Neurological Sciences (2019) 40:1683–1693
https://doi.org/10.1007/s10072-019-03916-1

ORIGINAL ARTICLE

Intracranial aneurysm rupture score may correlate to the risk of rebleeding before treatment of ruptured intracranial aneurysms

Qingyuan Liu[1,2,3,4] • Pengjun Jiang[1,2,3,4] • Jun Wu[1,2,3] • Maogui Li[1,2,3] • Bin Gao[5] • Yanan Zhang[6] • Bo Ning[7] • Yong Cao[1,2,3] • Shuo Wang[1,2,3]

Received: 5 January 2019 / Accepted: 24 April 2019 / Published online: 29 April 2019

Abstract

Background and objective Aneurysm rebleeding after rupture can result in a catastrophic outcome with high mortality and morbidity. In this study, we evaluated the correlation of IARS (intracranial aneurysm rupture score) and aneurysm rebleeding. The aim of this study was to explore the clinical utility of IARS for better clinical decision-making.

Method The patients with ruptured intracranial aneurysms between January 2017 and September 2018 were reviewed. Propensity scoring match was performed to construct a cohort. The morphological and hemodynamic parameters were obtained. The difference between stable aneurysms and rebleeding aneurysms was compared. Subsequently, the correlation of IARS and aneurysm rebleeding was studied.

Results The matching process constructed a cohort, including 5 rebleeding aneurysms and 15 stable aneurysms. By comparing the difference between stable aneurysms and rebleeding aneurysms, the statistical significance was found in diameter of neck ($p = 0.036$), aspect ratio ($p = 0.004$) and size ratio ($p = 0.029$), normalized wall shear stress average ($p = 0.026$), low shear area ratio ($p = 0.028$), oscillatory shear index (OSI) ($p = 0.031$), and deviated angle ($p = 0.025$). The IARS here had a strong correlation with the aneurysm rebleeding, and the interval from the first bleeding to the rebleeding tended to shorten with the increase of IARS ($R = 0.715$, $p = 0.027$). IARS had a good predicting value for the aneurysm rebleeding (area under the curve = 0.756, $p < 0.001$).

Conclusion Based on this preliminary study, intracranial aneurysm rupture score may correlate to the rebleeding in ruptured aneurysms. For ruptured aneurysms with high IARS scores, surgery should be given priority, and medical treatment is not recommended.

Keywords Intracranial aneurysms · Morphology · Hemodynamics · Computational fluid dynamics · Treatment priority

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating event with high mortality (45%) and high morbidity (40–50%)[1–3]. After aneurysm rupture, except for hemorrhage and ischemia events, rebleeding may also contribute to the poor prognosis[4–6]. Though timely treatment can effective improve the prognosis of aSAH patients[2, 7–9], for some reasons, part of patients cannot receive surgical treatment as soon as patients were sent to hospital. Considering some aneurysm under the risk of rebleeding within the first 24 h[5, 6, 10], it is important to

✉ Shuo Wang
captain9858@126.com

1 Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, No. 119 South 4th Ring West Road, Fengtai District, Beijing 100070, People's Republic of China

2 China National Clinical Research Center for Neurological Diseases, Beijing, People's Republic of China

3 Center of Stroke, Beijing Institute for Brain Disorders, Beijing, People's Republic of China

4 Beijing Key Laboratory of Translational Medicine for Cerebrovascular Diseases, Beijing, People's Republic of China

5 School of Life Science and BioEngineering, Beijing University of Technology, Beijing 100124, People's Republic of China

6 Department of Blood Transfusion, Beijing Tiantan Hospital, Capital Medical University, No. 119 South 4th Ring West Road, Fengtai District, Beijing 100070, People's Republic of China

7 Department of Neurosurgery, Guangzhou Red Cross Hospital, Jinan University, Guangzhou 510220, Guangdong, People's Republic of China

determine which aneurysm can receive medical treatment, and which aneurysm needs prioritized surgery.

Two main aspects are involved in the mechanism of aneurysm rupture, known as the structure of the aneurysm wall[11] and the internal hemodynamic features[12–14]. After aneurysm rupture, the morphological and hemodynamic features of an aneurysm would change, which may tend to reach a stable status. However, rebleeding after admission still occurred in 6%–22% of patients underlying aSAH[5, 6, 10, 15, 16]. Accordingly, it was hypothesized here that the hemodynamic condition of rebleeding aneurysms may not reach a stable status. Though the comorbidity is well controlled, this unstable status still can cause aneurysm rebleeding.

Our previous study built up a scoring stratification system, called as intracranial aneurysm rupture score (IARS), based on morphological and hemodynamic features of ruptured aneurysm[17]. This four-point system can discriminate the aneurysms with high rupture risk, which could also identify the unstable condition of an aneurysm.

The aim of this study was to investigate the morphological-hemodynamic features of aneurysms undergoing rebleeding. The relationship of the IARS to aneurysm rebleeding was further studied. The morphological and hemodynamic features from a group of matched patients were analyzed here. We believe that the present study can not only enhance the understanding of the rupture mechanism of the aneurysm but also assist doctors in making better medical decision.

Methods and material

Patient selected and inclusion/exclusion standards, study definition

The patients with intracranial aneurysms (IA) in our institution between January 2017 and September 2018 were reviewed. Patients were selected according to the following standards:

Inclusion criteria

(1) The aneurysm was identified by angiogram (CT/MR angiogram)
(2) An angiogram was performed after aneurysm rupture
(3) The patients were sent to our institution within 48 h as soon as aSAH were identified
(4) Clinical records were complete, or clinical history can be traced.

Exclusion criteria

(1) Patients related to other intracranial tumors, angiostenosis and angio-malformation (e.g., arteriovenous malformation, cavernous malformation, etc.)
(2) Angiogram was unsuitable for hemodynamic analysis
(3) Patients had family history of intracranial aneurysm or connective tissue disease
(4) Multiple aneurysms, dissecting aneurysms or aneurysms with thrombus
(5) Patients received special treatment in other medical institutions before admitting to our institution.
(6) Time from the first bleeding to rebleeding was more than 1 months.

