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Risk Assessment and Prediction of Rebleeding in Bleeding Gastroduodenal Ulcer

Background and Study Aims: The aims of this study were to identify risk factors for recurrence of hemorrhage in bleeding gastroduodenal ulcers after endoscopic injection therapy, and to develop a simple and relevant prognostic score which could be used to assess the early risk of recurrence and the residual risk of rebleeding.

Patients and Methods: A prospective study was conducted from January 1995 to December 1998, in 738 patients who were admitted to our department for acute bleeding peptic ulcer and who underwent endoscopic examination. Ulcers with active bleeding or signs of recent bleeding were treated with injection therapy using epinephrine (1/10 000) and 1% polidocanol.

Results: Multivariate analysis revealed that liver cirrhosis, recent surgery, systolic blood pressure below 100 mmHg, hematemesis, Forrest classification, and ulcer size and site were significantly predictive variables for the recurrence of hemorrhage. Among these, Forrest classification was the most important. The overall accuracy of the predictive model was 71% (95% CI = 63–79%). The model showed a better sensitivity of 90% for early rebleeding (< 48 hours) than for late rebleeding (≥ 48 hours) where the sensitivity was 65%. A prognostic score was obtained and patients were classified into four risk classes: very low (VL), low (L), high (H), and very high (VH). The rebleeding rates for the four classes were 0%, 7.9%, 31.8% and 67.9%, and the mortality rates were 5.9%, 8.6%, 13.9% and 35.7%, respectively. The residual risk of rebleeding after 48 hours was 0%, 3.3%, 10.4%, and 14.3% in the VL, L, H and VH classes, respectively. After 5 days the residual risk was under 4% in all classes.

Conclusions: This study demonstrates that the proposed prognostic score, which is easily obtained after emergency endoscopy, is useful in clinical practice because it can identify patients with different levels of rebleeding risk. It can be helpful in patient management and decision making for discharge.

Introduction

Gastroduodenal peptic ulcer is the most frequent cause of acute hemorrhage of the upper digestive tract, being responsible in about 50% of cases, with an overall mortality rate of 10 to 14% [1–4]. Endoscopic therapy represents the treatment of choice and provides effective control of bleeding peptic ulcers. The rate of initial hemostasis provided by injection therapy is greater than 90%, but the incidence of rebleeding remains high, from 10 to 30% [5–8]. Recurrence of hemorrhage is one of the most important factors affecting the prognosis, and early prediction and treatment of rebleeding would improve the outcome in such patients.

Several clinical factors and endoscopic signs have been found to be associated with further hemorrhage [8]. However, as individual factors, they lack predictive accuracy. Scoring systems and mathematical models have been proposed, to stratify patients into different outcome categories and improve the prediction of rebleeding, but usually their complexity has limited their application in routine clinical situations.

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While the stigmata that predict rebleeding in the absence of endoscopic therapy have been studied extensively, few studies have specifically investigated stigmata which are predictive of rebleeding after endoscopic therapy [9,10].

The aim of this study was to identify the clinical and endoscopic risk factors for rebleeding after endoscopic treatment, and to devise a mathematical model for assessing the risk of early rebleeding. In addition, we classified patients into four categories associated with an increasing risk of rebleeding.

Patients and Methods

All the patients with acute gastric and/or duodenal ulcer bleeding, who presented consecutively to our endoscopy service between January 1 1995 and December 31 1998 were included in this study. Our endoscopy service is the 24-hour referral center for emergency endoscopies in the city area. Previous gastroduodenal surgery or the presence of malignant ulcers were criteria for exclusion from the study.

Patients admitted to the study presented clinical signs and/or symptoms of recent or active gastroduodenal bleeding, i.e. hematemesis, coffee-ground vomit, melena, or anemia. After initial stabilization, all patients underwent emergency endoscopy within 2 hours of admission to our department. In all cases endoscopic examination confirmed active or recent bleeding from gastroduodenal ulcer. Endoscopy was performed in all cases by members of the same team of four experienced physicians who use the same criteria of diagnosis and treatment. Stigmata of active or recent bleeding were categorized according to the Forrest classification [11]. During the emergency endoscopy, all ulcers with active bleeding, a visible nonbleeding vessel, or an adherent clot (Forrest Ia, Ib, IIa, IIb) were treated by endoscopic injection with epinephrine (1/10 000) and 1% polidocanol. Lesions with a black ulcer base or a clean base (Forrest IIc, III) were treated by medication.

