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Original research

Timing of endoscopy for acute upper gastrointestinal bleeding: a territory-wide cohort study

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ABSTRACT

Objective While it is recommended that patients presenting with acute upper gastrointestinal bleeding (AUGIB) should receive endoscopic intervention within 24 hours, the optimal timing is still uncertain. We aimed to assess whether endoscopy timing postadmission would affect outcomes.

Design We conducted a retrospective, territory-wide, cohort study with healthcare data from all public hospitals in Hong Kong. Adult patients (age ≥18) that presented with AUGIB between 2013 and 2019 and received therapeutic endoscopy within 48 hours (n=6474) were recruited. Patients were classified based on endoscopic timing postadmission: urgent (t≤6), early (6<t≤24) and late (24<t≤48). Baseline characteristics were balanced with inverse probability of treatment weighting. 30-day all-cause mortality, repeated therapeutic endoscopy rate, intensive care unit (ICU) admission rate and other endpoints were compared.

Results Results showed that urgent timing (n=1008) had worse outcomes compared with early endoscopy (n=3865), with higher 30-day all-cause mortality (p<0.001), repeat endoscopy rates (p<0.001) and ICU admission rates (p<0.001). Late endoscopy (n=1601) was associated with worse outcomes, with higher 30-day mortality (p=0.003), in-hospital mortality (p=0.022) and 30-day transfusion rates (p=0.018).

Conclusion Compared with urgent and late endoscopy among patients who have received therapeutic endoscopies, early endoscopy was associated with superior outcomes especially among patients with non-variceal bleeding. This supports the notion that non-variceal AUGIB patients should receive endoscopy within 24 hours, but also emphasises the importance of prior resuscitation and pharmacotherapy.

Key messages

Question
⇒ Does the timing of endoscopy affect clinical outcomes in patients presenting with acute upper gastrointestinal bleeding?

Findings
⇒ In this retrospective, territory-wide, cohort study with 6474 patients, we observed significant more favourable outcomes among patients who received endoscopy between 6 and 24 hours after admission, compared with patients who received endoscopy within 6 hours and between 24 and 48 hours.

Meaning
⇒ Appropriate timing of endoscopy within 24 hours, after resuscitation and medical optimisation, is associated with better clinical outcomes in patients presenting with acute upper gastrointestinal bleeding.

INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) is a common medical emergency. In Western countries, its incidence was estimated to be over 100 cases per 100 000 adults per year.[1 2] Fortunately, the mortality rates of AUGIB have decreased over the past few decades, largely attributable to improvements in endoscopic and pharmacological therapies.[2] Currently, it is recommended that endoscopy should be performed within 24 hours on presentation to hospital, to identify the source of bleeding, risk-stratify patients and provide potential endoscopic treatments. However, there is limited clinical data regarding the optimal timing of endoscopy within the 24-hour period.[3–7] We have recently conducted a randomised controlled trial (RCT) to investigate the clinical outcomes of AUGIB patients receiving urgent (<6 hours) vs early (<24 hours) endoscopy. In this prospective trial of 512 patients, there was no significant difference in 30-day all-cause mortality or recurrent bleeding rates between the two groups[4]; although numerically, we observed more deaths in the urgent endoscopy (<6 hours) group, in contrast to the hypothesis that urgent endoscopy might improve outcomes. This raised the possibility that an adequate period of medical optimisation and acid suppression before endoscopy may lead to a better outcome, although proving this in another clinical trial would require a much larger sample size, given the between-group mortality difference of 2.3% in favour of early endoscopy.[4] Conflicting results have been observed in other clinical studies, with Cho *et al* favouring endoscopy within 6 hours with a lower mortality rate, while Laursen *et al* associated the lower mortality with an endoscopy timing of between 6 and 24 hours.[8 9]

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Significance of this study

What is already known on this subject?

⇒ It is commonly recommended that acute upper gastrointestinal bleeding (AUGIB) patient should receive endoscopic intervention within 24 hours.

What are the new findings?

⇒ Our results suggest that performing therapeutic endoscopy within 6–24 hours is associated with significantly better clinical outcomes, when compared with those performed ≤6 hours or 24–48 hours.

How might it impact on clinical practice in the foreseeable future?

⇒ This study emphasises the importance of adequate resuscitation and medical optimisation before endoscopy in patients presenting with AUGIB. Given that AUGIB is one of the most common inpatient diseases, we believe that our result has the potential to impact the management of patients around the world.

