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Integration of Hematoma Volume and Density Heterogeneity via the Harmonic Mean Is Associated With Improved Early Prediction of Hematoma Progression in Frontal Lobe Contusion: A Multicenter Retrospective Cohort Study

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Objective: Early hematoma progression (HPC) following frontal lobe contusion (FCL) is closely associated with secondary neurological deterioration and unfavorable outcomes. This study aimed to develop a quantitative noncontrast CT-based composite imaging marker—the volume-density integration index (VDII) ,constructed using the harmonic mean of baseline contusion volume and density coefficient of variation—and to evaluate its association with early HPC and incremental predictive value, as well as its incremental contribution beyond traditional imaging parameters.

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Methods: This multicenter retrospective cohort study included a development cohort of 341 patients with FCL from the General Hospital of Ningxia Medical University and an external validation cohort of 273 patients with FCL from The Second Affiliated Hospital, Hengyang Medical School, University of South China. Baseline hematoma volume (V) and density coefficient of variation (DCV) were extracted using 3D Slicer. VDII was constructed as the harmonic mean of V and DCV. Four logistic regression models were developed: VDII-only; a raw component model (Model 1: volume + DCV + clinical laboratory variables); an integrated model (Model 2: VDII replacing volume and DCV while retaining other variables); and an extended model (Model 3: Model 2 + blood glucose + albumin). Model performance was assessed using the area under the receiver operating characteristic curve (AUC), calibration, Brier score, decision curve analysis (DCA), and bootstrap internal validation.

Results: HPC occurred in 29.0% (training set), 28.3% (test set) and 21.0% (external set). In the testing set, VDII-only showed higher discrimination than volume-only (AUC 0.745 vs. 0.514, $P < 0.001$) and DCV-only (AUC 0.745 vs. 0.659, $P = 0.002$). In external validation, Model 2 achieved an AUC of 0.763 (95% CI: 0.698–0.824), compared with 0.699 (95% CI: 0.627–0.769) for Model 1; this difference was statistically significant after Bonferroni correction for multiple pairwise comparisons ($P < 0.001$). Model 3 did not significantly improve discrimination compared with Model 2 (AUC 0.758 vs. 0.763, $P = 0.649$). In multivariable analysis, lower standardized VDII was independently associated with higher risk of HPC (odds ratio [OR] 0.425, 95% confidence interval [CI]: 0.269–0.671, $P < 0.001$). Restricted cubic spline analysis suggested a nonlinear association between VDII and HPC risk (P for nonlinearity = 0.0007). Subgroup analysis showed that VDII had stronger predictive value in small-volume lesions (P for interaction = 0.005).

Conclusion: VDII, a harmonic mean-based imaging composite marker integrating hematoma volume and density heterogeneity, was associated with early HPC in patients with FCL and showed better discrimination than volume or DCV alone in the testing set. Replacing raw volume and DCV with VDII improved external discrimination compared with the raw component model in this retrospective cohort, whereas adding blood glucose and albumin did not provide a significant incremental benefit. These findings suggest that VDII may help early risk stratification, particularly in patients with small initial contusions; however, prospective validation and automated measurement workflows are needed before routine clinical implementation.

Keywords: frontal lobe contusion; hematoma progression; volume-density integration index; baseline hematoma volume; harmonic mean

1.Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. Its secondary injury process is complex and has significant dynamic changes [1]. Frontal lobe contusion (FCL) is a common and highly heterogeneous lesion type in TBI [2,3]. Because the bottom of the FCL is adjacent to bony raised structures such as the base of the anterior cranial fossa and the cribriform plate, when deceleration injury occurs, the brain tissue swings violently in the skull, and the micro-penetrating blood vessels are easily ruptured and bled by shear force; Even if initial non-enhanced CT (NCCT) shows only small hemorrhagic foci without obvious imaging abnormalities, 40%-50% of lobe contusion lesions still showed significant volume increase early after injury, that is, hematoma progression (HPC)[2-4], this process is closely related to secondary neurological deterioration, elevated intracranial pressure, increased need for emergency surgery and poor prognosis[4-7]. Therefore, how to identify high-risk individuals early in patient admission is of great clinical significance.

In traditional clinical practice, the assessment of the risk of FCL progression relies mostly on the clinical experience of neurosurgeons. However, the pathological background of FCL is complex, and the lesions often show "pepper salt"-like changes with irregular margins, multiple spotting hemorrhages and brain edema adjacent to the lobe contusion. This morphological complexity leads to significant heterogeneity in the interpretation of the above qualitative signs by different observers, and the Kappa consistency evaluation is generally at a low level [8,9].

In response to the problem of quantitative assessment of hematoma heterogeneity, some teams used the density coefficient of variation (DCV) of NCCT hematoma density as a quantitative indicator to assess internal heterogeneity of hematoma, and showed good effectiveness in predicting spontaneous cerebral hemorrhage expansion [10,11]. However, the relative indicator of DCV alone ignores the absolute physical size of the lesion; on the other hand, although the initial hematoma volume can reflect the spatial load, it cannot describe whether the interior is in active bleeding or unstable state. Neither the two dimensions of volume and heterogeneity alone are sufficient to fully characterize the risk of early progression of FCL, and there is an urgent need to integrate them into

a single quantitative indicator. Existing predictive models for traumatic hematoma expansion either rely on qualitative CT signs with poor inter-observer agreement or use volume or density heterogeneity alone, but no study has integrated these two dimensions into a single mathematically principled index specifically for FCL.

Based on the above background, this study proposes a new quantitative imaging indicator based on NCCT, the volume-density integration index (VDII), which uses a harmonic average formula to integrate baseline hematoma volume with DCV. Compared to simple additions or products, harmonic averaging has a unique advantage: it is more sensitive to smaller values, that is, when either dimension in volume or DCV is at a low level, VDII as a whole is significantly suppressed. This characteristic is highly consistent with the pathophysiology of FCL, that is, only when the lesion has a certain spatial scale and obvious internal heterogeneity are it more likely to be in a persistent active bleeding stage; while "large but uniform density" or "strong heterogeneity but small" lesions have relatively limited actual risk of progression. Therefore, whether VDII constructed based on the harmonic average formula can identify lesions at high risk of progression, providing a new assessment tool for early clinical risk stratification.

2. Method

2.1 Research design and ethics

This study adopted a **multicenter** retrospective cohort design **and is reported in accordance with the TRIPOD statement, with reference to the updated TRIPOD+AI recommendations to improve the transparency, completeness, and reproducibility of clinical prediction model research**[16]. The study followed the Declaration of Helsinki and was approved by the Ethics Committee of the General Hospital of Ningxia Medical University, Yinchuan, Ningxia, China (KYLL-2025-2410). The Second Affiliated Hospital, Hengyang Medical School, University of South China, Hengyang, China served as a participating external validation center. According to the local institutional procedure for multicenter retrospective studies, the external validation center did not perform a duplicate full ethics review but completed a simplified institutional confirmation procedure to assess local feasibility and compliance. The center formally acknowledged and relied on the ethics approval granted by the leading institution and confirmed the use of anonymized retrospective data from its site for this study. Written informed consent was obtained when required. For retrospective cases for which individual consent could not be obtained, the requirement for informed consent was waived according to the relevant ethics approval and local institutional procedure. All data were anonymized before analysis.

2.2 research object

The development cohort consecutively included FCL patients at Ningxia Medical University General Hospital (August 2020 to October 2025), and the external verification cohort continuously

included FCL patients at the Second Affiliated Hospital of South China University (January 2020 to December 2025). Inclusion criteria: (1) Emergency NCCT confirmed FCL;(2) The first NCCT was completed within 6 hours after the injury, and the follow-up NCCT was completed within 72 hours;(3) Glasgow Coma Scale (GCS) score ≥ 9 at admission;(4) Complete quantitative image analysis and clinical data were available. Exclusion criteria: (1) Patients undergoing emergency surgery immediately after admission;(2) GCS <9 ;(3) Patients with missing imaging or clinical data and unable to complete the analysis.

According to the events per variable (EPV) principle proposed by Riley et al.[17], a logistic regression model incorporating 8 predictive variables requires a minimum number of events of approximately $8 \times 10 / \text{event rate}$. The incidence of HPC in the development cohort is about 29%, so the minimum requirement is about 276 cases ($8 \times 10 / 0.29 \approx 276$). A total of 341 patients were included in the development cohort of this study, including 99 cases of HPC events, meeting the modeling requirements.

