

## RESEARCH ARTICLE

# Neutrophil-to-Lymphocyte ratio on admission predicts gastrointestinal bleeding in acute basal ganglia hemorrhage

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**Abstract**

**Background:** Gastrointestinal bleeding (GIB) is a potential contributing factor for poor prognosis of spontaneous basal ganglia hemorrhage (BGH). This study aimed to investigate the predictive value of new inflammatory biomarkers including neutrophil to lymphocytes (NLR) on admission and construct a nomogram for rapidly predicting GIB in acute BGH.

**Methods:** The retrospective study included all patients with acute BGH admitted from the emergency department in Huashan Hospital from July 2017 to January 2019. Multivariate analysis was conducted to evaluate the correlation between factors within 24 h and the occurrence of GIB within 7 days after BGH. The receiver operating characteristic (ROC) curve was performed to estimate the prediction ability of inflammatory biomarkers. A nomogram based on significant predictors was validated by ROC curve and calibration curve.

**Results:** A total of 122 patients were enrolled in this study, and the incidence of GIB was 23.0%. Patients with GIB had larger hematoma volume ( $\geq 30$  ml), lower Glasgow Coma Scale (GCS) score ( $\leq 8$ ) and increased inflammatory biomarkers on admission. ROC curve revealed that NLR had a high predictive value to the complication (area under the curve = 0.87). According to multivariate analysis, NLR, GCS score, and hematoma volume were main factors for nomogram, with good calibration and discrimination.

**Conclusions:** Neutrophil-to-lymphocyte ratio and GCS score within 24 h after the onset of acute BGH are the independent risk factors for GIB. The nomogram developed by these predictors may assist surgeons in rapidly assessing and preventing of GIB for BGH patients in earlier stage.

**KEYWORDS**

basal ganglia hemorrhage, gastrointestinal bleeding, Glasgow Coma Scale, neutrophil-to-lymphocyte ratio, nomogram

Xuewei Jiang, Liangliang Zhou and Yinuo Chen contributed equally to this work.

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## 1 | INTRODUCTION

Hemorrhagic stroke (HS), of which primary intracerebral hemorrhage (PICH) constituted 26.2% and subarachnoid hemorrhage (SAH) 8.9%,<sup>1</sup> is the leading cause of death in stroke, and there are approximate 2.8 million global deaths due to HS every year.<sup>2</sup> The complications of PICH are also the major contributors to mortality and poor outcomes, which involve cerebral edema, seizures, venous thromboembolism, infections, and gastrointestinal bleeding (GIB).<sup>3-5</sup>

Gastrointestinal bleeding is also one of the most common complications in critically ill patients, with a reported prevalence rate of 7.2% among intracerebral hemorrhage (ICH) patients.<sup>4</sup> GIB contributes to malnutrition, impaired immunity, prolonging the time of hospitalization, poor outcome, and even mortality.<sup>6</sup> The mortality rate of ICH patients combined with GIB was 2.7 times higher than the patients without GIB.<sup>7</sup> This result emphasizes that the early detection and prevention for GIB are significant to patients. Multiple factors, such as age, Glasgow Coma Scale (GCS), pyohemia, hematoma volume, and hemorrhage location, showed relevance to GIB in ICH patients. Recently, neutrophil-to-lymphocyte ratio (NLR) as comprehensive laboratory parameters of inflammation in various diseases, including thyroid conditions, irritable bowel disease, and COVID-19 infection,<sup>8-12</sup> were also reported as a potential predictor for poor prognosis of stroke.<sup>13-15</sup> However, there are few studies focus on the prognostic value of NLR in GIB after stroke. Moreover, these previous studies could not reflect the accurate conditions for basal ganglia hemorrhage (BGH) which was the highest incidence of PICH due to confounding factors.<sup>16,17</sup> Therefore, we retrospectively reviewed patients with acute BGH to analyze the potential risk factors and compare the predictive ability of inflammatory markers on admission for GIB, then constructed a prediction model which presented as a nomogram to estimate the GIB risk rapidly and effectively.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients' selection

