Rebleeding in peptic ulcer bleeding – a nationwide cohort study of 19,537 patients

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ABSTRACT

Background: Rebleeding is a frequent complication of peptic ulcer bleeding (PUB). The associated prognosis remains rather unclear because previous studies generally also included non-ulcer lesions.

Objective: We aimed to identify predictors for rebleeding; clarify the prognostic consequence of rebleeding; and develop a score for predicting rebleeding.

Methods: Nationwide cohort study of consecutive patients presenting to hospital with PUB in Denmark from 2006–2014. Logistic regression analyses were used to identify predictors for rebleeding, evaluate the association between rebleeding and 30-day mortality, and develop a score to predict rebleeding. Patients with persistent bleeding were excluded.

Results: Among 19,258 patients (mean age 74 years, mean ASA-score 2.4), 10.8% rebled, and 10.2% died. Strongest predictors for rebleeding were endoscopic high-risk stigmata of bleeding (Odds Ratio [OR]: 2.12 [95% Confidence Interval (CI): 1.91–2.36]), bleeding from duodenal ulcers (OR: 1.87 [95% CI: 1.69–2.08]), and presentation with hemodynamic instability (OR: 1.55 [95% CI: 1.38–1.73]). Among patients with all three factors (7.9% of total), 24% rebled, 50% with rebleeding failed endoscopic therapy, and 23% died. Rebleeding was associated with increased mortality (OR: 2.04 [95% CI: 1.78–2.32]). We were unable to develop an accurate score to predict rebleeding.

Conclusion: Rebleeding occurs in ~10% of patients with PUB and is overall associated with a two-fold increase in 30-day mortality. Patients with hemodynamic instability, duodenal ulcers, and high-risk endoscopic stigmata are at highest risk of rebleeding. When rebleeding occurs in such patients, consultation with surgery and/or interventional radiology should be obtained prior to repeat endoscopy.

Introduction

Acute upper gastrointestinal bleeding (UGIB) is a common cause of hospital admission with annual incidences of 61–172 per 100,000 and mortality rates of 2–14% [1–4]. Peptic ulcer bleeding (PUB) accounts for around one-half of the patients with UGIB [1,3]. Rebleeding develops in 13–18% of patients with PUB [1,5,6] and constitutes one of the most important complications in these patients. Based on studies of UGIB in general, rebleeding is associated with a 3–5 fold increase in mortality as compared to patients without rebleeding [6,7]. The prognostic consequence of rebleeding in patients with PUB is unclear, because previous studies generally include a high number of patients with minor bleeding lesions in the upper GI-tract, including esophagitis, gastroduodenal erosions, and Mallory–Weiss tears [6,7]. Due to good prognosis and low risk of rebleeding from many of the non-ulcer causes of bleeding in these studies, the estimates of mortality risk with rebleeding may not be valid for patients with PUB.

Two meta-analyses found that patients with hemodynamic instability, active bleeding during endoscopy, large ulcer size or ulcers located in the duodenum or lesser gastric curvature have an increased risk of rebleeding following endoscopic therapy [8,9]. The majority of included studies were small and performed prior to the era of proton pump inhibitors (PPIs) and modern endoscopic therapy with avoidance of epinephrine monotherapy. This is problematic as both PPIs and modern endoscopic therapy are associated with reduced risk of rebleeding [10,11] and may have an impact on the natural course of rebleeding.

In 1993, Saeed et al. presented the Baylor bleeding score for prediction of rebleeding following endoscopic therapy [12]. The Baylor bleeding score is based on patient age, comorbidities, site and stigmata of bleeding. Although one initial study seemed positive [13], later studies found the Baylor bleeding score to be inaccurate in predicting rebleeding [14–16].

As there is uncertainty, we need new data on rebleeding in patients with PUB who have been treated according to...
current accepted management strategies. Based on an unselected nationwide prospective cohort of patients with PUB, who had successful hemostasis at index endoscopy, we aimed to: (1) describe characteristics of patients who develop rebleeding, time from index endoscopy to intervention for rebleeding and severity of rebleeding; (2) evaluate the prognostic impact of rebleeding on mortality; (3) identify predictive factors for rebleeding; and (4) construct a weighted risk score for prediction of rebleeding.