The development cohort was randomly divided into a training set (n=256) and a testing set (n=85) on a 75%:25% basis; the external verification cohort (n=273) was used for independent verification. See Figure 1 for patient inclusion process.

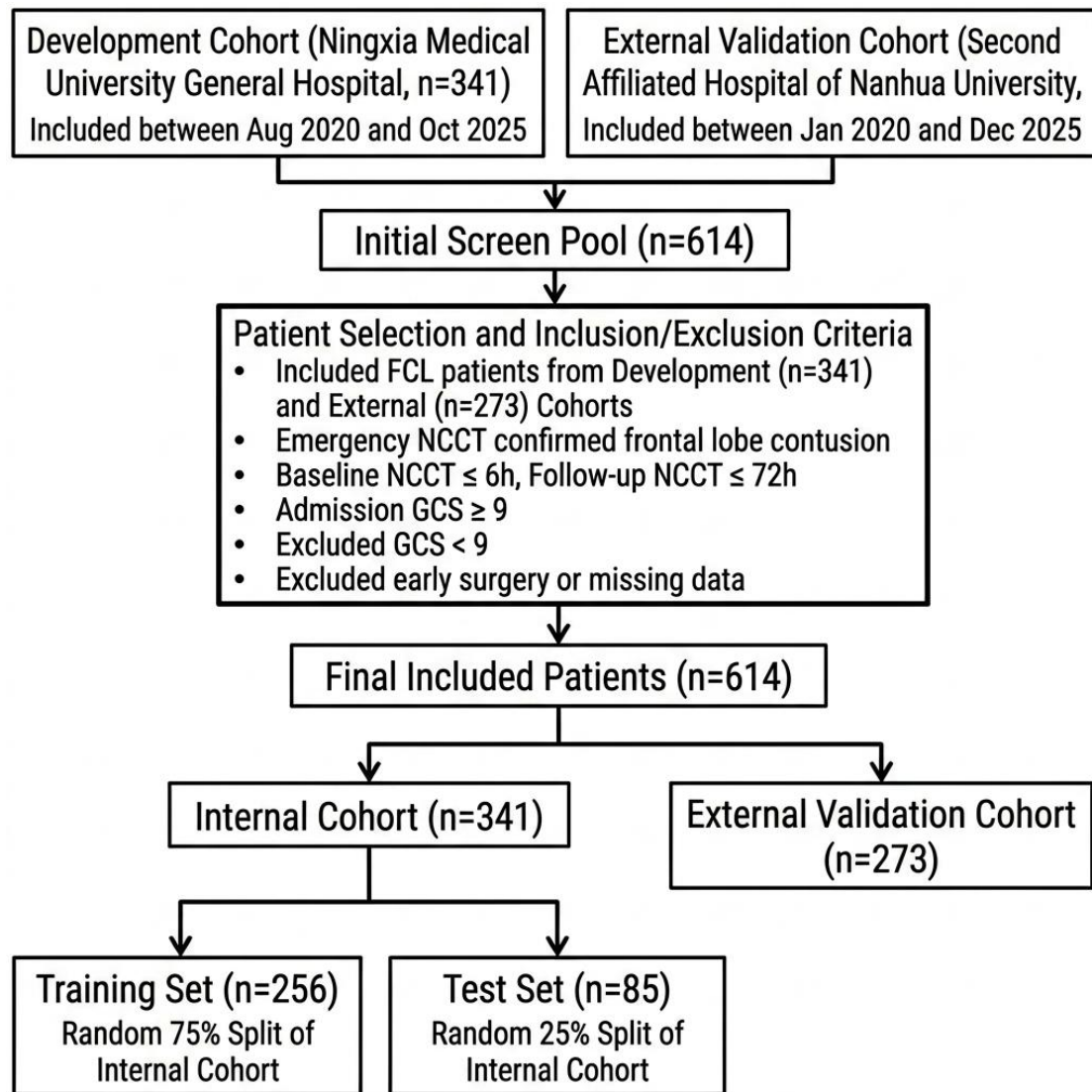


Figure 1 Flow chart of inclusion of study subjects

2.3 data collection

Clinical data were derived from a retrospective cohort database and included demographic characteristics (gender and age, etc.), medical history (hypertension, diabetes, coronary heart disease, etc.), baseline neurological score (GCS score), radiological characteristics (baseline hematoma volume, hematoma density standard deviation, DCV, etc.). Laboratory tests include hematology (sodium, potassium, glucose levels at admission; white blood cell, neutrophil, lymphocyte and platelet counts, D-dimer, etc.).

Derived indices: systemic inflammation response index (SIRI) = neutrophils $\times$ monocytes / lymphocytes; lymphocyte-to-monocyte ratio (LMR) = lymphocytes / monocytes.

2.4 Definition and measurement of baseline hematoma volume and density

All patients underwent routine NCCT scanning (GE *-slice spiral CT) upon admission. In order

to ensure the accuracy of quantitative analysis, all original DICOM images were imported into the 3DSlicer open source platform (version 5.8.1, www.slicer.org, Harvard University, USA) for three-dimensional segmentation. Two neurosurgeons with more than 5 years of clinical experience used the "SegmentEditor" module and set a threshold range (50–100 Hounsfield units [HU]) to initially define the hematoma area without knowing the patient's clinical outcome [18, 19]. Subsequently, manual delineation layer by layer combined with algorithm correction was used to remove adjacent bones and normal high-density tissues to obtain the three-dimensional region of interest (ROI) of the hematoma. The "LabelStatistics" module is used to automatically calculate the baseline contusion volume (V), CT mean (Mean) and density standard deviation (SD). The entire process took about 3 minutes on average, and there was good inter-observer agreement (intraclass correlation coefficient [ICC]=0.89).

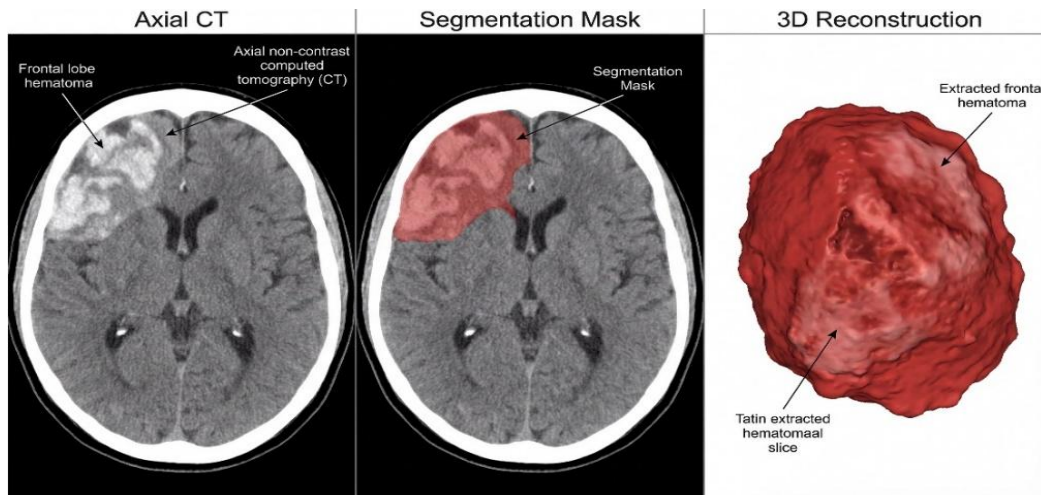


Figure 2. 3D Slicer segmentation illustration.

2.5 Construction of VDII

Referring to previous studies, the density coefficient of variation (DCV) is used to express the heterogeneity of hematoma density [10, 11, 20] and is defined as: $DCV = SD / Mean$.

SD is the standard deviation of CT values of hematoma area, Mean is the mean of CT values of hematoma area.

To balance the contributions of lesion volume and density heterogeneity, we introduced the volume-density integration index (VDII): $VDII = 2 / [(1 / V) + (1 / DCV)]$.

where V represents baseline contusion volume and DCV represents the density coefficient of variation. Because the harmonic mean is influenced by the smaller of the two components, VDII reflects the joint configuration of lesion size and density heterogeneity rather than either component alone. In the present cohort, lower standardized VDII values were associated with higher odds of

HPC. Therefore, the direction of association should be interpreted empirically within the context of the present outcome definition, which was based on relative volume increase. For regression modeling, VDII was standardized using the mean and standard deviation of the training set. **2.6**

outcome was defined

The primary outcome was HPC, defined as a $\geq 25\%$ increase in hematoma volume from baseline on NCCT performed within 72 hours after injury.

