Stability of unruptured intracranial aneurysms in the anterior circulation: nomogram models for risk assessment

Qingyuan Liu, MD,1,2 Xinyi Leng, PhD,4 Junhua Yang, MD,1,2 Yi Yang, MD,1,2 Pengjun Jiang, MD,1,2 Maogui Li, MD,1,2 Shaohua Mo, MD,1,2 Shuzhe Yang, MD,1,2 Jun Wu, MD,1 Hongwei He, MD,3 and Shuo Wang, MD1,2

1Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing; 2China National Clinical Research Center for Neurological Diseases, Beijing; 3Department of Neurointervention, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; and 4Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China

OBJECTIVE The probable stability of the lesion is critical in guiding treatment decisions in unruptured intracranial aneurysms (IAs). The authors aimed to develop multidimensional predictive models for the stability of unruptured IAs.

METHODS Patients with unruptured IAs in the anterior circulation were prospectively enrolled and regularly followed up. Clinical data were collected, IA morphological features were assessed, and adjacent hemodynamic features were quantified with patient-specific computational fluid dynamics modeling. Based on multivariate logistic regression analyses, nomograms incorporating these factors were developed in a primary cohort (patients enrolled between January 2017 and February 2018) to predict aneurysm rupture or growth within 2 years. The predictive accuracies of the nomograms were compared with the population, hypertension, age, size, earlier rupture, and site (PHASES) and earlier subarachnoid hemorrhage, location, age, population, size, and shape (ELAPSS) scores and validated in the validation cohort (patients enrolled between March and October 2018).

RESULTS Among 231 patients with 272 unruptured IAs in the primary cohort, hypertension, aneurysm location, irregular shape, size ratio, normalized wall shear stress average, and relative resident time were independently related to the 2-year stability of unruptured IAs. The nomogram including clinical, morphological, and hemodynamic features (C+M+H nomogram) had the highest predictive accuracy (c-statistic 0.94), followed by the nomogram including clinical and morphological features (C+M nomogram; c-statistic 0.89), PHASES score (c-statistic 0.68), and ELAPSS score (c-statistic 0.58). Similarly, the C+M+H nomogram had the highest predictive accuracy (c-statistic 0.94) in the validation cohort (85 patients with 97 unruptured IAs).

CONCLUSIONS Hemodynamics have predictive values for 2-year stability of unruptured IAs treated conservatively. Multidimensional nomograms have significantly higher predictive accuracies than conventional risk prediction scores.

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KEYWORDS unruptured intracranial aneurysm; stability; multidimensional predictive model; hemodynamics; nomograms; vascular disorders

Intracranial aneurysm (IA) is the main cause of non-traumatic subarachnoid hemorrhage, which has high morbidity and mortality.1,2 According to previous studies, unruptured IAs may exist in approximately 3% of the US population3,4 and in 6%-7% of the Chinese population.4 Despite the poor outcome of subsequent subarachnoid hemorrhage, endovascular or surgical management of unruptured IAs is associated with a considerable risk of postoperative complications such as ischemic stroke, re-current IA, and rebleeding.5 Therefore, patients with unruptured IAs may not benefit from such aggressive treatment, particularly those whose lesions have a low rupture risk.6 Thus, accurate stratification of the risk (or the stability) of unruptured IAs is crucial to guide treatment decisions in patients with these lesions.

Previous studies have indicated that clinical features of the patients, morphological features of the unruptured IAs, and adjacent hemodynamics may all affect the stability of...
IAS treated conservatively and that a multidimensional predictive model incorporating these factors may more accurately predict the risk of aneurysm rupture or growth in such cases, to assist in clinical decision-making. However, the predictive scores/models commonly used in clinical practice or research mostly only involve a part of these factors, which have limited predictive value, especially for small and large unruptured IAs. For instance, the PHASES (population, hypertension, age, size, earlier rupture, and shape) and ELAPSS (earlier subarachnoid hemorrhage, location, age, population, size, and shape) scores for aneurysm rupture or growth have been reported to be of limited predictive accuracy in previous studies. Of note, hemodynamics plays an important role in governing the risk of IA rupture and growth. Previous computational fluid dynamics (CFD) studies have revealed hemodynamic features of low- versus high-risk IAs and/or proposed predictive models involving hemodynamic indices to discriminate between low- and high-risk IAs. However, most of these studies were performed based on retrospective data, were conducted in patients with postruptured IAs, or used non-patient-specific conditions in CFD modeling, which might have hindered the applications of the hemodynamic models in further research or clinical practice.