Patients received blood transfusions before endoscopy if their hemoglobin level was below 8 g/dl. Patients with severe hemorrhagic shock, or with massive bleeding which could not be controlled with endoscopic therapy, underwent emergency surgery. All patients received intravenous ranitidine 50 mg three times a day and, after refeeding, omeprazole 20 mg twice a day. All patients underwent repeat endoscopy 48 hours after definitive haemostasis, or earlier in cases of clinical suspicion of recurrence.

Clinical suspicion of recurrence was defined as the presence of hematemesis, melena, hypovolemia or a decrease in haemoglobin level by 2 g/dl after initial stabilization. In all cases the clinical suspicion of recurrence was confirmed by endoscopy. The therapy of choice for recurrence was endoscopic injection therapy. Patients with rebleeding which could not be controlled by endoscopic therapy underwent emergency surgery.

We analysed recurrences which happened within 30 days of the acute bleeding episode. Biopsy-based *Helicbacter pylori* testing was not done during emergency endoscopy, but was carried out after ulcer healing. For this reason *H. pylori* test results were not included in the data analysis of the present study.

We considered three groups of variables, related to patient history, magnitude of bleeding, and endoscopic findings. The clinical variables related to patient history were: gender; age; bleeding at home or during hospitalization; previous peptic ulcer disease; previous gastrointestinal hemorrhage; intake of nonsteroidal anti-inflammatory drugs (NSAIDs), and/or anticoagulant drugs; associated diseases; recent surgical operations (within 30 days prior to the hemorrhage), or previous operations (more than 30 days). With regard to operations, we considered only major cardiovascular, thoracic, orthopedic, abdominal and neurosurgical procedures. Concomitant diseases were classified into seven groups: malignancies, liver cirrhosis, chronic renal failure, arterial hypertension, diabetes mellitus, rheumatic diseases, and peripheral vasculopathy (ischemic heart disease, cerebrovascular accidents, peripheral arteriopathy).

The variables related to the magnitude of bleeding were: hematemesis; coffee-ground vomit; melena; anemia; blood pressure; heart rate; hypovolemic shock; hematocrit and hemoglobin level at admission; and number of units of blood transfused before endoscopic treatment.

The endoscopic variables were: the number, size and site of peptic ulcers; the Forrest classification; and the presence of gastritis or duodenitis. Peptic ulcer sites were grouped as the fundus–corpus, the antropyloric region, the duodenal bulb, and the postbulbar region. In the case of multiple ulcers, we considered the lesion at greatest risk of recurrence according to the Forrest classification.

Statistical Methods

Sample size was planned following the formula proposed by Whittemore [12].

Continuous variables were categorized according the system shown in Table **1**. Variables with more than two categories were recorded using an appropriate variable coding scheme. As suggested by Kramer [13], cutoff points were defined according to the existing medical literature [1,10,14].

All the covariates of known clinical relevance, and those whose univariate test (chi-squared for categorical variables and Kendall's tau for ordinal variables) had a *P*-value of less than 0.25 were considered candidates for entry into the logistic model [15].

In the logistic regression model, we estimated the optimal cutoff point using the maximum discrimination point criterion which maximises the quantity: (sensitivity + specificity)/2 [16].

Many works in the field of statistical forecasting show that, for obtaining an unbiased estimate of the classification accuracy of a predictive model, the classic in-sample goodness-of-fit measures are not adequate [17,18]. In fact, they quantify the closeness of the model predictions to the in-sample data, but they usually give no information regarding the true out-of-sample prediction capabilities of the model. Data-splitting methods represent a valuable solution to the above problem. The sample is repeatedly and randomly divided in two subsets: the learning set and the

testing set [19]. The parameters of the model are estimated *n* times from the *n* learning sets, while the corresponding testing sets are used to calculate the (out-of-sample) percentages of correctly classified patients. The mean and 95% confidence intervals (95% CI) of the *n* "bootstrap" estimates give a reliable description of the true predictive performance of the model. The data-splitting estimate gives a prospective assessment of the predictive power of the model.

In the Discussion section, we use odds ratios as rough approximations of risk ratios (odds ratios are good estimates of risk ratios only for rare events) [20].

Univariate and multivariate analyses were undertaken using STATA 7.0 (chi-squared, Kendall's tau, and multivariate logistic regression model estimations) and MATLAB 5.3, together with the Stixbox toolbox (data splitting, repeated logistic regression model estimations, sensitivity and specificity data-splitting estimation) [21].

