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Apolipoprotein E- ϵ 4 allele is associated with perihematomal brain edema and poor outcomes in patients with intracerebral hemorrhage

Lei Huang^{1,2}, Qian Wu¹, Fei Ye¹, Wei Che¹, Xu Zhao¹, ChaoZhen Yang^{1,2}, Siying Ren¹, Guofeng Wu¹ & Likun Wang³✉

Intracerebral hemorrhage (ICH) poses significant disability and mortality risks and perihematomal edema (PHE) plays a crucial role in ICH prognosis. The ApoE- ϵ 4 allele has been implicated in exacerbating PHE and influencing neurological recovery post-ICH, yet, this specific association has not been explored much. This study aimed to investigate the correlation between ApoE- ϵ 4 allele, PHE, and clinical prognosis in patients with ICH. We conducted a prospective observational cohort study at the Affiliated Hospital of Guizhou Medical University from January 2020 to December 2023. We enrolled patients with supratentorial ICH patients and analyzed ApoE gene alleles, clinical baseline data, blood biochemical indices, and imaging findings. We considered ApoE- ϵ 4 carrier status as an exposure variable and compared PHE volumes between ApoE- ϵ 3 (ϵ 3/ ϵ 3) and ApoE- ϵ 4 (ϵ 2/ ϵ 4, ϵ 3/ ϵ 4, ϵ 4/ ϵ 4) carriers. We also compared clinical and imaging characteristics between the good prognosis group (modified Rankin score 0–3) and the poor prognosis group (modified Rankin score 4–6). Finally, we examined the association between ApoE ϵ 4 and PHE volume and poor prognosis at discharge. Among 153 patients, 63 (41%) carried ApoE- ϵ 4. ApoE- ϵ 4 carriers had significantly higher PHE volumes at 24 h and on days 5–7 compared to ApoE- ϵ 3 carriers. The poor prognosis group had a higher proportion of ApoE- ϵ 4 carriers (53.9% vs. 28.6%, $p = 0.001$) and increased PHE volumes. ApoE- ϵ 4 (OR 2.438, $p = 0.02$) and PHE (OR 1.048, $p = 0.015$) were independent predictors of poor prognosis. The area under the curve for ApoE- ϵ 4 was 0.627, and for PHE volume, it was 0.698. The ICH patients carrying the ApoE- ϵ 4 allele show severe PHE and poorer outcomes. Carrying ApoE- ϵ 4 gene is an independent predictor for poor outcomes in patients with ICH.

Trial registration: ClinicalTrials.gov, NCT05687201. Registered June 1, 2023, Effect of Apolipoprotein E on the Prognosis of Patients with Intracerebral Hemorrhage—Full Text View—ClinicalTrials.gov “prospective registered”.

Keywords Apolipoprotein E gene, Perihematomal edema, Outcome, Intracerebral hemorrhage

Intracerebral hemorrhage (ICH) is a critical cerebrovascular condition closely linked to high rates of disability and mortality¹. Predicting the prognosis of patients with ICH is essential to reduce its heavy health burden. Various predictors of poor outcomes following ICH include hematoma volume, hematoma expansion, and perihematomal edema (PHE). Post-onset hematoma not only causes direct mechanical injury, but also triggers secondary PHE, which is closely related to the inflammatory response². Both direct mechanical injury and secondary PHE are associated neurological deterioration and poor clinical prognosis³. PHE is defined as an increase in the water content of the brain tissue in the vicinity of a hematoma within the brain parenchyma, and is associated with inflammatory response, thrombin activation, blood–brain barrier (BBB) disruption,

¹The Affiliated Hospital of Guizhou Medical University, Guiyang 550004, Guizhou Province, People's Republic of China. ²Key Lab of Acute Brain Injury and Function Repair in Guizhou Medical University, Guiyang 550004, Guizhou Province, People's Republic of China. ³Emergency Department, The Affiliated Hospital of Guizhou Medical University, Guiyang 550004, Guizhou Province, People's Republic of China. ✉email: 769070308@qq.com

and hemoglobin-induced cytotoxicity⁴. Recent studies have increasingly highlighted the significant role of apolipoprotein E (ApoE) gene in the pathogenesis of ICH.

Polymorphisms in the ApoE gene, especially the $\epsilon 4$ polymorphisms, are associated with an increased risk of various neurological disorders^{5–7}. ApoE plays a key role in lipid metabolism, neuroinflammation, and neuronal repair, impacting several facets of neurological health⁸. Human ApoE protein manifests in three isoforms: ApoE- $\epsilon 2$, ApoE- $\epsilon 3$, and ApoE- $\epsilon 4$ ⁹. ApoE $\epsilon 4$ has been implicated in modulating BBB integrity and permeability¹⁰. There is growing evidence suggesting that ApoE $\epsilon 4$ may compromise BBB function, and affect neurovascular equilibrium^{11–13}. BBB disruption leads to enhanced permeability in the adjacent vasculature, allowing plasma constituents like water and proteins to enter the perihematoma area, and contributing to PHE¹⁴. PHE profoundly influences neurological recovery and the quality-of-life post-ICH¹⁵. Despite ApoE's well recognized role, relatively little research has explored its relationship with ICH. One study suggest that ApoE can influence the neurological prognosis following ICH in humans through its impact on PHE rather than hematoma size¹⁶. However, this study only assessed PHE extent through midline bias and did not provide a precise quantification of PHE. Many other studies have investigated ApoE gene polymorphisms as risk factors for ICH occurrence, but have not discussed their implications for prognosis^{17,18}. Our study aims to investigate the interactions between ApoE gene polymorphisms and outcomes in patients with ICH, and to further explore their relevance in a more reliable manner. We employed a more precise approach to assess PHE and investigate whether ApoE genotype alters clinical prognosis by influencing the neuroinflammatory response after ICH.

