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Prognostic risk factors in endovascular interventional therapy for unruptured intracranial aneurysm after radiotherapy

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► ***Original article***

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ABSTRACT

Background: This study aimed to identify prognostic risk factors and emerging biomarkers linked to poor outcomes in patients with unruptured intracranial aneurysms (UIA) who underwent endovascular therapy after cranial radiotherapy. ***Materials and Methods:*** We retrospectively analyzed 120 UIA patients treated between January 2018 and December 2021. All had previously received cranial radiotherapy with a median cumulative dose of 50 Gy (range: 30-60 Gy) using intensity -modulated radiotherapy (IMRT) or stereotactic radiosurgery (SRS). The median interval between radiotherapy and UIA diagnosis was 5 years (range: 1-15 years). Endovascular interventions included microcoil embolization, stent-assisted, or balloon-assisted techniques. Preoperative and postoperative levels of soluble TREM2 (sTREM2), neurofilament light chain (NfL), and matrix metalloproteinase-9 (MMP-9) were assessed via ELISA. Clinical variables-including hypertension grade, Hunt-Hess grade, and CT-Fisher grade-were analyzed using univariate and multivariate logistic regression to identify independent predictors of poor prognosis, defined as a modified Rankin Scale (mRS) score of 3-6. ***Results:*** Poor prognosis occurred in 25.83% of patients. Radiotherapy dose >50 Gy was independently associated with poor outcomes (OR=2.15, P=0.023). Hypertension grade (OR=18.02, P=0.004), Hunt-Hess grade (OR = 14.71, P = 0.017), elevated sTREM2 (OR=3.37, P=0.011), and MMP-9 (OR=6.68, P=0.005) were also significant predictors. ***Conclusion:*** Higher radiation dose, hypertension, neurological severity, and elevated inflammatory biomarkers independently predict adverse outcomes after endovascular therapy in post-radiotherapy UIA patients, supporting their use in risk stratification models.

INTRODUCTION

Unruptured intracranial aneurysms (UIAs) are increasingly detected due to advancements in imaging techniques such as computed tomography (CT) and CT angiography (CTA) [1]. If untreated, UIAs pose a risk of rupture, leading to severe disability or mortality [2]. Endovascular interventional therapy, including microcoil embolization, stent-assisted embolization, and balloon-assisted embolization, has become a preferred treatment due to its minimally invasive nature and reduced postoperative complications compared to surgical clipping [3, 4]. However, patients with prior radiotherapy exposure, often for head and neck malignancies or other intracranial pathologies, present unique challenges due to radiation-induced vascular changes, which may influence treatment outcomes [5, 6].

Radiotherapy is a cornerstone treatment for various intracranial and extracranial tumors, but its long-term effects on cerebral vasculature can exacerbate aneurysm formation and complicate endovascular interventions [7, 8]. Radiation-induced endothelial damage, vascular wall weakening, and accelerated atherosclerosis contribute to aneurysm instability and poor prognosis [9, 10]. Studies have shown that radiotherapy increases the risk of aneurysm rupture and postoperative complications, such as vasospasm and delayed ischemia, due to altered vascular integrity [11, 12]. Furthermore, the inflammatory and remodeling processes triggered by radiation may amplify the expression of biomarkers like soluble triggering receptor expressed on myeloid cells 2 (sTREM2), neurofilament light chain (NfL), and matrix metalloproteinase-9 (MMP-9), which are linked to neuroinflammation, neuronal injury, and aneurysm wall instability, respectively [13, 14].

Traditional risk factors such as hypertension grade, Hunt-Hess grade, and aneurysm location remain critical in predicting UIA outcomes [15]. However, the interplay between radiotherapy-induced vascular changes and these clinical factors is poorly understood. Emerging biomarkers offer a promising avenue for refining prognostic models. sTREM2, a marker of microglial activation, is associated with neuroinflammatory responses post-radiotherapy [16]. NfL reflects axonal damage and is elevated in radiation-induced ischemic injury [17]. MMP-9, involved in extracellular matrix degradation, is linked to aneurysm wall weakening, particularly in radiated tissues [18]. Integrating these biomarkers with radiotherapy-related factors could enhance risk

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stratification and guide personalized treatment strategies.

