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Title page

A new predictive model for microsurgical outcome of intracranial arteriovenous malformations: study protocol

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ABSTRACT

Introduction: Although microsurgical resection is currently the gold standard treatment modality for AVMs, microsurgery of these lesions is complicated due to the fact that they are very heterogeneous vascular anomalies. The Spetzler-Martin grading system and the supplementary grading system have demonstrated excellent performances in predicting the risk of AVM surgery. However, there are currently no predictive models based on multi-modal functional magnetic resonance imaging (fMRI). The purpose is to propose a predictive model based on multimodal fMRIs to assess the microsurgical risk of intracranial AVMs.

Methods and analysis: The study consists of two parts: the first part is to conduct a single-center retrospective analysis of 250 eligible patients to create a predictive model of AVM surgery based on multimodal fMRIs; the second part is to validate the efficacy of the predictive model in a prospective multi-center cohort study of 400 eligible patients. Patient characteristics, AVM features and multimodal fMRI data will be collected. The functional status at pretreatment and 6 months after surgery will be analyzed using the modified Rankin Scale (mRS) score. The patients in each part of this study will be dichotomized into two groups: those with improved or unchanged functional status (a decreased or unchanged mRS 6 months after surgery) and those with worsened functional status (an increased mRS). The first part will determine the risk factors of worsened functional status after surgery and create a predictive model. The second part will validate the predictive model and then a new AVM grading system will be proposed.

Ethics and dissemination: The study protocol and informed consent form have been reviewed and approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University (KY2016-031-01). The results of this study will be disseminated through printed media.

Trial registration number: ClinicalTrials.gov ID: NCT02868008

Key Words: inctracranial arteriovenous malformations (AVMs), predictive model, functional magnetic resonance imaging (fMRI), microsurgery

Strength and limitation of this study

Currently there are two grading systems (the Spetzler-Martin grading system and the supplementary grading system) in predicting the surgical outcomes of AVM resection. However, despite these two grading systems, surgical selection for AVM patients remains challenging, especially for those with eloquent AVMs. To ensure precision medicine and tailored treatment delivery, future grading scales that incorporate imaging features might replace the current grading systems. Based on this standpoint, we proposed this study. And in our previous studies, we have found that fMRI is a valuable tool in preoperative evaluation. We have also found that fMRI-guided inraoperative mapping allows optimal surgical planning and preservation of eloquent cortical areas adjacent to the AVMs. An fMRI-based predictive model might be superior to the current grading systems in predicting AVM surgery. However, many factors may influence this study. The second part of this study (validation set) is a prospective multicenter cohort study. Although these participating centers are well-known neurosurgical centers with high-volume AVM practices and high-level neurosurgical expertise in China, selection bias may exist between these centers.

INTRODUCTION

The incidence of intracranial arteriovenous malformations is estimated as 1.12–1.42 cases per 100,000 person-years.[1] The annual bleeding rate of untreated AVMs is reported to range from 0.78% to 34.3%, depending on AVM locations and patterns of venous drainage.[2-5] Intracranial AVMs are associated with high risk of morbidity and mortality.[6-9] Current treatment modalities for intracranial AVMs include microsurgical treatment, endovascular embolization, radiosurgical treatment and combination of two or three of the above. The risks associated with AVM treatment must be weighed against the natural history of hemorrhage.[10,11] However, the natural history of intracranial AVMs is still largely unknown.[1,11] Microsurgery offers the highest immediate cure rate and remains the gold standard treatment modality. However, microsurgical resection of intracranial AVMs, especially AVMs in eloquent locations, remains challenging and carries high risk of complications.

Currently, there are mainly two AVM grading systems that are commonly used in clinical practice: the Spetzler-Martin grading system and the supplementary grading system. The Spetzler-Martin grading system was first introduced by Spetzler and Martin in 1986 and consists of three factors: AVM size, location (eloquent or non-eloquent) and patterns of venous drainage.[12] The supplementary grading system was first proposed by Lawton et al. in 2010 and embodies three factors: patient age, bleeding, and diffuseness.[13] Both the two grading systems are well-designed in assessing the risks associated with AVM surgery. However, other factors may also influence the treatment outcomes besides the above six factors in the two grading systems.[11]

Functional MRI (fMRI) is a new imaging technique to identify the functional imaging of eloquent area of the brain. Diffuse tensor imaging (DTI) is a potential technique to map eloquent fiber tracts. Till now, in assessing the surgical risk of AVMs, there is no predictive model based on multi-modal fMRI. Small sample studies have reported that fMRI is a valuable tool for preoperative evaluation and treatment planning of brain AVMs.[14-24] In our previous studies of AVMs based on multimodal imaging techniques, we have found that the least distance from the AVM nidus to the activated cortex or the eloquent fiber tracts on fMRI studies is associated with surgical outcomes.[25-28] A 5-mm distance from the eloquent fibers may be a suitable safety margin for postoperative function preservation.[26-28] Based on our previous findings, we will create as well as validate a multimodal fMRI-based predictive model to assess the surgical risk in each individual AVM patient.

STUDY OBJECTIVE

The key purpose of this study is to create and validate a new predictive model for the surgical risk of intracranial AVMs. Based on this predictive model, we will propose a new supplementary grading system for intracranial AVMs.

METHODS AND ANALYSIS

Study designs

The study consists of two parts: the discovery set and the validation set. The discovery set is a retrospective analysis of 250 eligible AVM patients that were surgically treated at Beijing Tiantan Hospital (China National Clinical Research Center for Neurological Diseases) between June 2012 and June 2015. The validation set is a prospective cohort study of AVM patients that will receive surgical resection for their AVMs at five major neurosurgical centers in China between June 2016 and June 2019. The study design is presented in figure 1.

