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Assessment of Risks for Gastrointestinal Bleeding in Patients with Brain Injury

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Summary

The aim of the study was to develop a risk model for upper gastrointestinal tract (GIT) bleeding in patients with brain injury of various etiologies.

Material and methods. Case histories of 33 patients were included into a retrospective descriptive study: 22 patients had severe brain injury of various etiologies, and 11 patients after elective surgery for cerebral aneurisms with uneventful postop period were taken for comparison. The patients were grouped in two arms: Group 1 included patients with obvious signs of GIT bleeding (*N*=11) and Group 2 had no obvious signs of bleeding (*N*=22). Complaints, life and medical history, comorbidities, specialists' exams data, results of laboratory and instrumental examinations, therapeutic regimens were analyzed. Presence of disproportionate pathologic sympathetic overreaction to acute brain injury, i. e., paroxysmal sympathetic hyperactivity (PSH), was assessed on admission and on Days 1, 3 and 5 after brain injury.

Results. A model for upper GIT bleeding risk assessment was designed using logistic regression. The resulting model gains high quality rating: χ^2=33,78, 3; p<0,001; OR=315. The risk of upper GIT bleeding exceeded 95% in patients having combination of 4 symptoms in their medical history (presence of PSH on Day 1 after acute brain injury; Karnofsky performance scale index <75; lack of neurovegetative stabilization in the acute period of brain injury; gastric and/or duodenal ulcer).

Conclusion. Determining the risk factors thresholds enables stratification of patients by the risk for upper GIT bleeding. Modification of the identified four risk factors (presence of PSH on Day 1after acute brain injury; Karnofsky performance scale index <75; lack of neurovegetative stabilization in the acute period of brain injury; gastric and/or duodenal ulcer) will probably reduce the occurrence of upper GIT bleeding in patients with acute brain injury of various etiology.

Keywords: gastrointestinal bleeding; brain injury; risk assessment; paroxysmal sympathetic hyperactivity; logistic regression; gastric lesion; duodenal lesion; gastrointestinal tract

Conflict of interest. The authors declare no conflict of interest.

Introduction

Acute erosive lesions of the upper gastrointestinal tract have a multifactorial etiology and can complicate many diseases and worsen outcomes [1–5].

Acute gastric and duodenal lesions often develop in critically ill patients. The pathogenesis of these conditions is determined by a shift in the balance of aggressive versus protective factors [6]. The development of new treatments, as well as the improvement of existing ones, is a pressing issue in intensive care.

In 1867, T. Billroth demonstrated the relationship between surgical trauma and damage to the gastric and duodenal mucosa. In 1823, J. Swan described gastric mucosal defects in children after fire injury, while B. Curling described the so-called Curling ulcers in the middle of the 19th century. G. Selye elaborated the stress theory, coined the term «stress ulcer» and showed a causal relationship between psychosomatic diseases and the development of peptic ulcers [6–9].

Acute lesions of the GI mucosa are a common complication of severe brain injury. They were first described by G. Cushing and later named after him [10].

According to different authors, peptic bleeding in critical patients accounts for 5–47% of all gastrointestinal bleeding cases. This wide variation in data is due to the heterogeneity of the population, different definitions of gastrointestinal bleeding (GIB), and diagnostic difficulties. There is no single registry for GIB because of its multifactorial nature [7–9].

Risk factors for bleeding from damaged gastric and duodenal mucosa include lung ventilation, coagulation disorders, acute renal and hepatic failure, traumatic and other brain injury, paroxysmal sympathetic hyperactivity (PSH), and vary with disease severity [11–16].

Clinical signs of PSH include hyperhidrosis, fever, changes in heart rate, respiratory rate, blood pressure, mydriasis, and musculoskeletal system changes. Typically, non-medication, medical and preventive methods are used to treat PSH. The management is based on general intensive care principles (maintenance of adequate parameters of hemodynamics, gas exchange, blood volume, electrolyte balance, blood glucose, body temperature, and nutritional support). The first step in drug treatment is symptomatic therapy. In lack of efficacy, continuous opioids and propofol are suggested. After dexmedetomidine was introduced into practice, alpha-2 adrenergic agonists were successfully used for the treatment of PSH [16].