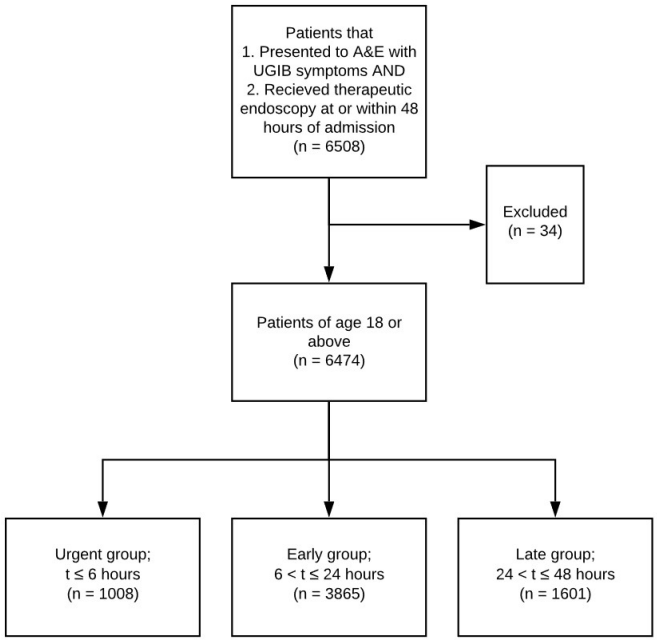

Figure 1 Patient inclusion criteria. A&E, accident & emergency department; UGIB, upper gastrointestinal bleeding.

On the other hand, a national audit conducted on 212 hospitals in the UK by Jairath *et al* showed no statistically significant difference for death and rebleeding between urgent, early and late groups, although timing definitions were differed slightly (<12 hours for urgent, as opposed to 6).[10] Other studies have also used different timings, such as before and after 12 hours,[11 12] or before and after 2–3 hours.[13 14]

In this study, we attempted to further investigate the effects of endoscopy timing on clinical outcomes of AUGIB patients, using computerised patient records in a propensity-score weighted cohort study. This approach enables us to analyse a large clinical dataset, to detect small effect size differences that would otherwise be formidable in prospective trials. We compared outcomes between three groups: endoscopy performed between 0 and 6 hours, between 6 and 24 hours, and between 24 and 48 hours. We hypothesise that for patients with AUGIB, therapeutic endoscopy performed within 6 hours of admission is associated with a higher 30-day all-cause mortality rate, compared with patients with endoscopy performed between 6 and 24 hours, or between 24 and 48 hours after admission.

METHODS

Study design

Clinical data were collected using the Clinical Data Analysis and Reporting System (CDARS), a computerised, territory-wide database with clinical information from all public hospitals in Hong Kong, which serves over ninety per cent of the city's inpatient medical service. AUGIB patients were identified by searching for patients newly admitted from the Accident and Emergency Department (AED) with a diagnosis of gastrointestinal bleeding, who underwent an oesophagogastroduodenoscopy (OGD) with a therapeutic modality within 48 hours of admission during the period of 2013–2019. Adult patients with an age of 18 or above were included. Based on the time interval difference between the admission time and index OGD time, patients were then divided into three groups: (1) urgent endoscopy group defined as a time difference of 6 hours or less, (2) early endoscopy group defined as a time difference of between 6 and 24 hours, and (3) late endoscopy group defined as a time difference of between 24 and 48 hours. The study flow is described in figure 1.

Baseline was taken as the time of patient admission into AED and patient characteristics are summarised in table 1 and online supplemental table 1. Bleeding severity is demonstrated using the modified Glasgow-Blatchford score (GBS). This is a condensed version of the GBS, which is based only on the objective and quantifiable elements of heart rate, blood pressure and biochemical parameters while also achieving performance similar to the full GBS. The score has a maximum of 16, as opposed to 23, and the fourth quartile of the score ranges from 10 to 16, as opposed to 12–23.[15 16] Individual components of the score are also reported in table 1. The inverse probability of treatment weighting (IPTW) method was employed to adjust for the baseline characteristics. Propensity score models were developed using generalised boosted models. The mean and maximum of both the standardised mean difference (SMD) and Kolmogorov-Smirnov statistic were used to determine the optimal number of trees. The stopping rule that produced the best balance was utilised.[17] Variables were considered well balanced if the SMD was less than 0.1.[18] Balanced characteristics include age, gender, blood pressure at admission, pulse rate at admission, use of antithrombotic drugs, use of proton-pump inhibitors (PPIs) or histamine 2 receptor antagonists, blood test results (including haemoglobin, platelet, urea, creatinine, urea:creatinine ratio and prothrombin time at admission), and comorbidities based on the Charlson Comorbidity Index (CCI).[19]

The outcomes of the three groups were compared after balancing these baseline characteristics. The primary endpoint was the 30-day all-cause mortality rate. Secondary outcomes included (1) need of repeating therapeutic endoscopy within 30 days, (2) average units of blood transfused within 30 days, (3) intensive care unit (ICU) admission within 30 days, (4) in-hospital mortality rate and (5) length of stay in hospital. Subgroup analysis was performed based on the presence of comorbid diseases. The cohort was further divided into two groups based on each patients' CCI score. A score of 3 or above was considered as having significant comorbidity burden, while a score of 2 or less was considered to be without significant comorbidity

