

ORIGINAL ARTICLE

Prognosis of variceal and non-variceal upper gastrointestinal bleeding in already hospitalised patients: Results from a French prospective cohort

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Abstract

Objectives: Patients who develop upper gastrointestinal bleeding (UGIB) while in hospital appear to have a poor prognosis. Our study aims at analysing the difference in outcome between in-patients (IPs) and out-patients presenting with variceal and non-variceal UGIB.

Methods: We conducted a multicentre prospective study by collecting data about variceal and non-variceal UGIB cases through 46 hospitals in France between November 2017 and October 2018. We then compared baseline demographic features, endoscopic findings and outcome between patients who developed variceal and non-variceal UGIB on admission (OPs) and those at least 24 h after hospitalisation (IPs). Our primary end-point was mortality and re-bleeding rates at 6 weeks of bleeding onset.

Results: A total of 2498 UGIB cases were identified, of whom 634 (25.4%) occurred in IPs. IPs were older than OPs (72.5 vs. 67.2 years old, $p < 0.001$) and had a higher rate of comorbidities (38.9% vs. 26.6%, $p < 0.0001$). Their bleeding was more severe with a Rockall score of >5 present in 40.9% (vs. 30.3% in OPs, $p < 0.0001$). The 6-week mortality rate was significantly higher in IPs when compared to OPs (21.7% vs. 8%, $p < 0.0001$). Prothrombin time $<50\%$ and rebleeding were the only independent predictors of mortality ($p = 0.001$ and 0.003 , respectively). Six-week rebleeding occurred more frequently among IPs (18.6% vs. 14.4%, $p = 0.015$) and predictors

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included female sex, active bleeding upon endoscopy and a Blatchford score >11 ($p = 0.017, 0.011$ and 0.008 , respectively).

Conclusion: IPs who develop variceal and non-variceal UGIB are more likely to be elderly with more comorbidities. They have a higher rate of mortality and rebleeding. Independent predictors of mortality were underlying coagulopathy and bleeding recurrence. An optimal bleeding management and efficient rebleeding prevention may improve outcome in these patients.

KEYWORDS

gastrointestinal bleeding, in-patients, non-variceal bleeding, peptic ulcer disease, portal hypertension, upper GI bleeding, upper GI endoscopy, variceal bleeding

Key Point

Summarize the established knowledge on this subject

- Upper gastrointestinal bleeding (UGIB) in already hospitalised patients (IPs) appears to have a worse prognosis when compared to UGIB in out-patients (OPs).
- Few studies have addressed this issue, most of which are retrospective. They found a poor short-term outcome in IPs without being able to identify modifiable risk factors that could affect the prognosis.

Significant and/or new findings of this study?

- We demonstrated in this prospective and multicentre study a greater 6-week mortality and rebleeding rates in IPs versus OPs.
- IPs were older and had a higher rate of comorbidities. Prothrombin time <50% and rebleeding were independently associated with a higher mortality rate in IPs.
- An appropriate bleeding management and an optimal rebleeding prevention plan might improve the outcome of UGIB in already hospitalised patients.

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) remains a common medical condition despite a decrease in its incidence by 23–33% over the last decades.^{1,2} Such decrease has been attributed to many factors including a higher proton pump inhibitors' (PPI) use and increasing preventive measures against non-steroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* (HP)-related peptic ulcer disease (PUD). A decline was also noted in the incidence of variceal bleeding probably due to advances in primary and secondary preventive measures.³ However, the mortality and rebleeding rates remained relatively unchanged and had even slightly increased, presumably due to the older age and the higher rate of comorbidities in these patients.^{1,2} In the French cohort that we have previously studied, upper gastrointestinal (GI) bleeders had a mortality rate of 8.3% and a rebleeding rate of 9.9%, with the two main aetiologies being PUD and portal hypertension.⁴

The occurrence of UGIB in hospitalised patients (IPs) constitutes a serious concern for gastroenterologists. Few studies have addressed this issue^{5–9} and reported an increase in mortality rate among IPs with UGIB when compared to out-patients (OPs). Only one report has found a significantly higher rebleeding rate in IPs.⁵

Many underlying factors may have contributed to the poorer prognosis including patients' comorbidities and bleeding severity.⁷ However, some authors suggested that the difference in outcome was not entirely explained by the demographic patients' characteristics nor the severity of bleeding.⁵ Further predictors of prognosis are yet to be elucidated to identify potentially modifiable risk factors that could improve the process of care in these patients.

Hence, the aim of this study was to compare the outcome of UGIB between IPs and OPs and to try to identify underlying factors, which might affect the prognosis.

METHODS

We prospectively collected data about patients who developed UGIB between November 2017 and October 2018 through 46 general hospitals across France.

Every patient aged 18 years old or more and who had a variceal or non-variceal UGIB upon presentation or during any hospitalisation, manifested by haematemesis and/or melena and/or acute drop in the haemoglobin (Hb) level with blood in the stomach

(identified while inserting a nasogastric tube or by performing endoscopic examination), was included.

