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A novel score for evaluating cerebral aneurysms treated with flow diversion: 4F-flow diversion predictive score

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Abstract

Background and purpose: Although grading scales for angiography outcomes following cerebral aneurysm treatment with flow diversion have been published, physicians have not widely adopted these scales in practice. The aim of this study is to propose and validate a novel Flow diversion Predictive Score (4F-FPS) grading scale based on previously established scales that is simple and reliable.

Methods: We retrospectively analyzed consecutive patients who underwent endovascular treatment for cerebral aneurysms with flow diversion between January 2014 and September 2019. The included patients were randomly divided into the derivation and validation group in a 70/30 ratio, respectively. Aneurysms were classified as incomplete or complete occlusion based on final angiography outcomes. 4F-FPS was derived to predict aneurysm occlusion from multivariate logistic regression analyses in the derivation group and validated with previously published grading scales in the validation group.

Results: Overall, 662 patients [mean age, 53.8 years; 72.5% (480/662) female] with 662 aneurysms treated with the Pipeline™ flow diverter were included [69.9% (463/662) derivation group, 30.1% (199/662) validation group]. The incidence of aneurysm occlusion was 82.7%. 4F-FPS demonstrated significant discrimination in 10-fold cross validation [mean receiver operating characteristic (ROC) area, 0.862 ± 0.055] and calibration (Cox & Snell R^2, 0.251; Nagelkerke R^2, 0.413) in the derivation group. The ROC area of 4F-FPS score in both the derivation and validation groups is the largest compared with previously published grading scales/scores ($p < 0.05$), which shows better sensitivity and specificity. The 4F-FPS score showed excellent prediction, discrimination, and calibration properties.

Conclusion: The 4F-FPS score is a simple and reliable tool to predict angiography outcome after flow diversion treatment. If widely adopted, it may provide a common language to be used in future reporting of flow diversion results for clinical trials and daily practice.

Clinical trial registration: http://www.clinicaltrials.gov. Unique identifier: NCT03831672

Keywords: endovascular treatment, flow diversion, grading scale, intracranial aneurysm, prediction

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Introduction

Over the last decade, flow diverters (FDs) have gained widespread global acceptance in the treatment of intracranial aneurysms, with overall complete occlusion rates of 75.0–85.5%.[1,2] Currently, there are four published grading systems for the classification of aneurysms after flow diversion treatment.[3–6] The O'Kelly-Marotta

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(OKM),[3] Kamran,[4] and Simple Measurement of Aneurysm Residual after Treatment (SMART) scales[5] are descriptive in nature and based on factors presumed to be important in the treatment of aneurysms by flow-diverting stents. These scales were developed based on factors assessed immediately after treatment, but they did not specifically examine their systems based on final angiography results. The Flow-Diverting Stent Score (FDSS) was developed using multivariate analysis of factors predictive of occlusion after flow diversion and nearly closes this gap;[6] however, the FDSS was developed based on the Raymond score,[7] which was specifically developed to describe angiography status after coiling embolization, and thus may not be suitable for flow diversion. No grading systems have been popularized in clinical practice due to their lack of verification and applicability, thus leaving an unmet clinical need.

To be clinically relevant, grading scales must be reliable, simple, memorable, and have predictive value for treatment-related risk or angiography outcome. Therefore, we established a novel Flow diversion Predictive Score (4F-FPS) grading system for the evaluation of cerebral aneurysms treated with flow diversion based on angiography outcomes. This study validated the reliability, discrimination, and calibration of the 4F-FPS and compared with previously published scores/scales.

Methods

Ethics statement

The study protocol was reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital (approval number KY 2018-098-02) and followed the declaration of Helsinki. All patients provided written informed consent.

Study design and ethics

The Postmarket, muLticenter, retrospective study on embolization of intracranial aneUrysmS with the Pipeline Embolization Device (PED; Covidien/Medtronic, Irvine, CA, USA) in China (PLUS) registry was a panoramic, consecutive, real-world cohort study designed to assess the safety and effectiveness of PED for embolization of intracranial aneurysms in the Chinese population. This is a subgroup study of the PLUS study.[8,9] Three of the 14 centers were excluded because of a lack of complete angiographic imaging data. All patients with intracranial aneurysms who underwent embolization using the PED between November 2014 and October 2019 in 11 centers and who provided written informed consent for the use of any recognizable patient photographs were included. Because the scores in this study were based on the results of imaging follow-up, 313 patients who lacked imaging follow-up were excluded. In addition, 196 patients with the following conditions were also excluded: (1) treated by parent vessel occlusion and (2) lacking complete array angiography images (e.g., lack of venous phase angiography). Therefore, a total of 662 patients (662/1171, 56.5%) were included in the present subgroup study. The decision to proceed with adjunctive coiling was left to the discretion of the treating physician who hopes to improve the cure rate (especially for large aneurysms) and reduce the risk of delayed aneurysmal rupture.[10] Generally, adjunctive coiling was considered when an aneurysm had a high imminent risk of rupture (e.g., irregular aneurysm with daughter sac, history of sentinel headache) or with large, giant aneurysms (lager aneurysms have a higher risk of delayed aneurysmal rupture).