Study participants

Patient demographic characteristics (age, sex, history of hemorrhage and preoperative functional status), AVM features (size, location, arterial supply, patterns of venous drainage, Spetzler-Martin grade and diffuseness) and multimodal MRI data (the least distance from the AVM to the eloquent cortex or the eloquent fiber tracts) will be provided. Patient functional status was or will be measured by the modified Rankin Scale (mRS) score. All patients in this study should meet the inclusion and exclusion criteria. For the prospective study part (validation set), informed written consent should be obtained from eligible adult patients or from the guardians of eligible pediatric patients. All patients in the prospective part of this study can withdraw at any time.

Inclusion criteria

1. Patients aged between 12 and 60 years.

2. Patients with a definite diagnosis of AVM confirmed by preoperative digital subtraction angiography (DSA).

3. Patients with complete multimodal MRIs: preoperative structural MRI, blood oxygen level-dependent (BOLD)-fMRI, time-of-flight magnetic resonance angiography (TOF-MRA), and DTI of the eloquent fiber tracts.

4. Patients opting for surgical management of their AVMs.

5. Patients without any treatment (microsurgery, radiosurgery, endovascular embolization, or multimodality treatment) before enrollment.

Exclusion criteria

1. Patients receiving emergency surgery due to acute intracranial hematoma and resultant brain hernia.

2. Patients experiencing an AVM-related hemorrhage in the past month before admission.

3. Patients without BOLD-fMRI and DTI data.

4. Patients with severe diseases that prevent them from microsurgical treatment.

5. Patients without written informed consent.

Multimodal fMRI data acquisition

Structural MRI scans, blood oxygen level dependent fMRI (BOLD-fMRI), diffusion tensor imaging (DTI) and time of flight MRA (TOF-MRA) were or will be performed on a 3T Siemens Tim Trio MRI scanner (Siemens Healthcare, Erlangen, Germany) as previously described.[22,24,29,30] For Bold-fMRI, maps of neural activity within motor, language or visual cortex were or will be generated as described in our previous publication.[31] The preoperative MRI data were or will be saved as DICOM format. The data were or will be transferred to an off-line iPlan 3.0 workstation (BrainLab, Feldkirchen, Germany) for analysis. The 3D model of the eloquent cortex (motor, language or visual), the fiber tracking of the eloquent fibers (corticospinal tract, the arcuate fasciculus, or the optic radiation) and the 3D anatomic structure of the AVMs were or will be reconstructed as described in our previous publications.[26-28,32,33]

AVM angioarchitecture (including the feeding artery, the nidus and the venous drainage) and AVM diffuseness will be acquired by the 3D MRA. The maximum diameter of the AVMs was or will be measured from the structural MRI on the axial, coronary and sagittal directions. The least distances from AVM to the eloquent cortex (AVM-EC) and eloquent fibers (AVM-EF) were or will be measured respectively on the axial, coronary and sagittal directions on 3D reconstruction of the AVM, the eloquent cortex and the eloquent fiber.

Treatment procedure

Preoperative multi-modality MRI reconstruction data (reconstruction of Bold-fMRI, DTI and TOF-MRA) were or will be displayed on a Kolibri WS 2.0 navigation system (BrainLab，Germany) during surgery. Craniotomy was or will be performed according to the preoperative plan based on the multimodal reconstruction data on the navigation system. After craniotomy, the feeding arteries, AVM nidus and draining veins of the AVM as well as adjacent eloquent cortex or eloquent fibers were or will be identified with the navigator's probe, as described in our previous publications.[31,32]

All microsurgical techniques or equipments such as intraoperative ultrasound and indocyanine fluorescence angiography (ICG) were or will be available during surgical resection. Motor evoked potential (MEP) and somatosensory evoked potential (SSEP) were or will be provided as needed for intraoperative monitoring.[31,32]

Outcome evaluation

The primary outcome is the change of functional status (mRS score) between two time points: at pretreatment and 6 months after microsurgery. Good outcome is defined as a decreased or unchanged mRS score (mRS 6 months after surgery minus pretreatment mRS ≤ 0). Poor outcome is defined as an increased mRS score (mRS 6 months after surgery minus pretreatment mRS > 0). The potential influencing factors for poor outcome will be collected. These factors are patient age, history of hemorrhage, preoperative mRS, AVM size, AVM location, deep arterial perforator supply, patterns of venous drainage, compactness and the least distance from AVM to eloquent cortex (AVM-EC) or eloquent fiber tract (AVM-EF) on multimodal fMRIs.

The second outcomes include AVM obliteration, headache and seizure outcome, surgical complications, and neurologic deficits (motor, language or visual deficits). AVM obliteration was or will be assessed by postoperative digital subtraction angiography (3 to 7 days after surgery). Seizure outcome was or will be assessed using the modified Engel scale (4 classes). The surgical complications include hemorrhagic stroke, intracranial infection, de novo seizures, and cerebral infarction within 6 months after surgery. Motor deficits were or will be assessed using muscle strength measured by muscle strength grading scale. Language deficits were or will be measured by Western Aphasia Battery (WAB) 6 months after surgery. Visual field deficits were or will be measured by visual field testing 6 months after surgery.