Patients' data collection and initial evaluation were performed and registered by the physician in charge on an online electronic case report form.

The study was approved by the "Committee for Personal Protection Sud-Méditerranée II" with the identification number 2017-AO1920-53 and the cohort was declared to the National Commission for computerised data and Liberties (CNIL) (declaration no. 2060169). The protocol was approved by our local ethics committee in agreement with French legislation on non-interventional studies in May 2017. It conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Patients (or their representatives) were provided with a written information about the study and asked to give their consent before their inclusion.

Study variables

In-hospital UGIB was defined as bleeding occurrence at least 24 h after admission for another reason.

Clinical data included age, sex, weight, past medical history, habits and medications in the past week. Comorbidities were weighted according to Charlson score.¹⁰ Excessive alcohol consumption was defined as more than three drinks per day (30 g). Pre-endoscopy assessment was based on haemodynamic and laboratory studies upon bleeding onset for IPs and upon presentation to the hospital for OPs. Vital signs were recorded including heart rate and blood pressure. Haemodynamic shock was defined as systolic blood pressure <100 mmHg with a heart rate of >100 beats/minute. We also evaluated the need for blood transfusion, coagulopathy correction, erythromycin infusion before endoscopy and the use of PPIs or somatostatin analogues. Laboratory studies included mainly complete blood count, coagulation studies, urea, creatinine, liver function test and albumin. We calculated the pre-endoscopic Rockall (Pre-RS) and Glasgow-Blatchford (GBS) prognosis scores^{11,12} for risk stratification in all patients and the Child-Pugh and MELD scores when appropriate. We considered a Pre-RS >5 and GBS >11 as high-risk features.^{11,12}

In patients who underwent endoscopy, the following variables were evaluated: the delay from bleeding onset to endoscopy, week-end versus week-day endoscopy, anaesthesia type, endoscopic findings and haemostatic treatment. Active bleeding upon endoscopy was defined as the presence of blood in the upper GI tract (oesophagus, stomach or duodenum). Patients with PUD had their ulcers classified according to the Forrest classification. The *HP* status was determined either by histological analysis or by serological testing.

The mortality and rebleeding rates were assessed during hospitalisation and then 6 weeks later by a follow-up check on patients' file if they were still hospitalised/re-hospitalised or by calling them (or their representatives) if they were already discharged. The reason

why we chose 6-week outcome rather than 28 days is due to the inclusion of variceal haemorrhage where outcome must be assessed at 6 weeks as recommended by the Baveno VI consensus.¹³ Thus, we tried to have a homogeneous assessment at 6 weeks of the whole study population including both variceal and non-variceal bleeding.

The death was defined as "bleeding related" when it resulted directly from uncontrolled bleeding in the absence of other potential factors or from a complication related to interventional procedure (endoscopy, anaesthesia, surgery) and as "non-bleeding related" when it resulted from another pathology related to cancer, sepsis/infection, heart failure, hepatic or renal failure and multiple organ dysfunction.

Study outcome

The main outcomes were 6-week mortality and re-bleeding rates.

Secondary outcomes included the length of hospital stay, the mortality and re-bleeding rates during the same hospitalisation and the need of surgical or radiological intervention.

Statistical analysis

We conducted a univariate analysis by comparing both groups of IPs and OPs using Student's *t*-test for quantitative variables and Chi-squared test or Fisher's exact test for qualitative variables. Quantitative variables were represented by mean (\pm standard deviation) and qualitative variables by numbers and percentages (%). The odds ratio (OR) and 95% confidence interval (CI) were calculated for each independent factor. A two-tailed *p*-value of <0.05 was considered statistically significant. A multivariate regression analysis was then performed to identify independent predictors of mortality and rebleeding in both groups. Variables with a *p*-value of ≤ 0.20 in the univariate regressions were included in the multivariate model. For OPs, the included variables were the following: rebleeding, age >80 years old, cirrhosis, Charlson score >3, haemodynamic instability, Hb <8 g/dl, GBS >11, PUD, anti-platelets use, Pre-RS >5, active bleeding upon endoscopy, portal hypertension and female sex. For IPs, we included rebleeding, body mass index (BMI) <20 or >30, anticoagulants, prothrombin time (PT) <50%, Charlson score >3, GBS >11, Pre-RS >5, haemodynamic instability, transfusion and female sex. The statistical analysis was performed using SPSS program version 18.0.

RESULTS

A total of 2536 patients were included during the 1-year study period. Thirty-eight patients were excluded because of incomplete data. Of the remaining 2498 patients, there were 634 (25.3%) IPs and 1864 (74.7%) OPs (Figure 1).

