

High-Mobility Group Box-1 as a Predictor for Malignant Brain Edema Following Mechanical Thrombectomy in Acute Ischemic Stroke Patients

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Background and Purpose: Emerging experimental evidence has established that high-mobility group box 1 (HMGB-1) plays a pivotal role in cerebral ischemia pathogenesis, primarily through mediating neuroinflammatory cascades following ischemic injury. This study sought to investigate the potential association between circulating HMGB-1 levels and the risk of malignant brain edema (MBE) in patients undergoing mechanical thrombectomy (MT).

Methods: This study prospectively recruited patients presenting with large vessel occlusive stroke in the anterior circulation and receiving MT treatment. Serum HMGB-1 levels were quantitatively assessed for all participants upon hospital admission. MBE was defined as defined as a midline shift of ≥ 5 mm observed on follow-up neuroimaging after MT. Multivariate logistic regression analyses were conducted to investigate the potential correlation between serum HMGB-1 concentrations and MBE development.

Results: Among the cohort of 261 eligible patients (mean age: 69.7 years; male: 166 [63.6%]), 59 individuals (22.6%; 95% confidence interval [CI]: 17.6%-28.3%) developed MBE. After adjusted for demographic characteristics and other potential confounders, multivariate logistic regression demonstrated that higher serum HMGB-1 levels were associated with an increased risk of MBE (odds ratios [OR], highest vs lowest quartile: 3.130; 95% CI, 1.077–9.098; $P = 0.036$). In addition, restricted cubic spline analysis revealed a dose-response relationship between elevated serum HMGB-1 levels and MBE risk (P for non-linearity=0.764).

Conclusion: This study confirmed that elevated circulating HMGB-1 levels were significantly associated with MBE after MT. These findings suggested that HMGB-1 could serve as a predictive biomarker for post-MT MBE risk, potentially enabling early identification of high-risk patients who may benefit from intensified monitoring or targeted therapeutic interventions.

Keywords: HMGB-1, brain edema, endovascular treatment, ischemic stroke

Introduction

Mechanical thrombectomy (MT) has emerged as a pivotal intervention for acute ischemic stroke caused by large vessel occlusion in the anterior circulation, significantly improving functional outcomes.¹ Nonetheless, malignant brain edema (MBE), a severe complication that arises in 10–20% of patients following MT, continues to pose a significant clinical challenge.² Even with successful reperfusion after MT, ischemic stroke patients who develop MBE exhibit markedly poorer clinical outcomes and elevated mortality rates.³ MBE is characterized by swift neurological decline, midline shift, and brain herniation, leading to mortality rates surpassing 50% within the first week post-MT.^{4,5} Previous studies have identified several key determinants of MBE, including basal cistern effacement, blood glucose levels, intravenous thrombolysis, baseline NIHSS score, collateral circulation grade, and postoperative revascularization grade.^{6,7} While the exact mechanisms of MBE after MT are still not completely understood, determining its risk factors may provide insights into molecular pathogenesis and reduce adverse outcomes after MT.

After ischemic stroke onset, brain tissue triggers a neuroinflammatory response, characterized by a marked increase in the expression of pro-inflammatory cytokines, such as TNF- α and IL-1 β .^{8,9} High-mobility group box-1 (HMGB-1), a nuclear protein that functions as a damage-associated molecular pattern molecule, plays a pivotal and multifaceted role in various pathological processes, including neuroinflammation and secondary brain injury.^{10–12} Experimental studies have consistently demonstrated that HMGB-1 significantly exacerbates pathological outcomes in ischemic stroke conditions, including increased infarct volume, aggravated cerebral edema, and enhanced blood brain barrier permeability.^{13–15} Also, HMGB1 may bind to fibrinogen and tissue plasminogen activator to amplify fibrinolytic enzymes and promote the release of matrix metalloproteinase-9, leading to the hemorrhage transformation.¹⁶ In patients with ischemic stroke undergoing reperfusion therapy, elevated HMGB1 levels have been found to be associated with both larger cerebral infarction volumes and poorer clinical outcomes.¹⁷ However, to date, the potential association between HMGB-1 and MBE post-MT has not been conclusively established.

We therefore perform this prospectively study to determine whether serum HMGB-1 levels can serve as an independent predictive biomarker for MBE in patients following MT treatment.

