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Serum occludin combined with clinical features for predicting early neurological deterioration in intracerebral hemorrhage

Серумски оклудин у комбинацији са клиничким карактеристикама у предвиђању раног неуролошког погоршања код интрацеребралног крварења

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SUMMARY

Introduction/Objective To evaluate the incremental predictive value of 24-hour serum occludin beyond clinical features and to develop and internally validate a clinically applicable risk prediction model.

Methods This was a single-centre prospective cohort study. Patients with spontaneous intracerebral haemorrhage (ICH) presenting within 24 hours of symptom onset were enrolled. The primary outcome, early neurological deterioration (END), was assessed at 72 hours post-admission. Variables for model development were selected using least absolute shrinkage and selection operator regression. A logistic regression model was constructed incorporating clinical and imaging factors and serum occludin levels measured at 24 hours post-admission. Model performance was evaluated using the area under the curve (AUC). Decision curve analysis was used to assess net clinical benefit across different risk thresholds.

Results Among the 600 enrolled patients, 210 (35.0%) developed END. The base model incorporating age, admission Glasgow Coma Scale score, ICH volume, intraventricular haemorrhage, location, surgical intervention and systolic blood pressure achieved an optimism-corrected AUC of 0.78 (95% CI: 0.74–0.82). The extended model with added 24-hour serum occludin significantly improved discrimination (AUC = 0.84, 95% CI: 0.81–0.87; ΔAUC = 0.06, p < 0.001), with greater clinical net benefit across threshold probabilities of 10%–40%. Category-free net reclassification improvement was 0.42 (95% CI: 0.28–0.56), and integrated discrimination improvement was 0.08 (95% CI: 0.05–0.11). Risk stratification at 10% and 20% thresholds demonstrated high sensitivity (87%) and specificity (79%) for the identification of the high-risk group.

Conclusion Twenty-four-hour serum occludin significantly enhances predictive performance for END and holds potential as an improved biomarker. However, external validation is necessary before widespread implementation.

Keywords: intracerebral haemorrhage; early neurological deterioration; occludin; blood–brain barrier; prediction model; Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis

САЖЕТАК

Увод/Циљ Проценити инкременталну предиктивну вредност серумског оклудин измереног 24 часа након пријема у односу на клиничке карактеристике, као и развити и интерно валидирати клинички применљив модел за предвиђање ризика.

Методе: Ова једносредишња проспективна кохортна студија обухватила је пацијенте са спонтаним интрацеребралним крварењем (*ICH*) примљене у року од 24 часа од почетка симптома. Примарни исход, рано неуролошко погоршање (*END*), процењиван је 72 часа након пријема. Варијабле за развој модела изабране су применом *LASSO* регресије. Конструисан је логистички регресиони модел који је укључивао клиничке и сликовне параметре, као и нивое серумског оклудинизмерене 24 часа након пријема. Перформансе модела процењене су коришћењем површине испод *ROC* криве (*AUC*). Анализа криве одлучивања (DCA) примењена је ради процене нето клиничке користи у различитим праговима ризика.

Резултати: Од укупно 600 укључених пацијената, код 210 (35,0%) развило се *END*. Основни модел, који је укључивао старост, *GCS* при пријему, волумен *ICH*, интравентрикуларно крварење, локализацију, хируршко лечење и систолни артеријски притисак, постигао је *AUC* коригован за оптимизам од 0,78 (95% *CI*: 0,74–0,82). Додавање серумског оклудиннакон 24 часа значајно је побољшало дискриминацију (*AUC* = 0,84; 95% *CI*: 0,81–0,87; *ΔAUC* = 0,06; *p* < 0,001), и већу нето клиничку корист у распону прагова ризика од 10% до 40%. Нето побољшање класификације без категорија (*NRI*) износило је 0,42 (95% *CI*: 0,28–0,56), док је интегрисано побољшање дискриминације (IDI) износило 0,08 (95% *CI*: 0,05–0,11). Стратификација ризика при праговима од 10% и 20% показала је високу осетљивост (87%) и специфичност (79%) у идентификацији пацијената високог ризика.