Results

The present study was conducted from January 1, 1995 to December 31, 1998. During this period, 1597 patients with acute nonvariceal upper gastrointestinal bleeding were seen at our endoscopic service. Among these, 738 patients (46.2%) with acute gastroduodenal bleeding ulcer were included in this study. Table **1** gives the general characteristics of the study population. Among the 738 patients, bleeding recurred in 98 patients (13.3%) within 30 days from the first observation, with a mean number of 1.44 rebleeding episodes. A single recurrence was observed in 67.3% (66 patients), two recurrences in 24.4% (24 patients), three in 4.1% (four patients), four in 2.1% (two patients) and five in 2.1% (two patients). The highest rebleeding rates were observed between 12 and 24 hours (20.4%) and between 24 and 48 hours (32.7%). In 18 cases (18.4%), the rebleeding time ranged from 96 hours to a maximum of 11 days after the first hemorrhagic episode. No rebleedings were observed after 11 days from the first bleeding.

Endoscopic injection therapy was performed in 447 patients (60.6%) with Forrest Ia, Ib, IIa and IIb ulcers, while those with Forrest IIc and III ulcers received only medical therapy. In patients with active bleeding, endoscopic injection therapy achieved hemostasis in 95.9% of cases. In four patients the bleeding was not controlled at first endoscopic treatment: two of these patients underwent emergency surgery and two patients died of hemorrhagic shock before surgery could be carried out.

Endoscopic examination was carried out in all cases of recurrence. Endoscopic treatment proved effective in 86.8% of cases of first rebleeding and in 62.5% of patients with two or more rebleedings. A total of 32 patients (4.3%) underwent emergency surgical operations after effective first endoscopic therapy: 25 for recurrent bleeding which was not controlled by endoscopic treatment, and seven for endoscopic complications which included gastric or duodenal perforation (six patients) and necrosis of the gastric wall (one patient).

The 30-day mortality rate was 10% in the whole sample: 51 deaths (8.5%) in the group without recurrence of bleeding and 23 deaths (23.5%) in the group with rebleeding ($P = 0.001$). Six patients died of hemorrhagic shock (8.1%), and the remaining patients died from causes unrelated to bleeding.

The results of the univariate analysis of clinical and endoscopic variables are presented in Table **1**. Among these, endoscopic findings, with the exception of the number of ulcers, showed the highest crude odds ratios. Gastritis or duodenitis was observed in association with peptic ulcer in 44% of patients ($n = 325$). This association was more frequent in Forrest III ulcers (116, 61.7%) than in Forrest II and Forrest I ulcers, with 156 cases (43.6%) and 53 cases (27.6%), respectively ($P < 0.01$).

The multivariate logistic model estimated for the risk of rebleeding is shown in Table **2** (Pearson's goodness-of-fit test, $P = 0.86$; Hosmer–Lemeshow test, $P = 0.77$). The significant predictive variables were: liver cirrhosis, recent surgery, systolic blood pressure at admission, hematemesis, Forrest classification, ulcer size, and ulcer site. Although univariate analysis showed a significant association between rebleeding and the covariate "bleeding during hospitalisation," multivariate analysis indicated that this variable had no predictive power and therefore could be excluded from the model. The estimated cutoff point of the model was 0.163. If the probability of rebleeding is higher than the threshold value, the patient is classified as being at risk, and vice versa. The sensitivity, specificity and total (in-sample) accuracy of the model were all equal to 76%. The mean values of sensitivity, specificity and total (out-of-sample) accuracy obtained by means of 10000 data-splitting operations were all approximately equal to 71% (95% CI = 63 – 79%). The bootstrap estimate of the cutoff point was 0.148 (95% CI = 0.11 – 0.20). The receiver operating characteristic (ROC) curve (Figure **1**) shows different levels of sensitivity and specificity for different cutoff points.

Figure **2** shows the residual percentage of rebleeding for patients correctly and incorrectly (false negatives) classified by the model. Within the false-negative group, only 13.4% of recurrences took place before 24 hours, whereas in the correctly classified patient group 42.5% of recurrences happened before 24 hours. In addition, patients in the false-negative group had a greater tendency to rebleed after 48 hours. This means that the proposed logistic model predicted short-term rebleeding with greater accuracy, whereas most of the classification errors related to later hemorrhagic events. This fact is more clearly illustrated in Figure **3**, which shows the sensitivity curves of the model for ulcers for early (< 48 hours) and late (≥ 48 hours) rebleeding compared with the sensitivity curve for overall rebleeding (dotted line). Taking a cutoff point of 0.163, the model had a markedly superior sensitivity for early rebleedings (89%) compared with later ones (66%).