2.7 Model building strategies

To compare the discriminative power of VDII with its individual components, we constructed single-indicator models containing only V, only DCV, and only VDII, and compared their AUCs. Based on clinical interpretability and previous analysis results, the following 4 models were constructed:

(1) VDII-only: standardized VDII alone.

(2) Model 1 (raw component model): hematoma density SD, DCV, baseline contusion volume, SIRI, LMR, GCS, eosinophil count, age.

(3) Model 2 (VDII integrated model): same clinical variables as Model 1, but DCV and baseline volume replaced by standardized VDII.

(4) Model 3 (extended model): Model 2 + blood glucose + albumin.

2.8 statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median (quartiles) depending on distribution, and categorical variables are expressed as frequencies and percentages. Inter-group comparisons were performed using independent sample t-test, Mann-Whitney U test, χ^2 test or Fisher's exact probability method.

Candidate variables are first screened using Least Absolute Shrinkage and Selection Operator (LASSO) regression combined with 10-fold cross-verification, followed by variable importance verification using the Boruta algorithm. Only the variables screened jointly by the two methods are retained for final modeling. Multivariate logistic regression was used to build a predictive model, report the odds ratio (OR) and its 95% confidence interval (95% CI), and use variance inflation factor (VIF) to assess multicollinearity.

The discriminative power of the model was evaluated using the AUC, and the 95% CI was calculated using the bootstrap method. The DeLong test was used to compare AUC between models.

Since a total of 6 pairs of pairwise comparisons were performed among the 4 models, the Bonferroni correction significance threshold was set at $P < 0.0083$. Model calibration capabilities were evaluated using the Hosmer-Lemeshow test, Brier score, calibration curves, and calibration intercept and calibration slope in external verification. Clinical application value was assessed using decision curve analysis (DCA). Model improvement was further quantified using integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI).

A restricted cubic spline (RCS) was used to assess the nonlinear relationship between VDII and HPC risk, setting 4 nodes (located at the 5th, 35th, 65th, and 95th percentile), and adjusting age, GCS score, hematoma density SD, SIRS, LMR, and eosinophil count based on previous literature, clinical experience, and variable screening results of this study. The robustness of the results was tested through bootstrap internal verification, integrated discrimination improvement (IDI), and complete-case sensitivity analysis. Calibration was assessed using the Brier score, calibration intercept, and calibration slope; the Hosmer-Lemeshow test was also reported but interpreted with caution due to its sample size dependence. All statistical analyses were completed in R software (version 4.5.1). Except for Bonferroni's correction for pairwise comparisons, all analyses showed a two-sided $P < 0.05$ as a statistical difference.

3. results

3.1 Subjects and Baseline Characteristics

A total of 341 patients with FCL were included in the development cohort and randomly divided into a training set ($n=256$) and a test set ($n=85$) on a 75%:25% ratio. The external validation cohort included 273 patients. The incidence rates of HPC in training set, test set, and external verification cohort were 29.0%, 28.3%, and 21.0%, respectively. See Figure 1 for the inclusion process of study subjects, and see Table 1 for baseline characteristics of the training and testing sets are shown in Supplementary Table S1. The distribution of VDII by HPC status is illustrated in Supplementary Figure S1.

Compared with the development cohort, patients in the external validation cohort were older (59.6 ± 14.8 years vs. 50.7 ± 15.8 years, $P < 0.001$), had a lower GCS (12.95 ± 2.30 vs. 13.76 ± 1.87 , $P < 0.001$), and had a higher raw VDII (0.40 ± 0.03 vs. 0.37 ± 0.04 , $P < 0.001$). These differences indicate population heterogeneity between the two centers, providing a basis for evaluating the generalizability of the model.

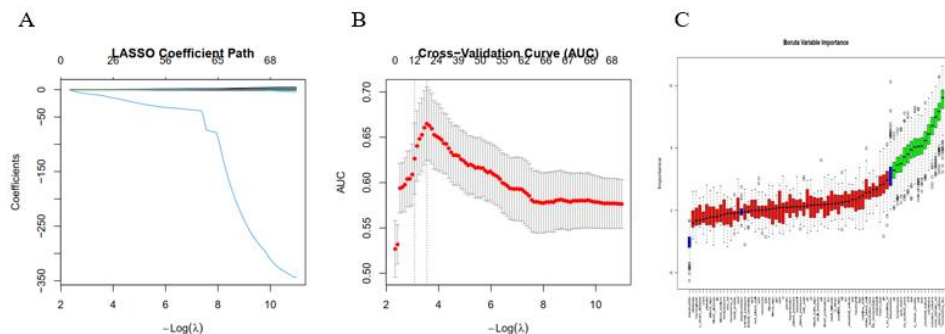
Table 1. Baseline characteristics of the development and external validation cohorts

Variable	Overall	Development	External	p
n	614	341	273	
age (mean (SD))	54.67 (16.01)	50.71 (15.84)	59.62 (14.82)	<0.001
GCS score (mean (SD))	13.40 (2.11)	13.76 (1.87)	12.95 (2.30)	<0.001
baseline contusion volume (mean (SD))	12.46 (10.54)	11.83 (12.42)	13.26 (7.50)	0.094
hematoma DCV (mean (SD))	0.20 (0.02)	0.19 (0.02)	0.20 (0.02)	<0.001
hematoma density SD (mean (SD))	13.11 (1.59)	12.88 (1.73)	13.39 (1.35)	<0.001
raw VDII (mean (SD))	0.38 (0.04)	0.37 (0.04)	0.40 (0.03)	<0.001
blood glucose (mean (SD))	8.05 (2.56)	8.02 (2.76)	8.08 (2.30)	0.779
albumin (mean (SD))	41.07 (4.48)	41.04 (4.93)	41.11 (3.85)	0.848
SIRI (mean (SD))	41.89 (44.39)	67.10 (44.56)	10.40 (12.90)	<0.001
LMR (mean (SD))	2.11 (2.68)	1.98 (1.88)	2.29 (3.43)	0.157
eosinophil count (mean (SD))	0.16 (0.48)	0.26 (0.63)	0.03 (0.05)	<0.001

3.2 Feature screening and model construction

LASSO regression combined with 10-fold cross-validation was used for preliminary variable screening, and Boruta algorithm was used to further verify the importance of variables. In the end, the two methods retained a total of 8 core characteristics, including GCS score, SIRI, LMR, eosinophil count, age, hematoma density SD, baseline contusion volume and hematoma DCV(Figure 3). Based on this, the original component model (Model1) was constructed.

Based on this, the standardized VDII was used instead of the baseline contusion volume and hematoma DCV to construct the VDII integrated model (Model 2); further, blood glucose and albumin were included to build the extended model (Model 3). Additionally, to evaluate the discriminative ability of VDII itself, a single-index model (VDII-only) that only included the standardized VDII was established. Full LASSO coefficients for all candidate variables are provided in Supplementary Table S2.

**Figure 3. Feature Screening Results**

(A).LASSO regression coefficient road map;(B). 10-fold cross verification to determine the

optimal λ value;(C). Importance analysis of Boruta characteristics

3.3 Model discriminant performance and external verification

In the training set, the AUC values for VDII-only, Model 1, Model 2, and Model 3 were 0.706 (95% CI 0.650–0.763), 0.710 (95% CI 0.645–0.765), 0.743 (95% CI 0.683–0.797), and 0.750 (95% CI 0.689–0.802), respectively. In the test set, the AUC values for the four models were 0.745 (95% CI 0.645–0.841), 0.711 (95% CI 0.608–0.807), 0.754 (95% CI 0.656–0.849), and 0.767 (95% CI 0.664–0.862), respectively. In the external validation cohort, the AUC values for VDII-only, Model 1, Model 2, and Model 3 were 0.785 (95% CI 0.720–0.846), 0.699 (95% CI 0.627–0.769), 0.763 (95% CI 0.698–0.824), and 0.758 (95% CI 0.695–0.821), respectively (Table 2, Figure 4).

