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Inflammatory score predicts early hematoma expansion and poor outcomes in patients with intracerebral hemorrhage

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Background: This study aimed to develop a prediction score named inflammatory score based on proper integration of several inflammatory markers and investigate whether it was associated with hematoma expansion and poor outcomes in patients with intracerebral hemorrhage (ICH).

Methods: This study involved a consecutive series of spontaneous ICH patients of two cohorts admitted within 24 hours after symptom onset. Inflammatory score (0–9) was developed with the combination of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, systemic immune-inflammation index, lactate dehydrogenase, and C-reactive protein. The authors investigated the association between inflammatory score and hematoma expansion and poor outcomes by using univariate and multivariate logistic regression analyses. The optimal cutoff point of inflammatory score was determined by receiver operating characteristic analysis in the development cohort and then validated.

Results: A total of 301 and 154 ICH patients were enrolled in the development and validation cohorts. Inflammatory score was significantly higher in patients with hematoma expansion and poor outcomes. The multivariate logistic regression analysis revealed inflammatory score was independently associated with hematoma expansion, secondary neurological deterioration within 48 hours, 30-day mortality, and 3-month poor modified Rankin scale (4–6). The diagnostic accuracy of inflammatory score exhibited by area under the curve showed numerically or statistically higher than most of the individual indicators. Moreover, inflammatory score greater than or equal to 5 was selected as the optimal cutoff point, which was further prospectively validated with high diagnostic accuracy.

Conclusions: The inflammatory score is a reliable predictor for early hematoma expansion and short-term and long-term poor outcomes with good diagnostic accuracies in ICH patients.

Keywords: hematoma expansion, inflammatory score, intracerebral hemorrhage, poor outcomes

Intracerebral hemorrhage (ICH) accounts for approximately a quarter of all stroke subtypes with high mortality and the survivors always have varying degrees of residual disability[1,2]. However, few medical and surgical treatments are clearly beneficial comparing with ischemic stroke[3]. Hematoma expansion, which is a determinant of poor outcom es, occurs in about 30% of ICH patients especially at the early stage[4]. Attenuating hematoma expansion is a compelling target for ICH treatment, while the outcomes have not been accordingly improved after curbing the growth of hematoma in several clinical trials[5]. It will be more helpful if a predictor can identify the risk of hematoma expansion and poor outcome rapidly and accurately. Thus the antiexpansion treatment to the patients with positive of such predictor is likely to provide clinical benefits.

HIGHLIGHTS

- We develop the inflammatory score with proper integration of some inflammatory markers.
- Inflammatory score independently predicts hematoma expansion and poor outcomes.
- Inflammatory score greater than or equal to 5 was the optimal cutoff point with high diagnostic accuracy.

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To date, more and more radiological signs have been demonstrated to predict hematoma expansion and unfavorable outcomes[6,7]. Besides, the parameters from laboratory tests are also regarded as practical predictors[8,9]. Inflammatory association is one of the important mechanisms. A cascade of inflammatory processes occurs around the hematoma hours after ICH onset and the injurious neuroinflammation participates in hematoma expansion and worsens the outcome[10]. Correspondingly, peripheral blood inflammatory biomarkers may help predict mortality and functional outcomes. Indicators derived from blood routine test such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune-inflammation index (SII) have been demonstrated to be associated with hematoma expansion and the prognosis of ICH[11–14]. Our previous study has revealed that serum lactate dehydrogenase (LDH) predicts hematoma expansion and poor outcomes in patients with ICH[15]. Moreover, as another important determinant of inflammatory response, C-reactive protein (CRP) has been also reported to be such an independent predictor[16]. However, in general, the accuracy of a single predictor is not good enough. Meanwhile, most of the cutoff points were obtained from a single center with relatively large variability. In addition, differences in the normal ranges of the parameters always exist between different medical institutions. These have limited the clinical application of the above findings.

In order to compensate for the above defects, we developed a prediction score named inflammatory score based on proper integration of the aforementioned markers. Then we validated whether the inflammatory score was associated with hematoma expansion and poor outcomes in patients with ICH.

Methods

Study population

This study contained two cohorts of spontaneous ICH patients aged 18 years or older admitted to a stroke unit within 24 hours after symptom onset.

Development cohort: a consecutive series of patients with primary ICH from Center 1 between January 1, 2012 and December 31, 2017 were enrolled for retrospective analysis. The enrolled patients all underwent admission blood routine, LDH and CRP tests along with both baseline and follow-up non-contrast computed tomography (NCCT) scan. The follow-up NCCT scan was performed within 24 hours after initial CT scan, which was the follow-up time of hematoma expansion. The exclusion criteria included: (1) secondary ICH (cerebral aneurysm, Moyamoya syndrome, arteriovenous malformation, tumor, trauma or hemorrhagic transformation from brain infarction); (2) primary intraventricular hemorrhage (IVH); (3) historical modified Rankin scale (mRS) score greater than 1; (4) refused to be enrolled. When analyzing hematoma expansion, the patients undergoing surgical evacuation before follow-up NCCT scan were excluded.

Validation cohort: consecutive primary ICH patients from two clinical centers between January 1, 2018 and June 30, 2021 were enrolled for prospective analysis. The inclusion and exclusion criteria were the same as in the development cohort. All patients or their next-of-kin gave their informed consent prior to inclusion in this study. This study was approved by and studied in accordance with the ethical standards of the Fudan University Ethics Committee. The work has been reported in line with the STROCSS criteria[17], Supplemental Digital Content 1, http://links.lww.com/JS9/A11. This study was registered with www.researchregistry.com (researchregistry7921). Hyperlink to the registration: https://www.researchregistry.com/register-now#home/registrationdetails/62839a62715011001ec2f619/

Imaging analysis

NCCT examinations were performed using a multidetector CT-scanner with contiguous axial 5-mm section thickness (Brilliance iCT; Philips Medical Systems, Cleveland, OH). Hematoma was three-dimensionally reconstructed and measured by 3D-Slicer software (Brigham Women's Hospital, Boston, MA, USA), which is a free open source software platform for biomedical research (http://www.slicer.org) according to previous studies[7]. Hematoma expansion was defined as an absolute increase greater than 6 ml or a proportional increase of more than 33% in the follow-up NCCT scan compared with the baseline NCCT scan[18].

Clinical data and outcome assessment

We recorded the essential clinical data including age, sex, the history of hypertension, diabetes mellitus, smoking, alcohol consumption, antiplatelet, and anticoagulation therapy. Also, the clinical and radiographic status on admission such as systolic and diastolic blood pressure, Glasgow coma scale (GCS) scores, the time of baseline NCCT, location of the hematoma (deep, lobar, and Infratentorial), and presence of IVH and hematoma volume were included. Meanwhile, laboratory testing including total white blood cells (WBC), the percentages (%) of neutrophils (N), lymphocytes (L) and monocytes (M), platelet count (PLT), LDH, CRP, prothrombin time (PT), activated partial thromboplastin time, and international normalized ratio (INR) were collected from admission blood work (the first examination). NLR, PLR, MLR, and SII were calculated as N/L, PLT/ (WBC × L%), M/L, and PLT × N/L.