Given the large number of risk factors, it is necessary to develop a mathematical model that enables the precise, sensitive, and specific identification of these factors from the general array in order to determine which of them are most crucial for patients with severe brain injury.

The study's methodology was based on the assumption that identifying important risk factors for the development of upper GI bleeding and their relationship to treatment outcomes would aid in the development of a successful plan for the prevention and treatment of this condition in patients with severe brain injury.

The aim of the study was to build a risk model for the development of overt upper gastrointestinal bleeding in patients with brain injury of various etiologies.

The study model was built on the basis of logistic regression, taking into account both quantitative and categorical variables as risk factors. The main idea of the model was to obtain the characteristics of the logistic function Ψ for the standard equation $y = \exp(\Psi) / (1 + \exp(\Psi))$.

Materials and Methods

The case histories of 33 patients treated in the Department of Anesthesiology and Intensive Care of the Russian Polenov Neurosurgical Institute between 1992 and 2022 were included in the retrospective descriptive study. Of these patients, 22 had severe brain damage of various etiologies (Table 1) and 11 (used as a comparison) had cerebrovascular aneurysms and an uneventful postoperative period after elective neurosurgical intervention.

Inclusion criteria were severe brain injury of various etiologies, age older than 18 years.

Non-inclusion criteria were brain malignancy, upper GI surgery, history of malignancy.

All patients were divided into two groups: without obvious signs of GI bleeding (*N*=22) and with overt GI bleeding (*N*=11). Criteria for overt GI bleeding were hematemesis, blood in GI aspirate, or melena. Clinically significant GI bleeding was defined as a combination of overt GI bleeding and hemodynamic changes or the need for blood transfusion or surgical intervention [17]. The fact of bleeding was confirmed according to the patient's medical record and/or upper endoscopy protocol.

Patients in the selected groups did not differ in age, Glasgow Coma Scores at hospital admission, and FOUR scores at ICU admission (Table 2).

Autonomic nervous system function was assessed using the PSH scales at admission and 1, 3, and 5 days after brain injury [16].

Seventy different clinical, assessment and laboratory parameters were analyzed (see Appendix).

The data obtained were analyzed using STATISTICA for Windows v10 software.

All quantitative variables had non-normal distributions and were analyzed using Mann–Whitney, Kolmogorov–Smirnov, and median χ^2 criteria. Frequency characteristics of qualitative parameters

Table 1. Etiology of brain injury.

Brain injury	Number of patients
Total	22
Subarachnoid hemorrhage	4
Spontaneous intracranial hemorrhage due to ruptured arteriovenous malformation	6
Closed head injury	3
Open head injury	1
Major ischemic type cerebrovascular accident	1
Hemorrhage after microsurgical removal of benign brain neoplasm	4
Hemorrhagic cerebrovascular accident with intracerebral hematoma	3

Table 2. Characteristics of the studied groups of patients, *M*±*SD*; *min*÷*max*; *Me* (*LQ*; *UQ*).

Parameters	Values in groups		*P*
	Without GIB, *N*=22	With GIB, *N*=11	
FOUR scale severity on admission to ICU	13.14±3.76; 5÷16; 16 (12; 16)	10.22±2.95; 5÷14; 10 (10;12)	0.051
Glasgow Coma Scale severity on hospital admission	14.86±0.47; 13÷15; 15 (15; 15)	12.91±2.07; 10÷15; 13 (10; 15)	0.073
Age, years	50.36±15.59; 21÷70; 54 (38; 64)	51.91±16.03; 31÷78; 48 (38; 71)	0.79

(gender, cerebral edema, performing neurovegetative stabilization regardless of PSH manifestations, etc.) were evaluated by nonparametric methods using Pearson's χ^2 and Fisher criteria. Critical thresholds and prognostic significance of risk factors in patients with hemorrhage were determined using the Classification Trees module. The odds ratio (OR) for GI bleeding was calculated using standard formulas. In the case of zero values in the four-way table, the Haldane correction was used for calculation.