Data gathering for the study was performed using Electronic Data Capture (EDC). All data were available online. The database included information on patient demographics (sex, age), aneurysm characteristics (size, location, morphological features), antiplatelet regimen, procedure details, instant angiography outcomes, neurological complications, and follow-up results. The first angiography follow-up was conducted at 3–6 months after PED implant. For patients who showed complete aneurysm occlusion at first angiography follow-up, further imaging and follow-up were not routinely performed. Patients who showed incomplete occlusion at first angiography follow-up had additional imaging performed up to 24 months or longer after the procedure. Retreatment was considered for patients who showed incomplete occlusion at 24 months. The imaging data of all patients were reviewed by three neuro-interventionists who were proficient in reviewing aneurysm angiography images and who were trained in determining the 4F-FPS score. After becoming proficient, they independently reviewed images and determined angiography scores for 662 aneurysms. Independent scoring was

repeated after a 2-week interval. The collected results were analyzed to assess inter- and intraobserver variability. Digital subtraction angiography was used to determine the degree of aneurysm occlusion immediately after PED placement, and the OKM grading scale was used to grade angiographic views.[3] The OKM grading scale is as follows: aneurysm filling is graded as A, complete (>95%); B, incomplete (5%–95%); C, neck remnant (<5%); or D, no filling (0%). Complete occlusion was defined as an OKM grade of D, and incomplete occlusion was defined as an OKM grade of A, B, or C. This definition is used for the assessment of immediate postoperative angiography and follow-up angiography for complete and incomplete occlusion.

Statistical analysis

Randomized grouping and model building. To develop and validate the predictive score, patient records were randomly divided into derivation and validation data sets (Figure 1). We selected approximately 70% of the data as the derivation data set (derivation group) using computerized random sampling; the remaining 30% constituted the validation data set (validation group). Patient characteristics were described with percentages, mean ± SD, or median and interquartile ranges as appropriate. Categorical variables were compared using the Fisher's exact test or Pearson's chi-square test. Continuous variables were compared between groups using the Mann–Whitney *U* test or Student's *t* test. Statisticians compared whether the baseline data of the two groups were statistically different; if the baseline data were different, groups were re-randomized. Regression coefficients (β) and odds ratios (ORs) were calculated using univariate and multivariate logistic regression models, respectively. A two-tailed *p*-value of <0.05 was considered statistically significant.

Predictive score derivation

The risk scale/score was developed from the derivation group. We first identified potential predictive factors of aneurysm occlusion with univariate analysis (incomplete occlusion = 0, complete occlusion = 1). Variables found to be significant ($p < 0.05$) were then included in a backward, stepwise, multivariable logistic regression model. We defined a $p < 0.05$ as meaningful for predicting occlusion in the final multivariable analysis. Variables were attributed points based on the relative regression coefficients, with the final predictive score defined as the sum of all points. Occlusion rate estimate was stratified by predictive score. We assessed the predictive score's calibration with the Hosmer–Lemeshow statistic, using the Cox & Snell R^2 and Nagelkerke R^2 as goodness-of-fit measures. Statistical analysis was carried out with SPSS Version 25 (IBM Corp., Armonk, NY, USA). The predictive score's discrimination was assessed by the 10-fold cross-validation test statistic to calculate sensitivity and specificity for the score model. Receiving operator characteristic (ROC) curves and area under the curve (AUC) were calculated. An AUC of 0.5 indicates no ability to discriminate between patients with or without occlusion, while an AUC of 1.0 indicates perfect discrimination. Calculations were performed with R software (V.4.0.2; R Foundation for Statistical Computing, http://www.R-project.org). We referred to a widely known risk scale derivation study conducted by Framingham Heart Study[11] to establish a scientific and convincing predictive grading system based on multivariate logistic regression coefficients.

Predictive score validation

To assess the performance of scoring systems in predicting aneurysm occlusion, parametric ROC curves were generated. We compared the differences in AUCs between the validation group and the derivation group. We then compared the new grading system, the 4F-FPS, with previously published scales (OKM, Kamran, SMART, FDSS) in the validation group, performing pairwise comparisons by examining AUCs (two-tailed tests, significance defined as $p < 0.05$). We followed the same model of pairwise comparisons in the derivation group. Calculations were performed with MedCalc Statistical Software (V.19.3.1; MedCalc Software bvba, Ostend, Belgium).

Data availability

The data not published within the article are available in a public repository and include accession numbers to the data sets. Data gathering for the study was performed using EDC. All data were available online. Any qualified investigator requesting access to the data must sign the data access and use agreement prior to obtaining access.