Sample size

According to the literature, in predicting the microsurgical outcome of brain AVMs, by comparing the area under the receiver operating characteristic (AUROC) curves corresponding to Spetzler-Martin grading system and supplementary Spetzler-Martin grading system models, the AUROC values of the Spetzler-Martin grading system and the supplementary Spetzler-Martin grading system are 0.69 and 0.58 respectively.[34] We hypothesize that the new predictive model can generate an AUROC value of 0.81. A significant difference of AUROC value between the new predictive model and the supplementary S-M grading system is 0.10. A sample size of 232 patients will meet the need of the

discovery set with a two-sided significance level of 5% and a power of 80%. In our AVM data base, we have 250 patients that meet the inclusion and exclusion criteria and these patients will be included in the discovery set. From June 2016 to June 2019, we will enroll 400 eligible patients from five neurosurgical centers with high-volume AVM practices and high-level neurosurgical expertise. The new model created from the discovery set will be validated in the prospective 400 eligible patients.

Statistical analyses to create a new predictive model

Statistical analyses will be performed using the Statistical Package for the Social Sciences software (version 20.0; SPSS Inc., Chicago, Illinois, USA). Patient characteristics and AVM features based on multimodal imaging will be summarized using descriptive statistics for continuous variables and categorical variables. These variables include patient demographics (age, sex, history of hemorrhage and pretreatment mRS scores), AVM features (size, cortical or deep location, eloquent or non-eloquent location, arterial supply, patterns of venous drainage, diffuseness and associated aneurysm) and multimodal imaging data (the least distance from the AVM to the eloquent cortex or to the eloquent fibers based on 3D reconstruction).

For the 250 patients in the discovery set, to create a predictive model for poor neurological outcome, we will analyze patient characteristics, AVM features and fMRI data by univariate and multivariate logistic regression analyses using poor outcome as the binary response. To assess the predictive ability of the multivariate model, we measured the area under the receiver operating characteristic (AUROC) curve based on the predicted values in the multivariate analyses. We will also measure the AUROC for Spetzler-Martin grading system and the supplementary grading system models. Comparison between the new predictive model and the current two grading system models will be performed based on AUROC. The multimodal fMRI-based predictive model then will be created.

Validation of the new predictive model

For the patients (a sample size of 400 eligible patients) in the multi-center prospective cohort study, the new predictive model will be verified in predicting poor outcomes. In the validation set, the new predictive model will also be compared with the current two existing grading systems by using the AUROC to predict poor neurological outcomes. If the new predictive model is superior to the Spetzler-Martin grading system and the supplementary grading system, the new model is validated and a new grading system will be proposed.

Data management

All data in the discovery set of 250 patients can be collected from our prospectively maintained AVM database at Beijing Tiantan Hospital. All data in the validation set will be prospectively collected using an electronic case report form (eCRF) through a study website. Five major neurological centers in China can access and manage patient information by login and password. All patients enrolled will be carefully monitored until 6 months after surgery. Data safety, data quality, monthly auditing and statistical analysis will be managed by a third party--SUN HEALTH (Beijing).,LTD, who shall be responsible for notifying any issues that will arise during the whole clinical trial. The whole trial will be supervised by Beijing Municipal Science & Technology Commission and China National Clinical Research Center for Neurological Diseases. Any issue occurring during the trial will be reported to these two oversight authorities. Recommendations from these two authorities will be forwarded to the principal investigators to balance the risk and benefit. The oversight authorities have the rights to terminate the trial if great risk occurs during the trial.

Duration of the study

The discovery set will include 250 eligible AVM patients that were surgically treated in Beijing Tiantan Hospital between June 2012 and June 2015. The validation set will enroll 400 eligible AVM patients that will receive microsurgical treatment in five major neurosurgical centers in China from June 2016 until June 2019.

ETHICS AND DISSEMINATION

The study is supported by Key Project of Beijing Municipal Science & Technology Commission (Grant No. D161100003816006). The first part of this study is a retrospective review of patients treated at one single center (Beijing Tiantan Hospital). The second part of this study is a prospective cohort study treated at five neurosurgical centers. To create and validate the multimodal fMRI-based predictive model for AVM surgery, all patients should have complete preoperative fMRI data and meet the inclusion and exclusion criteria. This study will be conducted in accordance with ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. Written informed consent will be obtained from each adult participant or from the guardian of each pediatric participant in the validation set. Professor Shuo Wang is the principal investigator of this clinical trial. Data collection, statistical analysis, interpretation and dissemination of study results will be managed under his direct supervision. The final results of this study will be disseminated through printed media in December 2019.

DISCUSSION

In 1986, Spetzler and Martin introduced the first AVM grading system (the Spetzler-Martin grading system) to estimate the risk of AVM surgery.[12] The Spetzler-Martin grading system is a 5-point scale that is based on AVM size, eloquent or non-eloquent AVM location, and patterns of venous drainage. According to S-M grading system, patients with asymptomatic grade 4 and 5 AVMs should not be surgically treated due to the high risk of surgical complications.[12] However, this standpoint is not universally accepted. Based on the original 5-tier Spetzler-Martin grading system, Spetzler and Ponce proposed a 3-tier classification for AVMs in 2011.[35] In this 3-tier classification, AVMs are divided into class A (S-M grade I and II AVMs), class B (S-M grade III AVMs) and class C (S-M grade IV and V AVMs). This 3-tier classification simplifies treatment recommendations. However, observation is still recommended for patients with asymptomatic class C (S-M grade IV and V) AVMs.[35]

In 2010, Lawton et al. proposed a supplementary grading system including three additional parameters that may affect surgical outcomes: patient age, hemorrhagic presentation and nidal diffuseness.[13] The authors proposed a full multivariable model (combination of S-M grading system and supplementary system) and a supplementary model. In analysis of 1009 patients, the authors found that the full multivariable model had the highest predictive accuracy.[34] However, surgical selection for AVM patients remains challenging. Just as described in a recent review in *Neurosurgery*, future grading scales may incorporate imaging features.[11] Multimodal fMRIs have proved to be a valuable tool in preoperative evaluation and surgical planning. In our clinical practice, we have found that the least distance from AVM to eloquent cortex or eloquent fibers based on multimodal imaging is significantly associated with surgical outcomes.[25-28] Based on our previous studies, we have designed this study to propose a multimodal MR imaging-based predictive model for surgical outcomes of intracranial AVMs. We will compare the predictive accuracy between the new predictive model and the current two grading systems. We hypothesize that the new predictive model in this study has the highest predictive accuracy.

