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Development and external validation of new nomograms by adding ECG 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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ABSTRACT

Objectives To develop new nomograms by adding ECG 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 university-affiliated tertiary hospital between January 2009 and March 2015.

Participants Adult patients with SAH were enrolled. Exclusion criteria were age <19 years, no baseline ECG, 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, ECG changes (ST depression or tall T wave), and three conventional scoring systems were selected to predict prognosis in patients with SAH using multi-variable 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 area under the receiver-operating characteristic curve value of 0.809, 0.812 and 0.772, respectively.

Strengths and limitations of this study

► Our nomograms are the first to combine ECG changes and other prognostic factors in patients with subarachnoid haemorrhage.
► Our nomograms are solely based on ECG 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.

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.

INTRODUCTION

Subarachnoid haemorrhage (SAH) is defined as haemorrhage in the subarachnoid space, and the reported incidence is 9–11 per 100 000 person years worldwide.[1] SAH accounts for 4% of all cerebrovascular diseases 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] These 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] 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 that 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 OR.[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
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 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 less than 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 in accordance with the inclusion and exclusion criteria. We collected
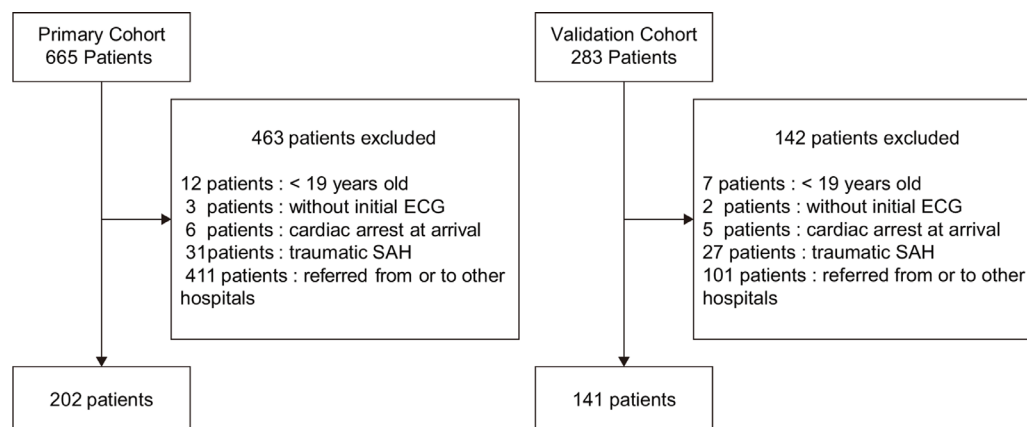
Figure 1 Flow diagram of the study subjects. ED, emergency department.

Table 1 Clinical characteristics of study populations

	Good outcome (n=111)	Poor outcome (n=91)	Total (n=202)	P value
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 (mm Hg)	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 (SD), unless otherwise indicated.
*median (IQR).
HH, Hunt and Hess; SAH, subarachnoid haemorrhage; WFNS, World Federation of Neurosurgical Societies.

sufficient data to score all variables in the established nomogram.

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.

Data collection

One investigator (J.YH) 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 and intracerebral haemorrhage 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
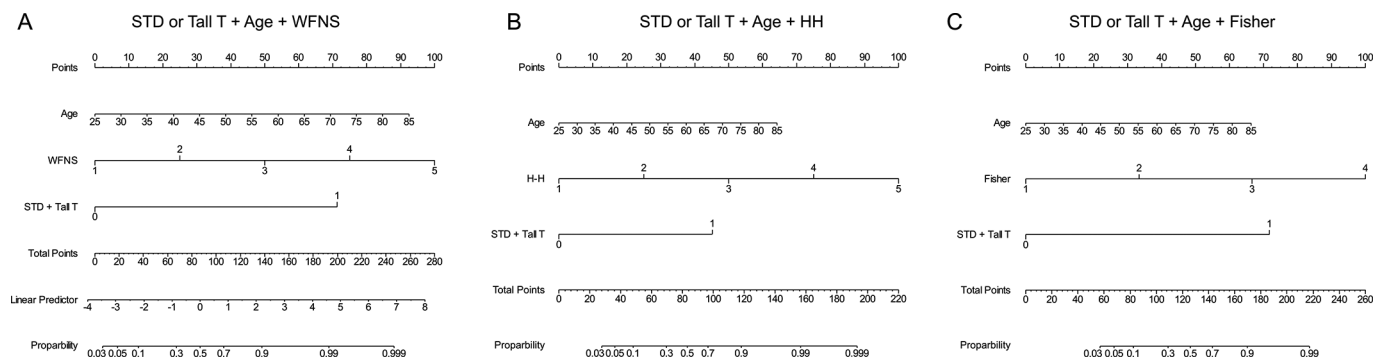
Figure 2 The newly developed nomograms. Nomograms for predicting 6 month prognosis among patients with subarachnoid haemorrhage incorporating World Federation of Neurosurgical Societies (WFNS) scale (A), Hunt and Hess (HH) system (B) and Fisher scale (C). The predicted probability (1/ (1+exp(-A))) of 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.