Demographic features

Patients' demographics are presented in Table 1. IPs were older than OPs with a mean age of 72.5 years (vs. 67.2 years for OPs, $p < 0.0001$). There were no significant differences in sex ratio or BMI between both groups ($p = 0.08$ and 0.58 , respectively). Among OPs, there were more smokers and excessive alcohol consumers ($p = 0.01$ and 0.02 , respectively).

Comorbidities

IPs had a greater rate of comorbidities, with a Charlson score of >3 present in 38.9% versus 26.6% in OPs ($p < 0.0001$). There were more patients with cirrhosis among OPs (22.5% vs. 16.4%, $p = 0.001$) without significant difference in the prevalence of severe liver dysfunction between both groups (Child-Pugh score >8 in 47.4% of IPs vs. 40.4% of OPs, $p = 0.22$).

Medications at bleeding onset

IPs were more likely to be on steroids, aspirin and heparin ($p < 0.0001$) while OPs were taking more frequently NSAIDs and oral anticoagulants ($p < 0.0001$ and 0.004 , respectively). The type of oral anticoagulant was similar in both groups [vitamin K antagonists and new oral anti-coagulants (NOAC), $p = 0.99$ and 0.63 , respectively]. PPI use was more prevalent in IPs (41.6% vs. 27.5%, $p < 0.0001$).

Bleeding severity assessment

IPs were more likely to have a pre-RS >5 (41% vs. 30.3% in OPs, $p < 0.0001$) and a GBS >11 (51% vs. 42.3% in OPs, $p < 0.0001$). Only 5.7% of the included OPs had a GBS of 0–1 in comparison with 2% of IPs ($p = 0.0001$, OR = 2.99, 95%CI = 1.64–5.49). Fifty percentage of these OPs were discharged home within 48 h. IPs had more haemodynamic instability (11.1% vs. 9.7% of OPs, $p = 0.03$), lower Hb level (8.6% vs. 9.1 g/dl, $p < 0.0001$) and a higher need for blood transfusion (53.8% vs. 47% in OPs, $p = 0.003$).

Endoscopic features

The great majority of patients ($>98\%$ in both groups) underwent endoscopy. Both IPs and OPs had their endoscopy done within 24 h of bleeding onset in more than 80% of cases. Endoscopic findings are shown in Table 2.

Peptic ulcer disease (PUD) and oesophagitis were more common in IPs when compared to OPs ($p < 0.0001$). There was no difference in the type of ulcers according to Forrest classification nor in the HP status between IPs and OPs. Variceal bleeding was observed predominantly in OPs (18.7% vs. 7.8% of IPs, $p < 0.0001$, OR = 0.42, 95% CI = 0.30–0.58).

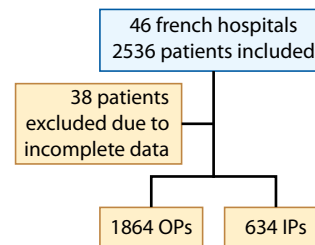


FIGURE 1 Patient selection diagram

IPs were more likely to have an active bleeding upon endoscopy (31.9% vs. 25.6% in OPs, $p = 0.003$, OR = 1.36, 95% CI = 1.11–1.68). Ulcers with high-risk stigmata (Forrest classes Ia–IIb) were treated in 84.6% of IPs and 76.9% of OPs ($p = 0.10$, OR = 1.65, 95% CI = 0.92–2.95). Endoscopic haemostasis in these patients was achieved by using a mechanical or thermal coagulation combined or not to adrenalin injection in 73.7% and 75.7% of IPs and OPs, respectively ($p = 0.77$, OR = 0.89; 95% CI = 0.51–1.56). Band ligation for oesophageal varices was achieved in 68.9% and 71.1% in IPs and OPs, respectively ($p = 0.86$, 95% CI = 0.89; 0.45–1.76).

Pre-endoscopic management

Octreotide was started for suspected variceal bleeding in 84% of cirrhotic OPs versus 57.6% of cirrhotic IPs ($p < 0.0001$, OR = 4.0, 95% CI = 2.50–6.41). Variceal or portal hypertensive gastropathy-related bleeding was then confirmed in 57 IPs and 357 OPs. Among these, octreotide was already started in 39/57 IPs (68.4%) and 302/357 OPs (84.6%) ($p = 0.005$, OR = 0.39, 95% CI = 0.21–0.74).

OPs received more intravenous PPIs (86.9% vs. 78.6% of IPs, $p < 0.0001$) and had their coagulopathy corrected in 13.4% of cases versus 7.5% of IPs ($p < 0.0001$).

The cause of coagulopathy in OPs who had a PT of $<50\%$ (the equivalent of 19.2 s) was related to oral anticoagulant treatment in 50.1% (vs. 35.4% in IPs, $p = 0.01$, OR = 1.83, 95% CI = 1.15–2.92) and to cirrhosis in 42.2% of cases (vs. 40.6% in IPs, $p = 0.81$, 95% CI = 1.07; 0.67–1.69). 24% of IPs with PT $<50\%$ had neither cirrhosis nor anticoagulant treatment (vs. 7.6% of OPs, $p < 0.0001$, OR = 0.28; 95% CI = 0.15–0.51).

