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ORIGINAL RESEARCH

Association Between Blood-Brain Barrier Disruption and Stroke-Associated Pneumonia in Acute Ischemic Stroke Patients After Endovascular Therapy: A Retrospective Cohort Study

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Background: Stroke, particularly due to large vessel occlusion (LVO), is a major cause of mortality and disability globally. Endovascular therapy (ET) significantly improves outcomes for acute ischemic stroke (AIS) patients, but complications such as stroke-associated pneumonia (SAP) increase mortality and healthcare costs. This study investigates the association between blood-brain barrier (BBB) disruption and the increased risk of SAP and explores the relationship between BBB disruption and medium-term functional outcomes.

Methods: The retrospective cohort study was performed on AIS patients enrolled between January 2019 to February 2023 who underwent ET. Patients were divided into two groups: BBB disruption and without BBB disruption. Multiple logistic regression model was conducted to measure the association between BBB disruption and SAP. Mediation analysis was used to estimate the potential mediation effects on the associations of BBB disruption with SAP. A restricted cubic spline (RCS) regression model was used to further outline the connection between the highest CT value of hyperattenuated lesions areas and the risk of SAP.

Results: The study included 254 patients who underwent endovascular therapy, with 155 patients in the BBB disruption group (exposure) and 99 patients in the without BBB disruption group (control). Multiple logistic regression analysis revealed a significantly increased risk of SAP in patients with BBB disruption (OR = 2.337, 95% CI: 1.118–4.990, p = 0.025). Furthermore, mediation analysis suggested that this association may be partly due to malignant cerebral oedema and haemorrhagic transformation. The study found an inverse L-shaped dose-response relationship between the maximum CT values of BBB disruption areas and the incidence of SAP. SAP partially mediated the association between BBB disruption and 3-month poor functional outcome.

Conclusion: BBB disruption are a potential risk factor for SAP. BBB disruption may affect short- and medium-term prognosis of patients after ET in part through SAP.

Keywords: acute stroke, stroke-associated pneumonia, hyperattenuated lesions, endovascular therapy, blood-brain barrier disruption

Background

Stroke is recognized as the second primary cause of death in high-income nations.[1,2] The Global Burden of Disease (GBD) study reported a substantial increase in stroke incidence and mortality from 1990 to 2019.[3] However, the burden

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of stroke is markedly higher in low- and middle-income countries, where healthcare infrastructure and resources for prevention and treatment are often insufficient.[4] In China, stroke has become the leading cause of death, with a significant increase in both the incidence and mortality rates over the past decades.[5] Data from 2020 show that stroke incidence reached 505.2 per 100,000 person-years, with 2.3 million stroke-related deaths.[6] Acute ischemic stroke caused by large vessel occlusion (LVO), which accounts for approximately one-third of stroke cases, is particularly concerning due to its association with severe disability and significantly higher mortality rates, making it a critical focus for treatment and prevention strategies.[7] In recent years, endovascular therapy (ET) has evolved as a promising treatment modality for patients with acute ischemic stroke and LVO, markedly improving outcomes in this group.[8] Nevertheless, in instances of severe stroke complications, the potential advantages of endovascular therapy may be diminished or negated. Stroke-Associated Pneumonia (SAP), a notable early complication of cerebral infarction, markedly increases not only the mortality risk but also healthcare expenditures and hospitalization expenses.[9] Recent studies have shown that pneumonia is one of the leading causes of death following ET, contributing to 26.2% of post-procedural mortality within the first 90 days.[10] The incidence of SAP varies from 7.1% to 38%, with higher rates particularly noted in Neurological Intensive Care Units (NICU).[11–14] The identification of early-stage risk factors for SAP is thus essential to enable effective preventative and therapeutic strategies. Existing research has identified several risk factors correlated with SAP, such as advanced age, male gender, severity of stroke, level of consciousness, dysphagia, use of proton pump inhibitors, admission to Intensive Care Units (ICU), atrial fibrillation, hypertension, diabetes, and chronic obstructive pulmonary disease (COPD).[13,15,16] However, there is a paucity of knowledge concerning the specific factors influencing SAP in patients with Acute Ischemic Stroke (AIS) undergoing endovascular therapy.

Hyperattenuated intracerebral lesions (HALs) often appear in post-interventional cranial CT scans after intra-arterial reperfusion therapy for acute ischemic stroke, occurring in 56% to 71.8% of cases.[17–20] These HALs are primarily attributed to substantial disruption of the blood-brain barrier (BBB), which plays a crucial role in maintaining cerebral homeostasis by regulating the passage of molecules between the bloodstream and the brain.[18] BBB disruption has been extensively studied in the context of ischemic stroke and is recognized as a key factor that exacerbates brain injury, contributing to complications such as cerebral edema, hemorrhagic transformation, and unfavorable clinical outcomes.[17,21,22] Studies have shown that HALs, as markers of BBB disruption, are predictive of adverse prognostic outcomes, including higher rates of hemorrhagic transformation and poor functional recovery.[17–21] Nevertheless, a noteworthy clinical observation has emerged in recent years. Patients who undergo endovascular therapy and develop HALs seem to exhibit a heightened susceptibility to SAP. Despite the existing body of research on BBB disruption and their relation to cerebral injuries, the connection between BBB disruption and SAP remains insufficiently explored. Therefore, the primary objective of this study is to evaluate the association between significant BBB disruption and SAP and to elucidate the relationship between BBB disruption, SAP and medium-term functional outcome.

Methods

Participants

The participants enrolled in this study were drawn from the "New DSA Parameters for Forebrain Perfusion Assessment (ClinicalTrials.gov Identifier: NCT03607565, Registration Date: July 15, 2018)" project, conducted at the Department of Neurology, Xi'an NO.3 hospital, during the period spanning January 2019 to February 2023. Inclusion criteria consisted of: (1) Acute Ischemic Stroke (AIS) resulting from acute occlusion of the extracranial or intracranial internal carotid artery, middle cerebral artery (M1 segment or proximal M2 segment); (2) Undergoing endovascular interventional treatment, including endovascular stent thrombectomy, aspiration thrombectomy, emergency balloon dilation, or emergency carotid or intracranial artery stenting; (3) Immediate post-operative CT imaging conducted following endovascular therapy. Exclusion criteria comprised: (1) Evidence of intracranial hemorrhage on the initial head CT scan upon admission; (2) Occurrence of posterior circulation cerebral infarction; (3) Presence of cerebral venous infarction; (4) Administration of intra-arterial thrombolysis; (5) Unavailability of follow-up head CT scans; (6) Mortality within the initial 48 hours after admission.

Data Collection

Three trained researchers extracted information on basic demographics and co-morbidities, such as hypertension, diabetes mellitus, atrial fibrillation, COPD, previous stroke, and current smoking status, from electronic medical records and data collected by the clinical team. In addition, baseline variables such as stroke severity, level of consciousness, dysphagia, use of proton pump inhibitors, occlusion site, stroke side, anesthesia method, endovascular therapy method, onset to groin puncture time, groin puncture to recanalization time, reperfusion status. Post-endovascular therapy complications, such as hemorrhagic transformation and cerebral edema with midline shift, were also noted. The preoperative stroke severity was assessed using the National Institute of Health Stroke Scale (NIHSS). Severe disturbance of consciousness was indicated by a Glasgow Coma Scale (GCS) score of ≤8. The reperfusion status was reported using the modified Thrombolysis in Cerebral Infarction (mTICI) grade, with successful reperfusion defined as a final mTICI grade of 2b-3.[23,24] Modified Rankin Scale at 3 months (mRS90) is assessed routinely 3 months after ischemic stroke per phone as part of the information from the local registry. Favorable outcome was defined as mRS 0–2. To guarantee adequate caloric and protein intake for patients in our intensive care unit who undergo endovascular treatments and experience dysphagia, we routinely insert nasogastric tubes. We exclude the placement of nasogastric tubes from the baseline parameters to simplify documentation and avoid redundant measurements.