Materials and methods

Study design and population

The study was conducted as a nationwide cohort study based on data from the Danish Clinical Register of Emergency Surgery (DCRES). DCRES is a nationwide database that includes prospectively collected data on consecutive patients admitted to Danish hospitals with verified PUB since 2006. The purpose of the database is to ensure a high quality of treatment and yearly reports are published with presentation of data on patients’ characteristics, treatment and outcome for all hospitals involved in treatment of PUB in Denmark. Danish hospitals are required by law to report data on all PUB patients to the DCRES. The reported data is compared to the National Patient Registry to ensure data accuracy and completeness. The DCRES has previously been described in greater detail [5].

Using DCRES we included patients admitted to hospital with PUB in Denmark during the period February 2006 to August 2014. In patients who were readmitted to hospital with PUB later in the inclusion period, only the initial hospitalization was included. In-patients who developed PUB during hospital admission for other reasons were also included in the study. Patients with persistent bleeding were excluded. An overview of included variables from the DCRES database is presented in Supplementary Appendix 1. Patients were followed until 30 days after time of admission to hospital or time from development of symptoms of bleeding in patients with in-hospital bleeding.

According to Danish law, review by an ethics board was not required for non-interventional observational studies [17]. The study was approved by the Danish Data Protection Agency (2014-41-3511). Our report follows STROBE guidelines [18].

Definitions

PUB was defined as presentation with hematemesis and/or melena, with subsequent upper endoscopy confirming the source to be peptic ulceration. Rebleeding was defined as redevelopment of symptoms of peptic ulcer bleeding within seven days of the initial endoscopy, associated with a significant decline in haemoglobin or confirmed by endoscopy, surgery, or imaging. Patients who were discharged from hospital but readmitted with rebleeding from an ulcer at the same location within seven days were also registered as having rebleeding. A list of further definitions used in the study is provided in Supplementary Appendix 2.

Statistical methods

Natural course and consequences of rebleeding

Rates of rebleeding, characteristics of patients developing rebleeding, time from index endoscopy to intervention for rebleeding, severity of rebleeding, and outcome were evaluated using descriptive statistics. Pearson’s chi-square test and Fischer’s exact test were used to compare proportions. Continuous data were compared using the Mann-Whitney U test.

Prognostic impact of rebleeding on 30-day mortality

Logistic regression analyses were used to estimate the association between rebleeding and 30-day mortality following adjustment for covariates. Regression models were constructed using backward elimination. Following inclusion of all candidate variables of interest, candidate variables with a p-value > .15 were evaluated and excluded from the model one by one if a comparison of the full and reduced models using likelihood ratio tests were associated with a p-value > .05. A description of included candidate variables is available in Supplementary Appendix 3. Rebleeding (yes/no) was included as a mandatory variable in all models. The outcome variable was 30-day mortality (yes/no). Results were presented as Odds Ratios (ORs) with 95% confidence intervals (CIs).

The appropriateness of the underlying assumptions (collinearity, linearity of independent variables and log odds) was examined graphically and statistically. Goodness of fit was evaluated using the Hosmer–Lemeshow test.

Based on clinical reasoning, evaluation of potential first order multiplicative interactions was performed using interaction terms. Potential interaction between rebleeding and age, and rebleeding and high ASA-score was analysed.

Due to interaction between ASA-score and rebleeding, we undertook two sensitivity analyses: (1) Estimation of the association between rebleeding and 30-day mortality when only including patients with ASA-score 1–2; and (2) estimation of the association between rebleeding and 30-day mortality when only including patients with ASA-score 3–4.

Predictive factors for rebleeding

Logistic regression analyses were used to identify predictive factors for rebleeding. Regression models were constructed using backward elimination similar to the method previously described. The candidate variables listed in Supplementary appendix 3, were also included as candidate variables in the model on predictive factors for rebleeding. Rebleeding (yes/no) was included as the outcome variable. Presentation of data, test of underlying assumptions, and goodness of fit were performed as previously described.

Risk score for prediction of rebleeding

Based on the identified predictors for rebleeding, a weighted risk score for early prediction of rebleeding was sought. The weight of each variable was determined based on the corresponding OR in the developed regression model. The
discriminative ability of the model for predicting rebleeding was evaluated by calculation of area under the receiver operating characteristic curves (AUROC). In order to keep the score as simple as possible, we excluded variables that did not contribute to an increase in AUROC. An AUROC of at least 0.80 was considered necessary for the model to have any clinical justification.

