**Original Article:**

**Gastroduodenal Ulcer Bleeding: The Prognosis of Rebleeding**

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**Abstract:**

**Purposes:** The study’s purpose was to develop a prognostic scale for identifying patients at high or low risk of recurrent ulcer bleeding (RB). **Methods:** To identify the factors influencing RB, a retrospective single-centre study of 240 patients with ulcerative bleeding was carried out. The first group included 52 patients with RB, the second group included 188 patients who did not have RB. The authors identified criteria associated with the development of recurrent ulcerative bleeding. The identified criteria were included in the recurrent bleeding prognostic scale. To assess the quality of the prognosis of the developed predictive system and compare it to analogous, a single-centre retrospective study was carried out, which included 100 patients with ulcerative bleeding. The efficiency of the elaborated predictive system was compared to the mGBS and RS scales using the ROC-analysis approach. **Results:** The following criteria influenced the development of rebleeding: shock index, the number of erythrocytes, urea and total blood protein, ulcer localization along the lesser curvature of the stomach and the posterior wall of the duodenum, Type 2A, 2C, and 3 hemostasis according to Forrest. The developed scale demonstrated a higher quality of the RB prognosis in comparison with the mGBS and RS (AUROC - 0.877, 0.784, and 0.731, respectively). The sensitivity was 90.5%, the specificity was 78.5%. **Conclusion:** The developed scale can be used to identify patients with a low or high risk of recurrent ulcer bleeding. With further study of the effectiveness of the scale, it is possible to shift the threshold value for changing the indicators of specificity and sensitivity. **Key Words:** Ulcerative gastroduodenal bleeding, Rebleeding, Risk assessment, Prognostic scale

**Introduction:**

Bleeding from the upper gastrointestinal tract remains an acute and complex problem in emergency surgery. In the structure of non-varicose bleeding, the most common causes are stomach and duodenal ulcers. (1) The global incidence of ulcerative bleeding does not appear to be decreasing, with 20-50 cases per 100,000 people these days. (2) Despite eradication therapy, the use of current proton pump inhibitors (PPIs), and the development of therapeutic endoscopy, ulcerative bleeding mortality remains high, ranging from 5 to 10% in different countries, according to the authors. (3) This type of bleeding complicates the underlying disease and makes surgical therapy more difficult. (4-6) Old age, decompensated comorbidity, and rebleeding are thought to be the main reasons for a negative outcome in the treatment of patients with ulcerative bleeding. (7) According to the authors’ observations, recurrent ulcer bleeding occurs in 12.4-17.3% of cases. (8, 9) Recurrent bleeding is a major medical consequence that increases the risk of lethal outcome. (10,11) Despite the suggested predictors, the difficulty of anticipating ulcer rebleeding remains relevant today. (12-14) The study’s objective was to develop a prognostic scale to identify patients with high and low risk of rebleeding and then compare the quality of the prognosis of the elaborated scale to analogous.

**Materials and Methods**
The study was carried out in two stages. At the first stage, a prognostic scale was developed. For this purpose, the authors performed a retrospective analysis of the treatment outcomes of 240 patients with ulcer bleeding admitted to the surgical department of the Beloretsk Central District Hospital between 2008 and 2018. The inclusion criteria were clinical manifestations of gastroduodenal bleeding (vomiting of fresh or altered blood, melena, collapse); a stomach or duodenal ulcer as a source of bleeding; gastroscopy, clinical and biochemical analyses performed within 2 hours after admission. The exclusion criteria were age less than 18 years, the presence of varicose veins of the esophagus or stomach, and signs of bleeding from the lower gastrointestinal tract. The patients were divided into two groups. Group 1 included 52 patients with RB, and group 2 included 188 patients without RB. The characteristics of the comparison groups are presented in Table 1.
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At the second stage, the quality of the prognosis of the elaborated scale was assessed and compared to the most cited up-to-date prognostic systems: Glasgow-Blatchford score (GBS) and Rockall score (RS). The authors performed a retrospective analysis of the treatment outcomes of 100 patients with ulcer bleeding who were admitted to the Ufa Emergency Hospital’s surgical departments in 2019. The inclusion and exclusion criteria were similar to those in the first stage. Table 2 presents the general characteristics of the studied group of patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (with RB)</th>
<th>Group 2 (without RB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity, n</td>
<td>52</td>
<td>188</td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, years (IQR)</td>
<td>55 (44.70)</td>
<td>55 (45.63)</td>
</tr>
<tr>
<td>Maximum, years</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Minimum, years</td>
<td>92</td>
<td>88</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>44 (84.6%)</td>
<td>142 (75.5%)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>8 (15.4%)</td>
<td>46 (24.5%)</td>
</tr>
</tbody>
</table>