Imaging Definitions of BBB Disruption

BBB disruption was defined as hyperattenuated intracerebral lesions (HALs) exhibited on a CT scan immediately after endovascular therapy.[17] These images illustrate the extravasation of contrast medium administered during the procedure into the extracellular spaces, resulting from an increased permeability of the BBB.[17] We have adopted the term introduced by Nikoubashman et al who defined HALs after endovascular therapy as non-solid visually distinctive parenchymal hyperdense areas diagnosed within 4.5 h after recanalisation, with a diameter of at least 0.1 cm^2, and without a space occupying effect, and with an increased density of at least 5 maximum Hounsfield Units (HUmax) compared to the unaffected contralateral,[18] Supplementary Figure S1 shows the typical presentation of BBB disruption in patients with acute large vessel occlusion in anterior circulation.

CT Imaging and BBB Disruption Measurement

Head CT scans were conducted utilizing two distinct scanner platforms (Somatom Definition Flash, Siemens, Erlangen, Germany, and OPTIMA CT680, GE Healthcare, Chicago, Illinois, US), with digital image management and storage facilitated through the Picture Archiving and Communication System (PACS) software. Post-endovascular therapy, head CTs were promptly rescanned, documenting the maximum CT value within the HALs regions. The median temporal interval between the immediate head CT scan and the final image of the therapy was 40 minutes. All patients underwent a CT scan 24 hours after the initiation of treatment to assess for complications related to intracranial hemorrhage. A third CT scan was performed 72 hours after treatment began to evaluate for complications associated with cerebral edema. HALs are predominantly observed in immediate CT scans post-endovascular treatment, particularly around the infarction area. The CT values of these BBB disruption areas were ascertained using an automated detection software integrated within the PACS system. The minimum, maximum and mean HU of hyperdense areas were calculated based on visually defined Regions of Interest (ROI). Our statistical analyses were centred on the maximum HU as it indicates the area of most severe BBB disruption within the designated volume.[18]

Radiological data were collected by neuroradiologists, each with over five years of experience and proficient in the imaging system. All data were independently analysed by a neurologist and a neuroradiologist. Discrepancies were resolved through consensus. In cases where consensus could not be reached, a third reviewer was consulted for adjudication.

Outcome Measures

The primary outcome was the presence of SAP in patients after endovascular therapy. According to the consensus published in 2015 by the Pneumonia in Stroke Consensus Group (PISCES), composed of UK multidisciplinary experts, it

is recommended to define SAP as a new occurrence of pneumonia within the first seven days of onset in stroke patients with non-mechanical ventilation. The diagnosis of definite SAP in this investigation conformed to the PISCES criteria, encompassing at least one of the subsequent: (1) fever > 38° C; (2) leukopenia or leukocytosis; (3) for adults > 70 years, altered mental status with no other recognized cause. Moreover, at least two of the following conditions should be exhibited: (1) new onset of purulent sputum, or change in character of sputum over a 24 h period, or increased respiratory secretions, or increased suctioning requirements; (2) new onset or worsening cough, or respiratory rate; rales, crackles, or bronchial breath sounds; (3) worsening gas exchange. Pathological X-ray imaging findings were also mandatory.[25] All patients were diagnosed by two experienced neurologists blind to the results of the clinical and laboratory evaluations. If there was no consensus, a third expert reader made the final diagnosis. The secondary outcome was medium-term functional outcome. Modified Rankin Scale at 3 months (mRS90) is assessed routinely 3 months after ischemic stroke per phone as part of the information from the local registry. Favorable outcome was defined as mRS 0–2.

Statistical Analysis

Baseline summary statistics are delineated as proportions for categorical variables and as medians (interquartile range) or means ± standard deviation (SD) for continuous variables. The distribution of continuous variables was evaluated for normality using the Shapiro–Wilk test. Differences in categorical data between groups were assessed using the Chi-square test or Fisher's exact test, as appropriate. For continuous variables, the Mann–Whitney *U*-test was utilized owing to the non-normal distribution of the data.

In order to explore the interrelationships among exposure, outcomes, and intervention variables, and to select a minimal yet sufficiently comprehensive set of covariates for adjusting confounding factors, we employed DAGitty v3.1 software to create a Directed Acyclic Graph (DAG). The construction of this DAG was grounded in scholarly literature and expert opinion. This approach aims to elucidate the complex interactions between these variables, thereby increasing the effectiveness and precision of our study.[26]

We utilized logistic regression models to estimate the Odds Ratios (ORs) and 95% Confidence Intervals (CIs) pertaining to the association between BBB disruption and SAP. This analysis involved the utilization of four distinct models, each designed to progressively incorporate potential confounding variables, thereby enhancing the robustness of the observed associations. Model 1 was a crude model without any adjustments. Model 2 was adjusted for age and sex. Model 3 incorporated additional adjustments for comorbidities and partial clinical parameters. Lastly, Model 4 was a fully adjusted model.

Stratified and interaction analyses were conducted to assess the potential differential effects of BBB disruption across various subgroups. Baseline characteristics, including age, sex, comorbidities, and clinical parameters, were used as modifiers in the stratification. Interaction terms between these baseline characteristics and BBB disruption were introduced in the logistic regression models to evaluate the statistical significance of any observed interactions. Subgroup analyses were conducted to investigate the heterogeneity of the association between BBB disruption and SAP across different patient demographics and clinical conditions. The presence of interaction was evaluated by including a multiplicative term in the model, and a p-value of less than 0.05 was considered indicative of a statistically significant interaction.

We identified potential mediating variables and a minimal set of confounding factors using a Directed Acyclic Graph. Mediation analyses were then performed utilizing the "mediation" package in R, employing bootstrap simulation methods with 5000 iterations. The direct effect referred to the effects of the baseline BBB disruption on SAP without a mediator. The indirect effect referred to the effects of the baseline BBB disruption on SAP impairment through the mediators. We calculated the proportion of mediation via dividing the indirect effect by total effect. The same confounding variables as used in the association analysis were controlled here.

We collected data on the outcome SAP, the continuous predictor variable maximum CT value of BBB disruption areas and covariates. Possible nonlinear relationships between the change in CT value and SAP were examined by a logistic regression model with RCS. The knots between 3 and 7 were tested respectively, and the model with lowest Akaike information criterion value was selected for RCS. Finally, we used RCS with 3 knots at the 10th, 50th, and 90th centiles. The reference value was set depending on the RCS shape. When interpreting the results of an RCS analysis, the

median value of the predictor variable was chosen as the reference value. If the curve exhibited a U-shape, Inverted U-shape, or L-shape, the inflection point (ie, the point where the curve changed its direction) was set as a cut-off value. The inflection point represented a turning point or boundary between different patterns of association between the predictor variable and the outcome. In cases where the RCS analysis revealed a U-shaped, Inverted U-shaped, or L-shaped curve, with a clearly identifiable inflection point, the data were divided into two distinct segments based on this inflection point. This segmented logistic regression allowed for a more nuanced understanding of the relationship between the predictor variable and the outcome in each segment, as it accounted for the distinct patterns of association in different parts of the curve.

To visualise the flow and distribution of critical events, an alluvial diagram was created for the variables NIHSS, BBB disruption, SAP and mRS90. The NIHSS was partitioned into quartiles for visualisation purposes. The alluvial plot was visualized using the online OmicShare tools (https://www.omicshare.com/tools).

To assess the robustness of our primary findings, we conducted sensitivity analyses with different approaches: (1) using the inverse probability of treatment weighting (IPTW) derived from propensity scores to further control for confounding.[27] (2) Initially, we employed Lasso regression (Least Absolute Shrinkage and Selection Operator) to re-select the covariates requiring adjustment. Lasso regression is an effective technique for variable selection and regularization, which assists in enhancing the prediction accuracy and interpretability of the statistical model.[28] Following the re-selection of covariates, we conducted logistic regression analysis again to estimate the association between BBB disruption and SAP, adjusting for the newly selected set of covariates. This step aimed to verify whether the association observed in the main analysis remains consistent even after a rigorous variable selection process.(3) E-value Analysis: Furthermore, we utilized the E-value method for sensitivity analysis. The E-value quantifies the required strength of an unmeasured confounder that could explain away the observed association, while also considering the effect of the measured confounders. By applying the E-value method, we aimed to gauge the robustness of our findings against potential unmeasured confounding. The E-value calculation provides a benchmark to evaluate how robust the observed associations are to potential unmeasured or uncontrolled confounding.[29]

The statistical analyses in our study were conducted using R software version 4.2.2, along with the rms package and MSTATA software. A two-tailed P-value of less than 0.05 was considered statistically significant.