Therefore, in this prospective study we aimed to develop a multidimensional model and nomogram to predict the 2-year stability of unruptured IAs treated conservatively, incorporating clinical features of the patients, morphological features of the unruptured IAs, and adjacent hemodynamic features obtained with patient-specific CFD modeling.

**Methods**

**Subjects and Study Design**

This study of the prediction of IA rupture in Chinese people, also named the Intracranial Aneurysm Rupture Project in the Chinese Population (IARP-CP; registration no. ChiCTR1900024547), is a prospective study aiming to investigate factors related to the stability of unruptured IAs and to establish a multidimensional predictive model. The study was approved by institutional ethics committees. Informed consent was obtained from each patient enrolled.

We enrolled patients between the ages of 18 and 75 years with unruptured IAs in the anterior circulation identified by CT angiography (CTA), who were asymptomatic and who had received conservative treatment for at least 2 years. The flowchart of patient enrollment is presented in Fig. 1. All patients recruited were followed up by outpatient visits and with follow-up CTA examinations.
fter the 2-year follow-up, among 355 appropriate patients, we further excluded 1) 21 patients lost to follow-up; 2) 11 patients who received surgical or endovascular treatment during the 2-year follow-up; and 3) 7 patients who did not complete the planned examinations. This study ultimately included 316 patients with 369 unruptured IAs.

Among the included patients, those enrolled between January 2017 and February 2018 formed the primary cohort (231 patients with 272 unruptured IAs) to develop a predictive model, and those enrolled between March 2018 and October 2018 formed the validation cohort (85 patients with 97 unruptured IAs). The ratio of numbers of unruptured IAs in the primary and validation cohorts was approximately 3:1.

The demographic information (e.g., age, male sex, history of smoking and alcohol consumption); comorbidities (i.e., history of hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, and ischemic stroke); and medications (dosage, frequency, and duration) were collected. We defined patients taking aspirin (including standard and low-dose aspirin) at least 3 times per week as aspirin users. 19

According to their alcohol consumption, the included patients were classified as regular alcohol users (drinking once or more per week) and others. 20 Based on their smoking status, patients were classified as current smokers and others. 21

Morphological features of the unruptured IAs were assessed in baseline CTA images, and adjacent hemodynamic features were quantified in patient-specific CFD models built based on the baseline CTA. The baseline PHASES 22 and ELAPSS 23 scores were calculated. The item “population” was counted as 0 in these two scores for all patients in the current study.

All patients were followed up for at least 2 years by outpatient visits every 6 to 12 months. Follow-up CTA was performed at each visit to document changes in the unruptured IAs. The primary endpoint was rupture of the aneurysm within 2 years, growth in the aneurysm size of more than 20% or 1 mm, or appearance of irregularity in the aneurysm pouch at any follow-up visit (compared with the baseline). 24, 25 If they were not defined as unstable IAs (uIAs), the lesions were otherwise considered as stable IAs (sIAs). For the unclear time point of an unruptured IA’s growth, we could not calculate the time from diagnosis of unruptured IAs to their growth. Hence, in this current study we investigated the stability of ruptured IAs at 2 years after diagnosis. The unstable rate was defined as the proportion of uIAs in the primary or validation cohort, or in a certain subgroup of IAs.

Aneurysm Morphology Assessment

CTA source images in the Digital Imaging and Communications in Medicine format were imported into Mimics 17.0 (Materialize) and reconstructed for further analyses. Morphological features of the aneurysms and adjacent arteries were assessed in reconstructed 3D CTA images, by two investigators (M.L. [investigator 1] and J.Y. [investigator 2]) who were blinded to the clinical information.