This study aims to explore the characteristics of ApoE- $\epsilon 4$ allele carriers in relation to the development of PHE following ICH, and to elucidate the impact of this genetic variant on the clinical prognosis of ICH.

Methods

Study design

This prospective cohort study on spontaneous ICH was conducted at the Affiliated Hospital of Guizhou Medical University from January 2020 to December 2023. Venous blood samples were collected from hospitalized patients to verify APOE genotyping. Additionally, detailed data were collected for each patient, including demographic characteristics, medical history, clinical features, imaging information, Glasgow Coma Scale (GCS) scores, National Institutes of Health Stroke Scale (NIHSS) scores¹⁹, presence of comorbidities like pulmonary infection, gastrointestinal bleeding, hypertension, diabetes mellitus, smoking status, and alcohol consumption. Within 24 h of admission, venous blood markers were analyzed for routine blood parameters, liver and renal function, coagulation profiles, electrolyte levels, and lipid indices.

The inclusion criteria were as follows: ① Diagnosis of supratentorial ICH confirmed through unenhanced CT scanning; ② Patients were categorized based on venous blood collection into ApoE- $\epsilon 4$ ($\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, $\epsilon 4/\epsilon 4$) gene (ApoE- $\epsilon 4$ genotype) and ApoE- $\epsilon 3$ ($\epsilon 3/\epsilon 3$) gene (non-ApoE- $\epsilon 4$ genotype) groups.

The exclusion criteria were as follows: ① Patients with infratentorial ICH; ② Patients with ApoE- $\epsilon 2$ ($\epsilon 2/\epsilon 2$) genotype based on venous blood collections; ③ Age younger than 18 years of age; ④ ICH caused by trauma, anticoagulation therapy, or antiplatelet therapy; ⑤ Patients admitted to the hospital with diseases that might impact inflammatory responses, such as infective meningitis and systemic infections; ⑥ Patients with residual neurological deficits from previous strokes; ⑦ Patients with concurrent tumors, severe liver and kidney dysfunction, or cardiac insufficiency.

This study was approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University (approval number: 2024031 K), and informed consent was obtained from the patients or their legal representatives. Our study was executed in accordance with the WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

Sample size

The sample size of this study was determined using the formula for comparing two sample proportions. Based on preliminary test results, the incidence of ApoE- $\epsilon 4$ in the test and control groups was known to be 28.6% and 53.9% respectively. Selecting $\alpha = 0.05$ (two-sided test), the sample sizes required for the test and control groups were calculated as 77 and 76, respectively. Using the “Tests for Two Proportions” tool of the PASS 2021 software (version V21.0.3), the degree of certainty was calculated to be 0.91 which exceeded the recommended threshold of 0.8. Therefore, 77 cases were included in the test group and 76 cases were included in the control group, resulting in a total of 153 study subjects. This approach ensures the scientific rigor of the study design.

PHE volume calculation

The DICOM format data of the patient's head CT was imported into the 3D Slicer software (Version 5.0.3, www.slicer.org). The Editor module was selected to complete a 3D reconstruction of the edema around the ICH for hematoma calculation. Edema volume was calculated by automatically identifying and marking the edema area by setting a threshold (20–33HU).

Hematoma volume calculation

These data were imported into 3D-Slicer for analysis. In the Editor module, thresholds were set with a lower limit of 50 Hounsfield units (HU) and an upper limit of 100 HU. The edge contours of the hematoma were depicted layer by layer using the Draw Effect. After all layers were labeled, the Make Model Effect was selected. Finally, the Models module was used to check the volume of the hematoma and obtain other relevant information.

ApoE genotype testing

Upon admission, peripheral venous blood samples were collected for ApoE genotype testing. The procedure involved extracting leukocytes from the samples using erythrocyte lysate, followed by DNA extraction through

adsorption and centrifugation. The prepared samples were loaded into PCR reaction tubes and then inserted into the PCR instrument, where appropriate parameters were set for amplification. After amplification, baseline and fluorescence thresholds were established. The fluorescence signals from the VIC and FAM channels were captured for ApoE gene analysis, while the signals of the ROX channel were captured for standard gene analysis. ApoE genotypes were determined based on the number of amplification cycles counted.

Treatment of the Patients

All patients in this study received standardized medication according to the guidelines for managing hypertensive ICH. Some ICH patients were treated with stereotactic minimally invasive surgery (SMIS) after evaluation by two experienced neurosurgeons. All patients underwent follow-up CT scans on day 1 and a CT or MRI on day 7 after ICH.

Outcomes

The primary outcome was a good prognosis, defined by a modified Rankin Scale (mRS) score of 0–3 at 1 month following ICH occurrence. A score exceeding 3 indicated a poor prognosis²⁰. The secondary outcome involved recording and comparing complications during hospitalization between the two groups.

Statistical analysis

Statistical analyses were conducted using the SPSS software (Version 26.0, IBM Corp). Normal distributed data were presented as mean \pm standard deviation (SD), and compared between groups using the independent samples t-test. Skewed data were expressed as median (M) with the first (Q1) and third (Q3) quartiles, and group comparisons were performed using the Mann–Whitney U test. Categorical variables were analyzed with the Chi-square (χ^2) test. Multivariate binary logistic regression was conducted to identify independent prognostic factors for ICH patients. The predictive accuracy of PHE and ApoE- $\epsilon 4$ was assessed using Receiver Operating Characteristic (ROC) curves, and the optimal diagnostic threshold was determined based on the maximum Youden index. Statistical significance was set at a p value less than 0.05.

Results

A total of 330 patients presenting with spontaneous ICH were admitted to the Affiliated Hospital of Guizhou Medical University. Exclusion criteria led to the exclusion of 177 patients, comprising those with ApoE- $\epsilon 2$ genotype ($n=70$), infratentorial ICH ($n=49$), and other miscellaneous cases ($n=58$).