In this study, rebleeding was diagnosed when the magnitude of subarachnoid, intracerebral, or intraventricular blood significantly increased on CT after admission, and the magnitude of bleeding did not increase and keeps stable at/before admission. The aneurysm underwent rebleeding before surgical intervention was identified as the rebleeding aneurysm, whereas the aneurysm without rebleeding before surgical intervention was identified as the stable aneurysm.

The study was approved by the institutional review board of Tiantan hospital. Written informed consents were obtained from all participants or their legally authorized representatives and privacy of patients was effectively protected.

Perioperative management and surgical intervention

In our institution, all surgeries were performed by two experienced vascular neurosurgeons (S.W. and Y.C., both worked as neurosurgeons for more than 20 years). All patients would receive antihypertensive treatment after admission. Acute lowering of systolic pressure to 120–140 mmHg was the target[18, 19].

All patients with Hunt-Hess I–II received surgical intervention within 72 h after admission. However, once patients' condition progressively deteriorated, an emergency surgical intervention would be performed.

For patients with Hunt-Hess grade III–V at admission, immediate surgical intervention was not recommended[19]. For those patients, conservative treatment was usually recommended until the Hunt-Hess "degraded." The patients who did not receive immediate surgical intervention would have a standard care following the guideline[19]. After admission, a CT would perform per 24 h, or when patients' condition deteriorated. Only surgical intervention was considered when patient's condition continued to deteriorate, or radiological examination found a significant rebleeding or a sign of cerebral hernia.

Image data and clinical information collection, vascular modeling, rebleeding event confirmation, and radiological morphology

The Digital Imaging and Communications in Medicine (DICOM) data of angiogram performed after admission were collected and converted into reordered slices (about 0.5 mm per slice). The DICOM data were introduced into Mimics 17.0 (Mimics Research 17.0, Materialize, Belgium) and reconstructed for further studies.

Clinical information was collected from electronical medical records regarding to age, gender, history of hypertension, history of smoking, Hunt-Hess grade at admission, time from the first bleeding to the rebleeding, blood pressure at admission, and blood pressure before rebleeding/surgery (24 h before rebleeding/surgery). Modified Fisher grade and aneurysm site was collected from radiological data. Patients' functional outcome was assessed by using modified Rankin scale according to the status on discharge.

Rebleeding events were confirmed by two experienced neurosurgeons (P.J and J.W, who were blind to patients' information) according to the bleeding presentation on CT after admission.

Measurement of morphological parameters was performed by the same neurosurgeons (P.J and J.W) based on the vascular model. Length (L), diameter of body (D), diameter of neck (d), perpendicular height (H), diameter of parent artery (P), and aneurysm volume were measured here[17]. The mentioned parameters were measured twice, and the average was taken. Aspect ratio (AR), size ratio (SR), undulation index (UI), ellipticity index (EI), and nonsphericity index (NSI) were calculated[20].

CFD simulating and hemodynamic parameters

All models were meshed under STAR-CCM (STAR-CCM+ 12, Siemens, German), creating 4 to 5 million unites of finite tetrahedral and prism elements. The simulations were performed in STAR-CCM fluid workstation (STAR-CCM+ 12, Siemens, German). The Navier-Stokers equation served as the solver in pulsatile blood. By using transcranial Doppler ultrasound, the pulsatile waveform was obtained with its magnitude scaled to the desired mean flow rate. The pulsatile waveforms of the internal carotid artery from a representative patient were applied for further analyses. Blood was assumed as the incompressible Newtonian fluid with density $\rho = 1056$ kg/m3 and viscosity $\mu = 0.0035$ Poise. Pulsatile curve acted as the velocity inlet boundary condition, and free-traction boundary condition was achieved at the outlet. When the residuals are less than 10^{-5}, the results will be considered converged[21]. A time step of 0.0001 s was used, giving 800 steps per cardiac cycle (total 0.8 s per cycle). Four pulsatile cycles were simulated. The last cycle was yielded for further studies.

The instantaneous WSS and pressure were time-averaged over a cycle. The oscillatory shear index (OSI) and relative resident time (RRT) were calculated. Also, the spatially average WSS, pressure, RRT and OSI over the aneurysm surface were calculated. For each model, pressure maximum (PM), pressure average (PA), WSS maximum (WSSM), WSS average (WSSA), and WSS gradient (WSSG) were obtained from the IA region, and parent pressure average (pPA), parent WSS average (pWSSA) were acquired from the parent artery region. Low WSS was defined to be less than 10% of WSS of parent artery[22]. The normalization of pressure and WSS was based on hemodynamic status of parent artery. The normalized pressure average (NPA), normalized WSS average (NWSSA), normalized pressure maximum (NPM) and normalized WSS maximum (NWSSM) were calculated by the following equations (Eqs. (1), (2), (3), (4)), respectively. The measurement of deviated angle (DA) was referenced in our previous study[17].

$$\mathrm{NPA} = \frac{PA}{\mathrm{pPA}} \tag{1}$$

$$\mathrm{N}WSSA = \frac{WSSA}{pWSSA} \tag{2}$$

$$\mathrm{NPM} = \frac{PM}{\mathrm{pPM}} \tag{3}$$

$$\mathrm{N}WSSM = \frac{WSSM}{pWSSM} \tag{4}$$

After collecting above parameters, the intracranial aneurysm rupture score (IARS) was then calculated according to our previous work. In this study, IARS ≥ 2 was thought as high-risk group.

Propensity score match and study groups

To balance the comparability of rebleeding aneurysms and stable aneurysms, a propensity score matching was performed to match patients using STATA (12SE, STATA Corporation, American). The propensity scores were calculated using a logistic regression model consisting of the input variables: age, gender, history of hypertension, history of smoking, and aneurysm site. The matching rate was 1:3 for rebleeding aneurysms to stable aneurysms. The final matched group was proven to be properly matching using $\chi 2$ testing to validate the equivalence of individual variables between all groups.

Statistical analysis

Measurement variables were compared by chi-square test or Fisher's exact test. Continuous variables were first assessed visually by P–P plots and the Shapiro-Wilk test and then compared by the independent samples' t test. The receiver operating characteristic curve (ROC) analysis was performed to examine the predicting value of IARS to rebleeding. The area under the curve (AUC) was calculated. An AUC > 0.7 was thought as a statistical significance. The results were expressed in 95% confidence intervals. A p value of < 0.05 was assumed to be statistically significant. Statistical analysis was performed using SPSS 22.0 (IBM, American).

