International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Prognostic Significance of Serum NLRP3 in Spontaneous Intracerebral Hemorrhage

Yong Cai, Yijun Ma, Chao Tang, Wei Li, Xuan Lv, Zhijie Xie, Jun Wang

Department of Neurosurgery, First People's Hospital of Linping District, Hangzhou, Zhejiang, People's Republic of China

Correspondence: Jun Wang, Department of Neurosurgery, The First People's Hospital of Linping District, Hangzhou, Zhejiang, People's Republic of China, Email wangjun57188@163.com

Background: Nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) is involved in secondary brain injury after acute intracerebral hemorrhage (ICH). The objective of this study was to determine its ability to predict early neurological deterioration (END) and 3-month neurological outcome after ICH.

Methods: In this prospective cohort study, serum NLRP3 levels were measured in 128 patients with sICH and 100 healthy controls. National institute of health stroke scale (NIHSS) scores and hematoma volumes were recorded. Post-ICH END and 3-month poor outcome (modified Rankin Scale (mRS) scores of 3–6) were documented. The results were assessed using multivariate analysis.

Results: Serum NLRP3 levels in sICH patients increased significantly as compared to controls (P<0.001). Serum NLRP3 levels were independently correlated with hematoma volumes (β=0.046; 95% confidence interval (CI), 0.020–0.072; P=0.001) and NIHSS scores (β=0.071; 95% CI, 0.004–0.139; P=0.039), independently forecasted END (OR=1.268; 95% CI, 0.892–1.801; P=0.036) and poor prognosis at post-ICH 3 months (OR=1.448; 95% CI, 1.006–2.085; P=0.046), and were predictive of them with areas under receiver operating characteristic curve at 0.788 (95% CI, 0.706–0.855) and 0.805 (95% CI, 0.725–0.870) separately. Serum NLRP3 levels, along with the two independent predictors, that are NIHSS scores and hematoma volumes, are combined to establish prediction models of END and poor prognosis. The models worked well by applying a series of statistical methods.

Conclusion: Increased serum NLRP3 levels after ICH are independently associated with bleeding severity, END and adverse outcomes of patients, meaning that serum NLRP3 may be a potential prognostic biomarker of sICH.

Keywords: intracerebral hemorrhage, disease severity, early neurological deterioration, outcome, NLRP3

Introduction

Spontaneous intracerebral hemorrhage (sICH) is one of the common cerebrovascular diseases, characterized by rapid progression and high mortality, and nearly half of the patients have neurological dysfunction of varying degrees.[1] Patients with an elevated national institute of health stroke scale (NIHSS) scores of ≥4 points within 24 hours of admission are usually considered as having early neurological deterioration (END).[2] Mitochondrial dysfunction, cellular excitotoxicity, erythrocyte lysis, inflammatory responses and oxidative stress can exacerbate brain tissue damage after sICH and lead to END.[3–6] Notably, END, one of the early serious complications of sICH, very often emerges as a contributor to poor prognosis of patients, and consequently becomes a conventional outcome variable.[7,8] Some biomarkers, such as dickkopf-1, matrix metalloproteinase-9 and S100B, have gradually attracted the attention of scientists with respect to anticipation of poor outcome after sICH.[9–11]

Nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) is recognized as an important factor in the inflammatory response, and its over-activation is involved in the development of many diseases, such as chronic obstructive pulmonary disease, asthma and coronary artery disease.[12–14] NLRP3 promotes the release of inflammatory factors such as interleukin (IL)-1 and IL-18 after the development of acute brain injury diseases such as ischemic stroke, traumatic brain injury (TBI) and neonatal hypoxic ischemic encephalopathy. This process can mediate the neuroinflammatory response, exacerbate neurological damage and affect the recovery of neurological

Received: 20 November 2024
Accepted: 5 February 2025
Published: 12 February 2025

© 2025 Cai et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

function.[15–17] Expression of NLRP3 was significantly elevated in the brain tissue of mice with traumatic brain injury, and inhibition of NLRP3 can effectively improve the neurological function of mice.[18] Notably, serum NLRP3 levels in patients with aneurysmal subarachnoid hemorrhage were closely correlated with the severity of the disease at the time of patient admission, and higher NLRP3 levels were significantly correlated with delayed cerebral ischemic as well as poor prognosis.[19] These results suggest that NLRP3 may be a potential prognostic predictive biomarker for acute brain injury disease. In this prospective cohort study, we sought to determine serum NLRP3 levels and further explore its association with disease severity, END, and neurologic prognosis in patients with sICH.

Materials and Methods

Study Populations

This prospective cohort study was completed from October 2021 to July 2023 at The First People's Hospital of Linping District (Hangzhou, China). We consecutively included patients with first-ever sICH. The inclusion criteria were in the following: (1) acute sICH with clinical manifestation of acute neurologic deficit and confirmation of new brain bleeding lesions by computed tomography (CT) scan; (2) admission within 24 hours of symptom onset; and (3) non-surgical treatment. Exclusion criteria were as follows: (1) age <18 years; (2) history of previous neurologic diseases; (3) pregnancies or severe underlying systemic diseases or malignancies; (4) surgical operation or infection within recent 1 month; (5) incomplete data, unavailability of blood samples, missed visits or refusal to participate in the study. Individuals, for whom physical examination, were done at the Physical Examination Center of The First People's Hospital of Linping District during the same period, were selected as the control group. The study was conducted in accordance with the principles set forth in the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the First People's Hospital of Linping District (No.2021–045), registered in Chinese Clinical Trial Registry (clinical trial number: ChiCTR2500095785). Written informed consent forms were completed by the controls themselves and the legal representatives of the patients separately.

Data Acquisitions

Comprehensive and detailed data were collected, including age, sex, previous underlying diseases (hypertension, diabetes mellitus and hyperlipidemia), smoking and alcohol consumption. Vital signs (systolic arterial pressure and diastolic arterial pressure) were observed and recorded on admission. Two kinds of time parameters were recorded as follows: time from symptom onset to admission and time from symptom onset to blood collection. Biochemical parameters, such as blood leukocytes, blood c-reactive protein (CRP) levels and blood glucose levels, were routinely tested on admission. Immediately after arrival at the emergency department, a CT scan of the head was performed and hematoma volumes were calculated according to the ABC/2 method,[20] as well as the presence of intraventricular hemorrhage and the location of the hemorrhage were clarified. Disease severity was assessed using NIHSS scores and hematoma volumes.[21]

Immune Analysis

Peripheral venous blood samples were collected from patients with sICH on admission to the hospital and from healthy controls during routine physical examinations. To quantify the serum NLRP3 levels, serum samples were obtained by centrifugation at 3000×g for 10 minutes and subsequently stored in a refrigerator at −80°C for further testing. An enzyme-linked immunosorbent assay (ELISA) kit (Niulai Biotech, Wuhan, China) was adopted to detect serum NLRP3 levels. The assay range was 35–1400 pg/mL with a sensitivity of 8.75 pg/mL, intra- and inter-plate coefficients of variation were less than 10%. To ensure accuracy and reliability, all samples were measured twice by the same technician who was unaware of the patient's clinical information to ensure unbiased testing and analysis. Using Bland-Altman plots, there was a good agreement between the double measurements for all participants (Supplementary Figure 1).