The morphological features of interest included the aneurysm size (maximum length of the aneurysm), dome diameter, perpendicular height, vessel angle, aneurysm inclination angle, surface area, aneurysm volume, and diameter of the parent artery (Supplementary Fig. 1). Each index of an aneurysm was measured twice by both investigators, and the average of 4 measurements was obtained for subsequent analyses. Aspect ratio, size ratio (SR), height-to-width ratio, undulation index, and nonsphericity index were then calculated 26 (definitions and formulas provided in Supplementary Table 1). The location, lateralization, bifurcation, and irregular shape of an aneurysm were recorded by the same investigators, and discrepancies were solved by consulting a senior neurosurgeon (J.W.). An irregular shape was defined as small blebs or secondary aneurysms protruding from the aneurysm fundus or bi- or multilobular aneurysm fundus. 27

CFD Modeling and Quantification of the Hemodynamic Features

CFD modeling based on CTA and quantification of the hemodynamic parameters were performed using STAR-CCM+ 12 (Siemens). In each case, the 3D vessel geometry was meshed with 4–5 million finite tetrahedral and prismatic elements. We defined the C2 (petrous) segment of the internal carotid artery (ICA) as the parent artery. A patient-specific pulsatile waveform was used as the velocity inlet boundary condition. The pulsatile waveform was obtained at the C1 (cervical) segment of the ICA with carotid ultrasound by using OriginPro 2018b (OriginLab Corp.), which was exported to a comma-separated value file to be used in CFD modeling. The mass flow rate based on mean flow velocities from a population-based study 28 was implemented at the outlet. Blood was defined as a newtonian fluid with density \( \rho = 1056 \text{ kg/m}^3 \) and viscosity \( \mu = 0.0035 \text{ poise} \). The vascular wall was assumed to be rigid. The Navier-Stokes equation was solved, and the results were considered converged, with the residuals reaching below \( 10^{-5} \). A time step of 0.001 seconds was used, giving 800 steps per cardiac cycle (0.8 seconds per cycle). Three pulsatile cycles were simulated, and the last cycle was used for the following analyses.

In each case, the pressure average, wall shear stress (WSS), WSS maximum, WSS average (WSSA), and WSS gradient in the systolic phase were obtained from the dome region. The oscillatory shear index (OSI) and relative resident time (RRT) of the dome throughout the cardiac cycle were calculated. With the value of a pressure or WSS metric at the parent artery as the reference, the normalized pressure average, normalized WSSA (NWSSA), and normalized WSS maximum of the aneurysm dome were calculated. Low WSS was defined as WSS lower than 10% of WSSA of the parent artery, and low shear area ratio (LSAR) of the dome was calculated (the formulas are given in Supplementary Table 1).

Statistical Analysis

Categorical variables were presented as numbers and percentages. Continuous variables with normal distribution were presented as means and standard deviations, and as medians and interquartile ranges if distribution was nonnormal. We compared the differences between two groups in continuous variables using Student t-tests or Wilcoxon rank-sum tests, and compared the differences in categorical variables using chi-square tests or Fisher’s
Demographic and Clinical Features

Results

Morphological and Hemodynamic Features

Independent Predictors of the Primary Endpoint in the Primary Cohort and Multidimensional Risk Prediction Nomograms
NWSSA (p < 0.001), LSAR (p < 0.001), and RRT (p < 0.001) as predictors for uIA.

Aneurysm-based multivariate logistic regression was then performed with these parameters. Hypertension (OR 3.55, 95% CI 1.42–8.89; p = 0.007); location (p = 0.005); irregular shape (OR 4.76, 95% CI 1.90–11.93; p = 0.001); SR (OR 1.24, 95% CI 1.01–1.53; p = 0.042); NWSSA ($\times 10^{-1}$) (OR 0.58, 95% CI 0.43–0.77; p < 0.001); and RRT (OR 1.18, 95% CI 1.07–1.30; p = 0.001) were found to be independent predictors for the stability of unruptured IAs treated conservatively (Table 3). Patient-based multivariate analysis had similar results (Supplementary Table 5).

Two nomograms integrating all independent predictors for the 2-year stability of unruptured IAs were developed: the C+M model (Fig. 3A) and C+M+H model (Fig. 3B). Four representative cases are shown in Supplementary Figs. 2–5. The calibration plot showed substantial agreement between the prediction by each nomogram and the actual observation, in the probability of stable unruptured IA at 2 years (Fig. 4A).