Using the coefficients of the estimated logistic model, it is possible to calculate a prognostic score which utilizes four clinical variables, i.e. liver cirrhosis (LV), recent surgery (RS), blood pressure (BP), and hematemesis (HM), and three endoscopic variables, ulcer size (S), ulcer site (L), and Forrest class (F). Values for these variables can be easily collected at the time of the first endoscopic examination. The prognostic score is then given by:

Table 1 Variables analysed in relation to rebleeding with crude odds ratios and 95 % confidence intervals

	Type of data	*Missing values*	*Cases* n	%	*Rebleeding* n	%	*Odds*	*95% CI*	*P-value*
All cases			738		98	13.3			
Variables and categorization									
Patient history									
Gender	Categorical	0							
Female			257	34.8	32	12.5	Reference		0.63
Male			481	65.2	66	13.7	1.12	0.71 to 1.76	
Age	Continuous	0							
< 60			207	28.1	29	14.0	Reference		0.17
60 – 69			152	20.6	25	16.5	1.21	0.68 to 2.16	
70 – 79			211	28.6	28	13.3	0.94	0.54 to 1.64	
≥ 80			168	22.8	16	9.5	0.65	0.34 to 1.23	
NSAID use	Categorical	67							
No			313	46.7	48	15.3	Reference		0.48
Yes			358	50.0	48	13.4	0.85	0.55 to 1.32	
Anticoagulant use	Categorical	65							
No			598	88.9	80	13.4	Reference		0.02
Yes			75	11.1	18	24.0	2.04	1.15 to 3.65	
No. of drugs taken	Continuous	67							
0			111	16.5	19	17.1	Reference		0.94
1 – 3			490	73.0	64	13.1	0.73	0.42 to 1.27	
> 3			70	10.4	13	18.6	1.10	0.51 to 2.41	
Past ulcer bleeding	Categorical	70							
No			520	77.9	68	13.1	Reference		0.88
Yes			148	22.1	20	13.5	1.04	0.61 to 1.78	
Past ulcer disease	Categorical	74							
No			348	52.4	52	14.9	Reference		0.27
Yes			316	47.6	38	12.0	0.78	0.50 to 1.22	
Liver cirrhosis	Categorical	66							
No			629	93.6	86	13.7	Reference		0.01
Yes			43	6.4	12	27.9	2.44	1.21 to 4.94	
Malignancy	Categorical	67							
No			602	89.7	82	13.6	Reference		0.07
Yes			69	10.3	15	21.7	1.76	0.95 to 3.27	
Chronic renal failure	Categorical	67							
No			609	90.8	84	13.8	Reference		0.13
Yes			62	9.2	13	21.0	1.66	0.86 to 3.19	
Hypertension	Categorical	67							
No			466	69.5	71	15.2	Reference		0.39
Yes			205	30.6	26	12.7	0.81	0.50 to 1.31	
Diabetes mellitus	Categorical	67							
No			590	87.9	87	14.8	Reference		0.57
Yes			81	12.1	10	12.3	0.81	0.40 to 1.64	
Vasculopathy	Categorical	67							
No			475	70.8	74	15.6	Reference		0.20
Yes			196	29.2	23	11.7	0.72	0.44 to 1.19	
Rheumatic diseases	Categorical								
No			637	94.9	92	14.4	Reference		0.97
Yes			34	5.1	5	14.7	1.02	0.39 to 2.71	
No. of illnesses	Continuous	67							
0			136	20.3	22	16.2	Reference		0.30
1			245	36.5	25	10.2	0.59	0.32 to 1.09	
> 1			290	43.2	50	17.2	1.08	0.62 to 1.87	
Recent surgery	Categorical	65							
No			621	92.2	82	13.2	Reference		0.01
Yes			52	7.7	16	30.7	2.92	1.55 to 5.52	
Previous surgery	Categorical	70							
No			530	79.3	73	13.7	Reference		0.41
Yes			138	20.8	23	16.7	1.24	0.74 to 2.08	