**Symptoms:**
- Vomiting, n (%) 27 (51.9%) 92 (48.9%)
- Melena, n (%) 41 (78.8%) 141 (75%)
- Collapse, n (%) 23 (44.2%) 42 (22.3%)

**Localisation:**
- Stomach, n (%) 32 (61.5%) 119 (63.3%)
- Duodenum, n (%) 20 (38.5%) 69 (36.7%)

**Forrest bleeding rate:**
- IA, n (%) 2 (3.8%) 0
- IB, n (%) 10 (19.2%) 25 (13.3%)
- 2A, n (%) 16 (30.8%) 24 (12.7%)
- 2B, n (%) 14 (26.9%) 50 (26.6%)
- 2C, n (%) 5 (9.6%) 57 (30.3%)
- 3, n (%) 2 (3.8%) 27 (14.4%)
- No data 3 (5.8%) 5 (2.7%)

**Negative outcomes:**
- Operative treatment, n (%) 41 (78.8%) 14 (7.4%)
- Post-operative lethality, n (%) 11 (26.8%) No
- Lethality, n (%) 14 (26.9%) 14 (7.4%)

**Table 1: Characteristics of comparison groups**

**Table 2: The general characteristics of the study group (to compare the quality of the prognosis)**

**Statistical processing**

Statistical processing was performed using the IBM SPSS Statistics v.23 software (developed by IBM Corporation). The normality of the distribution of quantitative variables was checked using the Kolmogorov-Smirnov test. The mean values of the variables of the independent groups were compared using the Student’s t-test (with a normal distribution) or the Mann-Whitney U test (with non-normal distribution). The nominal data were compared using Pearson’s chi-squared test (%). The odds ratio (OR) was used as a quantitative measure of effect when comparing relative values. To assess the diagnostic significance of quantitative signs and the choice of threshold values to prognosticate a certain outcome, the ROC curves analysis method and the Youden index calculation were used. To build a prognostic model, the discriminant analysis method was used. To determine the quality of the predictive model, the ROC analysis method with the determination of the area under the curve (AUROC) was used, as well as the calculation of sensitivity and specificity using the standard method. Differences in indicators were considered statistically significant at a significance level of p<0.05.

**Results**

**Identifying Significant Variables**

The following clinical, laboratory and endoscopic criteria were selected as potentially related to the RB onset: age, gender, type of vomiting (fresh blood or “coffee grounds”), melena, ulcerative and alcohol history, ulcer localization, Forrest type of hemostasis, ulcer type (acute or chronic), heart rate (HR), systolic blood pressure (SBP), shock index (SHI), red blood cell count, the quantity of hemoglobin, urea, creatinine, and total protein. It is important to note that all data, including laboratory tests, were obtained within the first two hours after the patient was admitted.

The analysis results revealed that the studied groups had statistically significant differences in the following variables: SHI, erythrocytes, total protein, urea, ulcer localization, and the state of hemostasis according to the Forrest classification (Table 3).

Considering that the ulcer localization and the hemostasis type according to Forrest are multifactorial signs, their relationship with the RB onset was calculated as follows: the RB percentage, the chi-square index and OR of the RB onset were calculated for each sign. The following endoscopic signs were associated with the RB onset: ulcer localization along the lesser gastric curvature - Pearson’s chi-square test p=0.014, OR=2.37 (95% CI: 1.18 - 4.74); ulcer localization along the duodenum posterior wall - Pearson’s chi-square test p=0.002, OR=3.84 (95% CI: 1.69 - 8.73); Forrest 2A ulcer bottom condition - Pearson chi-square test p=0.003, OR=3.17 (95% CI: 1.55 - 6.48); Forrest 2C+3 ulcer bottom condition - Pearson chi-square test p=0.001, OR=0.24 (95% CI: 0.10 - 0.56).