Follow-up and Clinical Outcomes

Patients were routinely followed up until the completion of 3 months after sICH by trained interviewers who were unaware of baseline characteristics and prognostic factors. Neurologic function at 3 months after stroke was assessed using the modified Rankin scale (mRS) score. mRS scores of 3–6 indicate a poor outcome.[22]

Statistical Analysis

Data were statistically analyzed using the SPSS 26.0 (IBM Corp. Armonk, NY, USA) and MedCalc 9.6.4.0 (MedCalc Software, Mariakerke, Belgium), and graphs were drawn using the GraphPad Prism 9.0 (GraphPad Software Inc., La Jolla, CA, USA) and R software (version 4.2.4 https://www.r-project.org). Quantitative data's normality was evaluated using the Shapiro–Wilk test test, with normally distributed data expressed as mean ± standard deviation and non-normally distributed data as median (upper and lower quartiles). Qualitative data were presented as counts (percentages). Comparisons of qualitative data were performed between two groups using the $\chi 2$ test or Fisher exact test; non-normally distributed quantitative data, using the Mann–Whitney *U*-test; and normally distributed quantitative data, using the *t* test. Spearman correlation test was done for correlation detection between variables. A multifactorial linear regression model was developed to reveal variables, which were independently associated with serum NLRP3 levels and mRS scores. Variables of independent association with the occurrence of END and 3-month prognostic outcome after ICH were identified by multifactorial logistic regression, and the associated odds ratio (OR) and 95% confidence interval (CI) were reported. A receiver operating characteristic (ROC) curve was constructed to investigate the predictive ability of serum NLRP3 levels on the occurrence of END and adverse outcomes in patients with sICH, the area under the curve (AUC) was estimated, and the Z-tests were applied to compare the AUC. Nomogram models were configured to describe the predictive ability of serum NLRP3 levels, NIHSS scores, and hematoma volumes on the risk of END and poor outcome. A calibration curve model was constructed to examine the stability of the predictive model, and a decision curve was drawn to discover the clinical application value of the predictive model. A two-tailed $P < 0.05$ was taken as statistically significant difference.

Results

Characteristics of the Study Populations

A total of 159 patients with sICH were initially enrolled. Based on predetermined criteria, 128 patients were finally included in the study (Supplementary Figure 2). In addition, 100 contemporaneous healthy physical examinees were recruited as a control group. Significant differences were not found between patients and controls in terms of age, gender, smoking and alcohol consumption (all $P>0.05$). While percentages of hypertension, diabetes and hyperlipidemia were significantly higher in patients than in controls (Supplementary Table 1, all $P<0.05$).

Correlation Analysis Between Serum NLRP3 Levels and Disease Severity

As shown in Figure 1, serum NLRP3 levels of patients were significantly higher at admission than those of healthy controls (median: 2.84 ng/mL vs 0.54 ng/mL). By applying the Spearman correlation analysis, serum NLRP3 levels were significantly correlated with NIHSS scores, hematoma volumes, age, intraventricular hemorrhage, blood glucose levels, blood leukocyte count, and blood CRP levels (all $P<0.05$; Supplementary Table 2). There were consistent results as verified by the univariate linear regression analysis (all $P<0.05$; Supplementary Table 2). NIHSS scores and hematoma volumes were firmly affirmed as the two classical indicators for objective assessment of impairments of consciousness levels as well as severity of hemorrhage. When variables of significant differences in univariate analyses were entered in the multivariate linear regression model, NIHSS scores (Figure 2A) and hematoma volumes (Figure 2B) remained independently associated with serum NLRP3 levels (all $P<0.05$; Table 1).

Correlation Analysis Between mRS Scores and Disease Severity

Neurological functional assessment of patients by the mRS was in application of the current study. A significantly positive correlation of serum NLRP3 levels was found with mRS scores ($P < 0.001$; Figure 3A), and the levels were substantially elevated in order of the scores ($P < 0.001$; Figure 3B). As shown in Supplementary Table 3, apart from serum NLRP3 levels, other variables of close pertinence to mRS scores consisted of hematoma volumes, NIHSS scores, expansion of hemorrhage into intraventricular system, blood glucose levels, blood CRP levels and blood leukocyte count (all $P<0.05$). Analogous findings appeared by using the univariate linear regression analysis (all $P<0.05$; Supplementary Table 3). In Table 2, with the inclusion of significantly different variables as listed in Supplementary Table 3 in the

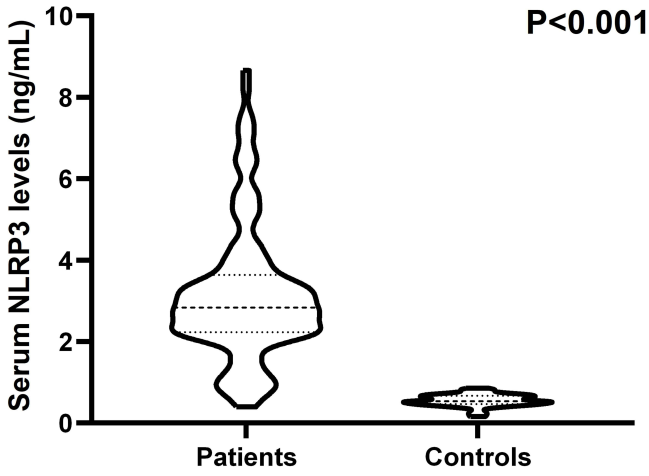

Figure 1 Change of serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels after spontaneous intracerebral hemorrhage. Serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels of patients were significantly higher than those of healthy controls (P<0.001). NLRP3 indicates nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3.

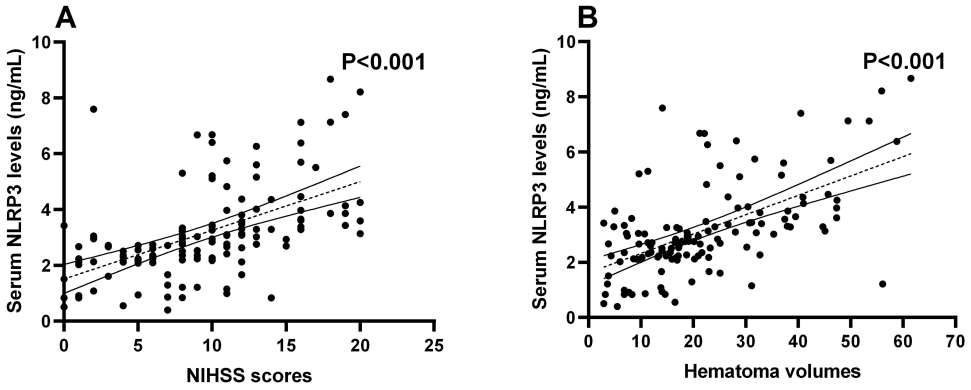

Figure 2 Correlograms describing relationships between admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels and hemorrhage severity of spontaneous intracerebral hemorrhage. (**A**) Correlograms illustrating the relationship between admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels and baseline national institute of health stroke scale scores after spontaneous intracerebral hemorrhage. (**B**) Correlograms illustrating the relationship between serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels and baseline hematoma volumes after spontaneous intracerebral hemorrhage. Admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels were obviously correlated with hemorrhage severity of spontaneous intracerebral hemorrhage (both P<0.001). NLRP3 denotes nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3.
Abbreviation: NIHSS, national institute of health stroke scale.

multivariate model, NIHSS scores, hematoma volumes and serum NLRP levels were retained to be independently correlated with post-stroke mRS scores (all P<0.05).