Overall, replacing baseline contusion volume and DCV with VDII was associated with improved discrimination of Model 2 compared with Model 1 in the external validation cohort. Because six possible pairwise comparisons among the four models were planned, Bonferroni correction was applied and the adjusted significance threshold was set at $P \leq 0.0083$. In the testing set, none of the selected pairwise comparisons reached statistical significance after correction. In the external validation cohort, Model 2 significantly outperformed Model 1 ($P \leq 0.001$), and Model 3 also outperformed Model 1 ($P \leq 0.001$). However, Model 3 did not significantly improve upon Model 2 ($P = 0.649$). The difference between VDII-only and Model 1 was nominally significant ($P = 0.020$) but did not meet the Bonferroni-corrected threshold.

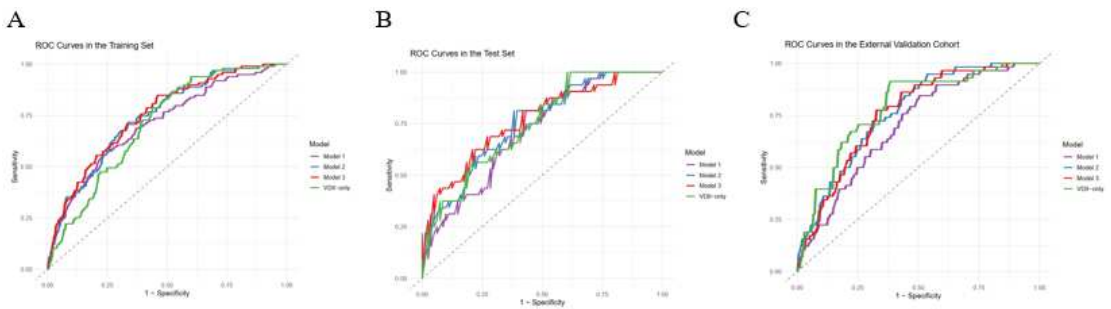


Figure 4. ROC curves of four models in different data sets
(A) Training set;(B) Test set;(C) External verification queue

Table 2. Discriminative performance of the four models in the training, testing, and external validation sets

Dataset	Model	AUC	95% CI
Training	VDII-only	0.706	[0.650, 0.763]
Training	Model 1	0.71	[0.645, 0.765]
Training	Model 2	0.743	[0.683, 0.797]
Training	Model 3	0.75	[0.689, 0.802]
Testing	VDII-only	0.745	[0.645, 0.841]
Testing	Model 1	0.711	[0.608, 0.807]

Testing	Model 2	0.754	[0.656, 0.849]
Testing	Model 3VDII-	0.767	[0.664, 0.862]
External validation	only	0.785	[0.720, 0.846]
External validation	Model 1	0.699	[0.627, 0.769]
External validation	Model 2	0.763	[0.698, 0.824]
External validation	Model 3	0.758	[0.698, 0.821]

Table 3. Pairwise DeLong comparisons among the four models in the testing set

Comparison	AUC_Difference	Z_Statistic	P_Value
Model 2 vs Model 1	0.043	1.182	0.237
Model 3 vs Model 2	0.012	0.77	0.441
Model 3 vs Model 1	0.055	1.352	0.176
VDII-only vs Model 1	0.034	0.636	0.525

Table 4. Pairwise DeLong comparisons among the four models in the external validation set

Comparison	AUC_Difference	Z_Statistic	P_Value
Model 2 vs Model 1	0.064	5.736	<0.001
Model 3 vs Model 2	-0.005	-0.455	0.649
Model 3 vs Model 1	0.06	3.999	<0.001
VDII-only vs Model 1	0.086	2.328	0.02

3.4 Single indicator comparison and incremental value analysis

To further evaluate the advantages of VDII over its constituent components, we compared the discriminative performance of the three indicators: baseline contusion volume, hematoma DCV, and VDII. In the test set, the AUCs of the three were 0.514 (95% CI 0.382–0.642), 0.659 (95% CI 0.537–0.766), and 0.745 (95% CI 0.643–0.836), respectively, suggesting that the discriminative ability of VDII was significantly superior to that of the individual volume or DCV (Table 5). Full details of single imaging marker performance are shown in Supplementary Table S11.

IDI analysis further supports the above results. In the test set and external verification queue, the IDI of Model2 compared to Model1 were 0.0366 and 0.0409, respectively, indicating that the overall discrimination of the model was improved by integrating the baseline contusion volume and the hematoma DCV into VDII. In contrast, Model 3 's external verification IDI compared to Model2 is only 0.0028, prompting limited additional gains from adding bloodglucose and albumin. Detailed IDI and NRI values are provided in Supplementary Table S7.

Table 5. Discriminative performance of single imaging indicators in the testing set

Model	AUC	CI_Lower	CI_Upper	95% CI
Volume-only	0.514	0.382	0.642	[0.382, 0.642]
DCV-only	0.659	0.537	0.766	[0.537, 0.766]
VDII-only	0.745	0.643	0.836	[0.643, 0.836]

3.5 Multivariable logistic regression

Multivariate logistic regression analysis showed that in Model 2, standardized VDII was independently associated with HPC (OR = 0.425, 95% CI 0.269–0.671, $P < 0.001$); in Model 3, this association remained stable (OR = 0.404, 95% CI 0.252–0.646, $P < 0.001$). Additionally, the GCS score was also independently associated with HPC in Model 2 and Model 3, with OR values of 0.791 (95% CI 0.692–0.903, $P < 0.001$) and 0.774 (95% CI 0.674–0.888, $P < 0.001$), respectively.

The effect direction of SIRI was consistent in both models, but neither reached statistical significance. There was no significant association between bloodglucose and albumin and HPC; at the same time, there was no significant improvement in the discriminatory performance of Model 3 compared with Model 2 (DeLong's test $P = 0.649$), suggesting that adding these two variables did not bring additional gains (Table 6, Figure 5). Variance inflation factors for Model 2 and Model 3 are provided in Supplementary Table S4.

Table 6. Multivariable logistic regression analyses for Model 2 and Model 3

Model	Variable	OR	Lower95	Upper95	P
Model 2	hematoma density SD	1.168	0.915	1.491	0.211
Model 2	SIRI	0.993	0.985	1	0.06
Model 2	LMR	0.995	0.842	1.177	0.956
Model 2	GCS score	0.791	0.692	0.903	0.001
Model 2	eosinophil count	1.408	0.913	2.171	0.121
Model 2	age	0.994	0.978	1.01	0.455
Model 2	standardized VDII	0.425	0.269	0.671	0.001
Model 3	hematoma density SD	1.22	0.948	1.568	0.122
Model 3	SIRI	0.992	0.984	1	0.055
Model 3	LMR	0.99	0.835	1.175	0.911
Model 3	GCS score	0.774	0.674	0.888	0.001
Model 3	eosinophil count	1.388	0.902	2.135	0.136
Model 3	age	0.996	0.978	1.013	0.614
Model 3	standardized VDII	0.404	0.252	0.646	0.0001
Model 3	blood glucose	1.028	0.935	1.13	0.568
Model 3	albumin	1.054	0.998	1.113	0.057

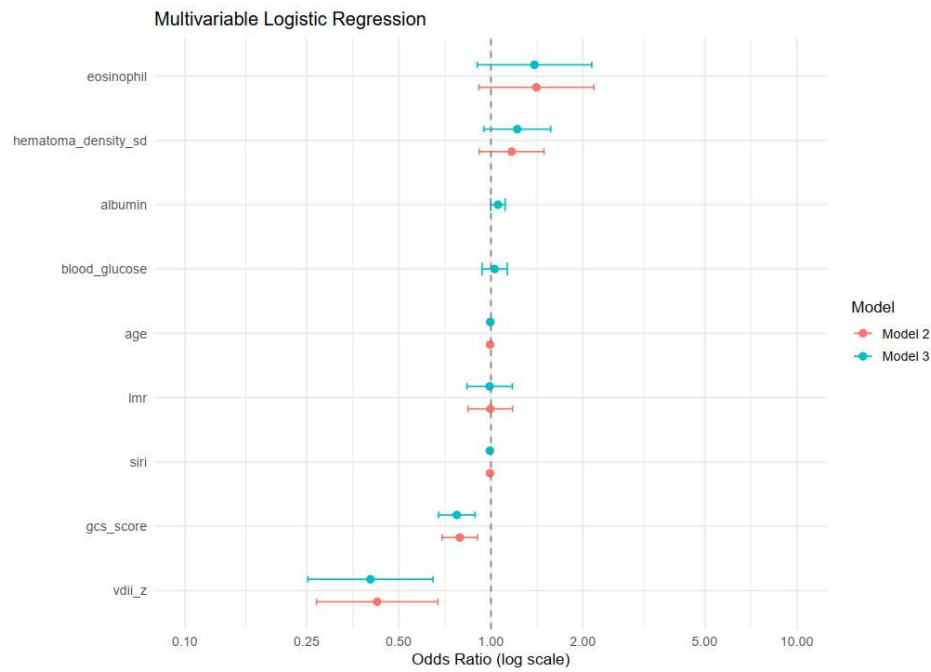


Figure 5. Forest plot of Model 2 and Model 3

3.6 multicollinearity analysis

Multicollinearity analysis showed that VIF values in Model 2 ranged from 1.11 to 3.10, and in Model 3 from 1.05 to 2.96, indicating no significant multicollinearity (Figure 6, Supplementary Table S4). The correlation matrix of all candidate predictors is shown in Supplementary Table S3.

