INFORMED CONSENT FORM

Official Title: Development and Validation of a Hemorrhage Risk Prediction Model for Moyamoya Disease Based on 5T MRI and Metabolomic Features: A Prospective Cohort Study

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Principal Investigator: Shaosen Zhang, MD, Attending Neurosurgeon, Department of Neurosurgery, Beijing Hospital

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Project source: Qihang Special Project of the Central High-Level Hospital Clinical Research Project, 2025

Protocol title: Development and Validation of a Hemorrhage Risk Prediction Model for Moyamoya Disease Based on 5T MRI and Metabolomic Features

Informed consent form version and date: Version 3.0, January 6, 2026

Study site: Beijing Hospital

Responsible department: Department of Neurosurgery

Principal investigator: Shaosen Zhang

Principal investigator title: Attending Physician

Because you may meet the enrollment conditions of the study "Development and Validation of a Hemorrhage Risk Prediction Model for Moyamoya Disease Based on 5T MRI and Metabolomic Features," we invite you to participate in this study. Please read this informed consent form carefully and make your decision about participation with due consideration. The study physician or research staff will be glad to discuss and explain any content of this form that you do not understand. Before deciding whether to participate, you may discuss fully with your family and friends. If you are participating in another study, please be sure to inform your study physician or research staff.

This study will be conducted by Dr. Shaosen Zhang of Beijing Hospital, funded by the Qihang Special Project of the Central High-Level Hospital Clinical Research Project.

1. Why is this study being conducted?

1.1 Study background

Moyamoya disease (MMD) is a rare cerebrovascular disease characterized by stenosis or occlusion of the distal bifurcation of the internal carotid artery and the formation of collateral networks at the base of the brain. In China, the annual incidence between 2016 and 2018 was estimated at 1.14 per 100,000 population, showing a significant upward trend over the years. MMD presents predominantly as ischemic or hemorrhagic manifestations; hemorrhagic-type MMD has an annual hemorrhage rate of 17% and a mortality between 6.8% and 20%, with a worse prognosis than the ischemic type, and can lead to severe disability and even death. At present, the etiology of MMD-related hemorrhage remains unclear; autopsy findings and imaging studies suggest that dilatation and rupture of collateral vessels are the likely cause of hemorrhage in MMD. It is therefore essential to clarify the mechanisms underlying the formation, expansion, and rupture of collateral vessels.

1.2 Study purpose

To extract important biological features of MMD-related hemorrhage based on 5T MRI and metabolomic techniques, and to construct a prediction model.

2. How many people will take part in this study?

This study will be conducted at Beijing Hospital only, and a total of 525 research participants are planned to be enrolled.

3. How long will this study last?

The study period of this project is from June 2025 to December 2027. Each research participant will receive 1 year of follow-up observation.

This study may be partially or completely terminated under the following circumstances:

- **Termination for safety:** The quality control committee may recommend terminating the study after considering the number and/or severity of adverse events occurring during the study.
- **Termination for effectiveness considerations:** The investigators and study organizers will comprehensively evaluate all available safety and tolerability data. The study may be stopped if the investigators and study organizers determine that the available data provide sufficient grounds.

You may choose to withdraw from the study at any time without losing any benefits to which you would otherwise be entitled. If you decide to withdraw during the study, we encourage you to discuss this with your physician first. For your safety, a relevant examination may be performed after withdrawal.

4. Is participation voluntary?

Your participation in this study is voluntary. If you decline to participate, you will not be subject to any penalty or loss of benefits to which you are otherwise entitled.

5. How will the study be conducted?

If you sign this informed consent form and agree to participate in this study, you will enter the following study procedures:

5.1 Screening

Inclusion criteria:

1. Moyamoya disease or moyamoya syndrome diagnosed by digital subtraction angiography (DSA).
2. Able to undergo 5.0T magnetic resonance imaging (MRI).

Exclusion criteria:

1. Refusal to sign the informed consent form for any reason.
2. Claustrophobia or other conditions preventing completion of imaging acquisition.
3. Revascularization surgery already performed in both cerebral hemispheres.
4. Any hemorrhage event within 1 month before enrollment.