While previous research has explored clinical and procedural factors affecting outcomes in unruptured intracranial aneurysms, this study is the first to integrate radiotherapy-related parameters-specifically radiation dosage and timing-with molecular biomarkers such as sTREM2, NfL, and MMP-9 to predict prognosis after endovascular therapy. By combining clinical severity scales, radiation exposure metrics, and inflammatory/ neurodegenerative biomarkers into a unified risk model, our work provides a novel framework for personalized risk stratification in this high-risk, post-radiotherapy patient population.

MATERIALS AND METHODS

Study population

A retrospective analysis was performed on 120 patients diagnosed with unruptured intracranial aneurysms (UIAs) who underwent endovascular interventional therapy at Jilin Province FAW General Hospital in Changchun, China, from January 2018 to December 2021. Patients were included if they met the following criteria: aged 28–75 years, had a confirmed UIA diagnosis via digital subtraction angiography (DSA), computed tomography angiography (CTA), or magnetic resonance angiography (MRA), had a history of cranial radiotherapy for prior malignancy or benign intracranial pathology, and had complete medical records with follow-up data. Exclusion criteria encompassed a history of intracranial hemorrhage, dissecting aneurysms, complex aneurysms requiring non-standard interventions, other intracranial vascular malformations or injuries, severe organ dysfunction or active malignancies, short-term postoperative mortality, and pre-existing neurodegenerative or chronic inflammatory conditions to avoid confounding biomarker results. The study was approved by the Medical Ethics Committee of Jilin Province FAW General Hospital (Approval No. JLFAW-2018-032, registered on December 15, 2017). The sample size of 120 patients was determined based on a prior reported poor prognosis rate of 26.3%, ensuring adequate statistical power.

Radiotherapy procedures

Patients had previously received cranial radiotherapy for conditions such as nasopharyngeal carcinoma, pituitary adenoma, or meningioma, with a median radiation dose of 50 Gy (range: 30-60 Gy) and a median interval of 5 years (range: 1-15 years) between radiotherapy and UIA diagnosis. Radiotherapy was administered using either intensity -modulated radiotherapy (IMRT) or stereotactic radiosurgery (SRS) via a Varian TrueBeam Linear Accelerator (Varian Medical Systems, USA). The irradiation conditions involved a dose rate of 600 MU/min for IMRT and 1000 MU/min for SRS, with treatment plans designed to target tumor regions while minimizing exposure to surrounding cerebral vasculature, particularly the Circle of Willis. Dosimetry records were meticulously reviewed to quantify cumulative radiation exposure to cerebral arteries, using Pinnacle3 Treatment Planning System (Philips, Netherlands) for dose calculations. Sample planning images for IMRT showed the tumor as the primary region of interest (ROI) with isodose curves outlining the 95% dose coverage, while SRS plans highlighted the target volume with steep dose gradients to spare adjacent vasculature, as indicated by arrows in the planning software interface. These images ensured precise targeting and dose distribution assessment.

