Development and validation of a novel nomogram to predict aneurysm rupture in patients with multiple intracranial aneurysms: a multicentre retrospective study

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ABSTRACT
Background and purpose Approximately 15%–45% of patients with unruptured intracranial aneurysms have multiple intracranial aneurysms (MIAs). Determining which one is most likely to rupture is extremely important for treatment decision making for MIAs patients. This study aimed to develop and validate a nomogram to evaluate the per-aneurysm rupture risk of MIAs patients.

Methods A total of 1671 IAs from 700 patients with MIAs were randomly dichotomised into derivation and validation sets. Multivariate logistic regression analysis was used to select predictors and construct a nomogram model for aneurysm rupture risk assessment in the derivation set. The discriminative accuracy, calibration performance and clinical usefulness of this nomogram were assessed. We also developed a multivariate model for a subgroup of 158 subarachnoid haemorrhage (SAH) patients and compared its performance with the nomogram model.

Results Multivariate analyses identified seven variables that were significantly associated with IA rupture (history of SAH, alcohol consumption, female sex, aspect ratio >1.5, posterior circulation, irregular shape and bifurcation location). The clinical and morphological-based MIAs (CMB-MIAs) nomogram model showed good calibration and discrimination (derivation set: area under the curve (AUC)=0.740 validation set: AUC=0.772). Decision curve analysis demonstrated that the nomogram was clinically useful. Compared with the nomogram model, the AUC of multivariate model developed from SAH patients had lower value of 0.730.

Conclusions This CMB-MIAs nomogram for MIAs rupture risk is the first to be developed and validated in a large multi-institutional cohort. This nomogram could be used in decision-making and risk stratification in MIAs patients.

INTRODUCTION
Multiple intracranial aneurysms (MIAs) are encountered in approximately 15%–45% of patients with intracranial aneurysms (IAs). The Japanese ‘small unruptured IA verification study’ found that patients with MIAs are at a higher risk of IA growth and rupture. Compared with single IA cases, MIAs were also found to be associated with unfavourable outcomes after rupture. In addition, patient counselling in the elective setting is very challenging because good models for specifically predicting subarachnoid haemorrhage (SAH) in these patients are lacking; instead, information is extrapolated from varied data sets including patients with both single IA and MIAs. Moreover, the treatment strategy for patients with MIAs is typically complex and is driven by evaluation of rupture risks of each IA (particularly when considering endovascular management). Therefore, to prevent the catastrophic consequences of IA rupture, it is clinically important to identify and prophylactically treat the IA that is most likely to rupture.

Several studies characterised ruptured IAs in SAH patients with MIAs, and found that the aspect ratio (AR), irregular shape, size and size ratio (SR) could identify the ruptured IA. However, those studies only included MIAs patients with SAH and not those without. Although those studies may aid in identifying responsible IAs in these patients with SAH, they may not be adequately helpful in treatment decision making of MIAs patients without SAH, that is, whether to treat or manage conservatively and to identify the IA that should be treated. This may be attributed to the fact that decision making requires comprehensive consideration of the characteristics of both patients and IAs.

Significant demographic, clinical and morphological (CMB) differences are found between patients with single IA and MIAs, indicating that the underlying pathogenesis of MIAs may differ from that of single IA. Given the lack of analyses of large data samples, the true relevance of potential MIAs predictors remains unknown, and the existing...
scoring system is not suitable for these patients. One of
the most popular models for predicting the IA rupture
risk, the Population, Hypertension, Age, Size, Earlier
SAH and Site (PHASES) score, was developed using 8382
participants from six prospective cohort studies to predict
patient’s risk of IA rupture.11 However, the PHASES score
only used the characteristics of the largest IA when eval-
uating MIAs patients, and data of other coexisting IA(s)
were ignored. In addition, previous studies showed that
one-quarter of the largest IAs did not rupture in patients
with SAH and MIAs.12 Thus, it is necessary to develop
a new method for assessing the rupture risk of each IA
among MIAs patients to improve clinical decision making,
especially in patients without SAH.

In this study, we aimed to identify the independent risk
factors for IA rupture in a large multi-institutional cohort
of MIAs patients. We also aimed to develop and validate
a nomogram model for rupture risk assessment of each IA,
and evaluate its clinical usefulness in aiding clinical deci-
dion making and improving ongoing treatment efforts.

