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Optimal timing of endoscopy in patients with acute upper gastrointestinal bleeding

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ABSTRACT

Endoscopy is the gold standard for evaluating and treating acute upper gastrointestinal bleeding (UGIB). The optimal timing of endoscopy is a very important consideration in the overall management of UGIB, but there is on going uncertainty regarding timing of the procedure, particularly in those with more severe bleeding. This is reflected by inconsistencies between current guidelines. Although evidence suggests endoscopy should be undertaken within 24 h for all admitted patients with UGIB, a small group of patients with severe bleeding or high-risk features may require more urgent endoscopy. The exact timing of the procedure in this high-risk group remains unclear, with recent data suggesting that performing endoscopy too early may be associated with worse outcome. In this article we examine the evidence for optimal timing of endoscopy in patients presenting with UGIB and suggest a clinical approach to this important aspect of patient management.

Introduction

The optimal timing of endoscopy in acute upper gastrointestinal bleeding (UGIB) remains somewhat controversial. This is reflected by variations in current recommendations regarding the interval between presentation and endoscopy. It is generally accepted that endoscopy within 24 h is appropriate for most patients with UGIB [1–5]. However, the organisation of this, particularly at weekends in smaller centres remains challenging. Over recent years, studies have described the accurate early identification of patients at very low risk of poor outcome after UGIB, in whom admission can be avoided and early outpatient endoscopy arranged [6–8]. At the other end of the spectrum, the optimal timing of endoscopy in patients who are acutely unwell with severe bleeding has not been clearly defined. In this article we will discuss the relevant issues regarding timing of endoscopy based on current evidence. We will assess the role of clinical parameters and risk scores in determining when endoscopy should be performed in a patient presenting with UGIB, and discuss the impact of out-of-hours presentation on timing of endoscopy and patient outcomes.

Current evidence on optimal timing of endoscopy in acute upper gastrointestinal bleeding

Randomised control trials

Among the numerous studies evaluating the association between timing of endoscopy and patient outcomes, there have only been three published randomised controlled trials (RCTs) [9–11]. These studies collectively comprised of a total of 528 patients and differed significantly in their design. Two of the studies only included haemodynamically stable patients [10,11]. The study by Lee et al. excluded patients with haemodynamic instability, cirrhosis, comorbid illness requiring intensive care, coagulopathy and those with recent UGIB [10] whereas the analysis by Bjorkman and colleagues excluded patients who started bleeding whilst in hospital and those with a Rockall score of >5 [11]. The results from both studies reported no significant difference in the rates of mortality between patients who were endoscoped early ($\leq$2 h in the Lee study and $\leq$6 h in the Bjorkman study) compared to those who were endoscoped later.

The study by Lin et al. included 325 patients and was unique in that the patients were risk stratified into three groups according to their nasogastric aspirates - clear, coffee-ground or bloody [9]. 36% of the patients included in the study were haemodynamically unstable. The patients were then randomised to receive 'early' endoscopy within 12 h of presentation or 'delayed' endoscopy at more than 12 h

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after presentation. The analysis again showed no difference in the rate of mortality between the early and the delayed group. However, patients with a bloody aspirate who received early endoscopy had a lower volume of blood transfusion requirement (mean, 450 ml *vs.* 666 ml; $p < 0.001$) and shorter length of hospital stay (mean, 4 vs. 14.5 days, $p < 0.001$). The overall relative risk of 30-day mortality in these three studies was 0.81 [1] (see Fig. 1).

None of these three RCTs demonstrated any statistically significant difference in the rates of re-bleeding, or surgery due to continued bleeding, between patients endoscoped earlier or later. The studies by Lee and Lin specifically assessed re-bleeding rates. In haemodynamically stable patients, Lee reported a re-bleeding rate of 5.40% in patients endoscoped ≤2 h compared with 3.70% in patients who underwent endoscopy later. In Lin's study, the rate of re-bleeding was similar in both groups at 3.70% in the early endoscopy group (≤12 h) versus 4.90% for the delayed endoscopy group (>12 h). Rates for surgery due to continued bleeding were analysed in all three studies. Comparing early versus later endoscopy, the rates of surgery were 5.7 *vs* 7.4%, 3.6 *vs* 1.9% and 2.1 *vs* 2.2% in Lin, Lee and Bjorkman's study respectively.

Major cohort studies looking at timing of endoscopy

Both retrospective and prospective cohort studies have tried to evaluate the effect of timing of endoscopy on patient outcomes (see Table 1). However, the interpretation of the results from these studies is complicated by the heterogeneity in their design, the variation in the follow-up period and various modes of endoscopic therapy used. In this section we discuss the results of the five retrospective and four prospective cohort studies that appear to focus on timing of endoscopy and it's effect on clinical outcomes [12–20].

The two largest retrospective cohort studies were carried out in the United States. In the earlier study dating from 1994 [12], 909 hospitalised patients who presented with UGIB and underwent endoscopy across 13 hospitals were included. The study evaluated the association between "early" endoscopy (≤24 h) and patient outcomes with. 64% of patients underwent endoscopy within 24 h. There was no statistically significant difference in the rate of recurrent bleeding or surgery (odds ratio 0.70; $P = 0.15$) however, the length of hospital stay was significantly shorter in the early endoscopy group (5.0 *vs* 6.4 days; $P < 0.001$). Patients deemed at high-risk of re-bleeding, defined as those with ulcer disease and visible vessels, active bleeding or arterial spurting, and those with varices, benefitted from early endoscopy resulting in lower re-bleeding and rates of surgery.

In the other large U.S. retrospective study from 2004, a nationwide sample of 2592 patients aged 66yrs and over who underwent inpatient or outpatient endoscopy for a principal diagnosis coded as peptic ulcer bleeding were included [13]. 1854 patients (71.5%) underwent endoscopy within 24 h. The authors reported no significant difference in mortality between the early and delayed endoscopy groups. Patients who underwent endoscopy within 24 h had shorter length of hospital stay (−1.95 days, 95% CI, −2.60 to −1.29) and reduced likelihood of surgery (odds ratio, 0.37; 95% CI, 0.21–0.66).