We retrospectively reviewed the patients who underwent acute BGH and were admitted from the emergency department in Huashan Hospital between July 2017 and January 2019. The inclusion criteria were as follows: (1) diagnosed with spontaneous basal ganglia hemorrhage by CT/MRI in accordance with Chinese guidelines for diagnosis and treatment of intracerebral hemorrhage 2019<sup>18</sup>; (2) hospitalized within 24 h of symptom onset; (3) age >18 years; (4) underwent conservative treatment during hospitalization. And exclusion criteria: (1) having a previous history of GIB, blood system diseases, tumor, arterial aneurysm, cerebral aneurysm, arteriovenous malformation, or stroke. (2) having severe abnormal renal and liver function, endocrine system, digestive system, autoimmune disease, acute infection, or received a blood transfusion within 3 months before admission; (3) using hormones, immunosuppressor (e.g., corticosteroids) for prolonged treatment, drugs

for anticoagulant, platelet function, or antibiotics within 1 month before admission; (4) having a surgical operation or trauma prior to the onset of BGH. (5) incomplete clinical data; (6) did not agree to participate in this present study. This retrospective study was approved by the Ethics Committee of the Huashan Hospital Affiliated to Fudan University (approval number HIRB-2015-256; registration date: October 22, 2015). Written consent to participate in the study was provided by all patients.

According to the occurrence of GIB, the patients were divided into GIB group and no GIB group.

### 2.2 | Definition of gastrointestinal bleeding

Gastrointestinal bleeding within 7 days after admission was recorded. The judgment of GIB was based on clinical symptoms and laboratory test results.<sup>19</sup> In detail: (1) bloody or tarry vomit, or gastrointestinal drainage juice, hematochezia. (2) Hemoglobin decreased to 2 g/dl accompanied with blood pressure reduction. (3) Occult blood test for vomit, gastrointestinal drainage juice, or feces was positive. GIB was diagnosed as any episode of these criteria occurring during the hospitalization.

### 2.3 | Data collection

Data of all patients were recorded from our database: demographics, medical history, vital signs, laboratory test values, and GCS score within 24 h after the onset of BGH, and hospital stay. Imaging data included intraventricular hemorrhage and hematoma volume calculated using the ABC/2 method.<sup>20</sup> NLR was calculated by dividing the absolute neutrophil count (ANC) by the absolute lymphocyte count (ALC), and lymphocyte-to-monocyte ratio (LMR) was calculated by dividing the ALC by the absolute monocyte count (AMC).<sup>21</sup>

### 2.4 | Statistical analysis

SPSS Statistic v.22.0, MedCalc 15.8 and R software (4.1.2) were used for analysis in this study. Data normality was assessed by the Kolmogorov-Smirnov test. Normal distribution data were presented as mean  $\pm$  SD, while non-normal distribution data were presented as median and range interquartile (0.25-0.75). Independent Student's *t*-test and rank-sum test (Mann-Whitney U test) were respectively used for comparison between two groups. The chi-square test and Fisher's exact test were used for the comparison of the categorical data between two groups. Multivariate logistic regression was conducted for identifying the independent risk factors. Receiver operating characteristic (ROC) curves were made to compare the predictive ability and identify the cutoff value of inflammatory markers. The nomogram was made according to the contribution of risk factors, and the discrimination and calibration were validated by the ROC curve and calibration curve. All significant difference was defined as  $p < 0.05$ .

### 3 | RESULTS

#### 3.1 | Patient characteristics

The study included 122 patients in total, with 84 (68.9%) male patients. The average age of overall patients was  $61.2 \pm 14.5$  years old, and the mean hospital stay was  $13.1 \pm 4.3$  days. 28 (23.0%) patients suffered from GIB with longer hospital stays ( $p < 0.05$ ). Univariate testing showed GCS score and hematoma volume on admission had significant statistical differences between the two groups ( $p < 0.05$ ; Table 1).