Among the 96 IPs who had a PT of $<50\%$, only 19 (19.8%) had their coagulopathy corrected, as compared to 121 of the 367 OPs (33%) with same PT values ($p = 0.012$, OR = 0.50, 95% CI = 0.29–0.87). The correction was performed using vitamin K, fresh frozen plasma, prothrombin complex concentrates, NOAC antagonist or tranexamic acid.

Outcome

Mortality

Six-week mortality rate was significantly higher among IPs (21.7% vs. 8.8%, $p < 0.0001$, OR = 2.86, 95% CI = 2.23–3.66). The death

TABLE 1 Patients' characteristics

	IPs n = 634 (%)	OPs n = 1864 (%)	p-Value	OR; 95% CI
Demographic features				
Female gender	226 (35.6)	595 (31.9)	0.08	1.18; 0.98-1.43
Age (years), mean	72.5 ± 13.8	67.2 ± 16.8	<0.0001	
Smoker	138/627 (22.0)	497/1839 (27.1)	0.01	0.76; 0.61-0.94
Alcohol (>30 g/day)	139/627 (22.2)	491/1840 (26.7)	0.02	0.78; 0.63-0.96
BMI, mean	25.9 ± 5.5	25.7 ± 6	0.58	
Comorbidities				
Charlson score >3	247 (38.9)	496 (26.6)	<0.0001	1.76; 1.45-2.12
Cirrhosis	104 (16.4)	420 (22.5)	0.001	0.67; 0.53-0.85
CHILD PUGH >8	45/95 (47.4)	149/369 (40.4)	0.22	1.32; 0.84-2.09
MELD >16	38/82 (46.3)	127/351 (36.2)	0.09	1.52; 1.93-2.47
Cardiac disease (HF, IHD)	199 (31.4)	489 (26.2)	0.01	1.29; 1.06-1.57
Drug intake				
No treatment	164 (25.9)	761 (40.8)	<0.0001	0.50; 0.41-0.61
PPI	264 (41.6)	512 (27.4)	<0.0001	1.87; 1.55-2.26
NSAID	26 (4.1)	175 (9.4)	<0.0001	0.41; 0.27-0.62
Steroids	52 (8.2)	73 (3.9)	<0.0001	2.18; 1.51-3.15
Aspirin	210 (33.1)	472 (25.4)	<0.0001	1.45; 1.19-1.77
Other antiplatelets	94 (14.8)	244 (13.1)	0.28	1.15; 0.89-1.49
Heparin	194 (30.6)	61 (3.3)	<0.0001	13.3; 9.5-17.6
Therapeutic	78/194 (40.2)	18/61 (29.5)	0.17	1.60; 0.86-2.99
Oral anticoagulants	99 (15.6)	381 (20.4)	0.004	0.70; 0.56-0.89
VKA	54/99 (54.5)	213/381 (55.9)	0.99	0.10; 0.64-1.55
NOAC	45/99 (45.5)	168/381 (44.1)	0.63	0.76; 0.54-1.07
Laboratory studies				
Haemoglobin (g/dl)	8.6 ± 2.2	9.14 ± 3.0	<0.0001	
Urea (mmol/L)	16.1 ± 13.5	13.4 ± 10.2	<0.0001	
Creatinin (µmol/L)	147.8 ± 95	124.4 ± 86	0.02	
Platelets count (g/L)	239.6 ± 132	215.2 ± 114	<0.0001	
Prothrombin time (%)	71.2 ± 20.3	69.6 ± 22.6	0.5	
Albumin (g/L)	27.8 ± 7.6	28.7 ± 6.1	0.23	
H. pylori status				
Positive	30/295 (10.1)	123/902 (13.6)	0.12	0.72; 0.47-1.09
Bleeding severity assessment				
Haemodynamic instability	70 (11.1)	178 (9.7)	0.03	1.11; 0.83-1.50
Initial transfusion	340 (53.8)	874 (47.0)	0.003	1.31; 1.1-1.58
Pre-RS >5	253 (40.9)	553 (30.3)	<0.0001	1.60; 1.32-1.92
GBS >11	305 (50.9)	768 (42.3)	<0.0001	1.42; 1.18-1.70

Abbreviations: BMI, body mass index; CI, confidence interval; HF, heart failure; GBS, Glasgow-Blatchford score; IHD, ischaemic heart disease; IPs, in-patients; NOAC, new oral anti-coagulants; NSAID, non-steroidal anti-inflammatory drugs; OPs, out-patients; OR, odds ratio; PPI, proton pump inhibitor; pre-RS, pre-endoscopic Rockall score; VKA, vitamin K antagonists.