Table 1 Summarised table on patient characteristics before and after matching

	Before IPTW				After IPTW			
	Early	Urgent	Late	SMD	Early	Urgent	Late	SMD
n	3865	1008	1601		3865	1008	1601	
Male (%)	2700 (69.9)	729 (72.3)	1076 (67.2)	0.074	2698 (69.8)	719 (71.3)	1093 (68.3)	0.044
Age (mean (SD))	67.11 (17.04)	66.37 (16.93)	70.15 (15.76)	0.153	67.66 (16.76)	67.36 (16.77)	68.13 (16.46)	0.031
Antithrombotic use (%)	463 (12.0)	127 (12.6)	229 (14.3)	0.046	475 (12.3)	128 (12.7)	202 (12.6)	0.008
Bleeding severity								
Modified GBS (mean (SD))	8.30 (3.21)	9.37 (2.81)	7.91 (3.33)	0.316	8.36 (3.21)	8.54 (3.18)	8.26 (3.16)	0.059
Pulse (mean (SD))	88.95 (17.14)	89.94 (17.95)	87.91 (17.58)	0.077	88.84 (17.17)	88.88 (17.60)	88.56 (17.06)	0.012
Systolic BP (mean (SD))	127.75 (22.63)	122.71 (22.77)	129.05 (23.33)	0.184	127.42 (22.72)	126.3 (21.99)	127.71 (22.53)	0.042
Haemoglobin ($\times 10^9$/L) (mean (SD))	8.97 (2.79)	8.18 (2.64)	9.28 (2.76)	0.270	8.93 (2.77)	8.81 (2.73)	9.02 (2.73)	0.050
Urea (mmol/L) (mean (SD))	13.83 (8.49)	15.50 (8.63)	13.72 (9.13)	0.136	14.02 (8.63)	14.24 (8.18)	13.9 (8.57)	0.027
Comorbidities								
Cancer (%)	309 (8.0)	90 (8.9)	163 (10.2)	0.051	321 (8.3)	82 (8.1)	146 (9.1)	0.023
Cardiac diseases (%)	171 (4.4)	48 (4.8)	96 (6.0)	0.047	182 (4.7)	44 (4.4)	80 (5.0)	0.016
Hepatic diseases (%)	109 (2.8)	56 (5.6)	38 (2.4)	0.110	116 (3.0)	31 (3.1)	40 (2.5)	0.025
Renal diseases (%)	119 (3.1)	37 (3.7)	61 (3.8)	0.027	124 (3.2)	32 (3.2)	56 (3.5)	0.010
Diabetes mellitus (%)	323 (8.4)	120 (11.9)	175 (10.9)	0.079	356 (9.2)	100 (9.9)	152 (9.5)	0.016
Bleeding aetiologies								
Neoplasm (%)	107 (2.8)	29 (2.9)	65 (4.1)	0.047	108 (2.8)	29 (2.9)	62 (3.9)	0.040
Peptic ulcers (%)	3518 (91.0)	889 (88.2)	1432 (89.4)	0.062	3509 (90.8)	898 (89.1)	1441 (90.0)	0.037
Varices (%)	160 (4.1)	66 (6.5)	56 (3.5)	0.094	166 (4.3)	47 (4.7)	59 (3.7)	0.033
Other (%)	504 (13.0)	99 (9.8)	259 (16.2)	0.127	506 (13.1)	106 (10.5)	247 (15.4)	0.098
Endoscopic therapies								
Injection (%)	3405 (88.1)	903 (89.6)	1373 (85.8)	0.078	3401 (88.0)	914 (90.7)	1377 (86.0)	0.098
Clipping (%)	890 (23.0)	267 (26.5)	401 (25.0)	0.053	901 (23.3)	265 (26.3)	403 (25.2)	0.047
Thermocoagulation (%)	2746 (71.0)	680 (67.5)	1094 (68.3)	0.052	2736 (70.8)	698 (69.2)	1101 (68.8)	0.029
Banding (%)	92 (2.4)	44 (4.4)	33 (2.1)	0.088	97 (2.5)	31 (3.1)	34 (2.1)	0.044
Others (%)	245 (6.3)	59 (5.9)	111 (6.9)	0.029	247 (6.4)	59 (5.9)	104 (6.5)	0.016

All the clinical details are provided in online supplemental table 1.
BP, blood pressure; GBS, Glasgow-Blatchford score; IPTW, inverse probability treatment weighting; SMD, standardised mean difference.

burden.[20] Subgroup analysis was also performed based on variceal versus non-variceal bleeding.

Statistical analysis

Data were analysed with the R Project for Statistical Computing software, V.3.6.0. Due to violation of proportional hazards, the 30-day all-cause mortality rate and 30-day repeated endoscopic therapy rate was analysed using weighted Cox regression for non-proportional hazards and the results were given as average HRs.[21–23] The 30-day ICU admission rate was calculated using regular Cox proportional hazards regression. These three outcomes were also assessed with the Kaplan-Meier method. Variables were selected for multivariate analysis from patient characteristics (online supplemental table 1) with a forward stepwise method, with a p value cut-off of ≤0.1. χ^2 test was used to compare differences in the 30-day transfusion rate and in-hospital mortality rate, while analysis of variance was used to compare differences in length of stay.