Results

Demographic and clinical information

A total of 97 appropriate patients with aSAH were reviewed in this study. Five patients were identified as undergoing rebleeding ranged in age from 49 to 68 years (mean, 58.4 ± 6.0 years). The rebleeding rate is 5.2%. The clinical information of patients underwent rebleeding are listed in Table 1. The clinical difference between patients with rebleeding aneurysms and stable aneurysms was summarized in Table 2. The CT at the first bleeding and rebleeding was shown in Fig. 1, separately. The rate of female to male was 3:2. Almost all (4/5, 80.0%) had a history of hypertension. The average time from the first bleeding to the rebleeding was 43.4 ± 37.4 h. After standardly caring, the blood pressure of 80% patients was controlled within a reasonable range. Eighty percent of patients with stable aneurysm, whereas only 40% of patients underwent rebleeding, had a good outcome with mRS < 3.

Matching process yielded 15 patients with stable aneurysm to 5 patients with rebleeding aneurysm. The significant difference did not find in Hunt-Hess grade at admission ($p = 0.605$) and the modified Fisher grade at admission ($p = 0.788$). It is noteworthy that blood pressure of almost patients was significantly increased at admission and was well controlled after standard care, yet the differences were not statistically significant ($p = 0.605$ for blood pressure at admission, and $p = 0.788$ for blood pressure after standard care).

After rebleeding, three patients (case1, 2, 5) received emergency surgery, and one patient (case 4) received emergency endovascular intervention after rebleeding. One patient (case 3) died because of acute cerebral hernia.

Hemodynamic and morphological differences

The hemodynamic and morphological features of rebleeding aneurysms were listed in Table 3. One aneurysm with daughter sac reached four points of IARS, which implied a severely unstable status. Eighty percent of rebleeding aneurysms were identified as high-risk aneurysms.

The hemodynamic and morphological difference was summarized in Table 4. Statistically significant difference was found in morphological parameters, including d ($p = 0.036$), AR ($p = 0.004$), and SR ($p = 0.029$). Significant difference was also found in hemodynamic parameters, such as NWSSA ($p = 0.026$), LSAR ($p = 0.028$), OSI ($p = 0.031$), and DA ($p = 0.025$). The rebleeding aneurysms were found with a narrow neck (lower d), a more obvious irregular shape (larger AR and SR) (Fig. 1) and a more significantly unstable hemodynamic condition (NWSSA was lower, DA, LSAR, and OSI were higher in rebleeding aneurysms than those in stable aneurysms) (Fig. 2).

Correlation between IARS and rebleeding and ROC analysis

Analysis of the relationship of IARS and rebleeding was further performed. The percentage of rebleeding increased with the increase of IARS (Fig. 3 A). Rebleeding occurred in up to 44.4% (4/9) of the high-risk aneurysms, but only 9.1% (1/11) of the low-risk aneurysms (Table 5 A). In addition, we also found that the interval from the first bleeding to the rebleeding tended to shorten with the increase of IARS ($R = 0.715$, $p = 0.027$) (Fig. 3 B).

Subsequently, the ROC analyses of IARS to rebleeding were performed. The results summarized in Table 5 B, revealed a good predicting value of IARS to rebleeding with an AUC as 0.793 (Fig. 3 C).

Discussion

The intracranial hemorrhage caused by IAs rupture can endanger patients' lives in the acute stage and cause severe cerebral ischemia in the late stage[2, 23]. The aneurysm rebleeds are the vital risk factors related to the poor prognosis[4, 6, 10]. Accordingly, the identification of the potential IAs to rebleed can contribute to the decision of treatment ordering. Based on our previous studies[17, 24], the present study made the first effort to explore the hemodynamic and morphological features of rebleeding aneurysms and find the predicting method for this disastrous event.

Table 1 Clinical information of patients undergoing rebleeding

No.	Gender	Age (years)	History of hypertension	Previous or current smoking history	Hunt-Hess grade at admission	Time from the first bleeding to the rebleeding (hours)	Blood pressure at admission (mmHg)	Blood pressure before rebleeding (mmHg)
1	Female	57	Yes	No	II	15	150/86	125/59
2	Female	49	Yes	No	II	36	175/94	128/69
3	Male	68	No	No	III	98	153/83	125/59
4	Male	63	Yes	Yes	III	6	180/90	113/71
5	Female	59	Yes	Yes	III	23	182/91	146/82

Table 2 Demographic and clinical differences between rebleeding group and stable group

Characteristics	Total, $n = 20$	Rebleeding group $n = 5$	Stable group $n = 15$	p value
Gender				N/A
Male	7	2	5	
Female	13	3	10	
Age (years)	57.7 ± 6.4	58.4 ± 6.0	57.5 ± 6.7	N/A
Hypertension				N/A
Yes	10	3	7	
No	10	2	8	
Ever-or-now smoker				N/A
Yes	10	2	8	
No	10	3	7	
Hunt-Hess grade at admission				0.605
Grade I–II	11	2	9	
Grade III–V	9	3	6	
Modified Fisher grade at admission				0.788
Grade I–II	7	2	5	
Grade III–IV	13	3	10	
Blood pressure at admission				0.580
< 160/90 mmHg	6	2	4	
> 160/90 mmHg	14	3	11	
Blood pressure before bleeding/surgery				0.766
< 140/80 mmHg	16	4	12	
> 140/80 mmHg	4	1	3	
Aneurysm site				N/A
Internal carotid artery	3	1	2	
Middle cerebral artery	9	2	7	
Anterior communicating artery	8	2	6	
Treatment after admission or outcome				N/A
Surgery	11	3	8	
Endovascular intervention	8	1	7	
Dead	1	1	0	
Modified Rankin scale on discharge				N/A
1–2	14	2	12	
3–5	6	3 (one dead)	3	

N/A is not further evaluated

Clinical factors related to the rebleeding in ruptured aneurysms

In our present cohort, three patients, including a dead, had a bad outcome in rebleeding group. The rate of poor outcome was as high as 60%, which is consistent with previous studies[4–6, 10, 25]. In our present cohort, rebleeding occurred in only 25% of patients with safe blood pressure, which implied that intensive lowering of blood pressure can significantly decrease the rate of rebleeding[15, 16]. Interestingly, blood pressure of almost patients with rebleeding (except one patient) was controlled within a reasonable range after admission. So, though elevated blood pressure is a risk factor for aneurysm rebleeding, rebleeding still occurred in some aneurysms with safe blood pressure. Therefore, clinical features are insufficient to predict the risk of rebleeding, features of aneurysms are also risk factors for rebleeding. Early identification of these aneurysms is important for clinical decision-making and treatment ordering.