Relationship Between Serum NLRP3 Levels and END After sICH

The sICH patients as enrolled in the study were categorized into END group and non-END group. A collective of 35 patients (27.3%) presented with END. A comparison of baseline characteristics between END and non-END groups was shown in Supplementary Table 4. Serum NLRP3 levels at admission were significantly higher in patients with END than in those without (P<0.001; Figure 4). In addition, age, NIHSS scores, hematoma volumes, blood leukocyte count, blood CRP levels, blood glucose levels, serum NLRP3 levels, and percentage of intraventricular hemorrhage were significantly higher in patients with END, as compared with those without (Supplementary Table 4, all P<0.05). Results were of consistence by operating the univariate logistic regression analysis (P<0.05; Table 3). Those factors as confirmed substantially distinct on univariate analyses were given entry into the multifactorial logistic regression model, and as a consequence, NIHSS scores, hematoma volumes and serum NLRP3 levels were independently predictive of END

Table 1 Correlative Analysis of Serum NLRP3 Levels Using Multivariate Linear Regression Analysis in Acute Spontaneous Intracerebral Hemorrhage

Variables	β	95% CI	VIF	P value
Age (years)	0.008	−0.012–0.028	1.170	0.421
Intraventricular hemorrhage	−0.503	−1.225–0.250	1.303	0.189
NIHSS scores	0.071	0.004–0.139	2.195	0.039
Hematoma volumes (mL)	0.046	0.020–0.072	2.287	0.001
Blood CRP levels (mg/mL)	0.005	−0.034–0.044	1.197	0.805
Blood leucocyte count ($\times 10^9$/L)	0.024	−0.069–0.117	1.120	0.608
Blood glucose levels (mmol/L)	0.075	−0.020–0.169	1.322	0.120

Abbreviations: NIHSS, national institute of health stroke scale; CRP, C-creation protein; β, beta; 95% CI, 95% confidence interval; VIF, variance inflation factor; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3.

happenings (all P<0.05; Table 3). Moreover, the ROC analysis was in process for elucidating the ability of serum NLRP3 levels to differentiate the possibility of END after sICH. The AUC of serum NLRP3 levels was presented as 0.788 (95% CI 0.706–0.855). About 3.02 ng/mL was identified as a cutoff value of serum NLRP3 levels to serve as the optimal threshold for the prognostication of END, thereby generating a sensitivity value of 69.1% and a specificity value of 83.6% (Figure 5A). Also, within the context of ROC analysis, the AUCs of the NIHSS scores and hematoma volumes were 0.792 (95% CI, 0.711–0.859) and 0.799 (95% CI 0.719–0.865) separately (Figure 5B), which, relative to serum NLRP3 levels, had numerically higher predictive value (P=0.918 and 0.084 successively). In Figure 5B, the prognostic discriminatory power of serum NLRP3 levels combined with NIHSS scores and hematoma volumes (AUC=0.872; 95% CI 0.801–0.924) was significantly higher than serum NLRP3 levels (P=0.034), NIHSS scores (P=0.024), and hematoma volume alone (P=0.035).

As shown in Supplementary Figure 3, serum NLRP3 levels, NIHSS scores, and hematoma volumes were forced into the nomogram model to predict the associated risk. The points corresponding to the above three variables were summed to calculate the total number of points, and different points corresponded to different survival probabilities, which were 0.1=59.0, 0.3=99.2, 0.5=124.4, 0.7=149.6, and 0.9=189.8, respectively. In addition, the model was stable in the framework of the calibration curve assessment (Supplementary Figure 4), and decision curves were established, suggesting that the model may have a high clinical validity (Supplementary Figure 5).

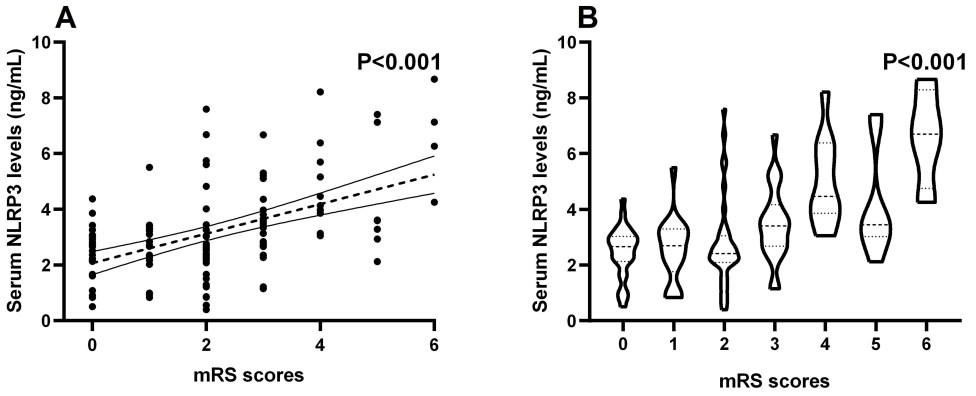

Figure 3 Boxplot and correlogram describing relationships between serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels and 3-month modified Rankin scale scores of spontaneous intracerebral hemorrhage. (**A**) Correlogram illustrating the relationship between serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels and 3-month modified Rankin scale scores after spontaneous intracerebral hemorrhage. (**B**) Boxplot illustrating admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels among patients with different 3-month modified Rankin scale scores after spontaneous intracerebral hemorrhage. Admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels were extremely pertinent to 3-month modified Rankin scale scores of spontaneous intracerebral hemorrhage (both P<0.001). NLRP3 denotes nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3.
Abbreviation: mRS, modified Rankin scale.

https://doi.org/10.2147/IJGM.S507518

Table 2 Correlative Analysis of Modified Rankin Scores Using Multivariate Linear Regression Analysis in Acute Spontaneous Intracerebral Hemorrhage

Variables	β	95% CI	VIF	P value
Age (years)	0.007	−0.011–0.026	1.177	0.429
Intraventricular hemorrhage	0.237	−0.460–0.934	1.322	0.503
NIHSS scores	0.064	0.001–0.128	2.275	0.046
Hematoma volumes (mL)	0.037	0.012–0.062	2.525	0.004
Blood CRP levels (mg/mL)	−0.003	−0.039–0.032	1.198	0.853
Blood leucocyte count ($\times 10^9$/L)	0.022	−0.063–0.108	1.123	0.608
Blood glucose levels (mmol/L)	0.007	−0.081–0.094	1.349	0.883
Serum NLRP3 levels (ng/mL)	0.171	0.005–0.338	1.646	0.043

Abbreviations: NIHSS, national institute of health stroke scale; CRP, C-creation protein; β, beta; 95% CI, 95% confidence interval; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3; VIF, variance inflation factor.