Because peripheral blood is an easily accessible sample in hospitals and strongly correlated to homeostasis, they are always used for the predictors searching for many acute and chronic diseases. Hence, we firstly compared the peripheral inflammatory cells within 24 h after the onset of stroke in two groups. White blood cell count (WBC) and ANC significantly increased in the GIB group ( $p < 0.001$ ), while ALC remarkably decreased in this group ( $p < 0.001$ ). AMC had no obvious change between the two groups ( $p > 0.05$ ). After calculating, patients with GIB had higher NLR and lower LMR ( $p < 0.001$ ). These results suggest WBC, ANC, ALC, and NLR, LMR may be the risk factors for gastrointestinal bleeding in basal ganglia hemorrhage patients. (Table 1).

In addition, we also compared some main indexes of liver, kidney, and cardiac function in peripheral blood on admission. No significant differences were found between the two groups ( $p > 0.05$ ; Table S1).

#### 3.2 | The predictive capability of inflammatory markers

Based on the ROC curve, NLR had the best predictive ability for GIB among other inflammatory markers. The best cutoff value of NLR was 6.75, with a sensitivity of 86%, specificity of 73%, and the area under ROC curve (AUC) at 0.87 (95% CI: 0.79–0.93,  $p < 0.001$ , Figure 1, Table 2).

#### 3.3 | Independent risk factors for GIB

Furtherly, multivariate regression analysis identified the significant factors ( $p < 0.05$ ) in univariate analysis. The results suggested that GCS score (odds ratio [OR]: 3.18; 95% confidence interval [CI]: 1.17–8.59,  $p = 0.023$ ), NLR (OR: 1.45; 95% CI: 1.25–1.67,  $p < 0.001$ ) were the independent risk factors for GIB in the acute stage of BGH. (Table 3).

#### 3.4 | Construction and validation of the nomogram model

As the multivariate analysis and ROC curve showed, NLR and GCS score were selected as significantly independent parameters in this nomogram ( $p < 0.05$ ). Hematoma volume was considered as one of the potential risk factors for GIB in previous studies,<sup>7</sup> so we involved

TABLE 1 Baseline characteristics and outcomes of all patients with or without GIB

Variable	Patients	Patients with GIB	Patients without GIB	p value
No, patients (n, %)	122	28 (23.0)	94 (77.0)	
Age, (years, mean $\pm$ SD)	$61.2 \pm 14.5$	$59.9 \pm 12.9$	$61.7 \pm 14.9$	0.583
Hospitalization days, (days, mean $\pm$ SD)	$13.1 \pm 4.3$	$14.5 \pm 3.3$	$12.6 \pm 4.4$	0.042
In-hospital mortality, (n, %)	24 (19.7)	8 (28.6)	16 (17.0)	0.177
Sex (male, n%)	84 (68.9)	22 (78.6)	62 (65.9)	0.206
ICH volume (ml, n%)				
$\geq 30$	58 (47.5)	19 (67.9)	39 (41.5)	0.014
$< 30$	64 (52.5)	9 (32.1)	55 (58.5)	
GCS (n, %)				
$\leq 8$	50 (41.0)	19 (67.9)	31 (33.0)	$< 0.001$
$> 8$	72 (59.0)	9 (32.1)	63 (67.0)	
IVH (n, %)	52 (42.6)	12 (42.9)	40 (42.6)	0.977
WBC ( $10^9/L$ )	$10.2 \pm 3.1$	$12.3 \pm 2.4$	$9.6 \pm 3.1$	$< 0.001$
ANC ( $10^9/L$ )	$8.1 \pm 2.9$	$10.5 \pm 2.4$	$7.4 \pm 2.8$	$< 0.001$
ALC ( $10^9/L$ )	$1.4 \pm 0.5$	$1.0 \pm 0.4$	$1.5 \pm 0.5$	$< 0.001$
AMC ( $10^9/L$ )	0.6 (0.5, 0.8)	0.7 (0.4, 0.8)	0.6 (0.4, 0.7)	0.245
NLR	5.7 (3.9, 8.7)	10.5 (7.3, 15.1)	4.9 (3.6, 7.0)	$< 0.001$
LMR	2.2 (1.6, 2.8)	1.7 (1.1, 2.4)	2.3 (1.7, 3.0)	$< 0.001$