Continuation on next page

Table 1 Continuation

	Type of data	*Missing values*	*Cases* n	%	*Rebleeding* n	%	*Odds*	*95% CI*	*P-value*
Bleeding during hospitalization	Categorical	0							
No			444	60.2	50	11.3	Reference		0.05
Yes			294	39.8	48	16.3	1.54	1.00 to 2.36	
Magnitude of bleeding									
Symptoms	Categorical	0							
Melena			443	60.0	41	9.3	Reference		< 0.01
Hematemesis			105	14.2	20	19.1	2.31	1.29 to 4.14	
Hematemesis + melena			136	18.4	31	22.8	2.89	1.73 to 4.84	
Other symptoms			54	7.3	6	11.1	1.23	0.50 to 3.04	
Hematemesis	Categorical	0							
No			497	67.3	47	9.5	Reference		< 0.01
Yes			241	32.7	51	21.2	2.57	1.67 to 3.95	
Shock	Categorical	49							
No			636	92.3	74	11.6	Reference		< 0.01
Yes			53	7.7	21	39.6	4.98	2.73 to 9.09	
Systolic blood pressure	Continuous	61							
> 100			604	89.2	68	11.3	Reference		< 0.01
≤ 100			73	10.8	30	41.1	5.50	3.24 to 9.34	
Heart rate	Continuous	61							
≤ 100			580	85.7	68	11.7	Reference		< 0.01
> 100			97	14.3	23	23.7	2.32	1.33 to 4.05	
Haematocrit	Continuous	48							
> 30			315	45.6	34	10.8	Reference		0.04
≤ 30			375	54.4	61	16.3	1.61	1.02 to 2.52	
Haemoglobin level	Continuous	48							
> 10			320	46.4	35	10.9	Reference		0.05
≤ 10			370	53.6	60	16.2	1.58	1.01 to 2.46	
Units of blood transfused	Continuous	43							
0			332	47.8	35	10.5	Reference		< 0.01
1 – 4			314	45.2	44	14.0	1.38	0.86 to 2.22	
> 4			49	7.0	17	34.7	4.51	2.27 to 8.94	
Endoscopic									
Ulcer size	Continuous	0							
< 1			224	30.4	14	6.3	Reference		< 0.01
1 – 2			386	52.3	44	11.4	2.06	1.03 to 3.61	
> 2			128	17.3	40	31.3	5.72	3.53 to 13.16	
Gastritis/duodenitis	Categorical	0							
No			413	56.0	66	16.0	Reference		0.02
Yes			325	44.0	32	9.9	0.57	0.37 to 0.90	
Forrest classification	Categorical	0							
III			188	25.5	2	1.1	Reference		< 0.01
IIc			103	14.0	10	9.7	10.00	2.15 to 46.57	
IIb*			106	14.4	18	17.0	19.02	4.32 to 83.79	
IIa*			149	20.2	29	19.5	22.48	5.27 to 95.92	
Ib*			137	18.6	26	19.0	21.78	5.07 to 93.55	
Ia*			55	7.5	13	23.6	28.79	6.26 to 132.4	
Ulcer location	Categorical	0							
Stomach			295	40.0	36	12.2	Reference		0.58
Duodenum			443	60.0	62	14.0	1.17	0.75 to 1.82	
Ulcer location	Categorical	0							
Antrum-pylorus			173	23.4	12	6.9	Reference		< 0.01
Postbulbar region			129	17.5	14	10.9	1.63	0.73 to 3.66	
Bulb			314	42.6	48	15.3	2.42	1.25 to 4.69	
Fundus–corpus			122	16.5	24	19.7	3.29	1.57 to 6.87	
No. of ulcers	Continuous	0							
1			599	81.2	80	13.7	Reference		0.90
> 1			139	18.8	18	13.0	0.97	0.56 to 1.67	

* With endoscopic therapy.

Table **2** Significant predictor variables for rebleeding

Variables and categories	*Logistic model (n = 627)* B	*SE*	*P*	*Exp(B)*	*95% CI*
Patient history					
Liver cirrhosis (LV)					
No	Reference				
Yes	0.83	0.43	0.05	2.30	1.00 to 5.29
Recent surgery (RS)					
No	Reference				
Yes	0.92	0.38	0.02	2.50	1.19 to 5.28
Magnitude of bleeding					
Systolic blood pressure (BP)					
> 100	Reference				
≤ 100	1.30	0.31	< 0.01	3.68	1.99 to 6.81
Hematemesis (HM)					
No	Reference				
Yes	0.45	0.26	0.09	1.57	0.94 to 2.61
Endoscopic					
Forrest classification					
III	Reference				
IIc (F1)	1.91	0.81	0.02	6.78	1.39 to 33.01
IIb* (F2)	2.42	0.78	< 0.01	11.30	2.47 to 51.64
IIa* (F3)	2.36	0.76	< 0.01	10.60	2.39 to 46.98
Ib* (F4)	2.67	0.76	< 0.01	14.47	3.27 to 64.05
Ia* (F5)	2.59	0.82	< 0.01	13.38	2.69 to 66.66
Ulcer size					
< 1	Reference				
1 – 2 (S1)	0.42	0.34	0.22	1.53	0.78 to 2.98
> 2 (S2)	1.53	0.38	< 0.01	4.61	2.20 to 9.64
Ulcer location					
Antrum–pylorus	Reference				
Postbulbar region (L1)	0.17	0.46	0.71	1.19	0.49 to 2.90
Bulb (L2)	0.67	0.38	0.07	1.96	0.94 to 4.09
Fundus-corpus (L3)	0.94	0.42	0.03	2.56	1.12 to 5.83
Constant	– 5.56	0.81	< 0.01		