Missing data were handled with multiple imputation. The vast majority (>99%) of laboratory parameters are complete; nevertheless, 55% of the pulse rate and systolic blood pressure data at admission were missing due to the structure of CDARS. Given similar proportions of missing vital signs data across different groups, the missing data were assumed to be missing at random.[24] Multiple imputation was used to impute the missing data, as this approach has been shown to produce reliable estimates with minimal bias using missing at random data, even if a significant proportion is missing.[25 26]

Sensitivity analyses were performed to assess the robustness of our findings. Five different approaches of sensitivity analyses were undertaken: (1) complete-case analysis, which restricted the analysis only to those cases with complete (ie, no missing) data; (2) analysis without IPTW balancing, which might better simulate the true characteristics of patients in both groups; (3) effect of weekend (vs weekday) on the statistics of timing analyses; (4 and 5) two alternative timings (4 and 8 hours, respectively) rather than the 6 hours cut-off for the urgent group.

All clinical data were anonymised by the CDARS, and all potential patient identifiers were removed on return of database searches.

RESULTS

We identified 6474 adult patients who were admitted for AUGIB and received a therapeutic OGD within 48 hours. The urgent group had 1008 patients, the early group had 3865 patients and the late group had 1601 patients (table 1 and online supplemental table 1). The urgent group received endoscopy at a mean of 4.08 hours (SD=1.19) after admission, the early group received endoscopy at a mean of 15.6 hours (SD=5.29) after admission and the late group received endoscopy at a mean of 32.3 hours (SD=7.74) after admission. After balancing, bleeding severity according to the modified GBS was well balanced and situated at a score of approximately

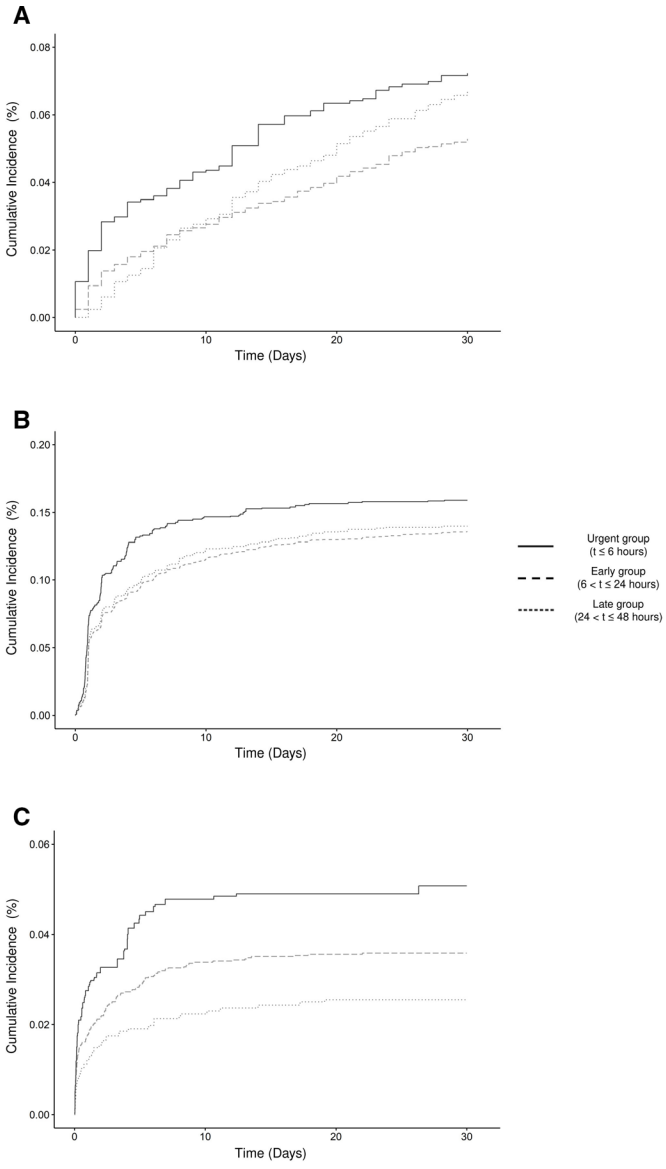

Figure 2 Kaplan-Meier plots for (A) 30-day mortality, (B) 30-day repeat therapeutic OGD, (C) 30-day ICU admission after index endoscopy. ICU, intensive care unit; OGD, oesophagogastroduodenoscopy.