**Handling of missing data**

The prevalence and pattern of missing data was evaluated and found not to be missing completely at random (Little's test: \( p < .001 \)). Missing data was handled using multiple imputation [19]. All outcomes and baseline variables were included in the imputation model and 20 imputations were used.

**Sample size estimation**

The required sample size was estimated based on the work of Peduzzi et al. [20] with an expected rate of rebleeding of 13%, 30-day mortality rate of 10%, and inclusion of 15 covariates in the regression models. A minimum of 1200 patients were needed in the regression model identifying predictive factors for rebleeding and more than 1500 patients were needed in the regression model on the association between rebleeding and 30-day mortality.

**Software**

Data were analysed using STATA 14.0 (StataCorp, College Station, Texas, USA).

**Results**

**Population**

Based on data from DCRES, 20,897 hospital admissions of 19,537 patients with PUB were identified. Following exclusion of patients with persistent bleeding \((n = 279)\), a total of 19,258 patients were included in the study. Patient characteristics are shown in Table 1. A total of 2,071 patients (10.8%) developed rebleeding within seven days and 131 patients (0.68%) were lost at follow-up 30 days from admission to hospital.

We identified many differences in patients' characteristics (Table 1). In particular, patients developing rebleeding were characterized by presence of high-risk stigmata of bleeding at ulcer site at endoscopy \((1,463/2,071 (72\%) \text{ vs. } 8,160/17,180 (48\%); \ p < .001\), bleeding from duodenal ulcers \((1,380/2,071 (70\%) \text{ vs. } 8,313/17,180 (50\%); \ p < .001\), and presentation with hemodynamic instability \((592/2,071 (29\%) \text{ vs. } 2,795/17,180 (16\%); \ p < .001\) when compared with patients who did not experience any rebleeding episodes. In accordance with this, rebleeding rates were higher for patients who had hemodynamic instability at time of presentation \((592/3,387 (17\%) \text{ vs. } 1,456/15,756 (9\%); \ p < .001\), high-risk stigmata of bleeding at endoscopy \((1,463/9,623 (15\%) \text{ vs. } 583/9,350 (6.2\%); \ p < .001\), or bleeding from duodenal ulcers \((1,380/9,693 (14\%) \text{ vs. } 594/8,833 (6.7\%); \ p < .001\) compared with patients without hemodynamic instability, high-risk stigmata of bleeding, or duodenal ulcers, respectively.

Among patients who developed rebleeding, the ability to achieve endoscopic hemostasis at repeat endoscopy was considerably lower than the overall rate of initial endoscopic hemostasis \((1,380/1,769 (78\%) \text{ vs. } 10,291/10,913 (94\%); \ p < .001\). In patients with rebleeding, 1,380/1,994 (69%) had successful hemostasis at repeat endoscopy, 501/1,994 (25%) underwent surgery \((208/1,994 (10\%) \text{ without preceding repeat endoscopy), 52/1,994 (2.6\%) \text{ received interventional radiology following failed endoscopic treatment, 44/1,994 (2.2\%) \text{ did not undergo further interventions following repeat endoscopy, despite lack of endoscopic hemostasis, and in 17/1,994 (0.9\%) the interventions performed were not clearly registered (Supplementary Appendix 4).}

**Table 1. Patients characteristics.**

| General characteristics | No rebleeding \(n = 17,180\) | Rebleeding \(n = 2,071\) | Total \(n = 19,258\) | \(p\) Value |
|-------------------------|-----------------------------|--------------------------|---------------------|-----------|
| Age (years, median [95% CI]) | 74.2 [48–91] | 75.7 [51–90] | 74.4 [48–91] | .003 |
| Sex, male | 9,326 (54) | 1,160 (56) | 10,491 (54) | .14 |
| ASA-score (mean, [95% CI]) | 2.4 [1–4] | 2.6 [1–4] | 2.4 [1–4] | <.001 |
| High alcohol consumption | 2,512 (16) | 347 (18) | 2,859 (16) | .004 |
| Daily smoking status | 5,304 (35) | 736 (41) | 6,040 (35) | <.001 |
| Medication | | | | |
| Aspirin | 7,660 (45) | 850 (42) | 8,514 (45) | .004 |
| NSAIDs | 4,415 (27) | 643 (33) | 5,060 (28) | .002 |
| AC/ADP-RI | 3,106 (18) | 316 (16) | 3,422 (18) | .002 |
| Steroids | 1,388 (8.5) | 226 (11) | 1,614 (8.8) | .001 |
| In-hospital bleeding | 3,622 (29) | 531 (36) | 4,154 (30) | <.001 |
| Hemodynamic instability | 2,795 (16) | 592 (29) | 3,388 (18) | <.001 |
| Blood tests | | | | |
| Hemoglobin (g/dL, median [95% CI]) | 8.9 (5.2–13.7) | 8.1 (4.7–12.4) | 8.9 (5.2–13.5) | <.001 |
| Creatinine (µmol/L, median [95%CI]) | 85 (48–219) | 89 (47–242) | 86 (48–221) | <.001 |
| Ulcer characteristics | | | | |
| Duodenal ulcer | 8,313 (50) | 1,380 (70) | 9,693 (52) | <.001 |
| High-risk stigmata of bleeding' | 8,160 (48) | 1,463 (72) | 9,629 (51) | <.001 |
| Length of hospital stay (days, median [95% CI]) | 4 [1–16] | 8 [2–31] | 4 [1–19] | <.001 |
| In-hospital mortality | 745 (4.3) | 339 (16.4) | 1,085 (5.6) | <.001 |
| 30-day mortality | 1,505 (8.8) | 441 (21.4) | 1,947 (10.2) | <.001 |