Both short-term and long-term functional outcomes were evaluated. Secondary neurological deterioration was defined (1) early hemicraniectomy under standardized criteria or (2) secondary decrease of GCS of greater than 3 points, both within the first 48 hours after symptom onset[19]. We also recorded the mortality at 30 days. Moreover, long-term functional outcome was assessed by using mRS at 3 months after ICH onset. It was performed through in-person interviews by trained senior physicians or a phone call by trained study staffs. Patients were dichotomized into poor outcome (mRS 4–6) and good outcome (mRS 0–3) as reported by previous studies[18,20].

Inflammatory score

This prediction score included combination of NLR, PLR, MLR, SII, LDH, and CRP. The cutoff points were dependent on the upper normal limits (UNLs) and lower normal limits (LNLs) of each blood index rather than certain values like most of other researches. The critical values were obtained from the integration of our clinical practice and previous studies[11–16]. The positive inflammatory indicators were shown as follows:

1. NLR ≥ 1.4 × N% (UNL)/L% (LNL)
2. PLR ≥ PLT (UNL)/ [WBC (UNL) × L% (LNL)]

Table 1

Individual components and calculation of inflammatory score

Variables	Points
Inflammatory indicators based on blood routine test (positive as follows)	
NLR ≥ 1.4 × N% (UNL)/L% (LNL)	If there is any positive indicator, 2 points will be counted
PLR ≥ PLT (UNL)/ [WBC (UNL) × L% (LNL)]	If there are still positive indicators, score 1 point for each
MLR ≥ M% (UNL)/L% (LNL)	Total: 0–5 points
SII ≥ 0.8 × PLT (UNL) × N% (UNL)/L% (LNL)	
LDL	
≥ 0.9 (UNL)	2
< 0.9 (UNL)	0
CRP	
≥ UNL	2
< UNL	0
Total	0–9

CRP, C-reactive protein; L, lymphocytes; LDH, lactate dehydrogenase; LNL, lower normal limit; M, monocytes; MLR, monocyte-to-lymphocyte ratio; N, neutrophils; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelets; SII, systemic immune-inflammation index; UNL, upper normal limit; WBC, white blood cells.

3. MLR ≥ M% (UNL)/L% (LNL)
4. SII ≥ 0.8 × PLT (UNL) × N% (UNL)/L% (LNL)
5. LDH ≥ 0.9 (UNL)
6. CRP ≥ UNL

As to items 1–4, if there was any positive indicator, two points would be scored. Meanwhile, if there were still other positive indicators, score one point for each. With regard to items 5 and 6, score 2 points for every positive indicators. Thus, the inflammatory score was created with a total score ranging from 0 to 9 (Table 1).

Statistical analysis

Statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA) by statisticians blinded to the groups. Data for continuous variables were summarized as means with SDs or medians with interquartile ranges (IQRs) when appropriate and analyzed using two-tailed Student *t*-test, one-way analysis of variance, Mann–Whitney *U*-test, or Kruskal–Wallis *H*-test determined by the data distribution and the number of variables. Data for categorical variables were expressed as a percentage and compared using χ^2-test or the Fisher exact test (two-tailed). *P* less than 0.05 was considered statistically significant. We used univariate analysis for comparing the variables to determine the possible significant predictors for hematoma expansion and poor outcomes. Predictors significant at *P* less than 0.05 from the univariate analysis were subsequently tested in the multivariable logistic regression analysis for the independent associations with hematoma expansion and poor functional outcomes. Variables known to be associated with hematoma expansion and poor outcomes based on multiple external data sets were also included in the multivariate model. Multicollinearity was also analyzed using the variance inflation factor (VIF) test to identify the high degree of correlations among the variables. The covariables were considered to have multicollinearity when VIF greater than 5[21]. We first removed all components that made up inflammatory scores to avoid the possibility of adding the same variables twice. If there were still any variable with VIF greater than 5, the variable with the highest VIF that could also scarcely affect the results were manually removed and the VIF test was re-performed until all variables in the regression model had VIF less than 5 so as to avoid the influence of multicollinearity to a great extent[22,23]. Receiver operating characteristic (ROC) curves were generated to estimate the ability of the variables for diagnosing hematoma expansion and poor outcomes and the area under curve (AUC) was also calculated for evaluating diagnostic accuracies. The cutoff points of inflammatory score for predicting hematoma expansion and poor outcomes were also determined according to Youden's Index (sensitivity + specificity – 1). Correspondingly, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated in the development and validation cohorts. Diagnostic accuracies evaluated by AUC were compared using the DeLong test package in MedCalc (MedCalc Software Ltd., Ostend, Belgium).

Results

Baseline characteristics

After application of the inclusion and exclusion criteria, 301 patients (109 excluded) and 154 patients (54 excluded) with primary ICH were enrolled in the development and validation

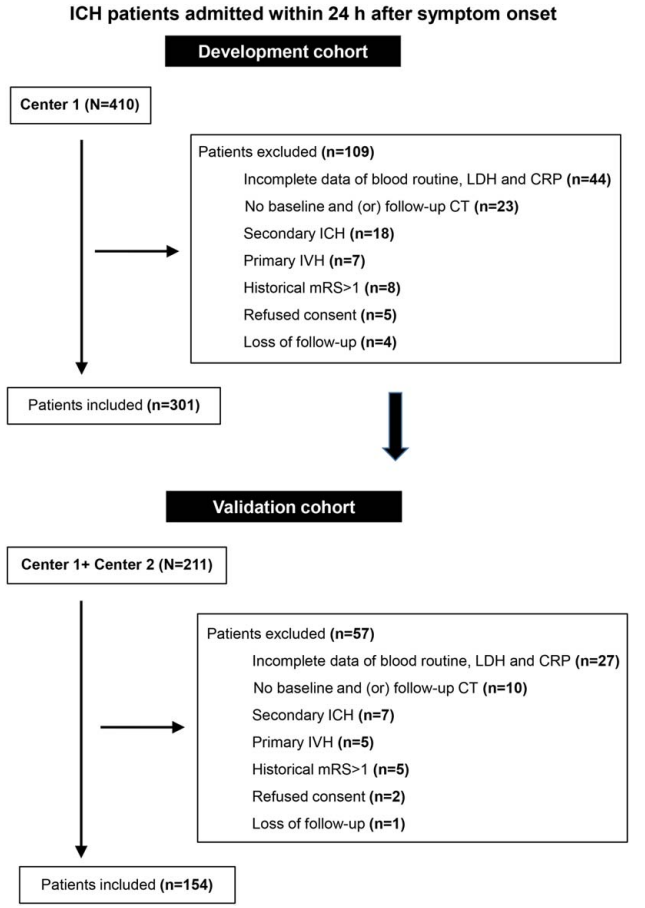

Figure 1. Flowchart of study patients. CT indicates computed tomography; CRP, C-reactive protein; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; LDH, lactate dehydrogenase; mRS, modified Rankin scale.