9, which falls near the upper boundary of the third quartile of said score.[15 16]

Thirty-day and in-hospital mortality rates

In the Cox regression analyses, we observed the highest 30-day all-cause mortality rate in the urgent endoscopy group (within 6 hours) and the lowest mortality rate in the early endoscopy group (between 6 and 24 hours). Taking the early group as a reference, the urgent group had an adjusted HR (aHR) of 1.43 (95% CI 1.24 to 1.65, p<0.001), while the late group (between 6 and 24 hours) had an aHR of 1.25 (95% CI 1.078 to 1.449, p=0.003) (figure 2 and table 2). Similarly, both the urgent and late groups had significantly more in-hospital deaths compared with the early group (urgent 6.2% vs early 4.3%, p=0.017; late 5.8% vs early 4.3%, p=0.022) (online supplemental table 2).

Repeat therapeutic endoscopy and other secondary endpoints

We analysed the rebleeding rate using Cox regression analyses. Compared with the early group, we observed a higher rate of repeat therapeutic endoscopy in the urgent group (aHR 1.22, 95%CI 1.11 to 1.33, p<0.001). The respective rate for the late endoscopy group was not significantly different (aHR 1.04, 95%CI 0.94 to 1.15, p=0.426) (figure 2 and table 2).

Similarly, when compared with the early group, patients in the urgent group were more likely to require an ICU admission after index endoscopy (aHR 1.40, 95%CI 1.18 to 1.67, p<0.001), while the late group had a lower rate of admission (aHR 0.72, 95%CI 0.58 to 0.88, p=0.002) (figure 2 and table 2). Next, we further compared the average units of blood transfused within 30 days of admission between the three groups. Patients in the urgent and the late group received numerically more units per patient, although the difference was only statistically significant for the late group (p=0.018). Regarding the length of stay, there was no significant difference was observed between the three groups (p>0.050) (online supplemental table 2).

Subgroup analysis based on medical comorbidities

The cohort was further divided into two groups, based on the comorbidity scores of the patients. A total of 5350 patients had no significant comorbidity, while 617 patients had a CCI score of 3 or above. Notably, the urgent endoscopy group fared worse especially for patients without significant comorbidity, with significantly higher 30-day all-cause mortality (aHR 1.69, 95%CI 1.38 to 2.07, p<0.001), 30-day repeat therapeutic endoscopy (aHR 1.29,

Table 2 Outcomes of endpoints on mortality, repeat endoscopy and ICU admission

		Univariate		Multivariate	
Outcomes	**Timing**	**HR (95% CI)**	**P value**	**aHR (95% CI)**	**P value**
30-day all-cause mortality					
	Early	Reference	NA	Reference	NA
	Urgent	1.412 (1.222 to 1.631)	<0.001	1.430 (1.237 to 1.653)	<0.001
	Late	1.263 (1.090 to 1.464)	0.002	1.250 (1.078 to 1.449)	0.003
30-day repeat therapeutic endoscopy					
	Early	Reference	NA	Reference	NA
	Urgent	1.221 (1.112 to 1.340)	<0.001	1.215 (1.107 to 1.334)	<0.001
	Late	1.034 (0.939 to 1.139)	0.491	1.040 (0.944 to 1.145)	0.426
30-day ICU admission after index endoscopy					
	Early	Reference	NA	Reference	NA
	Urgent	1.429 (1.202 to 1.699)	<0.001	1.403 (1.180 to 1.669)	<0.001
	Late	0.706 (0.574 to 0.869)	0.001	0.716 (0.582 to 0.881)	0.002

aHR, adjusted HR; ICU, intensive care unit; NA, not available.

95%CI 1.17 to 1.44, p<0.001) and 30-day ICU admission (aHR 1.55, 95%CI 1.28 to 1.87, p<0.001) rates. In contrast, there was no significant difference in outcomes among patients with significant comorbid diseases (online supplemental table 3).

Subgroup analysis based on bleeding aetiologies

The cohort was further analysed based on the aetiology of variceal versus non-variceal upper gastrointestinal bleeding. A total of 286 patients had variceal bleeding, while 6188 patients had non-variceal bleeding. Urgent endoscopy timing was associated with worse outcomes in patients with non-variceal bleeding, with the urgent group having significantly higher 30-day all-cause mortality (aHR 1.43, 95%CI 1.23 to 1.67, p<0.001), 30-day repeat therapeutic endoscopy (aHR 1.25, 95%CI 1.14 to 1.38, p<0.001) and 30-day ICU admission (aHR 1.42, 95%CI 1.19 to 1.69, p<0.001) rates. In contrast, urgent timing was not associated with any significant difference in outcomes among patients with variceal bleeding. Instead, late endoscopy was associated with increased risk of 30-day repeat therapeutic endoscopy rates (aHR 1.732, 95%CI 1.25 to 2.39, p=0.001) and 30-day ICU admission rates (aHR 6.61, 95%CI 1.95 to 22.40, p=0.002) (online supplemental table 4).

