±46.4 msec vs. 486.0±47.5 msec, p=0.04). However, multivariable logistic analysis revealed that QTc prolongation was not independently associated with poor prognosis in patients with SAH.[20] Other ECG changes associated with poor prognosis in patients with SAH are ST depression and non-specific ST segment changes (NSSTC).[17] Sudden increased in intracranial pressure compresses the brain triggering a sympathetic discharge. This creates a relative ischaemic state of the myocardium and causes ischaemic changes on the ECG. ST depression and NSSTC were found to be significantly associated with mortality or poor neurologic outcome.[17 22] Furthermore, the combination of tall T waves, tall P waves, large U waves, and prolonged QT has been associated with increased mortality. [23] In our study, ST depression or tall T waves were also independently associated with poor prognosis.

In addition to ECG changes, reports have suggested that other factors may be associated with prognosis among patients with SAH.[8 11 24-26] In our study, patient age was significantly associated with prognosis. Age was found to be a major independent prognostic factor in many studies.[24-26] This could

be explained by the fact that the aged brain may have less ability to recover from initial bleeding. Increased initial bleeding among aged patients also explains the poor outcomes.[24]

Classification and scoring systems to predict the prognosis of patients with SAH have been developed since 1956. The most broadly used systems are the HH system and WFNS scale.[7] The HH system divides disease status into five grades based on patient symptoms and level of consciousness.[10] Although this system is a good reflection of patient prognosis, the demarcation between each grade is ambiguous because of less clearly defined scales of consciousness.[7] To overcome this shortcoming, the WFNS scale uses the GCS as the prognostic predictor and the neurologic deficit was added to the differentiation between WFNS grades 2 and 3. However, there was occasional overlap between grades 2 and 3 and the predicted outcomes may not differ substantially.[27 28] To reduce the ambiguity between WFNS grades 2 and 3, a modified WFNS scale was developed.[9] However, the modified WFNS scale failed to show any significant prognostic differences between grades 3 and 4.[23]

The association between radiological findings and patient outcome has been previously reported.[7] In 1980, Fisher et al. developed a scale assigning a grade according to the pattern of blood demonstrated on the initial CT scan for the prediction of cerebral vasospasm after SAH.[6] Although it was designed to predict vasospasm, the predictive value of patient outcome has also been reported. However, the Fisher scale was designed when radiological technology resolution was only 10% of the current resolution. In the clinical context, it is uncommon for blood clots less than 1 mm in true thickness to occur in the subarachnoid space and to have no blood visible on the initial CT scan. Therefore, Fisher grades 1 and 2 were uncommon.[7]

Several advances,including the refinement of neurosurgical techniques, have taken place in SAH management since these scales were developed. Furthermore, reports found that the demarcation of the grades using these scales was ambiguous. To overcome these issues, we developed simple models by adding age and ECG changes to the existing models. The nomogram can generate an individual probability of a clinical event, such as mortality, by integrating prognostic variables.[21] With this advantage, a nomogram is being utilised to predict disease prognosis in different fields. Our nomograms used only three prognostic factors, such as existing scoring systems, age, and ECG changes. The existing scoring systems are widely used. Age and ECG changes are easily and readily

obtainable during the patient's admission at the ED. Our nomograms were the first approach to combine ECG changes and other prognostic factors in patients with SAH. This combination approach had more accurate predictive power than those of conventional scoring system alone, and there was excellent agreement between predicted and observed probabilities of 6-month prognosis.

Our study has several limitations. First, this study was a retrospective analysis; therefore, the results could differ from those of other centres, and the predictive probability could be overestimated more than in a prospective study. Second, we excluded patients referred from or to other hospitals, and this raises the possibility of selection bias. However, the patients were excluded because initial ECG could not be obtained or patients' prognosis could not be evaluated. Finally, interval from the onset of symptoms to arrival at the ED differs for each patient. ECG changes may not have been visible when patients presented late to the ED. We need to assess the applicability of our new nomograms in future prospective studies and validate them in a multi-centre study.

CONCLUSIONS

We developed new nomograms using only three independent variables: ECG changes including ST depression or tall T wave formation, age, and widely used conventional scoring systems, such as the WFNS scale, HH systems, and Fisher scale. Our new nomograms are valuable in predicting the 6-month prognosis of patients with SAH at an early stage after ED admission. Our new models are superior to the WFNS scale, HH systems, and Fisher scale in predicting prognosis and are readily available.

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COMPETING INTERESTS

The authors declare that they have no competing interest.