Закључак Серумски оклудин измерен 24 часа након пријема значајно побољшава предиктивне перформансе за *END* и представља обећавајући биомаркер. Ипак, неопходна је спољашња валидација пре шире клиничке примене.

Кључне речи: интрацеребрално крварење; рано неуролошко погоршање; оклудин; крвно-мождана баријера; модел предикције; *TRIPOD*

INTRODUCTION

Spontaneous intracerebral haemorrhage (ICH) accounts for 10%–15% of all strokes, with 90-day mortality rates approaching 40% and only 20–30% of survivors achieving functional independence [1, 2]. Early neurological deterioration (END) typically occurs within 72 hours of onset and is a critical indicator affecting prognosis [3]. It is usually defined as a decrease in Glasgow Coma Scale (GCS) score ≥2 points or an increase in National Institutes of Health Stroke Scale (NIHSS) score ≥4 points within 24–72 hours of admission [4], with an incidence rate of 20–40% [5].

The mechanisms of END are complex, including haematoma expansion (occurring in about 30% of patients within 24 hours), perihaematomal oedema (PHE), intraventricular haemorrhage (IVH) and systemic complications [6, 7]. Early neurological deterioration remains common even in the absence of haematoma growth, suggesting that secondary brain injury, such as blood–brain barrier (BBB) disruption, also plays an important role [3].

Current clinical prediction models (such as the ICH score and FUNC score) are mainly based on baseline clinical and imaging variables, with limited ability to predict END [8, 9]. Although the recent SIGNALS score has improved discrimination to AUC values of around 0.78 [10], there remains scope for optimisation through integration of biomarkers reflecting underlying pathophysiological processes, particularly BBB disruption.

The integrity of the BBB depends on tight junction proteins, particularly occludin, a 65-kDa transmembrane protein critical for regulating permeability [11, 12]. Following ICH, thrombin-mediated matrix metalloproteinase (MMP) activation, oxidative stress and inflammation degrade occludin, disrupting the BBB and promoting PHE and secondary injury [13]. Experimental data show that occludin degradation is an early event: serum levels rise within hours after stroke and correlate with BBB damage [14], and occludin-deficient mice have worse outcomes [15]. In ICH, preliminary evidence links serum occludin to PHE volume [16], but findings are limited by small sample sizes and the lack of multivariable adjustment. Therefore, this prospective study aims to evaluate the incremental predictive value of 24-hour serum occludin beyond baseline clinical–imaging models and to develop a clinically applicable risk prediction tool for END in patients with ICH following Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.

METHODS

Study design and ethical approval

This single-centre prospective cohort study was conducted in accordance with the TRIPOD statement [17]. The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Baotou Medical College. Written informed consent was obtained from all participants or their legally authorised representatives before enrolment.

Study population and selection criteria

Patients presenting to the hospital's department with spontaneous ICH between February 2022 and August 2024 were screened for eligibility. The inclusion criteria were as follows: (1) spontaneous supratentorial or infratentorial ICH confirmed by non-contrast head computed tomography, (2) time from symptom onset to hospital admission ≤24 hours, (3) age 18–85 years and (4) availability for blood sample collection at both baseline and 24-hour timepoints. The exclusion criteria were as follows: (1) secondary ICH due to arteriovenous malformation, tumour, trauma or anticoagulation-related haemorrhage (international normalised ratio >3.0 at presentation); (2) immediate post-surgical loss to follow-up or inability to assess END; (3) severe hepatic failure (Child–Pugh class C) or renal failure (estimated glomerular filtration rate <15 mL/min/1.73 m²); (4) concurrent enrolment in other interventional trials; (5) life expectancy <3 months due to terminal illness; and (6) prior disability with modified Rankin Scale score >3 before the current ICH [18].

Sample size calculation and statistical power

Based on the principle of events per predictor parameter ≥20 [19], the inclusion of 10–12 predictor variables would require 200–240 END events. Assuming an END incidence rate of 35% [4], the target sample size was 600 participants. According to Riley's criteria [20], a shrinkage factor ≥0.90 was ensured to reduce overfitting. Considering a 5% loss to follow-up, 630 participants were planned for enrolment.