ADP-RI: anticoagulants or adenosine diphosphate receptor inhibitors; ASA: American Society of Anesthesiologists; CI: confidence interval; NSAIDs: nonsteroidal anti-inflammatory drugs.

'High-risk stigmata of bleeding at ulcer base was defined as active bleeding, non-bleeding visible vessel or an adherent clot at ulcer base.
Time to intervention for rebleeding
The index endoscopy was performed within 24 h from time of hospital admission, or time from development of symptoms of bleeding in patients with in-hospital bleeding, in 15,487/19,258 (80.4%) of patients. The median time from index endoscopy to intervention for rebleeding was 33.5 h [95% CI: 4.0–133] (Figure 1). Among patients with rebleeding, 1152/1455 (79%) underwent hemostatic intervention within 72 h from the index endoscopy.

Prognostic impact of rebleeding on 30-day mortality
Patients who developed rebleeding had a markedly higher 30-day mortality rate when compared to patients who did not develop rebleeding (441/2,060 (21%) vs. 1,505/17,060 (8.8%); p < .001). Following adjustment for covariates, rebleeding was associated with an overall OR of 2.04 [95% CI: 1.78–2.32] for 30-day mortality. Regression analyses on the association between rebleeding and mortality were complicated by interaction between rebleeding and comorbidity (Table 2). When adjusting for interaction, rebleeding was associated with an OR of 2.56 [95% CI: 2.00–3.26] for 30-day mortality in patients with an ASA-score of 1–2, corresponding to none or minor comorbidity, and an OR of 1.88 [95% CI: 1.62–2.19] in patients with and ASA-score of 3–5 indicating presence of severe comorbidity.

Predictive factors for rebleeding
Several factors were found to be associated with increased risk of rebleeding (Table 3). The strongest predictors were related to the characteristics of the bleeding episode including high-risk stigmata of bleeding in ulcer base (OR: 2.12 [95% CI: 1.91–2.36]), bleeding from duodenal ulcers (OR: 1.87 [95% CI: 1.69–2.08]), and presentation with hemodynamic instability (OR: 1.55 [95% CI: 1.38–1.73]). Furthermore, higher ASA-score, age ≥ 70 years, anaemia, use of NSAIDs or steroids, daily smoking status, and in-hospital status were also related to increased risk of rebleeding within seven days.

Table 2. Association between rebleeding and 30-day mortality among 18,831 patients with peptic ulcer bleeding.