Results

Descriptive Statistics

Between January 2019 and February 2023, our database recorded 2650 eligible patients. Of these, 355 emergency NICU patients underwent digital subtraction angiography (DSA). Among them, 254 met the inclusion criteria and were included in the study. For an overview of the included patients, refer to Figure 1. Out of the 254 patients, BBB disruption was found in 155 patients (61.0%). Additionally, 99 patients (39.0%) were diagnosed with SAP (Table 1). The study participants had a median age of 67 years, and there was a slight difference in age between the groups (P=0.058). The gender distribution was almost identical (P=0.980). The patients without BBB disruption group had a higher prevalence of hypertension and diabetes mellitus (P=0.008 and P=0.016, respectively), while the BBB disruption group had a higher prevalence of atrial fibrillation (P<0.001). The patients with BBB disruption also had significantly higher preoperative NIHSS scores and dysphagia occurrence (P<0.001). Different anesthesia and endovascular therapy methods were used, with significant variations in the application of local anesthesia and SWIM technique (P<0.001). Post-interventional results showed a considerably higher occurrence of hemorrhagic transformation and stroke-associated pneumonia in the patients with BBB disruption (P<0.001).

Association Between BBB Disruption and SAP

Based on the existing literature and expert insights, we have identified several potential confounding factors, mediators, and effect modifiers. These variables have been incorporated into a directed acyclic graph (DAG), which has guided our modeling strategy (Figure 2). Using the DAG, we ultimately determined the minimally sufficient adjustment set (MSAS) to include: The following factors were considered in the study: age, sex, diabetes mellitus, previous stroke, stroke

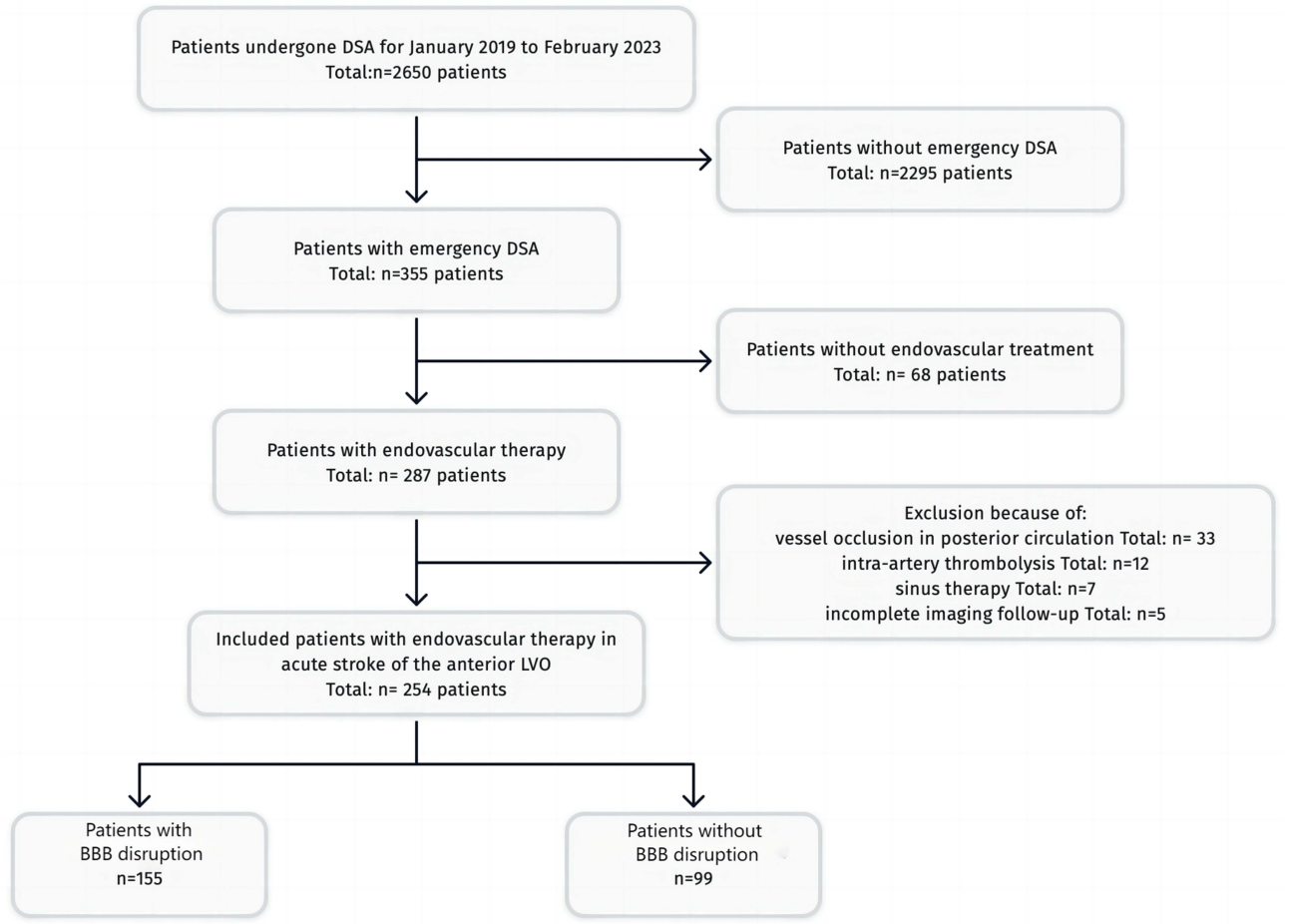

Figure 1 Flow diagram of patient identification and imaging findings.
Abbreviations: BBB, blood-brain barrier; DSA, digital subtraction angiography; LVO, large vessel occlusion.

severity (measured by the preoperative NIHSS score), level of consciousness (indicated by the preoperative GCS score), dysphagia, anesthesia method, occlusion site, time from onset to groin puncture, and reperfusion status (assessed using the modified TICI score). The analysis revealed a statistically significant correlation between BBB disruption and SAP

Table 1 Demographic and Clinical Variables of the Study Cohort

Variables	All Patients			
	All (n=254)	BBB Disruption		P
		No (n=99)	Yes (n=155)	
Demographics				
Age, median (IQR),y	67(58.0–76.0)	64(56.0–74.0)	69(59.0–77.0)	0.058
Male, n (%)	146(57.5)	57(57.6)	89(57.4)	0.980
Medical History				
Hypertension, n (%)	143(56.3)	66(66.7)	77(49.7)	**0.008**
Diabetes mellitus, n (%)	57(22.4)	30(30.3)	27(17.4)	**0.016**
Atrial fibrillation, n (%)	104(40.9)	27(27.3)	77(49.7)	**<0.001**
COPD, n (%)	20(7.9)	9(9.1)	11(17.1)	0.565
Previous stroke, n (%)	43(16.9)	13(13.1)	30(10.8)	0.197
Smoking, n (%)	82(32.3)	31(31.3)	51(32.9)	0.792

(*Continued*)

Table 1 (Continued).