CONTRIBUTORSHIP STATEMENT

YSP designed this study with JYH, IP, and SPC. JYH, JSY, and MJK contributed to the data acquisition. HSL and YSP performed the data analysis. JYH and YSP drafted this manuscript, and all other authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board of our hospital [no. 4-2015-0345]. Written informed consent was waived by the ethics committee.

DATA SHARING

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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FIGURE LEGENDS

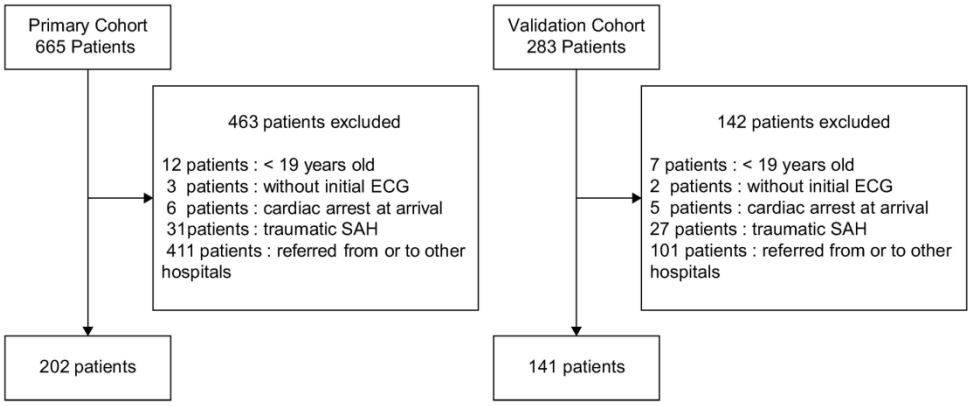
Figure 1. Flow diagram of the study subjects. ED, emergency department; ECG, electrocardiogram

Figure 2. The newly developed nomograms. Nomograms for predicting 6-month prognosis among patients with subarachnoid haemorrhage incorporating World Federation of Neurosurgical Societies scale (A), Hunt and Hess system (B), and Fisher scale (C). The predicted probability (1/(1+exp(-A))) of each nomogram is as follows: predicted probability = 1/(1+exp(-A)), A) where A = -6.4930 + 0.0666 * age + 1.0802 * WFNS grade + 3.0820 * STD or tall T, B) where A = -8.4664 + 0.0671 * age + 1.5685 * HH grade + 2.8352 * STD or tall T, C) where A = -9.4180 + 0.0557 * age + 1.6794 * Fisher grade + 3.6150 * STD or tall T. By calculating the total number of points and locating it on the total point scale, we can easily draw a straight line down to estimate the predicted prognosis. For example, if a 50-year-old patient had ST depression on initial ECG with a WFNS score of 3, a final score of 160 could be attained as the sum of each corresponding score (39 points for age, 50 points for WFNS 3, and 71 points for ST depression) and the predicted probability of poor prognosis was 95.9%. STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

Figure 3. Performance of the nomograms incorporating the World Federation of Neurosurgical Societies scale (A), Hunt and Hess system (B), and Fisher scale (C).
Receiver operating characteristic (ROC) curves of the nomograms are on the top line. The discrimination ability of the newly developed nomograms was good, with an AUC value of 0.912 (95% CI, 0.871 to 0.954), 0.913 (95% CI, 0.872-0.955), and 0.885 (95% CI, 0.839-0.931), respectively. The calibration curves are on the bottom line. All calibration plots (dotted lines) show close approximation to the logistic calibration (solid lines), indicating excellent agreement between the predicted and observed probabilities of the 6-month prognosis. STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

Figure 4. External validation of the nomograms incorporating the World Federation of

Neurosurgical Societies scale (A), Hunt and Hess system (B), and Fisher scale (C). Receiver operating characteristic (ROC) curves of the nomograms are on the top line. The discrimination ability of newly developed nomograms was good, with an AUC value of 0.809 (95% CI, 0.735-0.884), 0.812 (95% CI, 0.737-0.886), and 0.772 (95% CI. 0.691-0.852), respectively. The calibration curves are on the bottom line. The calibration plots presented good agreement between the nomogram prediction and actual observation. AUC, area under the curve; CI, confidence interval; HH, Hunt and Hess; STD, ST depression; WFNS, World Federation of Neurosurgical Societies



Flow diagram of the study subjects./ ED, emergency department; ECG, electrocardiogram