TABLE 2 Endoscopic features

	IPs n = 634 (%)	OPs n = 1864 (%)	p-Value	OR; 95% CI
Endoscopy done	622 (98.1)	1831 (98.2)	0.63	0.85; 0.43-1.67
Week-end endoscopy	97 (15.6)	427 (23.3)	<0.0001	0.60; 0.48-0.77
General anaesthesia	208 (33.4)	549 (30)	0.11	1.17; 0.96-1.42
Pre-endoscopy management				
Time to endoscopy <24 h	523 (84.1)	1543 (84.3)	0.99	1.00; 0.78-1.27
Prior erythromycin infusion	136 (21.6)	409 (22)	0.81	0.97; 0.78-1.2
Intravenous PPI	495 (78.6)	1618 (86.9)	<0.0001	0.55; 0.43-0.69
Oral PPI	100 (15.9)	131 (7)	<0.0001	2.40; 1.89-3.40
Octreotide in cirrhotic patients	60/104 (57.6)	355/420 (84.5)	<0.0001	4.0; 2.50-6.41
Coagulopathy correction	47 (7.5)	250 (13.4)	<0.0001	0.52; 0.37-0.72
Vitamin K	21 (44.7)	87 (34.8)	0.25	1.51; 0.80-2.84
FFP	16 (34)	85 (34)	1	1.0; 0.52-1.53
PCC	7 (14.9)	57 (22.8)	0.26	0.59; 0.25-1.39
Tranexamic acid	3 (6.4)	15 (6)	1	1.07; 0.29-3.84
NOAC antagonist	0 (0)	6 (2.4)	0.6	-
Endoscopic findings				
No abnormalities	48 (7.7)	202 (11.0)	0.02	0.67; 0.48-0.94
Peptic ulcer disease	310/572 (54.2)	722/1626 (44.4)	<0.0001	1.48; 1.22-1.79
Forrest Ia	10/292 (3)	20/701 (2.8)	0.63	1.21; 0.56-2.61
Forrest Ib	43/292 (14.7)	96/701 (13.7)	0.67	1.09; 0.74-1.60
Forrest IIa	23/292 (7.8)	52/701 (7.4)	0.80	1.07; 0.64-1.78
Forrest IIb	41/292 (14)	79/701 (11.2)	0.22	1.29; 0.86-1.93
Forrest IIc	44/292 (15)	112/701 (15.9)	0.79	0.93; 0.64-1.36
Forrest III	131/292 (44.8)	342/701 (48.8)	0.26	0.85; 0.65-1.12
Oesophagitis	131/572 (22.9)	265/1626 (16.3)	<0.0001	1.52; 1.21-1.93
Variceal bleeding	45/572 (7.8)	305/1626 (18.7)	<0.0001	0.42; 0.30-0.58
Portal hypertensive gastropathy	12/572 (2.1)	52/1626 (3.2)	0.18	0.65; 0.34-1.22
Cancer	33/572 (5.8)	84/1626 (5.2)	0.58	1.12; 0.74-1.7
AVM	31/572 (5.4)	80/1626 (4.9)	0.64	1.11; 0.72-1.7
Dieulafoy lesion	7/572 (0.6)	14/1626 (0.6)	0.44	1.43; 0.57-3.55
Active bleeding	183 (31.9)	418 (25.6)	0.003	1.36; 1.11-1.68
Endoscopic treatment				
Non-variceal bleeding				
Endoscopic haemostasis	163 (26.2)	364 (19.9)	0.001	1.43; 1.16-1.77
Treatment of Forrest Ia to IIb ulcers	99/117 (84.6)	190/247 (76.9)	0.10	1.65; 0.92-2.95
Mechanical/thermal therapy ^a	73/99 (73.7)	144/190 (75.7)	0.77	0.89; 0.51-1.56
Argon plasma coagulation	20/163 (12.2)	32/364 (8.8)	0.27	1.45; 0.80-2.62
Haemospray ^b	24/163 (14.7)	44/364 (12.1)	0.48	1.25; 0.73-2.14
Other ^c	20/163 (12.2)	98/364 (26.9)	0.0003	0.38; 0.22-0.64

TABLE 2 (Continued)

	IPs n = 634 (%)	OPs n = 1864 (%)	p-Value	OR; 95% CI
Variceal bleeding				
Band ligation for oesophageal varices	31/45 (68.9)	217/305 (71.1)	0.86	0.89; 0.45–1.76
Gastric varices' obturation	3/45 (6.7)	5/305 (1.6)	–	–
Oesophageal stent or Balloon tamponade	1/45 (2.2)	4/305 (1.3)	–	–
Non-endoscopic treatment				
TIPS	3/45 (6.7)	17/305 (5.6)	0.49	1.21; 0.34–4.3

Note: Mechanical/thermal therapy^a is complementary to the previous raw "treatment of Forrest Ia to IIb ulcers" which signifies that treatment of those ulcers was done by mechanical or thermal therapy in 73/99 (73.7) and 144/190 (75.7) of IPs and OPs respectively.