Clinical data collection

All clinical variables were obtained within 24 hours of admission. Intracerebral haemorrhage volume, PHE volume and IVH were calculated as previously described [14, 21, 22]. Intracerebral haemorrhage location was categorised as deep (basal ganglia or thalamus), lobar (involving cortical–subcortical regions), infratentorial (cerebellum or brainstem) or mixed based on epicentre determination. Computed tomography was performed using a 64-slice GE Revolution scanner (GE Healthcare Medical Systems, Slough, UK and Milwaukee, WI). Haematoma (40–80 Hounsfield units) and PHE (15–33 Hounsfield units) volumes were measured using a validated semi-automated segmentation method with manual correction [23]. All imaging measurements were performed by two trained radiologists blinded to clinical data and biomarker results, with inter-rater reliability assessed using intraclass correlation coefficients. Serum occludin concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Human Occludin ELISA Kit, catalogue #SEA145Hu, Cloud-Clone Corp., Houston, TX, USA) according to the manufacturer's instructions.

Early neurological deterioration was defined as a decrease in GCS score of ≥2 points between baseline assessment (within 6 hours of admission) and the 72-hour evaluation, excluding deterioration attributable to sedation, seizures or other reversible causes [4].

Data management and missing data handling

Data were entered into the REDCap system with logic checks and audit trails implemented. Little's missing completely at random test indicated that data were missing at random ($p = 0.18$), and multiple imputation by chained equations was performed ($m = 20$), with models including all predictor variables, outcomes and auxiliary variables (e.g. length of hospital stay, discharge disposition). Continuous variables were imputed using predictive mean matching, whereas binary and multicategory variables were imputed using logistic and multinomial logistic regression, respectively. Imputation convergence was verified through trace plots and distribution comparisons. All analyses were performed across the imputed datasets, and results were pooled according to Rubin's rules [20, 24].

Statistical analysis

Statistical analyses followed a prespecified plan using R version 4.3.1. Descriptive statistics were used to compare END and non-END groups using appropriate parametric or non-parametric tests. Model development employed a two-stage approach: least absolute shrinkage and selection operator regression with 10-fold cross-validation for variable selection, followed by ridge regression for coefficient estimation. The base model incorporated core clinical–imaging variables, whereas the extended model additionally included 24-hour serum occludin. Internal validation was performed using bootstrap resampling (2,000 iterations) to obtain optimism-corrected performance estimates. Model performance was assessed using AUC with 95% CIs, and Brier scores. The incremental value of occludin was evaluated through ΔAUC, net reclassification improvement (NRI), integrated discrimination improvement (IDI) and decision curve analysis. Risk stratification used prespecified cut-off points at 10% and 20% predicted probability, with sensitivity analyses examining model robustness across patient subgroups and alternative END definitions.

Ethics: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of First Affiliated Hospital of Baotou Medical College.

RESULTS

Study population and flow

A total of 687 patients with spontaneous ICH were screened, of whom 87 were excluded, leaving 600 patients included in the study. The mean age was 64.2 ± 13.5 years, 358 (59.7%) were men and the median time from onset to admission was 8.4 (4.2–14.7) hours. Early neurological deterioration occurred in 210 patients (35.0%), consistent with the sample size assumptions.

Baseline characteristics and measurement reliability

Patients who developed END were older and had lower admission GCS scores, larger baseline ICH and 24-hour PHE volumes, higher rates of IVH, more frequent emergency surgery and higher serum occludin concentrations (all $p < 0.001$) (Table 1).

Variable selection and model development

Least absolute shrinkage and selection regression selected eight predictors for the base model (Figure 1). Time to blood draw and antiplatelet and anticoagulant use were forced into the model. Occludin was added to the extended model ($\beta = 0.18$). After adjustment, 24-hour serum occludin remained independently associated with END (odds ratio per ng/mL: 1.23, 95% CI: 1.16–1.31, $p < 0.001$). Other predictive factors are shown in Table 2.