5.2 Study measures/procedures

If you agree to participate, please sign this informed consent form. The study includes the following core elements:

(1) Baseline data collection

The following information will first be collected by the physician in the outpatient or ward office. All of these data are derived from routine clinical records or examinations:

- Demographic information: age; sex; occupation; education level; household income status; medical insurance status; residence;
- History of previous hemorrhage;
- Modified Rankin Scale (mRS) score;
- Traditional risk factors for hemorrhage (hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, atrial fibrillation, smoking, alcohol consumption, etc.);
- Neurological function assessment (NIHSS score, GCS score, Fisher grade [SAH], Hunt-Hess grade [SAH], WFNS grade [SAH]);
- Pre-onset medications (antiplatelet agents, antihypertensive agents, lipid-lowering agents, hypoglycemic agents, anticoagulants, etc.);
- Blood pressure at admission (mmHg);
- Laboratory tests at admission, such as complete blood count, blood glucose, glycated hemoglobin, blood lipids, liver and kidney function, etc.;
- Neuroimaging examinations at admission, including NCCT, CTA, CTP, and DSA data.

All examination and test results and medical records described above can be obtained and reviewed 7 working days after completion of the outpatient or inpatient process.

(2) Main study procedures

- Patient screening: determination of eligibility according to the inclusion and exclusion criteria described above.
- Informed consent: the attending physician will explain to you and your relatives the possible risks and benefits of this study, and will inform you that, whether or not you agree to participate, you will receive the best available treatment. If you and your family agree to participate, you will sign the informed consent form. This process will be witnessed by another physician or nurse.

After enrollment, eligible patients will first undergo routine imaging assessment, including CTA, CTP, multimodal multi-sequence MRI, and DSA, to preliminarily evaluate the involved brain regions and the course and perfusion of intra- and extracranial vessels in MMD, to construct the clinical imaging database of MMD, and to upload the original images to the imaging platform for unified management. Thereafter, the 5T MRI examination and blood and urine sample collection required by this study will be completed. The 5T MRI data and the metabolomic results from the blood and urine samples are research content and cannot produce information with actual clinical diagnostic or therapeutic value; however, if you need them, you may request the relevant results from the researchers 7 working days later.

(3) 5.0T MRI acquisition protocol

All MRI examinations will be performed on a 5T whole-body MR scanner (Siemens Healthcare, Erlangen, Germany). All scans will use a birdcage transmit coil and a 32-channel receive head coil (Nova Medical, MA, USA). The following data will be collected from each participant: T1-weighted magnetization-prepared rapid gradient echo (T1W MPRAGE), TOF-MRA, 3D ASL, and HR-VWI. Two TOF-MRA protocols were

optimized to visualize fine collateral vessels. To assess the reproducibility of the method, a whole-brain isotropic TOF-MRA at 0.40 mm isotropic resolution (Gval) will be acquired with the following parameters: field of view (FOV) = 205 × 175 × 107 mm³, 6 slabs, repetition time (TR) = 18 ms, echo time (TE) = 4.03 ms, flip angle (FA) = 22°, bandwidth (BW) = 158 Hz/Px, generalized autocalibrating partially parallel acquisitions (GRAPPA) factor = 3, acquisition time (TA) = 9 min 28 s. For Gapp, a single-slab TOF-MRA was optimized to shorten the acquisition time. The imaging slab will be placed in an oblique axial orientation, covering the middle cerebral artery (MCA) territory and the base of the basal ganglia region. Detailed parameters are: FOV = 180 × 135 × 52 mm³, resolution = 0.23 × 0.23 × 0.36 mm³, TR = 15 ms, TE = 3.57 ms, FA = 20°, BW = 151 Hz/Px, GRAPPA factor = 2, TA = 8 min 20 s. Structural images will be obtained with T1W MPRAGE using the following parameters: FOV = 224 × 224 × 179 mm³, resolution = 0.70 × 0.70 × 0.70 mm³, TR = 3000 ms, TE = 3.23 ms, inversion time = 1050 ms, FA = 8°, BW = 320 Hz/Px, GRAPPA factor = 3, TA = 5 min 54 s.

(4) Biospecimen collection

Before surgery, 5 mL of venous blood will be drawn from each patient and centrifuged within 20 minutes to separate the plasma; 10 mL of urine will also be collected from each patient before surgery. All biospecimens will be frozen at −80 °C for long-term storage to construct the MMD biobank, for exploring novel biomarkers and performing clinical validation.

Trimming the superficial temporal artery is a necessary routine step during superficial temporal artery-middle cerebral artery bypass surgery, and the trimmed arterial remnant is not normally retained. In this study, if a patient undergoes direct bypass surgery, the superficial temporal artery remnant trimmed during surgery will be retained and stored in formalin for the long term. After paraffin embedding and sectioning, the tissue will be used for immunostaining to cross-validate the biomarkers.

6. What are the risks of participating in this study?

This study is an observational study and does not involve actual intervention in the disease.

Except for study information published in an orderly arrangement by the research group, all of your personal information will be kept confidential. Your name, telephone number, contact information, and other basic information will not be disclosed to non-research personnel, organizations, unrelated third parties, or media.