The model for estimating the risk of GIB in patients with brain injury of different etiologies was created using logistic regression (Logistic Regression in the Nonlinear Estimation module). First, the models with regression coefficient analysis were used, and then the model for estimating the risk of GIB was built. It included 4 most significant variables (Table 3).

Binary categorical variables were coded as 1 (yes) or 0 (no). For 4 variables (no neurovegetative stabilization performed, PSH severity 1 day after brain injury, history of gastric mucosal injury, and Karnofsky index at hospital admission), we found a significant association with GIB and analyzed them in detail.

To verify the effectiveness of the GIB risk assessment model, a «test» group was created. For this purpose, 10 case histories of patients treated in the Department of Anesthesiology and Intensive Care in 2023 were randomly selected. Of these, 6 had no GI bleeding and 4 had GI bleeding. Inclusion and non-inclusion criteria remained unchanged. The model was verified by checking for signs of overt GI bleeding, such as severe manifestations of PSH 24 hours after brain injury, history of gastric mucosal injury, and changes in Karnofsky index at hospital admission.

Adequacy of sample size was evaluated using Lehr's formula and Altman's nomogram. The characteristic studied was gastrointestinal bleeding in patients with brain injury. The power of the study was 0.80.

Results and Discussion

Autonomic nervous system function was evaluated based on the assessment of PSH (Table 4).

The quantitative parameters assessed in the study are summarized in Table 5.

Logistic regression tools were used to build a model to assess the risk of upper GI bleeding.

This model helped to calculate the probability of overt upper GI bleeding as a function of the severity of a given set of parameters. The positive effect was predicted at $y>0.5$ and the negative effect was predicted at $y\leqslant 0.5$.

We determined the strength of the effect of a single factor or group of factors on the probability of occurrence of the expected event (overt bleeding). The logistic function was calculated as

$$\Psi=A1\times X1+A2\times X2+A3\times X3+A4\times X4+B$$ [20–22].

The parameters of the logistic function Ψ of the optimal model are shown in Table 6.

Using the coefficients from the table, we obtained Ψ to estimate the risk of GIB in patients with brain injury of various etiologies. The formula obtained was

$$\Psi=0.029\times X1+8.69\times X2+0.1\times X3+6.07\times X4-15.27$$

Each of the regression coefficients describes the magnitude of the contribution of the corresponding factor. A positive regression coefficient indicates a factor which elevation increases the overall risk. A negative coefficient indicates a factor that decreases risk as its value drops. The magnitude

Table 3. The most significant parameters for building a model of the GIB risk.

Parameter	Abbreviation
Karnofsky scale on admission to the hospital	KAROA
Performing neurovegetative stabilization regardless of PSH manifestations (0 — no; 1 — yes)	NVS
Peptic (gastric and/or duodenal) ulcer disease detected prior to admission (0 — no; 1 — yes)	PUD
Manifestations of PSH 24 hours after brain injury	PSH1

Table 4. PSH scores at 1,3 and 5 days after brain injury (*M±SD*); (*min÷max*).

Parameter	Values in the groups		*P*
	Without GIB, *N*=22	With GIB, *N*=11	
PSH1	0.27±0.70(0÷2)	3.09±2.02 (1÷7)	<0.001
PSH3	0.42±0.77 (0÷2)	2.36±1.80 (0÷5)	0.003
PSH5	0.44±0.77 (0÷2)	2.55±1.37 (0÷5)	<0.001

Примечание. PSH1, 3, 5 — manifestations of paroxysmal sympathetic hyperactivity 1, 3, 5 days after brain injury. Presented are *M±SD* and range (in brakets).

Table 5. Quantitative parameters in the studied groups.