### Comparison in the Accuracies of Different Predictive Models in the Primary Cohort

The C+M+H nomogram model had the highest predictive accuracy (AUC 0.94, 95% CI 0.91–0.97), followed by the C+M nomogram model (AUC 0.87, 95% CI 0.84–0.93), the PHASES score (AUC 0.68, 95% CI 0.60–0.75), and the ELAPSS score (AUC 0.58, 95% CI 0.49–0.67) for the 2-year stability of unruptured IAs in the primary cohort (Fig. 4B and Supplementary Table 6).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary Cohort, n = 272</th>
<th>Validation Cohort, n = 97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>43 (19.3%) 18 (36.7%)</td>
<td>25 (30.5%) 5 (33.3%)</td>
</tr>
<tr>
<td>ICA</td>
<td>168 (75.3%) 19 (38.8%)</td>
<td>51 (62.2%) 4 (26.7%)</td>
</tr>
<tr>
<td>AcomA/ACA</td>
<td>12 (5.4%) 12 (24.5%)</td>
<td>6 (7.3%) 6 (40.0%)</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>56 (25.1%) 29 (59.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Irregular shape</td>
<td>21 (9.4%) 28 (57.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aneurysm size in mm</td>
<td>3.9 (3.4–5.3)</td>
<td>4.0 (3.4–7.1) 6.2 (5.2–7.6) 0.544</td>
</tr>
<tr>
<td>Dome diam in mm</td>
<td>3.1 (2–4.6)</td>
<td>3.3 (2–5.2) 4.2 (3.1–5.2) 0.841</td>
</tr>
<tr>
<td>Height in mm</td>
<td>3.1 (2.2–4.1) 4.1 (2.9–4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VA in $^\circ$</td>
<td>15.0 (10.9–27.4)</td>
<td>16.8 (13.3–42.7) 16.1 (14.1–24.0) 0.735</td>
</tr>
<tr>
<td>AA in $^\circ$</td>
<td>88.6 (78.8–98.3)</td>
<td>88.4 (82.3–100.6) 84.9 (78.0–89.4) 0.364</td>
</tr>
<tr>
<td>Vol in mm$^3$</td>
<td>25.1 (9.3–56.8) 38.4 (17.8–75.3)</td>
<td>0.023</td>
</tr>
<tr>
<td>Surface area in mm$^2$</td>
<td>38.7 (18.2–68.8) 61.5 (29.3–115.9)</td>
<td>39.6 (19.1–144.8) 76.7 (39.5–186.1) 0.841</td>
</tr>
<tr>
<td>AR</td>
<td>1.1 (0.9–1.4) 1.2 (0.9–1.6)</td>
<td>1.1 (0.9–1.5) 1.3 (0.8–1.9) 0.647</td>
</tr>
<tr>
<td>SR</td>
<td>1.2 (0.8–1.7) 3.5 (2.4–4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UI</td>
<td>0.2 (0.1–0.4) 0.4 (0.2–0.5)</td>
<td>0.035</td>
</tr>
<tr>
<td>NSI</td>
<td>0.1 (0.1–0.3) 0.2 (0.1–0.4)</td>
<td>0.016</td>
</tr>
<tr>
<td>Bottleneck factor</td>
<td>1.1 (0.9–1.3) 1.2 (1–1.4)</td>
<td>0.010</td>
</tr>
<tr>
<td>Height-to-width ratio</td>
<td>1.3 (1–1.6) 1.5 (1.3–2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WSSA in Pa</td>
<td>2.5 (1.4–4.1) 2.2 (1.2–3.3)</td>
<td>2.4 (1.3–4.0) 2.3 (1.0–4.5) 0.786</td>
</tr>
<tr>
<td>NWSSA, $\times 10^{-1}$</td>
<td>5.6 (3.8–6.6) 2.3 (1.6–3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WSSM in Pa</td>
<td>6.5 (3.5–10.0) 6.4 (3.9–10.5)</td>
<td>6.8 (3.3–10.2) 8.5 (3.1–14.1) 0.498</td>
</tr>
<tr>
<td>NWSSM</td>
<td>1.6 (0.8–2.9) 1.2 (0.6–2.4)</td>
<td>0.014</td>
</tr>
<tr>
<td>PA in kPa</td>
<td>2.3 (1.6–2.9) 2.3 (1.7–2.9)</td>
<td>0.994</td>
</tr>
<tr>
<td>NPA</td>
<td>0.6 (0.4–0.8) 0.6 (0.4–0.8)</td>
<td>0.037</td>
</tr>
<tr>
<td>WSSG</td>
<td>7.9 (5.6–10.7) 6.9 (15.4–27.0)</td>
<td>7.2 (5.8–11.7) 5.8 (4.8–85) 0.087</td>
</tr>
<tr>
<td>LSAR</td>
<td>0.22 (0.12–0.38) 0.36 (0.24–0.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OSI, $\times 10^{-2}$</td>
<td>0.9 (0.8–1.2) 1.1 (0.9–1.4)</td>
<td>0.241</td>
</tr>
<tr>
<td>RRT</td>
<td>4.6 (2.7–6.6) 9.7 (6.0–13.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PHASES score</td>
<td>1 (0–3) 3 (2–4) &lt;0.001</td>
<td>2 (1–4) 4 (2–7) 0.264</td>
</tr>
<tr>
<td>ELAPSS score</td>
<td>7 (4–14) 7 (1–11) 0.049</td>
<td>7 (4–12) 8 (4–11) 0.327</td>
</tr>
</tbody>
</table>