METHODS

Study population

We retrospectively obtained data regarding cerebro-
vascular images and medical records from a consecu-
tive series of patients with at least two saccular IAs from
three centres (Beijing Tiantan Hospital, Beijing Hospital
and Peking University International Hospital) in China
between September 2015 and December 2018. Aneu-
rysms were divided into ruptured and unruptured groups
depending on whether they were ruptured at admission.
In patients with SAH, we only included those in whom
the responsible IA could be identified; they included:
(1) patients who underwent treatment by clipping in
whom the ruptured IA was confirmed through micro-
scopic visual assessment and (2) patients who under-
went either endovascular or no treatment; in these cases,
we included only those with a definitive haemorrhage
pattern on computed tomographic images (localised to
one IA). Examples of definitive haemorrhage patterns are
provided in online supplemental figure S1. Patients with
fusiform or dissecting IAs, other cerebrovascular diseases,
IAs previously treated at other neurological centres, and
incomplete clinical and imaging data were excluded.

Clinical presentation

Data were collected regarding the following: age, sex, pres-
ence of hypertension (yes/no; diagnosed by the general
practitioner before admission and requiring medical
treatment), smoking, both current and previous (pre-
viously smoked regularly and quit at least 1 year before
admission), alcohol consumption (yes/no; current or
previous intake ≥5 drinks per day),12 presence of cardi-
ovascular disease (yes/no; angina pectoris, myocardial
infarction or peripheral vascular disease), and previous
stroke (yes/no; transient ischaemic attack or stroke).

MIAs morphology

All patients in this study had digital subtraction angiog-
raphy (DSA) images and three-dimensional (3D) recon-
structions. All DSA angiograms and 3D reconstructions
of the 1671 IAs were re-evaluated and measured by two
researchers on a 0.1 mm scale; they were supervised by
two senior neurointerventionists with 15 years of expe-
rience (online supplemental figure S2). The AR (dome
height/neck width), SR (maximum IA height/average
of the parent diameter), and bottleneck factors (dome
width/neck width) were calculated. IAs were categorised
as regular or irregular (with multiple lobes, daughter sacs
or other types of wall protrusions). The inflow angle was
defined as the angle from the parent artery into the IA,
and the outflow angle was defined as that at which the
IA flowed outward to the distal parent artery. The main
branching angle was defined as the angle of the parent
artery (in case of a sidewall IA) or that between the parent
artery and the daughter branch most approaching 180°
in (case of a bifurcation IA).5 All the associated angles
were measured on a 1° scale (online supplemental figure
S2). For bifurcation IAs, the branching to parent ratio
was defined as the ratio of the sum of the diameters of
the branch vessels to the diameter of the parent artery
(in case of a sidewall IA, the branching to parent ratio was set
to 1). The neck to parent ratio was defined as the ratio of
the neck width to the parent artery diameter.

Statistical analyses

Continuous and categorical variables of patients’ baseline
characteristics have been presented as means±SD and
percentages, respectively. The 1671 IAs were randomly
divided into two subsets with similar event rates, namely,
the derivation subset (1171/1671, 70%) and the valida-
tion subset (500/1671, 30%). Mean imputation was
used with low missing data; 20 factors with complete data
(gender, age, SAH history, number of IAs, hypertension,
diabetes, hypercholesterolaemia, heart diseases, history
of stroke, smoking, drinking, size, neck, AR, branching
to parent ratio, neck to parent ratio, SR, posterior circu-
lation (PC, basilar tip, basilar-superior cerebellar artery,
vertebral artery-posterior inferior cerebellar artery, or
vertebrobasilar junction), irregular shape and bifur-
cation location) and three factors with less than 10%
missing data (inflow angle (missing 31/1671, 1.9%),
outflow angle (missing 31/1671, 1.9%) and branching
angle (missing 35/1671, 2.1%)) were included in this
study. Both, complete case and imputed data set analyses
showed similar results.

Development and validation of the nomogram

Multivariate logistic regression analysis was performed
for per-aneurysm rupture risk in MIAs patients using a
forward stepwise method that included all variables with
a p<0.20 on univariate analysis. After logistic regression
analysis and risk factor calculation, we ranked nomogram
variables using their p values and effect values to generate
the nomogram model. Collinearity of combinations of
variables in the derivation set was evaluated by variation inflation factors (VIF, with values < 2 being considered non-significant). Overall performance was determined using the Brier score, ranging from 0 (excellent prediction) to 1 (worst prediction). Nomogram discrimination was assessed using the C-statistic to calculate sensitivity and specificity for prediction at each cut-off point. The C-statistic represents the area under the receiver operating characteristic curve (AUC); values of 0.5 and 1.0 indicate no and perfect ability to discriminate between patients with or without IAs, respectively. Calibration was assessed using the Hosmer-Lemeshow test and calibration curves. The decision curve analysis (DCA) was then used to determine the clinical net benefit associated with the use of the novel model in comparison to the unadjusted logistic models of other independent risk factors. The reference of DCA was calculated by treating all IAs, while treating none was set as zero-net benefit. For any given probability threshold, the risk model with the greater net benefit would be the preferred model.