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.

Data analysis

Statistical analysis was performed using SAS (V.9.2) and R package (V.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 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 multi-variable 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 re-samples. The predictive accuracy and calibration of the new nomograms were then externally validated with data derived from another ED (validation set; n=141). A value of p<0.05 was considered statistically significant.
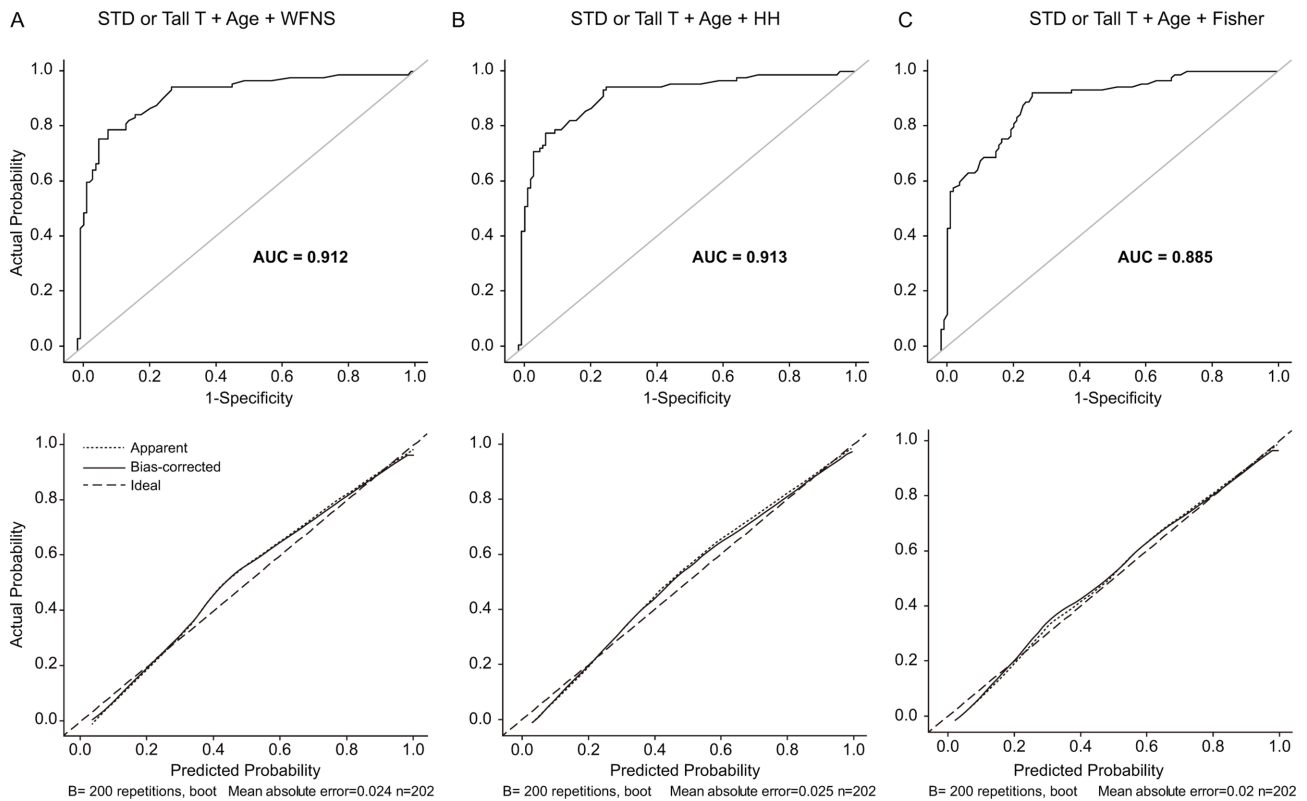
Figure 3 Performance of the nomograms incorporating the World Federation of Neurosurgical Societies scale (A), Hunt and Hess system (B) and Fisher scale (C). Receiver-operating characteristic curves of the nomograms are on the top line. The discrimination ability of the newly developed nomograms was good, with an area under the receiver-operating characteristic curve (AUC) value of 0.912 (95% CI, 0.871 to 0.954), 0.913 (95% CI, 0.872 to 0.955) and 0.885 (95% CI, 0.839 to 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. HH, Hunt and Hess; STD, ST depression; WFNS, World Federation of Neurosurgical Societies.

RESULTS

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 (figure 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.