Relationship Between Serum NLRP3 Levels and 3-month Clinical Outcome After sICH

A total of 44 cases (34.4%) had a poor outcome at 3 months after stroke. Serum NLRP3 levels were significantly higher in patients with poor outcome than in those with good outcome (P<0.001; Figure 6). Supplementary Table 5 shows that the NIHSS scores, hematoma volumes, intraventricular hemorrhage, blood glucose levels, blood leukocyte count, blood CRP levels, and serum NLRP3 levels of patients with poor outcome were significantly different from those of patients with good outcome (all P<0.05). As demonstrated via univariate logistic regression analysis, the preceding distinctions were still existent (P<0.05; Table 4). By consolidating those variables of significant disparity into the multifactorial logistic regression model, the independent predictors of poor outcome were serum NLRP3 levels, alongside with NIHSS scores and hematoma volumes (all P<0.05; Table 4). Alternatively, there was the operation of the ROC analysis for deciphering the capability of serum NLRP3 levels to distinguishing poor outcome at 3 months after sICH. The AUC of serum NLRP3 levels was yielded at 0.805 (95% CI 0.725–0.870). By utilization of the Youden method, serum NLRP3 levels were chosen at 3.10 ng/mL, which acted as the optimal threshold for the anticipation of poor outcome at 3 months after stroke with a sensitivity of 75.0% and a specificity of 77.4% (Figure 7A). Additionally, via employment of the ROC

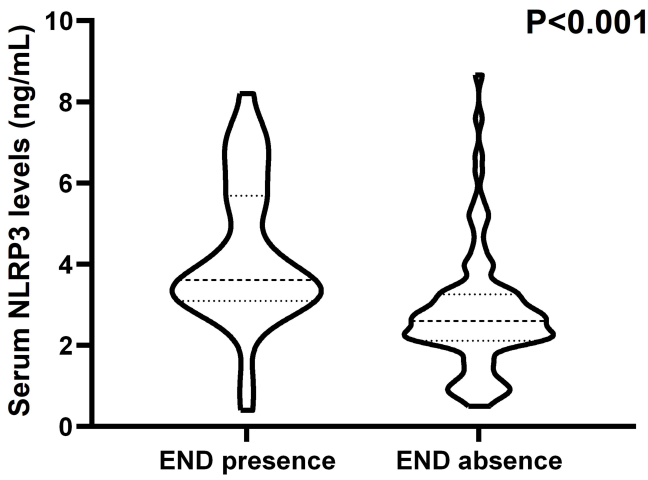

Figure 4 Boxplot illustrating baseline serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels between patients with early neurological deterioration and those without after spontaneous intracerebral hemorrhage. Baseline serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels were substantially higher in patients with early neurological deterioration than in those without in patients with spontaneous intracerebral hemorrhage (P<0.001). NLRP3 denotes nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3.
Abbreviation: END, early neurological deterioration.

Table 3 Univariate and Multivariate Logistic Regression Analysis of Predictors for Early Neurological Deterioration After Spontaneous Intracerebral Hemorrhage

Variables	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Age (years)	1.035 (1.001–1.070)	0.034	1.000 (0.962–1.040)	0.982
Gender (male/female)	1.676 (0.766–3.669)	0.196	–	–
Hypertension	1.442 (0.631–3.292)	0.385	–	–
Diabetes mellitus	2.257 (0.893–5.708)	0.085	–	–
Hyperlipidemia	0.580 (0.227–1.485)	0.256	–	–
Current smoking	1.667 (0.680–4.082)	0.264	–	–
Alcohol consumption	1.395 (0.593–3.280)	0.446	–	–
Admission time (h)	0.995 (0.925–1.070)	0.893	–	–
Blood-collection time (h)	0.989 (0.921–1.062)	0.755	-	-
Intraventricular hemorrhage	4.870 (1.761–13.467)	0.002	1.977 (0.534–7.316)	0.307
Superficial cerebral hemorrhage	1.016 (0.402–2.566)	0.973	-	-
Basal ganglia hemorrhage	1.118 (0.502–2.492)	0.785	-	-
Subtentorial hemorrhage	0.802 (0.270–2.384)	0.691	-	-
NIHSS scores	1.275 (1.149–1.414)	<0.001	1.211 (1.065–1.378)	0.042
Hematoma volume (mL)	1.094 (1.055–1.134)	<0.001	1.053 (1.013–1.115)	0.032
Blood CRP levels (mg/mL)	1.065 (1.005–1.128)	0.032	1.011 (0.939–1.089)	0.774
Blood leucocyte count ($\times 10^9$/L)	1.230 (1.058–1.431)	0.007	1.154 (0.958–1.390)	0.131
Blood glucose levels (mmol/L)	1.190 (1.041–1.359)	0.011	0.962 (0.801–1.155)	0.679
Blood potassium levels (mmol/L)	1.315 (0.560–3.088)	0.530	-	-
Serum NLRP3 levels (ng/mL)	1.702 (1.306–2.218)	<0.001	1.268 (0.892–1.801)	0.036

Abbreviations: NIHSS, national institute of health stroke scale; CRP, C-creation protein; 95% CI, 95% confidence interval; CRP, C-creation protein; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3.

analysis for analyzing predictive powers of the NIHSS scores and hematoma volumes, their AUCs were 0.823 (95% CI, 0.745–0.884) and 0.823 (95% CI, 0.745–0.885) successively (Figure 7B), which was higher as opposed to that of the serum NLRP3 levels, but these sorts of differences did not reach a significant state (P=0.677 and P=0.740). Subsequently,

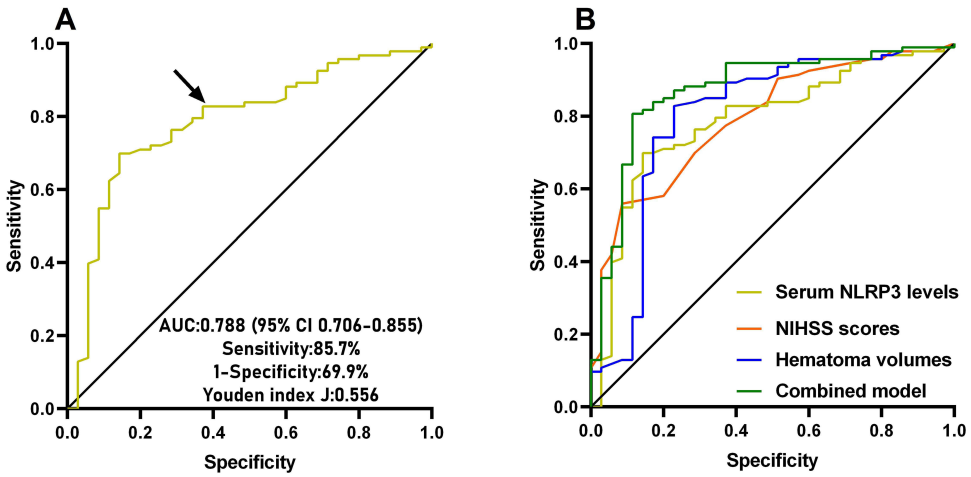

Figure 5 Receiver operating characteristic curve displaying relationship between admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels and the presence of early neurologic deterioration after spontaneous intracerebral hemorrhage. (**A**) Receiver operating characteristic curve for admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels to predict early neurological deterioration after spontaneous intracerebral hemorrhage. (**B**) Receiver operating characteristic curve for admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels, baseline national institute of health stroke scale scores, baseline hematoma volumes and the combination model to predict early neurological deterioration after spontaneous intracerebral hemorrhage.Serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels occupied effective predictive ability for early neurological deterioration after hemorrhagic stroke. NLRP3 means nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3.