In total, 153 met the study inclusion criteria. Among them, 63 ICH patients were classified into the ApoE- $\epsilon 4$ group based on the venous blood collection test results, while the remaining 90 ICH patients were categorized into the ApoE- $\epsilon 3$ ($\epsilon 3/\epsilon 3$) group (Fig. 1). Baseline characteristics of these patients were analyzed and categorized into two groups based on their ApoE genotypes (Table 1).

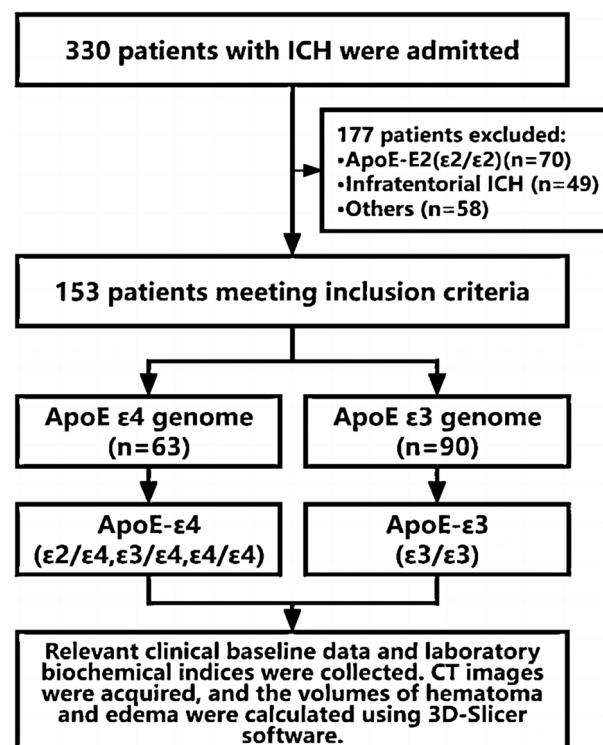


Fig. 1. Flowchart of patient inclusion.

Factors	ApoE-ε3(n = 90)	ApoE-ε4(n = 63)	F/Z/χ ²	p
Age (years)	59.21 ± 12.51	60.08 ± 12.34	0.089	0.672
Gender (male)	66 (73.3)	40 (63.5)	1.686	0.194
History of hypertension	70 (77.8)	52 (82.5)	0.52	0.471
History of diabetes	9 (10)	2 (3.2)	2.587	0.108
Hematoma ruptured into ventricles	32 (35.6)	26 (41.3)	0.514	0.473
Pulmonary infection	61 (67.8)	38 (60.3)	0.903	0.342
Gastrointestinal hemorrhage	24 (26.7)	16 (25.4)	0.031	0.86
Systolic pressure (mmHg)	167.5 (148.5–191)	160 (149–188)	−0.74	0.459
Diastolic pressure (mmHg)	99.58 ± 17.46	98.37 ± 18.95	0.22	0.684
Surgery	52 (57.8)	29 (46)	2.052	0.152
GCS	11 (8–13)	10 (4–13)	−1.89	0.059
NIHSS	13 (8–17)	17 (8–35)	−2.159	0.031
Imaging features				
ICH volume (mL), 1–24 h	20.65 (10.89–40.36)	16.03 (7.72–41.94)	−1.034	0.301
PHE volume (mL), 1–24 h	8.12 (3.12–16.27)	11.06 (6.8–22.46)	−2.875	0.004
ICH volume (mL), 5–7 days	7.89 (4.93–10.4)	11.1 (4.8–15.15)	−1.92	0.055
PHE volume (mL), 5–7 days	4.14 (2.29–8.02)	13.77 (8.04–30.91)	−4.911	0
Routine blood test				
White blood cell count (×10 ⁹)	9.02 (7.11–11.85)	9.07 (7.35–12.38)	−0.53	0.596
Absolute neutrophil value (×10 ⁹)	7.41 (4.74–10.23)	7.01 (5.1–9.99)	−0.2	0.841
Absolute Lymphocytes (×10 ⁹)	1.05 (0.75–1.58)	1.45 (0.92–2.03)	−2.773	0.006
Erythrocyte count (×10 ⁹)	4.62 ± 0.66	4.69 ± 0.72	1.053	0.492
Hemoglobin content (g/L)	142.77 ± 19.14	141.39 ± 22.57	2.191	0.684
Platelet count (×10 ⁹)	195.5 (164.5–233.25)	186 (153–214)	−1.055	0.292
Liver and Kidney Function Electrolytes				
K (mmol/L)	3.76 ± 0.36	3.65 ± 0.49	0.901	0.135
Na (mmol/L)	140.74 ± 3.25	141.27 ± 3.19	0.317	0.328
Cl (mmol/L)	103.27 ± 3.82	103.76 ± 4.26	1.566	0.457
Ca (mmol/L)	2.23 (2.13–2.31)	2.2 (2.12–2.28)	−1.483	0.138
Mg (mmol/L)	0.85 ± 0.11	0.83 ± 0.11	0	0.301
Creatinine (μmol/L)	64.7 (50.97–79.96)	64.4 (52–80.8)	−0.523	0.601
UA (μmol/L)	340.75 ± 119.71	336.47 ± 114.88	0.272	0.825
Venous blood glucose (mmol/L)	6.91 (5.99–8.57)	6.97 (6.01–9.52)	−0.43	0.667
Alanine aminotransferase (U/L)	16.45 (11.21–27.22)	16.4 (11.7–21.5)	−0.99	0.322
Aspartate aminotransferase (U/L)	23.2 (17.55–31.22)	21.2 (17.4–26.2)	−1.299	0.194
Total bilirubin (μmol/L)	12.6 (7.9–18.6)	9.86 (7–14.6)	−2.324	0.02
Direct bilirubin (μmol/L)	4.1 (2.78–6.12)	3 (2.4–4.2)	−2.697	0.007
Indirect bilirubin (μmol/L)	8.48 (5.1–13.12)	7.37 (4.9–10.26)	−1.729	0.084
Total protein (g/L)	69.56 ± 6.47	70.67 ± 7.74	2.512	0.336
Albumin (g/L)	44.4 (41.47–46.61)	43.2 (39.7–45.4)	−1.85	0.064
Coagulation				
Prothrombin time (s)	13 (12.4–13.52)	12.6 (12.1–13.2)	−2.386	0.017
International standardized ratio	1 (0.95–1.05)	0.99 (0.94–1.03)	−0.817	0.414
Plasminogen activity (PTA)	101.76 (93.59–113.04)	105.6 (96.93–116)	−1.289	0.197
Activated partial thromboplastin time (s)	33.7 (30.42–36)	33.8 (31–36.6)	−0.063	0.95
Fibrinogen (g/L)	3.01 (2.51–3.73)	3.08 (2.43–3.73)	−0.024	0.981
Prothrombin time (s)	17.15 (16.1–18.32)	17.2 (16.4–18.1)	−0.371	0.711
Cardiac enzymes				
Creatine kinase (U/L)	97.56 (73.47–161.03)	110 (66.5–198)	−0.163	0.87
Creatine kinase-MB (U/L)	17.17 (12.72–22.1)	14.85 (11.9–18.88)	−1.608	0.108
Continued				