The morphological factors related to the aneurysm rebleeding

By analyzing the radiological features from the IAs before rebleeding, the relationship between morphological features and the risk of rebleeding was investigated. The d, AR, and

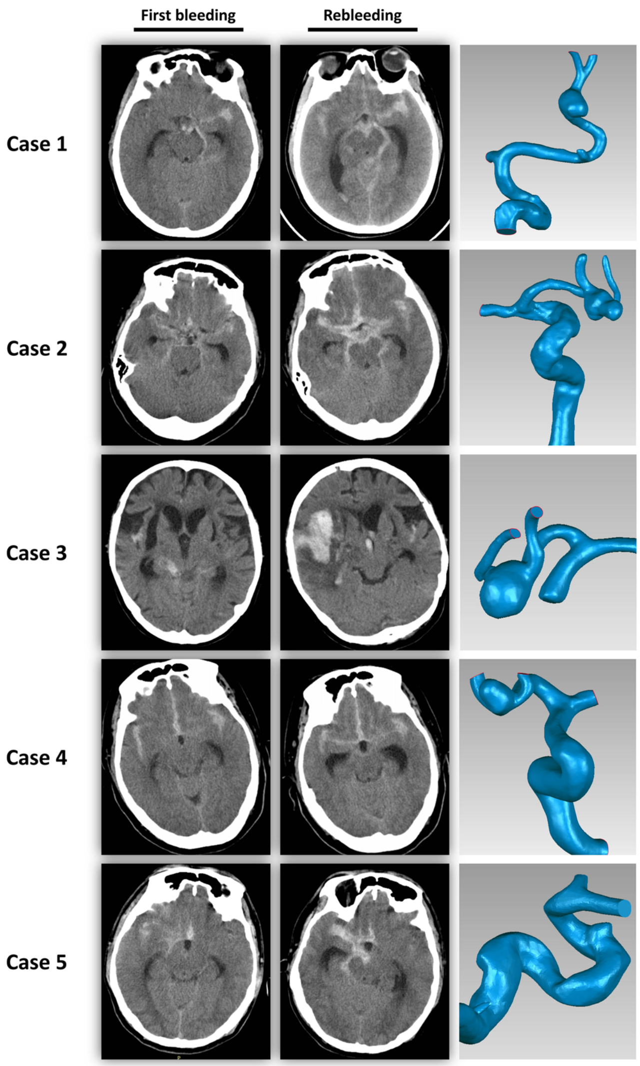

Fig. 1 The CT at the first bleeding and rebleeding of all patients with rebleeding aneurysm, and the reconstructed models of all rebleeding aneurysms

SR were significantly different between rebleeding aneurysms and stable aneurysms.

The AR reflecting the irregular shape of IA can serve as a reliable predictor for aneurysm rupture[26], and includes the effect from narrow aneurysm neck (small d) to aneurysm rupture. However, the threshold of this parameter is various from 1.18 to 2.3 though the predicting value is reliable[22, 26, 27]. In our current cohort, the mean AR of stable aneurysms was 1.4, whereas, the mean AR of rebleeding aneurysms was 2.0, which suggested that these aneurysms may have a more significantly irregular shape with higher risk of rupture. Therefore, once accidents occurred, such as a sudden increase in blood pressure, these aneurysms are more likely to rebleed.

The SR can reflect the relative size of aneurysm and parent artery[28]. The predicting value of this parameter to aneurysm rupture has been evaluated in our previous study and other relative studies[17, 22, 26, 28, 29]. In addition, a meta-analysis found that aneurysm size was a predictor for aneurysm rebleeding[30], which implied that SR may reflect the risk of rebleeding. SR > 2.3 is a risk factor related to aneurysm rupture. Though the morphological features would change after aneurysm rupture[31], the SR of rebleeding aneurysm was still over 2.3. Therefore, we thought that rebleeding aneurysms may not reach a stable status after bleeding stopping. It is not difficult to understand that an accident can trigger the occurrence of rebleeding.

The hemodynamic factors related to the aneurysm rebleeding

In addition to morphological features, we also found that several hemodynamic parameters, including NWSSA, LSAR, OSI, and DA, were significantly different between rebleeding aneurysms and stable aneurysms.

NWSSA can reflect the whole status of WSS in an aneurysm, and the LSAR is the area of low WSS. The WSS, important for normal proliferation, is the friction between blood and endothelial cell[14, 22, 32, 33]. The low WSS can cause inflammatory infiltration and cell apoptosis[11, 34–39]. Thus, the large LSAR means a large area of severe damage of the vascular wall. The area of an aneurysm wall exposed to a WSS below 10% of the mean arterial WSS was applied in some previous studies[22, 40]. Both of Jou et al. and Skodvin et al. demonstrated this parameter as an independent risk factor for IA rupture[31, 40]. In our previous work and current work, the result revealed that an aneurysm with LSAR > 0.3 has a high

Table 3 Morphological and hemodynamic features of rebleeding aneurysms

No.	Daughter sac	Aneurysm site	L (mm)	D (mm)	AR	SR	DA (°)	WSSA (Pa)	NWSSA	LSAR	OSI	IARS
1	No	MCA	12.0	8.2	1.9	3.5	26.9	1.1	0.14	0.55	0.012	3
2	No	AcomA	8.5	7.6	2.2	2.8	23.6	1.2	0.19	0.43	0.004	2
3	No	MCA	9.3	7.8	2.1	3.3	34.4	2.3	0.21	0.67	0.006	2
4	Yes	AcomA	8.3	9.7	2.0	2.9	36.5	2.5	0.23	0.41	0.009	4
5	No	ICA	6.2	5.9	1.7	0.5	22.6	3.3	0.27	0.34	0.007	1

MCA is the middle cerebral artery; AcomA is the anterior communicating artery

Table 4 Morphological and hemodynamic differences between rebleeding group and stable group