A study by Schacher et al. attempted to determine whether immediate endoscopy made a difference to clinical outcomes [14]. This retrospective cohort study included 81 patients with bleeding peptic ulcer who were divided into two groups. One group of patients underwent endoscopy in the emergency department within three hours ($n = 43$) and the second group received standard therapy with endoscopy within 48 h ($n = 38$). The authors reported that early endoscopy (within 3 h) did not improve patient outcomes, with similar rates of recurrent bleeding, persistent bleeding, medical complications, need for surgery, length of stay and mortality. The patients in the early endoscopy group received significantly higher rates of endotherapy (77% *vs* 47%; $P = 0.006$) but this did not translate into improvements in clinically relevant outcomes as described above.

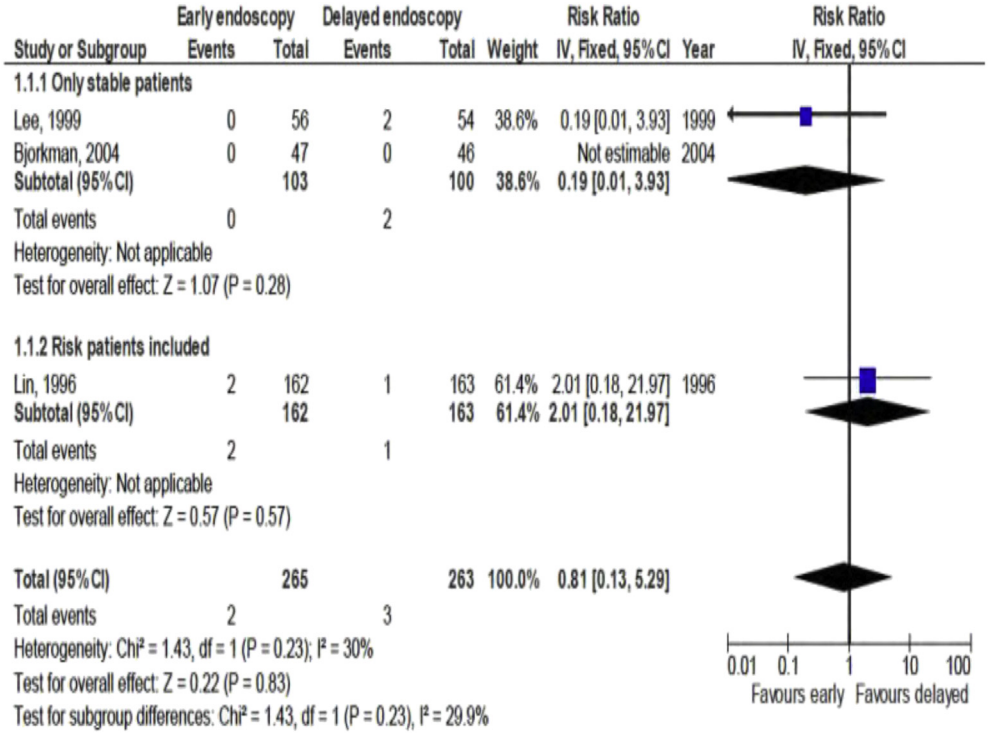

Fig. 1. Randomised studies evaluating 30-day mortality in early endoscopy versus delayed endoscopy.

Table 1
Randomised and large cohort studies evaluating the effect of timing of endoscopy.

Source	Design	Patient number	Patient characteristic	Follow-up period	Comparison
Lin [9]	RCT, Single centre	325	HD stable and unstable	60 days	Early (within 12 h) vs delayed (>12 h) endoscopy
Lee [10]	RCT, Single centre	110	HD stable	30 days	Early endoscopy (in ED within 2 h) vs endoscopy in 1–2 days
Bjorkman [11]	RCT, Multi-centre	93	HD stable	N/A	Urgent (pre-hospitalisation) vs elective (after admission) endoscopy
Lim [17]	PCT, Single centre	934	HD stable and unstable	Length of patient stay	All cause in-hospital mortality in high-risk vs low-risk patients
Cho [18]	PCT, Single centre	962	HD stable and unstable	28 days	Urgent (<6 h) vs elective (6–48 h) endoscopy
Cooper [12]	RtCohort study, Multicentre	909	HD stable and unstable	Length of stay	Early (within 24 h) vs delayed (>24 h) endoscopy
Schacher [14]	RtCohort study, Single centre	81	HD stable and unstable	14 days	Early endoscopy in ED vs delayed endoscopy (within 24 h of hospitalisation)
Targownik [15]	RtCohort study, Multicentre	169	HD unstable	30 days	Rapid endoscopy (<6 h) vs early endoscopy (6–24 h)
Tai [16]	RtCohor study, Single centre	189	HD stable and unstable	Length of stay	Emergency endoscopy (<8 h) vs urgent endoscopy (8–24 h)
Cooper [13]	RtCohort study,, Nationwide	2592	HD stable and unstable	30 days	Early (within 24 h) vs delayed (>24 h) endoscopy
Laursen [20]	Nationwide cohort study	12,601	HD stable and unstable	Length of stay	Effect of timing and ASA status on in-hospital mortality
Jairath [19]	Prospective national audit	4478	HD stable and unstable	Length of stay	Early (<12 h) vs later (>24 h) endoscopy

RCT: randomised controlled trials, PCT: Prospective cohort trial, Rt: Retrospective, HD: haemodynamically, ED: emergency department, ASA: American Society of Anaesthesiologists.

The remaining two retrospective studies tried to evaluate the effect of endoscopy performed within 6 or 8 h [15,16]. One study from Canada looked at clinical outcomes of 169 haemodynamically unstable patients over a 5 year period [15]. 77 patients underwent early endoscopy within 6 h of presentation whereas the control group of 92 patients received endoscopy between 6 and 24 h. The group that underwent early endoscopy had an increased prevelance of high-risk endoscopic lesions compared to the control group (57% *vs* 37%, $P = 0.012$) as well as use of endotherapy (53% *vs* 37%, $P = 0.043$). However, they did not find any difference in overall adverse clinical outcomes between the two groups (25% in early group *vs* 23% in control group, $P > 0.2$), including mortality, rebleeding, need for surgery, transfusion requirements and length of hospital stay. Even though the study assessed outcomes in haemodynamically unstable patients, the majority of the patients included in the study would be considered relatively low-risk with a mean pre-endoscopic Rockall score of 3.2 in the early-endoscopy group versus 3.3 in the control group. Additionally, less than half of the patients in each group had a pre-endoscopic Rockall score of greater than 5.