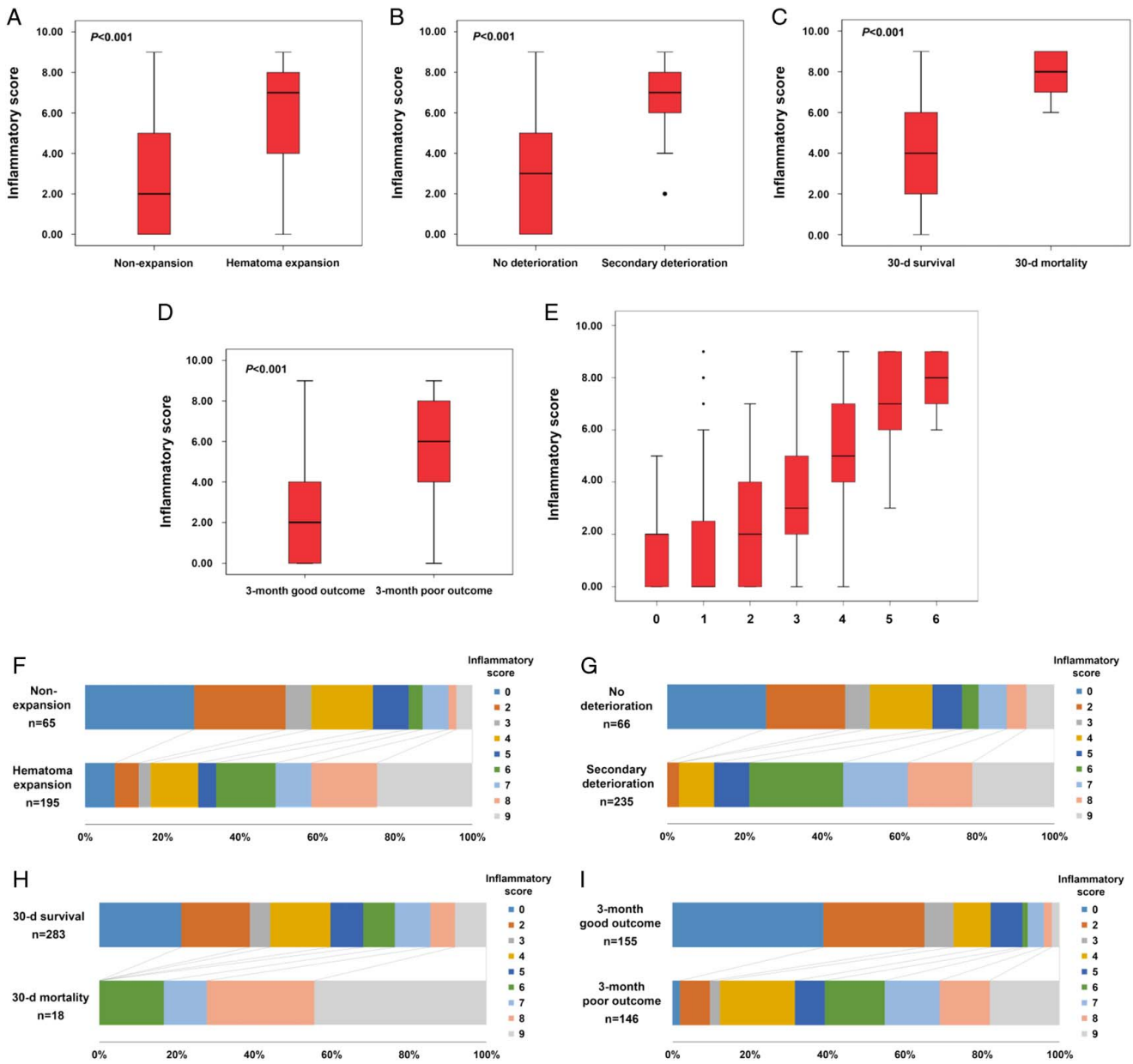

Figure 2. (a–d) Differences of inflammatory score between intracerebral hemorrhage (ICH) patients with and without hematoma expansion (a), secondary neurological deterioration within 48 hours (b), 30-day mortality (c), and 3-month poor modified Rankin scale (mRS) (d). (e) The inflammatory scores in each mRS score (from 0 to 6). Details of each inflammatory score in ICH patients with or without hematoma expansion (f), secondary neurological deterioration within 48 hours (g), 30-day mortality (h), and 3-month poor modified Rankin scale (mRS) (i).

cohorts respectively for analysis (Fig. 1).

In the development cohort, 222 males and 79 females with the average age of (61.4 ± 13.1) years met inclusion criteria. The baseline GCS score was 15 (IQR: 12–15) with the baseline hematoma volume of 14.8 (IQR: 6.7–31.4) ml. IVH was found in 87 patients (25.9%). As this cohort contains only single center and the UNLs and LNLs of the parameters were as follows: WBC ($3.5–9.5 \times 10^9$/L) neutrophils (40–75%), lymphocytes (20–50%), monocytes (3–10%), PLT ($125–350 \times 10^9$/l), LDH (125–245 U/l), and CRP (0–8.2 mg/l), each inflammatory indicator had unique critical value: NLR greater than or equal to 5.25, PLR greater than or equal to 184, MLR greater than or equal to 0.5, SII greater than or equal to 1050×10^9/l, LDH greater than or equal to 220 U/L, CRP greater than or equal to 8.2 mg/L. After excluding 51 patients undergoing surgical evacuation before follow-up NCCT scan, 65 of 260 patients (25.0%) was observed hematoma expansion. Secondary neurological deterioration within 48 hours occurred in 66 patients (21.9%) and 19 patients (6.3%) died at 30 days after ICH. One hundres and fifty-five patients (51.5%) had 3-month poor mRS (4–6) (Table 2).

One hundred and fifty-four patients (male: 110) were included in the validation cohort with average age of 64.0 (13.7). The median baseline GCS score was 15 (IQR: 13–15) with the baseline