Factors	ApoE-ε3(n = 90)	ApoE-ε4(n = 63)	F/Z/χ ²	p
Lipid profile				
Triglyceride (mmol/L)	1.13 (0.77–1.9)	1.13 (0.87–1.76)	−0.114	0.91
Total cholesterol (mmol/L)	4.21 ± 1.167	4.22 ± 1.057	0.007	0.952
High density lipoprotein (mmol/L)	1.16 (0.95–1.48)	1.12 (0.98–1.32)	−0.99	0.322
Low density lipoprotein (mmol/L)	2.58 ± 0.989	2.72 ± 1.007	0.158	0.434

Table 1. Comparison of ICH and PHE volumes and baseline data. ICH, intracerebral hemorrhage; PHE: Perihematoma brain edema; ApoE-ε3, apolipoprotein E gene, coded by the ε3 allele; ApoE-ε4, apolipoprotein E gene, coded by the ε4 allele.

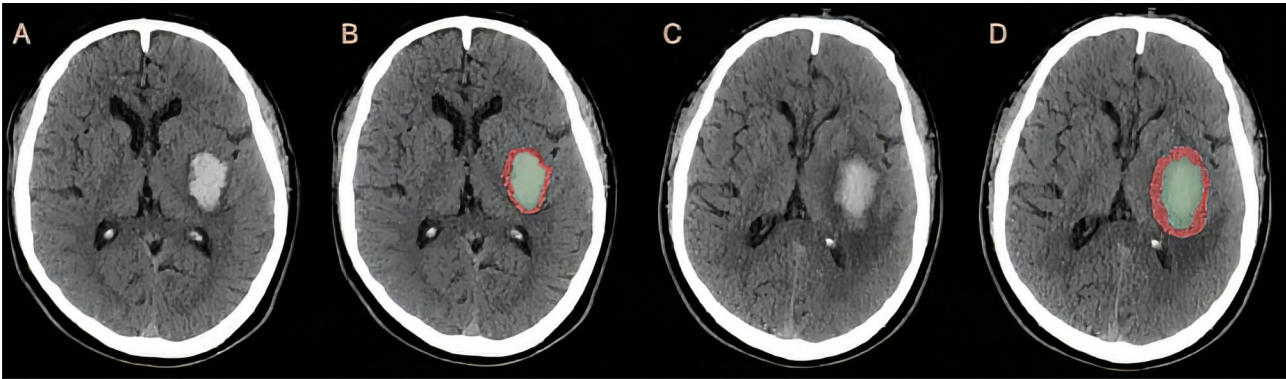


Fig. 2. Hematoma and perihematoma edema after cranial CT scan and 3D Slicer processing. (A) Hematoma on cranial CT scan within 24 h of ICH onset; (B) Corresponding schematic diagram after 3D Slicer measurement, with the green area depicting the hematoma (about 12 ml) and the red area depicting the PHE (about 3 ml); (C) The cranial CT scan on the 7th day post ICH show partial absorption of hematoma compared to the previous scan, alongside significant exacerbation of PHE; D: Measurement by the 3D Slicer suggests a slight decrease in the green area compared to the previous scan (approximately 9 ml), with a notable increase in the red area (approximately 11 ml).

All patients’ CT scans (General Electric Medical Systems, Milwaukee, WI) were performed using standard clinical parameters (axial 3-mm-thick slices). Experienced neuroimaging specialists used the 3D-Slicer to measure ICH and PHE volumes²¹ (Fig. 2). All scans were conducted on the same scanner.

The ApoE-ε4 and ApoE-ε3 groups exhibited similar baseline characteristics, including sex, age, history of hypertension, history of diabetes, and volume of ICH. However, when compared to ApoE-ε3 carriers, patients carrying the ApoE-ε4 allele showed markedly increased PHE within 24 h before the disease onset. The median and interquartile range (IQR) of PHE values were 11.06 [6.8–22.46] in the ApoE-ε4 group and 8.12 [3.12–16.27] in the ApoE-ε3 group ($p = 0.004$), respectively. This trend of increased PHE in the ApoE-ε4 group persisted into the later stages of ICH, specifically on days 5–7 post-onset. Median PHE measurements during this period were 13.77 [8.04–30.91] in the ApoE-ε4 group, which is significantly higher than 4.14 [2.29–8.02] observed in the ApoE-ε3 group ($p = 0.000$) (Fig. 3).