In another retrospective study by Tai et al. from Taiwan [16], the authors compared clinical outcomes of 189 patients with UGIB, who underwent early endoscopy within 8 h of presentation ($n = 88$) or between 8 and 24 h of presentation ($n = 101$). The patients that underwent early endoscopy had more high-risk endoscopic lesions than the later group with significantly more actively bleeding ulcers and more exposed vessels (19% *vs* 8%, $P = 0.03$; and 34% *vs* 12%, $P < 0.001$ respectively). Consequently, the early endoscopy group also received more endoscopic intervention (50% *vs* 21%), with 40% of the early endoscopy group receiving combination modality to achieve endoscopic haemostasis compared to 15% in the 'delayed' group. Similar to the previously described studies, there was no statistically difference in clinical outcomes (mortality, rebleeding, length of hospital stay or volume of transfusion) between the two groups.

A prospective cohort trial, assessing the timing of endoscopy based on risk assessment scores was carried out in Singapore at a university hospital with 24-h access to endoscopy [17]. All adult patients undergoing endoscopy over an 18-month period for UGIB (coffee-ground vomitus, haematemesis or melaena) were included in the study. A total 934 patients were recruited and of these 77.6% underwent endoscopy within 24 h. The patients were risk-stratified into low-risk (Glasgow Blatchford score (GBS) < 12) and high-risk (GBS ≥ 12) groups. The authors then analysed whether the timing of endoscopy had any effect on inpatient mortality between the two groups. In the low-risk group ($n = 837$) the timing was not associated with inpatient mortality, however in the high-risk group ($n = 97$), presentation-to-endoscopy was the only factor associated with all-cause in-hospital mortality (adjusted OR, 1.09; 95% CI, 1.02–1.17).

The authors suggested that for patients with GBS ≥12, endoscopy within 13 h may lower mortality. We describe this aspect in more detail in the section below on use of pre-endoscopic risk scoring systems to guide timing of endoscopy.

In another prospective cohort trial by Cho et al. [18], 961 consecutive patients with GBS of greater than 7 who underwent endoscopy for UGIB were recruited over a 9 year period. They were divided into urgent (within 6 h) and elective (6–48 h) groups according to the time to endoscopy after presentation. 571 patients underwent urgent endoscopy. The authors reported that there were significant differences in mortality rates between the urgent and elective groups (1.6% *vs* 3.8% respectively). The number of transfused packed red blood cells, need for endoscopic therapy and radiological embolisation were also higher in the elective group. However, rebleeding rates and length of hospital stay were similar between the two groups.

Patient outcomes in relation to timing of endoscopy was examined in 4478 patients with non-variceal UGIB in the 2007 UK prospective national audit [19]. The authors reported that earlier endoscopy (within 12 h) was not associated with lower mortality or need for surgery compared with later endoscopy (>24 h). However, later endoscopy was associated with a longer risk adjusted hospital stay (1.7 extra days, 96% CI 1.39–1.99; $P < 0.001$).

When considering early endoscopy in patients with UGIB, it is important to ensure that any haemodynamic instability is addressed with appropriate resuscitation, in addition to optimizing

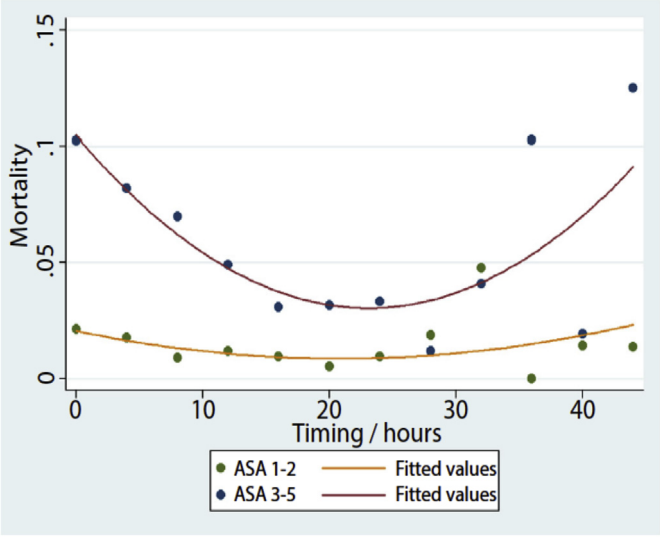

Fig. 2. Association between timing of endoscopy and in-hospital mortality in haemodynamically stable patients. For ASA 1 to 2: no association with in-hospital mortality (OR, 0.59; 95% CI, 0.33−1.05; P = 0.075) or 30-day mortality (OR, 1.02; 95% CI, 0.50−2.09; P Z = 0.96). For ASA 3 to 5: lower in-hospital mortality (OR, 0.48; 95% CI, 0.34-0.67; P < 0.001)and 30-day mortality (OR, 0.73; 95% CI, 0.53−1.01; P = 0.059) Used with permission of Elsevier.

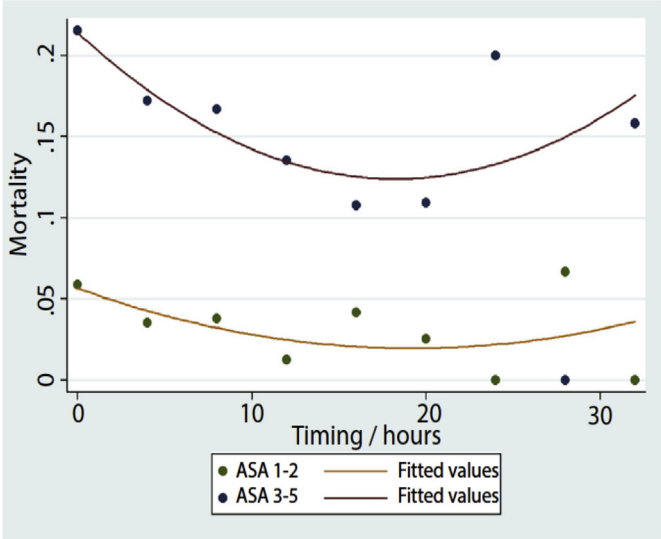

Fig. 3. Association between timing of endoscopy and in-hospital mortality in haemodynamically unstable patients. For ASA 1 to 5: Endoscopy between 6 and 24 h associated with lower in-hospital mortality (OR, 0.73; 95% CI, 0.54-0.98; P = 0.035) and lower 30-day mortality (OR, 0.66; 95% CI, 0.46-0.95; P = 0.025) Used with permission of Elsevier.