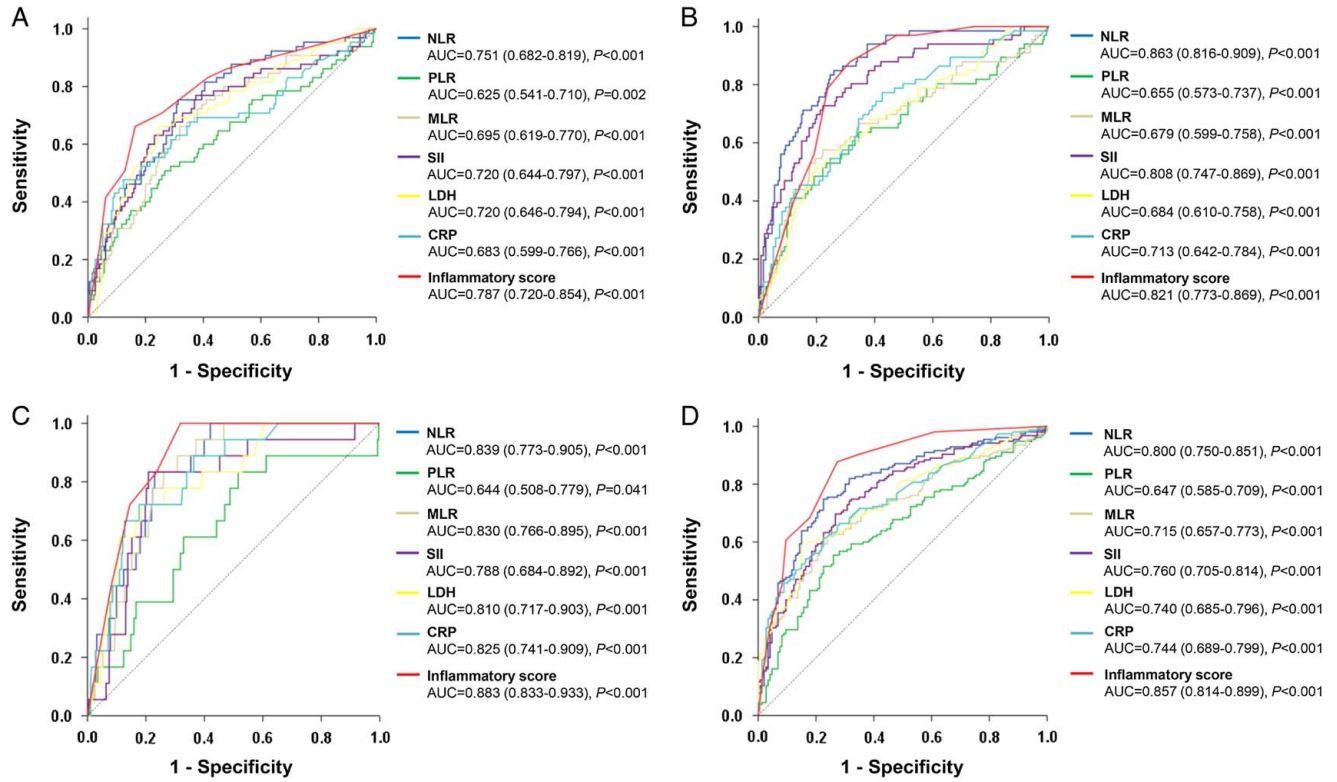

Figure 3. Receiver operating characteristic (ROC) curves of inflammatory score for predicting hematoma expansion and poor outcomes. (a) Hematoma expansion. (b) Secondary neurological deterioration within 48 hours. (c) Thirty-day mortality. (d) Three-month poor modified Rankin scale (mRS). AUC, area under curve; CRP, C-reactive protein; LDH, lactate dehydrogenase; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

hematoma volume of 11.5 (IQR: 5.3–30.1) ml. Hematoma expansion was observed in 37 patients (26.4%). Poor outcomes were evaluated as follows: secondary neurological deterioration within 48 hours (32 patients, 20.8%); 30-day mortality (nine patients, 5.8%); 3-month poor mRS (4–6) (76 patients, 49.4%). The baseline characteristics of the development and validation cohorts were well-balanced ($P > 0.05$) (Table 2). The following UNLs and LNLs were used in Center 2: parameters in blood routine test (the same as Center 1), LDH (135–225 U/l) and CRP (0–10.0 mg/l).

Inflammatory score for predicting hematoma expansion

In the development cohort, the values of each inflammatory indicator were much higher in patients with hematoma expansion than patients without hematoma expansion (Supplemental Figs 1, 2A, Supplemental Digital Content 1, http://links.lww.com/JS9/A12). Meanwhile, the proportion of high scores in patients with hematoma expansion was markedly higher than those without hematoma expansion (Fig. 2F). The incidence of hematoma expansion increased with higher scores, which reached 51.6% in patients with the highest score of 9 (Table 4). Univariate analysis displayed significant differences in sex (male) ($P = 0.009$), history of diabetes mellitus ($P = 0.027$), baseline GCS scores ($P < 0.001$), time to the baseline NCCT ($P = 0.001$), baseline hematoma volume ($P < 0.001$), WBC counts ($P < 0.001$), ANC ($P < 0.001$), ALC ($P < 0.001$), NLR ($P < 0.001$), PLR ($P < 0.001$), MLR ($P < 0.001$), SII ($P < 0.001$), LDH ($P < 0.001$), CRP ($P < 0.001$), INR ($P = 0.018$), PT ($P = 0.010$), and inflammatory score ($P < 0.001$) for hematoma expansion prediction (Table 3). Subsequently, after removing INR to avoid multicollinearity, the multivariate logistic regression analysis revealed that inflammatory score [odds ratio (OR): 2.475, 95% confidence interval (CI): 1.672–3.662, $P < 0.001$] was independently associated with hematoma expansion (Table 3). The AUC of inflammatory score in ROC analysis was 0.787 with 95% CI of 0.720–0.854 ($P < 0.001$), numerically higher than other inflammatory indicators, indicating inflammatory score was appropriate for diagnosing hematoma expansion. The accuracy was statistically higher than PLR ($P = 0.003$) and CRP ($P = 0.049$) (Fig. 3A). The optimal cutoff point for predicting hematoma expansion was 5 with Youden's Index of 0.452.

Independent association of inflammatory score with poor outcomes

Both short-term and long-term poor outcomes were included in our work so as to assess functional outcomes and expectably, the results were consistent with each other. Comparing with those with good outcomes, ICH patients with poor outcomes had much higher NLR, PLR, MLR, SII, LDH, CRP as well as inflammatory score [secondary neurological deterioration within 48 h (7.0, IQR: 6.0–8.0 vs. 3.0, IQR: 0–5.0); 30-day mortality (8.0, IQR: 7.0–9.0 vs. 4.0, IQR: 1.0–6.0); 3-month poor mRS (4–6) (6.0, IQR: 4.0–8.0 vs. 2.0, IQR: 0–4.0)] (Supplemental Figs 1, 2B–D,