Authors' contributions

SW has obtained research funding and is the principal investigator of the study. YC, YZ and SW have developed this study protocol. XT, JW, YC, YZ and SW have participated in the final design of the study.

Funding statement

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Competing interests statement

None.

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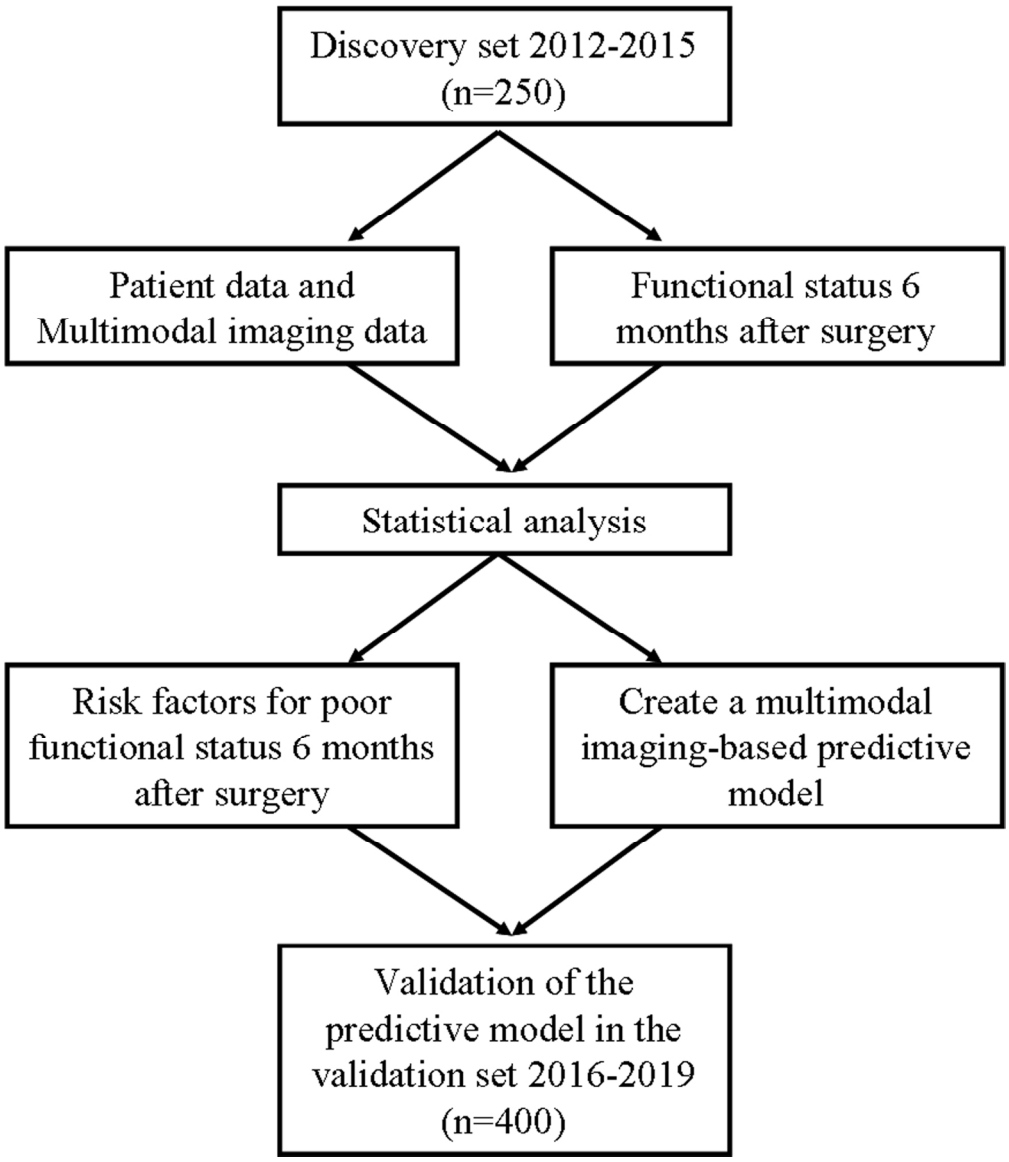
Figure legends

Figure 1. Diagram of the study protocol.



146x168mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Page 1
	2b	All items from the World Health Organization Trial Registration Data Set Page 1
Protocol version	3	Date and version identifier Page 1, Page 9
Funding	4	Sources and types of financial, material, and other support Page 10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Page 10
	5b	Name and contact information for the trial sponsor Page 10
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities Page 9
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Page 9
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Page 4
	6b	Explanation for choice of comparators Page 4
Objectives	7	Specific objectives or hypotheses Page 4

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Page 5
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Page 5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Page 5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Page 6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Page 5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Page 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure 1) Page 7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Page 7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Page 8-9
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Page 9-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Page 9-10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Page 9-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Page 9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) NA

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Page 9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Page 9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Page 9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Page 9

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Page 9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Page 10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Page 9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Page 11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Page 9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions Page 9
	31b	Authorship eligibility guidelines and any intended use of professional writers Page 9
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Page 9
Appendices		NA
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Title page

A new predictive model for microsurgical outcome of intracranial arteriovenous malformations: study protocol

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ABSTRACT

Introduction: Although microsurgical resection is currently the first-line treatment modality for AVMs, microsurgery of these lesions is complicated due to the fact that they are very heterogeneous vascular anomalies. The Spetzler-Martin grading system and the supplementary grading system have demonstrated excellent performances in predicting the risk of AVM surgery. However, there are currently no predictive models based on multi-modal magnetic resonance imaging techniques. The purpose is to propose a predictive model based on multimodal MRI techniques to assess the microsurgical risk of intracranial AVMs.