https://doi.org/10.2147/IJGM.S507518

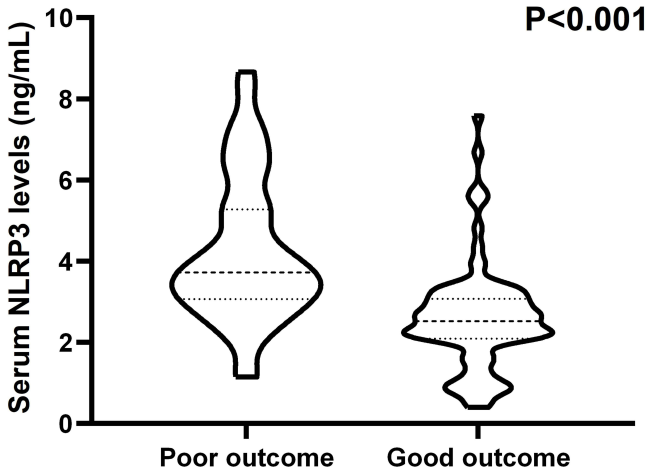

Figure 6 Boxplot illustrating baseline serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels between patients with poor outcome and good outcome after spontaneous intracerebral hemorrhage. Baseline serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels were substantially higher in patients with poor outcome than in those with good outcome after spontaneous intracerebral hemorrhage (P<0.001). NLRP3 denotes nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3.

a combined binary logistic regression model was built by adding serum NLRP3 levels, NIHSS scores and hematoma volumes. As for predicting 3-month poor outcome after stroke, this model exhibited significantly higher power (AUC=0.887; 95% CI 0.820–0.936) than serum NLRP3 levels (P=0.019), NIHSS scores (P=0.018) and hematoma volumes (P=0.039) alone (Figure 7B).

Table 4 Univariate and Multivariate Logistic Regression Analysis of Predictors for 3-month Poor Prognosis After Spontaneous Intracerebral Hemorrhage

Variables	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Age (years)	1.047 (1.013–1.081)	0.006	1.009 (0.968–1.052)	0.678
Gender (male/female)	1.873 (0.894–3.921)	0.096	–	–
Hypertension	1.703 (0.781–3.714)	0.181	–	–
Diabetes mellitus	1.821 (0.738–4.491)	0.193	–	–
Hyperlipidemia	1.655 (0.743–3.685)	0.217	–	–
Current smoking	1.314 (0.553–3.121)	0.537	–	–
Alcohol consumption	0.735 (0.315–1.719)	0.478	–	–
Admission time (h)	0.984 (0.918–1.054)	0.640	–	–
Blood-collection time (h)	0.980 (0.917–1.048)	0.563	-	-
Intraventricular hemorrhage	10.345 (3.173–33.731)	<0.001	3.506 (0.759–16.195)	0.108
Superficial cerebral hemorrhage	1.222 (0.518–2.884)	0.647	-	-
Basal ganglia hemorrhage	0.667 (0.317–1.401)	0.284	-	-
Subtentorial hemorrhage	1.543 (0.594–4.005)	0.373	-	-
NIHSS scores	1.347 (1.202–1.509)	<0.001	1.131 (0.983–1.301)	0.035
Hematoma volumes (mL)	1.124 (1.077–1.173)	<0.001	1.048 (0.997–1.103)	0.036
Blood CRP levels (mg/mL)	1.113 (1.048–1.183)	0.001	1.069 (0.988–1.156)	0.097
Blood leucocyte count ($\times 10^9$/L)	1.162 (1.011–1.336)	0.035	1.085 (0.890–1.323)	0.422
Blood glucose levels (mmol/L)	1.291 (1.123–1.483)	<0.001	1.033 (0.851–1.255)	0.740
Blood potassium levels (mmol/L)	1.578 (0.701–3.550)	0.270	-	-
Serum NLRP3 levels (ng/mL)	2.040 (1.494–2.786)	<0.001	1.448 (1.006–2.085)	0.046

Abbreviations: NIHSS, national institute of health stroke scale; CRP, C-creation protein; 95% CI, 95% confidence interval; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3.

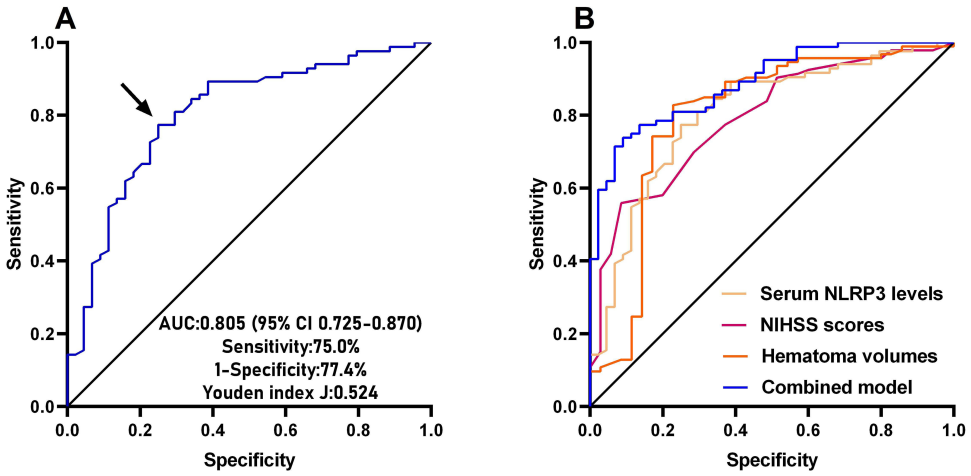

Figure 7 Receiver operating characteristic curve showing relationship between admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels and the presence of poor outcome after spontaneous intracerebral hemorrhage. (**A**) Receiver operating characteristic curve for admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels to predict poor outcome after spontaneous intracerebral hemorrhage. (**B**) Receiver operating characteristic curve for admission serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 levels, baseline national institute of health stroke scale scores, baseline hematoma volumes and the combination model to predict poor outcome after spontaneous intracerebral hemorrhage.Serum nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 exhibited markedly high prognostic predictive ability in humans with acute intracerebral hemorrhage. NLRP3 denotes nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3.