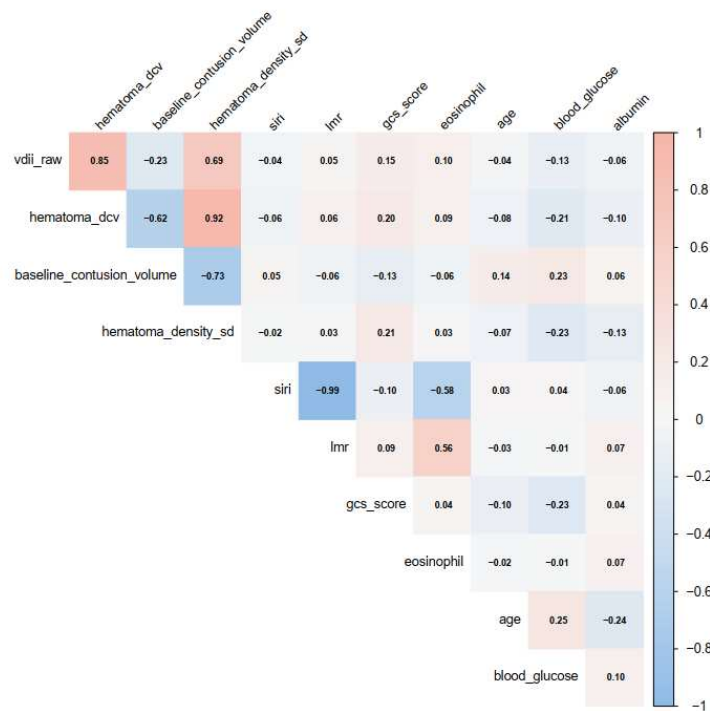


Figure 6. Heat map of correlations among predictors

3.7 Calibration and overall prediction performance

In the test set, the Brier scores for VDII-only, Model 1, Model 2, and Model 3 were 0.173,

0.180, 0.168, and 0.160 respectively. In the external validation cohort, the corresponding Brier scores were 0.145, 0.166, 0.149, and 0.152 respectively. Overall, the prediction error of Model 2 was lower than that of Model 1, and it performed better than Model 3 in the external validation.

The external calibration analysis revealed that the calibration intercept values for Model 1, Model 2, and Model 3 were -0.549, -0.421, and -0.465 respectively, and the corresponding calibration slopes were 0.915, 1.233, and 1.125 respectively. Considering the overall discriminative ability and calibration performance, Model 2 demonstrated a better balance between discrimination and calibration in the external validation (Figure 7). External calibration metrics and Hosmer-Lemeshow test results are summarized in Supplementary Tables S9 and S10. Calibration curves for Model 1, Model 3, and VDII-only are provided in Supplementary Figure S2.

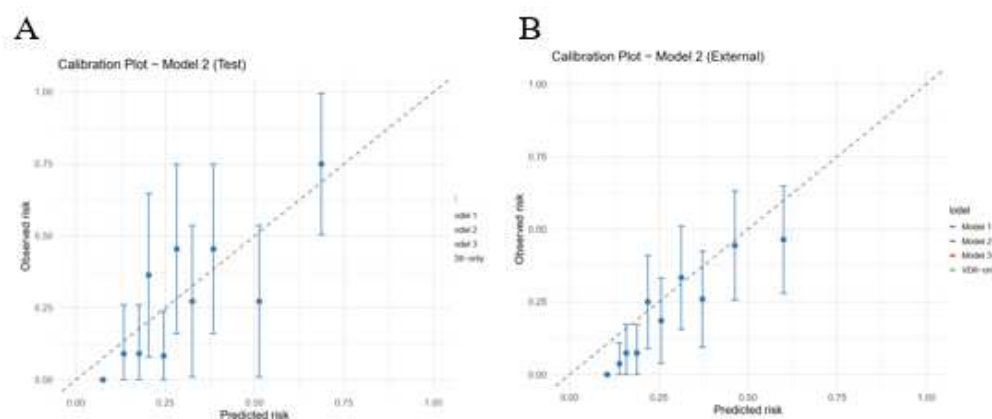


Figure 7. Model 2 calibration curve
(A) test set;(B) external verification queue

3.8 robustness analysis

The internal validation of Bootstrap shows that the optimism-corrected AUC for VDII-only, Model 1, Model 2, and Model 3 are 0.707, 0.679, 0.716, and 0.716 respectively (Supplementary Table S5). Although the apparent AUC of Model 3 is slightly higher than that of Model 2, after optimism correction, the performance of both is basically the same, and Model 2 still outperforms Model 1.

The results of the complete-case sensitivity analysis are highly consistent with the main analysis: the AUC for VDII-only, Model 1, Model 2, and Model 3 are 0.745, 0.711, 0.754, and 0.767 (Supplementary Table S6) respectively, supporting the robustness of the main results.

3.9 RCS analysis of VDII and HPC risk

Based on previous literature, clinical experience, and multivariate screening results of this study, age, GCS score, hematoma densitySD, SIRI, LMR and eosinophil count were selected as

potential confounding factors for adjustment. RCS analysis showed a significant nonlinear association between VDII and HPC risk (overall $P < 0.001$, nonlinear $P=0.0007$) (Figure 8). The overall trend shows that the HPC risk gradually decreases with the increase in VDII; in the lower VDII range, the risk decrease is more obvious, while in the higher VDII range, the curve tends to flatten out.