Sensitivity analyses

We performed five different sensitivity analyses to testify the reliability of our results. Restricting our analyses to include only cases with complete data, we observed consistent associations with 30-day all-cause mortality and need of repeat endoscopy, at approximately half the original cohort size. In the analysis without IPTW balancing, all results were consistent with the original analyses. We additionally tested for the impact of weekend versus weekday on the timing analyses on all the three outcomes. We observe no significant effect of admission time on the association between endoscopy timing and clinical outcomes (online supplemental table 5). Finally, we also tested the associations using alternative timings, setting the cut-offs at four or 8 hours for the urgent group, rather than 6 hours in the original study design. All the observed associations were replicated with both the 4 and 8 hours cut-off (online supplemental table 5).

DISCUSSION

Our findings demonstrate that urgent endoscopy (t≤6 hours) has worse outcomes compared with early endoscopy (6<t≤24 hours). In contrast, the outcomes for late timing (24<t≤48 hours) were more variable. Among AUGIB patients receiving therapeutic endoscopies, an urgent endoscopy timing was associated with higher 30-day all-cause mortality, in-hospital mortality and increased ICU admission rates. Late endoscopy timing was also associated with increased 30-day all-cause mortality, in-hospital mortality rates and 30-day transfusion rate, compared with the early endoscopy group but were also associated with a lower rate of ICU admission after endoscopy. When also taking into account bleeding aetiology, the results were only consistent with non-variceal bleeding. For variceal bleeding, only late endoscopy was associated with worse outcomes, with higher rates of repeated endoscopy and ICU admission.

Our findings can potentially be explained by the longer medical optimisation time that patients in the early group had when compared with the urgent group. There is likely time for a primary and secondary survey, fluid resuscitation, blood transfusion, as well as the pharmacological therapies to take effect. Patients with active bleeding may have large amounts of fresh blood or clots in the stomach, possibly obscuring the site of injury and rendering endoscopic haemostasis difficult.[27] Gastric acid suppression, especially with the potent intravenous PPI infusion, has been demonstrated to improve outcomes in AUGIB patients.[28] On the flip side, with too much time before intervening, haemostasis might not be achieved without endoscopic therapy and the patient may deteriorate too significantly, which could have resulted in the higher mortality rate of the late endoscopy group.

This finding contrasts with some previous hypotheses. While it is a common consensus that endoscopy should be performed within 24 hours of admission,[3–7] previous study findings were conflicting over the precise timing of endoscopy: one study suggested that urgent endoscopy was superior,[8] one suggested that early endoscopy was superior,[9] while some suggested no significant difference, including our recently published RCT.[4 12 27 29 30] Among these studies, there were four retrospective cohort studies and three RCTs. In this study, we used a retrospective territory-wide cohort that is larger than all but one of the aforementioned studies. This means that our study would possess a greater statistical power, to detect a difference that previous studies may have missed or would otherwise be formidable for a prospective trial. The only study that had a larger cohort size was by Laursen *et al*, which observed similar results as our study. This also highlights the importance of sample size and statistical power.

The difference in outcomes between our study and other studies may also be partly explained by controlling the clinical characteristics of patients between groups. This would lead to inevitable differences between groups and hence bias in the comparison. Although background differences can be addressed by randomisation in RCTs, bias could still arise due to exclusion of patients with hypotensive shock or continual bleeding. Rigorous propensity weighting with IPTW, as in this study, allows us to minimise differences between groups to enable a meaningful comparison of endoscopy timing, ceteris paribus. This is especially relevant as the early and urgent groups are likely to exhibit differing baseline characteristics that would confound the clinical outcomes.

While our results indicated that early endoscopy timing may be superior to urgent endoscopy, the results of the subgroup analyses suggest that there are more subtle aspects for different patients. In the comorbidity subgroup analysis, patients with comorbid diseases were less affected by the endoscopy timing. This difference may be explained that suggests comorbid illnesses, as opposed to the gastrointestinal bleeding, are more frequently the main causes of death among AUGIB patients.[31–34] Thus, the presence of comorbidities would have a greater impact on the overall outcome, negating the impact of endoscopy timing and gastrointestinal bleeding outcome. In a similar fashion, variceal bleeding was less affected by the endoscopy timing, as only late endoscopy was associated with worse outcomes. This is concurrent with previous findings that suggested that the outcome of variceal bleeding is more dependent on other prognostic factors (such as the severity of liver disease)[35] and is associated with a poorer prognosis compared with non-variceal bleeding, contributing the most to the mortality rate of AUGIB in the USA.[36] Analogously, in our cohort, the 30-day death rate among variceal bleeding patients was higher than that among non-variceal bleeding patients. Hence, the presence of a bleeding variceal may already have devastated the overall outcome, rendering the endoscopy timing effect negligible.

The sensitivity analyses mostly yielded congruent results, which suggest that the results of our primary analysis are reliable. The main deviation in results occurred with the complete case analysis, in which the 30-day all-cause mortality was for the urgent group was almost significant, while the 30-day ICU admission was not significant for both timings. With a halving of cohort size, it is may have reduced the power of the study, hence resulting in an insignificant.