relevant comorbidities prior to endoscopy. This is highlighted by a recent large Danish prospective cohort study of patients with peptic ulcer bleeding [20]. Laursen and colleagues reported data on 12,601 patients over an 8-year period from a nationwide database. Using descriptive statistics and logistic regression with backward elimination for adjustment of confounders, they correlated the optimal time frame for endoscopy with regard to in-hospital mortality. The patients were stratified according to their haemodynamic status at presentation and also their American Society of Anaesthesiologists (ASA) score.

They found that among haemodynamically stable patients with an ASA score of 3−5, in-hospital mortality was lower in those who were endoscoped between 12 and 36 h from presentation (OR = 0.48; 95% CI 0.34−0.67) (see Fig. 2). For haemodynamically unstable patients, the optimum time for endoscopy appeared to be between 6 and 24 h after presentation (OR = 0.73; 95% CI 0.54−0.98) (see Fig. 3). The resultant "U-shaped" association found in these patient groups suggests that in patients with major comorbidities or those with haemodynamic instability, the first few hours of hospital admission might be best used for patient resuscitation and optimization of comorbidities, for example correction of severe anemia and coagulopathy, and investigation and rapid treatment of possible infection. The authors however pointed out that endoscopy should not be delayed in patients with severe haemodynamic instability who are not responding to intensive resuscitation.

Timing of endoscopy in suspected variceal bleeding

In patients with suspected variceal bleeding (those with known cirrhosis and/or varices, or signs of chronic liver disease), it has been suggested that endoscopy should be performed following appropriate resuscitation and within 12 h of presentation [21−25]. However, the evidence base for this time-period is weak. Other major variceal bleeding guidelines state that endoscopy should be undertaken with 24 h, unless the patient is unstable with severe bleeding in which case it is required immediately after resuscitation [26]. Interestingly, a recent paper assessing the association of timing of endoscopy with outcomes in 274 consecutive patients with variceal bleeding, reported no difference in 6-week mortality between those having endoscopy ≤12 h *versus* >12 h, after correction for confounding variables [27]. These patients should also be given prompt antibiotics and vasoactive drug therapy in view of the strong evidence of benefit from these medications in patients with cirrhosis and suspected varices [21−26].

Timing of endoscopy in patients with UGIB who have been taking antithrombotic medication

A recent international cohort study of 619 patients requiring endoscopic therapy for UGIB reported that 44% were taking an antiplatelet or anticoagulant drug at presentation, with 25% taking more than one of these medications [28]. With regard to timing of endoscopy, if the patient has been taking anticoagulants, undertaking endoscopic therapy with INR <2.5 appears safe [29], and successful endoscopic therapy can be achieved in the majority of patients with an INR between 1.3 and 2.7 [30]. The safety of endoscopic therapy in patients with INR higher than this is unclear and in clinical practice the timing of endoscopy will depend on the clinical situation including haemodynamic parameters and the severity of bleeding. In case of life-threatening UGIB in patients on warfarin, it has been suggested that prothrombin complex concentrate (PCC) and vitamin K should be given and the patient adequately resuscitated prior to performing endoscopy [31]. The management of patients with UGIB who are taking anti-platelet or anticoagulant drugs is discussed in detail in another chapter in this publication.

Does out-of-hours presentation affect timing of endoscopy and outcomes?

Out-of-hours presentation (i.e. at weekends, evenings and overnight) is associated with reduced staff availability, lack of subspecialist cover and limited ancillary services in many hospitals. The relationship between out-of-hours admissions and mortality has been examined in many studies [32−37], with a majority

concluding that patients admitted out-of-hours with non-variceal UGIB, have a higher mortality and longer length of in-patient stay compared to patients admitted during weekdays. There are several factors that have been implicated as possible explanations for this 'weekend effect' including lower staffing levels, less experienced healthcare providers, limited availability of subspecialists (including endoscopy and interventional radiology) and poor continuity of care. It has also been suggested that patients presenting at weekends or overnight may be more unwell, with more significant comorbidities or older age compared with those admitted during weekdays [38,39].

There have been three large systematic reviews and meta-analyses evaluating the effects on mortality and clinical outcomes for patients presenting with UGIB out-of-hours and their conclusions are fairly consistent with regards to the effect of out-of-hours admission on mortality [37,40,41]. They found that patients admitted with non-variceal UGIB out-of-hours had higher in-hospital mortality compared to patients admitted during in-hours. Interestingly, there was no significant difference in mortality in patients with variceal bleeding. The recently published systematic review and meta-analysis by Xia and colleagues analysed 20 cohort studies [41]. Their analysis showed that patients with UGIB who were admitted out-with routine working hours had a significantly higher overall mortality with a pooled OR of 1.11 (95% CI 1.04–1.18, $p = 0.006$). Patients admitted out-of-hours were also less likely to receive endoscopy within 24 h of admission (OR 0.60, 95% CI 0.54–0.68; $p < 0.001$). Similar to meta-analyses described above, the higher mortality in this patient group was only noted in patients with non-variceal bleeding. Interestingly, patients admitted out-of-hours to hospitals that provided a 24/7 endoscopy service, did not show an increased risk of mortality compared to patients admitted during normal working hours ($p = 0.904$) [41].

Whether the increase in mortality reported at weekends is directly related to the timing of endoscopic intervention is unclear. A study by a group in the U.S. used a large database of national hospital discharges (the Nationwide Inpatient Sample) to identify patients hospitalised for peptic-ulcer related UGIB between 1993 and 2005. They found that even though patients admitted at the weekend had to wait longer for endoscopy (2.21±0.01 *vs* 2.06±0.01 days; $P < 0.0001$), this delay did not appear to mediate the higher mortality they found for weekend admissions [35]. Further data including randomised trials are required to determine whether a delay in timing of endoscopy in patients admitted out-of-hours with UGIB directly affects mortality. However, it seems logical to aim to provide out-of-hours specialist services where possible (or a clear pathway to another hospital) to allow prompt endoscopy and therapy as needed for patients who present with UGIB at these times.