Table 2

The baseline characteristics of the development and validation cohort

Characteristics	Development cohort ($n=301$)	Validation cohort ($n=154$)	*P* value
Age, y, mean (SD)	61.4 (13.1)	64.0 (13.7)	0.051
Sex, male, n (%)	222 (73.8)	110 (71.4)	0.597
History, n (%)			
Hypertension	204 (67.8)	115 (74.7)	0.128
Diabetes mellitus	42 (14.0)	24 (15.6)	0.640
Smoking	57 (18.9)	29 (18.8)	0.978
Alcohol consumption	27 (9.0)	12 (7.8)	0.671
Antiplatelet therapy	20 (6.6)	6 (3.9)	0.232
Anticoagulation therapy	5 (1.7)	5 (3.2)	0.275
Clinical/radiographic status on admission			
SBP (mm Hg), mean (SD)	171.0 (29.3)	168.1 (29.3)	0.359
DBP (mm Hg), mean (SD)	95.4 (16.3)	94.0 (16.5)	0.426
GCS score, median (IQR)	15 (12–15)	15 (13–15)	0.637
Time to the baseline NCCT (min), median (IQR)	213.0 (122.0–340.0)	176.5 (103.8–283.8)	0.031
Hematoma location, n (%)			
Deep	216 (71.8)	114 (74.0)	0.609
Lobar	63 (20.9)	32 (20.8)	0.970
Infratentorial	22 (7.3)	8 (5.2)	0.390
IVH	87 (28.9)	40 (26.0)	0.510
Hematoma volume (ml), median (IQR)	14.8 (6.7–31.4)	11.5 (5.3–30.1)	0.227
Laboratory testing			
WBC ($\times 10^9$/L), median (IQR)	9.1 (7.1–12.1)	9.2 (7.2–11.9)	0.956
Neutrophils (%), mean (SD)	75.8 (12.8)	76.8 (10.9)	0.449
Lymphocytes (%), mean (SD)	15.6 (9.0)	15.4 (9.0)	0.851
Monocytes (%), mean (SD)	6.5 (2.4)	6.5 (2.4)	0.886
PLT ($\times 10^9$/L), mean (SD)	205.5 (64.6)	195.7 (56.1)	0.111
NLR, median (IQR)	5.3 (3.1–9.7)	5.3 (3.3–9.7)	0.643
PLR, median (IQR)	163.5 (120.0–225.0)	149.5 (113.5–223.7)	0.450
MLR, median (IQR)	0.43 (0.31–0.73)	0.45 (0.29–0.74)	0.642
SII ($\times 10^9$/L), median (IQR)	1084.9 (619.7–1956.7)	1006.6 (665.3–1765.6)	0.844
vLDH (U/L), median (IQR)	203.0 (170.0–241.0)	194.0 (169.0–243.0)	0.472
CRP (mg/L), median (IQR)	8.5 (3.5–28.2)	10.3 (4.9–24.4)	0.330
INR, median (IQR)	0.96 (1.01–1.06)	1.01 (0.96–1.07)	0.795
APTT (s), median (IQR)	25.3 (22.3–29.0)	24.1 (22.0–28.4)	0.213
PT (s), median (IQR)	11.7 (11.1–12.4)	11.7 (11.1–12.5)	0.900
Inflammatory score, median (IQR)	4.0 (2.0–7.0)	4.0 (2.0–7.0)	0.962

APTT, activated partial thromboplastin time; CRP, C-reactive protein; DBP, diastolic blood pressure; GCS, Glasgow coma scale; INR, international normalized ratio; IQR, interquartile range; IVH, intraventricular hemorrhage; LDH, lactate dehydrogenase; MLR, monocyte-to-lymphocyte ratio; NCCT, noncontrast computed tomography; NLR, neutrophil-to-lymphocyte ratio; PT, prothrombin time; SBP, systolic blood pressure; SII, systemic immune-inflammation index; WBC, white blood cells.

Supplemental Digital Content 1, http://links.lww.com/JS9/A12). Inflammatory score in ICH patients with or without poor outcomes were also detailed, showing that high scores accounted for a large proportion of patients with both short-term and long-term poor outcomes (Figs 2G–I). Generally, the probability of poor outcomes increased along with the rising of the inflammatory score (Table 4). The variable PT in 30-day mortality and 3-month poor mRS was excluded from the multivariate regression models in order to reduce the influence of multicollinearity. The VIFs of the variables in each regression model were shown in Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/JS9/A12. Multivariate logistic regression analysis revealed that inflammatory score independently predicted secondary neurological deterioration within 48 hours (OR: 1.949, 95% CI: 1.199–3.167, $P=0.007$); 30-day mortality (OR: 3.254 95% CI: 1.236–8.569, $P=0.017$); 3-month poor mRS (4–6) (OR: 2.190, 95% CI: 1.642–2.922, $P<0.001$) after ICH (Table 5). ROC curves of the independent predictive factors for poor outcomes were plotted and the AUCs, 95% CIs, and *P* values of inflammatory score were as follows: secondary neurological deterioration within 48 hours (0.821, 0.773–0.869, $P<0.001$); 30-day mortality (0.883, 0.833–0.933, $P<0.001$); 3-month poor mRS (4–6) (0.857, 0.814–0.899, $P<0.001$). The diagnostic accuracy of inflammatory score exhibited by AUC showed numerically higher than other inflammatory indicators except NLR in secondary neurological deterioration within 48 hours. Statistical differences of AUCs existed between inflammatory score and PLR ($P<0.001$), MLR ($P=0.003$), LDH ($P=0.003$), and CRP ($P=0.014$) (secondary neurological deterioration within 48 h); PLR ($P=0.001$) (30-d mortality); PLR ($P<0.001$), MLR ($P<0.001$), SII ($P=0.006$); LDH ($P=0.001$), and CRP ($P=0.002$) (3-month poor mRS) (Figs 3B–D). Moreover, the inflammatory scores in each mRS score (from 0 to 6) were also detailed, indicating that inflammatory scores increased with the aggravation of outcomes (Fig. 2E). The optimal cutoff points for predicting secondary neurological deterioration within 48 hours, 30-day mortality, and 3-month poor mRS were 5, 5, and 4 with Youden's indices of 0.564, 0.597, and 0.603, respectively.

Table 3

Univariate and multivariate analysis of the potential predictors for hematoma expansion

	Hematoma expansion		
Variables	**OR**	**95% CI**	***P* value**
Age	0.986	0.965–1.007	0.196
Sex	2.765	1.285–5.953	0.009
History			
Hypertension	1.205	0.659–2.203	0.545
Diabetes mellitus	2.359	1.139–4.885	0.021
Smoking	1.349	0.693–2.627	0.378
Alcohol consumption	0.516	1.171–1.556	0.240
Antiplatelet therapy	1.424	0.518–3.913	0.493
Anticoagulation therapy	9.339	0.954–91.410	0.055
Clinical/radiographic status on admission			
SBP	1.009	0.999–1.019	0.086
DBP	1.004	0.985–1.023	0.701
GCS score	0.743	0.660–0.835	< 0.001
Time to the baseline NCCT	0.995	0.992–0.997	< 0.001
Hematoma location			
Deep	1.173	0.615–2.237	0.628
Lobar	0.970	0.491–1.918	0.931
Infratentorial	0.531	0.115–2.461	0.419
IVH	1.638	0.882–3.041	0.118
Hematoma volume	1.040	1.024–1.057	< 0.001
Laboratory testing			
WBC	1.238	1.130–1.356	< 0.001
Neutrophils (%)	1.102	1.063–1.143	< 0.001
Lymphocytes (%)	0.885	0.845–0.927	< 0.001
Monocytes (%)	0.954	0.839–1.085	0.476
Platelets	0.999	0.994–1.004	0.647
NLR	1.167	1.101–1.237	< 0.001
PLR	1.006	1.003–1.009	0.001
MLR	5.526	2.477–12.330	< 0.001
SII	1.001	1.000–1.001	< 0.001
LDH	1.013	1.007–1.018	< 0.001
CRP	1.019	1.011–1.027	< 0.001
INR	48.367	1.928–1213.410	0.018
APTT	1.028	0.984–1.074	0.212
PT	1.336	1.072–1.665	0.010
Inflammatory score	2.235	1.761–2.837	< 0.001
Multivariate analysis			
Sex	1.554	0.566–4.260	0.392
Diabetes mellitus	1.831	0.687–4.880	0.227
Anticoagulation therapy	2.184	0.161–29.578	0.557
GCS score	0.947	0.780–1.150	0.583
Time to the baseline NCCT	0.995	0.992–0.998	0.001
Hematoma volume	1.014	0.994–1.034	0.168
WBC	1.007	0.879–1.153	0.924
Neutrophils (%)	1.039	0.986–1.316	0.078
Lymphocytes (%)	1.167	0.973–1.399	0.097
INR	Removed		
PT	1.260	0.995–1.594	0.055
Inflammatory score	2.475	1.672–3.662	< 0.001

APTT, activated partial thromboplastin time; CI, confidence interval; CRP, C-reactive protein; DBP, diastolic blood pressure; GCS, Glasgow coma scale; INR, international normalized ratio; IVH, intraventricular hemorrhage; LDH, lactate dehydrogenase; MLR, monocyte-to-lymphocyte ratio; NCCT, noncontrast computed tomography; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PT, prothrombin time; SBP, systolic blood pressure; SII, systemic immune-inflammation index; WBC, white blood cells.