Materials and Methods

Study Sample

This study prospective recruited acute ischemic stroke patients with large vessel occlusion who underwent MT at Nanjing First Hospital from September 2019 to July 2021. The inclusion criteria were as follows: (1) age ≥ 18 years; (2) occlusion of the internal carotid artery or middle cerebral artery confirmed by preoperative imaging; (3) received MT treatment using a stent retriever and/or aspiration system. Patients were excluded if they diagnosed with a concomitant aneurysm, arteriovenous malformation, moyamoya disease, or hematological system diseases. This study was approved by the Ethics Committee of Nanjing First Hospital and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the participants' parent/legal guardian/next of kin to participate in the study.

Data Collection

Baseline data comprising demographic characteristics, clinical parameters, procedural details, and laboratory findings were collected and analyzed. Neurological deficits at admission were assessed using the National Institutes of Health Stroke Scale (NIHSS) score. Baseline infarct volume was evaluated via the Alberta Stroke Program Early Computed Tomography Score (ASPECTS). Stroke etiology was categorized according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification criteria.¹⁸ Collateral status was evaluated with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology grading system,¹⁹ and categorized as either poor (grades 0–1) or good (grades 2–4).²⁰ Furthermore, successful vascular recanalization was defined as achieving a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b–3.^{20–22}

Blood Sampling

Venous blood samples were collected within 24 hours of admission. Serum HMGB1 levels were quantified using a commercially available enzyme-linked immunosorbent assay kit (IBL International, Hamburg, Germany) following the manufacturer's protocol. The intra- and inter-assay coefficients of variation for the biochemical assays were 3.2% and 1.3%, respectively. The limit of detection was 0.2 ng/mL. All procedures strictly adhered to the manufacturer's guidelines and were performed by a laboratory technician blinded to clinical data.

Outcome Measures

A follow-up CT scan was performed 24–72 hours after MT. According to previous studies,^{23,24} MBE was diagnosed according to the following criteria: (1) parenchymal hypoattenuation involving $\geq 50\%$ of the middle cerebral artery territory, accompanied by local mass effect (eg, sulcal effacement or lateral ventricular compression); (2) Midline shift ≥ 5 mm at the septum pellucidum or pineal gland, with concurrent effacement of the basal cisterns. Two board-certified

neurologists, blinded to clinical data, independently evaluated all imaging parameters. Discrepancies in interpretation were resolved through consensus discussion, and unresolved cases underwent adjudication by a senior neuroradiologist.

Statistical Analysis

Patients were stratified into MBE and non-MBE groups. Categorical variables are reported as frequencies (%) and compared with the chi-square test or Fisher's exact test. Continuous variables are presented as mean \pm standard deviation or medians and analyzed using the Mann–Whitney *U*-test, *t*-test, Kruskal–Wallis test, and one-way analysis of variance, when appropriate. Binary logistic regression analysis was utilized to explore the relationship between HMGB-1 levels and MBE adjusting for age, sex, and covariates with *P* value < 0.1 in the univariate analysis. Furthermore, to characterize the nonlinear association between serum HMGB-1 concentrations and MBE risk, restricted cubic splines with 3 knots positioned at the 5th, 55th, and 95th percentiles were applied.²⁵ For all analyses, *P* < 0.05 was regarded as significant. All analyses were performed using SPSS version 25.0 (IBM, New York, NY), and R statistical software version 4.3 (R Foundation, Vienna, Austria).

Results

Patient Characteristics

This study initially screened 283 patients who underwent MT. Among them, we excluded 14 patients who did not receive treatment with a stent retriever or aspiration system, 5 patients with concurrent conditions such as aneurysms, arteriovenous malformations, moyamoya disease, or leukemia, and 3 patients lacking follow-up imaging data for assessing MBE. After exclusions, the final analysis included 261 patients (mean age: 69.7 years; male: 166 [63.6%]). The NIHSS score was 13.0 (IQR, 10.0–17.0), the baseline ASPECTS was 9.0 (IQR, 8.0–9.0), and the time from onset to recanalization was 360.0 (IQR, 248.0–569.0) minutes. Of those, 120 (46.0%) patients were identified as large artery atherosclerosis, 114 (43.7%) as cardioembolism, 27 (10.3%) as undetermined stroke/others etiology. The median HMGB-1 levels were 6.9 (IQR, 4.2–11.8) ng/mL. Baseline characteristics of the study sample stratified by the quartile of HMGB-1 levels were shown in Table 1. Increasing quartile of HMGB-1 was associated with hypertension (*P* = 0.037), diabetes (*P* = 0.076), and MBE (*P* = 0.006).