Parameters	Total, n = 20	Rebleeding group n = 5	Stable group n = 15	*p* value
D (mm)	7.9 ± 1.7	7.8 ± 1.4	7.9 ± 1.8	0.953
d (mm) *	5.1 ± 1.3	4.0 ± 1.4	5.4 ± 1.2	0.036
L (mm)	8.3 ± 3.0	9.1 ± 1.8	8.1 ± 3.3	0.614
H (mm)	6.9 ± 2.3	6.7 ± 1.7	7.0 ± 2.5	0.795
AR *	1.6 ± 0.4	2.0 ± 0.2	1.4 ± 0.4	0.004
SR *	2.1 ± 0.7	2.6 ± 1.2	1.8 ± 0.5	0.029
UI	0.08 ± 0.06	0.09 ± 0.10	0.08 ± 0.04	0.924
EI	0.11 ± 0.03	0.10 ± 0.06	0.11 ± 0.03	0.710
NSI	0.15 ± 0.06	0.15 ± 0.13	0.14 ± 0.03	0.906
PM (Pa)	4103.5 ± 1918.6	3233.8 ± 1303.4	4393.4 ± 2037.2	0.252
PA (Pa)	1879.8 ± 464.6	1845.0 ± 462.4	1891.3 ± 480.9	0.853
WSSM (Pa)	5.3 ± 3.8	6.0 ± 3.3	5.0 ± 4.0	0.628
WSSA (Pa)	2.2 ± 1.0	2.1 ± 0.9	2.3 ± 1.1	0.698
NPM	1.05 ± 0.37	0.93 ± 0.28	1.09 ± 0.40	0.417
NPA	0.52 ± 0.20	0.55 ± 0.10	0.52 ± 0.22	0.759
NWSSM	0.57 ± 0.22	0.61 ± 0.31	0.56 ± 0.19	0.686
NWSSA*	0.30 ± 0.17	0.21 ± 0.05	0.33 ± 0.18	0.026
WSSG (Pa/m)	9.9 ± 5.9	7.5 ± 2.3	10.8 ± 6.5	0.298
LSAR *	0.35 ± 0.15	0.48 ± 0.13	0.31 ± 0.14	0.028
OSI *	0.0048 ± 0.0034	0.0076 ± 0.0030	0.0039 ± 0.0031	0.031
RRT	7.3 ± 1.1	7.5 ± 1.0	7.2 ± 1.1	0.576
DA (°) *	23.7 ± 6.0	28.8 ± 6.3	22.1 ± 5.1	0.025

*is the parameter with statistically significant difference

risk of rupture[17]. However, after aneurysm rupture, though WSS increased and LSAR decreased to reach a stable status, rebleeding aneurysms still had a low NWSSA and a LSAR > 0.3. Thus, though aneurysm rupture can stabilize the hemodynamic status, for rebleeding aneurysms, bleeding stopped before aneurysm reaching a stable status.

OSI can reflect the stability of internal blood flow in aneurysm. High OSI can change the endothelial surface adhesion molecules and aggravate the damage in the vascular wall[41]. Meng et al. reported that this parameter can be used to predict the risk of aneurysm rupture[22]. In our stratification study, the OSI was demonstrated as a good predictor for IA rupture[17]. In our current study, increased OSI with more than 0.008 was found in rebleeding aneurysms, which did also reflect the unstable status.

DA is the deviation of the real bloodstream to the direction of normal vessel. The magnitude of DA can reflect the impact effect. We studied this parameter in a previous work and confirmed the relationship of DA and aneurysm rupture. An aneurysm with DA > 35° has a high risk of natural rupture because the direct impact effect from blood flow. However, though increasing DA was also found in rebleeding aneurysms comparing to stable aneurysms, the mean DA of those aneurysms was under 35°, and a DA > 35° was found in only two rebleeding aneurysms. For this phenomenon, we thought aneurysm rupture can change morphological features, which can obviously influence the direction of flow and makes an aneurysm tend to be stable. Thus, an aneurysm with DA < 35°may have a high risk of rebleeding.

IARS and treatment ordering

Our IARS system can predict the risk of rebleeding. Although the bleeding stopped in some rupture IAs, they did not reach the stable condition and may rebleed once a “trigger” occurred (it may be transiently increasing blood pressure and so on). The rebleeding occurred in 44.4% of high-risk aneurysms (4/9) and 9% of low-risk aneurysms (1/11). Therefore, the medical treatment is suitable for the aneurysms with IARS < 2, but not a reasonable choice for the aneurysms with IARS ≥ 2 regardless of the Hess-Hunt grade. To avoid rebleeding, we recommended an immediate surgical intervention for the high-risk aneurysms, and a priority should give to aneurysms with higher IARS scores. However, given large population of patients with high-risk aneurysms would occur, for the aneurysms with IARS score as 2 points, we believe that a short-time observation is acceptable (within 72 h[19]). Even if