Validation of inflammatory score

As the cutoff points of inflammatory score for predicting hematoma expansion, secondary neurological deterioration within 48 hours, 30-day mortality, and 3-month poor mRS were 5, 5, 5, and 4, we selected 5 for the optimal cutoff point for both hematoma expansion and poor outcomes prediction. Then we prospectively validated the diagnostic accuracy of inflammatory score greater than or equal to 5 points for predicting hematoma expansion and poor outcomes. The AUCs of ROC curves were 0.728 (hematoma expansion), 0.801 (secondary neurological deterioration within 48 h), 0.786 (30-d mortality), and 0.785 (3-month poor mRS). Meanwhile, high mRS scores are more likely in patients with inflammatory score greater than or equal to 5 points (Supplemental Fig. 2, Supplemental Digital Content 1, http://links.lww.com/JS9/A12). In addition, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of inflammatory score greater than or equal to 5 were showed in Table 5.

Discussion

In the current study, we created a new score system called inflammatory score by using several well-known inflammatory markers. Although these markers were all reported to be associated with hematoma expansion and poor outcomes in previous studies[11–16], several limitations still exist when applied to clinical practice. Single predictor always fails to reflect comprehensive characteristics with unsatisfactory sensitivity and specificity. Besides, an appropriate cutoff point which can promote a direct clinical use has more advantages than the simple correlation. However, the testing methods for these parameters may differ among different medical institutions, leading to even marked differences in the normal ranges. Therefore, the cutoff points of the same parameter obtained from different single centers are always difficult to unify. For example, the cutoff points of NLR to predict poor outcome at 90 days from two different studies were 4.58 and 6.28, respectively[11,24]. As a result, these findings could hardly be popularized on a large scale due to the lack of a consistent standard.

In our inflammatory score, the optimal cutoff points were calculated by using the normal upper and lower limits according to the integration of our clinical practice and reported results, so that it can be applied to every center without limitations to the difference of testing methods and normal ranges. Generally, the changing trends of the UNLs and LNLs of each parameter in blood routine test are more or less consistent. In other words, if the UNL and LNL of one parameter are higher in one laboratory than another, it is quite possible that the UNLs and LNLs of other parameters are also higher. Therefore, ratios have more advantages when calculating optimal cutoff points using UNLs and LNLs. Our validation cohort included two centers and the results are in good agreement with development cohort. Moreover, the proper combination of each indicator is another advantage of inflammatory score. As NLR, PLR, MLR, and SII are all based on blood routine test, any other positive indicator after the first determined indicator was only scored one point. Expectedly, this double-center study reveals inflammatory score is independently associated with hematoma expansion and poor outcomes in ICH patients, which is supported by four parts of results. First of all, the inflammatory score in patients with hematoma expansion and short-term and long-term poor outcomes were significantly higher than that in the negative groups and the incidence of hematoma expansion and poor outcomes increased with higher scores. Then the univariate and the

Table 4

Performance of inflammatory score for hematoma expansion and poor outcomes in the development and validation cohorts

	Hematoma expansion		Secondary neurological deterioration within 48 hours		Thirty-day mortality		Three-month poor mRS (4–6)	
Inflammatory score	Development cohort ($n=65$)	Validation cohort ($n=37$)	Development cohort ($n=66$)	Validation cohort ($n=32$)	Development cohort ($n=18$)	Validation cohort ($n=9$)	Development cohort ($n=155$)	Validation cohort ($n=76$)
Individual points, *n* (%)								
0	5 (8.3)	1 (2.7)	0	0	0	0	3 (5.0)	2 (5.4)
2	4 (8.0)	3 (11.5)	2 (4.0)	2 (7.7)	0	0	12 (24.0)	10 (38.5)
3	2 (13.3)	0	0 ()	0	0	0	4 (26.6)	0
4	8 (18.2)	5 (35.7)	6 (13.6)	0	0	0	30 (68.2)	7 (50.0)
5	3 (12.5)	6 (40.0)	6 (25.0)	7 (46.7)	0	1 (6.7)	12 (50.0)	8 53.3
6	10 (38.5)	3 (25.0)	16 (61.5)	3 (25.0)	3 (11.5)	0	24 (92.3)	8 (66.7)
7	6 (21.4)	5 (62.5)	11 (39.3)	4 (50.8)	2 (7.1)	0	22 (78.6)	6 (75.0)
8	11 (47.8)	3 (27.3)	11 (47.8)	4 (36.4)	5 (21.7)	3 (27.3)	20 (87.0)	11 (100)
9	16 (51.6)	11 (44.0)	14 (45.2)	12 (48.0)	8 (25.8)	5 (20.0)	28 (90.3)	24 (96.0)
Categorized score, *n* (%)								
<5	19 (11.6)	9 (11.1)	8 (4.7)	2 (2.9)	0	0	49 (29.0)	19 (22.9)
≥ 5	46 (47.9)	28 (47.5)	58 (43.9)	30 (35.3)	18 (10.2)	9 (10.6)	106 (80.3)	57 (80.3)
Accuracy of score ≥ 5 (%)								
Sensitivity	70.8	75.7	87.9	93.8	100	100	68.4	75.0
Specificity	74.4	69.9	68.5	66.4	59.7	57.2	82.2	82.1
PPV	47.9	47.5	43.9	42.3	13.6	12.6	80.3	80.3
NPV	88.4	88.9	95.3	97.6	100	100	71.0	77.1
Accuracy	73.5	71.7	72.8	72.1	62.1	59.7	75.1	78.6
Total accuracy of score ≥ 5 (%)								
Sensitivity	72.5		89.8		100		70.6	
Specificity	72.8		67.8		58.9		82.1	
PPV	47.7		43.3		13.3		80.3	
NPV	88.6		96.0		100		73.0	
Accuracy	72.8		72.5		61.3		76.3	

mRS, modified Rankin scale; NPV, negative predictive value; PPV, positive predictive value.

following multivariate logistic regression analysis revealed that inflammatory score could be regarded as an independent predictor. In addition, ROC analysis suggested that inflammatory score was appropriate for diagnosing hematoma expansion and poor outcomes and had its own advantages compared with other single inflammatory indicators. Finally, inflammatory score greater than or equal to 5 was validated as an appropriate predictor of hematoma expansion and poor outcomes with good accuracies.