We acknowledge weaknesses in our study. Our study only included patients that required therapeutic endoscopy, who were patients with greater AUGIB severity. By only focusing on these

patients, the generalisability of this study may be limited, as patients with resolved bleeding have not been included. Nonetheless, our study was able to isolate the independent variable of time while keeping other dependent variables constant using IPTW, allowing us to better demonstrate the effect of time itself. These results may be suitably interpreted in the context of bleeding of moderate to high severity, which strongly suggests worse outcomes with urgent endoscopy timings when compared with early timings. Second, despite the stringent balancing of multiple patient characteristics on hospital admission, unrecognised factors and uncollected clinical data were inevitable and could not be accounted for. For example, syncope, one element of the GBS,[37] was not available in the computerised records. Hence, the full GBS could not be calculated as we did for our recent RCT study. Additionally, there may be residual confounding due to hidden confounders. Third, a significant proportion of the pulse rate and blood pressure data were missing. While multiple imputation was reported to produce reliable estimates (even up to 80% missing data), its true validity in this study cannot be evaluated. This may have introduced bias to our results. Fortunately, the results of our sensitivity analyses were consistent for at least for two of three outcomes, indicating that our results are most probably reliable. Finally, it can sometimes be difficult to differentiate between variceal versus non-variceal bleeding for patients with chronic liver disease. As such, the best endoscopy timing for these patients may not be so easily perceivable. This can be pertinent, given the demographic shift in bleeding aetiology consequential to availability of antiviral therapies, variceal screening, primary prophylaxis and liver transplantation.

In conclusion, we observed a lower mortality rate in non-variceal AUGIB patients receiving early endoscopy between 6 and 24 hours, compared with patients receiving urgent endoscopy within 6 hours, and those receiving endoscopy later between 24 and 48 hours of hospital admission. Results of this study suggest that most AUGIB patients need not be rushed to endoscopy immediately. Rather, active resuscitation and optimal medical treatment should be initiated as appropriate, then with endoscopy performed within 24 hours of presentation.

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Contributors SW conceived the study. CLG extracted the data, performed the analysis and drafted the manuscript. LHSL, RNSL, WYM, RSYT, TCFY, WKKW, GLHW, FKLC, JL and JJYS provided important intellectual input and revised the manuscript. JJYS and SW managed and supervised the study. All authors critically reviewed and agreed to be accountable for the study.

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Supplementary Table 1. Patient characteristics before and after matching. SMD stands for standardised mean difference. PPI stands for proton-pump inhibitor. IPTW, inverse probability treatment weighting; SMD, standardised mean difference; SD, standard deviation; BP, blood pressure; GBS, Glasgow-Blatchford score; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist.