AA = aneurysm inclination angle; AR = aspect ratio; diam = diameter; NPA = normalized pressure average; NSI = nonsphericity index; NWSSM = normalized WSSM; PA = pressure average; UI = undulation index; VA = vessel angle; WSSG = WSS gradient; WSSM = WSS maximum.

Unless otherwise indicated, values are expressed as the number of patients (%) or median (IQR). Boldface type indicates statistical significance.
Validation of the Nomograms for 2-Year Stability of Unruptured IAs

Eighty-five patients (mean age 60.0 years) with 97 unruptured IAs were enrolled in the validation cohort. Among all parameters of interest, only patient age ($p = 0.034$) and IA located at bifurcation ($p = 0.037$) were significantly different between the primary cohort and the validation cohort (Supplementary Table 7).

In the validation cohort, 15 IAs ruptured or grew during follow-up. Demographic characteristics and morphological-hemodynamic characteristics of the validation cohort are presented in Tables 1 and 2, respectively. Thirty-eight

![Image](image-url)

**FIG. 2.** The morphological and hemodynamic characteristics of representative cases. Lower WSS was found in the uIAs compared with the sIAs. In a cardiac cycle, uIAs showed a higher OSI and RRT compared with sIAs. LSA = LSAR. Figure is available in color online only.

**TABLE 3.** Aneurysm-based logistic regression analyses for independent predictors of uIAs in the primary cohort assessed using backward stepdown selection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Hypertension; yes vs no</td>
<td>4.24</td>
<td>(2.19–8.19)</td>
</tr>
<tr>
<td>Locations</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>AcomA/ACA</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>ICA</td>
<td>0.42</td>
<td>(0.16–0.49)</td>
</tr>
<tr>
<td>MCA</td>
<td>3.70</td>
<td>(1.79–7.65)</td>
</tr>
<tr>
<td>Irregular shape; yes vs no</td>
<td>12.83</td>
<td>(6.23–26.42)</td>
</tr>
<tr>
<td>SR</td>
<td>1.85</td>
<td>(1.51–2.27)</td>
</tr>
<tr>
<td>NWSSA, $\times 10^{-5}$</td>
<td>0.46</td>
<td>(0.37–0.59)</td>
</tr>
<tr>
<td>RRT</td>
<td>1.26</td>
<td>(1.17–1.37)</td>
</tr>
</tbody>
</table>

Boldface type indicates statistical significance.
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(44.7%) patients had a history of hypertension. Fifty-five (56.7%) unruptured IAs were located in the ICA, 30 (30.9%) in the MCA, and 12 (12.4%) in the AcomA/ACA. Twelve (14.6%) sIAs and 8 (53.3%) uIAs were irregular (p < 0.001). The median SRs were 1.4 (0.8–2.3) and 4.4 (3.7–7.0) for sIAs and uIAs, respectively (p < 0.001). The median NWSSA was 0.49 (0.28–0.65) for sIAs and 0.22 (0.16–0.35) for uIAs (p < 0.001).