Can pre-endoscopic scoring systems help guide the timing of endoscopy?

Risk stratification in UGIB is discussed in detail in another chapter of this publication. Here we review the potential use of risk scores to direct the timing of endoscopy. Early (pre-endoscopic) use of risk-stratification tools can categorise patients into low-risk and high-risk groups [1,3,5,42]. The Glasgow Blatchford score (GBS), the pre-endoscopy (aka "clinical" or "admission") Rockall score (RS) and AIMS65 are the most widely used scores to risk stratify patients with UGIB before endoscopy.

The GBS has been found to out-perform the pre-endoscopy RS and AIMS65 in predicting need for intervention or death [7,43] and in predicting specific interventions such as endoscopic therapy, blood transfusion, or radiological or surgical intervention (see Fig. 4). Although the original study suggested that only a GBS of

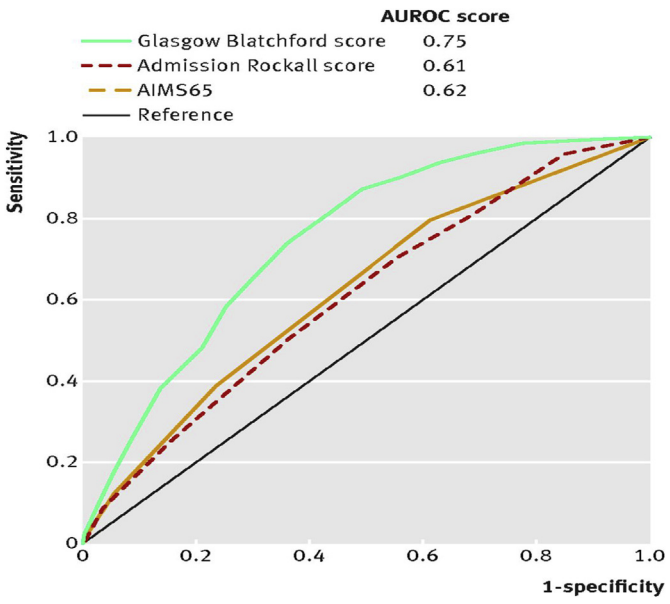

Fig. 4. Comparison of pre-endoscopic scores in predicting the need for endoscopic treatment. GBS (AUROC 0.75) is superior to AIMS65 (0.62) and Admission Rockall scores (0.61; $P < 0.001$ for both). AUROC = area under the receiver operating characteristic curve. This figure is used with permission of the BMJ Publishing Group Ltd.

zero was safe for discharge [44], several subsequent studies have recommended extending the low-risk threshold to GBS ≤1, to identify patients who will not require transfusion or any haemostatic intervention and will survive [8,43,45]. As a result of these data, many centres now calculate GBS when patients present with UGIB, and if GBS is ≤ 1, they do not admit these patients, but offer an early outpatient diagnostic endoscopy.

At the other end of the spectrum, the existing risk scores for UGIB appear less accurate in the identification of high-risk patients. As mentioned earlier in this article, an observational study by Lim et al. attempted to determine whether a 'high-risk' group of patients could benefit from having endoscopy performed sooner than the currently recommended 24 h target [17]. Their study reported that in higher risk patients, defined as GBS ≥12, the presentation-to-endoscopy time was significantly longer in those who died than those who had survived. Multivariate analysis of this higher-risk group showed that in those patients who underwent endoscopy more than 13 h after presentation, all-cause in-hospital mortality was significantly higher compared to those who were endoscoped within 13 h (44% *vs* 0% respectively; $P < 0.001$).

The interim results of a randomised controlled study from Hong Kong which compared urgent (<6 h) with standard (<24 h) endoscopy in high risk patients with UGIB, defined as GBS ≥ 12, did not find any difference in clinical outcomes [46]. However the final published results of this important study are awaited.

A recent international multicentre study of 3012 consecutive patients presenting with UGIB found that all existing scores were relatively inaccurate at predicting need for endoscopic therapy, and also mortality, with AUROCs for GBS, AIMS65 and pre-endoscopy Rockall score for these endpoints all <0.80 [43]. Although GBS of ≥7 appeared best at predicting the need for endoscopic treatment, the AUROC of 0.75 may limit the clinical utility of using this to direct patient management (see Fig. 4).

Another score called the T-score, has been recently described to prioritise patients who are likely to have high-risk endoscopic stigmata and therefore need endoscopic intervention. A T-score of ≤6, corresponding to high-risk patients, was found to be able to

predict the presence of high-risk endoscopic stigmata and the need for an early endoscopy with a sensitivity and specificity of 30% and 96% respectively. The positive predictive value was reported to be 74.5% whereas the negative predictive value was 76.4% [47,48]. How this information relates to timing of endoscopy remains unclear. External validation of this score is also required.

Other characteristics of 'high-risk' patients that have been highlighted in randomised and observational studies and who might be considered for urgent endoscopy, have included evidence of haemodynamic shock with hypotension and tachycardia, a bloody nasogastric aspirate, GBS $\geq$ 7–12, persistent in-hospital haematemesis and comorbid illness such as cirrhosis [9,17,18].

Timing of endoscopy and economic considerations

There appears to be an economic argument for stable patients with low risk of mortality to undergo early endoscopy. Lee and colleagues reported that the cost of care was significantly less for patients who underwent early endoscopy, within two hours of presentation [10]. This was mainly due to the fact that 46% of patients in the study group were discharged directly from the emergency department after endoscopy and did not require a hospital stay. None of the patients who were discharged suffered an adverse outcome. This study was however carried out in the United States and the results may not be broadly applicable, as the provision of endoscopy in emergency departments is not generally available worldwide.