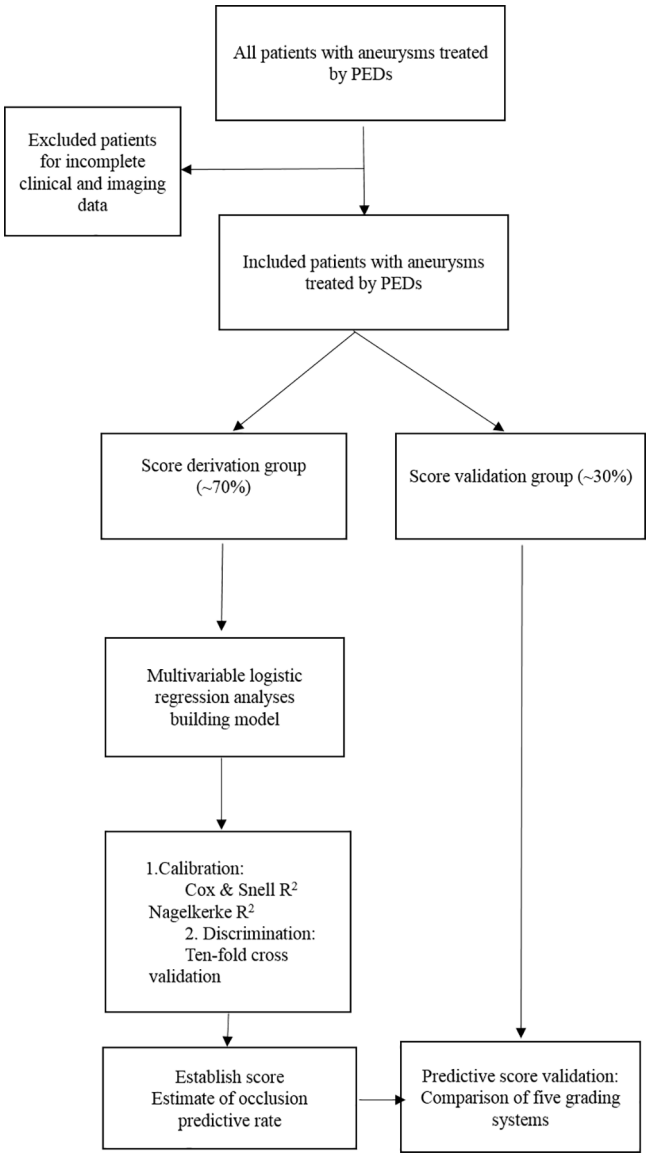

Figure 1. Flowchart of study processes.

Assessment of inter- and intraobserver variability

SPSS Version 25 statistical software was used to analyze and assess the inter- and intraobserver agreement of the 4F-FPS score and calculate Cohen's kappa coefficient. The kappa value was between –1 and + 1. The resulting kappa statistic was interpreted to determine the inter- and intraobserver agreement using the following criteria: ⩽0.40, poor agreement; 0.40–0.75, fair to good agreement; and ⩾0.75, excellent agreement.[4,12]

Results

Study population

There were 765 consecutive patients with intracranial aneurysms who underwent endovascular treatment using PED and had angiography follow-up at least once. After excluding 103 subjects for incomplete clinical and imaging data, 662 patients met inclusion criteria for analysis, with 463 (69.9%) in the derivation group and 199 (30.1%) in the validation group.

Table 1. Comparison of baseline characteristics between the derivation and validation groups.

	Derivation group ($n = 463$)	Validation group ($n = 199$)	*p*-value
Sex			0.893
Female	335 (72.4%)	145 (72.9%)	
Age	54.1 ± 11.4	53.0 ± 10.9	0.236
Aneurysm size	12.86 ± 8.16	12.35 ± 7.36	0.446
Aneurysm location			0.324
Anterior circulation	402 (86.8%)	167 (83.9%)	
Posterior circulation	61 (13.2%)	32 (16.1%)	
Aneurysm forms			0.970
Fusiform	60 (13.0%)	26 (13.1%)	
Circumferential	403 (87.0%)	173 (86.9%)	
Collateral artery			0.471
No	395 (85.3%)	174 (87.4%)	
Yes	68 (14.7%)	25 (12.6%)	
Degree of stasis			0.687
Extending into the arterial or capillary phase	137 (29.6%)	62 (31.2%)	
Extending into the venous phase or no blood flow	326 (70.4%)	137 (68.8%)	
Coherent inflow jet			0.057
Yes	64 (13.8%)	17 (8.5%)	
No	399 (86.2%)	182 (91.5%)	
Residual contrast filling			0.326
Residual contrast filling <50% of the aneurysm volume	231 (49.9%)	91 (45.7%)	
Residual contrast filling ⩾50% of the aneurysm volume	232 (50.1%)	108 (54.3%)	
Final angiography outcomes			0.610
Incomplete occlusion	82 (17.7%)	32 (16.1%)	
Complete occlusion	381 (82.3%)	167 (83.9%)	

Baseline characteristics

Baseline characteristics of the derivation and validation groups are shown in Table 1. There was no significant difference between the two groups. Incidence of aneurysm occlusion was 82.7%. There were 335 (72.4%) female patients in the derivation group with an average age 54.1 ± 11.4 years, whereas there were 145 (72.9%) female