Methods and analysis: The study consists of two parts: the first part is to conduct a single-center retrospective analysis of 201 eligible patients to create a predictive model of AVM surgery based on multimodal fMRIs; the second part is to validate the efficacy of the predictive model in a prospective multi-center cohort study of 400 eligible patients. Patient characteristics, AVM features and multimodal fMRI data will be collected. The functional status at pretreatment and 6 months after surgery will be analyzed using the modified Rankin Scale (mRS) score. The patients in each part of this study will be dichotomized into two groups: those with improved or unchanged functional status (a decreased or unchanged mRS 6 months after surgery) and those with worsened functional status (an increased mRS). The first part will determine the risk factors of worsened functional status after surgery and create a predictive model. The second part will validate the predictive model and then a new AVM grading system will be proposed.

Ethics and dissemination: The study protocol and informed consent form have been reviewed and approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University (KY2016-031-01). The results of this study will be disseminated through printed media.

Trial registration number: ClinicalTrials.gov ID: NCT02868008

Key Words: inctracranial arteriovenous malformations (AVMs), predictive model, functional magnetic resonance imaging (fMRI), microsurgery

Strength and limitation of this study

The study is designed to provide a new supplementary grading scale in predicting surgical outcomes of brain arteriovenous malformations.

The new predictive model based on multimodal MR imaging techniques may be superior to currently existing AVM grading systems.

Selection bias may exist in the prospective phase of the study that consists of patients treated by different neurosurgeons at different neurosurgical centers.

INTRODUCTION

The incidence of intracranial arteriovenous malformations is estimated as 1.12–1.42 cases per 100,000 person-years.[1] The overall annual bleeding rate of untreated AVMs is reported to range from 2.10% -4.12%.[1-5] Intracranial AVMs are associated with high risk of morbidity and mortality.[6-9] Current treatment modalities for intracranial AVMs include microsurgical treatment, endovascular embolization, radiosurgical treatment and combination of two or three of the above. The risks associated with AVM treatment must be weighed against the natural history of hemorrhage.[10,11] However, the natural history of intracranial AVMs is still largely unknown.[1,11] Microsurgery offers the highest immediate cure rate.[11] However, microsurgical resection of intracranial AVMs, especially AVMs in eloquent locations, remains challenging and carries high risk of complications.

Currently, there are mainly two AVM grading systems that are commonly used in clinical practice: the Spetzler-Martin grading system and the supplementary grading system. The Spetzler-Martin grading system was first introduced by Spetzler and Martin in 1986 and consists of three factors: AVM size, location (eloquent or non-eloquent) and patterns of venous drainage.[12] The supplementary grading system was first proposed by Lawton et al. in 2010 and embodies three factors: patient age, bleeding, and diffuseness.[13] Both the two grading systems are well-designed in assessing the risks associated with AVM surgery. However, other factors may also influence the treatment outcomes besides the above six factors in the two grading systems.[11]

Functional MRI (fMRI) is a new imaging technique to identify the functional imaging of eloquent area of the brain. Diffuse tensor imaging (DTI) is a potential technique to map eloquent fiber tracts. Till now, in assessing the surgical risk of AVMs, there is no predictive model based on multi-modal fMRI. Small sample studies have reported that multimodal MR techniques (fMRI, DTI and TOF-MRA) are valuable tools for preoperative evaluation and treatment planning of brain AVMs.[14-24] In our previous studies of AVMs based on multimodal imaging techniques, we have found that the least distance from the AVM nidus to the eloquence (the activated cortex or the eloquent fiber tracts) on fMRI and DTI studies is associated with surgical outcomes.[25-28] A 5-mm distance from the eloquent fibers may be a suitable safety margin for postoperative function preservation.[26-28] Based on our previous findings, we will create as well as validate a multimodal MRI technique-based predictive model to assess the surgical risk in each individual AVM patient.

STUDY OBJECTIVE

The key purpose of this study is to create and validate a new predictive model for the surgical risk of intracranial AVMs. Based on this predictive model, we will propose a new supplementary grading system for intracranial AVMs.

METHODS AND ANALYSIS

Study designs

The study consists of two parts: the discovery set and the validation set. The discovery set is a retrospective analysis of 201 eligible AVM patients from our brain AVM database of a prospective randomized controlled clinical trial -- FMRINAVMS (Functional Magnetic Resonance Imaging (fMRI) Navigation in Intracranial Arteriovenous Malformation Surgery. ClinicalTrials.gov Identifier: NCT01758211) at Beijing Tiantan Hospital (China National Clinical Research Center for Neurological Diseases) between September 2012 and September 2015.[29] The validation set is a prospective cohort study of AVM patients that will receive surgical resection for their AVMs at five major neurosurgical centers in China between June 2016 and June 2019. The study design is presented in figure 1.