As shown in Supplementary Figure 6, serum NLRP3 levels, NIHSS scores and hematoma volumes were integral to establish a combined model as graphically shown in the nomogram in order to judge the associated risk. The points relative to the above three variables were added up to produce the total points, and different aggregate scores mirrored variable survival possibility, which were 0.1=59.4, 0.3=88.8, 0.5=107.3, 0.7=125.8 and 0.9=155.3 separately. Simultaneously, the model was of satisfactorily stability in the context of the calibration curve assessment (Supplementary Figure 7) and was of rather clinical benefit in the help of decision curve analysis (Supplementary Figure 8).

Discussion

sICH appears as a serious cerebrovascular disease of severe effects on people's health. Acknowledgedly, NIHSS scores and hematoma volumes are in frequent utilization of clinical work of severity assessment and prognosis prediction, and their high applicabilities have been validated in numerous studies.[23] NLRP3 has been confirmatory as a firm association with neuroinflammatory responses after acute brain injury diseases; however, clinical data are scarce regarding post-sICH serum NLRP3 levels.[24] Serum NLRP3 levels were determined in this cohort of patients subsequent to sICH, with further exploration of its relation to severity, END occurrence and long-term neurologic outcome of patients. The chief results are that (1) serum NLRP3 levels of patients with sICH were significantly higher at admission compared with those of healthy controls; (2) patients' serum NLRP3 levels were significantly positively correlated with hematoma volume and NIHSS scores; (3) serum NLRP3 levels significantly differentiated between patients at risk of END or poor outcome and the other remainders; (4) serum NLRP3 may be an independent predictor of the development of END and 3-month poor outcome following ICH. Overall, all the preceding data point to the notion that serum NLRP3 may hold a promise to become a use prognostic biomarker of sICH.

NLRP3, as one of the cores of the inflammatory response, plays a key role in the pathogenesis and development of inflammatory and immune responsive illnesses, and its overactivation is involved in the development of a variety of diseases.[25,26] In immune diseases, the pyrin domain of NLRP3 can interact with the pyrin domain of apoptosis-associated speck-like protein to initiate the assembly of inflammasome.[27] This interaction is one of the important ways that NLRP3 participates in the immune response. In some cases, reduced or absent NLRP3 activity can lead to an inadequate immune response, which increases the risk of infection.[28,29] It has been found that when injury occurs, NLRP3 undergoes conformational changes and regulates the activation of caspase-1 to promote the maturation, secretion, and release of

https://doi.org/10.2147/IJGM.S507518

precursor IL-1β and precursor IL-18, which mediate neuroinflammatory responses, exacerbate neurological impairments, and affect the recovery of neurological function.[30] Thus, NLRP can be an activator of immune and inflammation in the whole body.

Reportedly, the expressions of NLRP3 inflammatory vesicles in glial cells were significantly increased in brain tissues of ICH mice, and it may be involved in the processes of secondary brain injury after ICH through mediating cellular pyroptosis pathway.[31] Moreover, NLRP3 RNAi markedly attenuated inflammation and brain damage after ICH and revealed that NLRP3 RNAi-encoded recombinant adenovirus may have potential value as an anti-inflammatory treatment for ICH.[32] In the TBI mouse model, NLRP3 expression was elevated in mouse brain tissues. Moreover, NLRP3-knockout mice had significantly less severe brain injury and lighter inflammatory mediators in brain lysates, and preserved more cognitive functions compared to wild-type mice. In addition, the application of NLRP3 inhibitors effectively improved the neurological function of TBI mice.[33] Therefore, upregulation of NLRP3 expressions in brain tissues after acute brain injury diseases may lead to disruption of the blood–brain barrier, brain edema worsening and even neuronal death, thus aggravating brain tissue injury.[34,35] On the contrary, inhibition of NLRP3 activity may suppress neuroinflammation in animals with acute brain injury, thereby improving neurological function.[36] In summary, NLRP3 may be a potential therapeutic target for acute brain injury diseases.

In a clinical study of aneurysmal subarachnoid hemorrhage, patients with delayed cerebral ischemia had significantly higher serum NLRP3 levels than those without delayed cerebral ischemia, and patients with a poor prognosis had higher serum NLRP3 levels; furthermore, serum NLRP3 levels were correlated with Glasgow coma scale scores, modified Rankin scores, Hunt-Hess grades, and World Federation of Neurosurgical Societies grades.[19] Interestingly, serum NLRP3 concentrations were significantly higher in patients with malignant brain edema secondary to acute ischemic stroke than in those with nonmalignant brain edema and showed a significantly positive correlation with NIHSS score.[37] In a study of 270 patients with TBI, serum NLRP3 levels were significantly elevated in the early phase of the disease and were strongly correlated with the prognosis of the patients, and there was also a significant difference in cerebrospinal fluid NLRP3 levels between patients with good and poor prognosis.[38] The results of these three clinical studies are firmly suggestive of conception that NLRP3 may be a potential prognostic predictive biomarker of patients with acute brain injury diseases.

The mRS is preferably applied for neurological assessment.[39] END is only an adverse event, which is very frequently regarded as an outcome variable of interest.[40,41] In this prospective cohort study including 128 patients with sICH, serum NLRP3 levels were significantly elevated in patients after sICH. We explored the relationships between serum NLRP3 levels, disease severity and mRS score at 3 months after stroke with investigation of each outcome variable's associative factors by the multivariate analysis and found that serum NLRP3 levels were independently associated with NIHSS score and hematoma volume, and mRS score was independently associated with NIHSS score, hematoma volume, and serum NLRP3 levels. In addition, all results are based on the statistical analysis, showing differences in serum NLRP3 levels as statistical significance of $P < 0.001$ between the two subgroups formed in accordance with END or poor prognosis. Thus, the clinical values of serum NLRP3 levels are existent, as verified by areas under ROC curve of 0.788 and 0.805 for predicting END and poor prognosis, respectively. In this cohort, some conventional confounding variables, such as hypertension, diabetes mellitus, hyperlipidemia and so forth, were gathered.[42–44] By establishing the binary logistic regression models, serum NLRP3 levels were of revelation as an independent association with END and 3-month adverse outcomes in patients with sICH. Therefore, we concluded that serum NLRP3 level may be closely associated with disease severity in sICH and can effectively predict END and poor prognosis with similar predictive ability as NIHSS score and hematoma volume. Subsequent nomogram models, calibration curves, and decision curves validated the predictive ability and value of the models. Statistically, serum NLRP3 levels were effective in differentiating the risk of occurrence of both END and adverse outcome after sICH. Thus, our study provides further evidence to support the view that serum NLRP3 may be a potential biochemical variable for assessing the severity of sICH and predicting clinical outcomes.