Parameter	Характеристики	Values in the groups		*P*
		Without GIB, *N*=22	With GIB, *N*=11	
Karnofsky Index on admission to the hospital	*M±SD*	77.73±21.59	41.82±23.16	0.001
	min÷max	20÷90	20÷80	
	Me (*LQ*; *UQ*)	90 (80; 90)	40 (20; 60)	
Manifestations of PSH 24 hours after brain injury	*M±s.d*	0.27±0.70	3.09±2.02	<0.001
	min÷max	0÷2	1÷7	
	Me (*LQ*; *UQ*)	0 (0; 0)	2 (2; 5)	

Table 6. Factors for assessing the risk of overt bleeding.

Parameters of the model	Designation of variables	Value of coefficients A1-A4	Rank of predictive value
KAROA	X1	0.029	2
NVS	X2	8.69	3
PUD	X3	0.1	4
PSH1	X4	6.07	1
Intercept	B	–15.27	—

of the regression coefficients determines the impact on overall risk. Prognostic significance is a «side effect» of model building [18–20].

The constructed model includes the following values: χ^2=33.78, 3; P<0.001; odds ratio 315 (95% CI: 11.8–8,400). Increased 95% CI is explained by the small sample size. We calculated the key features of the model including sensitivity 90.9%, specificity 100%, diagnostic accuracy 97.0%, positive predictive value 100%, negative predictive value 95.7%.

Thus, a comprehensive assessment of the risk of the upper GI bleeding for an individual patient depends on all the parameters included in the equation. The importance of some parameters may be balanced by the contribution of others.

The key values of Ψ were used to assess the risk of GIB: Ψ<–2.94 indicated the risk of less than 5%, Ψ<0 indicated the risk of less than 50%, Ψ>0 indicated the risk of more than 50%, while Ψ>2.94 represented the risk of more than 95% (see Fig. 1).

Using the classification tree building module, we identified critical threshold criteria. Figure 2 shows how the threshold for the Karnofsky index and PSH was determined when the patient was admitted to the hospital.

Risk factors for the development of overt GI bleeding and their thresholds were as follows: KAROA⩽75 (OR=34.0), NVS=1 (OR=10.0), PUD=1 (OR=17.5), PSH1⩾1 (OR=128.1).

Figure 3 illustrates the variations in the risk of GIB in relation to changes in several parameters. The efficiency of the identified thresholds is demonstrated in Table 7.

Performance testing of the model on the test group showed that there were no false negatives and only one false positive. The characteristics of the obtained model of GIB risk assessment in the test group were as follows: sensitivity — 100%, specificity — 83.3%, diagnostic accuracy — 90%, positive predictive value — 80%, negative predictive value — 100%.

Meanwhile, the positive Ψ values in 4 patients with GIB were in the range of 6.24–24.45, indicating a risk of GIB of more than 95%. The positive value of Ψ in one patient without GIB could be explained by the greater adaptive capacity of this 19-year-old individual or by the influence of as yet unidentified genetic factors.

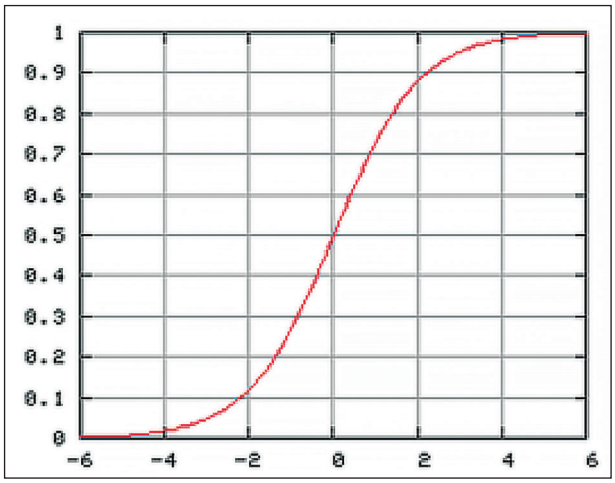

Fig. 1. Logistic curve.
Note. To assess the risk of GIB, Ψ (horizontal axis) was calculated from real data (X1–X4), and then y = exp(Ψ) / (1 + exp(Ψ)) was calculated using the logistic curve, and the probability of GIB was determined (vertical axis).