B is the coefficient of the variable in the logistic regression model and SE its standard error. *P* is the statistical significance for the hypothesis that *B* = 0. Exp(*B*) is the odds ratio and 95% CI the 95% confidence interval of exp(*B*). * With endoscopic injection therapy.

0.83 LV + 0.92 RS + 1.30 BP + 0.45 HM + 1.91 F1 + 2.42 F2 + 2.36 F3 + 2.67 F4 + 2.59 F5 + 0.42 S1 + 1.33 S2 + 0.17 L1 + 0.67 L2 + 0.94 L3

In order to identify four classes of patients with an increasing risk of rebleeding, we estimated three cutoff points for the prognostic score: if the score is less than 1.66, the patient is classified as being at very low risk (VL); if the score is higher than 5.75, 3.91, or 1.66, the patient is classified as being at very high risk (VH), high risk (H), or low risk (L), respectively. Table **3** shows the distribution of the patient sample in the four risk classes. The rebleeding rate in these classes consistently rose, from 0% in the VL class to 7.9%, 31.8%, and 67.9%, in the L, H, and VH classes, respectively. After 48 hours the residual risk of rebleeding decreased to 3.3%, 10.4% and 14.3% for the L, H and VH groups, respectively, as shown in Figure **4**. After 5 days, all categories of patients showed a residual risk lower than 4%, which decreased to 0% after 11 days.

The mortality rates for the VL, L, H, and VH groups, were 5.9%, 8.6%, 13.9%, and 35.7%, respectively.

Discussion

Endoscopic therapy has proved effective in control bleeding in acute peptic ulcer, but the recurrence rate is still 10 – 30% [5 – 8]. The recurrence of bleeding is one of the most important factors affecting prognosis. In our study, the observed mortality was three times higher in patients with rebleeding, as is reported in the literature [22]. The early identification of patients with an increased risk of recurrence may improve the outcome.

In our study we used endoscopic injection with a combination of epinephrine and polidocanol because this technique is widely used and is one of the most effective endoscopic treatments [9,23]. The timing of endoscopic monitoring, the usefulness of endoscopic re-treatment, and appropriate treatment for recurrence are still matters of debate [24,25].

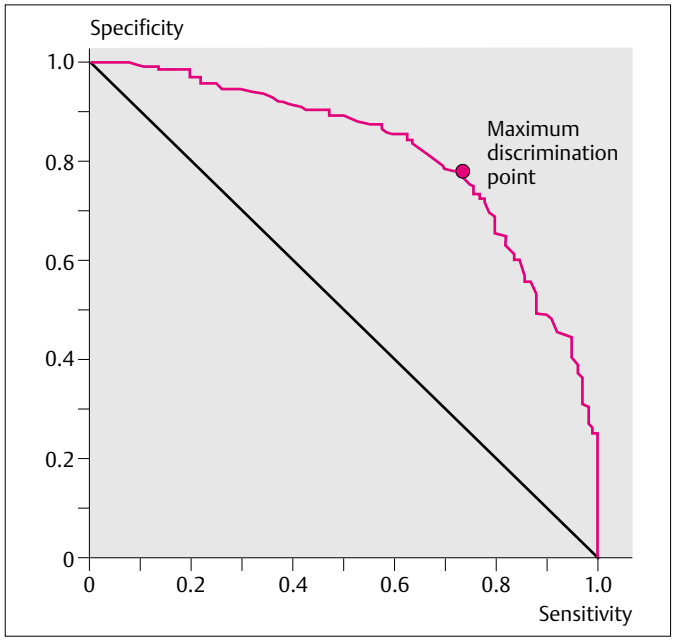

Figure 1 ROC curve. Sensitivity and specificity for various cutoff points of the prognostic score