| Variable                          | Univariate OR [95% CI] | Multivariate OR [95% CI] | p Value |
|-----------------------------------|------------------------|--------------------------|---------|
| Rebleeding                        | 2.80 [2.49–3.15]       |                          |         |
| ASA-score 1–2                     | 2.56 [2.00–3.26]       | <.001                    |         |
| ASA-score 3–5                     | 1.88 [1.62–2.19]       | <.001                    |         |
| General characteristics           |                        |                          |         |
| Age                               |                        |                          |         |
| <70 years                         | (Reference)            | (Reference)              |         |
| 70–79 years                       | 1.79 [1.56–2.05]       | <.001                    |         |
| ≥80 years                         | 3.28 [2.91–3.70]       | <.001                    |         |
| Male sex                          | 0.96 [0.87–1.05]       | <.001                    |         |
| High ASA-score                    | 5.01 [4.47–5.61]       | <.001                    |         |
| No rebleeding                     | -                      |                          |         |
| Rebleeding                        | 3.90 [3.41–4.46]       | <.001                    |         |
| High alcohol consumption          | 0.98 [0.86–1.13]       | <.001                    |         |
| Daily smoking status              | 0.91 [0.82–1.01]       | 0.10                     |         |
| Medication                        |                        |                          |         |
| Aspirin                           | 1.13 [1.03–1.25]       | <.001                    |         |
| Anticoagulants /ADP-RI            | 0.95 [0.84–1.07]       | <.001                    |         |
| NSAIDs                            | 0.94 [0.85–1.05]       | <.001                    |         |
| Steroids                          | 2.28 [1.99–2.62]       | <.001                    |         |
| Bleeding characteristics          |                        |                          |         |
| Hemodynamic instability           | 2.46 [2.22–2.73]       | <.001                    |         |
| High-risk stigmata of bleeding    | 1.95 [1.77–2.16]       | <.001                    |         |
| Duodenal ulcer                    | 1.86 [1.69–2.06]       | <.001                    |         |
| Time of admission to hospital     |                        |                          |         |
| Weekend                           | 1.07 [0.96–1.19]       |                          |         |
| Year                              | 0.98 [0.96–0.99]       | <.001                    |         |
| In-hospital bleeding              | 1.93 [1.72–2.16]       | <.001                    |         |

ADP-RI: anticoagulants or adenosine diphosphate receptor inhibitors; ASA: American Society of Anesthesiologists; CI: confidence interval; OR: Odds ratio; NSAIDs: nonsteroidal anti-inflammatory drugs; Year: year of hospital admission. Variables registered with “•” in Multivariate, adjusted OR were removed from the model during backwards elimination (p > .15). For details on how the variables were handled in the model please refer to the section on statistical methods.

Development of a risk scoring system
Despite identification of ten predictive factors associated with rebleeding, it was not possible to construct a weighted risk score that had an acceptable discriminative ability for prediction of rebleeding above the predetermine threshold (AUROC ≥ 0.80).

Rebleeding triad
Ninety percent of patients who developed rebleeding had one or more of the following findings: 1. high-risk stigmata of bleeding in the ulcer base, 2. duodenal ulcers, and 3. presentation with hemodynamic instability. All three conditions were present in 1,439/18,213 (7.9%) of patients. This subgroup had a rebleeding rate of 23.8% [95% CI: 21.6–26.1%] that often could not be controlled by endoscopic therapy (49.7% [95% CI: 47.1–52.3%]) and had a 30-day mortality rate of 23.4% [95% CI: 21.2–25.7%]. Patients fulfilling two out of the three conditions (5,426/18,213; 30%) had a rebleeding rate of 15.9% [95% CI: 14.9–16.9%] and a 30-day mortality rate of 13.0% [95% CI: 12.1–13.9%]. Among patients with none of the three conditions present (4,399/18,213; 24%), only 3.6% [95% CI: 3.0–4.2%] developed rebleeding. The Rebleeding Triad had an AUROC [95% CI] of 0.67 [0.65–0.68] for predicting rebleeding. Further details on the...
Table 3. Predictive factors for rebleeding among 18,876 patients with peptic ulcer bleeding.