In the present study, we also developed a multivariate model for a subgroup of 400 MIAs in 158 SAH patients, and compared its performance in discrimination and calibration based on all 1671 IAs in 700 patients; p < 0.05 was considered statistically significant. All calculations were performed using SPSS V.25.0 and R software packages. The major R software packages used in this study are shown in online supplemental table S1.

RESULTS
Study population
The database review from September 2015 to December 2018 in three centres identified 782 consecutive MIAs patients. After exclusion, a total of 1671 IAs were analysed from 700 consecutive patients with MIAs (1171 IAs in the derivation set and 500 IAs in the validation set). The flowchart of this study is shown in online supplemental figure S3. The baseline characteristics and univariable analysis results between the ruptured and unruptured groups of 1671 MIAs are summarised in online supplemental table S2. The characteristics of the patients and IAs in the derivation and validation cohorts have been compared in online supplemental table S3. No significant differences were noted between the derivation and validation sets. For all 1671 MIAs, the proportions of ruptured IAs were 8.9%, 10.8% and 9.5% in the derivation set, validation set, and entire cohort, respectively.

Univariate and multivariate analyses
The results of univariate analysis are shown in table 1. The following variables were significant in the derivation cohort: a history of SAH, size, AR, branching and neck to parent ratio, SR, PC, irregular shape, bifurcation location, inflow angle and branching angle. The results of univariate analysis for 158 SAH patients with 400 MIAs are shown in online supplemental table S4.

Multivariable logistic regression including all 1671 MIAs revealed that seven variables: SAH history (OR, 5.094; 95% CI 2.848 to 8.929; p < 0.001), alcohol consumption (OR, 2.022; 95% CI 1.016 to 3.920; p < 0.04), female sex (OR 1.856; 95% CI 1.053 to 3.395; p = 0.038), AR > 1.5 (OR 2.375; 95% CI 1.507 to 3.698; p < 0.001), PC (OR 2.772; 95% CI 1.561 to 4.460; p < 0.001), irregular shape (OR 1.883; 95% CI 1.225 to 2.897; p < 0.004) and bifurcation location (OR 1.762; 95% CI 1.118 to 2.745; p = 0.013) were significantly associated with MIAs rupture risk (table 2).

When the probability of IA rupture generated by the nomogram was between 0.10 and 0.65, DCA revealed that the CMB-MIAs nomogram conferred more benefit than either the treat-all or treat-none strategy in the validation and derivation groups (figure 3).

DISCUSSION
We developed and validated an evaluation tool based on 1671 MIAs from a multicentre database to evaluate
rupture risks of individual IAs in patients with MIAs. Our CMB-MIAs nomogram comprised seven readily available independent risk factors of IA rupture. The categorical variables by order of decreasing multivariate predictive effect were: SAH history, PC, AR >1.5, alcohol consumption, irregular shape, female sex and bifurcation location.

To the best of our knowledge, this study is the first to attempt to establish a reliable nomogram for evaluating rupture risks of each IA in MIAs patients to improve informed decision making.

The presence of MIAs represents a greater risk than that of a single IA due to the higher complication rate.
associated with both IA rupture and treatment, which may involve complex management issues.\textsuperscript{13} \textsuperscript{14} The management of MIAs remains particularly challenging owing to variations in anatomical distribution, difficulties in determining IAs at higher risk of rupture and poor overall outcomes in cases of SAH.\textsuperscript{15} The treat-all or treat-none strategies can be ineffective or expensive. Thus, it is essential to identify IAs that are most likely to rupture.\textsuperscript{16} \textsuperscript{17}