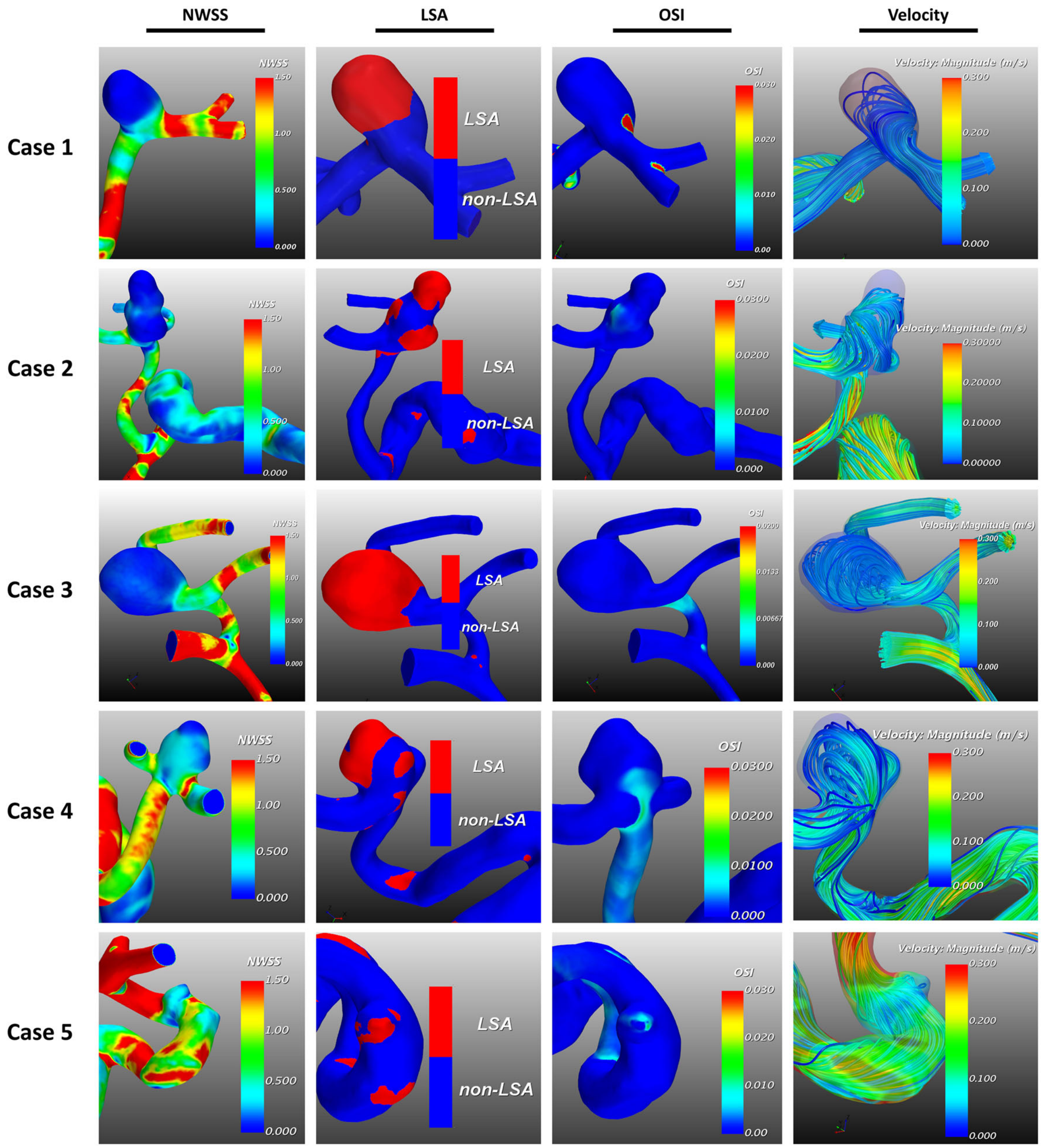

Fig. 2 The hemodynamic features of all rebleeding aneurysms

a surgery is considered, it can be done following the aneurysms with IARS score as 3–4 points.

In the developing countries, e.g., China, treatment ordering is important for the intervention of IAs. This is primarily because of a large patient population but the limitation of medical resources[42]. This phenomenon means that a patient may have to wait for a long time for appropriate treatment before aneurysm rupture, or immediately gets medical intervention after aneurysm rupture. In this condition, the prognosis is not guaranteed. Therefore, the treatment ordering is important to assist doctors in clinical decision-making. Our IARS system can evaluate the rebleeding potential of IAs, which can identify the targeted aneurysms from the ruptured aneurysms and give priority to intervention.

Limitations

There were several limitations in the present study. First and foremost, the inlet boundary condition was from a representative patient, which could affect the result of CFD since this method is sensitive to velocity and waveform[43]. However, in the IARS system, we used normalized parameters, which can

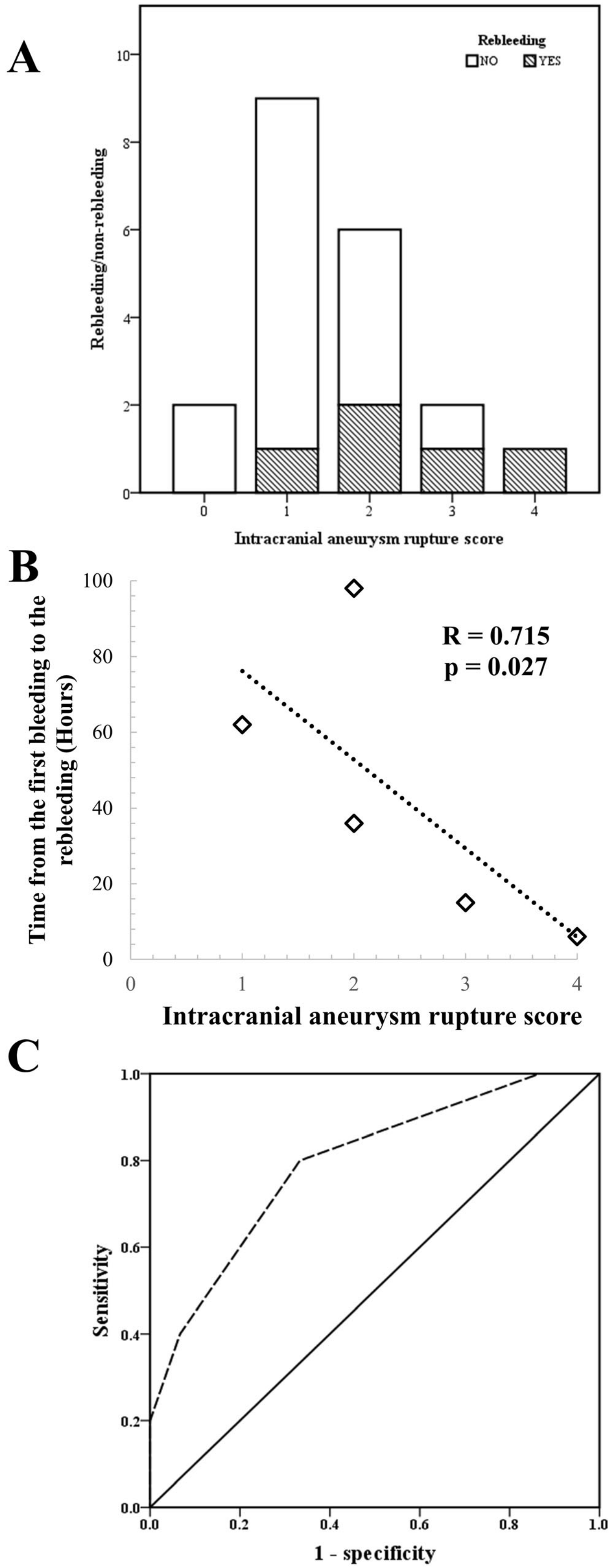

Fig. 3 **a** The distribution of rebleeding aneurysms in each IARS score; **b** the correlation of time from the first bleeding to rebleeding and IARS score; **c** the predicting value of IARS to the risk of rebleeding