| Variable                      | Univariate OR (95% CI) | Multivariate, adjusted OR (95% CI) | p Value |
|-------------------------------|------------------------|-----------------------------------|---------|
| General characteristics       |                        |                                   |         |
| • Age ≥70 years               | 1.18 [1.08–1.30]       | 1.21 [1.08–1.34]                  | .001    |
| • Male sex                    | 1.07 [0.98–1.17]       |                                   |         |
| • ASA-score                   |                        |                                   |         |
| 1 (Reference)                 | (Reference)            |                                   |         |
| 2                             | 1.18 [0.99–1.39]       | 1.05 [0.88–1.25]                  | NS      |
| 3                             | 1.73 [1.46–2.04]       | 1.27 [1.06–1.52]                  | .009    |
| 4                             | 2.35 [1.89–2.92]       | 1.42 [1.13–1.79]                  | .003    |
| • High alcohol consumption    | 1.20 [1.06–1.36]       |                                   |         |
| • Daily smoking status         | 1.29 [1.17–1.42]       | 1.26 [1.13–1.40]                  | <.001   |
| Medication                    |                        |                                   |         |
| • Aspirin                     | 0.88 [0.80–0.96]       |                                   |         |
| • Anticoagulants /ADP-RI      | 0.82 [0.72–0.93]       |                                   |         |
| • NSAIDs                      | 1.33 [1.20–1.47]       | 1.27 [1.15–1.41]                  | <.001   |
| • Steroids                    | 1.41 [1.22–1.63]       | 1.21 [1.04–1.41]                  | .016    |
| Blood tests                   |                        |                                   |         |
| • Hemoglobin (g/dL)           | 0.88 [0.86–0.89]       | 0.93 [0.91–0.95]                  | <.001   |
| • Creatinine (μmol/L)         | 1.00 [1.00–1.00]       |                                   |         |
| Bleeding characteristics      |                        |                                   |         |
| • Hemodynamic instability     | 2.09 [1.88–2.31]       | 1.55 [1.38–1.73]                  | <.001   |
| • High-risk stigmata of bleeding | 2.69 [2.42–2.98]     | 2.12 [1.91–2.36]                  | <.001   |
| • Duodenal ulcer              | 2.29 [2.08–2.53]       | 1.87 [1.69–2.08]                  | <.001   |
| Weekend admission to hospital  | 1.06 [0.96–1.18]       |                                   |         |
| In-hospital bleeding           | 1.39 [1.24–1.54]       | 1.15 [1.03–1.29]                  | .016    |

ADP-RI: anticoagulants or adenosine diphosphate receptor inhibitors; ASA: American Society of Anesthesiologists; CI: confidence interval; OR: odds ratio; NSAIDs: nonsteroidal anti-inflammatory drugs. Variables registered with “-“ in Multivariate, adjusted OR were removed from the model during backwards elimination (p > .15). For details on how the variables were handled in the model please refer to the section on statistical methods.

**Missing data**

There were missing values for rebleeding (n = 7), age (n = 70), ASA-score (n = 349), use of low-dose aspirin (n = 287), use of NSAIDs (n = 953), use of anticoagulants or ADP receptor inhibitors (n = 280), use of steroids (n = 917), alcohol use (n = 1,475), smoking status (n = 2,232), time of hospitalisation (n = 85), circulatory status at presentation (n = 108), hemoglobin level (n = 34), creatinine level (n = 222), time of endoscopy (n = 257), location of ulcer (n = 725), stigmata of bleeding at ulcer base (n = 278), outcome of index endoscopy (n = 42), length of hospital stay (n = 200), and 30-day mortality (n = 131).

**Discussion**

This nationwide cohort study shows that 10.8% of patients with PUB develop rebleeding within seven days. Rebleeding increases the risk of 30-day mortality with an OR 1.88–2.56 depending on level of comorbidity and is associated with an overall 30-day mortality rate of 21.4%. High-risk stigmata of bleeding in the ulcer base (active bleeding, visible vessel, or an adherent clot), bleeding from duodenal ulcers, and presentation with hemodynamic instability are important predictors of rebleeding.

Rockall et al. identified predictors for mortality among 3,981 patients with UGIB in the UK [6]. The authors found that rebleeding was associated with an overall OR of death of 5.57, but noted that the impact of rebleeding was highest in patients with a relatively low risk of death defined as a Rockall score of 3–4. In patients with higher risk of death, demonstrated by higher Rockall scores (5–8), rebleeding was associated with a two- to threefold increase in mortality. An Italian study of 1,020 patients with non-variceal UGIB showed that rebleeding was associated with an adjusted OR of 30-day mortality of 3.27 [7]. The present study shows that rebleeding is a significant predictor for 30-day mortality in PUB, but the prognostic impact may be somewhat less than indicated by previous studies. We believe this is explained by differences in case mix, as the aforementioned studies included patients with very different sources of UGIB (e.g., Mallory–Weiss tears, erosive disease, varices, tumors). In line with the findings by Rockall and colleagues in overall UGIB [6], we found that the prognostic impact of rebleeding on mortality depended on patients’ baseline risk. Rebleeding increases the relative risk of death most in patients with an ASA-score of 1–2 (Table 2), but as expected, the absolute risk of death is lower in these patients compared with patients with an ASA-score of 3–5 (4 vs. 18%).