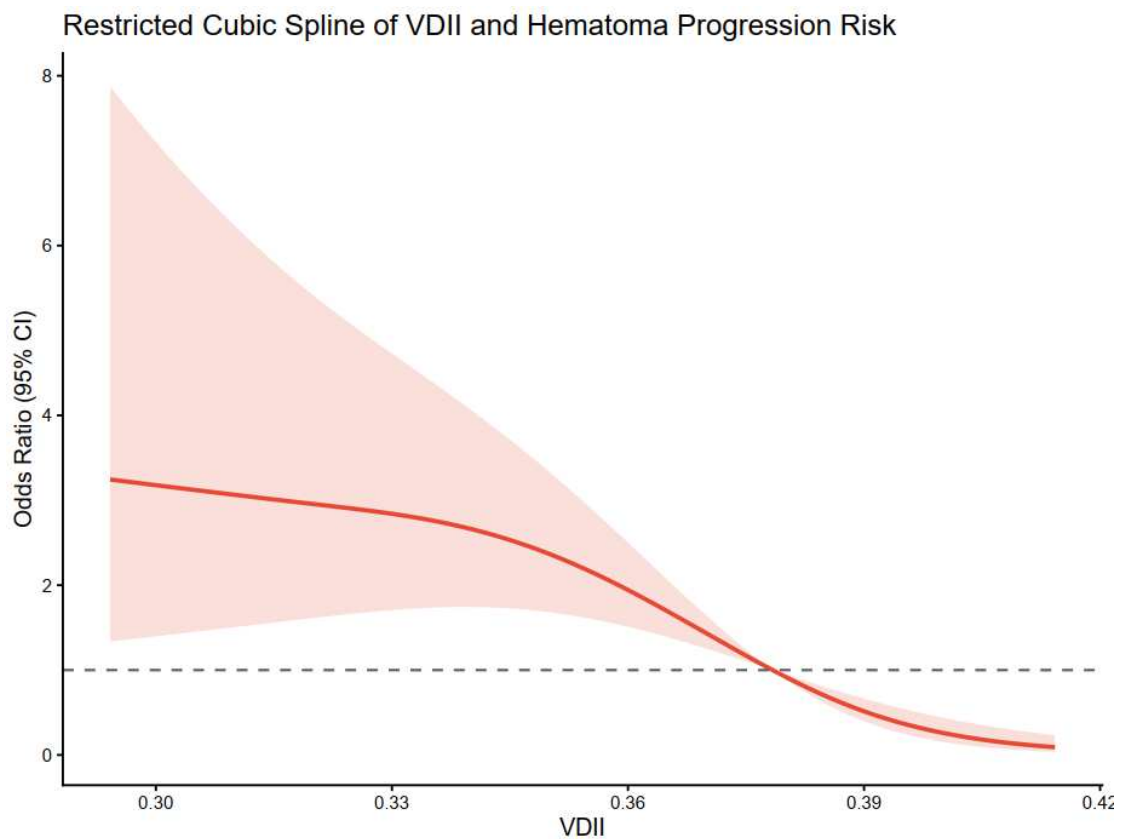


Figure 8. Restrictive cubic spline curve of VDII versus HPC risk

3.10 Clinical Decision Analysis

DCA shows (Figure 9) that within clinically relevant threshold probabilities, the VDII-based model generally has a higher net benefit than Model1. Especially in the external verification queue, the decision curve of Model2 is generally above that of Model1, while Model 3 does not show the additional advantage of being more stable than Model2.

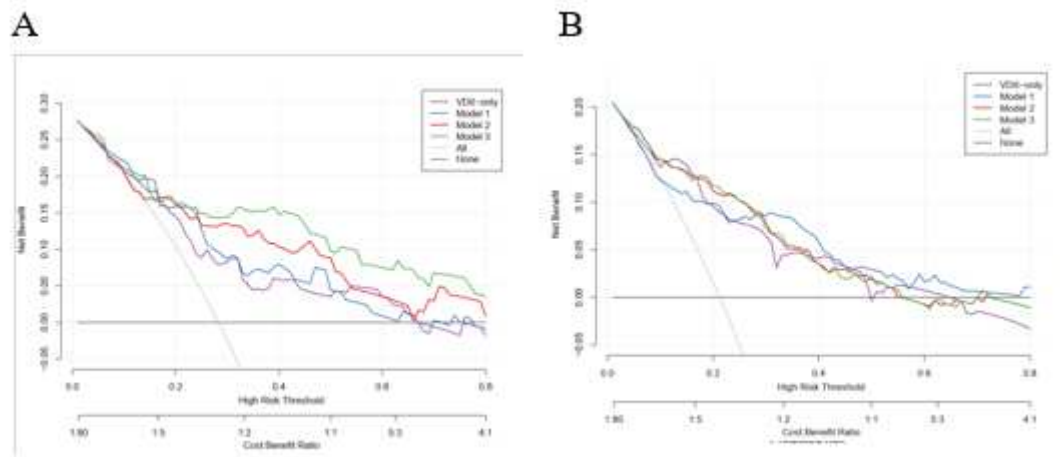


Figure 9. Decision curve analysis of four models
(A) test set; (B) external verification queue

3.11 subgroup analysis

Subgroup analysis showed that the overall direction of the association between VDII and HPC was consistent across subgroups of different age, GCS level and lesion volume, and no obvious opposite trend was observed. In the low hematoma volume subgroup, the predictive effect of VDII was stronger (OR = 0.26, 95% CI 0.16 - 0.44), while the effect was relatively weaker in the high volume subgroup (OR = 0.58, 95% CI 0.44 - 0.76), and the interaction $P = 0.005$ (Figure 10, Supplementary Table S8), suggesting that the risk stratification effect of VDII in small-volume lesions may be more obvious.

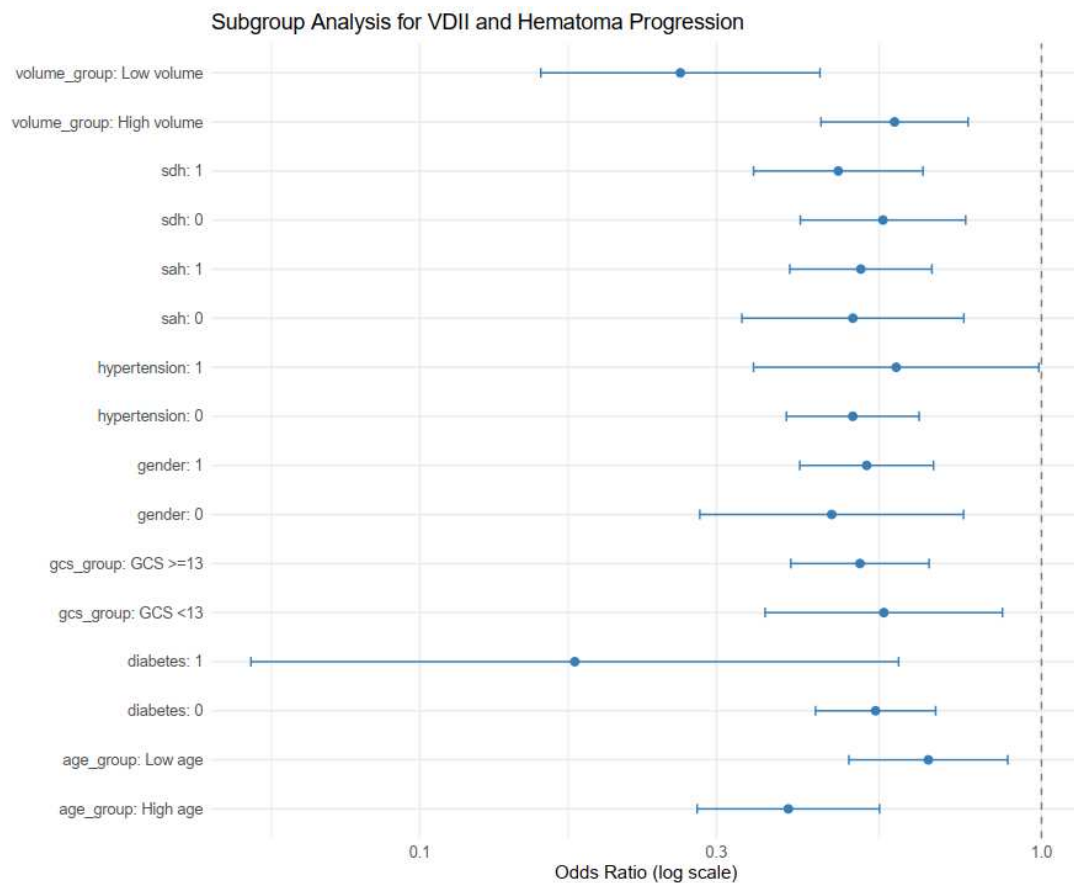


Figure 10. Forest plot of predicted effects of VDII in different subgroups

3.12 Norms and clinical applicability

Build a nomogram based on Model2 to achieve personalized risk prediction. The nomogram integrates GCS score, SIRS, LMR, eosinophil count, age, hematoma density SD, and VDII (Figure 11) to facilitate rapid risk stratification early in patient admission.

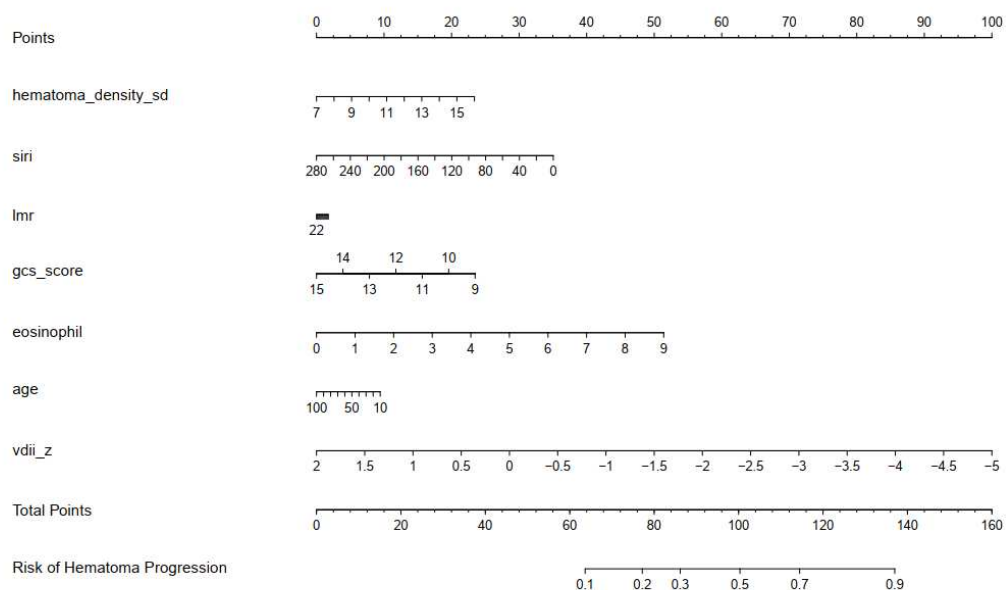


Figure 11. Nomogram built based on Model2

3.13 case show

Representative cases illustrating VDII-based risk stratification are shown in Figure 12.