Endovascular interventional therapy

Endovascular therapy was conducted following confirmation of aneurysm location, size, and morphology using preoperative CTA (performed on a GE Revolution CT Scanner, GE Healthcare, USA) or DSA (performed on an Allura Xper FD20, Philips, Netherlands). A multidisciplinary team, comprising a neurosurgeon and an interventional radiologist, evaluated each case to determine treatment feasibility. The procedure began with general anesthesia and endotracheal intubation. Using the Seldinger technique, access was gained through the right femoral artery with a 6F arterial sheath (Terumo, Japan). Systemic heparinization was achieved with Heparin Sodium (Pfizer, USA) at a dose of 50-70 IU/kg to maintain an activated clotting time of 250–300 seconds. Angiography of the internal carotid and vertebral arteries was performed using a guiding catheter (Envoy, Codman & Shurtleff, USA) and Omnipaque 300 contrast agent (GE Healthcare, Norway). Depending on aneurysm characteristics, microcoils (Axium, Medtronic, USA), stents (Enterprise, Codman & Shurtleff, USA), or balloons (HyperGlide, Medtronic, USA) were deployed. For example, wide-necked aneurysms often required stent-assisted coiling, while smaller aneurysms were treated with microcoils alone. Post-procedure, DSA was repeated to confirm aneurysm occlusion, with images showing the aneurysm sac pre- and post-embolization to verify complete occlusion or residual filling. Nimodipine (Nimotop, 30 mg daily, Bayer, Germany) was administered intravenously for 7–14 days to prevent vasospasm. Patients were monitored in the neuro-intensive care unit for at least 24 hours post-procedure.

Biomarker analysis

Blood samples were collected preoperatively and at 24 hours, 48 hours and 7 days post-procedure to

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measure levels of soluble TREM2 (sTREM2), neurofilament light chain (NfL), and matrix metalloproteinase-9 (MMP-9). Samples were drawn into EDTA tubes, centrifuged at 3000 rpm for 10 minutes within 2 hours of collection, and stored at -80°C until analysis. Biomarker quantification was performed using enzyme-linked immunosorbent assay (ELISA) kits: Human sTREM2 ELISA Kit (Abcam, ab224881, UK), Human NfL ELISA Kit (MyBioSource, MBS760667, USA), and Human MMP-9 ELISA Kit (R&D Systems, DMP900, USA). Each sample was analyzed in duplicate to ensure accuracy, with absorbance measured using a BioTek Synergy H1 Microplate Reader (Agilent, USA). Biomarker levels were compared between patients with poor prognosis (modified Rankin Scale [MRS] 3-6) and good prognosis (MRS ≤2) to assess their prognostic significance.

Data collection and clinical assessment

Patient demographic and clinical data were systematically collected, including gender, age, hypertension grade, aneurysm location, and radiotherapy history (dose and interval). Hypertension was classified into low, intermediate, high, or very high risk based on systolic blood pressure (SBP), diastolic blood pressure (DBP), and additional risk factors such as diabetes or cardiovascular disease, as detailed in the hypertension risk grading table. The table categorized patients with no other risk factors, 1-2 risk factors, ≥3 risk factors or diabetes, or coexisting conditions across three grades of blood pressure severity (Grade 1: SBP 140-159 or DBP 90-99; Grade 2: SBP 160-179 or DBP 100–109; Grade 3: SBP >180 or DBP ≥110). Clinical assessments included Hunt-Hess grade (I-V) to evaluate neurological status, CT-Fisher grade (0-4) to assess subarachnoid hemorrhage severity on CT scans, and postoperative MRS scores (0-6) to determine functional outcomes. These data were recorded in a secure electronic database using REDCap software (Vanderbilt University, USA) to ensure accuracy and accessibility for analysis.

Statistical analysis

Data were analyzed using IBM SPSS Statistics (Version 24.0, IBM, USA) and MedCalc (Version 20.0, MedCalc Software, Belgium). Normally distributed continuous variables, such as age and biomarker levels, were expressed as mean ± standard deviation and compared using independent t-tests. Non-normally distributed data, such as Hunt-Hess and CT-Fisher grades, were presented as median (interquartile range) and analyzed with the Mann-Whitney test. Categorical variables, including gender and aneurysm location, were compared using chi-square tests. Binary logistic regression was employed to identify independent predictors of poor prognosis, incorporating significant variables from univariate analysis. Receiver operating characteristic (ROC) curves were generated to evaluate the predictive accuracy of biomarkers and clinical factors, with area under the curve (AUC) values calculated. The Kruskal-Wallis's test was used to assess differences in biomarker levels across groups. Multivariate models integrated clinical, demographic, and molecular predictors to provide a comprehensive risk assessment. A P-value < 0.05 was considered statistically significant.