Study participants

Patient demographic characteristics (age, sex, history of hemorrhage and preoperative functional status), AVM features (size, location, arterial supply, patterns of venous drainage, Spetzler-Martin grade and diffuseness) and the lesion to eloquence distance (LED) obtained by multimodal MRI techniques. The LED means the least distance from the AVM to the eloquent cortex or the eloquent fiber tracts. Patient functional status was or will be measured by the modified Rankin Scale (mRS) score. All patients in this study should meet the inclusion and exclusion criteria. Since the patients in the retrospective phase were chosen from the database of a prospective randomized controlled trial, written informed consent has already been obtained from the patients or their relatives.[29] For the prospective study part (validation set), informed written consent should be obtained from eligible adult patients or from the guardians of eligible pediatric patients. All patients in the prospective part of this study can withdraw at any time.

Inclusion criteria

1. Patients aged between 12 and 60 years.

2. Patients with a definite diagnosis of AVM confirmed by preoperative digital subtraction angiography (DSA).

3. Patients with complete multimodal MRIs: preoperative structural MRI, blood oxygen

level-dependent (BOLD)-fMRI, time-of-flight magnetic resonance angiography (TOF-MRA), and DTI of the eloquent fiber tracts.

4. Patients opting for surgical management of their AVMs.

5. Patients without any treatment (microsurgery, radiosurgery, endovascular embolization, or multimodality treatment) before enrollment.

Exclusion criteria

1. Patients receiving emergency surgery due to acute intracranial hematoma and resultant brain hernia.

2. Patients experiencing an AVM-related hemorrhage in the past month before admission.

3. Patients without BOLD-fMRI and DTI data.

4. Patients with severe diseases that prevent them from microsurgical treatment.

5. Patients without written informed consent.

Multimodal MRI data acquisition

Structural MRI scans, blood oxygen level dependent fMRI (BOLD-fMRI), diffusion tensor imaging (DTI) and time of flight MRA (TOF-MRA) were or will be performed on a 3T Siemens Tim Trio MRI scanner (Siemens Healthcare, Erlangen, Germany) as previously described.[22,24,30,31] For Bold-fMRI, maps of neural activity within motor, language or visual cortex were or will be generated as described in our previous publication.[29] The preoperative MRI data were or will be saved as DICOM format. The data were or will be transferred to an off-line iPlan 3.0 workstation (BrainLab, Feldkirchen, Germany) for analysis. The 3D model of the eloquent cortex (motor, language or visual), the fiber tracking of the eloquent fibers (corticospinal tract, the arcuate fasciculus, or the optic radiation) and the 3D anatomic structure of the AVMs were or will be reconstructed as described in our previous publications.[26-28,32,33]

AVM angioarchitecture (including the feeding artery, the nidus and the venous drainage) and AVM diffuseness will be acquired by the 3D MRA. The maximum diameter of the AVMs was or will be measured from the structural MRI on the axial, coronary and sagittal directions. The lesion to eloquence distances (the LED: the least distances from AVM to the eloquent cortex and eloquent fibers) were or will be measured respectively on the axial, coronary and sagittal directions on 3D reconstruction of the AVM, the eloquent cortex and the eloquent fiber. All the multimodal MR data from different centers will be collected by two neuroradiologists.

Treatment procedure

Preoperative multi-modality MRI reconstruction data (reconstruction of Bold-fMRI, DTI and TOF-MRA) were or will be displayed on a Kolibri WS 2.0 navigation system (BrainLab，Germany) during surgery. Craniotomy was or will be performed according to the preoperative plan based on the multimodal reconstruction data on the navigation system. After craniotomy, the feeding arteries, AVM nidus and draining veins of the AVM as well as adjacent eloquent cortex or eloquent fibers were or will be identified with the navigator's probe, as described in our previous publications.[29,32]

All microsurgical techniques or equipments such as intraoperative ultrasound and indocyanine fluorescence angiography (ICG) were or will be available during surgical resection. Motor evoked potential (MEP) and somatosensory evoked potential (SSEP) were or will be provided as needed for intraoperative monitoring.[29,32]

Outcome evaluation

For the retrospective phase, a nurse clinician, under the supervision of a neurologist, performed the outcome evaluation at presentation and at the last follow-up through telephone or patient routine clinical visit. For the prospective phase, patient outcome will be assessed by a physician or a nurse clinician from each of the five participating centers. All the physicians or nurse clinicians have been professionally trained in evaluating patient outcomes (including using the mRS) before the study.

For the retrospective phase, we will analyze the change of functional status (mRS score) between two time points: at pretreatment and at the final follow-up. For the propective phase, the primary outcome is the change of mRS score between two time points: at pretreatment and 6 months after microsurgery. Good outcome is defined as a final mRS score of 0-2 and poor outcome is defined as a final mRS >2. Improved outcome is defined as a decreased or unchanged mRS score (mRS 6 months after surgery minus pretreatment mRS ≤ 0). Worsened outcome is defined as an increased mRS score (mRS 6 months after surgery minus pretreatment mRS >0). The potential influencing factors for worsened outcome will be collected. These factors are patient age, history of hemorrhage, preoperative mRS, AVM size, AVM location, deep arterial perforator supply, patterns of venous drainage, diffuseness and the LED on multimodal MR images.

For the prospective phase, the second outcomes include AVM obliteration, headache and seizure outcome, surgical complications, and neurologic deficits (motor, language or visual deficits). AVM obliteration will be assessed by postoperative digital subtraction angiography (3 to 7 days after surgery). Seizure outcome will be assessed using the modified Engel scale (4 classes). The surgical

complications include hemorrhagic stroke, intracranial infection, de novo seizures, and cerebral infarction from the surgical date to 6 months after surgery. Motor deficits will be assessed using muscle strength measured by muscle strength grading scale. Language deficits will be measured by Western Aphasia Battery (WAB) 6 months after surgery. Visual field deficits will be measured by visual field testing 6 months after surgery.