Variables	All Patients			
	All (n=254)	BBB Disruption		P
		No (n=99)	Yes (n=155)	
Clinical Parameters				
Preoperative NIHSS, median (IQR)	14(9–19)	11(7–17)	16(12–20)	**<0.001**
Preoperative GCS≤8, n (%)	21(8.3)	3(3.0)	18(11.6)	**0.015**
Dysphagia, n (%)	168(66.1)	38(38.4)	130(83.9)	**<0.001**
Proton pump inhibitors, n (%)	163(64.2)	62(62.6)	101(65.2)	0.681
Occlusion site, n (%)				0.308
Internal carotid artery	94(37.0)	35(35.4)	59(38.1)	
M1 segment of MCA	140(55.1)	53(53.5)	87(56.7)	
M2 segment of MCA	20(7.9)	11(11.1)	9(5.8)	
Stroke side, n (%)				0.224
Left	129(50.8)	55(55.6)	74(47.7)	
Right	125(49.2)	44(44.4)	81(52.3)	
Anesthesia method, n (%)				**<0.001**
Local anesthesia	66(26.0)	37(37.4)	29(18.7)	
Conscious sedation	164(64.6)	49(49.5)	115(74.2)	
General anesthesia	24(9.4)	13(13.1)	11(7.1)	
Endovascular therapy method, n (%)				**<0.001**
SWIM	95(37.4)	24(24.2)	71(45.8)	
ADAPT	75(29.5)	31(31.3)	44(28.4)	
Balloon or/and Stenting	46(18.1)	29(29.3)	17(11.0)	
SWIM or ADAPT + Balloon or/and Stenting	38(15.0)	15(15.2)	15(15.2)	
Onset to groin puncture time, median (IQR), min	360.0(246.0–579.0)	362.0(256.0–701.0)	352.0(240.0–482.0)	0.060
Groin puncture to recanalization time, median (IQR), min	110.0(80.0–162.0)	112.0(81.0–164.0)	110.0(80.0–160.0)	0.776
Modified TICI score < 2b, n (%)	28(11.0)	9(9.1)	19(12.3)	0.432
Clinical Parameters After Endovascular Therapy				
Hemorrhagic transformation, n (%)	73(28.7)	3(3.0)	70(45.2)	**<0.001**
Cerebral edema with midline shift, n (%)	23(9.1)	5(5.1)	18(11.6)	0.075
Outcome				
SAP, n (%)	99(39.0)	19(19.2)	80(51.6)	**<0.001**
mRs90 0–2, n (%)	129(50.8)	75(75.8)	54(34.8)	**<0.001**

Notes: Data are reported as n (%), proportion or median (IQR). Bold values for a p-value below the threshold (<0.05).

Abbreviations: ADAPT, a direct aspiration first-pass technology; BBB, blood-brain barrier; COPD, chronic obstructive pulmonary disease; DSA, digital subtraction angiography; GCS, Glasgow coma scale; IQR, interquartile range; LVO, large vessel occlusion; MCA, middle cerebral artery; NIHSS, national institutes of health stroke scale; SAP, stroke-associated pneumonia; SWIM, solitaire retriever stent combined with intracranial support catheter aspiration for mechanical thrombectomy; TICI, treatment in cerebral ischemia.

across all models (Table 2). Model 1, adjusted solely for BBB disruption, showed that patients with BBB disruption had an OR of 4.491 (95% CI: 2.478–8.111, $p < 0.001$) for developing SAP. In Model 2, after further adjustment for age and sex, the association remained strong with an OR of 4.286 (95% CI: 2.342–7.841, $p < 0.001$). Model 3, which included adjustments from Model 2 as well as diabetes mellitus, previous stroke, preoperative NIHSS, and preoperative GCS≤8, showed a slightly attenuated yet significant OR of 3.278 (95% CI: 1.711–6.281, $p < 0.001$). Finally, Model 4 was further adjusted for dysphagia, anesthesia method, occlusion site, onset to groin puncture time, and modified TICI score < 2b. The association between BBB disruption and SAP still exists, although with a lower OR of 2.337 (95% CI: 1.118–4.990, $p = 0.025$). These results emphasize the increased risk of SAP in patients who experience BBB disruption after endovascular therapy, even after accounting for multiple potential confounding variables.

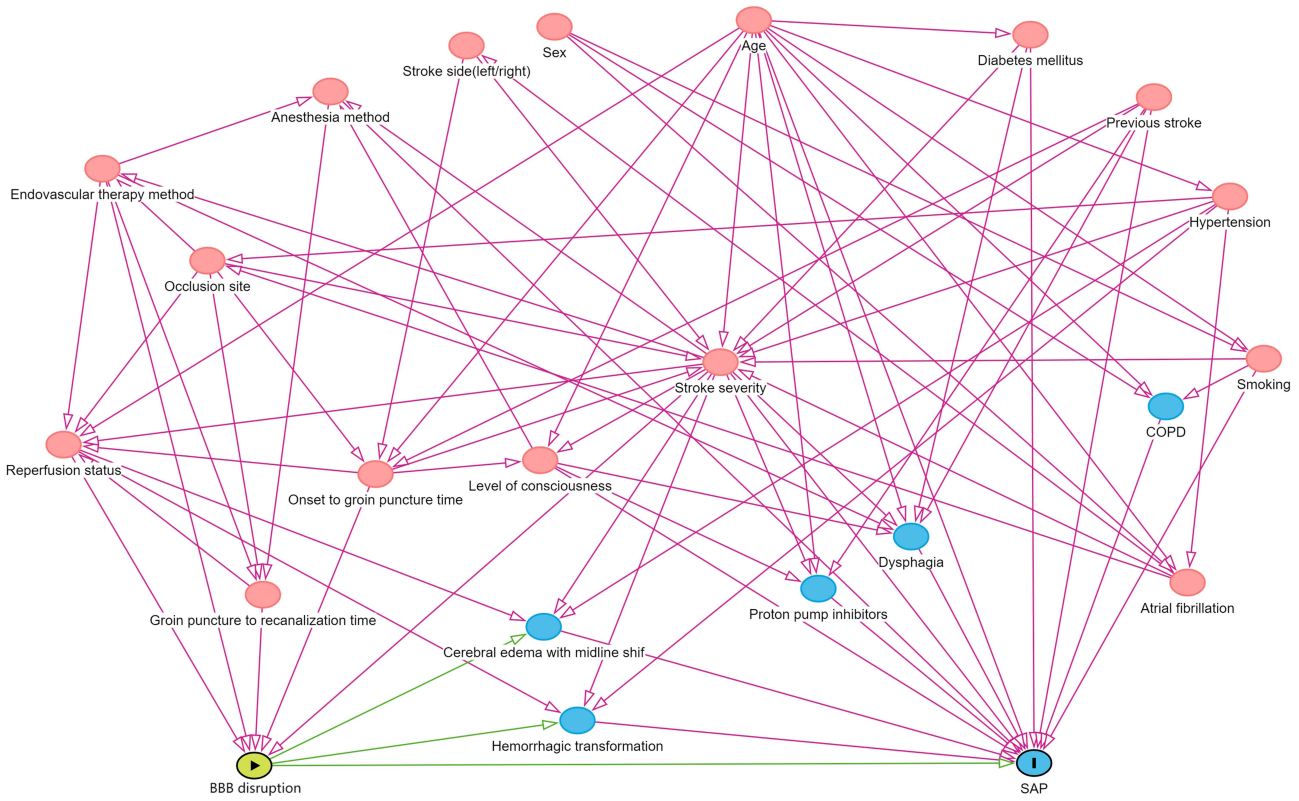

Figure 2 Directed acyclic graph(DAG) representing relationships between covariates and primary predictor and outcome. Red circles represent ancestors of the exposure and outcome (ie confounders) and blue circles represent ancestors of the outcome (ie causal determinants of the outcome). Green lines represent causal paths, and red lines represent biasing paths. The minimally sufficient adjustment set (MSAS) was determined using DAGitty f(v3.1 *https://dagitty.net/dags.html*), a software for creating causal diagrams to minimize confounding bias in epidemiology. The final MSAS was determined to be the following: Age, Sex, Diabetes mellitus, Previous stroke, Stroke severity (Preoperative NIHSS score), Level of consciousness (Preoperative GCS score), Dysphagia, Anesthesia method, Occlusion site, Onset to groin puncture time, Reperfusion status (Modified TICI score).
Abbreviations: BBB, blood-brain barrier; GCS, Glasgow coma scale; NIHSS, national institutes of health stroke scale; TICI, treatment in cerebral ischemia score.