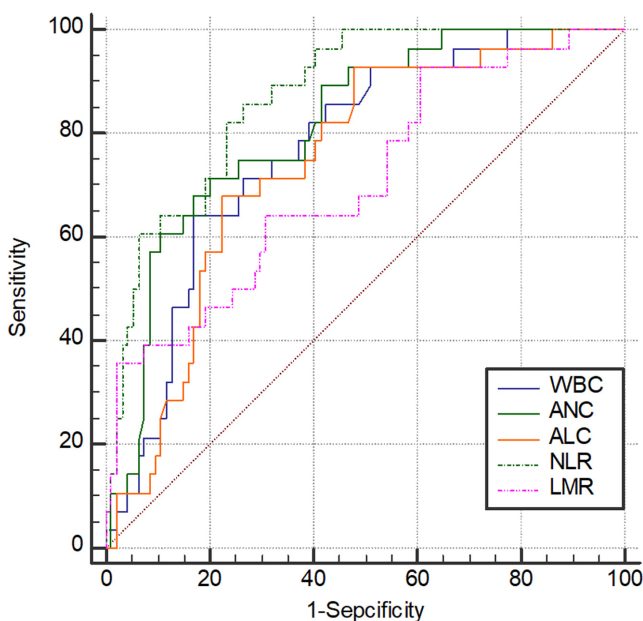
Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; GCS, Glasgow Coma Scale; GIB, gastrointestinal bleeding; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cells.

this variable into the model (Figure 2). The calibration curve showed good agreements that the prediction curve and the ideal line were approximately consistent (Figure 3A). Meanwhile, the AUC was 0.819 (95% CI 0.732–0.906; Figure 3B), indicating that this model had good discrimination.

## 4 | DISCUSSION

In this study, we observed hematoma volume, GCS score, and changes in inflammatory markers (WBC, ANC, ALC, NLR, LMR) on admission were related to GIB in patients. Moreover, NLR showed a good predictive value for GIB among these inflammatory markers.

As one of important complications after ICH which contributed to adverse clinical outcomes, GIB had an incidence of 4.9%–30% in the literature.<sup>17,22–24</sup>



**FIGURE 1** Receiver operating characteristic (ROC) curve of inflammatory markers for prediction of gastrointestinal bleeding (GIB).

	Sensitivity	Specificity	PPV	NPV	Cutoff	AUC (95%CI)	<i>p</i>
WBC	0.64	0.83	0.51	0.88	12.06	0.77 (0.68–0.84)	<0.001
ANC	0.70	0.82	0.50	0.90	9.39	0.82 (0.73–0.88)	<0.001
ALC	0.68	0.78	0.46	0.88	1.07	0.75 (0.66–0.82)	<0.001
NLR	0.86	0.73	0.48	0.94	6.75	0.87 (0.79–0.93)	<0.001
LMR	0.35	0.97	0.81	0.82	1.16	0.71 (0.62–0.79)	<0.001

Note: Receiver operating characteristic (ROC) curve analysis of predictive power of peripheral inflammatory cells on admission for GIB in acute BGH. NLR showed the best predictive power compared with other cells (AUC: 0.87; 95% CI: 0.79–0.93,  $p < 0.001$ ).

Abbreviations: AUC, the area under the curve; GIB, gastrointestinal bleeding; NPV, negative predictive value; PPV, positive predictive value.