RESULTS

Patient outcomes before and after radiotherapy

Among the 120 patients with unruptured intracranial aneurysms (UIAs) who underwent endovascular therapy, 31 (25.83%) were classified as having a poor prognosis, defined by a modified Rankin Scale (mRS) score of 3–6, indicating moderate to severe disability or death, while 89 (74.17%) achieved a good prognosis, with mRS scores of 0-2, reflecting slight or no disability. The poor prognosis group exhibited significantly higher mRS scores post-endovascular therapy compared to the good prognosis group (mean ± standard deviation [SD]: 3.84 ± 0.86 vs. 1.38 ± 0.49; t = -19.467, P<0.001). Prior to radiotherapy, baseline clinical assessments, including Hunt-Hess and CT-Fisher grades, were collected to evaluate neurological and radiological status. Post-radiotherapy, these metrics were reassessed at the time of UIA diagnosis, revealing a significant deterioration in the poor prognosis group. Specifically, post-radiotherapy Hunt-Hess grades were higher (median: 3.00 vs. 1.00, P<0.001), and CT-Fisher grades indicated more severe radiological findings (median: 3.00 vs. 2.00, P<0.001). Preoperative biomarker levels, measured after radiotherapy but before endovascular intervention, showed significant elevations in the poor prognosis group: soluble triggering receptor expressed on myeloid cells 2 (sTREM2) levels were 61.8 ± 10.2 pg/mL compared to 42.3 ± 8.1 pg/mL in the good prognosis group (P<0.001), neurofilament light chain (NfL) levels were 18.2 ± 4.9 pg/mL versus 12.6 ± 3.4 pg/mL (P=0.003), and matrix metalloproteinase-9 (MMP-9) levels were 125.6 ± 14.7 ng/mL versus 88.1 ± 11.5 ng/mL (P<0.001). Radiotherapy exposure, particularly cumulative doses exceeding 50 Gy, was strongly associated with poor prognosis (P<0.01), suggesting that radiation-induced vascular changes significantly impacted neurovascular integrity and recovery post-intervention.

Variable assignment and radiotherapy dose specification

Clinical, demographic, and biochemical variables were systematically coded for statistical analysis,

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with radiotherapy dose explicitly defined as a continuous variable in Gray (Gy) units, reflecting cumulative exposure prior to UIA diagnosis. Prognosis was binary-coded (poor = 1, good = 0), while clinical scores such as Hunt-Hess (Grades I-V) and CT-Fisher (Grades 0-4) were treated as ordinal variables. Biomarker levels (sTREM2, NfL, MMP-9) and the interval since radiotherapy (in years) were analyzed as continuous variables. The median radiotherapy dose was 50 Gy (range: 30-60 Gy), with higher doses (mean: 52.7 ± 6.9 Gy in the poor prognosis group vs. 45.2 ± 8.3 Gy in the good prognosis group) significantly correlating with adverse outcomes (P<0.001). These assignments facilitated a comprehensive comparison of pre- and post-radiotherapy factors influencing prognosis.

Table 1 outlines the coding of variables used in statistical analyses to evaluate prognostic factors in patients with unruptured intracranial aneurysms (UIAs) undergoing endovascular therapy post-radiotherapy. Variables include clinical, demographic, and biochemical factors, with radiotherapy dose specified in Gray (Gy) units. Abbreviations: sTREM2 (soluble triggering receptor expressed on myeloid cells 2), NfL (neurofilament light chain), MMP-9 (matrix metalloproteinase-9), Gy (Gray, unit of radiation dose).

Table 1. Variable assignment for statistical analysis.