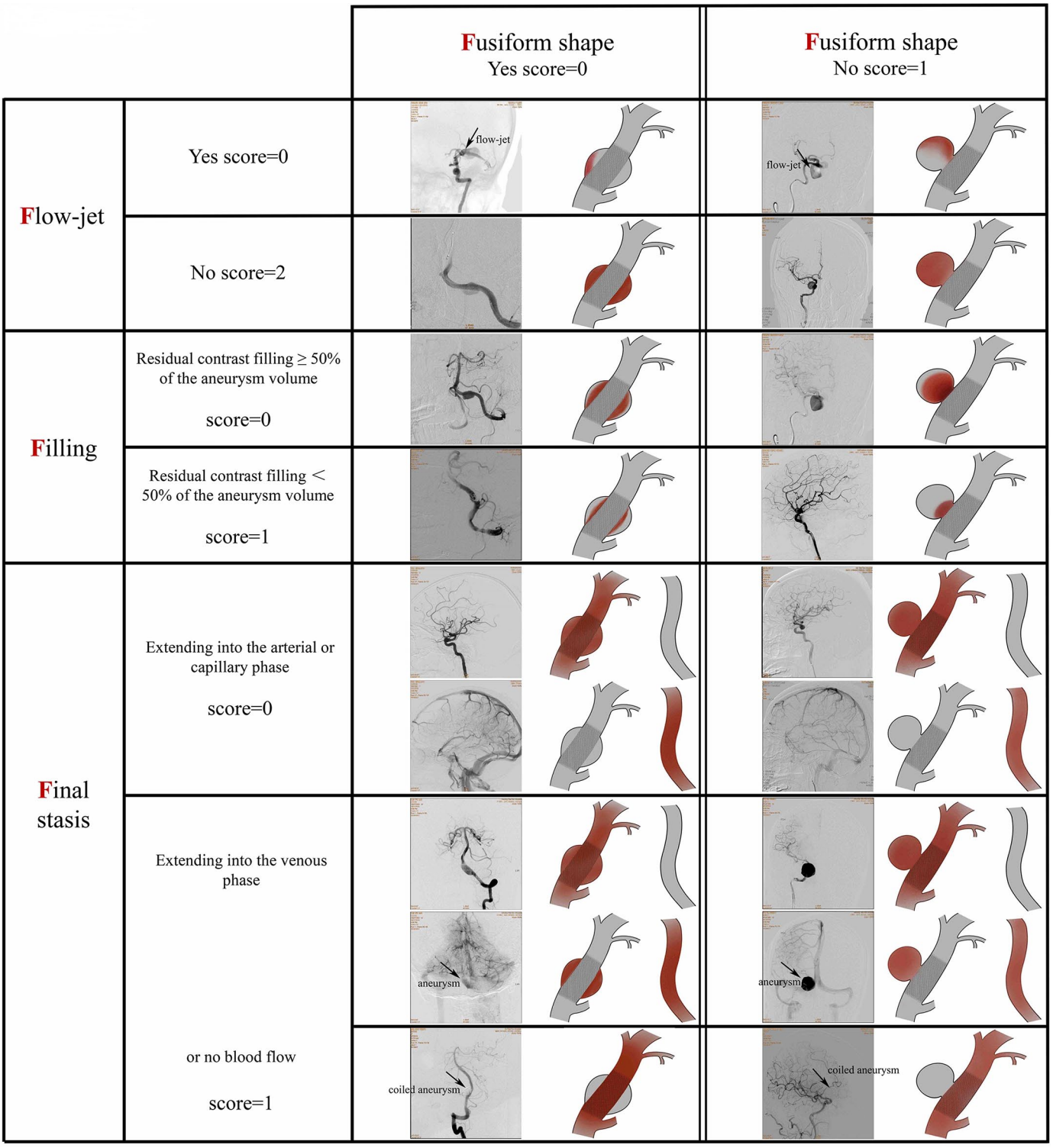

Figure 2. Diagrammatic illustration of the 4F-Flow diversion Predictive Score (4F-FPS). Final scores are determined by adding the values from each of the four variables.

patients in the validation group with an average age 53.0 ± 10.9 years. In the derivation group, 61 (13.2%) aneurysms were located in the posterior circulation, whereas 32 (16.1%) aneurysms were located in the posterior circulation in the validation group. The average size of aneurysms was

Table 2. Univariate and multivariate logistic analysis score derivation group for predictors of occlusion.

Variable	Score derivation group ($n = 463$)							
	Univariate analysis				Multivariate analysis			
	β	OR	95% CI	*p*-value	β	OR	95% CI	*p*-value
Female	0.376	1.457	0.875–2.427	0.148				
Age	0.003	1.003	0.983–1.024	0.760				
Aneurysm size	−0.021	0.979	0.952–1.006	0.131				
Posterior circulation	0.402	1.495	0.682–3.277	0.316				
Circumferential aneurysm	1.467	4.336	2.416–7.781	<0.0001	1.356	3.881	1.948–7.734	<0.0001
Collateral artery	−0.982	0.374	0.210–0.667	0.001				
Extending into the venous phase or no blood flow	1.730	5.643	3.399–9.368	<0.0001	1.832	6.249	3.222–12.121	<0.0001
Coherent inflow jet	2.029	7.604	4.282–13.502	<0.0001	2.373	10.728	5.146–22.367	<0.0001
Residual contrast filling <50% of the aneurysm volume	2.188	8.915	4.576–17.368	<0.0001	1.145	3.141	1.464–6.739	0.003

β, regression coefficient; CI, confidence interval; OR, odds ratio.

12.86 ± 8.16 mm in the derivation group and 12.35 ± 7.36 mm in the validation group. All patients underwent angiographic follow-up, with a mean follow-up time of 9.0 ± 7.5 months. Individual grading scores for aneurysms treated with flow diversion are reported in Supplementary Table 1. In total, 226 (48.8%) patients were treated with a PED with coiling in the derivation group, and 98 (49.2%) patients were treated with a PED with coiling in the validation group (Supplemental Table 2).

Predictive score derivation

On multivariate analysis, circumferential aneurysm [β = 1.356, OR = 3.881, 95% confidence interval (CI) = 1.948–7.734], extending into the venous phase or no blood flow (β = 1.832, OR = 6.249, 95% CI = 3.222–12.121), coherent inflow jet (β = 2.373, OR = 10.728, 95% CI = 5.146–22.367), and residual contrast filling <50% of the aneurysm volume (β = 1.145, OR = 3.141, 95% CI = 1.464–6.739) were independent predictive factors for aneurysm occlusion on follow-up angiography (Table 2). Thus, we derived the 4F-FPS based on regression coefficients, with the grading system derivation process (Table 3) and scoring rules for each factor (Table 4). A diagrammatic representation of the 4F-FPS characteristics is found in Figure 2. Estimates of occlusion predictive rate based on 4F-FPS score are shown in Table 5. Discrimination and calibration measures for the 4F-FPS score in the derivation group are shown in Supplementary Table 3. The mean AUC (0.862 ± 0.055) and calibration (Cox & Snell R^2, 0.251; Nagelkerke R^2, 0.413) in the derivation group showed strong prediction, discrimination, and calibration properties.