Incidence and Predictors of MBE

During the hospitalization, 59 individuals (22.6%; 95% confidence interval [CI]: 17.6%–28.3%) diagnosed with MBE. Table 2 summarized the results of the binary logistic regression of MBE. Univariate logistic regression analysis demonstrated that hypertension (odds ratio [OR], 1.512; 95% CI, 1.082–4.772; *P* = 0.030), NIHSS score (OR, 1.091; 95% CI, 1.045–1.139; *P* = 0.001), poor collateral status (OR, 4.325; 95% CI, 2.166–7.635; *P* = 0.001), successful vascular recanalization (OR, 0.135;

Table 1 Baseline Characteristics of the Patients Stratified by the Quartiles of HMGB1 Levels

Variables	First Quartile, n = 62 (<4.2 ng/mL)	Second Quartile, n = 68 (4.2–6.9 ng/mL)	Third Quartile, n = 64 (7.0–11.8 ng/mL)	Fourth Quartile, n = 67 (>11.8 ng/mL)	P value
Age, year	67.9 \pm 11.5	69.7 \pm 12.1	69.1 \pm 14.7	71.8 \pm 10.5	0.327
Male, n (%)	39 (62.9)	44 (64.7)	43 (67.2)	40 (59.7)	0.839
Hypertension, n (%)	41 (66.1)	53 (77.9)	39 (60.9)	54 (80.6)	0.037
Diabetes, n (%)	13 (20.0)	22 (32.4)	10 (15.6)	21 (31.3)	0.076
Hyperlipidemia, n (%)	4 (6.5)	7 (10.3)	8 (12.5)	9 (13.4)	0.589
Coronary heart disease, n (%)	6 (9.7)	11 (16.2)	7 (10.9)	12 (17.9)	0.457
Smoking, n (%)	27 (43.5)	29 (42.6)	26 (40.6)	21 (31.3)	0.456
Systolic blood pressure, mmHg	135.2 \pm 23.4	138.9 \pm 21.9	134.8 \pm 23.0	136.5 \pm 22.6	0.723
Diastolic blood pressure, mmHg	84.7 \pm 13.9	81.7 \pm 11.9	82.7 \pm 14.6	81.9 \pm 13.6	0.593
Baseline NIHSS, score	12.0 (8.0, 15.0)	14.0 (10.0, 18.0)	14.0 (10.0, 18.0)	13.0 (11.0, 19.0)	0.162
Baseline ASPECTS, score	9.0 (8.0, 9.0)	8.5 (8.0, 9.0)	9.0 (8.0, 9.0)	8.0 (8.0, 9.0)	0.294
Time from onset to recanalization, min	396.5 (253.0, 706.0)	353.5 (242.0, 541.5)	360.5 (242.5, 535.0)	353.0 (256.0, 535.0)	0.509
Time from onset to blood draw, h	20.5 (13.0, 24.0)	19.0 (14.0, 24.0)	17.0 (12.0, 23.0)	19.0 (13.0, 23.0)	0.420

(Continued)

Table 1 (Continued).

Variables	First Quartile, n = 62 (<4.2 ng/mL)	Second Quartile, n = 68 (4.2–6.9 ng/mL)	Third Quartile, n = 64 (7.0–11.8 ng/mL)	Fourth Quartile, n = 67 (>11.8 ng/mL)	P value
Cause of stroke, n (%)					0.244
Large artery atherosclerosis	27 (43.5)	37 (54.4)	26 (40.6)	30 (44.8)	
Cardioembolism	30 (48.4)	24 (35.3)	27 (42.2)	33 (49.3)	
Others/unknown	5 (8.1)	7 (10.3)	11 (17.2)	4 (6.0)	
Malignant brain edema, n (%)	7 (11.3)	17 (25.0)	11 (17.2)	24 (35.8)	0.006
Prior IVT treatment, n (%)	25 (40.3)	33 (48.5)	33 (51.6)	29 (43.3)	0.577
Poor collateral status, n (%)	33 (53.2)	38 (55.9)	34 (53.1)	38 (56.7)	0.966
Successful recanalization, n (%)	55 (88.7)	58 (85.3)	60 (92.2)	53 (79.1)	0.094
Occlusive vessel, n (%)					0.154
Internal carotid artery	22 (35.5)	25 (36.8)	13 (20.3)	23 (34.3)	
Middle cerebral artery	40 (64.5)	43 (63.2)	51 (79.7)	44 (65.7)	
Laboratory data					
Total cholesterol, mmol/L	4.1 ± 1.1	4.3 ± 1.3	4.2 ± 1.1	4.2 ± 1.2	0.925
Triglyceride, mmol/L	1.0 (0.8, 1.4)	1.1 (0.8, 1.6)	1.0 (0.7, 1.5)	1.1 (0.8, 1.8)	0.509
High-density lipoprotein, mmol/L	1.1 ± 0.3	1.3 ± 0.3	1.1 ± 0.3	1.3 ± 0.2	0.557
Low-density lipoprotein, mmol/L	2.2 (1.8, 2.9)	2.3 (1.8, 3.0)	2.7 (2.0, 3.1)	2.4 (1.7, 3.1)	0.510
Baseline glucose levels, mmol/L	6.9 ± 2.2	7.4 ± 2.7	7.0 ± 2.4	7.4 ± 2.2	0.532
Hyper-sensitive C-reactive protein, mg/L	7.9 (4.3, 20.9)	12.1 (4.4, 22.9)	10.2 (4.0, 29.4)	12.5 (4.4, 28.2)	0.512