Stratified and Interaction Analyses

In our cohort study, stratified analyses demonstrated consistent associations across various subgroups with the primary outcomes, as detailed in Figure 3. Analysis of age-stratified data revealed substantial associations, with no significant interaction effects observed (P for interaction = 0.725). This trend was consistent across other stratified factors, including sex, diabetes mellitus status, history of previous stroke, preoperative NIHSS and GCS scores, anesthesia method,

Table 2 Association of BBB Disruption and SAP in All Endovascular Patients

	Estimate	SE	Z	p	Odds Ratio	95% CI Lower	95% CI Upper
Modle1	1.502	0.302	4.980	**<0.001**	4.491	2.478	8.111
Modle2	1.455	0.308	4.721	**<0.001**	4.286	2.342	7.841
Modle3	1.187	0.332	3.580	**<0.001**	3.278	1.711	6.281
Modle4	0.847	0.379	2.237	**0.025**	2.337	1.118	4.990

Notes: Estimates represent the log odds of "SAP = Yes" vs "SAP = No". The bolded values indicate statistically significant. Model 1 was adjusted for HALs; Model 2 included Model 1 additionally adjusted for Age, Sex; Model 3 included Model 2 additionally adjusted for Diabetes mellitus, Previous stroke, Preoperative NIHSS, Preoperative GCS≤8; Model 4 included Model 3 additionally adjusted for Dysphagia, Anesthesia method, Occlusion sit, Onset to groin puncture time and Modified TICI score < 2b.
Abbreviations: BBB, blood-brain barrier; CI, confidence intervals; GCS, Glasgow coma scale; NIHSS, national institutes of health stroke scale; SAP, stroke-associated pneumonia; SE, standard error; TICI, treatment in cerebral ischemia score; Z, the z-score.

BBB disruption	NO	Yes	Adjusted OR (95% CI)	P value	P for interaction
Overall	99 (100%)	155 (100%)	2.11 (1.07-4.24)	0.033	
Age					0.725
<67	55 (56%)	69 (45%)	1.88 (0.67-5.40)	0.23	
≥67	44 (44%)	86 (55%)	1.94 (0.76-5.11)	0.171	
Sex					0.305
Female	42 (42%)	66 (43%)	2.76 (0.94-9.05)	0.075	
Male	57 (58%)	89 (57%)	1.65 (0.65-4.12)	0.283	
Diabetes mellitus					0.388
No	69 (70%)	128 (83%)	2.61 (1.21-5.83)	0.016	
Yes	30 (30%)	27 (17%)	0.61 (0.09-3.34)	0.58	
Previous stroke					0.207
No	86 (87%)	125 (81%)	1.78 (0.82-3.90)	0.144	
Yes	13 (13%)	30 (19%)	5.44 (1.04-34.33)	0.051	
Preoperative NIHSS					0.499
<14	67 (68%)	55 (35%)	1.43 (0.50-4.08)	0.502	
≥14	32 (32%)	100 (65%)	2.88 (1.15-7.53)	0.027	
Preoperative GCS≤8					0.121
No	96 (97%)	137 (88%)	1.75 (0.86-3.58)	0.124	
Yes	3 (3.0%)	18 (12%)	18.06 (1.04-801.13)	0.066	
Dysphagia					0.078
No	61 (62%)	25 (16%)	7.54 (1.45-56.97)	0.023	
Yes	38 (38%)	130 (84%)	1.57 (0.74-3.37)	0.245	
Anesthesia method					0.781
LA	37 (37%)	29 (19%)	4.02 (0.97-18.31)	0.059	
CS	49 (49%)	115 (74%)	2.13 (0.88-5.42)	0.1	
GA	13 (13%)	11 (7.1%)	0.61 (0.02-10.04)	0.738	
Occlusion site					0.533
MCA-M1 or M2	64 (65%)	96 (62%)	2.62 (1.16-6.11)	0.022	
Internal carotid artery	35 (35%)	59 (38%)	1.48 (0.40-5.58)	0.553	
Onset to groin puncture time					0.813
<360 min	46 (46%)	79 (51%)	1.98 (0.77-5.16)	0.155	
≥360 min	53 (54%)	76 (49%)	2.17 (0.79-6.22)	0.136	
Modified TICI score					0.693
≥2b	90 (91%)	136 (88%)	1.98 (0.96-4.16)	0.065	
<2b	9 (9.1%)	19 (12%)	2.23 (0.22-23.48)	0.48	

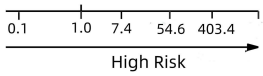

Figure 3 Association of BBB disruption and SAP stratified by participant characteristics. Continuous variables were dichotomized based on their median values. Each stratification controlled for all factors except the stratification factor itself. P-interaction was assessed by combining the variables' cross-product term in the same model. **Abbreviations**: BBB, blood-brain barrier; CI, confidence intervals; GCS, Glasgow coma scale; MCA, middle cerebral artery; NIHSS, national institutes of health stroke scale; OR, odds ratios; TICI, treatment in cerebral ischemia score.

occlusion site, time from onset to groin puncture and modified TICI scores. While these subgroups showed significant associations in certain instances, their interaction effects did not indicate notable discrepancies. A potentially noteworthy observation was made in the dysphagia subgroup, where the interaction effect approached statistical significance (P for interaction = 0.078). This suggests a possible, yet not statistically confirmed, dependency of the relationship on dysphagia status.

Mediation Analyses

Based on our analysis using DAG, we identified potential mediators in the relationship between BBB disruption and SAP risk as the occurrence of cerebral edema with midline shift and hemorrhagic transformation after endovascular therapy. Table 3 shows the mediating effects of complications post-endovascular therapy on the association between BBB disruption and SAP risk. We found a significant indirect effect of BBB disruption on SAP risk through cerebral edema with midline shift (Coefficient: 0.0267, 95% CI: 0.0013 to 0.052, P=0.048), accounting for 15.1% (95% CI: 1.2% to 48.3%) of the proportions mediated. Additionally, hemorrhagic transformation, particularly the PH subtype,

Table 3 Mediation Analysis for the Associations Between BBB Disruption and SAP

Independent Variable	Mediator	Indirect Effect		Direct Effect		Proportion Mediated, % (95% CI)
		Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value	
BBB disruption	Cerebral edema with midline shift	0.0267 (0.0013, 0.0520)	**0.048**	0.1499 (0.0285, 0.2746)	**0.024**	15.1 (1.2, 48.3)
BBB disruption	HT	0.0712 (0.0130, 0.1412)	**0.020**	0.1481 (0.0286, 0.2731)	**0.024**	32.5 (5.0, 84.2)
BBB disruption	PH[1]	0.0602 (0.0203, 0.1217)	**0.004**	0.1500 (0.0283, 0.2663)	**0.028**	28.6 (8.3, 74.7)

Notes: The bolded values indicate statistically significant. The mediation analyses were adjusted for all confounding factors. 1. The radiographic definition of Hemorrhagic transformation is generally classified by the European Cooperative Acute Stroke Study (ECASS). On CT scans, the severity of HT is divided into two stages: hemorrhagic infarction (HI) and parenchymal hemorrhage (PH) with or without mass effect.
Abbreviations: BBB, blood-brain barrier; CI, confidence interval; HT, hemorrhagic transformation; PH, parenchymal hemorrhage; SAP, stroke-associated pneumonia.

significantly mediated the relationship, with proportions mediated of 32.5% (95% CI: 5.0% to 84.2%) and 28.6% (95% CI: 8.3% to 74.7%), respectively.

The Dose-Response Relationships

In this study, constrained cubic splines (RCS) based on the multivariable adjusted model are utilized to provide a nuanced modeling of the association between the maximum CT values observed within the BBB disruption regions and the risk of SAP. As depicted in Figure 4, the RCS analysis revealed a nonlinear association (P-Nonlinear=0.025), with an inflection