**Formation of the prognosis scale**

The ulcer localization along the lesser curvature or the posterior wall of the duodenum and the hemostasis type according to Forrest (2A, 2C, 3) are dichotomous variables, which means there are only two options: "yes" or "no". For quantitative variables, a threshold value had to be determined. The ROC-curves method was used to select the cut-off point. To calculate a suitable threshold value, two methods were used: 1) the threshold value corresponds to the point on the ROC curve, where the values of sensitivity (Se) and specificity (Sp) are as close to each other as possible; 2) the threshold value corresponds to the point at which the Youden index will be maximum (calculated by the Se+Sp-1 formula). The following threshold values were calculated: Se=1; erythrocytes - 3.0; total protein - 58.0 g/l; urea - 8 mmol/l.
To assess the degree of influence of each variable on the likelihood of rebleeding, we used the method of multivariate statistical analysis - the discriminant analysis. After drawing up the discriminant equation, at one of the stages, the standardized coefficients of the discriminant variables were calculated, which enabled for the estimate of each variable’s relative contribution to the differences between the groups. Coefficients that were inconvenient to use were transferred to the corresponding points. Table 4 shows the final prognosis scale.

The currently existing prognostic systems can be divided into three groups:
1) a scale that includes only endoscopic criteria: Rockall scales, including endoscopic and clinical criteria: Rockall Blatchford score, AIMS65 scale, etc.;
2) a scale that includes only clinical criteria: Glasgow score, Forrest scale, etc.;
3) scales, including endoscopic and clinical criteria: Rockall score, PESR bleeding recurrence prediction system.

Table 3: Revealing statistically significant differences in 2 groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Statistically significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54.9±2.6</td>
<td>54.2±1.2</td>
<td>Student’s t-test p=0.783</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>98 (IR 85-119)</td>
<td>90 (IR 86-100)</td>
<td>Mann-Whitney U test p=0.024</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>110 (IR 90-120)</td>
<td>110 (IR 100-120)</td>
<td>Mann-Whitney U test p=0.043</td>
</tr>
<tr>
<td>Shock index</td>
<td>0.92 (IR 0.77-1.2)</td>
<td>0.82 (IR 0.72-0.96)</td>
<td>Mann-Whitney U test p=0.002</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>2.84±0.13</td>
<td>3.19±0.07</td>
<td>Student’s t-test p=0.02</td>
</tr>
<tr>
<td>Hemoglobin, g/l</td>
<td>90±4</td>
<td>98±2</td>
<td>Student’s t-test p=0.071</td>
</tr>
<tr>
<td>Urea, mmol/l</td>
<td>12.5 (IR 8.9-15.8)</td>
<td>7.8 (IR 6.2-10.5)</td>
<td>Mann-Whitney U test p=0.001</td>
</tr>
<tr>
<td>Creatinine, μmol/l</td>
<td>112.2 (IR 85.6-158.8)</td>
<td>85.5 (IR 70-107.8)</td>
<td>Mann-Whitney U test p=0.001</td>
</tr>
<tr>
<td>Total protein, g/l</td>
<td>55.3±0.9</td>
<td>61.9±0.6</td>
<td>Student’s t-test p=0.001</td>
</tr>
</tbody>
</table>

Table 4: The bleeding recurrence prognosis system

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Number of points</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHI exceeding or equalling to 1</td>
<td>+1</td>
</tr>
<tr>
<td>Erythrocytes less than 3</td>
<td>+1</td>
</tr>
<tr>
<td>Total protein less than or equals to 58 g/l</td>
<td>+4</td>
</tr>
<tr>
<td>Urea exceeding 8 mmol/l</td>
<td>+4</td>
</tr>
<tr>
<td>Ulcer localized along the lesser gastric curvature</td>
<td>+2</td>
</tr>
<tr>
<td>Ulcer localized on the duodenum back wall</td>
<td>+3</td>
</tr>
<tr>
<td>2A Forrest hemostasis type</td>
<td>+2</td>
</tr>
<tr>
<td>2C or 3 Forrest hemostasis type</td>
<td>-3</td>
</tr>
</tbody>
</table>