Model performance and validation

A nomogram (Figure 2) enables bedside risk estimation. Risk groups may be interpreted as low risk (<0.10), intermediate risk (0.10–0.20), and high risk (>0.20). The bootstrap-corrected AUC was 0.78 (95% CI: 0.74–0.82) for the base model, improving to 0.84 (95% CI: 0.81–0.87) with the inclusion of occludin. The Brier score decreased from 0.18 to 0.15. The addition of occludin yielded ΔAUC = 0.06 (95% CI: 0.04–0.08, $p < 0.001$), NRI = 0.42 (95% CI: 0.28–0.56, $p < 0.001$) and IDI = 0.08 (95% CI: 0.05–0.11, $p < 0.001$). Decision curve analysis (Figure 3) demonstrated superior net benefit for the extended model across 10%–40% risk thresholds.

Sensitivity and subgroup analyses

The results remained robust in patients not undergoing surgery (AUC = 0.83 *vs.* 0.77), across different bleeding locations (deep, lobar or subarachnoid; ΔAUC = 0.05–0.07) and blood sampling times (< 8 hours or ≥ 8 hours), complete-case analysis (n = 581) and alternative definitions of END (NIHSS ≥4, n = 542) (all $p < 0.001$, Table 3).

DISCUSSION

This prospective study demonstrates that 24-hour serum occludin provides substantial independent and incremental predictive value for END beyond standard clinical–imaging variables in ICH. The extended model achieved excellent performance (AUC = 0.84), improved reclassification (NRI = 0.42, IDI = 0.08) and greater net clinical benefit across relevant decision thresholds. These findings highlight the clinical value of serum occludin as a promising biomarker with demonstrable net clinical benefit across a range of decision thresholds. This enhancement in predictive accuracy supports the utility of serum occludin in improving patient stratification and clinical decision-making.

Compared with previous studies that focused only on ischaemic stroke or small-sample correlation analyses, this study systematically verified the independent contribution of occludin by fixing the 24-hour detection time point, strictly adjusting for confounding factors using multivariable correction and applying modern evaluation methods such as NRI and IDI [15, 17]. Notably, the basic model's AUC of 0.78 aligns with existing ICH prediction scores (such as the ICH score and FUNC score) [9, 10], whereas the inclusion of occludin led to a clinically meaningful improvement in predictive accuracy, emphasising the importance of integrating biomarkers into clinical prediction models.

From a mechanistic perspective, post-ICH thrombin activation, MMP-9 activation and oxidative stress are known to degrade occludin, leading to BBB disruption, PHE and secondary brain injury [12, 14]. Importantly, our study shows that occludin retains predictive value even after adjustment for PHE volume, suggesting that it reflects subclinical BBB dysfunction that may not be captured by imaging alone. This finding is consistent with previous studies highlighting the role of occludin in BBB integrity and its correlation with neurological outcomes in patients with stroke [15].

The clinical applicability of our model is substantial. Patients classified as low risk (<10%) may avoid unnecessary intensive care unit admission, whereas patients at high risk (>20%) may be prioritised for interventions such as closer monitoring or early therapeutic strategies. The 24-hour sampling window used in this study is clinically feasible, and the nomogram developed provides a practical tool for bedside risk estimation, supporting applicability in routine clinical practice.

However, several limitations should be acknowledged. First, the single-centre design of this study limits generalisability, and external validation in diverse settings is required before widespread clinical adoption. Second, the sample size in some subgroups, such as patients with subacute ICH (n = 70), was relatively small, and further studies including larger cohorts are needed to confirm these findings. Additionally, this study used a single serum occludin measurement at 24 hours post-admission, which does not capture potential dynamic changes in occludin levels over time. Longitudinal monitoring of occludin and other BBB biomarkers may provide more comprehensive insights into the progression of ICH and END. Finally, although this study focused on serum occludin, other BBB markers were not assessed, and future research should explore the synergistic effects of combining multiple biomarkers to improve predictive accuracy.