It is recognised that endoscopy carried out within the first 24 h of admission is likely to be more cost effective than leaving it longer than 24 h. This is largely due to the ability to discharge patients once endoscopy is undertaken, provided no major stigmata of bleeding or other significant pathology is identified which would require in-patient management [49]. In addition, an economic analysis undertaken as part of the UK NICE guidelines suggested that centres managing >330 patients with UGIB per year would find it cost-effective to organize and resource 7-day endoscopy lists, to enable patients to undergo endoscopy within 24 h [1]. This allows early discharge of many patients deemed low-risk after endoscopy and reduces in-patient stay for those admitted at weekends or holidays. A recent UK cost analysis study reported that the mean in-hospital costs for a patient with UGIB were estimated to be £2458, with 60% of the cost due to in-patient bed-days [50].

Current guidelines

The recommendations on timing of endoscopy for patients with UGIB from the major guidelines published over the past 8 years are summarised in Table 2. Several recommendations are not consistent across the guidelines. The UK National Institute of Clinical Excellence (NICE) recommend an endoscopy within 24 h of admission for all haemodynamically stable patients with UGIB [1]. However, those who are haemodynamically unstable should have endoscopy within two hours of optimal resuscitation. These recommendations were adopted by the British Society of Gastroenterology (BSG). Interestingly, the large 2007 UK audit of patients presenting with UGIB reported that only 50% of underwent endoscopy within 24 h [51].

The European Society of Gastrointestinal Endoscopy (ESGE) and American Society for Gastrointestinal Endoscopy (ASGE) guidelines advise that most patients who are hospitalised with UGIB should undergo 'early' endoscopy within 24 h whereas 'very early' endoscopy within 12 h is reserved for those with high-risk clinical features [3,4]. These are consistent with the recommendations put forward by the American College of Gastroenterology on the timing of endoscopy, which also emphasise the importance of resuscitative efforts to correct and optimise haemodynamic parameters and other medical comorbidities [5]. The most recent international guidelines were published in 2018 by the Asia-Pacific Working Group consensus and recommend endoscopic intervention within 24 h of onset of bleeding in patients admitted with UGIB [42]. However they state that very high risk patients who are haemodynamically unstable should have endoscopy performed as soon as they are stabilised with resuscitation. These and other guidelines acknowledge that very low-risk patients defined by GBS 0–1 could be managed as out-patients.

Current guidelines on the timing of endoscopy in patients with variceal bleeding are summarised in Table 3. Most of these recommend performing endoscopy within the first 12 h of admission [22–24]. However, the British Society of Gastroenterology variceal bleeding guidelines advise endoscopy within 24 h, although note that unstable patients with severe bleeding should undergo endoscopy immediately after resuscitation [26].

Summary

When patients present with UGIB, the decision on timing of endoscopy should take into account their haemodynamic status, comorbidities and laboratory parameters, which together help to assess their risk of poor outcome. Most published studies report no difference in mortality between early and delayed endoscopy. However, these results must be treated with caution as well-designed RCTs and high-quality data are lacking.

There appears to be a group of very low risk patients identified by GBS$\leq$1 who can be discharged from the emergency department

Table 2
Current major guidelines on timing of endoscopy in AUGIB.

Source	Year updated	Recommendation on timing of endoscopy in non variceal upper gastrointestinal bleeding
Asia-Pacific Working Group [42]	2018	Urgent endoscopy (within 12 h) after resuscitation and stabilisation of patients with haemodynamic shock and signs of upper GI bleeding Endoscopy within 24 h for other patients admitted with UGIB
European Society of Gastrointestinal Endoscopy (ESGE) [3]	2015	Very early (<12 h) upper GI endoscopy may be considered in patients with high risk clinical features Early ($\leq$24 h) upper GI endoscopy following haemodynamic resuscitation
UK NICE (adopted by British Society of Gastroenterology) [1]	2012	Urgent endoscopy in unstable patients with severe acute upper gastrointestinal bleeding. Offer endoscopy within 24 h of admission to patients with upper gastrointestinal bleeding.
American Society of Gastrointestinal Endoscopy (ASGE) [4]	2012	Urgent endoscopy (<24 h) is recommended for patients with history of malignancy, or cirrhosis, presentation with haematemesis and signs of hypovolaemia and Hb < 8 d/dL
American College of Gastroenterology [5]	2012	9. Endoscopy within 24 h of admission, following resuscitative efforts to optimise haemodynamic parameters and other medical problems In patients with higher risk clinical features (e.g., tachycardia, hypotension, bloody emesis or nasogastric aspirate in hospital) endoscopy within 12 h may be considered.

Table 3
Current society guidelines on timing of endoscopy in suspected variceal haemorrhage.

Source	Year updated	Recommendations on timing of endoscopy in variceal bleeding
European Association for the Study of the Liver (EASL) [22]	2018	Gastroscopy should be performed within the first 12 h after admission once haemodynamic stability has been achieved.
American Association for the study of liver diseases AASLD) [23]	2016	Endoscopy should be performed within 12 h of admission and once the patient is haemodynamically stable
Baveno VI Consensus [21]	2015	Following haemodynamic resuscitation, patients with UGIB and features suggesting cirrhosis should undergo gastroscopy within 12 h of presentation
British Society of Gastroenterology Variceal bleeding guidelines (BSG) [26]	2015	Offer endoscopy to unstable patients with severe acute upper gastrointestinal bleeding immediately after resuscitation. Offer endoscopy within 24 h of admission to all other patients with upper gastrointestinal bleeding
American Society for Gastrointestinal Endoscopy (ASGE) [24]	2014	Recommend performing endoscopy urgently (within 12 h of admission) in patients with suspected acute variceal haemorrhage
Asia-Pacific Association for Study of the Liver (APASL) [25]	2011	Endotherapy should be done as soon as possible under resuscitation preferably within 6 h of admission

with early out-patient endoscopy planned. For patients who do require admission, undertaking endoscopy within 24 h seems appropriate. This also has an economic benefit, allowing early hospital discharge for many patients.

Patients presenting with UGIB and haemodynamic instability and/or suspected variceal bleeding, require prompt resuscitation prior to endoscopy. In addition, relevant comorbidities should be addressed. This higher risk group may need urgent endoscopy within 6–12 h.

Although some studies have suggested using GBS $\geq$12 to identify patients who will benefit from urgent endoscopy, this has not been confirmed. It seems logical to use haemodynamic and clinical assessment and blood parameters to identify those patients who require urgent endoscopy.