ECG changes of patients with SAH

Of the 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 two patients (1.8%); p<0.001 and 9 patients (9.9%) vs. one 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) s vs 458.1 (39.1) s; p=0.002).

Nomograms for the prediction of prognosis

In this study, we established three nomograms incorporating each scoring system (figure 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 to 0.955) vs 0.826 (0.772 to 0.879); p<0.001 and 0.885 (0.839 to 0.931) vs 0.746 (0.687 to 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 (figure 3).

External validation of the nomograms

The new nomograms were externally validated using the independent dataset (figure 1) listed in table 2. The

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 (SD), unless otherwise indicated.
*Median (IQR).
HH, Hunt and Hess; STD, ST depression; WFNS, World Federation of Neurosurgical Societies.

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 (figure 4).

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.
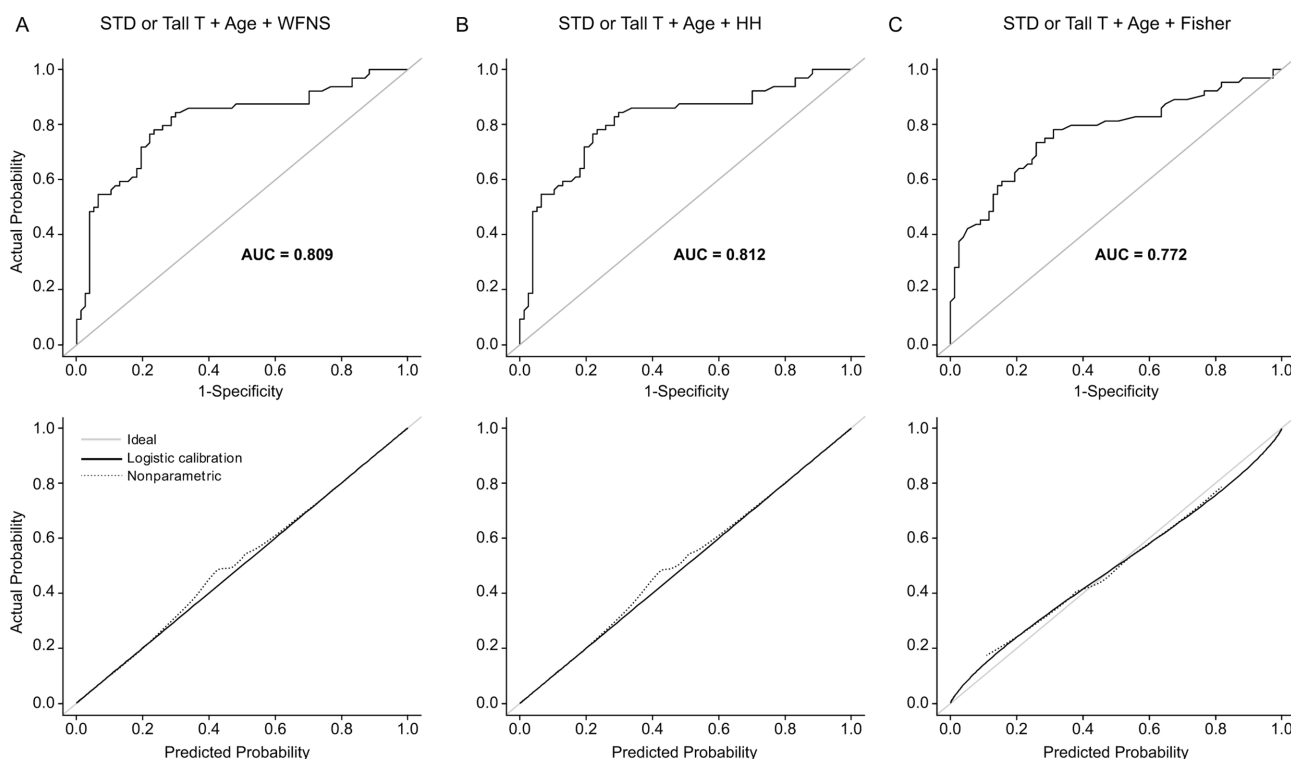
Figure 4 External validation of the nomograms incorporating the World Federation of Neurosurgical Societies (WFNS) scale (A), Hunt and Hess system (HH) (B) and Fisher scale (C). Receiver operating characteristic curves of the nomograms are on the top line. The discrimination ability of newly developed nomograms was good, with an area under receiver-operating characteristic curve (AUC) value of 0.809 (95% CI, 0.735 to 0.884), 0.812 (95% CI, 0.737 to 0.886), and 0.772 (95% CI. 0.691 to 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.

non-survivor; 464.9±46.4 ms vs. 486.0±47.5 ms, p=0.04). However, multi-variable 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] A sudden increase 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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