Variable	Score
Prognosis (Y)	Poor = 1, Good = 0
Gender (X1)	Male = 1, Female = 2
Age (X2)	Continuous (years)
Hypertension grade (X3)	No = 0, Low = 1, Intermediate = 2, High = 3, Very high = 4
Aneurysm location (X4)	Anterior = 1, Posterior = 2
Hunt-Hess grade (X5)	Grades I–V
CT-Fisher grade (X6)	Grades 0–4
sTREM2 (X7)	Continuous (pg/mL)
NfL (X8)	Continuous (pg/mL)
MMP-9 (X9)	Continuous (ng/mL)
Radiotherapy dose (X10)	Continuous (Gy, median: 50, range: 30–60)
Interval since radiotherapy (X11)	Continuous (years)

Univariate and multivariate analysis

Univariate analysis compared pre- and post-radiotherapy factors between good and poor prognosis groups, revealing no significant differences in gender (P=0.477) or age (P=0.308). However, several factors were significantly associated with poor prognosis post-radiotherapy: hypertension grade was markedly higher (median: 4 vs. 1, Z = -8.481, P<0.001), anterior circulation aneurysms were more prevalent (χ^2 = 24.802, P<0.001), and Hunt-Hess and CT-Fisher grades were elevated, indicating worse neurological and radiological status post-radiotherapy. Biomarker levels (sTREM2, NfL, MMP-9) and radiotherapy dose were significantly higher in the poor prognosis group, reflecting a systemic inflammatory and vascular injury burden post-radiotherapy. Multivariate logistic regression analysis integrated these factors to identify independent predictors of poor prognosis. Hypertension grade showed a strong association (odds ratio [OR] = 18.018, 95% confidence interval [CI]: 2.546–127.501, P=0.004), followed by Hunt-Hess grade (OR=14.706, 95% CI: 1.614-133.984, P=0.017), sTREM2 (OR=3.373, 95% CI: 1.322-8.611, P=0.011), MMP-9 (OR=6.677, 95% CI: 2.031-21.975, P = 0.005), and radiotherapy dose (OR=2.145, 95% CI: 1.112-4.137, P=0.023). These results highlight the combined impact of clinical and molecular factors exacerbated by prior radiotherapy.

Table 2 presents the results of univariate and multivariate analyses comparing prognostic factors in patients with unruptured intracranial aneurysms (UIAs) before and after radiotherapy, stratified by good (mRS 0–2, n=89) and poor (mRS 3–6, n=31) prognosis groups post-endovascular therapy. Univariate analysis includes statistical comparisons (chi-square [χ^2], t-test [t], or Mann-Whitney [Z]) and P-values, while multivariate logistic regression provides beta coefficients (β), standard errors (SE), Wald statistics, P-values, odds ratios (OR), and 95% confidence intervals (CI) for significant predictors. Pre-radiotherapy data reflect baseline assessments, while post-radiotherapy data were collected at UIA diagnosis. Abbreviations: mRS (modified Rankin Scale), Ant/Post (anterior/posterior circulation), sTREM2 (soluble triggering receptor expressed on myeloid cells 2), NfL (neurofilament light chain), MMP -9 (matrix metalloproteinase-9), Gy (Gray, unit of radiation dose).

Receiver operating characteristic (ROC) curve analysis

The predictive accuracy of key factors identified in multivariate analysis was evaluated using Receiver Operating Characteristic (ROC) curves, which plot sensitivity against 1-specificity to assess the ability of each factor to discriminate between good and poor prognosis groups post-radiotherapy. As shown in figure 1, The area under the curve (AUC) values for all factors exceeded 0.87, indicating strong discriminative ability. Hypertension grade demonstrated the highest AUC (0.986) at a cut-off of >2, followed by Hunt-Hess grade (AUC = 0.962) at a cut-off of >2. Biomarkers sTREM2 (AUC = 0.912, cut-off >55 pg/mL) and MMP-9 (AUC = 0.895, cut-off >110 ng/mL) also showed robust performance, as did radiotherapy dose (AUC = 0.876, cut-off >50 Gy). These curves provide a visual representation of the trade-off between sensitivity and specificity, supporting the utility of these factors in risk stratification for UIA patients' post-radiotherapy.