Table 7. Frequency of GIB with respect to risk factors.

Number of points	Values in groups, *N* (%)		Total, *N*	*P*
	Without GIB, 22 (66.67)	With GIB, 11 (33.33)	With and without GIB, 33	
Performing neurovegetative stabilization regardless of PSH manifestations (0 — no; 1 — yes)				
0	11 (91.67)	1 (8.33)	12	0.007
1	11 (52.38)	10 (47.62)	21	
Peptic (gastric and/or duodenal) ulcer disease detected prior to admission (0 — no; 1 — yes)				
0	21 (77.78)	6 (22.22)	27	0.046
1	1 (16.67)	5 (83.33)	6	
Karnofsky Index on admission to the hospital				
>75	17 (94.44)	1 (5.56)	18	<0.001
⩽75	5 (33.33)	10 (66.67)	15	
Manifestations of PSH 24 hours after brain injury				
<1	19 (100.00)	0 (0.00)	19	<0.001
⩾1	3 (21.43)	11 (78.57)	14	

Note. Fisher's criterion was used in the calculations.

Limitations of the presented model include a wide (95%) confidence interval due to the small sample size, sensitivity of 90.7%, power of 0.80, use of a history parameter (history of GI mucosal injury), correlated predictors (manifestations of PSH and neurovegetative stabilization), scale-based assessment of PSH.

Conclusion

The logistic regression model predicted the risk of GIB in patients with brain injury of different etiology with high sensitivity, accuracy and specificity. Significant risk factors for GIB included PSH severity on day 1 after brain injury, history of gastric mucosal injury, and Karnofsky index at hospital admission. Thus, identification of risk factor thresholds allows stratification of patients into risk groups for development of upper GI bleeding, while management of risk factors may help reduce the incidence of upper GI bleeding in patients with brain injury.

Supplement

The following 70 parameters were analyzed: sex, age of the patient; number of full days of neurovegetative stabilization without and with the administration of a sedative; length of hospital stay; Karnofsky Index scores on admission to the hospital, on admission to the intensive care unit, and on discharge; PSH scores on admission to the hospital; FOUR scores on admission to the intensive care unit; systolic blood pressure on admission to the intensive care unit; systolic blood pressure on admission to the hospital; the fact of prescription and timing of neurovegetative stabilization before the manifestations of paroxysmal sympathetic hyperactivity and after their appearance; repeated brain surgery; death; pneumonia; lung ventilation longer than 24 and 48 hours; temporary tracheostomy; cerebral edema and cerebrospinal fluid flow abnormalities on CT or MRI; ventriculoperitoneal shunt; systemic inflammatory response; meningitis; hepatitis; recurrent hemorrhagic lesions of the brain; administration of anticoagulants, antiplatelet agents, corticosteroids, administration of corticosteroids at a dose of more than 8 mg per day for 2 days, administration of non-steroidal anti-inflammatory drugs more than once per day for at least 3 days, administration of proton pump inhibitors, antacids, H2 histamine antagonists, upper endoscopy prior to hospitalization; history of gastric and/or duodenal ulcer disease; blood in stool and/or vomit during hospitalization; tube feeding during treatment; coagulopathy; sepsis; increase in urea and creatinine levels more than 1.5 times the upper limit of normal; hemoglobin and