Table 5 Risk category and the result if ROC analysis

A. Risk category			
Intracranial aneurysm rupture score		Rebleeding (*n*, %)	
Low risk ($n = 11$)	0 ($n = 2$)	0 (0.0%)	
	1 ($n = 9$)	1 (11.1%)	
High risk ($n = 9$)	2 ($n = 6$)	2 (33.3%)	
	3 ($n = 2$)	1 (50.0%)	
	4 ($n = 1$)	1 (100.0%)	
B. ROC analysis			
IARS rebleeding	AUC	95% Confidence interval	*p* value
	0.793	0.559–0.967	0.025

reduce the effects exerted by this problem[43]. Second, the morphology can significantly influence the hemodynamics. For the change of morphology and hemodynamics after indiscoverable aneurysm rupture[44], our conclusion may be limited. Third, the small sample size (only five rebleeding aneurysms were included) would limit our conclusion. However, after the recent improvement of perioperative management, the rate of rebleeding were significantly decreased, and we believe that the current results are the best available. Indications remain the focus in aneurysm treatment, and the present study has its clinical utility to help clinical work determine the treatment method and ordering though there are some limitations.

Conclusion

After the first aneurysm rupture, aneurysms, which may rebleed at a short period, still have an unstable status with large AR and SR, decreasing NWSSA and increasing DA, LSAR and OSI. Based on this preliminary study, intracranial aneurysm rupture score (IARS) may correlate to the rebleeding in ruptured aneurysms. For aneurysms with high IARS scores, surgery should be given priority, and medical treatment is not recommended after rupture.

Authors' contribution Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Q.L. Analysis and interpretation of data: Q.L, P.J. Drafting the article: Q.L. Critically revising the article: all authors. Reviewing submitted version of manuscript: all authors. Approving the final version of the manuscript on behalf of all authors: S.W. Administrative/technical/material support: S.W and B.G. Study supervision: S.W and J.W.

Funding This study was supported by the National Natural Foundation of China (Grant No. 81471210 and 81671129, Recipient: Shuo Wang) and Major special projects in the 13th five-year plan (Grant No.2016YFC1301800, Recipient: Shuo Wang).

Compliance with ethical standards

Conflict of interest All authors certify that we have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Szklener S, Melges A, Korchut A, Zaluska W, Trojanowski T, Rejdak R, Rejdak K (2015) Predictive model for patients with poor-grade subarachnoid haemorrhage in 30-day observation: a 9-year cohort study. BMJ Open 5:e007795
2. Cordonnier C, Demchuk A, Ziai W, Anderson CS (2018) Intracerebral haemorrhage: current approaches to acute management. Lancet. 392:1257–1268
3. Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ (2009) Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurol 8:635–642
4. Kienzler J, Marbacher S, Remonda L, Soleman J, Ai Schlaeppi J, Leupold U, Fandino J (2016) Outcome after in-hospital rebleeding of rupture of intracranial aneurysms. J Neurol Surg A Cent Eur Neurosurg 77:207–221
5. Jaechan P, Hyunjin W, Dong-Hun K, Yong-Sun K, Young KM, Im Hee S et al (2015) Formal protocol for emergency treatment of ruptured intracranial aneurysms to reduce in-hospital rebleeding and improve clinical outcomes. J Neurosurg 122:383
6. Rosenørn J, , Eskesen V, Schmidt K, Rønde F. The risk of rebleeding from ruptured intracranial aneurysms. J Neurosurg 1987;67:329–332
7. Fisher CM, Kistler JP, Davis JM (1980) Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery. 6:1–9
8. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Jr CE, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery. 2006;59:21–27
9. Ko SB, Choi HA, Carpenter AM, Helbok R, Schmidt JM, Badjatia N, Claassen J, Connolly ES, Mayer SA, Lee K (2011) Quantitative analysis of hemorrhage volume for predicting delayed cerebral ischemia after subarachnoid hemorrhage. Stroke 42:669–674
10. Hijdra A, van Gijn J, Nagelkerke NJ, Vermeulen M, van Crevel H (1988) Prediction of delayed cerebral ischemia, rebleeding, and outcome after aneurysmal subarachnoid hemorrhage. Stroke 19: 1250–1256
11. Frosen J, Tulamo R, Paetau A, Laaksamo E, Korja M, Laakso A et al (2012) Saccular intracranial aneurysm: pathology and mechanisms. Acta Neuropathol 123:773–786
12. Dolan JM, Kolega J, Meng H (2013) High wall shear stress and spatial gradients in vascular pathology: a review. Ann Biomed Eng 41:1411–1427
13. Meng H, Xiang J, Liaw N. The role of hemodynamics in intracranial aneurysm initiation. 2012;7:40–57
14. Meng H, Tutino VM, Xiang J, Siddiqui A (2014) High wss or low wss? Complex interactions of hemodynamics with intracranial aneurysm initiation, growth, and rupture: toward a unifying hypothesis. AJNR Am J Neuroradiol 35:1254–1262
15. Gian Marco DM, Hector L, J Michael S, Lord AS, Velander AJ, Andres F, et al. Impact of premorbid hypertension on haemorrhage severity and aneurysm rebleeding risk after subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 2014;85:56–59
16. Lin QS, Ping-Chen LYX, Lin ZY, Yu LH, Dai LS et al (2016) Systolic blood pressure variability is a novel risk factor for rebleeding in acute subarachnoid hemorrhage: a case-control study. Medicine 95:e3028
17. Jiang P, Liu Q, Wu J, Chen X, Li M, Li Z, Yang S, Guo R, Gao B, Cao Y, Wang S (2018) A novel scoring system for rupture risk stratification of intracranial aneurysms: a hemodynamic and morphological study. Front Neurosci 12
18. American Society of Anesthesiologists Task Force on Perioperative Blood M (2015) Practice guidelines for perioperative blood management: an updated report by the American Society Of Anesthesiologists task force on perioperative blood management. Anesthesiology. 122:241–275
19. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT et al (2012) Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 43:1711–1737
20. Dhar S, Tremmel M, Mocco J, Kim M, Yamamoto J, Siddiqui AH, Hopkins LN, Meng H (2008) Morphology parameters for intracranial aneurysm rupture risk assessment. Neurosurgery. 63:185–197
21. Tian Z, Zhang Y, Jing L, Liu J, Zhang Y, Yang X (2016) Rupture risk assessment for mirror aneurysms with different outcomes in the same patient. Front Neurol 7:219
22. Xiang J, Natarajan SK, Tremmel M, Ma D, Mocco J, Hopkins LN, Siddiqui AH, Levy EI, Meng H (2011) Hemodynamic-morphologic discriminants for intracranial aneurysm rupture. Stroke 42:144–152
23. Lovelock CE, Molyneux AJ, Rothwell PM (2007) Oxford vascular S. change in incidence and aetiology of intracerebral haemorrhage in oxfordshire, Uk, between 1981 and 2006: a population-based study. Lancet Neurol 6:487–493
24. Jiang P, Wu J, Chen X, Ning B, Liu Q, Li Z, Li M, Yang F, Cao Y, Wang R, Wang S (2018) Quantitative proteomics analysis of differentially expressed proteins in ruptured and unruptured cerebral aneurysms by itraq. J Proteome 182:45–52
25. Torner JC, Kassell NF, Wallace RB, Adams HP (1981) Preoperative prognostic factors for rebleeding and survival in aneurysm patients receiving antifibrinolytic therapy: report of the cooperative aneurysm study. Neurosurgery. 9:506–513
26. Dhar S, Tremmel M, Mocco J, Kim M, Yamamoto J, Siddiqui AH, Hopkins LN, Meng H (2008) Morphology parameters for intracranial aneurysm rupture risk assessment. Neurosurgery. 63:185–196 discussion 196–187
27. Ghosh S, Dey S, Tjoumakaris S, Gonzalez F, Rosenwasser R, Pascal J, Jallo J (2013) Association of morphologic and demographic features of intracranial aneurysms with their rupture: a retrospective analysis. Acta Neurochir Suppl 115:275–278
28. Tremmel M, Dhar S, Levy EI, Mocco J, Meng H (2009) Influence of intracranial aneurysm-to-parent vessel size ratio on hemodynamics and implication for rupture: results from a virtual experimental study. Neurosurgery 64:622–630 discussion 630–621
29. Rahman M, Smietana J, Hauck E, Hoh B, Hopkins N, Siddiqui A, Levy EI, Meng H, Mocco J (2010) Size ratio correlates with intracranial aneurysm rupture status: a prospective study. Stroke. 41: 916–920
30. Boogaarts HD, Lieshout JH, Van, Amerongen MJ, Van, Joost DV, Verbeek ALM, J André G, et al. Aneurysm diameter as a risk factor for pretreatment rebleeding: a meta-analysis. J Neurosurg 2015;122:921, 928