Even after you sign this informed consent form, you retain all your legal rights.

7. What are the benefits of participating in the study?

You may have no direct medical benefit from participating in this study. We hope that the information obtained from your participation will provide a basis for benefiting future patients with the same condition as yours.

8. Apart from participating in this study (or if I do not participate), do I have other medical options?

Participating in this study may or may not improve your health, and it will not affect your choices regarding treatment methods.

9. Will my information be kept confidential?

We will keep your study records confidential as required by law. Relevant laws in China provide safeguards for the security of privacy, data, and authorized access. Unless required by applicable law, your name, identification number, address, telephone number, or any information that could directly identify you will not be disclosed outside Beijing Hospital. For study information transferred outside Beijing Hospital, a unique number will be used to represent you, and the coded information will be securely stored at Beijing Hospital. When study information and data are published in scientific meetings or journals, your identity will not be disclosed.

10. Who may review the study records, and to whom is this information disclosed?

To ensure that this study complies with the relevant laws and regulations, your records may be reviewed. Reviewers include the national and hospital administrative authorities and the Beijing Hospital Ethics Committee.

11. Will I need to pay to participate in the study?

Participating in this study will not bring you medical costs beyond your routine medical care.

12. What compensation will I receive?

Participants in this study will receive the 5T MRI examination free of charge.

13. What if I am injured as a result of the study?

If an injury related to the study occurs during the research process, Beijing Hospital will immediately provide the corresponding diagnosis, treatment, and nursing care, will bear the corresponding medical expenses, and will provide compensation in accordance with the relevant laws and regulations of China.

14. Do I have the right to withdraw from the study?

You have the right to withdraw from the study at any stage at any time without discrimination or retaliation, and your medical treatment and rights and interests will not be affected.

In principle, after you withdraw, the researchers will securely store your relevant information until it is destroyed, and will not continue to use or disclose such information during this period. However, in the following rare circumstances, the researchers will continue to use or disclose your relevant information even after you have withdrawn from the study or after the study has ended:

- If removal of your information would affect the study results;
- To provide limited information for research, teaching, or other activities (such information will not include your name, identification number, or other personally identifying information);
- When the ethics committee and government regulatory authorities need to supervise the study, they may request access to all study information, including information related to your participation.

15. Will I be informed promptly of information that may affect my continued participation?

If information is obtained that may affect your continued participation in the study, you or your guardian will be notified in a timely manner.

16. Can the study be terminated?

If the scientific research administration department terminates this study, we will notify you promptly.

17. What do I need to do if I participate in the study?

- Provide accurate past medical history and current condition information.
- Accept follow-up for 1 year after enrollment in the study.
- Inform the researchers of any health problems that occur during the study period.
- You may ask questions at any time about anything that is unclear.

18. Whom should I contact if I have questions or difficulties?

If you have questions related to the study or to study-related injury, please contact Shaosen Zhang at 18611284839, or contact the researcher who obtained your signature on the informed consent form; the name and telephone number are provided on the signature page.

If you have any questions concerning your rights and interests, please contact the Beijing Hospital Ethics Committee at 010-85138105, or by email at bjyyec@126.com.

INFORMED CONSENT FORM — SIGNATURE PAGE

Research participant statement

I have carefully read this informed consent form. I have had the opportunity to ask questions, and all questions have been answered to my satisfaction. I understand that participation in this study is voluntary, and that I may choose not to participate in this study, or withdraw at any time after notifying the researcher, without discrimination or retaliation, and that none of my medical treatment, rights, or interests will be affected as a result.

If I require other diagnosis/treatment, or if I do not comply with the study plan, or for other reasonable causes, the researcher may terminate my continued participation in this study.

I voluntarily agree to participate in this study, and I will receive a signed copy of the informed consent form.

Research participant signature: _____ Date: ____ year ____ month ____ day

Research participant telephone (mobile): _____

If the research participant is unable to sign the informed consent form due to incapacity or other reasons, or if the research participant is a minor, the form shall be signed by their guardian.

Guardian signature: _____ Date: ____ year ____ month ____ day

Relationship to the research participant: _____

Telephone (mobile): _____

Reason why the research participant cannot sign the informed consent form: _____

If the research participant or their guardian is unable to read, an impartial witness will witness the entire informed consent process, and sign and date the form.

Impartial witness signature: _____ Date: ____ year ____ month ____ day

Telephone (mobile): _____

Researcher statement

I have accurately conveyed the content of the informed consent form to the research participant and have answered the research participant’s questions. The research participant voluntarily agrees to participate in this study.

Researcher signature: _____ Date: ____ year ____ month ____ day

Researcher telephone (mobile): _____