The ROC analysis method was used to calculate the threshold value, after which the risk of the RB onset becomes high. After constructing the ROC curve, it turned out that the maximum value of sensitivity and specificity (86.5% and 82.3%, respectively) was reached with a value of 6.5 points. Youden’s index also had a maximum value at this point: 0.865+0.823-1=0.688. Thus, the value of 6.5 points was taken as a cut-off point, that is, with a score of 7 or more, the risk of RB is considered high.

At the next stage, the prognosis quality of the elaborated scale was checked and compared to analogues. The scores were calculated according to the elaborated scale, the mGBS and RS. In the study group of patients, the number of points on the original scale ranged from 3 to 12 points, on the mGBS scale - from 0 to 14 points, and on the RS scale - from 1 to 7 points. The prognosed negative outcome was the RB onset. The ROC-curve was plotted and the area under it calculated (AUROC). The curve is shown in Graph 1.

The AUROC indices were: for the elaborated scale - 0.877 (95% CI: 0.820-0.934), for mGBS - 0.784 (95% CI: 0.696-0.872), for RS - 0.731 (95% CI: 0.634-0.829). Based on the ROC analysis, we can say that the developed scale has a higher quality of the RB forecast than its analogues. The sensitivity and specificity indicators of the developed scale were calculated according to the standard method. The sensitivity was 90.5%, the specificity was 78.5%. The overall prognosis accuracy was 81%.

**Discussion**

Our study demonstrates that ulcerative bleeding is still an issue today. We saw no change in the incidence across the 10-year follow-up period. According to our data, ulcerative bleeding is the most common type of non-variceal bleeding, accounting for half of all cases (51 %). The death rate was 6.25 % over the study period. RB is still a common complication of the disease, occurring in 21.7 % of the cases. The mortality rate in the patients with RB was 26.9%, while the mortality rate in the group with a relapse-free course of the disease was just 0.5 %. Further investigation revealed that recurrent bleeding in peptic ulcer disease is one of the leading causes of death, with rebleeding raising the risk of death tenfold compared to patients without relapse (p<0.001, OR=68.9, 95% CI: 8.8-539.7). As a result, one of the possible strategies to reduce mortality is to prognosticate recurrent bleeding and prevent it.

The currently existing prognostic systems can be divided into three groups:
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2) a scale that includes only clinical criteria: Glasgow-Blatchford score, AIMS65 scale, etc.;
3) scales, including endoscopic and clinical criteria: Rockall score, PESR bleeding recurrence prediction system.

Graph 1: ROC-curve for the “recurrent bleeding” outcome

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The lack of endoscopic criteria in the composition of various prognostic systems is one of their drawbacks. The endoscopic picture (ulcer localization, hemostasis type), according to our findings, has a significant impact on the development of RB. Complex multistage calculation processes and difficult-to-remember thresholds are other disadvantages of some scales. That makes using these scales in daily work more difficult, which is why prognostic systems aren’t widely used. Additional difficulties arise from the criteria that can be interpreted differently by two experts, adding a high level of subjectivity into risk assessment.

Conclusion
The purpose of the study was to develop a simple and easy-to-use prognostic system including clinical, laboratory, and endoscopic criteria. The study made it possible to identify the use prognostic systems isn’t wide applicability only for ulcerative bleeding. Thus, we believe that the new scale is more convenient to use than the interval type used in many other prognostic systems. The new scale outperformed the mGRBS and RS in terms of predicting RB. A limitation of the study could be the fact that it is a retrospective single-centre research with a small sampling. Also, the scale’s applicability only for ulcerative bleeding should be considered its specific feature. Larger multicentre prospective studies are needed to confirm our findings.

References