In conclusion, very low-risk patients with UGIB defined by GBS $\leq$1 do not require admission (unless required for another reason) and can be managed as out-patients. There is a small high-risk group who may require urgent endoscopy (eg within 6–12 h) following resuscitation. The majority of patients will be between these two extremes and should undergo endoscopy within 24 h. This provides prompt diagnosis, therapy if required, and allows early discharge where appropriate.

Practice points

- In patients with UGIB, endoscopy offers accurate diagnosis, aids assessment of prognosis and allows provision of endoscopic therapy if required
- For the majority of patients, endoscopy within 24 h of presentation is appropriate
- Very low-risk patients can be identified by GBS$\leq$1 on presentation; these patients can avoid admission (unless required for another reason) with early out-patient endoscopy arranged
- A small high-risk group with haemodynamic instability and severe bleeding or those with suspected varices may require more urgent endoscopy within 6–12 h after appropriate resuscitation

Research agenda

- Adequately powered randomised controlled trials are required to help clarify the optimal timing of endoscopy in patients presenting with severe UGIB and haemodynamic instability
- Detailed controlled studies are required to help define the optimal timing of endoscopy in patients presenting with suspected variceal bleeding
- High quality studies are required to help identify higher-risk patients with UGIB who will benefit from further resuscitation and management of comorbidities prior to endoscopy

Conflict of interest statement

None.

References

[1] Acute upper gastrointestinal bleeding: management. London: National Institute for Health and Clinical Excellence: Guidance; 2012.
[2] Barkun AN, Bardou M, Kuipers EJ, Sung J, Hunt RH, Martel M, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med 2010;152(2):101–13.
[3] Gralnek IM, Dumonceau JM, Kuipers EJ, Lanas A, Sanders DS, Kurien M, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European society of gastrointestinal endoscopy (ESGE) guideline. Endoscopy 2015;47(10):a1–46.
[4] Hwang JH, Fisher DA, Ben-Menachem T, Chandrasekhara V, Chathadi K, Decker GA, et al. The role of endoscopy in the management of acute nonvariceal upper GI bleeding. Gastrointest Endosc 2012;75(6):1132–8.
[5] Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol 2012;107(3):345–60. quiz 61.
[6] Stanley AJ, Ashley D, Dalton HR, Mowat C, Gaya DR, Thompson E, et al. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. Lancet 2009;373(9657):42–7.
[7] Laursen SB, Hansen JM, Schaffalitzky de Muckadell OB. The Glasgow Blatchford score is the most accurate assessment of patients with upper gastrointestinal hemorrhage. Clin Gastroenterol Hepatol 2012;10(10). 1130-5 e1.
[8] Mustafa Z, Cameron A, Clark E, Stanley AJ. Outpatient management of low-risk patients with upper gastrointestinal bleeding: can we safely extend the Glasgow Blatchford Score in clinical practice? Eur J Gastroenterol Hepatol 2015;27(5):512–5.
[9] Lin HJ, Wang K, Perng CL, Chua RT, Lee FY, Lee CH, et al. Early or delayed endoscopy for patients with peptic ulcer bleeding. A prospective randomized study. J Clin Gastroenterol 1996;22(4):267–71.
[10] Lee JG, Turnipseed S, Romano PS, Vigil H, Azari R, Melnikoff N, et al. Endoscopy-based triage significantly reduces hospitalization rates and costs of treating upper GI bleeding: a randomized controlled trial. Gastrointest Endosc 1999;50(6):755–61.
[11] Bjorkman DJ, Zaman A, Fennerty MB, Lieberman D, Disario JA, Guest-Warnick G. Urgent vs. elective endoscopy for acute non-variceal upper-GI bleeding: an effectiveness study. Gastrointest Endosc 2004;60(1):1–8.
[12] Cooper GS, Chak A, Way LE, Hammar PJ, Harper DL, Rosenthal GE. Early endoscopy in upper gastrointestinal hemorrhage: associations with recurrent bleeding, surgery, and length of hospital stay. Gastrointest Endosc 1999;49(2):145–52.
[13] Cooper GS, Kou TD, Wong RC. Use and impact of early endoscopy in elderly patients with peptic ulcer hemorrhage: a population-based analysis. Gastrointest Endosc 2009;70(2):229–35.
[14] Schacher GM, Lesbros-Pantoflickova D, Ortner MA, Wasserfallen JB, Blum AL, Dorta G. Is early endoscopy in the emergency room beneficial in patients with bleeding peptic ulcer? A "fortuitously controlled" study. Endoscopy 2005;37(4):324–8.
[15] Targownik LE, Murthy S, Keyvani L, Leeson S. The role of rapid endoscopy for