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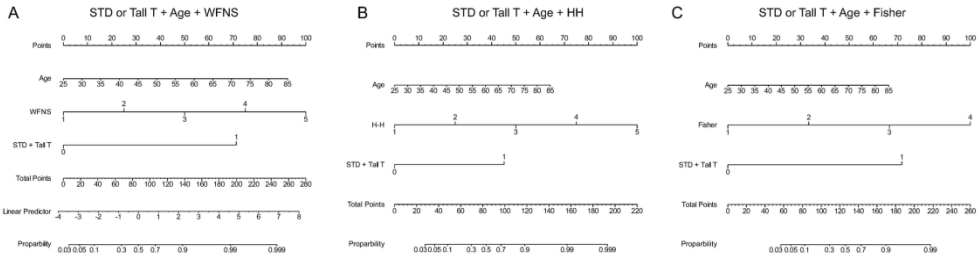
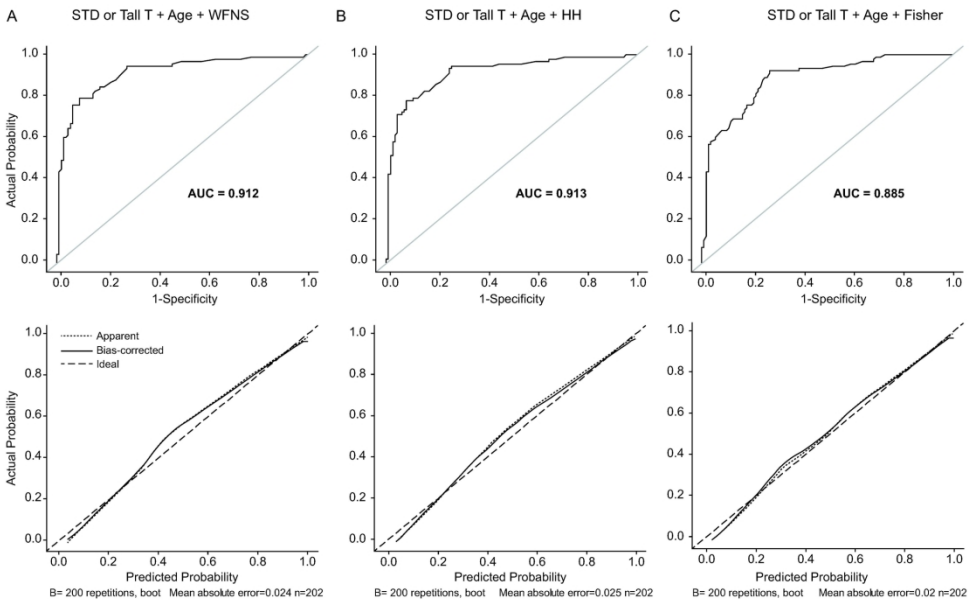


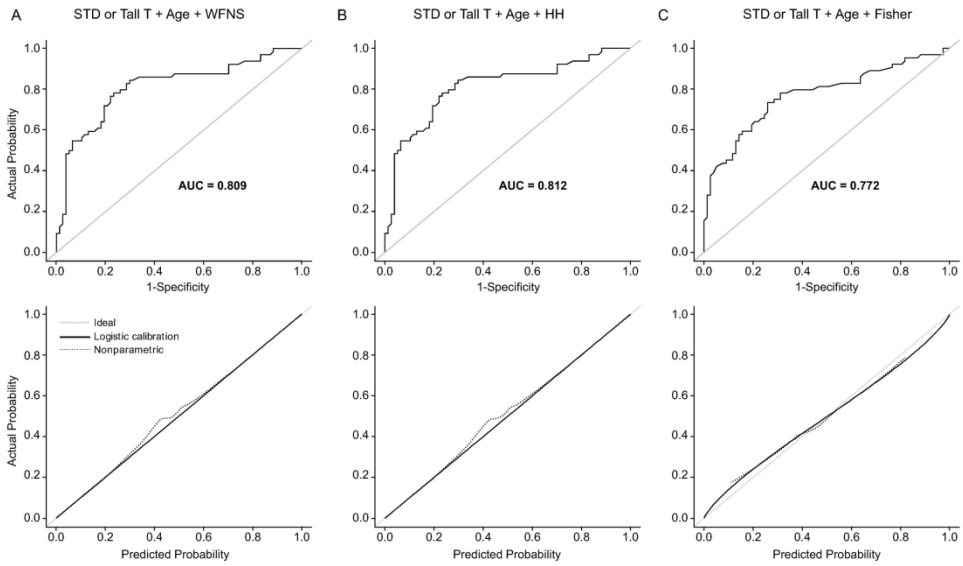
The newly developed nomograms./ Nomograms for predicting 6-month prognosis among patients with subarachnoid haemorrhage incorporating World Federation of Neurosurgical Societies scale (A), Hunt and Hess system (B), and Fisher scale (C). The predicted probability (1/(1+exp(-A))) of each nomogram is as follows: predicted probability = 1/(1+exp(-A)), A) where A = -6.4930 + 0.0666 * age + 1.0802 * WFNS grade + 3.0820 * STD or tall T, B) where A = -8.4664 + 0.0671 * age + 1.5685 * HH grade + 2.8352 * STD or tall T, C) where A = -9.4180 + 0.0557 * age + 1.6794 * Fisher grade + 3.6150 * STD or tall T. By calculating the total number of points and locating it on the total point scale, we can easily draw a straight line down to estimate the predicted prognosis. For example, if a 50-year-old patient had ST depression on initial ECG with a WFNS score of 3, a final score of 160 could be attained as the sum of each corresponding score (39 points for age, 50 points for WFNS 3, and 71 points for ST depression) and the predicted probability of poor prognosis was 95.9%. STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