More and more attentions have been paid to searching for a perfect laboratory testing parameter that predicts hematoma expansion and/or outcomes in ICH patients. The parameter should be easily available with close association with the pathophysiology of ICH. Three main aspects of mechanisms are concerned. Markers related to microvascular integrity such as matrix metalloproteinases-9 (MMP-9) and low-density lipoprotein cholesterol which result in the breakdown of the blood–brain barrier (BBB) are one of the three kinds of predictors[25,26]. Meanwhile, parameters that alter the coagulation status are associated with hematoma expansion owing to the increase of bleeding risk and hemostasis prevention. Hypocalcemia and high INR belong to such factors[8,27]. Inflammatory-associated factors contribute to another kind of mechanism, which is the focus of our research. Multiple mechanisms may be involved in the effects of neuroinflammation on hematoma expansion. Inflammatory responses, as a pathological hallmark of ICH, has the ability to induce activation of MMPs, especially MMP-9, which degrade basal lamina and brain microvessels resulting in BBB breakdown and lead to hematoma expansion[28,29]. Meanwhile, neuroinflammation after ICH promotes the release of variable cytokines[30]. The cytokines such as interleukin-1β cause injury of brain vascular endothelial cells[31]. The damage of the integrity of vessels close to the site of initial bleeding may bring out hematoma expansion. Moreover, inflammatory activation commonly induces coagulation abnormalities[32]. It has been demonstrated that neutrophil, lymphocyte, and WBC are major predictors to the occurrence of acute coagulopathy in ICH patients[33]. Therefore, inflammatory responses may also affect hematoma expansion via breaking the balance of coagulation. Neuroinflammation induced by ICH is characterized by increased activation of microglia/monocyte-derived macrophages and the subsequent release of proinflammatory and anti-inflammatory mediators[34]. Neutrophils are the earliest leukocytes recruited from peripheral blood into the brain[35]. It has been demonstrated the accumulation of neutrophils and macrophages perihematoma from day 1 after ICH in the postmortem tissue[36]. Meanwhile, lymphocytes are also found in low concentrations perihematoma[37]. The balance of platelet aggregation which is involved in hemostasis is broken after ICH. Platelets activation after ICH is predisposed by multiple factors and may elicit the effect of promoting hemostasis. However, activated platelets also release a range of potent chemical mediators that promote neuroinflammation[38]. Besides, platelets have the capability to recruit leukocytes including neutrophils, lymphocytes, and macrophage to sites of inflammation, contributing to the initiation or

Table 5

Univariate and multivariate analysis of the potential predictors for poor outcomes

	Secondary neurological deterioration within 48 hours			Thirty-day mortality			Three-month poor mRS (4–6)		
Variables	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Age	0.988	0.968–1.009	0.274	1.018	0.981–1.058	0.341	1.004	0.987–1.022	0.626
Sex	1.273	0.669–2.421	0.463	2.990	0.672–13.309	0.150	1.586	0.945–2.661	0.081
History									
Hypertension	0.789	0.445–1.398	0.416	1.713	0.549–5.349	0.354	0.883	0.544–1.432	0.613
Diabetes mellitus	0.439	0.165–1.165	0.098	2.557	0.862–7.589	0.091	1.303	0.675–2.515	0.431
Smoking	0.370	0.151–0.906	0.030	2.275	0.815–6.344	0.116	1.154	0.647–2.058	0.628
Alcohol consumption	0.263	0.061–1.138	0.074	1.290	0.280–5.935	0.744	0.733	0.331–1.623	0.444
Antiplatelet therapy	0.175	0.023–1.332	0.092	3.129	0.825–11.868	0.093	1.163	0.467–2.893	0.746
Anticoagulation therapy	0.888	0.098–8.087	0.916	4.013	0.434–38.747	0.218	0.623	0.103–3.783	0.607
Clinical/radiographic status on admission									
SBP	1.003	0.993–1.013	0.589	1.008	0.981–1.024	0.360	1.007	0.999–1.015	0.106
DBP	1.001	0.983–1.020	0.904	1.011	0.980–1.044	0.486	1.004	0.990–1.019	0.564
GCS score	0.680	0.614–0.754	< 0.001	0.682	0.597–0.779	< 0.001	0.526	0.434–0.638	< 0.001
Time to the baseline NCCT	0.999	0.998–1.001	0.527	0.996	0.993–1.000	0.079	0.999	0.998–1.000	0.091
Hematoma location									
Deep	0.614	0.343–1.096	0.099	0.598	0.224–1.598	0.305	1.562	0.942–2.590	0.084
Lobar	0.704	0.344–1.442	0.337	3.316	1.251–8.794	0.016	0.594	0.338–1.042	0.069
Infratentorial	2.696	1.098–6.621	0.030	0.734	0.093–5.788	0.769	0.938	0.394–2.233	0.884
IVH	2.602	1.473–4.597	0.001	4.280	1.061–11.443	0.004	2.249	1.340–3.773	0.002
Hematoma volume	1.063	1.045–1.081	< 0.001	1.045	1.029–1.061	< 0.001	1.100	1.072–1.129	< 0.001
Laboratory testing									
WBC	1.420	1.286–1.567	< 0.001	1.224	1.114–1.344	< 0.001	1.376	1.256–1.507	< 0.001
Neutrophils (%)	1.222	1.158–1.288	< 0.001	1.158	1.076–1.246	< 0.001	1.091	1.062–1.120	< 0.001
Lymphocytes (%)	0.780	0.727–0.836	< 0.001	0.785	0.694–0.887	< 0.001	0.867	0.835–0.900	< 0.001
Monocytes (%)	0.700	0.612–0.801	< 0.001	0.917	0.750–1.122	0.402	0.854	0.773–0.945	0.002
Platelets	0.996	0.991–1.000	0.068	0.997	0.989–1.004	0.375	0.997	0.994–1.001	0.121
NLR	1.210	1.146–1.277	< 0.001	1.071	1.029–1.114	0.001	1.263	1.178–1.355	< 0.001
PLR	1.005	1.003–1.008	< 0.001	1.003	1.000–1.007	0.079	1.006	1.003–1.009	< 0.001
MLR	2.829	1.524–5.250	0.001	2.588	1.341–4.996	0.005	12.267	4.938–30.474	< 0.001
SII	1.001	1.001–1.001	< 0.001	1.000	1.000–1.001	0.001	1.001	1.001–1.001	< 0.001
LDH	1.010	1.006–1.015	< 0.001	1.013	1.007–1.020	< 0.001	1.020	1.014–1.026	< 0.001
CRP	1.015	1.009–1.021	< 0.001	1.017	1.010–1.024	< 0.001	1.032	1.020–1.044	< 0.001
INR	5.858	0.792–43.306	0.083	13.323	1.502–118.187	0.020	16.300	1.132–234.663	0.040
APTT	1.000	0.956–1.046	0.999	1.073	1.005–1.145	0.034	1.012	0.975–1.051	0.525
PT	1.190	1.000–1.416	0.049	1.331	1.073–1.650	0.009	1.249	1.023–1.525	0.029
Inflammatory Score	2.574	1.979–3.348	< 0.001	4.465	2.235–8.918	< 0.001	3.180	2.474–4.088	< 0.001
Multivariate analysis									
Age	0.962	0.930–0.996	0.029	1.018	0.953–1.087	0.595	1.004	0.979–1.031	0.744
Smoking	0.041	0.004–0.457	0.009	-	-	-	-	-	-
GCS score	1.066	0.862–1.317	0.557	0.928	0.707–1.216	0.587	0.836	0.675–1.037	0.104
Lobar	-	-	-	1.817	0.224–14.769	0.576	-	-	-
Infratentorial hematoma	12.786	1.165–140.347	0.037	-	-	-	0.392	0.090–1.706	0.212
IVH	4.444	1.068–18.490	0.040	19.728	2.772–140.378	0.003	2.420	1.129–5.187	0.023
Hematoma volume	1.041	1.019–1.064	< 0.001	1.051	1.024–1.079	< 0.001	1.064	1.028–1.101	< 0.001
WBC	1.042	0.881–1.233	0.893	1.172	0.965–1.422	0.109	1.021	0.895–1.1656	0.754
Neutrophils (%)	1.092	0.972–1.226	0.140	1.026	0.868–1.212	0.765	0.977	0.948–1.007	0.136
Lymphocytes (%)	1.036	0.716–1.500	0.851	1.117	0.737–1.693	0.601	1.009	0.947–1.075	0.779
Monocytes (%)	1.162	0.758–1.781	0.490	-	-	-	0.942	0.801–1.109	0.473
INR	-	-	-	0.982	0.013–77.043	0.993	0.908	0.084–9.856	0.937
APTT	-	-	-	1.160	1.027–1.312	0.017	-	-	-
PT	1.126	0.883–1.435	0.339		Removed			Removed	
Inflammatory score	1.949	1.199–3.167	0.007	3.254	1.236–8.569	0.017	2.190	1.642–2.922	< 0.001