In the validation cohort, the C+M+H nomogram model had the best predictive accuracy (AUC 0.94), followed by the C+M nomogram model (AUC 0.91) and PHASES and ELAPSS scores, similar to findings in the primary cohort (Fig. 4B and Supplementary Table 6). The calibration curves are shown in Fig. 4A.

**Discussion**

The probable stability of IAs is the key in decision-making in the management of unruptured IAs. In this prospective cohort of patients with unruptured IAs in the anterior circulation, we identified several clinical, morphological, and hemodynamic factors that were independently associ-
ated with the 2-year stability of the unruptured IAs. We then developed and validated two multidimensional nomogram models for the 2-year stability of unruptured IAs in the anterior circulation—the C+M model and the C+M+H model, both of which had significantly higher predictive accuracies than the PHASES and ELAPSS scores.

The annual unstable rate of unruptured IAs was approximately 9.0%. The identification of IA growth remained controversial. Several standards were used to identify this event, e.g., a measurable increase in size > 1 mm of maximal diameter and appearance of irregularity. A recent study reported a growth rate of 4.0% per year. Our unstable rate was slightly higher than in previous studies because a combined definition of IA growth, including growth in the aneurysm size > 20% or 1 mm, was used in this study. This definition may allow us to identify more IAs as growing. However, this study could not clarify which definition of growth could more accurately suggest the risk of IA rupture, which needs further studies to investigate.

Similar to previous relevant studies, we found hypertension, irregular shape, aneurysm location, and SR as independent predictors for unruptured IAs’ stability. Hypertension has long been recognized as a risk factor for IA rupture. For instance, pooled analyses of data from 6 prospective cohort studies found that the rupture risk of IAs in patients with hypertension was approximately 1.4 times the risk of those without hypertension, which was included in the PHASES score. In addition, other prospective studies have also revealed the detrimental role of hypertension in IA rupture. Moreover, aneurysm size and location were also included in PHASES and ELAPSS scores as independent risk factors for IA rupture. In a systematic review, Kleinloog et al. also found irregular shape and SR (the relative size of aneurysm) to be predictors for IA rupture with a high level of evidence. In Dhar et al.’s report, SR was also a sensitive predictor for IA rupture. In a subsequent study, Etminan et al. used SR as an indicator for intervention in unruptured IAs. Findings related to the morphological features of IAs in this study were therefore consistent with previous studies.

More importantly, this study reinforced the idea that hemodynamic factors could be reliable predictors for unruptured IAs’ stability. Hemodynamics has been associated with the risk of IA rupture in previous studies, but the predictive value of hemodynamics remains controversial. Of note, previous studies have mostly investigated postruptured IAs, even though the morphology of IAs would change after rupture, which could greatly affect their hemodynamic features. In contrast, in this prospective study we built CFD models based on the morphology of unruptured IAs with patient-specific boundary conditions, and we assessed the baseline hemodynamic features. We then followed up

FIG. 4. The predictive accuracy and calibration curves of different models. A: The calibration plots show substantial agreement between the prediction by each nomogram and the actual observation. B: In the primary cohort, the C+M+H nomogram model had the highest predictive accuracy, followed by the C+M nomogram model. The PHASES and ELAPSS scores had lower predictive accuracies for the 2-year stability of unruptured IAs. The findings were replicated in the validation cohort. Figure is available in color online only.
with the patients to assess for IA stability, which reflected real-world situations in predicting IA stability in clinical practice. We found lower NWSSA to be associated with a higher risk of IA instability within 2 years. A possible explanation could be that chronic injury to the vascular wall due to blood flow patterns (low shear stress) could exaggerate inflammation infiltration, damage the normal organization, and increase the instability of the vascular wall.14,34,35