Major efforts have been made to stratify IAs based on rupture risk assessment. The most widely used methods include morphological analysis,\textsuperscript{4} \textsuperscript{18} clinical factor assessment\textsuperscript{1} \textsuperscript{19} and scoring systems,\textsuperscript{11} \textsuperscript{20} \textsuperscript{21} which are mainly based on clinical risk factors and morphological features. However, the existing scoring system is not suitable for MIAs. Although the PHASES\textsuperscript{11} and Earlier SAH, Location, Age, Population, Size, Shape\textsuperscript{21} scores are almost identical in terms of predictors, both use characteristics of the largest IA to categorise MIAs patients\textsuperscript{21} and may, therefore, be unsuitable for comparing coexisting IAs. For cases with MIAs, the unruptured IA treatment score\textsuperscript{20} evaluates each IA separately; however, most of the study population comprised patients with single IA. There are already some prediction models for evaluating the risk of rupture in those with IAs, including MIAs. Tominari \textit{et al} built a prediction model for 3-year rupture risk of IAs in Japanese patients, by including 6606 IAs in 5651 patients.\textsuperscript{22} They also considered each IA as a unit of analysis; in this

\begin{table}[h]
\centering
\caption{Multivariate analysis of all 1671 multiple aneurysms in 700 patients and 400 multiple aneurysms in 158 patients who presented with SAH}
\begin{tabular}{lcccc}
\hline
 & OR (95\% CI) & P value & VIF & OR (95\% CI) & P value & VIF \\
\hline
SAH history & 5.094 (2.848 to 8.929) & <0.001 & 1.026 & AR > 1.55 & 2.449 (1.302 to 4.641) & 0.006 & 1.218 \\
Irregular shape & 1.883 (1.225 to 2.897) & 0.004 & 1.025 & Irregular shape & 1.886 (1.070 to 3.336) & 0.028 & 1.120 \\
Alcohol use & 2.022 (1.016 to 3.920) & 0.040 & 1.400 & Neck > 4 mm & 1.994 (1.015 to 3.944) & 0.046 & 1.307 \\
Female & 1.852 (1.053 to 3.395) & 0.038 & 1.419 & PC & 2.522 (1.156 to 5.667) & 0.022 & 1.007 \\
AR > 1.5 & 2.371 (1.507 to 3.698) & <0.001 & 1.021 & Size & Ref & Ref \\
Bifurcation location & 1.762 (1.118 to 2.745) & 0.013 & 1.026 & <3 mm & Ref & Ref \\
PC & 2.722 (1.561 to 4.460) & <0.001 & 1.028 & 3 to 7 mm & 1.494 (0.738 to 3.093) & 0.270 & 1.617 \\
& & & & >7 mm & 3.240 (1.090 to 10.114) & 0.038 & 1.803 \\
\hline
\end{tabular}
\footnote{Model one was developed by all 1671 multiple aneurysms in patients with or without SAH; model 2 was developed by 400 multiple aneurysms in 158 patients with SAH. }\footnote{AR, aspect ratio; PC, posterior circulation; SAH, subarachnoid haemorrhage; VIF, variation inflation factors.}
\end{table}

Figure 1 Distribution of survey respondents by country, region, occupation and by hospital context. AR, aspect ratio; AUC, area under the curve; PC, posterior circulation; SAH, subarachnoid haemorrhage.

Figure 2 Calibration curves of the CMB-MIAs nomogram in the derivation (A) and validation (B) set. The predicted probabilities and the actual observed probability of aneurysm rupture were divided into ten groups to create a bar chart for in the derivation (C) and validation (D) set. CMB, clinical and morphological; MIA, multiple intracranial aneurysms.
In the study, we applied this score to evaluate the rupture risk of 1671 MIAs. The results showed that the AUC of their model for the 1671 MIAs in this cohort was 0.577; this was worse than that of our model (AUC=0.753). This may be attributed to the fact that although the study included a large sample of IAs, only 13.7% of derivation data and 12.7% of validation data were from MIAs patients; therefore, their model may be more suitable for single IA patients. In addition, this study may have selection bias. Some unruptured IAs with a high risk of rupture were treated and not included in the follow-up cohort. This necessitates the development of a prediction model specific for MIAs.

To date, several studies have focused on identifying risk factors for MIAs rupture. However, the populations were limited to MIAs patients with SAH, and the variables analysed were limited to IA morphological characteristics. These studies mainly intended to accurately identify ruptured IAs in SAH patients with MIAs. As we pooled individual patient data from three larger centres in China, we were able to analyse clinical risk factors and morphological features of IAs in MIAs patients with or without SAH; we were also able to calculate the absolute risks of individual IA rupture. In addition, we developed a multivariate model for SAH patients with MIAs (model 2). In this model, the AUC in the derivation and validation groups were 0.739 and 0.717, respectively; these results were worse than those of the model including all MIAs patients.