Predictive score validation

The relationship between prediction scores of different grading systems and aneurysm occlusion at final follow-up is shown in Supplementary Table 4. The 4F-FPS score was associated with the highest OR for aneurysm occlusion at final follow-up (OR = 4.890, 95% CI = 2.925–8.174). The performance of 4F-FPS scores between the validation group and the derivation group in predicting aneurysm occlusion is illustrated by the ROC curves in Figure 3(a). There was no

Table 3. Grading system derivation process.

Factors	Categories	Reference value (W_{ij})	βi	βi ($W_{ij} - W_{iREF}$)	Points $ij = D/B$, $B = 1.356$
Circumferential aneurysm	No	$0 = W_{1REF}$		0	0
	Yes	1	1.356	1.356	1
Extending into the venous phase or no blood flow	No	$0 = W_{2REF}$		0	0
	Yes	1	1.832	1.832	1
Coherent inflow jet	No	$0 = W_{3REF}$		0	0
	Yes	1	2.373	2.373	2
Residual contrast filling <50% of the aneurysm volume	No	$0 = W_{4REF}$		0	0
	Yes	1	1.145	1.145	1

β_i, regression coefficients of each factor of the logistic regression model; B, constant corresponding to each point value in the score; D = distance between each group of predictive factors and W_{iREF} ($D = [W_{ij} - W_{iREF}] \times \beta_i$); $Points_{ij}$, score corresponding to each factor category ($Points_{ij} = D/B = [W_{ij} - W_{iREF}] \times \beta i/B$); W_{ij}, reference value of each variable; W_{iREF}, basic risk reference value of each factor.

Table 4. 4F-FPS grading system scoring rules.

'4F' grading system components	Score
Fusiform shape	
Yes	0
No	1
Flow-jet	
Yes	0
No	2
Filling	
Residual contrast filling ⩾50% of the aneurysm volume	0
Residual contrast filling <50% of the aneurysm volume	1
Final stasis	
Extending into the arterial or capillary phase	0
Extending into the venous phase or no blood flow	1

Table 5. Estimate of occlusion predictive rate.

Point total	Estimate of occlusion predictive rate
0	0.058
1	0.193
2	0.481
3	0.782
4	0.933
5	0.982

Following is the formula for estimate of occlusion predictive rate:

$$\hat{p} = \frac{1}{1 + \exp\left(-\sum_{i=0}^{P} \beta_i X_i\right)},$$

where $\hat{p}$ is the estimate of occlusion predictive rate;

$\sum_{i=0}^{P} \beta_i X_i \approx$ constant term (multivariate logistic regression model) $+\beta_{ij} \times W_{ij} + B \times$ total predictive score

significant difference between the two groups for 4F-FPS score ($p = 0.265$). In the validation group, AUCs for the scores of 4F-FPS, OKM, Kamran, SMART, and FDSS were 0.894 (0.843–0.933), 0.807 (0.745–0.895), 0.835 (0.776–0.884), 0.845 (0.787–0.892), and 0.814 (0.753–0.866), respectively (Figure 3(b)). AUCs were comparable among these grading systems