There are several limitations in this study. First, this was a single-center study that included more than 100 patients with sICH, and a validation of conclusions is necessary based on a multicenter large-sample study. Second, we detected serum NLRP3 levels only at the admission time of patients, and accordingly measurements of serum NLRP3 levels at

multiple time points will be of more significance to aid in revelation of the temporal trend of serum NLRP3 levels after sICH, thereby providing support for clinical treatments. Third, controls in our study were not diseased of hypertension, diabetes and hyperlipidemia, while patients did not present with such conditions. This imbalance may affect serum NLRP3 levels, leading to inconsistency of results. However, to the best of our knowledge, no literature has shown that these chronic sicknesses could influence serum NLRP3 levels. Hence, to some extent, it is reliable of our result that serum NLRP3 levels may be significantly elevated after ICH. Undoubtedly, a supplementation of another control group with such chronic diseases is a better choice. Fourth, considering that NLRP3 is one of the markers of inflammasomes,[25] its specific mechanisms in secondary brain injury post-sICH should be further studied so as to aid in exploration of a new therapeutic agent of sICH. Last, it is unclear about superiority of serum NLRP3 in terms of predicting poor prognosis of sICH when compared with other prognostic factors, including other immune factors and inflammatory markers, and therefore, it may be a good job that more biomarkers are all together measured in future to assess their prognostic values.

Conclusion

By applying multivariate analysis, elevated serum NLRP3 levels are strongly related to disease severity, END and poor prognosis after sICH in this prospective cohort study, and serum NLRP3 levels display effective prognostic predictive ability under ROC curve, signifying that serum NLRP3 levels may have the potential to become a prognostic biomarker of clinical value in sICH.

Abbreviations

sICH, spontaneous intracerebral hemorrhage; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3; NIHSS, national institute of health stroke scale; END, early neurological deterioration; ROC, receiver operating characteristic; AUC, area under curve; mRS, modified Rankin scale; OR, odds ratio; CI, confidence interval; OS, overall survival; SD, standard deviation.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author Contributions

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.

Funding

This work is financially supported by the Medical and Health Research Project of Zhejiang province (No. 2023XY260).

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Hostettler IC, Seiffge DJ, Werring DJ. Intracerebral hemorrhage: an update on diagnosis and treatment. *Expert Rev Neurother*. 2019;19(7):679–694. doi:10.1080/14737175.2019.1623671
2. Amer HA, El-Jaafary SIM, Hmae S, Fouad AM, Mohammed SS. Clinical and paraclinical predictors of early neurological deterioration and poor outcome in spontaneous intracerebral hemorrhage. *Egypt J Neurol Psychiatr Neurosurg*. 2023;59(1):74. doi:10.1186/s41983-023-00675-x
3. Xiao A, Zhang Y, Ren Y, et al. GDF11 alleviates secondary brain injury after intracerebral hemorrhage via attenuating mitochondrial dynamic abnormality and dysfunction. *Sci Rep*. 2021;11(1):3974. doi:10.1038/s41598-021-83545-x
4. Hu X, Tao C, Gan Q, Zheng J, Li H, You C. Oxidative stress in intracerebral hemorrhage: sources, mechanisms, and therapeutic targets. *Oxid Med Cell Longev*. 2016;2016:3215391. doi:10.1155/2016/3215391