CONCLUSION

In conclusion, this prospective study demonstrates that 24-hour serum occludin significantly enhances END prediction in patients with ICH when added to comprehensive clinical–imaging models. The findings support conceptualising occludin not as an isolated independent predictor but as an enhancement factor providing incremental value by capturing BBB disruption not fully reflected in conventional variables. External validation and impact studies are required before clinical adoption, but

these results establish serum occludin as a promising biomarker warranting further investigation for personalised risk stratification in ICH management.

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Authors' contributions: Shuhai Shi: major role in the acquisition of data; drafted and revised the article; data collection and processing.

Chunyang Zhang: interpreted and analyzed the data; revised the article.

Jingli Cheng: design and conceptualized study; drafted and revised the article.

All authors have approved the final manuscript.

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Conflict of interest: None declared.

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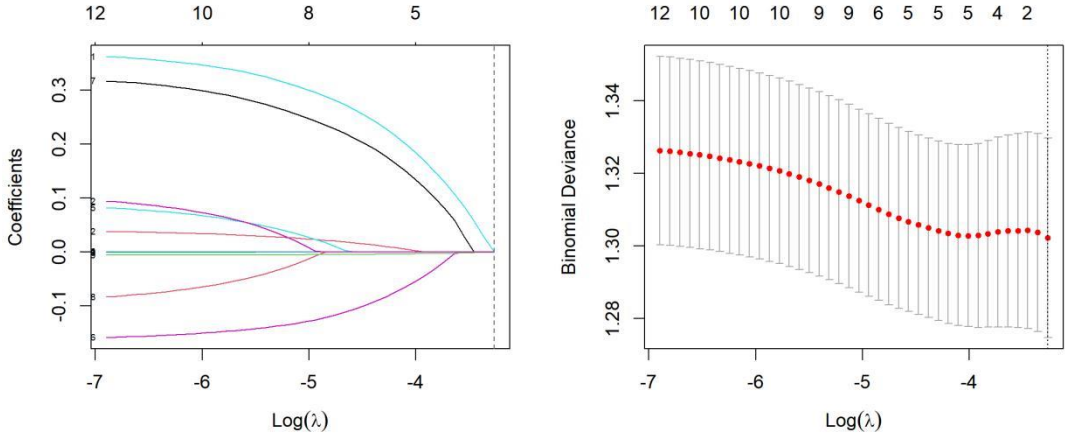

Figure 1. Variable selection process using LASSO regression**;** left: coefficient paths *vs*. log (lambda); optimal lambda (1-SE rule, dashed line) selected eight predictors; right: cross-validation deviance curve; numbers indicate variables retained at each lambda

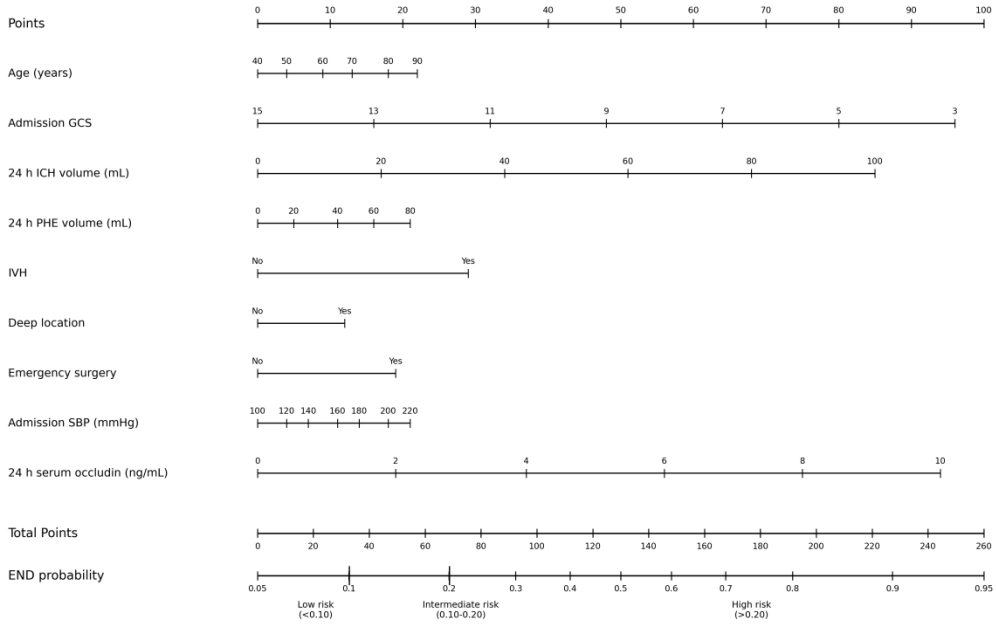

Figure 2. Nomogram for predicting end risk; risk groups may be interpreted as low risk (< 0.1), intermediate risk (0.1–0.2), and high risk (> 0.2)