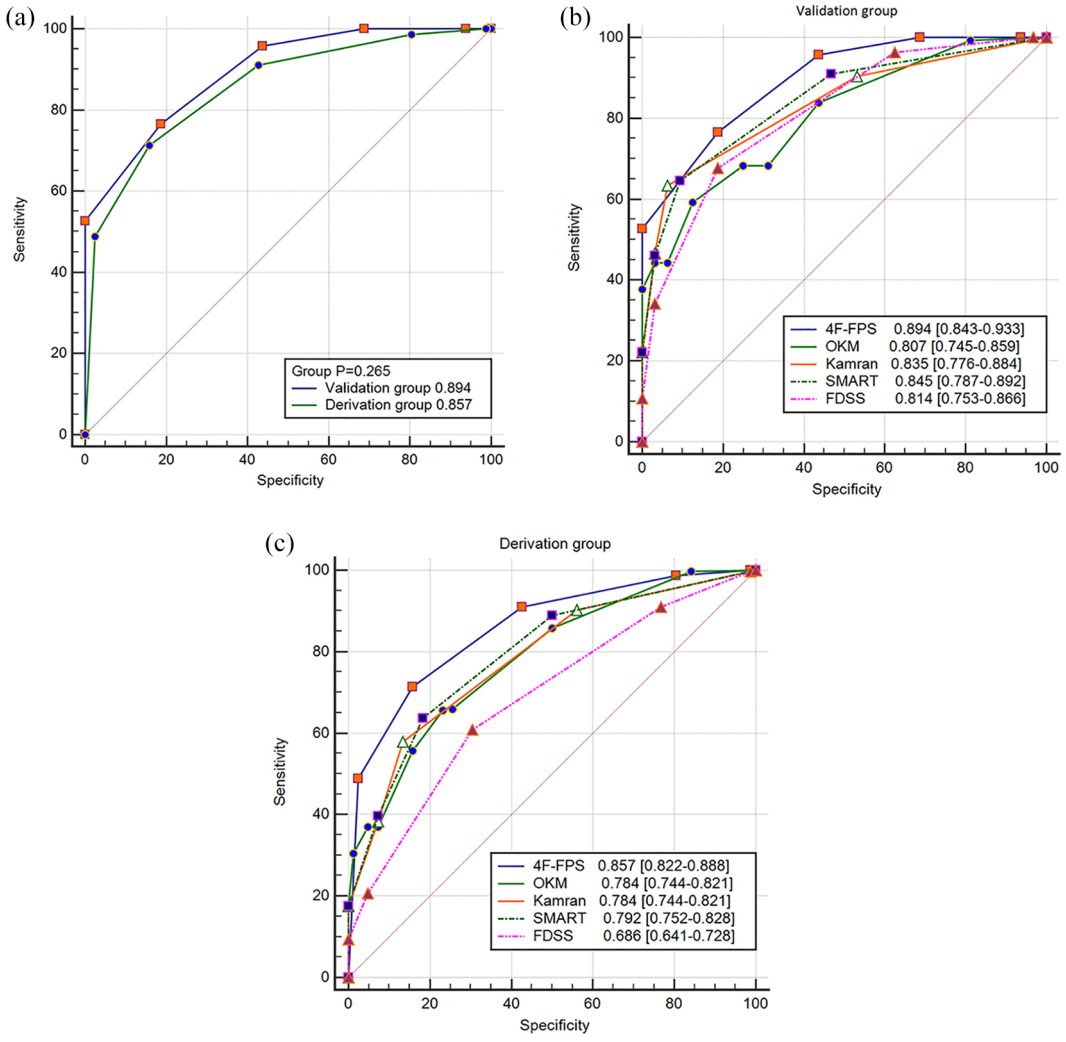

Figure 3. (a) Comparison of AUC differences between the validation group and the derivation group, derivation group AUC: 0.857 (0.822–0.888); validation group AUC: 0.894 (0.843–0.933). (b) Performance of grading systems in predicting aneurysm occlusion in the validation group. (c) Performance of grading systems in predicting aneurysm occlusion in the derivation group.

(Supplementary Table 5). In the derivation group, AUCs for the scores of 4F-FPS, OKM, Kamran, SMART, and FDSS were 0.857 (0.822–0.888), 0.784 (0.744–0.821), 0.784 (0.744–0.821), 0.792 (0.752–0.828), and 0.686 (0.641–0.728), respectively (Figure 3(c)). The pairwise comparison result of these grading scales/scores is shown in Supplementary Table 6. The AUC of 4F-FPS score in both the derivation and validation groups is the largest compared with other grading systems [validation group AUC: 0.894 (0.843–0.933), derivation group AUC: 0.857 (0.822–0.888)]. AUC areas of 4F-FPS score were statistically significant in pairwise comparisons with other grading scales/scores ($p < 0.05$), which showed better sensitivity and specificity. Three clinical neuro-interventionists used the 4F-FPS score to perform a total of 3972 times of scoring ($662 \times 3 \times 2$ times), and the average credibility kappa values of the interobserver and intraobserver reproducibility of measurements of the 4F-FPS score were 0.897 (95% CI = 0.857–0.936) and 0.944 (95% CI = 0.916–0.973), respectively, which showed excellent agreement.

Discussion

The PED was Food and Drug Administration approved in 2011,[13] marking it as the first commercially available FD, and its efficacy and safety have been demonstrated in clinical studies.[14,15] Many additional devices have since been brought to market, with their safety and efficiency having also been verified in studies.[16–18] As FD technology gains further traction, there is a need for a simple and easy-to-use grading system to evaluate treatment outcomes and standardize reporting of clinical results and trials.

The 4F-FPS grading system draws inspiration from previously published scales to predict outcomes following flow diversion treatment for intracranial aneurysms. The 4F-FPS was developed by examining a large 5-year cohort of patients, first deriving what would become the four independent predictors of aneurysm occlusion: fusiform shape, flow-jet, filling, and final stasis. We then validated the grading system in pairwise comparisons with previously published scales. All ROC and AUC metrics indicate that the 4F-FPS has strong reliability, accuracy, and predictive power, placing it equivalent or superior to the existing scales.

The 4F-FPS meets a critical, as-of-yet unmet clinical need to assess angiographic outcomes and predict occlusion outcomes following flow diversion treatment. Although the Raymond score[7] is relatively common and may initially appear suitable for this purpose, it would require aneurysms to show immediate occlusion after FD implantation, which they do not, and thus is not appropriate. Other authors have, respectively, published their OKM,[3] Kamran,[4] SMART,[5] and FDSS[6] grading systems, but none of these scales have been widely adopted by physicians. One study found that the inter-rater reliability between SMART, Kamran, and OKM scales is generally low[19]; another study compared the predictive capacity of all four aforementioned scales and found only FDSS was a significant predictor of final occlusion, but even it 'fell below the typical level for widespread clinical utility'.[20] Although each system has its own strengths, clearly none are able to meet demonstrated needs. That these scales have fallen somewhat short is less surprising considering that, of the four grading systems, only one (FDSS) was specifically developed based on final patient outcomes. The FDSS includes variables based on both initial and final treatment results, combining the Raymond score with the status of side branches, aneurysm size, and patient age; however, the Raymond score was originally developed to describe angiography status after coiling embolization, not flow diversion treatment. The FDSS is thus unable to fully capture blood flow status after FD implant. Notably, our study confirmed with significant ORs that such blood flow characteristics, extending into the venous phase or no blood flow, and coherent inflow jet, are independent predictive factors for final aneurysmal occlusion. In addition, contrast stasis after PED deployment is also a controversial factor for aneurysm occlusion that is not fully considered by the FDSS score. The Raymond–Roy occlusion classification used for coiled aneurysms does not address the results of flow modification treatments, but other classifications for extrasaccular FD treatment have defined flow stagnation as a determining feature.[3–5] However, flow stagnation does not necessarily have direct implications regarding the future or final treatment result.[21] Vakharia and colleagues[22] reported that the degree of aneurysm contrast stasis immediately after PED deployment is not significantly associated with 6- and 12-month angiographic occlusion rates. Our research fully considers the various factors of postoperative blood flow changes (residual contrast filling, final stasis, flow-jet) and verifies the predictive effect of these factors on occlusion. However, further external research is needed to verify the results.