195x53mm (300 x 300 DPI)



Performance of the nomograms incorporating the World Federation of Neurosurgical Societies scale (A), Hunt and Hess system (B), and Fisher scale (C)./
Receiver operating characteristic (ROC) curves of the nomograms are on the top line. The discrimination ability of the newly developed nomograms was good, with an AUC value of 0.912 (95% CI, 0.871 to 0.954), 0.913 (95% CI, 0.872-0.955), and 0.885 (95% CI, 0.839-0.931), respectively. The calibration curves are on the bottom line. All calibration plots (dotted lines) show close approximation to the logistic calibration (solid lines), indicating excellent agreement between the predicted and observed probabilities of the 6-month prognosis. STD, ST depression; WFNS, World Federation of Neurosurgical Societies; HH, Hunt and Hess.

202x125mm (300 x 300 DPI)



External validation of the nomograms incorporating the World Federation of Neurosurgical Societies scale (A), Hunt and Hess system (B), and Fisher scale (C)./ Receiver operating characteristic (ROC) curves of the nomograms are on the top line. The discrimination ability of newly developed nomograms was good, with an AUC value of 0.809 (95% CI, 0.735-0.884), 0.812 (95% CI, 0.737-0.886), and 0.772 (95% CI. 0.691-0.852), respectively. The calibration curves are on the bottom line. The calibration plots presented good agreement between the nomogram prediction and actual observation. AUC, area under the curve; CI, confidence interval; HH, Hunt and Hess; STD, ST depression; WFNS, World Federation of Neurosurgical Societies

209x125mm (300 x 300 DPI)

Reporting checklist for prediction model development and validation study.

Based on the TRIPOD guidelines.

		Reporting Item	Page Number
Title	#1	Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	#2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction	#3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4
	#3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	5
Source of data	#4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	#4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6,7
Participants	#5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	#5b	Describe eligibility criteria for participants.	6
	#5c	Give details of treatments received, if relevant	N/A

		The aim of this study was to identify the relationship between initial status and final prognosis and did not consider intermediate treatment.	
Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7
	#6b	Report any actions to blind assessment of the outcome to be predicted.	7
Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured	7,8
	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	7
Sample size	#8	Explain how the study size was arrived at.	7
Missing data	#9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	9 Figure 1
		We excluded patients referred from other hospitals because the initial ECG could not be obtained. We also excluded the patients without initial ECG. However, there were no missing data because all variables used were collected in usual practice.	
Statistical analysis methods	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.	8
	#10b	If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	8
	#10c	If you are validating a prediction model, describe how the predictions were calculated.	8
	#10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8
	#10e	If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done	8,11

Risk groups	#11	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	#12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors	9,11
Participants	#13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	9 Figure1
	#13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	9 Table1
	#13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	11 Table2
Model development	#14a	If developing a model, specify the number of participants and outcome events in each analysis.	9
	#14b	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	10,11
Model specification	#15a	If developing a model, present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Figure 2 foot print
	#15b	If developing a prediction model, explain how to the use it.	Figure 2 foot print
Model performance	#16	Report performance measures (with CIs) for the prediction model.	11
Model-updating	#17	If validating a model, report the results from any model updating, if done (i.e., model specification, model performance).	N/A
Limitations	#18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	15

Interpretation	#19a	For validation, discuss the results with reference to performance in the development data, and any other validation data	Figure 1 table2
	#19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	13,14,15
Implications	#20	Discuss the potential clinical use of the model and implications for future research	15
Supplementary information	#21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	N/A
Funding	#22	Give the source of funding and the role of the funders for the present study.	N/A