Another interesting finding is that RRT, not OSI, was a predictor for unruptured IAs’ stability. RRT could reflect the oscillation of WSS in a cardiac cycle, with a higher RRT reflecting more significant oscillatory flow over a cardiac cycle. A majority of previous studies have indicated the predictive value of OSI, but not RRT, for IA stability.7,8,15,16,18 Notably, a recent study gave a similar result—that RRT could predict the risk of IA rupture.36 Given that RRT is more susceptible to WSS and would be more significantly affected by the inlet conditions, we inferred that the use of patient-specific inlet conditions in the current study may partly explain the discrepancy between this study and previous ones in findings regarding RRT, which needs to be verified in future studies.

Based on these findings, we established two nomograms, using factors of different dimensions (i.e., clinical, morphological, and hemodynamic factors) to predict the 2-year stability of unruptured IAs treated conservatively, both of which showed high predictive accuracy, significantly higher than that of the PHASES and ELAPSS scores. In this study, the C+M+H nomogram had higher predictive accuracies in both the primary and validation cohorts, compared with the C+M nomogram. The stability of unruptured IAs is governed by numerous factors of multiple dimensions, and most previous predictive models or scores only partially took these factors into account. For instance, the PHASES and ELAPSS scores only considered clinical factors and limited morphological features of the IAs,22,23 which therefore had inadequate predictive accuracies for IA stability. In this sense, the C+M+H nomogram could more comprehensively picture the characteristics of the patients and the IAs, which hence had a high predictive accuracy. However, hemodynamic analyses may not be feasible in routine clinical practice, despite emerging semiautomatic analysis tools (e.g., AView).37 Therefore, we also developed and validated the C+M nomogram, composed of clinical and easily obtained morphological factors, which also showed a significantly higher accuracy than the PHASES and ELAPSS scores in predicting the 2-year stability of unruptured IAs. Both the nomograms could assist in clinical decision-making in the treatment strategy of unruptured IAs.

Limitations in the Current Study
First, the study only recruited patients with IAs in the anterior circulation, the findings of which may not be applicable in posterior circulation IAs. Second, the relatively short follow-up duration was not able to capture the long-term risk of unruptured IAs receiving conservative treatment. However, the nomograms had clinical utility to identify IAs at a high risk of rupture or further growth in 2 years and to guide timely intervention. Third, although patient-specific models were used for CFD analysis, we assumed a rigid vascular wall and the blood as a Newtonian fluid, which might have resulted in small errors in the hemodynamic simulation results. In fact, most of previous studies used similar assumptions for vessel wall and blood properties in CFD modeling. Fourth, given that patients in this study were all Chinese, we do not know whether the results are applicable to other populations. This limited the generalizability of our conclusions. Studies based on other populations are needed to further validate our conclusion. Fifth, we did not consider some factors—e.g., aneurysm wall enhancement—in predicting the risk of uIAs. Sixth, we validated the accuracy of our nomograms based on the same cohort, which may limit our conclusions. A further validation based on another independent cohort is needed. Despite these limitations, our study could provide insight into the role of hemodynamics in predicting the stability of unruptured IAs, and our nomograms could be used to discriminate high-risk unruptured IAs, which would help clinical decision-making.

Conclusions
In a prospective cohort of patients with unruptured IAs in the anterior circulation, we demonstrated the predictive value of hemodynamic features for the 2-year stability of unruptured IAs treated conservatively. We have also developed and validated two multidimensional nomogram models for the 2-year stability of unruptured IAs, and the C+M+H model had the highest predictive accuracy. The nomogram models warrant further validations in other populations, which may yield a valuable tool for individualized risk assessment of unruptured IAs in the anterior circulation.

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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Liu. Acquisition of data: Liu, J Yang, Y Yang, Jiang, Li, Mo, S Yang, Wu. Analysis and interpretation of data: Liu. Drafting the article: Liu. Critically revising the article: Leng. He. Approved the final version of the manuscript on behalf of all authors: Wang. Statistical analysis: Liu, Leng. Study supervision: Wang.

Supplemental Information
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Correspondence
Shuo Wang: Beijing Tiantan Hospital, Capital Medical University, Beijing, China. captain9858@126.com.