In addition, NIHSS scores on admission were higher in the ApoE-ε4 group, with a median of 17 [range 8–35], compared to a median of 13 [range 8–17] in the ApoE-ε3 group ($p = 0.031$) (Table 1).

The poor and good prognosis groups were comparable in terms of baseline characteristics, including sex, age, history of hypertension, history of diabetes, alcohol consumption, history of smoking, and volume of ICH. However, the percentage of ApoE-ε4 alleles was 53.9% in the poor outcome group, which was significantly higher than 28.6% in the good outcome group ($p = 0.001$). Similarly, the incidence of hematoma rupture into ventricles was 46.1% in the poor outcome group, which was significantly higher than 29.9% in the good outcome group ($p = 0.039$). The incidence of pulmonary infection in the poor outcome group (73.7%) was higher than the good outcome group (55.8%) ($p = 0.021$). Regarding PHE, patients in the poor outcome group exhibited a greater extent of edema both within the first 24 h after onset (14.46 [6.89–24.57] vs. 6.8 [2.68–12.45], $p = 0.000$) and on days 5–7 following onset (8.72 [3.88–22.52] vs. 5.35 [2.72–9.15], $p = 0.024$). The poor prognosis group demonstrated higher white blood cell counts, with a median of 10.25 [7.62–13.62], as opposed to 8.49 [7.14–10.69] in the good prognosis group ($p = 0.02$). The absolute neutrophil count was also markedly elevated in the poor prognosis group, with a median of 7.76 [5.20–11.44], in comparison to 6.77 [4.65–8.82] in the good outcome group ($p = 0.037$) (Table 2).

A binary logistic regression analysis was performed to include ApoE-ε4, pulmonary infection, hematoma rupture into the ventricle, PHE volume within 1–24 h of onset, white blood cell count, and absolute neutrophil values, focusing on variables that were identified as significant in the univariate analyses. (Table 3).

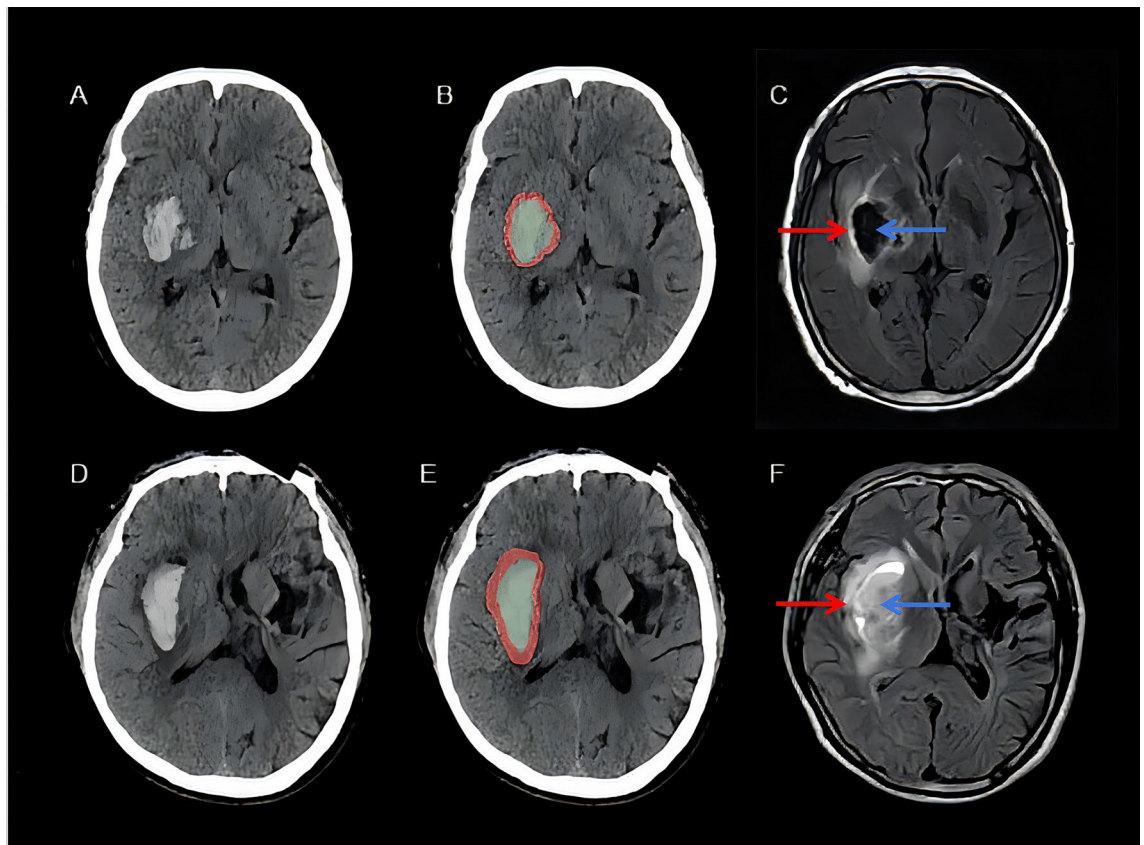


Fig. 3. Head CT and MRI images patients with ApoE ϵ 3 (A–C) and ApoE ϵ 4 (D–F). (A) and (D): head CT images before 3D-slicer processing; (B) and (E): corresponding head CT images after 3D slicer processing. The green area depicts hematoma and blue area depicts PHE. In (B), the hematoma measures approximately 13 ml, with PHE of approximately 7 ml. In (E), the hematoma measures approximately 14 ml, with PHE increased to approximately 20 ml; (C) and (F): MRI FLAIR images corresponding to A and D.