APTT, activated partial thromboplastin time; CI, confidence interval; CRP, C-reactive protein; DBP, diastolic blood pressure; GCS, Glasgow coma scale; INR, international normalized ratio; IVH, intraventricular hemorrhage; LDH, lactate dehydrogenase; MLR, monocyte-to-lymphocyte ratio; mRS, modified Rankin Scale; NCCT, noncontrast computed tomography; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PT, prothrombin time; SBP, systolic blood pressure; SII, systemic immune-inflammation index; WBC, white blood cells.

exacerbation of the inflammatory process[12,39]. Thus, high levels of platelets may reflect the aggravation of inflammatory response, which may have a greater impact on hematoma expansion. Therefore, the above-mentioned hematocytes in peripheral blood can to a great extent reflect the changes in the brain tissues. Considering single hematocyte may be affected by multiple factors, the appropriate combinations such as NLR, PLR, MLR, and SII not only reflect the changes of more than one hematocyte but

also prevent the influence of other factors, for example, exercise and dehydration[40]. LDH has been regarded as a crucial inflammatory biomarker and is also associated with vascular endothelial damage and angiogenesis[15]. Plasma CRP is likely to reflect evolving proinflammatory processes both in the brain after ICH and systemically. Besides, CRP can directly lead to BBB disruption and formation of brain edema[41], which is a promoter of hematoma expansion[42]. From this it appears that the components of our inflammatory score may elicit other effects beyond the predominant inflammatory mechanism to influence hematoma expansion and prognosis of ICH, which further enhances the accuracy and adequate of the score.

There have been multiple score systems for predicting hematoma expansion and (or) unfavorable outcomes comprising several parameters that fall into one or more of the three categories: clinical features, laboratory parameters and neuroradiological criteria. Morotti and colleagues created a five-point score called BAT score using NCCT features including one point for blend sign, two points for any hypodensity, and two points for timing of NCCT less than 2.5 hours. This score was able to predict hematoma expansion with the AUC of 0.77[43]. Another novel score was max-ICH score (0–10), which integrates National Institute of Health Stroke Scale (NIHSS) score, age, IVH, anticoagulation, and ICH volume (lobar and nonlobar). This score combining clinical and radiological features could predict 12-month functional outcome with the AUC of 0.81[44]. The two scores both include radiological findings. In comparison, the parameters from laboratory tests are relatively objective and easy to identify, thus increasing the accuracy of the score. It was also established an abnormal physiological score containing systolic blood pressure increase, serum glucose, body temperature, and warfarin use, which was independently associated with poor outcomes at 90 days after ICH[45]. Different from our score system, this score combined both clinical and laboratory parameters and only performed regression analysis rather than ROC analysis. Meanwhile, this study excluded ICH patients with a poor prognosis or large hematoma volume and lack further validation. Yang *et al*.[46] established F-NLR score with the combination of plasma fibrinogen and NLR, which could predict poor prognosis after ICH. Nevertheless, this score also depended on the cutoff values from a single center and the AUCs of 1-month mortality and 3-month poor outcome were both lower than the inflammatory score (0.809 vs. 0.883; 0.699 vs. 0.857). The inflammatory score that reflects the importance of inflammatory response in ICH consists of appropriate integration of blood inflammatory indicators. The laboratory tests only include three items: blood routine, myocardial enzymes, and CRP, which are easily detectable in almost every emergency room and ward with low costs and the results are rapidly available. Besides, previous scores generally predict either hematoma expansion or outcomes of ICH, while our inflammatory score is able to predict both. Especially, both of the short-term and long-term functional outcomes are involved. In brief, the aforementioned advantages enhance the clinical application value of inflammatory score. The inflammatory score may be regarded as an inclusion criterion of the trials to evaluate the effects of medical and surgical treatment after ICH. For example, further studies may investigate whether ICH patients with inflammatory score greater than or equal to 5 benefit from minimally invasive surgery.

Several limitations of this study should be considered when interpreting the results. The sample size was relatively small and only Chinese patients were included, which may cause sample selection bias and limit the generalizability of the findings in other cohorts. In order to address this issue, further study of global multicenter with large sample size should be performed. Moreover, prolonging follow-up time for 1 year or more may provide a comprehensive evaluation of the outcomes. Furthermore, in our study, we only recorded the inflammatory indicators within 24 hours after ICH rather than the changes of inflammatory score, which may also predict the outcomes. Besides, admission NIHSS score was not used to measure ICH severity. In addition, neuroinflammation is associated with the development of perihematomal edema which was not measured in the current study. Whether inflammatory score is able to predict perihematomal edema is an interesting topic for further investigation.

Conclusions

The current study suggests inflammatory score consisting of appropriate integration of NLR, PLR, MLR, SII, LDH, and CRP is independently associated with hematoma expansion and poor outcomes of different terms in ICH patients, including secondary neurological deterioration within 48 hours, 30-day mortality, and 3-month poor mRS. Moreover, inflammatory score greater than or equal to 5 is validated as an appropriate predictor of hematoma expansion and poor outcomes with good accuracies.

Ethical approval

This study was approved by and studied in accordance with the ethical standards of the Fudan University Ethics Committee.

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Author contribution

H.C. and C.H.: study design, data collection and analysis and drafting of the manuscript. Z.Z.: data analysis. Y.T., Q.D., and Q.G.: conception and design, acquisition of clinical data, revision and approval of the manuscript.

Conflicts of interest disclosure

None.

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Data statement

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

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