Abbreviations: AVM, arterio-venous malformation; CI, confidence interval; FFP, fresh frozen plasma; IPs, in-patients; NOAC, new oral anti-coagulant; OPs, out-patients; OR, odds ratio; PCC, prothrombin complex concentrate; PPI, proton pump inhibitor; TIPS, transjugular intrahepatic porto-systemic shunt.

^aWith or without adrenalin injection.

^bAlone or in combination with other treatment.

^cSclerosing agent or adrenalin injection or clipping for low-risk ulcers or tumoral lesions.

TABLE 3 Outcome

	IPs n = 634 (%)	OPs n = 1864 (%)	p-Value	OR; 95% CI
Same hospitalisation outcome				
Length of hospital stay, mean (days)	15.64 ± 16.3	8.65 ± 9.17	<0.0001	
Mortality	107 (16.8)	109 (5.8)	<0.0001	3.26; 2.45–4.34
Rebleeding	89 (14.2)	170 (9.2)	<0.0001	1.62; 1.23–2.14
Six weeks outcome				
Mortality	137 (21.7)	165 (8.8)	<0.0001	2.86; 2.23–3.66
Bleeding related death	15/137 (10.8)	34/165 (20.6)	0.02	0.47; 0.24–0.90
Rebleeding	113 (18.6)	256 (14.4)	0.015	1.35; 1.06–1.73
Need for radiological intervention	7/464 (1.5)	16/1346 (1.2)	0.59	1.27; 0.52–3.11
Need for surgical intervention	15/469 (3.2)	52/1355 (3.8)	0.53	0.83; 0.46–1.48

Abbreviations: CI, confidence interval; IPs, in-patients; OPs, out-patients; OR, odds ratio.

was bleeding related in only 10.8% of IPs versus 20.6% of OPs ($p = 0.02$, OR = 0.47, 95% CI = 0.24–0.90). The rate of mortality during the same hospitalisation was also more elevated in IPs (16.8% vs. 5.8% in OPs, $p < 0.0001$, OR 3.26, 95% CI = 2.45–4.34) (Table 3).

Rebleeding

Rebleeding rate at 6 weeks was greater in IPs when compared to OPs (18.6% vs. 14.4%, $p = 0.015$, OR = 1.35; 95% CI = 1.06–1.73). The rate of rebleeding during the same hospitalisation was also more prevalent among IPs (14.2% vs. 9.2% in OPs, $p < 0.0001$, OR = 1.62, 95% CI = 1.23–2.14).

Other secondary outcomes

IPs had a significantly longer hospital stay than OPs (15.64 vs. 8.65 days, $p < 0.0001$). However, there was no significant difference in the need of surgical or radiological intervention for uncontrolled bleeding between IPs and OPs ($p = 0.53$ and 0.59, respectively).

Outcome predictors

Results of the multivariate regression analysis of outcome predictors are shown in Table 4. Only two factors were found to be independent predictors of mortality in IPs: a PT <50% ($p = 0.001$) and rebleeding

TABLE 4 Independent outcome predictors according to multivariate analysis

	Outcome	Predictor	p-value	OR; 95% CI
IPs	Mortality	PT <50%	0.001	2.42; 1.43-4.08
		Rebleeding	0.004	2.13; 1.27-3.56
	Rebleeding	GBS >11	0.009	1.85; 1.17-2.94
		Active bleeding	0.01	1.82; 1.15-2.89
		Sex, female	0.016	1.76; 1.11-2.79
OPs	Mortality	Rebleeding	<0.0001	3.16; 2.02-4.94
		Pre-RS >5	<0.0001	2.67; 1.66-4.30
		Charlson >3	<0.0001	2.29; 1.50-3.50
		Haemodynamic instability	0.014	1.93; 1.14-3.26
		Cirrhosis	0.014	2.28; 1.18-4.41
	Anti-platelets	0.028	0.45; 0.22-0.92	
	Rebleeding	Active bleeding	<0.0001	2.14; 1.53-2.99
		Hb <8 g/dl	0.02	1.48; 1.06-2.06
		Charlson >3	0.04	1.47; 1.02-2.12

Abbreviations: CI, confidence interval; GBS, Glasgow-Blatchford score; Hb, haemoglobin; OR, odds ratio; Pre-RS, pre-endoscopic Rockall Score; PT, prothrombin time.