5. Li N, Guo J, Kang K, et al. Cytotoxic edema and adverse clinical outcomes in patients with intracerebral hemorrhage. *Neurocrit Care*. 2023;38(2):414–421. doi:10.1007/s12028-022-01603-2
6. Xi G, Hua Y, Bhasin RR, Ennis SR, Keep RF, Hoff JT. Mechanisms of edema formation after intracerebral hemorrhage: effects of extravasated red blood cells on blood flow and blood-brain barrier integrity. *Stroke*. 2001;32(12):2932–2938. doi:10.1161/hs1201.099820
7. Leira R, Dávalos A, Silva Y, et al. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. *Neurology*. 2004;63(3):461–467. doi:10.1212/01.wnl.0000133204.81153.ac
8. Kuohn LR, Witsch J, Steiner T, et al. Early deterioration, hematoma expansion, and outcomes in deep versus lobar intracerebral hemorrhage: the FAST trial. *Stroke*. 2022;53(8):2441–2448. doi:10.1161/STROKEAHA.121.037974
9. Wu X, Liu J, Tian D, Chen J, Li H. Associations of serum Dickkopf-1 levels with disease severity and 90-day Prognosis after spontaneous intracerebral hemorrhage: results from the prospective cohort study. *Neurosurg Rev*. 2024;47(1):528. doi:10.1007/s10143-024-02755-9
10. Cao D, Liu F, Liu Q, Feng J. Correlation analysis between TSP2, MMP-9 and perihematoma edema, as well as the short-term prognosis of patients with hypertensive intracerebral hemorrhage. *Ann Palliat Med*. 2021;10(10):10930–10937. doi:10.21037/apm-21-2553
11. Senn R, Elkind MS, Montaner J, Christ-Crain M, Katan M. Potential role of blood biomarkers in the management of nontraumatic intracerebral hemorrhage. *Cerebrovasc Dis*. 2014;38(6):395–409. doi:10.1159/000366470
12. Coll RC, Schroder K, Pelegrín P. NLRP3 and pyroptosis blockers for treating inflammatory diseases. *Trends Pharmacol Sci*. 2022;43(8):653–668. doi:10.1016/j.tips.2022.04.003
13. Wu Y, Di X, Zhao M, Li H, Bai L, Wang K. The role of the NLRP3 inflammasome in chronic inflammation in asthma and chronic obstructive pulmonary disease. *Immun Inflamm Dis*. 2022;10(12):e750. doi:10.1002/iid3.750
14. Hemenway G, Frishman WH. Therapeutic implications of NLRP3-mediated inflammation in coronary artery disease. *Cardiol Rev*. 2022;30(2):90–99. doi:10.1097/CRD.0000000000000391
15. Han PP, Han Y, Shen XY, Gao ZK, Bi X. NLRP3 inflammasome activation after ischemic stroke. *Behav Brain Res*. 2023;452:114578. doi:10.1016/j.bbr.2023.114578
16. Eagle SR, Basantani MK, Preszler J, et al. Interaction of obesity and proteins associated with the NLRP3 inflammasome following mild traumatic brain injury. *Sci Rep*. 2024;14(1):10178. doi:10.1038/s41598-024-61089-0
17. Ystgaard MB, Scheffler K, Suganthan R, et al. Neuromodulatory effect of NLRP3 and ASC in neonatal hypoxic ischemic encephalopathy. *Neonatology*. 2019;115(4):355–362. doi:10.1159/000497200
18. Yi HJ, Lee JE, Lee DH, et al. The role of NLRP3 in traumatic brain injury and its regulation by pioglitazone. *J Neurosurg*. 2019;133(4):1083–1091. doi:10.3171/2019.6.JNS1954
19. Xu B, Zhou Y, Zhang Z, Ma J, Lv K. Serum concentrations of NLRP3 in relation to functional outcome and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *Clin Chim Acta*. 2022;536:61–69. doi:10.1016/j.cca.2022.09.004
20. Dsouza LB, Pathan SA, Bhutta ZA, et al. ABC/2 estimation in intracerebral hemorrhage: a comparison study between emergency radiologists and emergency physicians. *Am J Emerg Med*. 2019;37(10):1818–1822. doi:10.1016/j.ajem.2018.12.036
21. Liao LY, Xu PD, Fang XQ, et al. Prevalence and clinical predictors of spasticity after intracerebral hemorrhage. *Brain Behav*. 2023;13(3):e2906. doi:10.1002/brb3.2906
22. Shah VA, Thompson RE, Yenokyan G, et al. One-year outcome trajectories and factors associated with functional recovery among survivors of intracerebral and intraventricular hemorrhage with initial severe disability. *JAMA Neurol*. 2022;79(9):856–868. doi:10.1001/jamaneurol.2022.1991
23. Zhang Y, Tian Y, Wei J, Xiang Y. Relationship of serum IL-12 to inflammation, hematoma volume, and prognosis in patients with intracerebral hemorrhage. *Emerg Med Int*. 2022;2022:8688413. doi:10.1155/2022/8688413
24. Yuan D, Guan S, Wang Z, et al. HIF-1α aggravated traumatic brain injury by NLRP3 inflammasome-mediated pyroptosis and activation of microglia. *J Chem Neuroanat*. 2021;116:101994. doi:10.1016/j.jchemneu.2021.101994
25. Thornton P, Reader V, Digby Z, et al. Reversal of high fat diet-induced obesity, systemic inflammation, and astrogliosis by the NLRP3 inflammasome inhibitors NT-0249 and NT-0796. *J Pharmacol Exp Ther*. 2024;388(3):813–826. doi:10.1124/jpet.123.002013
26. Song S, Guo R, Mehmood A, et al. Liraglutide attenuate central nervous inflammation and demyelination through AMPK and pyroptosis-related NLRP3 pathway. *CNS Neurosci Ther*. 2022;28(3):422–434. doi:10.1111/cns.13791
27. Li Z, Guo J, Bi L. Role of the NLRP3 inflammasome in autoimmune diseases. *Biomed Pharmacother*. 2020;130:110542. doi:10.1016/j.biopha.2020.110542
28. Yu H, Li Q, Zhu H, Liu C, Chen W, Sun L. Mesenchymal stem cells attenuate systemic lupus erythematosus by inhibiting NLRP3 inflammasome activation through Pim-1 kinase. *Int Immunopharmacol*. 2024;126:111256. doi:10.1016/j.intimp.2023.111256
29. Werner LE, Wagner U. Calcium-sensing receptor-mediated NLRP3 inflammasome activation in rheumatoid arthritis and autoinflammation. *Front Physiol*. 2023;13:1078569. doi:10.3389/fphys.2022.1078569
30. Gu L, Sun M, Li R, et al. Didymin suppresses microglia pyroptosis and neuroinflammation through the Asc/Caspase-1/GSDMD pathway following experimental intracerebral hemorrhage. *Front Immunol*. 2022;13:810582. doi:10.3389/fimmu.2022.810582
31. Yao ST, Cao F, Chen JL, et al. NLRP3 is required for complement-mediated caspase-1 and IL-1beta activation in ICH. *J Mol Neurosci*. 2017;61(3):385–395. doi:10.1007/s12031-016-0874-9
32. Yuan B, Shen H, Lin L, Su T, Zhong S, Yang Z. Recombinant adenovirus encoding NLRP3 RNAi attenuate inflammation and brain injury after intracerebral hemorrhage. *J Neuroimmunol*. 2015;287:71–75. doi:10.1016/j.jneuroim.2015.08.002
33. Irrera N, Pizzino G, Calò M, et al. Lack of the Nlrp3 inflammasome improves mice recovery following traumatic brain injury. *Front Pharmacol*. 2017;8:459. doi:10.3389/fphar.2017.00459
34. Ward R, Li W, Abdul Y, et al. NLRP3 inflammasome inhibition with MCC950 improves diabetes-mediated cognitive impairment and vasoneuronal remodeling after ischemia. *Pharmacol Res*. 2019;142:237–250. doi:10.1016/j.phrs.2019.01.035
35. Liu C, Yao K, Tian Q, et al. CXCR4-BTK axis mediate pyroptosis and lipid peroxidation in early brain injury after subarachnoid hemorrhage via NLRP3 inflammasome and NF-κB pathway. *Redox Biol*. 2023;68:102960. doi:10.1016/j.redox.2023.102960
36. Dodd WS, Noda I, Martinez M, Hosaka K, Hoh BL. NLRP3 inhibition attenuates early brain injury and delayed cerebral vasospasm after subarachnoid hemorrhage. *J Neuroinflammation*. 2021;18(1):163. doi:10.1186/s12974-021-02207-x
37. Wang Y, Huang H, He W, Zhang S, Liu M, Wu S. Association between serum NLRP3 and malignant brain edema in patients with acute ischemic stroke. *BMC Neurol*. 2021;21(1):341. doi:10.1186/s12883-021-02369-4

38. Chen W, Wang Z, Ye G, et al. Changes of NLRP3 in serum and cerebrospinal fluid of patients after moderate to severe traumatic brain injury and their predictive values for prognosis. *CNS Neurosci Ther*. 2024;30(9):e70009. doi:10.1111/cns.70009
39. Coleman CI, Concha M, Baker WL, et al. Agreement between 30-day and 90-day modified rankin scale score and utility-weighted modified rankin scale score in acute intracerebral hemorrhage: an analysis of ATACH-2 trial data. *J Clin Neurosci*. 2024;121:61–66. doi:10.1016/j.jocn.2024.02.009
40. Zhu W, Zhou J, Ma B, Fan C. Predictors of early neurological deterioration in patients with intracerebral hemorrhage: a systematic review and meta-analysis. *J Neurol*. 2024;271(6):2980–2991. doi:10.1007/s00415-024-12230-6
41. Deng L, Li ZQ, Yang WS, et al. Prehospital ultra-early neurological deterioration in intracerebral hemorrhage: definition, prevalence, and association with outcomes. *Cerebrovasc Dis*. 2023;52(4):471–479. doi:10.1159/000527545
42. Shah QA, Ezzeddine MA, Qureshi AI. Acute hypertension in intracerebral hemorrhage: pathophysiology and treatment. *J Neurol Sci*. 2007;261(1–2):74–79. doi:10.1016/j.jns.2007.04.036
43. Bahadar GA, Shah ZA. Intracerebral hemorrhage and diabetes mellitus: blood-brain barrier disruption, pathophysiology and cognitive impairments. *CNS Neurol Disord Drug Targets*. 2021;20(4):312–326. doi:10.2174/1871527320666210223145112
44. Almuklass AM, Alawad YA, Alanazi AS, et al. Hyperlipidemia and hypertension are associated with intracerebral hemorrhage incidence: a retrospective study. *Cureus*. 2023;15(1):e33236. doi:10.7759/cureus.33236

International Journal of General Medicine

Dovepress
Taylor & Francis Group

Publish your work in this journal

The International Journal of General Medicine is an international, peer-reviewed open-access journal that focuses on general and internal medicine, pathogenesis, epidemiology, diagnosis, monitoring and treatment protocols. The journal is characterized by the rapid reporting of reviews, original research and clinical studies across all disease areas. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/international-journal-of-general-medicine-journal