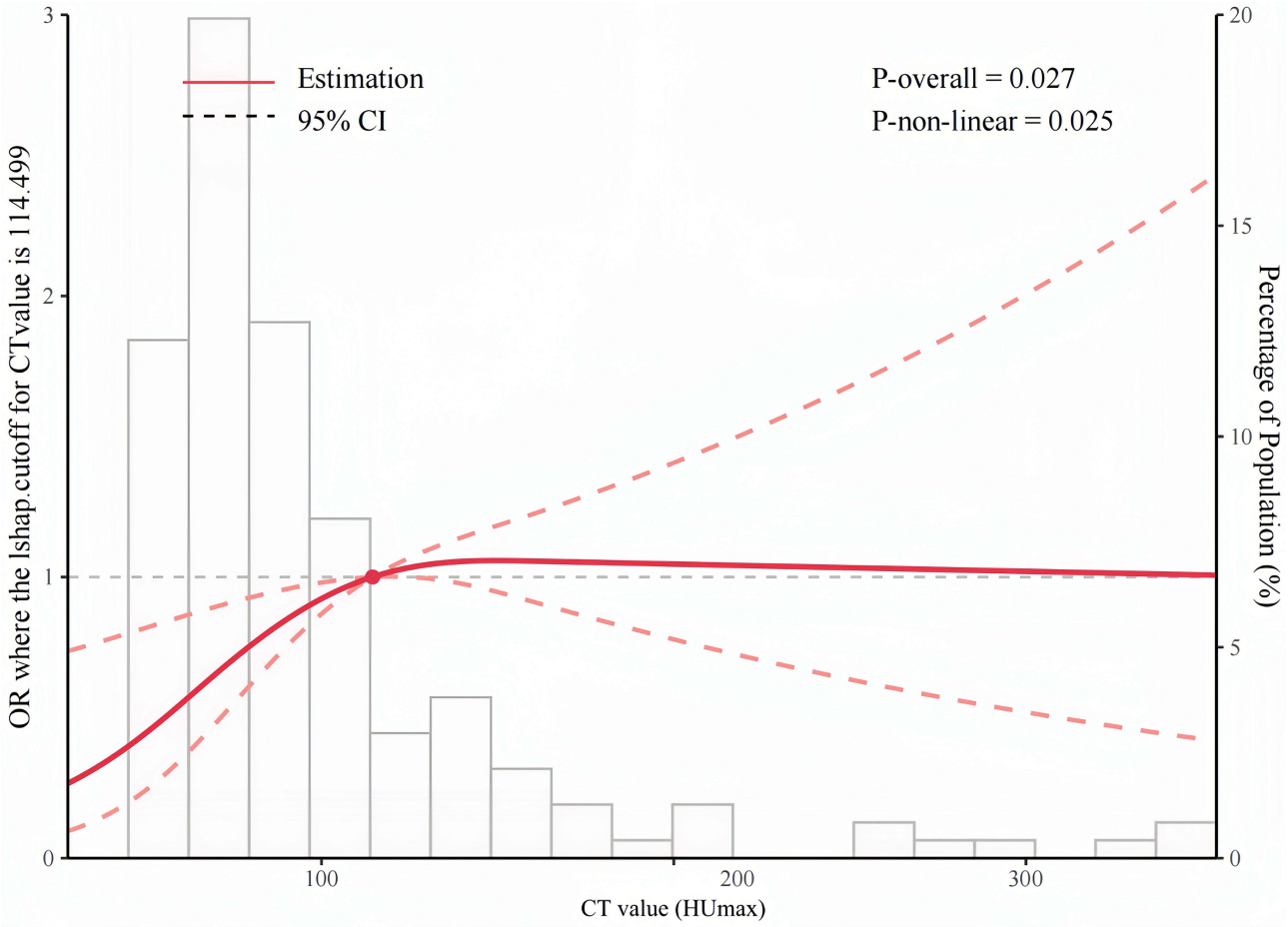

Figure 4 Restricted cubic spline (RCS) for the associations between maximum CT value and SAP. The lines represent odds ratios (ORs, solid lines) and 95% confidence intervals (CIs, long dashed lines) after multivariable adjustment for all confounding factors based on the RCS models. The reference values (OR = 1) were set at the 50th percentiles, and the knots were set at the 10th, 50th, and 90th percentiles of the maximum CT value. The histograms represent the distribution of CT value in our study, excluding values outside the 5th and 95th percentiles.
Abbreviations: CI, confidence intervals; OR odds ratios; SAP, stroke-associated pneumonia.

point at a CT value of 114 hUmax. This inflection point signifies a critical juncture in the CT value-SAP relationship. Following this, data stratification around this inflection point yielded two distinct groups: CT values < 114 (HUmax) and CT values≥114 (HUmax). Segmented logistic regression analysis was then applied to these groups to further investigate the relationship. For CT values below 114 hUmax, a noticeable and consistent increase in SAP risk was observed as the CT values intensified (OR=1.03, 95% CI: 1.02–1.04, P <0.001). However, an interesting observation arises beyond this CT threshold. Past the 114 hUmax, the escalation in SAP risk becomes less pronounced (OR= 1.00; 95% CI: 1.0–1.00, P = 0.63; Supplementary Table S1), suggesting a potential saturation in the risk profile with further increases in CT values.

Impact of BBB Disruption and SAP on Functional Outcome

The alluvial diagram depicted in Figure 5 illustrates the distribution of BBB disruption at different levels of stroke severity, as measured by the NIHSS scores. The diagram reveals a clear trend that the proportion of patients with BBB disruption increases with higher NIHSS scores. It is worth noting that half of the patients in the BBB disruption cohort were diagnosed with SAP, whereas only a small proportion of those without BBB disruption experienced this complication. The diagram also shows that SAP has a significant impact on intermediate-term functional outcomes, as measured by the modified Rankin Scale (mRS) 90 days after the intervention. Patients with SAP had predominantly unfavourable prognoses (mRS 3–6), in contrast to the non-SAP cohort, where a significantly larger proportion achieved favourable functional outcomes (mRS 0–2). It is clear from this chart that both BBB disruption and SAP are important crossroads in the developmental trajectory of patients. In our initial cohort of 254 patients who underwent a 3-month mRS evaluation, we observed that 129 patients (50.8%) had a favorable prognosis. Patients with BBB disruption had lower rates of

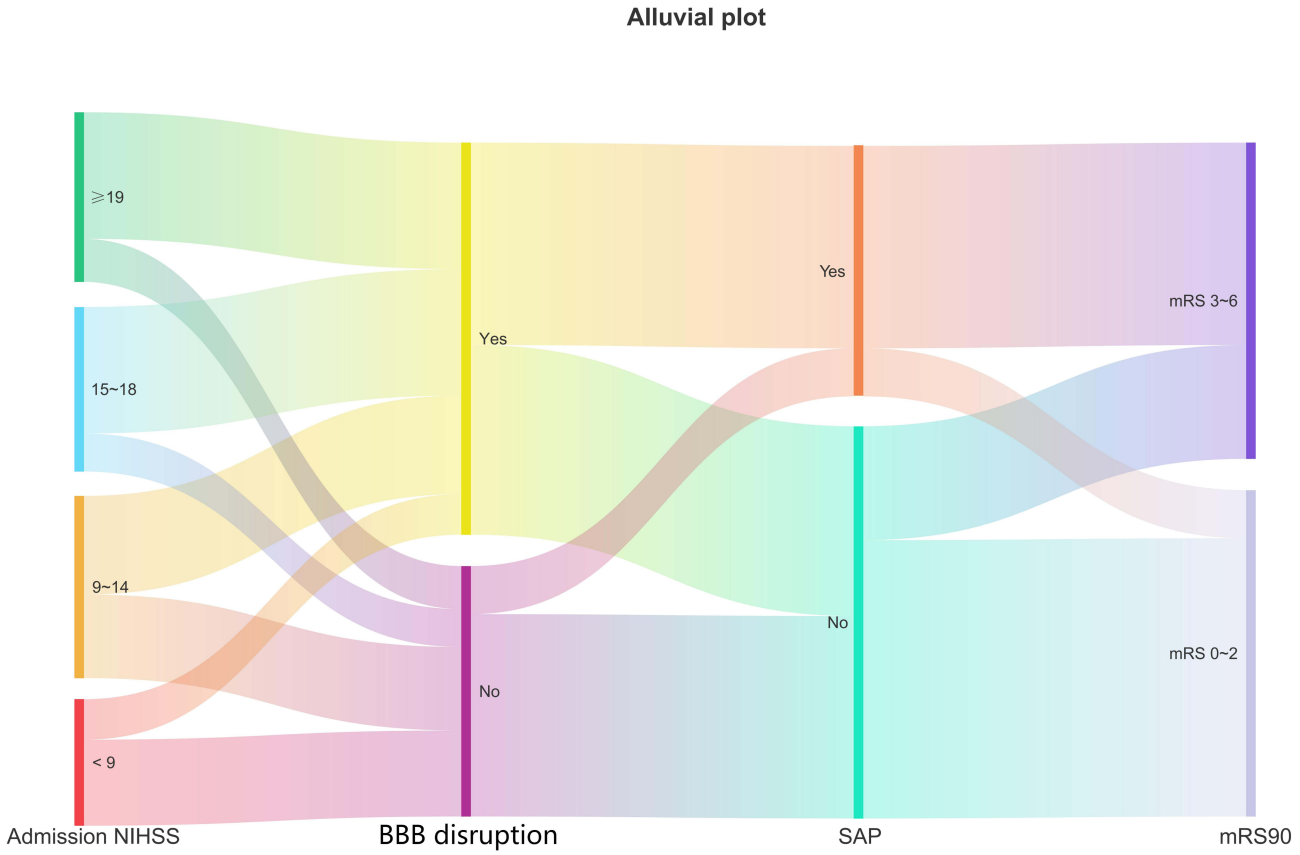

Figure 5 Alluvial diagram of the critical clinical events and outcomes (n = 254).
Abbreviations: BBB, blood-brain barrier; mRS90, modified Rankin Scale at 3 months after stroke; NIHSS, national institutes of health stroke scale; SAP stroke-associated pneumonia.

favorable outcome (34.8% vs 75.8%, p<0.001). The mediation analysis revealed that SAP partially mediates the association between BBB disruption and the 3-month poor functional outcome (Supplementary Table S2).