31. Skodvin TO, Evju O, Helland CA, Isaksen JG. Rupture prediction of intracranial aneurysms: a nationwide matched case-control study of hemodynamics at the time of diagnosis. J Neurosurg 2017:1–7
32. Goubergrits L, Schaller J, Kertzscher U, Petz C, Hege HC, Spuler A (2013) Reproducibility of image-based analysis of cerebral aneurysm geometry and hemodynamics: an in-vitro study of magnetic resonance imaging, computed tomography, and three-dimensional rotational angiography. J Neurol Surg A Cent Eur Neurosurg 74: 294–302
33. Etminan N, Buchholz BA, Dreier R, Bruckner P, Torner JC, Steiger HJ, Hänggi D, Macdonald RL (2014) Cerebral aneurysms: formation, progression, and developmental chronology. Transl Stroke Res 5:167–173
34. Chalouhi N, Jabbour P, Hasan D (2014) Inflammation, macrophages, and targeted imaging in intracranial aneurysms. World Neurosurg 81:206–208
35. Hosaka K, Hoh BL (2014) Inflammation and cerebral aneurysms. Transl Stroke Res 5:190–198
36. Penn DL, Witte SR, Komotar RJ, Sander Connolly E Jr (2014) The role of vascular remodeling and inflammation in the pathogenesis of intracranial aneurysms. J Clin Neurosci 21:28–32
37. Starke RM, Chalouhi N, Ali MS, Jabbour PM, Tjoumakaris SI, Gonzalez LF, Rosenwasser R, Koch W, Dumont A (2013) The role of oxidative stress in cerebral aneurysm formation and rupture. Curr Neurovasc Res 10:247–255
38. Starke RM, Chalouhi N, Ding D, Raper DM, McKisic MS, Owens GK et al (2014) Vascular smooth muscle cells in cerebral aneurysm pathogenesis. Transl Stroke Res 5:338–346
39. Yan L, Zhu YQ, Li MH, Tan HQ, Cheng YS (2013) Geometric, hemodynamic, and pathological study of a distal internal carotid artery aneurysm model in dogs. Stroke. 44:2926–2929
40. Jou LD, Lee DH, Morsi H, Mawad ME (2008) Wall shear stress on ruptured and unruptured intracranial aneurysms at the internal carotid artery. AJNR Am J Neuroradiol 29:1761–1767
41. Malek AM, Alper SL, Izumo S (1999) Hemodynamic shear stress and its role in atherosclerosis. JAMA. 282:2035–2042
42. Bian LH, Liu YF, Nichols LT, Wang CX, Wang YL, Liu GF, Wang WJ, Zhao XQ (2012) Epidemiology of subarachnoid hemorrhage, patterns of management, and outcomes in China: a hospital-based multicenter prospective study. CNS Neurosci Ther 18:895–902
43. Xiang J, Siddiqui AH, Meng H (2014) The effect of inlet waveforms on computational hemodynamics of patient-specific intracranial aneurysms. J Biomech 47:3882–3890
44. Skodvin TO, Johnsen LH, Gjertsen O, Isaksen JG, Sorteberg A (2017) Cerebral aneurysm morphology before and after rupture: Nationwide case series of 29 aneurysms. Stroke. 48:880–886