Abbreviations: ASPECTS, Alberta stroke program early CT score; IVT, Intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale.

Table 2 Logistic Regression Analysis of the Risk Factors with MEB

Variables	Univariate Regression Analysis		Multivariate Regression Analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, per 1-year increase	1.013 (0.988–1.038)	0.303	0.992 (0.960–1.026)	0.649
Male	1.512 (0.626–2.119)	0.650	1.296 (0.598–2.812)	0.511
Hypertension	2.272 (1.082–4.772)	0.030	2.571 (1.011–6.540)	0.047
Diabetes	1.009 (0.518–1.966)	0.978		
Hyperlipidemia	0.539 (0.719–1.622)	0.272		
Coronary heart disease	1.622 (0.746–3.531)	0.223		
Smoking	1.169 (0.649–2.107)	0.603		
Systolic blood pressure, per 1-mmHg increase	0.988 (0.985–1.011)	0.752		
Diastolic blood pressure, per 1-mmHg increase	1.001 (0.980–1.023)	0.925		
Baseline NIHSS score, per 1-score increase	1.091 (1.045–1.139)	0.001	1.099 (1.042–1.160)	0.001
Baseline ASPECTS, per 1-score increase	0.887 (0.695–1.133)	0.337		
Time from onset to recanalization, per 1-min increase	1.000 (0.999–1.001)	0.902		
Cause of stroke				
Large artery atherosclerosis	0.526 (0.211–1.132)	0.168		
Cardioembolism	0.562 (0.225–1.403)	0.217		
Others/unknown	Reference			
Prior IVT treatment	1.287 (0.720–2.301)	0.394		
Poor collateral status	4.325 (2.166–7.635)	0.001	4.352 (1.953–9.698)	0.001
Successful vascular recanalization	0.135 (0.063–0.288)	0.001	0.099 (0.039–0.254)	0.001
Occlusive vessel				
Internal carotid artery	1.512 (0.807–2.766)	0.180		
Middle cerebral artery	Reference			
Laboratory data				
Total cholesterol, per 1-mmol/L increase	0.850 (0.656–1.102)	0.219		
Triglyceride, per 1-mmol/L increase	1.172 (0.879–1.561)	0.280		
High-density lipoprotein, per 1-mmol/L increase	1.333 (0.923–1.619)	0.161		

(Continued)

Table 2 (Continued).

Variables	Univariate Regression Analysis		Multivariate Regression Analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Low-density lipoprotein, per 1-mmol/L increase	0.780 (0.556–1.094)	0.150	1.089 (0.943–1.257)	0.247
Baseline glucose levels, per 1-mmol/L increase	1.193 (1.063–1.339)	0.003		
Hyper-sensitive C-reactive protein, per 1-mmol/L increase	1.000 (0.997–1.004)	0.829		
HMGB1 quartile				
First	Reference		Reference	
Second	2.619 (1.004–6.834)	0.049	2.197 (0.737–6.547)	0.158
Third	1.631 (0.588–4.522)	0.347	1.593 (0.495–5.121)	0.435
Fourth	4.385 (1.727–11.133)	0.002	3.130 (1.077–9.098)	0.036

Notes: Multivariate regression model was adjusted for age, sex, hypertension, poor collateral status, successful recanalization, and baseline glucose levels.