high-risk patients with acute nonvariceal upper gastrointestinal bleeding. Can J Gastroenterol 2007;21(7):425–9.
[16] Tai CM, Huang SP, Wang HP, Lee TC, Chang CY, Tu CH, et al. High-risk ED patients with nonvariceal upper gastrointestinal hemorrhage undergoing emergency or urgent endoscopy: a retrospective analysis. Am J Emerg Med 2007;25(3):273–8.
[17] Lim LG, Ho KY, Chan YH, Teoh PL, Khor CJ, Lim LL, et al. Urgent endoscopy is associated with lower mortality in high-risk but not low-risk nonvariceal upper gastrointestinal bleeding. Endoscopy 2011;43(4):300–6.
[18] Cho SH, Lee YS, Kim YJ, Sohn CH, Ahn S, Seo DW, et al. Outcomes and role of urgent endoscopy in high-risk patients with acute nonvariceal gastrointestinal bleeding. Clin Gastroenterol Hepatol 2018;16(3):370–7.
[19] Jairath V, Kahan BC, Logan RF, Hearnshaw SA, Dore CJ, Travis SP, et al. Outcomes following acute nonvariceal upper gastrointestinal bleeding in relation to time to endoscopy: results from a nationwide study. Endoscopy 2012;44(8):723–30.
[20] Laursen SB, Leontiadis GI, Stanley AJ, Moller MH, Hansen JM, Schaffalitzky de Muckadell OB. Relationship between timing of endoscopy and mortality in patients with peptic ulcer bleeding: a nationwide cohort study. Gastrointest Endosc 2017;85(5):936–944 e3.
[21] de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63(3):743–52.
[22] European Association for the Study of the Liver, Electronic address eee, European Association for the study of the L. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69(2):406–60.
[23] Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017;65(1):310–35.
[24] Hwang JH, Shergill AK, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, et al. The role of endoscopy in the management of variceal hemorrhage. Gastrointest Endosc 2014;80(2):221–7.
[25] Sarin SK, Kumar A, Angus PW, Baijal SS, Baik SK, Bayraktar Y, et al. Diagnosis and management of acute variceal bleeding: Asian Pacific association for study of the liver recommendations. Hepatol Int 2011;5(2):607–24.
[26] Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, et al. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut 2015;64(11):1680–704.
[27] Yoo JJ, Chang Y, Cho EJ, Moon JE, Kim SG, Kim YS, et al. Timing of upper gastrointestinal endoscopy does not influence short-term outcomes in patients with acute variceal bleeding. World J Gastroenterol 2018;24(44):5025–33.
[28] Dunne PDJ, Laursen SB, Laine L, Dalton HR, Ngu JH, Schultz M, et al. Previous use of antithrombotic agents reduces mortality and length of hospital stay in patients with high-risk upper gastrointestinal bleeding. Clin Gastroenterol Hepatol 2018;17(3). 440–447.e2.
[29] Shingina A, Barkun AN, Razzaghi A, Martel M, Bardou M, Gralnek I, et al. Systematic review: the presenting international normalised ratio (INR) as a predictor of outcome in patients with upper nonvariceal gastrointestinal bleeding. Aliment Pharmacol Ther 2011;33(9):1010–8.
[30] Wolf AT, Wasan SK, Saltzman JR. Impact of anticoagulation on rebleeding following endoscopic therapy for nonvariceal upper gastrointestinal hemorrhage. Am J Gastroenterol 2007;102(2):290–6.
[31] ASoP Committee, Acosta RD, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointest Endosc 2016;83(1):3–16.
[32] Ananthakrishnan AN, McGinley EL, Saeian K. Outcomes of weekend admissions for upper gastrointestinal hemorrhage: a nationwide analysis. Clin Gastroenterol Hepatol 2009;7(3):296–302e1.
[33] Dorn SD, Shah ND, Berg BP, Naessens JM. Effect of weekend hospital admission on gastrointestinal hemorrhage outcomes. Dig Dis Sci 2010;55(6):1658–66.
[34] Ahmed A, Armstrong M, Robertson I, Morris AJ, Blatchford O, Stanley AJ. Upper gastrointestinal bleeding in Scotland 2000-2010: improved outcomes but a significant weekend effect. World J Gastroenterol 2015;21(38):10890–7.
[35] Shaheen AA, Kaplan GG, Myers RP. Weekend versus weekday admission and mortality from gastrointestinal hemorrhage caused by peptic ulcer disease. Clin Gastroenterol Hepatol 2009;7(3):303–10.
[36] Abougergi MS, Travis AC, Saltzman JR. Impact of day of admission on mortality and other outcomes in upper GI hemorrhage: a nationwide analysis. Gastrointest Endosc 2014;80(2):228–35.
[37] Gupta A, Agarwal R, Ananthakrishnan AN. Weekend effect" in patients with upper gastrointestinal hemorrhage: a systematic review and meta-analysis. Am J Gastroenterol 2018;113(1):13–21.
[38] Black N. Higher mortality in weekend admissions to the hospital: true, false, or uncertain? J Am Med Assoc 2016;316(24):2593–4.
[39] de Groot NL, Bosman JH, Siersema PD, van Oijen MG, Bredenoord AJ. Group Rs. Admission time is associated with outcome of upper gastrointestinal bleeding: results of a multicentre prospective cohort study. Aliment Pharmacol Ther 2012;36(5):477–84.
[40] Shih PC, Liu SJ, Li ST, Chiu AC, Wang PC, Liu LY. Weekend effect in upper gastrointestinal bleeding: a systematic review and meta-analysis. PeerJ 2018;6:e4248.
[41] Xia XF, Chiu PWY, Tsoi KKF, Chan FKL, Sung JJY, Lau JYW. The effect of off-hours hospital admission on mortality and clinical outcomes for patients with upper gastrointestinal hemorrhage: a systematic review and meta-analysis of 20 cohorts. United European Gastroenterol J 2018;6(3):367–81.
[42] Sung JJ, Chiu PC, Chan FKL, Lau JY, Goh KL, Ho LH, et al. Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding: an update 2018. Gut 2018;67(10):1757–68.
[43] Stanley AJ, Laine L, Dalton HR, Ngu JH, Schultz M, Abazi R, et al. Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study. BMJ 2017;356:i6432.
[44] Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. Lancet 2000;356(9238):1318–21.
[45] Laursen SB, Dalton HR, Murray IA, Michell N, Johnston MR, Schultz M, et al. Performance of new thresholds of the Glasgow Blatchford score in managing patients with upper gastrointestinal bleeding. Clin Gastroenterol Hepatol 2015;13(1):115–121 e2.
[46] Wong JCea. 785 urgent versus early endoscopy for upper gastrointestinal bleeding with glasgow-blatchford score ≥12. Gastroenterology 2015;148(4). S-154.
[47] Tammaro L, Di Paolo MC, Zullo A, Hassan C, Morini S, Caliendo S, et al. Endoscopic findings in patients with upper gastrointestinal bleeding clinically classified into three risk groups prior to endoscopy. World J Gastroenterol 2008;14(32):5046–50.
[48] Tammaro L, Buda A, Di Paolo MC, Zullo A, Hassan C, Riccio E, et al. A simplified clinical risk score predicts the need for early endoscopy in non-variceal upper gastrointestinal bleeding. Dig Liver Dis 2014;46(9):783–7.
[49] Laine L. Upper gastrointestinal bleeding due to a peptic ulcer. N Engl J Med 2016;375(12):1198.
[50] Campbell HE, Stokes EA, Bargo D, Logan RF, Mora A, Hodge R, et al. Costs and quality of life associated with acute upper gastrointestinal bleeding in the UK: cohort analysis of patients in a cluster randomised trial. BMJ Open 2015;5(4):e007230.
[51] Hearnshaw SA, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. Gut 2011;60(10):1327–35.