A meta-analysis reported that hemodynamic instability (OR: 3.3), active bleeding during endoscopy (OR: 1.7), large ulcer size >2 cm (OR: 2.8), and posterior duodenal ulcer location (OR: 3.8) increases the risk of rebleeding following endoscopic therapy [8]. The validity of these findings may have changed over time as the majority of studies included used H2-blockers for acid suppression and some studies only applied endoscopic monotherapy with injection of epinephrine [8]. The present study shows that many factors are associated with rebleeding including patients characteristics (age, comorbidty, smoking status), medication use (NSAIDs, steroids), and bleeding-related characteristics (level of anemia, hemodynamic instability, high-risk stigmata of bleeding at ulcer site, ulcer location). According to our data, the strongest predictors for rebleeding are high-risk stigmata of bleeding at ulcer site, bleeding from duodenal ulcers and presentation with hemodynamic instability. Data from a national audit in the UK found that rates of rebleeding among UGIB patients on aspirin (13%), warfarin (13%), or NSAIDs (12%) were similar compared with patients not taking any of these medications (14%) [1]. In line with this, our data indicate that use of low-dose aspirin or anticoagulants are not associated with increased risk of rebleeding following adjustment for confounding. In contrast, we did find that use of NSAIDs was more common among patients who developed rebleeding compared with those who did not (33 versus 27%; p < .001) and regression analyses indicate that use of NSAIDs is associated with rebleeding (OR: 1.27 [95% CI: 1.15–1.41]). A Korean study of 904 patients with PUB found that comorbidity (OR 2.9), use of multiple drugs (OR: 3.1), albumin level (OR: 0.51), and presentation with hematemesis or hematochezia (OR: 1.9) was associated with rebleeding [21]. The 30-day mortality rate among the 64 patients who developed rebleeding in that study was surprisingly low (1.0%) [21]. We were unable to evaluate the risk of...
rebleeding associated with low albumin level and presentation with hematemesis or hematochezia due to lack of data.

Strengths of our study include the nationwide inclusion of a large number of consecutive patients with prospective registration of data. Limitations include that we did not have access to data describing the type of endoscopic therapy applied, ulcer size, detailed ulcer location (e.g., posterior duodenal bulb, lesser curve of stomach), detailed comorbidities, medical treatment, and cause of death. As DCRES has stopped including data on PUB, we were not able to provide newer data in this study. One of the aims of this study was to describe time to rebleeding. Due to the nature of registration in the DCRES, we were only able to describe time from index endoscopy to the intervention (endoscopy, surgery, transarterial embolization) performed following development of symptoms of rebleeding. Despite this, our data clearly illustrates that the vast majority of rebleeding episodes occur within 72 h from the index endoscopy.

Although we identified several predictors associated with rebleeding (Table 3), we were not able to develop a risk score that had acceptable discriminative ability for early identification of patients at high risk for rebleeding. The reason for this is most likely that the association between the predictors and outcome is not as strong as one may think. It is interesting to note that among patients who developed rebleeding, 28% had ulcers without high-risk stigmata of bleeding (fibrin covered or hemat in ulcer base), 30% had gastric ulcers, and 71% were hemodynamically stable at presentation (Table 1).

In conclusion, rebleeding is a frequent and serious complication in PUB resulting in a twofold increased risk of death within 30 days. The majority of rebleeding episodes occur within 72 h from the index endoscopy. Our data indicate existence of a Rebleeding Triad consisting of (1) high-risk stigmata of bleeding in the ulcer base, (2) bleeding from duodenal ulcers, and (3) presentation with hemodynamic instability. Physicians should be aware that 7.9% of patients with PUB fulfil these three criteria and they have a 23% rate of rebleeding and a 24% rate of 30-day mortality. Consideration for a higher-level of care should be given to patients with these features. When rebleeding does occur in such patients, early consultation with interventional radiology and/or surgery is appropriate, and repeat endoscopy should be performed by a very experienced endoscopist because endoscopic treatment is unsuccessful in 50% of cases. Similarly, the Rebleeding Triad can be used for rapid identification of the 24% of patients who fulfil none of the aforementioned criteria and only have a 3.6% risk of developing rebleeding. These low-risk patients may be suitable for early hospital discharge.

Guarantor of the article

SBL is the study guarantor.

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Author contributions

The study was designed by SBL and OBSDM. SBL collected data. The statistics were performed by SBL and LL. SBL and AJS wrote the paper with considerable input from LL and OBSDM. All coauthors approved the final manuscript.

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