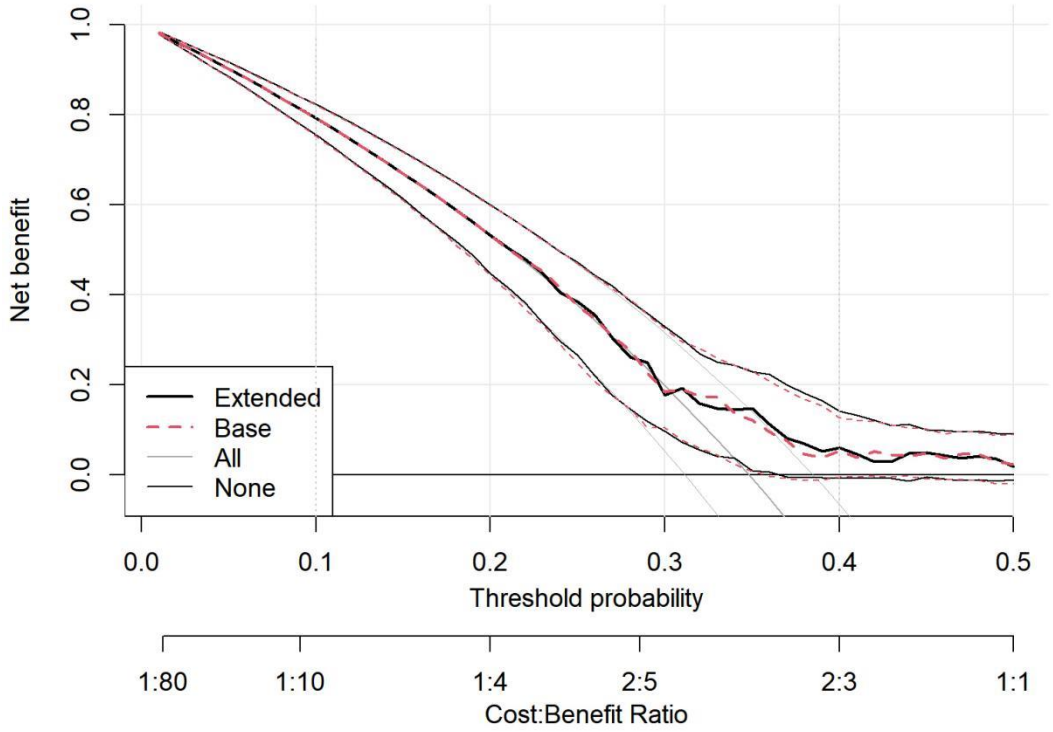

Figure 3. Decision curve analysis comparing models; net benefit across threshold probabilities (0–50%); extended model (solid black) outperforms base model (dashed gray) in clinically relevant range (10–40%), e.g., net benefit 0.22 *vs*. 0.17 at 15% threshold (equivalent to five additional true positives per 100 patients)

Table 1. Baseline characteristics (n = 600)