Abbreviations: ASPECTS, Alberta stroke program early CT score; CI, Confidence interval; HMGB1, High-mobility group box-1; IVT, Intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; OR, Odd ratio.

95% CI, 0.063–0.288; $P=0.001$), baseline glucose levels (OR, 1.193; 95% CI, 1.063–1.339; $P=0.003$), and HMGB-1 levels (fourth quartile vs first quartile, OR, 4.385; 95% CI, 1.727–11.133; $P=0.002$) were associated with increasing risk of MBE. After adjusting for potential confounders, higher HGMB-1 levels were identified as an independent predictor of MBE (fourth quartile vs first quartile, 3.310; 95% CI, 1.077–9.098; $P=0.036$) in multivariate logistic regression model.

In addition, restricted cubic spline analysis revealed a dose-response relationship between elevated serum HMGB-1 levels and MBE risk (P for non-linearity=0.764; Figure 1).

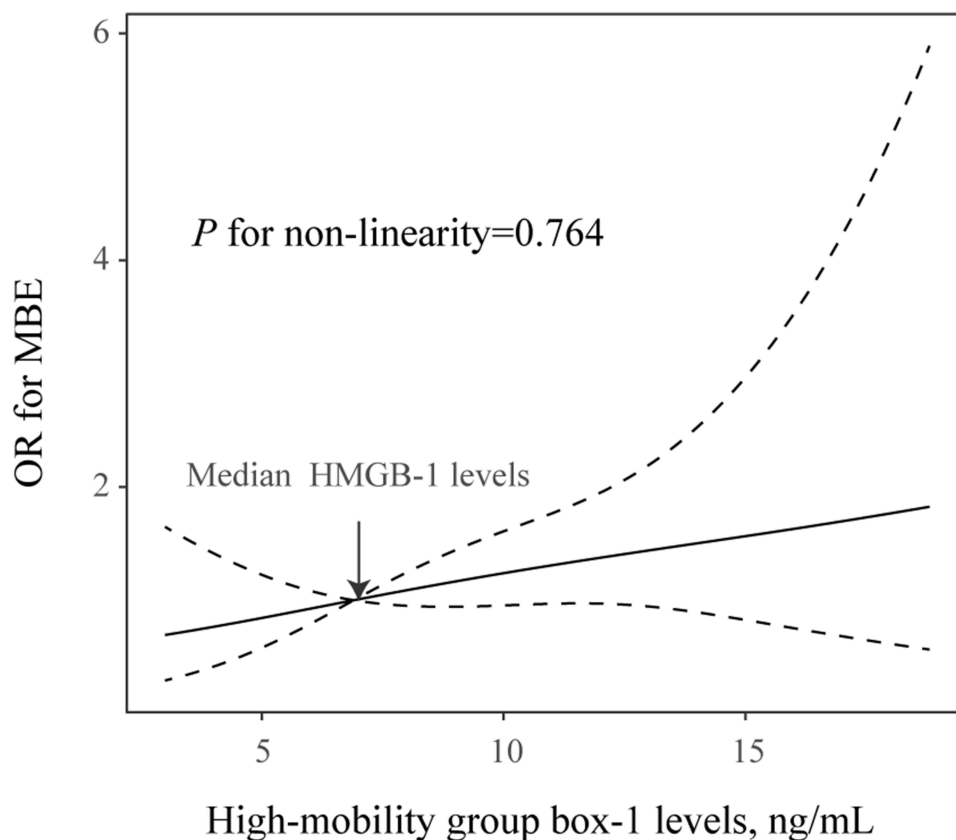


Figure 1 Restricted cubic spline was used to explore the pattern and magnitude of the association of HMGB-1 levels with MBE with three knots placed at the 5th, 55th, and 95th percentiles. The odd ratio was adjusted for the same covariates in the multivariate regression model. The median HMGB-1 level was used as the reference value. The solid line represents odd ratio, and dashed line indicates 95% confidence interval.

Discussion

To our best knowledge, this is the first study demonstrates a significant association between higher serum HMGB-1 levels and an increased risk of MBE following MT in patients with anterior circulation large vessel occlusion. Importantly, this association remained robust after adjustment for potential confounders, including age, sex, hypertension, poor collateral status, successful recanalization, and baseline glucose levels.