ROC curves were used to assess the predictive value of ApoE- ϵ 4 and PHE volume within 1–24 h of onset on patient prognosis. The sensitivity, specificity, positive and negative predictive values of ApoE- ϵ 4 for predicting patients with a poor prognosis were 0.539, 0.714, 0.650 and 0.611, respectively, and the Youden's index was 0.253. The corresponding area under the curve was 0.627 ($p = 0.007$). For PHE volume within 1–24 h after onset, the area under the curve was 0.698 (95% CI 0.616–0.780, $p = 0.000$), indicating a sensitivity of 84.2%, a specificity of 46.8%, and a Youden's index of 0.31 when the hematoma volume cutoff value was 4.77 (Fig. 4).

Discussion

The key finding of our study was that individuals carrying ApoE ϵ 4 exhibited more severe PHE within the first 24 h and on days 5 to 7 after ICH. This observation coincided with their higher NIHSS scores on admission, suggesting that ApoE ϵ 4 may adversely affect short-term prognosis. Our multifactorial analysis further revealed that the ApoE- ϵ 4 gene and larger initial edema volume were independent risk factors for poor outcomes in patients with ICH. These results may be attributed to the exacerbation of ApoE ϵ 4-induced neuroinflammatory responses, BBB dysfunction, and aggravation of perihematomal edema^{11,16,22}. Only one previous study has mentioned that ApoE ϵ 4 may affect the prognosis of ICH patients by influencing PHE¹⁶. However, our study identified ApoE ϵ 4 as an independent risk factor for poor outcomes in ICH patients and proposed for the first time that patients with ApoE ϵ 4 tend to have larger edema volumes compared to patients with ApoE ϵ 3.

ApoE- ϵ 4, a significant susceptibility factor for Alzheimer's disease, plays a pivotal role in BBB disruption and perivascular cell degeneration. This is evidenced by significant BBB disruption observed in the hippocampal and temporal lobe regions of ApoE- ϵ 4-carriers when compared to non-carriers. The disruption of BBB is implicated in the cognitive decline associated with ApoE- ϵ 4¹¹. A recent meta-analysis support our finding that ICH patients carrying the ApoE ϵ 4 gene face a higher risk of poor prognosis²³. However, no notable distinction was seen in patients with ApoE ϵ 4 gene in ischemic stroke and subarachnoid hemorrhage. Our study validated previous indications of APOE gene involvement in ICH prognosis and potential implications in PHE. However, the precise molecular mechanisms of ApoE- ϵ 4 in ICH have not been fully understood. Studies have shown that ApoE ϵ 4 plays a role in postprandial inflammatory responses in nutritionally vulnerable older adults²⁴. Research on traumatic cerebral hemorrhage suggests ApoE ϵ 4 is a risk factor for progressive hemorrhagic brain injury,

Factors	Good outcome(n = 77)	Poor outcome(n = 76)	F/Z/ χ^2	p
Age (years)	58.00 ± 11.43	61.16 ± 13.21	1.821	0.116
Gender (male)	56 (72.7)	50 (65.8)	0.865	0.352
History of hypertension	62 (80.5)	60 (78.9)	0.059	0.809
History of diabetes	8 (10.4)	3 (3.9)	2.379	0.123
Systolic pressure (mmHg)	162 (145.5–181)	168 (151.5–192.75)	– 1.451	0.147
Diastolic pressure (mmHg)	99.57 ± 17.45	98.36 ± 18.95	0.22	0.684
Smoking history	39 (50.6)	35 (46.1)	0.324	0.569
Drinking history	25 (32.5)	22 (28.9)	0.223	0.637
Hematoma ruptured into ventricles	23 (29.9)	35 (46.1)	4.255	0.039
Pulmonary infection	43 (55.8)	56 (73.7)	5.33	0.021
Gastrointestinal hemorrhage	16 (20.8)	24 (31.6)	2.31	0.129
Surgery	37 (48.1)	44 (57.9)	1.487	0.223
ApoE-ε4 (n, %)	22 (28.6)	41 (53.9)	10.169	0.001
Imaging features				
ICH volume (mL), 1–24 h	17.20 (8.46–37.98)	20.65 (11.99–51.64)	– 1.704	0.088
PHE volume (mL), 1–24 h	6.8 (2.68–12.45)	14.46 (6.89–24.57)	– 4.238	0
ICH volume (mL), 5–7 days	7.95 (4.89–12.37)	9.63 (4.87–13.91)	– 1.067	0.286
PHE volume (mL), 5–7 days	5.35 (2.72–9.15)	8.72 (3.88–22.52)	– 2.262	0.024
Routine blood test				
White blood cell count (×10 ⁹)	8.49 (7.14–10.69)	10.25 (7.62–13.62)	– 2.324	0.02
Absolute neutrophil value (×10 ⁹)	6.77 (4.65–8.82)	7.76 (5.20–11.44)	– 2.089	0.037
Absolute Lymphocytes (×10 ⁹)	1.17 (0.81–1.66)	1.17 (0.80–1.88)	– 0.546	0.585
Erythrocyte count (×10 ⁹)	4.62 ± 0.65	4.69 ± 0.72	1.053	0.492
Hemoglobin content (g/L)	142.77 ± 19.14	141.39 ± 22.57	2.191	0.684
Platelet count (×10 ⁹)	197 (163.5–233.5)	186 (155–215.5)	– 1.383	0.167
Liver and Kidney Function Electrolytes				
K (mmol/L)	3.73 ± 0.35	3.70 ± 0.48	4.019	0.705
Na (mmol/L)	140.74 ± 3.25	141.27 ± 3.19	0.317	0.328
Cl (mmol/L)	103.27 ± 3.82	103.76 ± 4.26	1.566	0.457
Ca (mmol/L)	2.24 (2.14–2.3)	2.20 (2.12–2.29)	– 1.365	0.172
Mg (mmol/L)	0.85 ± 0.11	0.83 ± 0.11	0	0.301
Creatinine (μmol/L)	62.1 (50.93–80.06)	68.95 (52.17–83.34)	– 1.062	0.288
UA (μmol/L)	340.75 ± 119.71	336.47 ± 114.88	0.272	0.825
Venous blood glucose (mmol/L)	6.9 (6.03–8.48)	6.93 (6–9.42)	– 0.336	0.737
Alanine aminotransferase (U/L)	18.7 (11.95–27)	15.05 (11.22–21.12)	– 1.573	0.116
Aspartate aminotransferase (U/L)	20.9 (17.3–29.9)	23.05 (18.00–30.3)	– 1.066	0.287
Total bilirubin (μmol/L)	11.8 (7.75–17.21)	11.34 (7.72–16.66)	– 0.447	0.655
Direct bilirubin (μmol/L)	3.57 (2.55–5.57)	3.55 (2.44–5.62)	– 0.002	0.999
Indirect bilirubin (μmol/L)	8 (5.05–12.05)	7.78 (5.04–10.84)	– 0.58	0.562
Total protein (g/L)	69.56 ± 6.47	70.67 ± 7.74	2.512	0.336
Albumin (g/L)	44.2 (42.17–46.09)	44.27 (39.47–45.94)	– 0.713	0.476
Coagulation				
Prothrombin time (s)	12.6 (12.2–13.2)	12.9 (12.3–13.5)	– 1.373	0.17
International standardized ratio	0.99 (0.95–1.02)	1 (0.95–1.05)	– 1.111	0.267
Plasminogen activity (PTA)	105.26 (98.49–115.58)	103.48 (93.91–113.87)	– 1.506	0.132
Activated partial thromboplastin time (s)	33.5 (31–35.95)	34.3 (30.27–36.85)	– 0.292	0.77
Fibrinogen (g/L)	2.99 (2.38–3.61)	3.09 (2.53–3.85)	– 0.998	0.318
Prothrombin time (s)	17.2 (16.3–18.2)	17.3 (16.22–18.17)	– 0.009	0.993
Cardiac enzymes				
Creatine kinase (U/L)	97.72 (67.75–156.56)	105.82 (75.25–191.42)	– 1.357	0.175
Creatine kinase-MB (U/L)	15.42 (11.98–19.52)	16.45 (12.34–22.58)	– 0.935	0.35
Continued				