Variable	Overall	END (n = 210)	No END (n = 390)
Age, years (mean ± SD)	64.2 ± 13.5	67.8 ± 12.4	62.3 ± 13.8
Male sex, n (%)	358 (59.7)	128 (61)	230 (59.0)
Time to admission, h (median [IQR])	8.4 [4.2-14.7]	7.9 [3.8-13.2]	8.7 [4.5-15.3]
Admission GCS (mean ± SD)	12.9 ± 3.2	11.2 ± 3.6	13.8 ± 2.1
Baseline ICH volume, mL (mean ± SD)	28.3 ± 23.5	38.6 ± 28.4	22.7 ± 19.3
24h ICH volume, mL (mean ± SD)	31.7 ± 25.8	42.1 ± 30.2	26.2 ± 21.4
24h PHE volume, mL (mean ± SD)	33.2 ± 26.4	42.3 ± 31.2	28.4 ± 22.7
IVH present, n (%)	247 (41.2)	122 (58.1)	125 (32.1)
Deep location, n (%)	312 (52)	118 (56.2)	194 (49.7)
Lobar location, n (%)	218 (36.3)	68 (32.4)	150 (38.5)
Infratentorial location, n (%)	70 (11.7)	24 (11.4)	46 (11.8)
Emergency surgery, n (%)	101 (16.8)	52 (24.8)	49 (12.6)
Admission SBP, mmHg (mean ± SD)	167.3 ± 28.4	172.8 ± 30.1	164.5 ± 27.2
Hypertension history, n (%)	448 (74.7)	162 (77.1)	286 (73.3)
Diabetes mellitus, n (%)	142 (23.7)	54 (25.7)	88 (22.6)
Antiplatelet use, n (%)	178 (29.7)	67 (31.9)	111 (28.5)
Anticoagulation use, n (%)	52 (8.7)	23 (11)	29 (7.4)
24h serum occludin, ng/mL (mean ± SD)	5.56 ± 3.12	7.82 ± 3.41	4.26 ± 2.18

END – early neurological deterioration; GCS – Glasgow Coma Scale; ICH – intracerebral hemorrhage; IVH – intraventricular hemorrhage; PHE – perihematomal edema; SBP – systolic blood pressure

Table 2. Final model coefficients

Predictor	Base Model β (OR, 95% CI)	Extended Model β (OR, 95% CI)	VIF
Age (per year)	0.02 (1.02, 0.99–1.05)	0.01 (1.01, 0.98–1.04)	1.24
Admission GCS (per point)	-0.20 (0.82, 0.77–0.87)	-0.18 (0.83, 0.78–0.89)	2.18
24h ICH volume (per 10 mL)	0.22 (1.24, 1.16–1.33)	0.19 (1.21, 1.13–1.3)	2.45
24h PHE volume (per 10 mL)	0.08 (1.08, 1.02–1.15)	0.06 (1.06, 1–1.13)	1.87
IVH presence	0.78 (2.18, 1.52–3.12)	0.65 (1.92, 1.33–2.76)	1.56
Deep location	0.32 (1.38, 0.96–1.98)	0.28 (1.32, 0.92–1.9)	1.43
Emergency surgery	0.51 (1.67, 1.09–2.56)	0.42 (1.52, 0.99–2.33)	1.38
Admission SBP (per 10 mmHg)	0.05 (1.05, 0.99–1.11)	0.04 (1.04, 0.98–1.1)	1.22
24h serum occludin (per ng/mL)	—	0.21 (1.23, 1.16–1.31)	1.64

GCS – Glasgow Coma Scale; ICH – intracerebral hemorrhage; VIF – variance inflation factor; SBP – systolic blood pressure;

all $p < 0.05$ except where OR crosses 1.0

Table 3. Sensitivity analyses (selected subgroups); all sensitivity analyses demonstrate consistent incremental value of occludin

Subgroup	n	Events	Base AUC	Extended AUC	ΔAUC	p-value
Non-surgical patients	513	167	0.77	0.83	0.06	< 0.001
Deep location	312	118	0.76	0.82	0.06	< 0.001
Lobar location	218	68	0.79	0.84	0.05	0.002
Infratentorial location	70	24	0.75	0.82	0.07	0.041
Early blood collection (<8h)	298	108	0.77	0.83	0.06	< 0.001
Late blood collection (≥8h)	302	102	0.79	0.84	0.05	0.001
Complete cases (no imputation)	581	204	0.78	0.84	0.06	< 0.001
Alternative END definition (NIHSS≥4)	542	187	0.76	0.82	0.06	< 0.001

AUC – area under the curve; END – early neurological deterioration