Sensitivity Analysis

The investigation into the relationship BBB disruption and SAP demonstrated remarkable stability across various sensitivity analyses. First, by reweighting the baseline data using the IPTW method based on propensity scores, we successfully balanced the differences in participant characteristics (Supplementary Table S3). The logistic regression outcomes post-weighting were congruent with our initial findings, suggesting that our core conclusions were not influenced by the initial attributes of the subjects (Supplementary Table S4). Second, during our main analyses, we used a DAG to determine the minimal sufficient adjustment set. We then employed multivariate logistic regression to evaluate the association between BBB disruption and SAP. It is important to note that relying solely on DAG to select covariates has limitations. DAG relies on prior expert knowledge and previous literature and might omit potential confounders if not captured in the graphical representation. To address this, we used LASSO regression to determine the minimal adjustment set statistically (Supplementary Figure S2). Reassuringly, upon performing multifactor logistic regression again with these variables, the results remained consistent with our primary analysis (Supplementary Table S5). Last, for the E-value method, our findings indicate an E-value of 2.42 for the point estimate and 1.31 for the confidence interval (Supplementary Figure S3). The purpose of using the E-value method is to assess the strength of our results against potential unmeasured confounding variables. This implies that a potential unmeasured confounder would need to have a risk ratio greater than 2.42 with both BBB disruption and SAP to reduce the significance of the observed effect, which further supports the robustness of our findings.

Discussion

To our knowledge, this research is the inaugural exploration of the association between BBB disruption and SAP following endovascular therapy. Our results imply that BBB disruption is associated with increased risk of SAP. This association may be partially ascribed to malignant cerebral edema and hemorrhagic transformation post-endovascular therapy in acute ischemic stroke patients. Additionally, we identified an inverse L-shaped dose-response curve between maximum CT values of BBB disruption areas and the incidence of SAP. This novel observation suggests that beyond a certain threshold, elevated CT values of BBB disruption areas do not linearly increase the risk of SAP, suggesting a potential saturation effect in this relationship. Finally, we found that the effect of BBB disruption on the functional outcome was partially mediated by the occurrence of SAP.

Hyperattenuated intracerebral lesions (HALs) are commonly observed on immediate CT scans following endovascular treatment for ischemic stroke. Our research found that 61.0% of patients developed HALs after endovascular treatment, which is consistent with previous studies.[17,18,20,30,31] The BBB is a unique and tightly regulated anatomical interface between circulating blood and the central nervous system(CNS) and is collectively formed by endothelial cells (ECs) the end-feet of astrocytes, and pericytes embedded in the basement membrane of capillary vessel.[32] Under normal conditions, an intact BBB selectively permits the passage of lipid-soluble molecules smaller than 400 Daltons.[33] One of the hallmark pathophysiological features of ischemic stroke is BBB disruption, which is characterized by an increased permeability due to the degradation of tight junctions (TJs) and an enhancement in endothelial vesicle transport.[34] As a result, there is an uncontrolled influx of blood-borne cells, fluid, and macromolecules such as iodinated contrast materials (eg, iodixanol, a water-soluble molecule with a molecular weight of 1550.182 Daltons), ultimately presenting as HALs on CT scans. Moreover, the more severe the disruption of the blood-brain barrier, the higher the concentration of the contrast agent and red cell that extravasates into the brain tissue, resulting in higher CT values in HALs region.[21] The duration and severity of brain tissue ischemia, reperfusion injury after vascular recanalization, and mechanical damage during thrombectomy are closely related to the BBB damage.[17,21] In addition, hypertension, diabetes, hyperlipidemia, age, and gender may also affect the permeability of the blood-brain barrier.[35]

Previous research has shown that BBB disruption is associated with higher rates of HT, malignant brain edema, and poor clinical outcomes, even after successful reperfusion.[17–19,22] Our study investigates the relationship between BBB disruption and the risk of SAP. The study found a significantly higher risk of SAP in cases where there was BBB disruption. Specifically, the risk was 2.3 times greater in the group with BBB disruption, characterized by HALs,

compared to the patients without BBB disruption group. Mediation analysis revealed that this association could be partially attributed to HT and malignant cerebral edema observed post endovascular treatment, with mediation proportions of 15.1% and 32.5%, respectively. This was particularly evident in cases of the PH subtype of hemorrhagic transformation, which accounted for 28.6% of the mediation effect. It is hypothesized that the pathway linking BBB disruption to SAP involves multiple mechanisms. The main mechanisms are likely to be HT, particularly PH, and malignant cerebral edema resulting from BBB disruption, which can worsen patients' levels of consciousness and dysphagia, thereby increasing the risk of aspiration. Reduced levels of consciousness may hinder protective reflexes, such as coughing and swallowing, which are crucial in preventing aspiration, a primary mechanism of SAP.[36] Additionally, the literature indicates a correlation between disturbances in consciousness and gastrointestinal dysfunctions, such as impaired lower esophageal sphincter function, delayed gastric emptying, and a predisposition towards reflux.[15] The clinical implications of using gastric tubes in patients with impaired consciousness are significant. While necessary for nutrition, these tubes can have a negative impact on the function of the lower esophageal sphincter, resulting in gastric reflux. Reflux increases the risk of aspiration and, as a result, the incidence of pneumonia.[37]

In addition to the mediating role of postoperative hemorrhage transformation and malignant cerebral edema in the relationship between BBB disruption and SAP, Stroke-Induced Immunosuppression (SIDS) may further explain the observed association. Traditionally, SAP was believed to be a secondary consequence of aspiration following a stroke. Previous clinical studies have suggested that aspiration and its associated risk factors, such as disturbances in consciousness and dysphagia, are the main causes of SAP.[38] However, relying solely on the aspiration theory does not fully explain the incidence of SAP,[39] and interventions aimed at preventing aspiration have proven only partially effective.[40] Growing experimental and clinical evidence suggests that stroke induces a rapid and transient state of immunosuppression, primarily regulated by the autonomic nervous system.[41–43] This condition, known as Stroke-Induced Immunosuppression Syndrome (SIDS), is characterized by a marked reduction in systemic cellular immune responses, including a rapid decline in peripheral blood lymphocyte subsets and functional inactivation of monocytes, leading to increased susceptibility to SAP.[44–46] In a multicenter, prospective clinical study, Sarah Hoffmann et al employed monocytic HLA-DR expression (mHLA-DR) as a biomarker for immunosuppression in their research on SAP, confirming that SIDS constitutes an independent risk factor for stroke-associated pneumonia.[47] Furthermore, some pathophysiological studies suggest that BBB disruption may serve as a critical pathological trigger for SIDS, with the extent of BBB damage potentially influencing the severity of SIDS.[48–50] SIDS is a specific immune response that occurs after ischemic stroke brain injury, typically emerging within 24 hours of stroke onset and lasting for several weeks.[44–46] BBB disruption plays a critical role in the development of SIDS. Normally, the central nervous system sends strong anti-inflammatory signals following peripheral organ injury, while a tight BBB preserves brain immunity. However, in the context of cerebral ischemia, brain-derived antigens, damage-associated molecular patterns (DAMPs), cytokines, and chemokines are released into the circulatory system through the damaged BBB, recruiting various immune cells (both resident and peripheral) to the affected area, thereby contributing to secondary brain damage. SIDS mitigates brain injury by preventing autoimmunity through the activation of the sympathetic and parasympathetic nervous systems and the hypothalamic-pituitary-adrenal axis.[44–46] However, this immunosuppressive state also results in a rapid reduction in T, B, and NK lymphocytes, increasing the risk of infection-related complications.[51] Our research confirms the significant mediation effects of hemorrhagic transformation and malignant cerebral edema. Additionally, we introduce SIDS as a key factor that may explain the heightened SAP risk associated with BBB disruption. However, it is important to note that the specific impact of BBB disruption on SAP risk mediated by SIDS requires further direct clinical evidence to be fully understood. We aim to explore this relationship further in future studies by incorporating markers for immunodepression, such as monocytic HLA-DR (mHLA-DR), as mediators to provide more direct clinical evidence of the link between BBB disruption and SAP.