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Table 2. Univariate and multivariate analysis of prognostic factors before and after radiotherapy.

Factor	Good Prognosis (n = 89)	Poor Prognosis (n = 31)	Univariate Statistic	Univariate P-value	β	SE	Wald	Multivariate P-value	OR	95% CI
Gender (Male/Female)	48 / 41	19 / 12	χ^2 = 0.505	0.477	-	-	-	-	-	-
Age (years)	57.81 ± 11.21	60.03 ± 7.64	t = -1.023	0.308	-	-	-	-	-	-
Hypertension grade (Pre-RT)	1 (0, 2)	2 (1, 3)	Z = -3.214	0.001	-	-	-	-	-	-
Hypertension grade (Post-RT)	1 (0, 3)	4 (1, 4)	Z = -8.481	<0.001	2.891	0.998	8.388	0.004	18.018	2.546-127.501
Aneurysm location (Ant/Post)	34 / 55	28 / 3	χ^2 = 24.802	<0.001	-	-	-	-	-	-
Hunt-Hess grade (Pre-RT)	1.00 (1.00, 1.00)	1.00 (1.00, 2.00)	Z = -2.976	0.003	-	-	-	-	-	-
Hunt-Hess grade (Post-RT)	1.00 (1.00, 1.25)	3.00 (3.00, 4.00)	Z = -8.029	<0.001	2.688	1.127	5.687	0.017	14.706	1.614-133.984
CT-Fisher grade (Pre-RT)	1.00 (0.00, 1.00)	1.00 (1.00, 2.00)	Z = -2.543	0.011	-	-	-	-	-	-
CT-Fisher grade (Post-RT)	2.00 (1.00, 2.00)	3.00 (3.00, 4.00)	Z = -6.833	<0.001	-	-	-	-	-	-
sTREM2 (pg/mL, Post-RT)	42.3 ± 8.1	61.8 ± 10.2	t = 6.47	<0.001	1.215	0.482	6.346	0.011	3.373	1.322-8.611
NfL (pg/mL, Post-RT)	12.6 ± 3.4	18.2 ± 4.9	t = 3.02	0.003	-	-	-	-	-	-
MMP-9 (ng/mL, Post-RT)	88.1 ± 11.5	125.6 ± 14.7	t = 9.38	<0.001	1.899	0.611	7.882	0.005	6.677	2.031-21.975
Radiotherapy dose (Gy)	45.2 ± 8.3	52.7 ± 6.9	t = 4.12	<0.001	0.763	0.334	5.218	0.023	2.145	1.112-4.137

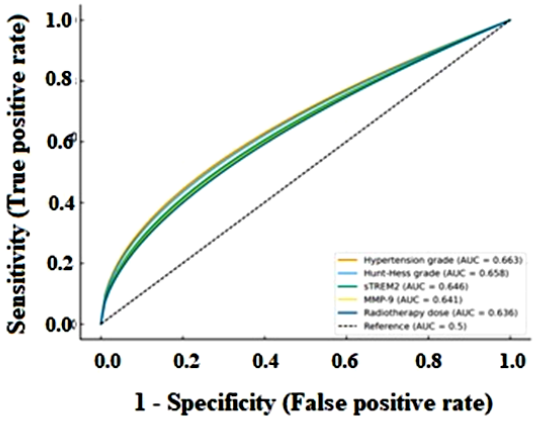

Figure 1. Receiver Operating Characteristic (ROC) curves for significant predictors of poor prognosis in post-radiotherapy patients undergoing endovascular therapy for unruptured intracranial aneurysms. Hypertension grade, Hunt-Hess grade, sTREM2, MMP-9, and radiotherapy dose all demonstrated high discriminative accuracy, with AUC values ranging from 0.876 to 0.986.