TABLE 5 Multivariate analysis of risk factors associated with 6-week mortality; all patients included

Risk factor	p-Value	OR	95% CI
Rebleeding	<0.0001	2.69	1.82-3.98
Age >80	0.53	1.15	0.74-1.78
Female sex	0.82	0.95	0.64-1.42
BMI <20 or >30	0.17	1.30	0.89-1.89
NSAIDs/aspirin/steroids use	0.71	0.93	0.64-1.35
Oral anticoagulant	0.89	0.97	0.60-1.56
Alcohol >30 g/day	0.66	0.90	0.55-1.45
Smoking	0.63	1.11	0.72-1.73
Cirrhosis	0.05	1.62	1.00-2.62
Charlson score >3	0.002	1.81	1.24-2.65
Haemodynamic instability	<0.0001	2.30	1.45-3.67
GBS >11	0.48	1.16	0.77-1.76
Pre-RS >5	0.018	1.65	1.82-2.51
Active bleeding	0.310	1.22	0.74-1.78
Haemoglobin <8 g/dl	0.166	1.30	0.64-1.89
In-patients	<0.0001	2.71	0.90-3.88

Note: Those were the risk factors having a significant *p* value concerning the association with mortality.

Abbreviations: BMI, body mass index; CI, confidence interval; GBS, Glasgow-Blatchford score; NSAIDs, non-steroidal anti-inflammatory drugs; Pre-RS, pre-endoscopic Rockall score; OR, odds ratio.

(*p* = 0.004). Predictors of rebleeding among IPs were the following: GBS >11 (*p* = 0.009), active bleeding upon endoscopy (*p* = 0.01) and female sex (*p* = 0.016). In OPs, independent predictors of mortality were the following: rebleeding (*p* < 0.0001), Pre-RS >5 (*p* < 0.0001), Charlson >3 (*p* < 0.0001), haemodynamic instability (*p* = 0.014), cirrhosis (*p* = 0.014) and anti-platelets use (*p* = 0.028). Predictors of rebleeding in OPs were: active bleeding (*p* < 0.0001), Hb < 8 g/dl (*p* = 0.02) and Charlson >3 (*p* = 0.04).

To strengthen our results, we added in Table 5 a multivariate analysis of mortality predictors among the whole study population including the IPs or OPs' status. This analysis confirmed that the IP status was independently associated with a higher 6-week mortality rate (*p* < 0.0001, OR = 2.71, 95% CI 0.90-3.88), beside rebleeding, Pre-RS >5, Charlson score >3 and haemodynamic instability.

DISCUSSION

We presented hereby a nationwide multicentre prospective study comparing the characteristics and outcome of UGIB between IPs and OPs through a large cohort of patients.

We demonstrated a 2.4-fold increase in six-week mortality rate in IPs when compared to OPs. Our observation is in agreement with previous studies where mortality rate in IPs was estimated between 9% and 39% and IP/OP mortality ratio between 2.3- and 6-fold.⁵⁻⁹ Rebleeding rate at 6 weeks was also significantly elevated in IPs, a finding, that is, however, in contrast with the majority of other similar studies that did not observe any considerable increase in bleeding

recurrence among IPs⁶⁻⁹ except for the study of Jairath et al.⁵ who noticed a 2-fold higher odds of rebleeding in IPs versus OPs. Perhaps, in our study, the longer follow-up period of 6 weeks rather than 28 days and the inclusion of variceal haemorrhage in addition to the non-variceal bleeding have allowed us to detect more rebleeding cases. Furthermore, IPs presented more criteria of clinical and biological severity, as represented by a higher Rockall and Blatchford scores as well as increased need for blood transfusion.

Many baseline differences were encountered explaining at least some of the disparities observed between both groups. First, IPs were found to be older than OPs and had a greater rate of comorbidities, making them more susceptible and vulnerable to GI bleeding. In addition, and despite the more prevalent use of PPI among IPs, their UGIB was mainly related to PUD and oesophagitis. This may be explained by the higher intake of aspirin and steroids, which are known to increase the risk of PUD-related haemorrhage especially in elderly and hospitalised patients, not to mention the risk of stress ulcers in this population.¹⁴⁻¹⁶ The *HP* status was however similar between the two groups. Other patient-related factors like the more prevalent renal failure and heparin use among IPs might constitute other potential predisposing factors for severe bleeding.

More interestingly, we found that mortality in OPs was more likely to be directly related to UGIB as opposed to IPs where death resulted more commonly from other causes (renal, hepatic or cardiac failure, sepsis, cancer, etc.), which raises the question of whether UGIB occurring in IPs is the direct cause of their poor prognosis or it is actually another manifestation of their complicated and declining clinical course.

We also noticed some dissimilarities in the process of care between the two groups. Intravenous PPI was less frequently used among IPs but whether this has negatively affected their prognosis is uncertain.¹⁷ Similarly, coagulopathy was less frequently corrected in IPs when compared to OPs. This might be explained by the fact that coagulopathy in OPs was more commonly caused by oral anticoagulants and, thus, its correction was feasible through vitamin K or NOAC antagonists and FFPs, which was not the case in IPs. Cirrhosis related coagulopathy was itself proportionate between both groups. Whatsoever, the prolonged PT in cirrhotic patients does not necessarily reflect a higher risk of bleeding¹⁸ and its correction would not improve outcome. In addition, more IPs with coagulopathy had neither cirrhosis nor anticoagulant treatment and their prolonged PT might be related to an underlying disseminated intravascular coagulation, which is hardly corrected or to vitamin K deficiency, which may be unnoticed in hospitalised patients.