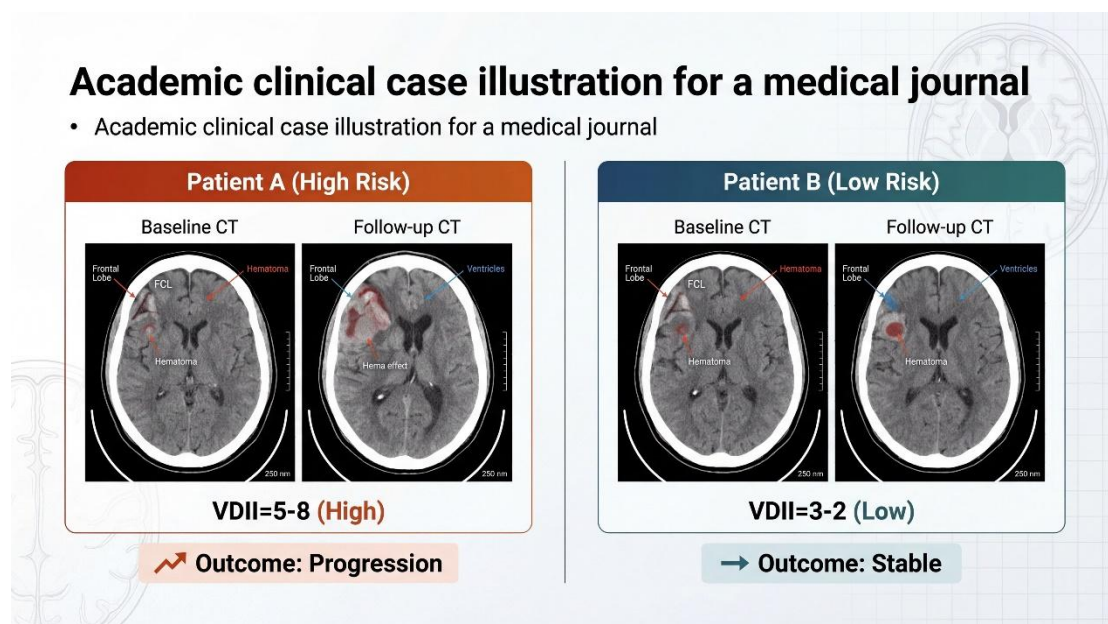


Figure 12. Representative case examples of VDII-based risk stratification.

4. discussion

In this multicenter retrospective cohort study of patients with FCL, we developed a harmonic mean-based composite imaging marker, VDII, to integrate baseline contusion volume and density heterogeneity. The main findings were as follows. First, VDII-only showed higher discrimination than volume-only or DCV-only in the testing set. Second, replacing raw volume and DCV with

VDII in a multivariable model improved discrimination in the external validation cohort compared with the raw component model. Third, adding blood glucose and albumin to the VDII-based model did not provide significant incremental discrimination in the external cohort. Fourth, lower standardized VDII was independently associated with higher odds of HPC, and the association appeared nonlinear. Finally, the association between VDII and HPC was stronger in patients with smaller baseline lesions. These findings suggest that VDII may capture complementary information from lesion size and density heterogeneity, but they should be interpreted cautiously given the retrospective design and the need for prospective validation. This study found that when baseline hematoma volume is used alone, its ability to discriminate HPC is very limited, and although DCV has certain predictive value, it is still significantly inferior to VDII. This result suggests that in FCL, it is difficult to fully characterize the risk of progression whether it is solely based on the size of the lesion or the dispersion of the density within the lesion. From a pathophysiological perspective, the progression of FCL is not just a simple enlargement of existing hematoma, but a dynamic process involving continuous rupture of microvessels, local tissue contusion, expansion of edema, and microcirculation disorders [2, 21, 22]. Lesion volume reflects spatial load, but does not indicate whether the interior of the lesion is still in an active bleeding or unstable coagulation state; while DCV reflects density heterogeneity. Although it can indirectly suggest that there is mixed old and new bleeding or uneven coagulation inside the lesion, its essence is a relative indicator and lacks constraints on the absolute physical size of the lesion. Therefore, a single volume parameter can easily miss "small and active" lesions, and a single heterogeneity parameter may overestimate "heterogeneous but limited" lesions [9 - 15, 20, 23]. The value of VDII lies in integrating these two complementary dimensions into a single index, thereby providing a more complete characterization of lesion instability.

The use of the harmonic mean was intended to summarize two complementary imaging dimensions within a single index. Unlike simple addition or multiplication, the harmonic mean is more influenced by the smaller component and therefore reflects the balance between lesion volume and density heterogeneity. However, the observed direction of association in this study deserves careful interpretation. Because HPC was defined as a relative increase in hematoma volume of at least 25%, smaller baseline lesions may be more likely to satisfy the outcome definition after a modest absolute increase. This may partly explain why lower VDII values were associated with

higher HPC risk and why the association was stronger in the low-volume subgroup. Therefore, VDII should not be interpreted simply as a marker indicating that “larger and more heterogeneous lesions are always at higher risk.” Rather, in the context of the present endpoint, VDII appears to provide an empirical summary of volume-density configuration that helps identify lesions more likely to show early relative progression.

In this study, the harmonic mean was used to construct VDII rather than simple addition or linear weighting. We believe that this construction method has certain pathological rationality. The harmonic average is more sensitive to low values, meaning that when either dimension of volume or density heterogeneity is low, the overall indicator is suppressed. Only when the lesion has both a certain spatial scale and significant internal heterogeneity can VDII fully express its potential risk characteristics. This "short board effect" is consistent with the clinical reality of FCL: lesions with large volume but relatively uniform interior may represent a relatively stable bleeding load; while lesions with obvious heterogeneity but small total volume may not be enough to show significant imaging progress in the short term. In contrast, lesions with both volume and heterogeneity are more likely to be in a continuous evolution stage [10, 11, 14, 15, 20, 22, 23]. Therefore, the superiority of VDII over its individual components does not only mean that "the two variables are better put together", but rather that an integrated approach that conforms to the dynamics of the lesion can more effectively capture image information that is truly related to progress.

In model comparison, replacing baseline volume and DCV with VDII was associated with improved discrimination of Model 2 compared with Model 1 in the external validation cohort, whereas the corresponding difference in the testing set did not reach statistical significance after correction. This finding suggests that the VDII-based model may offer a more parsimonious representation of lesion-level information, but it should not be interpreted as definitive evidence of universal superiority. Further validation in independent cohorts with standardized imaging protocols is needed. This result has more important significance than the simple increase in AUC. Because although the original component model contains more "subdivision information", there is certain correlation and redundancy between this information, and it is more sensitive to scanning conditions, lesion distribution and sample composition in different centers. In contrast, VDII expresses lesion structural risk in a more compact manner, reducing model complexity while improving generalization stability. Especially in this study, there were significant differences between the

external verification cohort and the development cohort in terms of age, GCS score, VDII level and some inflammation indicators, while Model2 still maintained good discriminative ability and calibration performance, indicating that the image information carried by VDII has good cross-center robustness [10, 24 - 29]. For clinical predictive models, this ability to migrate is often more practical than a slight performance improvement within the development set [16].