Sample size

The retrospective phase of the study includes 201 eligible AVM patients from our brain AVM database of a prospective randomized controlled clinical trial -- FMRINAVMS (Functional Magnetic Resonance Imaging (fMRI) Navigation in Intracranial Arteriovenous Malformation Surgery. ClinicalTrials.gov Identifier: NCT01758211) at Beijing Tiantan Hospital (China National Clinical Research Center for Neurological Diseases) between September 2012 and September 2015. We will use the data of these 201 patients to create the new predictive model. From June 2016 to June 2019, we will enroll 400 eligible patients from five neurosurgical centers with high-volume AVM practices and high-level neurosurgical expertise. The new model created from the retrospective phase will be validated in the prospective 400 eligible patients.

Statistical analyses to create a new predictive model

Statistical analyses will be performed using the Statistical Package for the Social Sciences software (version 20.0; SPSS Inc., Chicago, Illinois, USA). Patient characteristics and AVM features based on multimodal imaging will be summarized using descriptive statistics for continuous variables and categorical variables. These variables include patient demographics (age, sex, history of hemorrhage and pretreatment mRS scores), AVM features (size, cortical or deep location, eloquent or non-eloquent location, arterial supply, patterns of venous drainage, diffuseness and associated aneurysm) and multimodal imaging data (the least distance from the AVM to the eloquent cortex or to the eloquent fibers based on 3D reconstruction).

For the 201 patients in the discovery set, to create a predictive model for worsened neurological outcome, we will analyze patient characteristics, AVM features and multimodal MRI data by univariate and multivariate logistic regression analyses using worsened outcome as the binary response. To assess the predictive ability of the multivariate model, we measured the area under the receiver operating characteristic (AUROC) curve based on the predicted values in the multivariate analyses. We will also measure the AUROC for Spetzler-Martin grading system and the supplementary grading system

models. Comparison between the new predictive model and the current two grading system models will be performed based on AUROC. The multimodal MRI-based predictive model then will be created. According to our preliminary result, hemorrhagic presentation (H), diffuseness (D), deep venous drainage (V) and the lesion to eloquence distance (L) on multimodal MR imaging were independent predictors of worsened outcomes after AVM surgery. The predictive accuracy of the HDVL model is superior to the Spetzler-Martin grading system and the supplemented S-M grading system. The HDVL grading system (Hemorrhagic presentation, diffuseness, deep venous drainage and LED) will be proposed.

Validation of the new predictive model

For the patients (a sample size of 400 eligible patients) in the multi-center prospective cohort study, the new predictive model will be verified in predicting poor outcomes. In the validation set, the new predictive model will also be compared with the current two existing grading systems by using the AUROC to predict worsened neurological outcomes. If the new predictive model is superior to the Spetzler-Martin grading system and the supplementary grading system, the new model is validated and a new grading system will be proposed.

Data management

All data in the discovery set of 201 patients can be collected from our prospectively maintained AVM database at Beijing Tiantan Hospital. All data in the validation set will be prospectively collected using an electronic case report form (eCRF) through a study website. Five major neurological centers in China can access and manage patient information by login and password. All patients enrolled will be carefully monitored until 6 months after surgery. Data safety, data quality, monthly auditing and statistical analysis will be managed by a third party--SUN HEALTH (Beijing).,LTD, who shall be responsible for notifying any issues that will arise during the whole cohort study. The whole study will be supervised by Beijing Municipal Science & Technology Commission and China National Clinical Research Center for Neurological Diseases. Any issue occurring during the cohort study will be reported to these two oversight authorities. Recommendations from these two authorities will be forwarded to the principal investigators to balance the risk and benefit. The oversight authorities have the rights to terminate the study if great risk occurs during the study.

Duration of the study

The discovery set includes 201 eligible AVM patients that were surgically treated in Beijing Tiantan

Hospital between September 2012 and September 2015. The validation set will enroll 400 eligible AVM patients that will receive microsurgical treatment in five major neurosurgical centers in China from June 2016 until June 2019. The first participant was recruited for the prospective phase of the study on June 3rd, 2016.

ETHICS AND DISSEMINATION

The study is supported by Key Project of Beijing Municipal Science & Technology Commission (Grant No. D161100003816006). The first part of this study is a retrospective review of patients treated at one single center (Beijing Tiantan Hospital). The second part of this study is a prospective cohort study treated at five neurosurgical centers. To create and validate the multimodal fMRI-based predictive model for AVM surgery, all patients should have complete preoperative fMRI data and meet the inclusion and exclusion criteria. This study will be conducted in accordance with ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. Written informed consent will be obtained from each adult participant or from the guardian of each pediatric participant in the validation set. Professor Shuo Wang is the principal investigator of this cohort study. Data collection, statistical analysis, interpretation and dissemination of study results will be managed under his direct supervision. The final results of this study will be disseminated through printed media in December 2019.