The incidence of MBE has been documented in several studies. A previous investigation reported an MBE occurrence rate of 19.4% among patients undergoing MT.²⁶ Another cohort study demonstrated a higher MBE incidence of 26.9% in patients receiving MT for anterior circulation large vessel occlusive stroke.⁶ Our prospective study demonstrated that MBE was diagnosed in 22.6% of the patient cohort, a finding that aligns with above studies. Previous studies have identified several predictive factors for MBE in patients following MT,^{6,27-29} including advanced age, fasting blood glucose levels, hypertension, baseline NIHSS score, collateral circulation status, hematocrit levels, and unsuccessful recanalization. However, our current investigation did not demonstrate statistically significant associations between MBE and either age or hypertension. This discrepancy may be attributed to the heterogeneous definitions of MBE across different study populations. The establishment of standardized diagnostic criteria is therefore imperative to facilitate consistent research outcomes and enhance the clinical relevance of MBE-related studies.

Previous studies have identified MBE determinants including basal cistern effacement, blood glucose, thrombolysis, NIHSS score, collateral circulation, and revascularization grade.^{6,7} Although MT-related MBE mechanisms remain incompletely understood, this first demonstrates that elevated serum HMGB-1 levels predict MBE risk after MT in large vessel occlusive patients. The mechanisms by which serum HMGB-1 affects MBE after ischemic stroke are unclear, but several potential pathophysiological pathways have been suggested. The neuroinflammation and disruption of blood-brain barrier are likely to represent an important link between these 2 conditions. HMGB1 is released into the extracellular space either through passive diffusion following cellular necrosis or via regulated secretion by immunologically activated cells.³⁰ The neuroinflammatory pathway involves HMGB-1 activation of microglial and astroglial cells, triggering the release of pro-inflammatory cytokines through the TLR4/NF- κ B signaling pathway.^{31,32} This inflammatory cascade is further amplified by HMGB-1's ability to promote matrix metalloproteinase (MMP) activation, particularly MMP-9, which plays a dual role in MBE pathogenesis.^{33,34} Moreover, the MMP-9 contributes to BBB breakdown by degrading critical tight junction proteins (occludin and claudin-5) and the basement membrane, while simultaneously exacerbating neuroinflammation.^{35,36} The thrombectomy may potentiate these effects by inducing initial BBB disruption, thereby facilitating HMGB-1's pro-inflammatory actions and creating a vicious cycle of inflammation and edema formation. Other possible pathways include increasing oxidative stress, and inducing atherosclerosis and thrombosis.³⁷⁻³⁹ Currently, multiple HMGB1 antagonists are currently in various stages of research and development. These therapeutic agents are designed to counteract HMGB1-mediated inflammatory processes, immune dysregulation, and associated pathological conditions. Notable candidates comprise glycyrrhizin, specific anti-HMGB1 antibodies, and pharmacological compounds that modulate HMGB1 release or its post-translational modifications.⁴⁰ Further studies are needed to clarify its effect in ischemic stroke.

This study has several limitations that warrant consideration. First, the small sample size and single-center design may compromise statistical power and limit the generalizability of the findings. This is particularly relevant for etiologically defined subgroups (eg, large-territory infarction or specific stroke subtypes), where these limitations may introduce statistical bias and reduce the external validity of our conclusions. Second, the absence of longitudinal HMGB-1 assessment precludes the analysis of its temporal dynamics and potential prognostic value throughout the disease course. Third, potential confounding factors, including comorbidities and concomitant medications that may influence HMGB-1 expression, were not systematically evaluated. Finally, while our study identifies HMGB-1 as a potential risk factor for MBE, further research is needed to determine its clinical utility, including optimal measurement protocols, clinically significant thresholds, and integration into existing diagnostic or prognostic frameworks.

In conclusion, our study confirmed that higher HMGB-1 levels were significantly associated with as MBE after MT. These findings suggested that HMGB-1 may serve as a predictive biomarker for post-MT MBE risk, potentially allowing early identification of high-risk patients who could benefit from intensified monitoring or targeted therapy. In addition, the robust association observed underscores the need for preclinical trials of anti-HMGB-1 therapies in reperfusion injury models.

Data Sharing Statement

Data are available upon reasonable request to the corresponding author.

Ethical Approval

The Ethics Committee of Nanjing First Hospital approved this study. Written informed consent was obtained from the participants' parent/legal guardian/next of kin to participate in the study.

Author Contributions

XC and GC designed the study. XC, YE, YH, and WW obtained the data and carried out the analysis. XC wrote the manuscript. Important data analysis suggestions were made by GC and YE. YE, XX and GC revised the manuscript. All authors made a significant contribution to the work reported, whether that is 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 declare that there is no conflict of interest in this work.

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