To develop a data- and outcomes-driven, statistically robust, and clinically useful grading system, we followed the derivation model described by Wilson and colleagues[11] from the Framingham Heart Study. First, we designed our investigation of relevant predictive factors around research of previous studies, which had reported that adjunctive coiling, aneurysm size, incorporated branch vessel, age, sex, prior treatments, fusiform morphology, and smoking status were all relevant predictive factors for aneurysmal occlusion.[23–26] Furthermore, use of multiple PEDs was also a predictive factor and was associated with higher intracranial aneurysm occlusion rates and lower retreatment rates.[27] Putting all these likely factors into the regression models, we then confirmed which of these factors are related to final angiography outcomes. This kind of rigorous development sets the 4F-FPS apart from previously published scales, which were largely based simply on clinical judgment and best practices. Although

the FDSS reports similarly rigorous development, its data were based on a fairly small cohort of 171 patients,[6] whereas our study included nearly four times as many subjects, lending additional credibility to the 4F-FPS scale. In addition, our 4F-FPS system showed a high degree of sensitivity and specificity through statistical analysis, with excellent prediction, discrimination, and calibration properties. The ROC area of 4F-FPS score was the largest compared with other grading systems in both the derivation group and the validation group. AUCs were statistically significant among these grading systems, demonstrating that the 4F-FPS is preferred over the previously published scores.

Previous studies have found that early blood stagnation in the aneurysm is predictive of therapeutic success,[4,28] and one study developed a mathematical model congruent with the flow transport phenomena observed in cerebral aneurysms. The model was based on the washout of angiographic contrast medium from these aneurysms, which was used to provide quantitative indices to predict the likelihood of stable thrombus formation after stent placement.[29] However, another study suggested that early angiographic changes after FD placement are very frequent but are not correlated with the 12-month technical success of flow diversion techniques.[30] Our study showed that the changes in blood flow status (residual contrast filling, final stasis, flow-jet) after FD placement might be associated with aneurysm occlusion on follow-up angiography. Similarly, our results are consistent with the Kamran scale, which focuses on the percentage of the aneurysm dome that is filled instead of the actual level of contrast stasis in multiple frames. In addition, one study has confirmed that the occlusion time of cerebral aneurysms treated with FDs can be predicted by the hemodynamic conditions created immediately after device implantation, and low postimplantation flow velocity, inflow rate, and shear rate are associated with rapid occlusion times.[31] Our result showed that flow-jet ($\beta = 2.373$, OR = 10.728, 95% CI = 5.146–22.367) was a predictive factor for aneurysm occlusion. Similarly, the SMART score also categorizes the inflow jet of contrast on an injection immediately after flow diversion.[5]

Similar to the Spetzler–Martin scale for arteriovenous malformations,[32] the 4F-FPS consists of just four grading components, and each grading component can only receive a score of 0, 1, or 2. This type of simplicity makes the grading system straightforward and memorable for physicians and others who may use it. The average credibility kappa value of the interobserver and intraobserver reproducibility of measurements of the 4F-FPS score was 0.897 (95% CI = 0.857–0.936) and 0.944 (95% CI = 0.916–0.973), respectively, which showed excellent agreement. As a readily understandable and applicable grading system, the 4F-FPS may provide a common language needed to be used in future reporting of the flow diversion results. With further studies to verify its utility and additional familiarization, the 4F-FPS could be used to inform patient treatment plans leading up to intervention (e.g. adjunctive coiling or overlapping flow divert implant) and predict recanalization risk after treatment.

Limitations

The 4F-FPS system was based on physician interpretation of various factors, which occasionally led to discrepancies that were resolved; clinical application of the 4F-FPS likewise involves some level of subjective interpretation. Furthermore, external validation of this grading scale using data from other institutions is needed. The decision to proceed with flow diversion was up to surgeons performing the intervention, which could have introduced selection bias into the study population.

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Conflict of interest statement