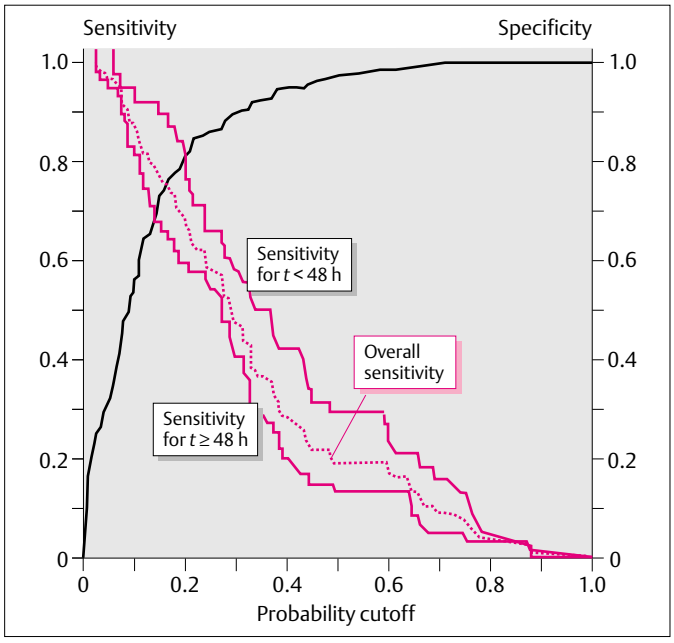

Figure 3 Sensitivity curves for early and late bleeding, and for bleeding overall. The overall specificity curve is also shown. For a cutoff point of 0.163, the model shows a sensitivity of 89 % for early rebleeding and 66 % for late rebleeding

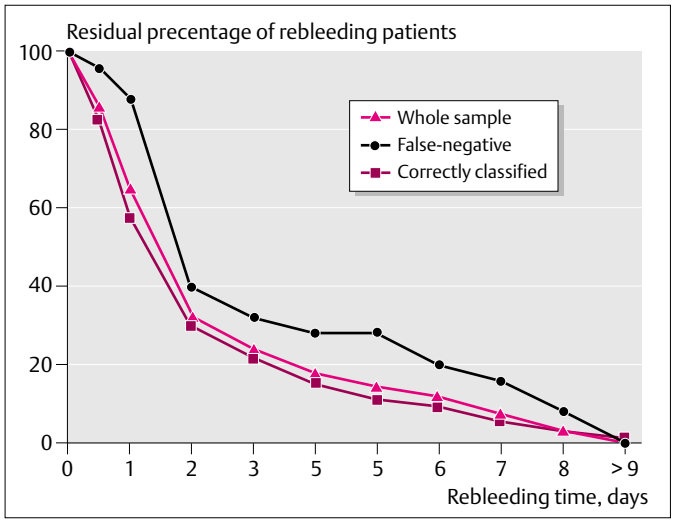

Figure 2 Residual percentage of rebleeding after admission, for correctly classified patients, patients with a false-negative result, and the whole sample

Table 3 Distributions of patients within the four risk classes: very low (VL), low (L), high (H) and very high (VH)

	VL	*L*	*H*	*VH*
No rebleeding				
n	121	281	118	9
%	100	92.1	68.2	32.1
Rebleeding				
n	0	24	55	19
%	0.0	7.9	31.8	67.9
Rebleeding time ≤ 48 h				
n	0	14	37	15
%	0.0	4.6	21.4	53.6
Rebleeding time > 48 h				
n	0	10	18	4
%	0.0	3.3	10.4	14.3
Mortality				
Alive				
n	111	279	149	18
%	94.1	91.5	86.1	64.3
Dead				
n	7	26	24	10
%	5.9	8.5	13.9	35.7

We adopted endoscopic injection as the treatment of choice for rebleeding in all patients, using emergency surgery only when endoscopy was not effective. Rates for emergency surgery reported in the literature vary from 10% to 20% of patients [8,22,26]. In this study, using a restrictive surgical policy, we have achieved a low emergency surgery rate of 4.6% with a mortality of 10%; this compares favorably with other studies, where death has occurred in 5 – 15% [9,22,23,27].