Vasopressors' provision in cirrhotics was surprisingly less prevalent in IPs than in OPs. The reason behind that is not obvious. One possible explanation could probably be due to the delay in having the gastroenterology consultation, which was not recorded in our study. Some specialties, whether they were medical or surgical, do not have the same initial approach to GI bleeding management as gastroenterologists, emergency medicine specialists or intensivists.

The access to endoscopy was assured within 24 h in similar proportion for IPs and OPs, which was not the case in the Canadian RUGBE study,⁶ where authors attributed some of the negative bleeding outcome in IPs to a limited early access to endoscopy compared to OPs.

While endoscopic therapy was performed predominantly in IPs group, the mortality and rebleeding rates were still higher than OPs. Treatment of ulcers with higher risk stigmata (Forrest Ia to IIb) was proportionate between IPs and OPs and the majority had a mechanical or thermal therapy whether it was combined or not to adrenalin injection. However, about quarter of these patients (OPs and IPs included) had adrenalin injection alone and a smaller proportion had even not receive endoscopic haemostasis, mostly patients with adherent clots (Forrest IIb). This has probably increased the risk of rebleeding.¹⁹

Many scores have been used for outcome prediction in patients presenting with UGIB but none has really distinguished between in and OPs. The most commonly used in practice are the Rockall (RS) and GBS. PT is not included in any of these two scores but it was comprised in a more recent model, the AIMS65.²⁰ This score was found to be more reliable in assessing the risk of UGIB related mortality when compared to RS and GBS.^{20,21} In our study, Pre-RS >5 independently predicted mortality in OPs but not in IPs after adjustment to other patients' related factors. On the other hand, GBS >11 was better in predicting rebleeding in IPs. While rebleeding was strongly associated with higher mortality in both groups, a PT of <50% was found to be an independent predictor of mortality among IPs. The existing risk stratification scores for UGIB are probably less reliable in IPs and other outcome predictors may have to be considered when we assess bleeding in these patients. In their study, Marmo et al.⁷ proposed a prediction model of mortality for IPs and OPs with UGIB, separately. Rebleeding was among the main predisposing factors of mortality in OPs but not in IPs, which is in contrast with our finding. This discrepancy is likely related to the fact that our Italian colleagues did not include variceal haemorrhage in their analysis, where rebleeding is a well-known predictor of 6-week mortality.²² In addition, haemodynamic instability and overall clinical status represented by the modified American Society of Anesthesiologists (ASA) class were the independent predictors of death in IPs while failure of endoscopic treatment and ASA class were the main determinants of mortality in OPs, besides rebleeding.

While we cannot draw conclusions about the causative effect of the association between the less prevalent coagulopathy correction in IPs with a PT of <50% and their poorer outcome, we think that a more efficient rebleeding prevention would reduce the mortality related to UGIB in hospitalised patients. Such preventive measures in variceal bleeding include a better provisioning of vasopressors and antibiotics, starting beta blockers and following a regular ligation protocol until variceal eradication. Non-variceal rebleeding can be prevented by an adequate PPI prescription, an appropriate endoscopic haemostasis according to the bleeding risk stigmata and by weighing the risk/benefit balance before resuming anti-coagulants or anti-platelets in high risk patients.

Our study presents several strengths including a prospective design as well as a large nationwide cohort of patients with UGIB related or not to variceal aetiology. In addition, it represents a real-life study showing the process of care followed in non-academic hospitals, which are not considered as big referral or tertiary care centers. Unique to our study was the six weeks follow-up period, which enhances the value of outcome assessment beyond hospital stay, but at

the same time, it limits the comparability of our results with previous studies where outcome was assessed mostly at 28 days except for variceal bleeding. Our study has however some limitations. For example, we were not able to precise the initial cause of hospitalisation among all IPs, which may have a substantial influence on their prognosis. In addition, we did not record the continuation of high dose PPI after endoscopic therapy for ulcers with high-risk stigmata neither the use of antibiotics in patients with cirrhosis, which may affect the risk of rebleeding in these groups. Another important limitation was the scarcity of data about the management of rebleeding. This should be particularly emphasised especially that bleeding recurrence was associated with a higher mortality. Moreover, it is important to note that the length of hospital stay was different between IPs and OPs and thus, the comparison of mortality during the same hospitalisation between both groups may not be accurate.

CONCLUSION

Patients who develop UGIB while in hospital have a poorer prognosis with higher 6-week mortality and rebleeding rates when compared to OPs. They are mostly elderly, severely ill and taking more aspirin and steroids. While endoscopic and pharmacological treatment as well as close monitoring for complications are essential in the management of these patients, other factors such as coagulopathy correction when possible and more importantly, an efficient rebleeding prevention may reduce the risk of death in this high-risk group.

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DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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APPENDIX

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