DISCUSSION

In 1986, Spetzler and Martin introduced the first AVM grading system (the Spetzler-Martin grading system) to estimate the risk of AVM surgery.[12] The Spetzler-Martin grading system is a 5-point scale that is based on AVM size, eloquent or non-eloquent AVM location, and patterns of venous drainage. According to S-M grading system, patients with asymptomatic grade 4 and 5 AVMs should not be surgically treated due to the high risk of surgical complications.[12] However, this standpoint is not universally accepted. Based on the original 5-tier Spetzler-Martin grading system, Spetzler and Ponce proposed a 3-tier classification for AVMs in 2011.[34] In this 3-tier classification, AVMs are divided into class A (S-M grade I and II AVMs), class B (S-M grade III AVMs) and class C (S-M grade IV and V AVMs). This 3-tier classification simplifies treatment recommendations. However, observation is still recommended for patients with asymptomatic class C (S-M grade IV and V) AVMs.[34]

In 2010, Lawton et al. proposed a supplementary grading system including three additional parameters that may affect surgical outcomes: patient age, hemorrhagic presentation and nidal

diffuseness.[13] The authors proposed a full multivariable model (combination of S-M grading system and supplementary system) and a supplementary model. In analysis of 1009 patients, the authors found that the full multivariable model had the highest predictive accuracy.[35] However, surgical selection for AVM patients remains challenging. Just as described in a recent review in *Neurosurgery*, future grading scales may incorporate imaging features.[11] Multimodal MRIs have proved to be a valuable tool in preoperative evaluation and surgical planning. In our clinical practice, we have found that the least distance from AVM to eloquent cortex or eloquent fibers based on multimodal imaging is significantly associated with surgical outcomes.[25-28] Based on our previous studies, we have designed this study to propose a multimodal MR imaging-based predictive model for surgical outcomes of intracranial AVMs. We will compare the predictive accuracy between the new predictive model and the current two grading systems. We hypothesize that the new predictive model in this study has the highest predictive accuracy.

Authors' contributions

SW has obtained research funding and is the principal investigator of the study. YC, YZ and SW have developed this study protocol. XT, JW, YC, YZ and SW have participated in the final design of the study.

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Competing interests statement

None.

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Figure legends

Figure 1. Diagram of the study protocol.

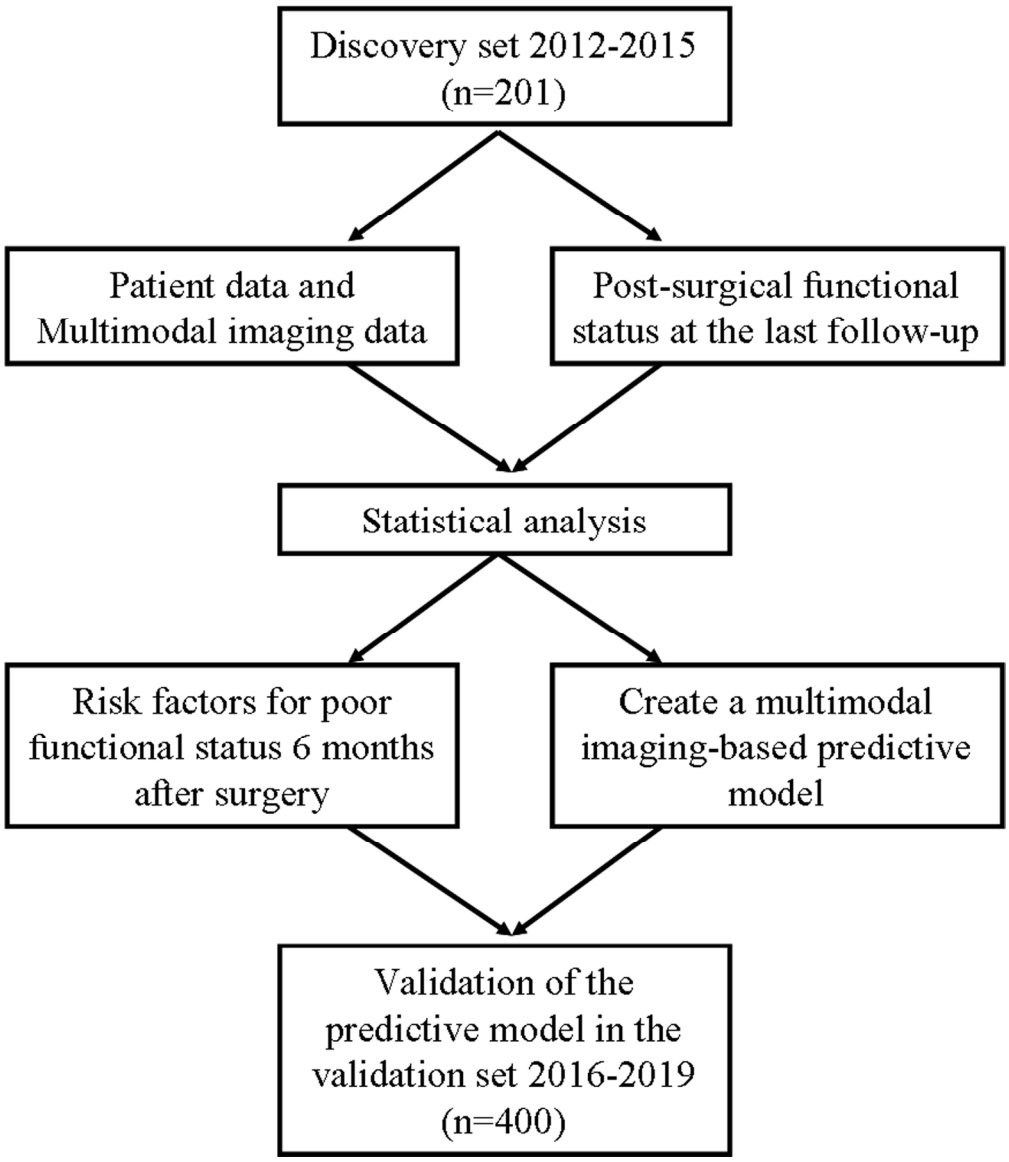

Figure 1. Diagram of the study protocol.

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