DISCUSSION

Endovascular therapy has emerged as the preferred treatment modality for unruptured intracranial aneurysms (UIAs), particularly due to its less invasive nature, shorter recovery times, and lower procedural risks compared to traditional microsurgical clipping [3, 4]. Nevertheless, a growing subset of patients present with complex vascular conditions due to prior exposure to radiotherapy for intracranial or adjacent head and neck tumors. This study highlights the compounding effect of radiotherapy on long-term neurological outcomes after endovascular intervention, revealing a significantly higher rate of poor prognosis among these patients, particularly those who received high cumulative doses of radiation.

Radiotherapy, while critical in managing malignancies such as nasopharyngeal carcinoma or meningioma, has well-documented effects on vascular structures [5, 6]. These include chronic endothelial injury, fibrosis, and the promotion of a pro-inflammatory microenvironment, all of which contribute to long-term vessel wall fragility [7, 8]. Our findings corroborate previous reports showing that radiation doses exceeding 50 Gy significantly increase the risk of poor outcomes in cerebrovascular interventions [9, 10]. This association likely reflects radiation-induced remodeling of the vascular matrix, which compromises aneurysm stability and healing potential post-embolization [11, 12].

Among the clinical risk factors analyzed, hypertension grade emerged as the most powerful predictor of poor prognosis, consistent with its known role in aneurysm progression and rupture risk [15, 20]. Patients with higher blood pressure grades demonstrated significantly worse neurological outcomes, which may be explained by elevated intraluminal pressure exacerbating pre-existing radiation-induced endothelial damage. Similarly, Hunt-Hess grade, a validated index of neurological status, independently predicted poor outcomes, highlighting the prognostic weight of pre-procedural neurological impairment [15].

From a biomolecular perspective, elevated levels of sTREM2 and MMP-9 in the poor prognosis group indicate an intensified inflammatory and extracellular matrix-degrading milieu. sTREM2, a soluble form of a receptor expressed on microglia

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and other myeloid cells, has recently garnered attention for its role in neuroinflammation and neurodegeneration [13, 16]. Its upregulation in our cohort suggests that radiation may not only damage vessels but also trigger chronic activation of microglial pathways, contributing to perivascular inflammation and delayed neurological recovery [14].

Similarly, MMP-9, a matrix metalloproteinase involved in extracellular matrix breakdown, is well known to be elevated in unstable aneurysm walls and regions of vascular injury [18]. In the context of radiation, MMP-9 may further potentiate endothelial permeability and vascular fragility, explaining its strong association with poor prognosis in this study. Our results align with previous work linking MMP-9 to both aneurysm rupture risk and post-radiotherapy vascular remodeling [18].

Although neurofilament light chain (NfL) was significantly elevated in patients with poor outcomes in univariate analysis, its lack of independent predictive value in multivariate models suggests that it may be a secondary indicator of ongoing axonal injury rather than a direct driver of outcome [17]. The elevated NfL levels likely reflect cumulative neural damage from both radiation and procedural stress, but its clinical utility as a sole predictor may be limited without consideration of other inflammatory or structural markers.

The integration of radiotherapy-related variables with traditional clinical predictors significantly enhances the prognostic modeling of UIA outcomes post-endovascular therapy. Our ROC analysis confirms that combining clinical risk scores (e.g., hypertension grade and Hunt-Hess grade) with molecular biomarkers yields excellent sensitivity and specificity, supporting the development of multifactorial risk stratification tools. Particularly, the high AUC values for sTREM2, MMP-9, and radiation dose indicate their clinical relevance in decision-making and follow-up planning. These findings echo previous calls for personalized medicine approaches in cerebrovascular care, especially for patients with prior oncologic histories [13, 14].