However, there are no accurate data about BGH patients, the most common type accounting for 40%–57% of ICH. Our results indicated 23% of BGH patients suffered from GIB in the acute stage. The high rate suggested BGH was more likely to cause bleeding in the digestive tract. Some scholars believed that age, GCS score, hematoma volume, and hemorrhage location had been revealed to be the risk factors for gastrointestinal bleeding in ICH patients.<sup>7</sup> However, the lack of unified inclusive criteria and the interactions of these factors, such as hematoma volume and hemorrhage location, might lead to a large bias in study results. After strictly controlling the inclusive criteria, our analysis results showed that the BGH patients with hematoma volume  $\geq 30$  ml and GCS score  $\leq 8$  within 24 h of onset were at high risk for GIB. This indicated large hematoma and severe neurological impairment were major disadvantages for the gastrointestinal tract. Interestingly, the same ripple effect on digestive system was also seen in other CNS diseases, such as traumatic brain injury and ischemic stroke, through autonomic nerve regulation, gut microorganism, and inflammation pathway.<sup>25,26</sup> Moreover, besides gastrointestinal bleeding, neurological impairment also caused multiple organ dysfunction.<sup>27,28</sup>

After analyzing the inflammatory markers furtherly, the change in total WBC, neutrophils, and lymphocytes had the strong association with digestive damage. The correlation between WBC fluctuation and GIB suggested the systemic inflammation caused by BGH might be the potential mechanism for the negative impacts of CNS injury on the digestive tract. Blood components leaked from broken cerebral vessels trigger an immediate inflammatory response by mobilizing and activating the inflammatory cells, including CNS residential immune cells such as microglia, astrocytes, and peripheral WBC.<sup>29</sup> What was accompanied by the activation of the immune cells were the raise of inflammatory cytokines, including TNF- $\alpha$ , IFN- $\gamma$ , IL-2, and IL-6.<sup>30</sup> Upregulating immune cells and inflammatory cytokines in circulation acted on various organs throughout the body and had different levels of undesirable effects depending on the intensity of inflammatory response, which was similar to sepsis-induced systemic inflammatory response syndrome (SIRS) to a certain extent.<sup>31</sup> In mice subjected to ICH, suppressing the systemic inflammatory response by splenectomy attenuated the secondary organ dysfunction, proving the inflammation-mediated non-CNS organ dysfunction after ICH.<sup>32</sup> Therefore, we believed ICH-induced

**TABLE 2** Predictive capability of inflammatory markers for GIB

systemic inflammatory response after BGH was an important pathway for gastrointestinal tract injury, although there were others involved.

The systemic inflammatory response following ICH constitutes the underlying mechanism for the potential prognostic value of inflammatory markers such as ANC, ALC, NLR, and LMR. Jiang, Chao