Risk scores are more reliable if they include already well-established risk factors for IA rupture. Most risk factors included in our model are known to cause IA rupture; these included the following: history of SAH, female sex, alcohol consumption, bifurcation location, location of PC, AR and IA shape. DCA evaluates whether a model is useful in clinical decisions and identifies the model leading to the best decision. In the present study, when the threshold probabilities were between 10% and 65%, DCA showed that the nomogram was more beneficial than either the treat-all or treat-none strategy (figure 3). These results indicate the clinical benefits of using the CMB-MIAs nomogram.
We found that IA size and number, and smoking status were not associated with IA rupture when other risk factors were considered. This does not imply that these factors are not important for MIAs rupture in isolation; it indicates that these factors were not significantly associated with IA rupture in addition to the seven predictors used. Aneurysm size was ranked the most important risk factor; physicians widely accept that larger IAs are more dangerous than smaller ones. However, a large cohort study of patients with IA SAH and MIAs revealed that the largest IA had not ruptured in 36 (29%) of 124 MIAs patients. Interestingly, for SAH patients with MIAs, IA size was significantly associated with IA rupture; the risk of IA rupture increased with size in the range of 3–15 mm, (online supplemental figure S5A). This suggests that IA size may help identify ruptured IAs in SAH patients; however, this is not necessarily applicable to all MIAs patients, and especially in those with IAs with irregular shapes (online supplemental figure S6). A previous study revealed that in MIAs patients, each IA is not associated with an increased risk of rupture; however, these patients are subject to the cumulative risk from all individual IAs. Similarly, we found that the IA number is not associated with an increased risk of rupture. In addition, compared with patients with three or more IAs, those with two IAs demonstrated more ruptures (online supplemental figure S5B). Regarding smoking status, we only had data regarding the time of IA detection, and not for the intensity and duration of smoking or passive smoking. The association between smoking and MIA rupture requires further in-depth research, with more detailed questionnaires or prospective studies. We found that hypertension was not a significant factor on univariate analysis in both, derivation and validation cohorts. However, statistical differences were observed between ruptured and unruptured groups in the entire cohort. This may be explained by the fact that the results of randomisation caused a slight change in the distribution of this subgroup. However, we believe that this will not significantly impact the results of multivariate because factors with p<0.2 have been incorporated into the multivariate analysis. The SR, in/outflow angle, branching angle, and neck width are widely used morphological indexes for IA stratification. Nevertheless, these factors were not significantly associated with IA rupture in our study.

Strengths and limitations of the present study

An important strength of this study is that it included a large number of MIAs patients with high-quality angiograms; this adequate sample number enabled the development of a multivariable prediction model for MIAs. Second, the inclusion of patients from three different centres improved the validity of our results. Third, the risk factors included in our prediction model are easy to retrieve from outpatient clinics; this will improve its utility in daily clinical practice.

Nevertheless, our study also has certain limitations. First, the retrospective nature of our study inevitably introduced bias, which may have affected our analysis. Prospective multicentre validation is needed to acquire high-level evidence for further clinical application. Second, although our nomogram exhibited favourable discriminatory and calibration ability regarding predictive value and net benefit in the derivation and validation cohort, it should be noted that our model was developed using data from patients treated at Chinese institutions. Thus, caution is needed when generalising our results to other countries and ethnicities. Third, our study did not include other factors that may be associated with aneurysm rupture, such as blood pressure levels, family histories and imaging indicators such as haemodynamic analysis and vascular wall enhancement on MRI. Fourth, morphological measurements may change during and after rupture. A large-scale prospective cohort study including unruptured MIAs is needed to investigate the CMB risk factors of both unruptured IAs that eventually rupture and those that do not. Finally, we excluded patients with MIAs in whom the ruptured IA could not be identified; this may have caused selection bias.

CONCLUSIONS

Using a large multicentre cohort, we first devised and validated a nomogram, that is simple to use, for clinically evaluating the per-aneurysm rupture risk of patients with MIAs. Data on the seven independent factors included this nomogram are easy to obtain; these include: SAH history, alcohol consumption, sex, AR >1.5, PC, irregular shape and bifurcation location. With favourable calibration and discrimination, this nomogram may be useful for decision making and risk stratification in patients with MIAs.

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Contributors DW and AL conceived and designed the study. FP, HN, YZ and WJ collected the data. PO, JL, YZ and ZW were responsible for quality control. XF and XT conceived of the project, analysed the data and wrote the paper. All authors helped organised and carried out the research. All authors read and approved the final manuscript.

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Data availability statement Some or all data, models or code generated or used during the study are available from the corresponding author by request.

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