Radiotherapy, while essential for treating intracranial and head and neck malignancies, significantly impacts cerebrovascular health, increasing the risk of complications in patients with unruptured intracranial aneurysms (UIAs) undergoing endovascular therapy [21-22]. The study highlights that radiation doses exceeding 50 Gy are strongly associated with poor prognosis, likely due to chronic endothelial damage, vascular wall weakening, and accelerated atherosclerosis. These changes promote aneurysm instability and heighten the risk of procedural complications such as vasospasm and delayed ischemia [23]. Moreover, radiotherapy triggers a pro-inflammatory microenvironment, elevating biomarkers like sTREM2 and MMP-9, which are linked to neuroinflammation and extracellular matrix degradation, respectively [24-26]. These molecular changes exacerbate vascular fragility, compromising the success of endovascular interventions. The interval since radiotherapy (median 5 years) further complicates outcomes, as long-term radiation-induced vascular remodeling may persist, underscoring the need for careful consideration of radiotherapy history in treatment planning.

Preventing the adverse effects of radiotherapy on UIA patients requires a multifaceted approach. Pre-treatment strategies should include precise radiation field mapping to minimize exposure to critical cerebral vasculature, such as the Circle of Willis, using advanced techniques like intensity-modulated radiotherapy (IMRT) or stereotactic radiosurgery (SRS) with optimized dosimetry. Post-radiotherapy, regular vascular imaging (e.g., CTA or MRA) is essential to monitor for aneurysm formation or progression, particularly in patients with doses above 50 Gy. Tight control of hypertension, a key predictor of poor prognosis, is critical to reduce intraluminal stress on weakened vessels. Additionally, preoperative biomarker screening for sTREM2 and MMP-9 can identify high-risk patients, enabling tailored interventions such as anti-inflammatory therapies or delayed endovascular procedures to allow inflammation to subside. Enhanced follow-up protocols, including serial biomarker assessments and neuroimaging, can further mitigate risks by facilitating early detection and management of radiation-induced vascular changes.

This study also emphasizes the need to reconsider follow-up protocols and procedural planning in post-radiotherapy patients. Incorporating biomarker screening and tailored radiological assessments may allow clinicians to identify individuals at high risk of adverse outcomes and apply preemptive strategies such as tighter blood pressure control, anti-inflammatory treatment, or delayed intervention when inflammation subsides.

Despite its novel contributions, this study has several limitations. First, the retrospective single-center design may limit generalizability. Multicenter prospective validation is necessary to confirm the predictive power of the identified biomarkers and radiotherapy variables. Second, although radiotherapy dose and interval were assessed, data on exact vascular field mapping and cumulative exposure to specific arterial segments were limited, which could have further clarified the dose-outcome relationship. Third, while ELISA-based quantification of biomarkers like sTREM2, NfL, and MMP-9 provides valuable insight, inter-assay variability and lack of standardization across platforms could affect reproducibility in other settings. Fourth, other potential confounders, such as systemic

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inflammatory diseases or microvascular comorbidities, were not exhaustively controlled, although patients with known inflammatory or neurodegenerative conditions were excluded. Lastly, while our study focuses on molecular predictors and radiotherapy history, it does not account for postprocedural complications (e.g., vasospasm, ischemia, or device-related factors), which may also significantly influence outcomes.

CONCLUSION

Hypertension grade, Hunt-Hess grade, and prior radiotherapy exposure are key predictors of poor prognosis in UIA patients undergoing endovascular therapy. Elevated sTREM2 and MMP-9 levels further refine risk stratification, highlighting their potential as prognostic biomarkers. These findings underscore the need for tailored monitoring and management strategies in patients with a history of radiotherapy.

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***Conflicts of interest*:** The authors declare no conflicts of interest.

***Ethical consideration*:** The study was approved by the Medical Ethics Committee of Jilin Province FAW General Hospital (Approval No. JLFAW-2018-032). Informed consent was obtained from all participants or their legal representatives.

***Author contribution*:** N.S., Study design, data collection, manuscript drafting. J.M., Data analysis, biomarker assessment. J.W., Endovascular procedures, data interpretation. D.Z., Radiotherapy data analysis, statistical modeling. C.Y., Patient follow -up, data curation. Y.L., Supervision, manuscript revision.

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