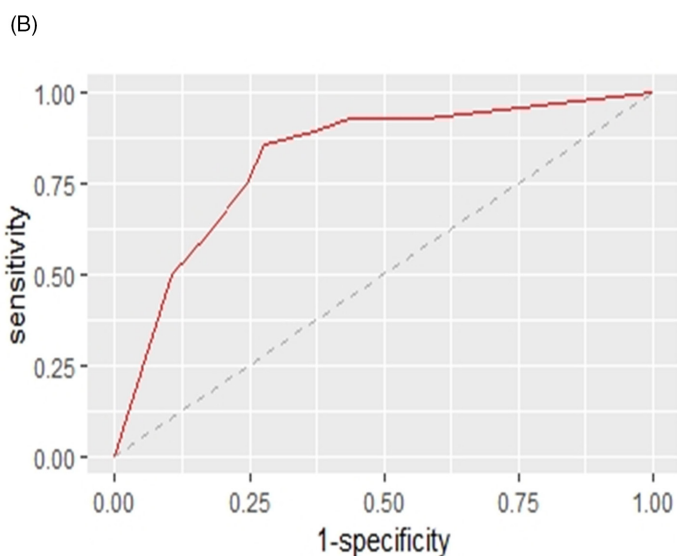
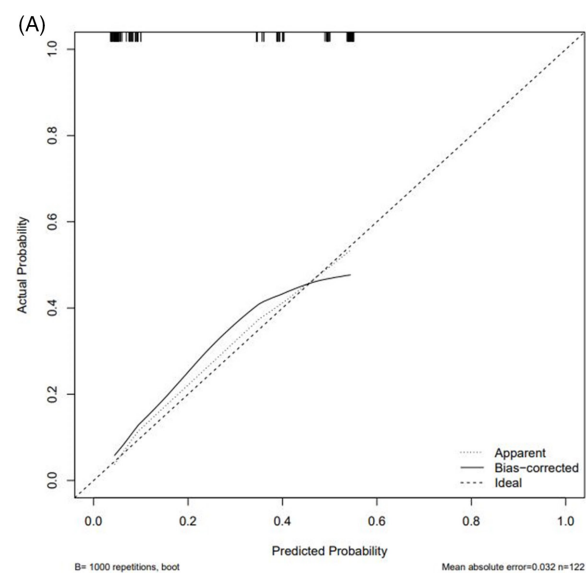
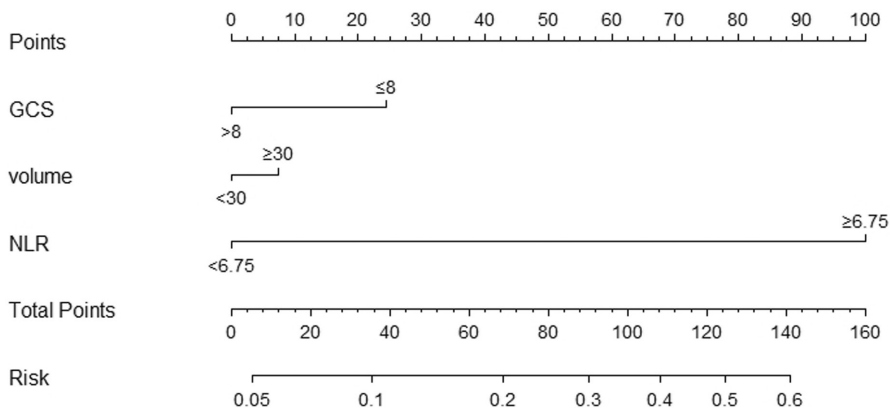
**TABLE 3** Multivariate logistic regression analysis of potential risk factors for GIB

	OR (95% CI)	<i>p</i> value
GCS	3.18 (1.17–8.59)	0.023
NLR	1.45 (1.25–1.67)	<0.001

Note: Multivariate logistic regression analysis was calculated for GIB, including parameters showing a statistical trend ( $p < 0.05$ ) in univariate testing. GCS (OR: 3.18; 95% CI: 1.17–8.59,  $p = 0.023$ ) and NLR (OR: 1.45; 95% CI: 1.25–1.67,  $p < 0.001$ ) were significantly associated with GIB.

Abbreviations: CI, confidence interval; GIB, gastrointestinal bleeding; OR, odds ratio.

**FIGURE 2** Nomogram for prediction of gastrointestinal bleeding (GIB) in acute basal ganglia hemorrhage (BGH). GCS, Glasgow Coma Scale; volume, hematoma volume; NLR, neutrophil-to-lymphocyte ratio.