Many patient-related variables are recognized as being associated with the occurrence of rebleeding [28,29]. In our study, only the presence of liver cirrhosis, and recent surgery in the 30 days before the bleeding episode, were associated with a significantly increased risk of rebleeding, roughly doubling that risk. Chronic renal failure, though associated with an increased risk, did not reach statistical significance, unlike the findings reported by other investigators [28]. However, it did correlate significantly with mortality (crude odds ratio = 4.28, $P < 0.01$). In our sample,

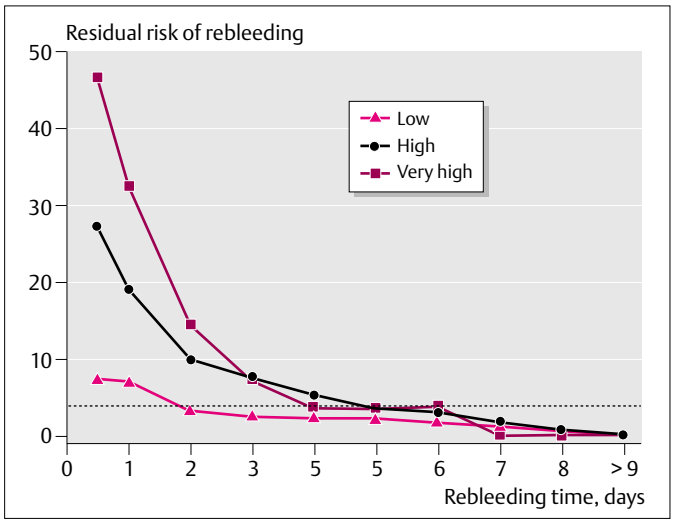

Figure 4 Residual risk of rebleeding according to different classes of risk (low, high and very high)

age was not found to be a risk factor, thus confirming the findings of other studies [30,31].

Amongst symptoms, the presence of hematemesis increased the risk by approximately 50%. Analysing the relationship between hematemesis and ulcer site, we found that ulcers located in the duodenum re-bled in about 25.0% of cases when associated with hematemesis, and in 10.0% of cases in the presence of other symptoms (melena, coffee-ground vomit, anemia). Moreover, hematemesis increased the risk of rebleeding in ulcers within the same Forrest class. Ulcers with active bleeding in patients with hematemesis re-bled in 28.2% of cases, and only in 14.0% of cases in the presence of other symptoms.

Endoscopic variables (in particular the Forrest classification) were found to be the most influential variables for the risk of rebleeding, in agreement with the data reported in the literature [10,14,26,32–38]. Patients with active bleeding (Forrest Ia and Ib) and those with signs of recent bleeding (Forrest IIa, IIb) showed an approximately tenfold greater risk of recurrence of hemorrhage than those with a clean ulcer base (Forrest III).

The predictive performance of our model yielded overall results similar to those reported by other authors [8,26]. These models are not widely applied in routine clinical situation on account of their complexity. In addition, time-dependent studies concerning the residual risk of rebleeding following therapeutic endoscopy are rare. In our study, in order to investigate this feature, we followed up all patients for 30 days after their acute episode.

Our model performed markedly better in predicting early rebleeding (< 48 hours) than late rebleeding, with sensitivities of 90% and 70%, respectively. We found that most recurrences were within the first 48 hours, but we observed rebleedings up to 11 days from the first observation.

To improve the clinical usefulness of the predictive model, we constructed a prognostic score and classified patients into four categories of increasing risk of recurrence and mortality. This categorization, obtained from seven variables, available after endoscopic examination, can be used to improve patient management and selection of appropriate treatment.

The patients belonging to the lowest risk class (VL) showed a recurrence of 0%. They should be discharged after the first endoscopic observation, provided that they are hemodynamically stable and without severe co-morbidity.

In the low risk (L) category, the recurrence rate was 7.9%, and most of the rebleedings happened in the first 48 hours. Only 3.3% of the recurrences took place after 48 hours. For this reason, clinical observation should be prolonged for at least 48 hours.

For patients belonging to the high risk (H) category, the recurrence rate was 31.8%. In this group of patients clinical observation is necessary because of the high risk of recurrence, but programmed endoscopic examinations and endoscopic treatment of recurrence achieved satisfactory results. To arrive at a residual risk of rebleeding of less than 4.0%, patients should stay in hospital for at least 5 days.

In the very high risk (VH) group, endoscopic injection therapy did not provide satisfactory results, with a recurrence rate of 67.9% and a mortality rate of 35.7%. These results might be improved by early elective therapy, such as surgery or second-look endoscopy with prophylactic sclerotherapy, an approach which has also been supported by other authors [4,9].

This study demonstrates that the proposed prognostic score, which is easily obtained after emergency endoscopy, can identify patients at different risk of rebleeding and can be helpful in patient management and decisions about discharge.

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