Factors	Good outcome(n = 77)	Poor outcome(n = 76)	F/Z/ χ^2	p
Lipid profile				
Triglyceride (mmol/L)	1.18 (0.77–1.88)	1.09 (0.85–1.61)	– 0.075	0.94
Total cholesterol (mmol/L)	4.31 ± 1.173	4.11 ± 1.062	0.078	0.325
High density lipoprotein (mmol/L)	1.11 (0.98–1.35)	1.15 (0.89–1.4)	– 0.335	0.737
Low density lipoprotein (mmol/L)	2.58 ± 0.989	2.72 ± 1.007	0.043	0.219

Table 2. Comparison of clinical information affecting the prognosis of patients with ICH. ICH, intracerebral hemorrhage; PHE: Perihematomal brain edema.

	P	Exp(B)	95% C.I. for EXP(B)	
			Lower	Upper
1-24 h PHE volume	0.015	1.048	1.009	1.088
White blood cell count	0.098	1.379	0.943	2.016
Absolute neutrophil value	0.199	0.781	0.536	1.138
ApoE-ε4	0.02	2.438	1.148	5.176
Pulmonary infection	0.151	1.786	0.81	3.939
Hematoma ruptured into ventricles	0.141	1.749	0.831	3.68
Constant	0	0.061		

Table 3. Binary logistic regression analysis affecting poor prognosis in patients with ICH.

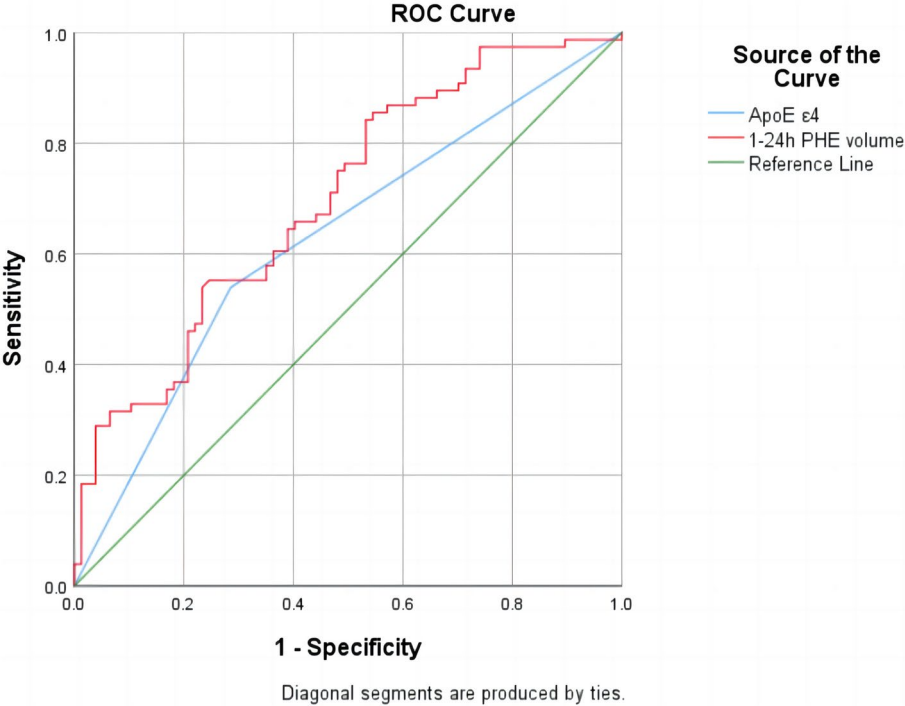


Fig. 4. Analysis of the predictive value of poor prognosis in patients with ICH.

but no correlation with prognosis was found, and the authors speculate that inflammation may lead to vascular hyperpermeability²⁵, which may provide new ideas for clinical and basic research.