Our study has revealed a nuanced aspect of the relationship between the maximum CT values of BBB disruption areas and the incidence of SAP. The RCS analysis showed an inverted L-shaped dose-response curve. This pattern indicates that as CT values increase, indicating more severe BBB disruption, there is an initial rapid rise in the incidence of SAP. However, once the CT values surpass a certain threshold, the rate of increase in SAP incidence notably slows down. This saturation effect suggests that while BBB disruption initially increases the risk of SAP, beyond a certain level

of BBB damage, other factors such as the severity and location of the stroke may become more important. These findings offer valuable guidance for clinical practice. The identification of a saturation point in the dose-response relationship suggests that early detection of mild to moderate BBB disruption could provide a critical window for intervention. Clinicians may consider early, targeted interventions, such as prophylactic antibiotic use or enhanced monitoring, to mitigate SAP risk before more severe BBB damage occurs. The radiological evidence supporting the link between BBB disruption and SAP also highlights the complexity of factors influencing SAP risk in stroke patients.

Our study found that BBB disruption was associated with poor prognosis at 3 months after stroke, which is consistent with a previous study by Mazighi.[17] Importantly, our analysis extends these findings by elucidating the role of SAP as a partial mediator of the relationship between BBB disruption and three-month poor functional outcome. This mediating role emphasizes the complex interplay between neurological injury and secondary complications such as SAP. Patients with BBB rupture in our cohort demonstrated a significantly higher incidence of SAP, which was subsequently associated with a poorer recovery trajectory in terms of mRS assessed at 90 days post- endovascular therapy. These insights may suggest that while BBB disruption directly contributes to functional deterioration, the subsequent development of SAP exacerbates these outcomes, thereby amplifying the overall impact on patient recovery. This dual pathway emphasizes the need for vigilant monitoring and potentially more targeted therapeutic strategies in patients who develop signs of BBB disruption after endovascular therapy.

From a clinical perspective, our findings suggest that patients presenting with BBB disruption after ET should be closely monitored for signs of SAP. The results indicate that early identification of BBB disruption on post-ET imaging could provide an opportunity for preventive interventions, potentially reducing the incidence of SAP and improving overall patient outcomes. Current clinical practice tends to focus on treating pneumonia after it occurs, but based on our findings, we recommend considering proactive measures for high-risk patients. For instance, implementing routine screening protocols for SAP in patients with significant BBB disruption—measured by HALs—could allow for earlier diagnosis and intervention. Strategies such as the judicious use of prophylactic antibiotics or enhancing post-ET pulmonary care could be explored to mitigate SAP risk in these patients. Furthermore, given the role of stroke-induced immunosuppression, efforts to modulate immune response in patients with BBB disruption could be another avenue for reducing pneumonia risk.

Additionally, as identified in our mediation analysis, complications such as hemorrhagic transformation and cerebral edema appear to partially mediate the relationship between BBB disruption and SAP. Therefore, close monitoring and active management of these complications could also reduce the occurrence of SAP, contributing to better functional outcomes at 3 months post-stroke.

Our study has several notable strengths. Firstly, it is the first to explore the association between BBB disruption post-endovascular therapy and SAP, shedding new light on this area. Secondly, we used DAG in our modeling approach to identify and adjust for potential confounding variables, thus strengthening the validity of our results. Furthermore, the study used advanced statistical methods, such as mediation analysis and constrained cubic splines, to analyze complex relationships and dose-response patterns. Stratified and interaction analyses provided deeper insights into how different factors might influence the association between BBB disruption and SAP. Lastly, a key strength of the study is the practical and accessible method of assessing BBB disruption using HALs on non-contrast CT scans post-mechanical thrombectomy. This simpler and more accessible approach enables earlier identification of high-risk SAP patients, facilitating timely clinical interventions. The study's clinical relevance is further underscored by its illumination of potential pathways and mechanisms linking BBB disruption to SAP, providing significant insights for both future research and clinical practice.

Several limitations should be acknowledged. Firstly, the retrospective cohort design is inherently prone to selection and information biases. Additionally, our findings are based on a single-center cohort, which limits their generalizability to diverse populations. Therefore, multi-center studies with larger sample sizes and varied demographics are necessary to validate and expand upon our results. Secondly, our reliance on CT imaging to identify BBB disruption introduces potential variability in interpretation. The assessment of HALs is subject to interobserver variability. Consistency of measurements may be affected by the use of different CT scanners and protocols across various centres. Finally, the discussion section highlights the potential mediating role of stroke-induced immunosuppression in the relationship

between blood-brain barrier disruption and secondary autoimmune processes. However, this conclusion is based on indirect evidence. Currently, there is no direct clinical data linking disruption of the blood-brain barrier to stroke-induced immunosuppression. To gain more concrete insights, future studies could employ biomarkers of immunosuppression.

Conclusion

This study explores the relationship between BBB disruption and SAP in acute ischemic stroke patients after endovascular therapy. The study shows BBB disruption are significantly associated with an increased risk of SAP, potentially mediated by hemorrhagic transformation, malignant cerebral edema, and potentially stroke-induced immunosuppression. Given this, hemorrhagic transformation and cerebral edema should be considered as critical factors in managing patients following endovascular therapy, as they may exacerbate the risk of pneumonia and other complications. Importantly, the study reveals a saturation effect, where beyond a certain threshold of BBB disruption, the risk of SAP no longer increases proportionally, indicating that early detection of mild to moderate BBB disruption may provide a critical window for intervention. Our study also confirms that BBB disruption negatively affects medium-term functional outcomes, partially mediated in part by SAP. Assessment of BBB disruption may have a role in prognostic staging of patients after endovascular therapy, and minimizing BBB disruption during procedures may help reduce pneumonia-related complications and improve midterm outcomes.

Abbreviations

AIS, Acute ischemic stroke; BBB, blood-brain barrier; CT, Computerized tomograph; CNS, Central nervous system; COPD, Chronic obstructive pulmonary disease; DAG, A directed acyclic graph; DSA, Digital subtraction angiography; ET, Endovascular therapy; GCS, Glasgow coma scale; HALs, Hyperattenuated Lesions; HUmax, Maximum Hounsfield Units; ICU, Intensive Care Unit; IPTW, Inverse probability of treatment weighting; IQR, Inter-quartile range; LVO, Large vessel occlusion; MSAS, Minimally sufficient adjustment set; NICU, Neurological Intensive Care Unit; NIHSS, National Institutes of Health Stroke Score; OR, Odds ratio; PACS, Picture archiving and communication system; RCS, Restricted cubic spline; ROI, Regions of Interest; PISCES, Pneumonia in Stroke Consensus Group; PS, Propensity score; SAP, Stroke-associated pneumonia; SD, standard deviation; SIDS, Stroke-induced immunodepression syndrome; SMD, Standardized mean difference; TICI score, Thrombolysis in cerebral infarction score.

Data Sharing Statement

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the principles of the Declaration of Helsinki. This study was approved by the institutional review board of Xi'an NO.3 hospital (number:syll-2022-079). In accordance with the guidelines of the Institutional Review Board of Xi'an NO.3 hospital, the requirement for informed consent was waived due to the retrospective nature of the study. All patient data were anonymized and de-identified prior to analysis to ensure confidentiality. No personally identifiable information was disclosed or published. The study adhered to the ethical principles of the Declaration of Helsinki and relevant local regulations regarding data protection and patient privacy.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing

the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All the authors have no competing interests.

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