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References

1. Gory B, Berge J, Bonafe A, *et al*. Flow diverters for intracranial aneurysms: the diversion national prospective cohort study. *Stroke* 2019; 50: 3471–3480.
2. Sweid A, Starke RM, Herial N, *et al*. Predictors of complications, functional outcome, and morbidity in a large cohort treated with flow diversion. *Neurosurgery* 2019; 87: 730–743.
3. O'Kelly CJ, Krings T, Fiorella D, *et al*. A novel grading scale for the angiographic assessment of intracranial aneurysms treated using flow diverting stents. *Interv Neuroradiol* 2010; 16: 133–137.
4. Kamran M, Yarnold J, Grunwald IQ, *et al*. Assessment of angiographic outcomes after flow diversion treatment of intracranial aneurysms: a new grading schema. *Neuroradiology* 2011; 53: 501–508.
5. Grunwald IQ, Kamran M, Corkill RA, *et al*. Simple measurement of aneurysm residual after treatment: the smart scale for evaluation of intracranial aneurysms treated with flow diverters. *Acta Neurochir* 2012; 154: 21–26.
6. Park MS, Mazur MD, Moon K, *et al*. An outcomes-based grading scale for the evaluation of cerebral aneurysms treated with flow diversion. *J Neurointerv Surg* 2017; 9: 1060–1063.
7. Roy D, Milot G and Raymond J. Endovascular treatment of unruptured aneurysms. *Stroke* 2001; 32: 1998–2004.
8. Luo B, Kang H, Zhang H, *et al*. Pipeline embolization device for intracranial aneurysms in a large Chinese cohort: factors related to aneurysm occlusion. *Ther Adv Neurol Disord* 2020; 13: 1–11.
9. Kang H, Zhou Y, Luo B, *et al*. Pipeline embolization device for intracranial aneurysms in a large Chinese cohort: complication risk factor analysis. *Neurotherapeutics*. Epub ahead of print 14 January 2021. DOI: 10.1007/s13311-020-00990-8.
10. Kang H, Luo B, Liu J, *et al*. Postoperative occlusion degree after flow-diverter placement with adjunctive coiling: analysis of complications. *J Neurointerv Surg*. 13 May 2021. DOI: 10.1136/neurintsurg-2021-017445.
11. Wilson PW, D'Agostino RB, Levy D, *et al*. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97: 1837–1847.
12. Senn S. Review of Fleiss, statistical methods for rates and proportions. *Res Synth Methods* 2011; 2: 221–222.
13. Patel PD, Chalouhi N, Atallah E, *et al*. Off-label uses of the pipeline embolization device: a review of the literature. *Neurosurg Focus* 2017; 42: E4.
14. Becske T, Brinjikji W, Potts MB, *et al*. Long-term clinical and angiographic outcomes following pipeline embolization device treatment of complex internal carotid artery aneurysms: five-year results of the pipeline for uncoilable or failed aneurysms trial. *Neurosurgery* 2017; 80: 40–48.
15. Hanel RA, Kallmes DF, Lopes DK, *et al*. Prospective study on embolization of intracranial aneurysms with the pipeline device: the premier study 1 year results. *J Neurointerv Surg* 2020; 12: 62–66.
16. Mohlenbruch MA, Herweh C, Jestaedt L, *et al*. The FRED flow-diverter stent for intracranial aneurysms: clinical study to assess safety and efficacy. *Am J Neuroradiol* 2015; 36: 1155–1161.
17. De Vries J, Boogaarts J, Van Norden A, *et al*. New generation of flow diverter (surpass) for unruptured intracranial aneurysms: a prospective single-center study in 37 patients. *Stroke* 2013; 44: 1567–1577.
18. Lubicz B, Van der Elst O, Collignon L, *et al*. Silk flow-diverter stent for the treatment of intracranial aneurysms: a series of 58 patients with emphasis on long-term results. *Am J Neuroradiol* 2015; 36: 542–546.
19. Mazur MD, Taussky P, Shah LM, *et al*. Inter-rater reliability of published flow diversion occlusion scales. *J Neurointerv Surg* 2016; 8: 1294–1298.
20. Raper DMS, Chen CJ, Kumar J, *et al*. Predicting outcomes for cerebral aneurysms treated with flow diversion: a comparison between 4 grading scales. *World Neurosurg* 2019; 128: e209–e216.
21. Cekirge HS and Saatci I. A new aneurysm occlusion classification after the impact of flow modification. *Am J Neuroradiol* 2016; 37: 19–24.
22. Vakharia K, Waqas M, Munich SA, *et al*. Is contrast stasis after pipeline embolization device

deployment associated with higher aneurysm occlusion rates. *World Neurosurg* 2020; 133: e434–e442.

23. Bender MT, Colby GP, Lin LM, *et al*. Predictors of cerebral aneurysm persistence and occlusion after flow diversion: a single-institution series of 445 cases with angiographic follow-up. *J Neurosurg* 2018; 130: 259–267.
24. Shapiro M, Becske T and Nelson PK. Learning from failure: persistence of aneurysms following pipeline embolization. *J Neurosurg* 2017; 126: 578–585.
25. Jabbour P, Chalouhi N, Tjoumakaris S, *et al*. The pipeline embolization device: learning curve and predictors of complications and aneurysm obliteration. *Neurosurgery* 2013; 73: 113–120.
26. Adeeb N, Moore JM, Wirtz M, *et al*. Predictors of incomplete occlusion following pipeline embolization of intracranial aneurysms: is it less effective in older patients? *Am J Neuroradiol* 2017; 38: 2295–2300.
27. Waqas M, Vakharia K, Gong AD, *et al*. One and done? The effect of number of pipeline embolization devices on aneurysm treatment outcomes. *Interv Neuroradiol* 2020; 26: 147–155.
28. Brinjikji W, Murad MH, Lanzino G, *et al*. Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. *Stroke* 2013; 44: 442–447.
29. Sadasivan C, Lieber BB, Gounis MJ, *et al*. Angiographic quantification of contrast medium washout from cerebral aneurysms after stent placement. *Am J Neuroradiol* 2002; 23: 1214–1221.
30. Labeyrie PE, Gory B, Sadeh-Gonike U, *et al*. Early angiographic changes of intra-aneurysmal flow after flow-diverter stent treatment are not predictive of therapeutic success. *Interv Neuroradiol* 2016; 22: 682–686.
31. Mut F, Raschi M, Scrivano E, *et al*. Association between hemodynamic conditions and occlusion times after flow diversion in cerebral aneurysms. *J Neurointerv Surg* 2015; 7: 286–290.
32. Spetzler RF and Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg* 1986; 65: 476–483.