**FIGURE 3** Calibration curve and receiver operating characteristic (ROC) curve of the nomogram for gastrointestinal bleeding (GIB). (A) The pointed line represents the apparent curve, the solid line represents the bias-correction one, and the dashed line represents the ideal one.  $B = 1000$  repetitions;  $n = 122$ , mean absolute error = 0.032. (B) The AUC was 0.819 (95% CI 0.732–0.906).

et al. analyzed the blood samples from ICH patients and reported that ICH induced an increase in the amounts of WBC, monocytes, and granulocytes and a reduction in lymphocytes in the acute phase. Additionally, the increase in WBC, monocytes, and granulocytes marking a systemic pro-inflammatory state was positively associated with hematoma volume,<sup>33</sup> while the meaning of lymphocytes reduction was still not clear. Meanwhile, some evidence suggested negatively regulatory lymphocytes, for example, regulatory T cells (Treg cells) declined at the early phase of ICH, which was contributing to poor neurological outcomes.<sup>34</sup> This phenomenon was also observed in ischemic stroke.<sup>35,36</sup> Hence, the reduction in lymphocytes possibly represented a loss of control over inflammation of the immune system in the initial stage of stroke, and together with macrophages, neutrophils reflected the unbalanced immune homeostasis. Similar to the above views, our data also showed that BGH patients with lower LMR, and higher NLR are more likely to have GIB.

More interestingly in our results, NLR had a stronger ability in predicting GIB compared with LMR, suggesting neutrophil might be more responsive to BGH and make a significant contribution

to digestive tract injury. NLR was usually considered as a sensitive marker for severity of diseases, such as cancer, infection, and stroke.<sup>15,37,38</sup> In ICH patients, NLR and ANC were synergistically on propagation of the inflammatory cascade which enhanced the IL-6 effects on the edema volume.<sup>39</sup> In experimental BGH, neutrophil infiltration with the high level of IL-6 and IL-1 $\beta$  was obvious in the intestine and blood circulation in acute stage.<sup>6,40</sup> It suggested that these activated cytotoxic factors played the important role in gut mucosal damage and barrier dysfunction. And on this basis, immune-mediated gut microbiota dysbiosis might in turn aggravate neuroinflammation.<sup>41</sup> However, the detailed interaction mechanism between cells and interleukins in digestive system remains to be investigated.

Based on identified variables, we developed a nomogram which was a diagram to make the prediction model visual and clearly displayed the relationship between variables and outcomes. This method gained widespread attention in predicting cancer prognosis.<sup>42</sup> In this study, the nomogram had high performance, with good discrimination and calibration assessed by ROC curve and the calibration plot. It illustrated the model can provide surgeons to effectively evaluate the occurrence of gastrointestinal tract injury at acute stage of BGH.

#### 4.1 | Limitations

The present study has several limitations. Firstly, the study is a retrospective single-center study. Our conclusions need to be validated in prospective and multicenter randomized controlled trials. Besides, it lacks the observation of the dynamic clinical indexes restricting a further exploration of the relationship between these indicators and GIB. Nevertheless, on account of the aim for short-term prediction for GIB in hospitals, initial clinical indexes have more diagnostic value. Finally, all the patients have been treated with proton pump inhibitors for at least 3 days to prevent stress ulcers. The proton pump inhibitor treatment may also have some effects on gastrointestinal bleeding.

#### 5 | CONCLUSIONS

In conclusion, GCS score ( $\leq 8$ ) and peripheral NLR on admission are the independent risk factors for the occurrence of GIB in acute BGH. NLR within 24h of the onset of BGH, as a new inflammatory indicator, is a sensitive predictor for GIB. The nomogram based on identified factors may help intensive care specialists to early predict gastrointestinal bleeding and choose alternative therapies for basal ganglia hemorrhage patients.

#### AUTHOR CONTRIBUTIONS

JXW, ZLL, and CYN had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JXD were involved in the study concepts and

design. All authors (JXW, ZLL, CYN, TYQ, and JXD) were involved in the acquisition, analysis, and interpretation of data. JXW, ZLL, CYN, and TYQ finished the analysis and the draft of the article. All authors read, critically revised, and approved the article.

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#### CONFLICT OF INTEREST

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the article.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions." cd\_value\_code="text

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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