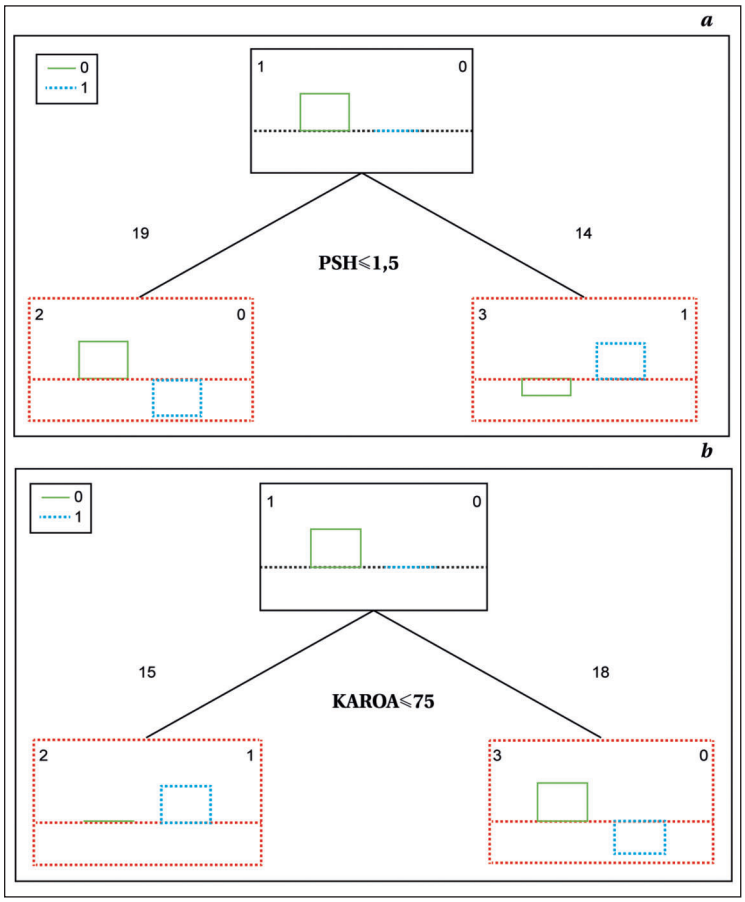

Fig. 2. Example of classification tree construction for PSH (*a*) and Karnofsky index (*b*) at patient admission to the hospital.
Note. Rectangles represent parts of classification trees; black solid lines represent splits; red dashed lines represent terminal nodes; green solid line represents a class without overt GI bleeding; blue dashed line represents a class with overt GI bleeding; numbers above rectangles indicate the number of observations that fell into nodes from the split; the number in the upper left corner of the rectangle is the ordinal number of the node; the number in the upper right corner indicates the predicted class.

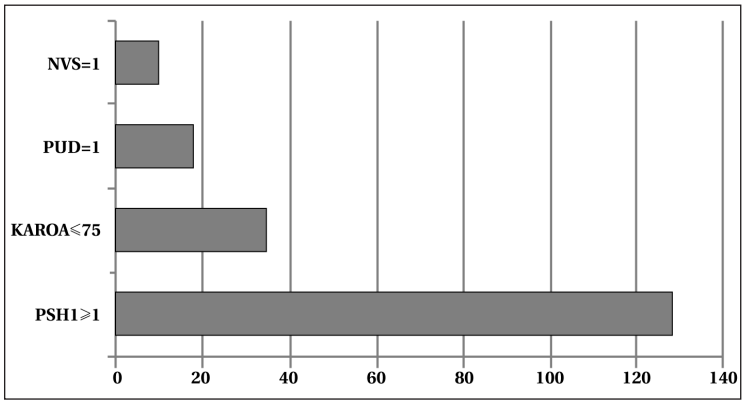

Fig. 3. Variation of the risk of GIB with changes in some parameters.

lactate levels on admission to hospital and after confirmation of brain injury; changes in vegetative (Kerdo) index and Glasgow Coma Scale scores during different periods; manifestations of PSH during different periods; inotropic support during hospitalization; body mass index; diabetes mellitus; documented mucosal lesions of the upper GI tract; documented gastrointestinal bleeding (blood in stool and/or vomiting with blood); documented clinically significant gastrointestinal bleeding.

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