The performance of the VDII-only model in external verification has been significantly better than the original component model, suggesting that VDII itself already contains strong risk information. This result suggests that lesion-level imaging characteristics may contain important information related to early HPC in FCL, although the relative contribution of systemic factors and post-admission management cannot be excluded. Further, after Model 3 added blood sugar and albumin to Model2, it did not achieve stable improvement in external verification, which also supports the above judgment. Although blood sugar and albumin reflect stress response, metabolic status and systemic inflammation background [30 - 35], they are greatly affected by blood collection timing, pre-hospital treatment, fluid replacement status and underlying diseases, and have limited cross-center stability. Therefore, the slight gain in the development cohort has not been stably transferred to the external population. In contrast, the quantitative imaging characteristics of the lesion itself are closer to the direct path for HPC. Therefore, considering model simplicity and the absence of significant incremental discrimination after adding glucose and albumin, Model 2 may be preferable to Model 3 for further validation.

The study also found a significant non-linear association between VDII and HPC risk, with an overall monotonic decreasing trend, with steeper risk changes in the low VDII interval and flatter risk changes in the higher interval. This result suggests that the risk reflected by VDII is not a simple linear accumulation, but more likely there is a critical interval from "unstable" to "relatively stable" lesions. The evolution of early lesions after trauma is itself significantly phased [21,22,36,37]: in the initial phase, microvascular persistent oozing, local coagulation formation and mechanical stress redistribution interact, and the lesion state is highly dynamic; as the lesion gradually stabilizes, the marginal contribution of further imaging changes to the risk of progression decreases. Therefore, RCS results not only support the inclusion of VDII as a continuous variable in the model, but also suggest that in future clinical applications, it may need to be interpreted in conjunction with nonlinear risk intervals, rather than simply understood as a fixed risk change per unit change.

Subgroup analysis further showed that VDII had a stronger predictive effect in low-volume lesions. This finding may have potential clinical implications. For larger lesions, doctors usually already have higher vigilance and adopt more aggressive review and monitoring strategies, so their subsequent management is more influenced by the overall condition and intervention measures; for lesions with small initial sizes, routine experience may tend to think that the risk is low, but some of them are still in a highly unstable stage and are more likely to be underestimated. VDII showed a stronger effect in this subgroup, suggesting that VDII may be particularly informative in patients with small initial lesions who are still at risk of early relative progression. [12, 37 - 39]. In other words, the most important clinical value of VDII may not be to strengthen our judgment of obviously high-risk large lesions, but to detect in advance those hidden high-risk lesions that are easily classified as low-risk under traditional experience but actually have a high tendency to progress.

In addition to discriminatory power, this study also showed that the VDII correlation model performed well in calibration and decision curve analysis. For predictive studies, high AUCs alone are not enough to support clinical applications, because true clinical decisions depend on whether individualized probability outputs are reliable and whether they can provide net benefits at different thresholds. Model2 achieved a lower Brierscore in both the test set and external verification cohort, and showed a higher net benefit in DCA than Model1, suggesting that the improvement brought by VDII is not simply an improvement in statistical fit, but has potential clinical transformation value. Combined with the research concepts of early risk identification, CT review strategies and time-sensitive intervention in the field of cerebral hemorrhage and cerebral contusion [4,37, 39,40], If validated prospectively, VDII may help inform CT follow-up strategies and early surveillance intensity in future clinical workflows.

This study has several limitations. First, although an external validation cohort was included, the study was retrospective and observational; therefore, selection bias, information bias, and residual confounding cannot be excluded. The results should be interpreted as associations rather than evidence that using VDII will necessarily improve clinical outcomes. Second, the study included only two tertiary centers in China, and the external validation cohort differed from the development cohort in age, GCS score, inflammatory indices, and VDII distribution. Although this heterogeneity provided an opportunity to test transportability, the generalizability of the model to

other regions, scanners, imaging protocols, and trauma systems remains uncertain. Third, patients with GCS ≤ 9 or those requiring immediate emergency surgery were excluded. Therefore, the findings may not apply to patients with severe TBI, rapidly deteriorating neurological status, or lesions requiring immediate operative intervention. Fourth, HPC was defined as a relative increase in hematoma volume of at least 25%. This definition may be more easily reached by small baseline lesions after a modest absolute increase, which may influence the observed association between VDII and HPC. Future studies should evaluate whether VDII performs similarly when alternative endpoints are used, such as absolute volume increase, combined absolute and relative expansion criteria, need for surgery, neurological deterioration, or functional outcome. Fifth, although segmentation was performed using 3D Slicer with good interobserver agreement, VDII measurement still required semi-automatic segmentation and manual correction. This workflow may limit real-time clinical implementation and may introduce measurement variability, especially in small or irregular contusions adjacent to bone. Sixth, VDII combines lesion volume and DCV, which are measured on different numerical scales. Although the harmonic mean was prespecified and standardized before modeling, the index may be sensitive to measurement scale, segmentation method, and CT acquisition parameters. Further methodological work is needed to evaluate alternative scaling strategies, robustness across scanners, and clinically interpretable thresholds. Seventh, treatment factors after admission, including hemostatic therapy, blood pressure management, fluid resuscitation, timing of repeat CT, and surgical decision-making, were not fully modeled and may have influenced hematoma progression. Eighth, the present study focused on early radiological progression rather than long-term neurological or functional outcomes. Therefore, the clinical utility of VDII for improving patient management and outcomes remains to be determined. Finally, although Model 2 showed favorable discrimination and calibration compared with Model 1 in the external cohort, the model has not yet undergone prospective validation, impact analysis, or automated deployment testing. Prospective multicenter studies with standardized imaging protocols and automated segmentation are required before VDII can be recommended for routine clinical decision-making.

5. conclusion

In this multicenter retrospective cohort study, VDII, a harmonic mean-based composite imaging

marker integrating baseline lesion volume and density heterogeneity, was associated with early HPC in patients with FCL. . VDII showed higher discrimination than volume or DCV alone in the testing set, and replacing raw volume and DCV with VDII improved external discrimination compared with the raw component model. Adding blood glucose and albumin did not provide significant additional benefit. Lower standardized VDII was independently associated with higher odds of HPC, with evidence of a nonlinear relationship, and the association appeared stronger in patients with smaller baseline lesions. These findings suggest that VDII may be useful for early radiological risk stratification, but prospective validation, standardized measurement, and assessment of clinical impact are required before routine implementation.

Abbreviations

HPC: hematoma progression; FCL: frontal lobe contusion; VDII: volume-density integration index; DCV: density coefficient of variation; NCCT: non-contrast computed tomography; GCS: Glasgow Coma Scale; SIRI: systemic inflammation response index; LMR: lymphocyte-to-monocyte ratio; AUC: area under the receiver operating characteristic curve; OR: odds ratio; CI: confidence interval; RCS: restricted cubic spline; DCA: decision curve analysis; IDI: integrated discrimination improvement; NRI: net reclassification improvement; LASSO: least absolute shrinkage and selection operator; VIF: variance inflation factor.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Ethics Committee of the General Hospital of Ningxia Medical University, Yinchuan, Ningxia, China (Approval No. KYLL-2025-2410) .

The Second Affiliated Hospital, Hengyang Medical School, University of South China participated as the external validation center. According to its local institutional procedures for multicenter retrospective studies, a duplicate full ethics review was not required. The center completed a simplified institutional confirmation process, formally acknowledged and relied on the ethics approval granted by the leading institution, and confirmed the legitimacy of using anonymized retrospective data from its institution for this study.

Because this was a retrospective study using anonymized clinical and imaging data, the requirement for individual informed consent was waived by the ethics committee of the leading institution and accepted by the participating external validation center according to its local institutional procedures. All data were de-identified before analysis.

Consent for publication

All authors read and agree to submit this manuscript to your journal.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no conflicts of interest relevant to this study.

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Authors' contributions

Guoqing Jiang is the sole first author. Liang Wu is the sole corresponding author. Guoqing Jiang and Liang Wu conceived and designed the study. Guoqing Jiang, Qinghua Zhang, Tao Wang, Zhanfeng Niu, Shengyu Sun, and Xvlei Hu were responsible for data collection and organization. Xianglong Liu and Yu Zhao performed the statistical analysis and model development. Li Ma, Lijuan Wang, and Xianglong Liu contributed to laboratory data interpretation and methodological support. Guoqing Jiang drafted the manuscript. Liang Wu and Xvlei Hu acquired the funding. Liang Wu and Yu Zhao contributed to methodology, writing-review and editing. All authors reviewed the final manuscript and approved the submitted version.

Additional declarations:

Originality: The authors confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

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Reporting Checklist: The authors confirm that they have followed the TRIPOD+AI statement for reporting clinical prediction models. A completed TRIPOD+AI checklist is provided as a supplementary file with this submission.

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