Our study not only confirmed the relationship between ApoE-ε4 and poor prognosis in ICH, but also found that patients carrying ApoE-ε4 gene exhibited more severe PHE. This finding implies subtype-specific effects of APOE on neuroinflammatory responses, potentially leading to persistent neurological impairment²⁶. First of all, ApoE-ε4 may exacerbate brain edema by compromising the integrity of BBB. Previous studies have indicated that ApoE-ε4 carriers are more prone to BBB dysfunction, resulting in increased vascular permeability, thereby aggravating edema and neuronal injury²⁷. Moreover, ApoE-ε4 may potentiate neuroinflammatory responses

and microglial activation, further promoting the release of inflammatory mediators and impairing tissue repair around the hematoma^{28,29}. Additionally, lipid metabolism associated with ApoE- ϵ 4 may contribute to the development of brain edema and hinder recovery³⁰. Consequently, ApoE- ϵ 4 not only exacerbates edema brain injury but also delays neural recovery through mechanisms involving neuroinflammation. While, previous studies have also found that ApoE- ϵ 4 aggravated cerebrovascular amyloidosis, leading to larger ICH³¹. However, our study did not find larger hematoma volumes in ApoE- ϵ 4 carriers, possibly due to the fact that amyloid ICH is more common in older patients and usually occurs at more superficial lobar sites³². Therefore, we hypothesized that the prognostic effect of ApoE- ϵ 4 in ICH effect may not directly relate to the course of amyloidosis. It has also been suggested that ApoE- ϵ 4 affects systolic blood pressure, which in turn increases the risk of cerebral small-vessel disease after ICH in the elderly. We observed no substantial disparity in blood pressure between ϵ 4-carrying and non- ϵ 4-carrying patients with ICH in our study.

The increase in PHE was particularly significant in the poor prognosis group, emphasizing its significance in the progression of ICH³³. Consistent with previous studies, increased PHE levels correlated with a greater risk of poor prognosis in patients with ICH¹⁵. It was noted that PHE progression typically peaked around 7 days after ICH³⁴. However, some patients who underwent surgical treatment had reduced hematoma volume and corresponding PHE. Nevertheless, we found that PHE volume even within 24 h of onset was a predictor of poor prognosis.

The present study is subject to several limitations. Firstly, the lack of stratification by etiology such as cerebral amyloid angiopathy(CAA)-related ICH, arteriolosclerosis-related ICH may introduce confounding variables, as prognosis and hematoma volumes vary among these groups. Secondly, the relatively small hematoma volumes, the single-center design, and the limited sample size may restrict the generalizability of our findings. To validate these results, future research should involve multicenter studies with larger cohorts. Thirdly, the follow-up period was limited to short- to mid-term outcomes, potentially failing to capture the long-term consequences of ICH. Therefore, extended follow-up studies are required for a more comprehensive evaluation. Fourthly, although our study primarily focused on the comparison between the ApoE- ϵ 4 and ApoE- ϵ 3 alleles, it did not include an analysis of the ApoE- ϵ 2 allele. The ApoE- ϵ 2 allele has been reported to exert protective effects in certain neurological conditions³⁵, and its potential role in ICH remains to be clarified. Future research should incorporate the ApoE- ϵ 2 allele to better elucidate its influence, particularly in comparison with ApoE- ϵ 3 and ApoE- ϵ 4. Lastly, we recognize the potential for implications of multiple hypothesis testing to increase the risk of false-positive findings. Although the sample size and exploratory analyses limit the feasibility of applying FDR correction in this study, we recognize the importance of controlling the false discovery rate in future research. Subsequent studies should aim to include larger cohorts to facilitate robust statistical corrections while maintaining adequate power. Despite these limitations, our findings underscore the significant influence of ApoE- ϵ 4 on PHE and its association with poor outcomes in ICH patients. These results lay the groundwork for further investigations into the molecular mechanisms underlying these associations and for validating our findings in larger and more diverse populations.

In summary, we found that the ApoE- ϵ 4 allele was associated with worsening PHE within 24 h and on days 5–7 after supratentorial ICH, consistent with previous observations linking ApoE- ϵ 4 to poor prognosis in ICH. A growing number of studies support our observations, suggesting that ApoE regulates the neuroinflammatory response in a subtype-specific manner. However, additional research is needed to confirm these findings and to explore in depth the pathophysiological mechanisms linking ApoE polymorphisms to PHE and ICH prognosis.

Data availability

The datasets collected and/or analyzed during this study are available from the corresponding author on reasonable request.

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Author contributions

L.H.: Conceptualized and designed the study, data collection, performed statistical analyses, and drafted the manuscript. Q.W., F.Y., W.C., X.Z., C.Y.: Contributed to data collection, and assisted in manuscript revisions. S.R.: Provided critical feedback on the study design, supervised the analysis, and revised the manuscript critically for important intellectual content. G.W., L.W.: Involved in the review and editing of the manuscript, ensuring consistency and clarity of the final draft. All authors have read and approved the final manuscript. Guarantor Statement: Likun Wang is the guarantor of this work and accepts full responsibility for the integrity of the study and the accuracy of the data presented. She also guarantees that all aspects of the manuscript meet the highest scientific standards.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

All procedures involving human subjects in this study were conducted in compliance with the ethical standards set by the national research committee and in accordance with the 1964 Helsinki Declaration and its subsequent revisions. The study received approval from the Guizhou Medical University Ethical Board (approval number: 2024031K).

Additional information

Correspondence and requests for materials should be addressed to L.W.

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