	Before IPTW				After IPTW			
	Early	Urgent	Late	SMD	Early	Urgent	Late	SMD
n	3865	1008	1601		3865	1008	1601	
Male (%)	2700 (69.9)	729 (72.3)	1076 (67.2)	0.074	2698 (69.8)	719 (71.3)	1093 (68.3)	0.044
Age (mean (SD))	67.11 (17.04)	66.37 (16.93)	70.15 (15.76)	0.153	67.66 (16.76)	67.36 (16.77)	68.13 (16.46)	0.031
Antithrombotic use (%)	463 (12.0)	127 (12.6)	229 (14.3)	0.046	475 (12.3)	128 (12.7)	202 (12.6)	0.008
PPI or H2RA use (%)	3602 (93.2)	815 (80.9)	1485 (92.8)	0.249	3544 (91.7)	910 (90.3)	1478 (92.3)	0.049
Bleeding severity								
Modified GBS (mean (SD))	8.30 (3.21)	9.37 (2.81)	7.91 (3.33)	0.316	8.36 (3.21)	8.54 (3.18)	8.26 (3.16)	0.059
Pulse (mean (SD))	88.95 (17.14)	89.94 (17.95)	87.91 (17.58)	0.077	88.84 (17.17)	88.88 (17.60)	88.56 (17.06)	0.012
Systolic BP (mean (SD))	127.75 (22.63)	122.71 (22.77)	129.05 (23.33)	0.184	127.42 (22.72)	126.3 (21.99)	127.71 (22.53)	0.042
Laboratory values								
Haemoglobin (g/dL) (mean (SD))	8.97 (2.79)	8.18 (2.64)	9.28 (2.76)	0.270	8.93 (2.77)	8.81 (2.73)	9.02 (2.73)	0.050
Platelets (x10^9/L) (mean (SD))	231.13 (106.06)	224.34 (103.76)	228.05 (100.01)	0.044	229.88 (106.99)	227.37 (97.50)	227.48 (98.83)	0.016
Urea (mmol/L) (mean (SD))	13.83 (8.49)	15.50 (8.63)	13.72 (9.13)	0.136	14.02 (8.63)	14.24 (8.18)	13.9 (8.57)	0.027
Creatinine (μmol/L) (mean (SD))	108.80 (110.31)	118.03 (109.93)	119.00 (137.80)	0.058	110.27 (111.87)	109.48 (94.82)	117.08 (135.36)	0.043
Urea-creatinine ratio (mean (SD))	143.64 (64.36)	150.41 (65.17)	133.59 (62.71)	0.175	143.94 (64.68)	145.88 (65.90)	139.1 (62.48)	0.070
Prothrombin time (secs) (mean (SD))	13.87 (8.17)	14.27 (8.47)	14.53 (10.46)	0.049	14.03 (8.66)	13.72 (7.34)	13.9 (7.90)	0.027
Charlson Comorbidity Index								
Cancer (%)	299 (7.7)	87 (8.6)	158 (9.9)	0.050	309 (8.0)	79 (7.8)	141 (8.8)	0.025
Metastatic disease (%)	104 (2.7)	27 (2.7)	50 (3.1)	0.018	108 (2.8)	22 (2.2)	46 (2.9)	0.032
Congestive heart failure (%)	135 (3.5)	34 (3.4)	79 (4.9)	0.052	143 (3.7)	34 (3.4)	62 (3.9)	0.019
Myocardial infarction (%)	53 (1.4)	21 (2.1)	25 (1.6)	0.037	54 (1.4)	16 (1.6)	26 (1.6)	0.007
Stroke (%)	176 (4.6)	50 (5.0)	91 (5.7)	0.034	182 (4.7)	49 (4.9)	83 (5.2)	0.013
Peripheral vascular disease (%)	30 (0.8)	13 (1.3)	14 (0.9)	0.034	31 (0.8)	12 (1.2)	13 (0.8)	0.030
Mild liver disease (%)	76 (2.0)	41 (4.1)	26 (1.6)	0.099	81 (2.1)	22 (2.2)	27 (1.7)	0.023
Severe liver disease (%)	71 (1.8)	43 (4.3)	24 (1.5)	0.111	77 (2.0)	21 (2.1)	24 (1.5)	0.029
Pulmonary diseases (%)	123 (3.2)	34 (3.4)	74 (4.6)	0.050	131 (3.4)	37 (3.7)	56 (3.5)	0.011
Moderate-severe kidney disease (%)	119 (3.1)	37 (3.7)	61 (3.8)	0.027	124 (3.2)	32 (3.2)	56 (3.5)	0.010
Diabetes mellitus (%)	273 (7.1)	107 (10.6)	158 (9.9)	0.084	305 (7.9)	88 (8.7)	136 (8.5)	0.021
Diabetes complications (%)	75 (1.9)	26 (2.6)	38 (2.4)	0.029	77 (2.0)	20 (2.0)	34 (2.1)	0.006
Dementia (%)	30 (0.8)	14 (1.4)	23 (1.4)	0.042	35 (0.9)	10 (1.0)	18 (1.1)	0.013
Connective tissue disease (%)	6 (0.2)	4 (0.4)	3 (0.2)	0.031	8 (0.2)	2 (0.2)	3 (0.2)	0.008
Paraplegia (%)	15 (0.4)	3 (0.3)	7 (0.4)	0.015	15 (0.4)	4 (0.4)	6 (0.4)	0.003
Bleeding aetiologies								
Neoplasm (%)	107 (2.8)	29 (2.9)	65 (4.1)	0.047	108 (2.8)	29 (2.9)	62 (3.9)	0.040
Peptic ulcers (%)	3518 (91.0)	889 (88.2)	1432 (89.4)	0.062	3509 (90.8)	898 (89.1)	1441 (90.0)	0.037

Varices (%)	160 (4.1)	66 (6.5)	56 (3.5)	0.094	166 (4.3)	47 (4.7)	59 (3.7)	0.033
Other (%)	504 (13.0)	99 (9.8)	259 (16.2)	0.127	506 (13.1)	106 (10.5)	247 (15.4)	0.098
Endoscopic therapies								
Injection (%)	3405 (88.1)	903 (89.6)	1373 (85.8)	0.078	3401 (88.0)	914 (90.7)	1377 (86.0)	0.098
Clipping (%)	890 (23.0)	267 (26.5)	401 (25.0)	0.053	901 (23.3)	265 (26.3)	403 (25.2)	0.047
Thermocoagulation (%)	2746 (71.0)	680 (67.5)	1094 (68.3)	0.052	2736 (70.8)	698 (69.2)	1101 (68.8)	0.029
Banding (%)	92 (2.4)	44 (4.4)	33 (2.1)	0.088	97 (2.5)	31 (3.1)	34 (2.1)	0.044
Others (%)	245 (6.3)	59 (5.9)	111 (6.9)	0.029	247 (6.4)	59 (5.9)	104 (6.5)	0.016

Supplementary Table 2. Chi-square test on outcomes. SD, standard deviation **.**

	Early	Urgent	*P*-value	Late	*P*-value
n	3865	1008		1601	
Length of Stay (mean (SD))	6.49 (9.01)	7.28 (12.07)	0.058	6.96 (11.75)	0.148
In-hospital Mortality Rate (%)	166 (4.3)	62 (6.2)	0.017	93 (5.8)	0.022
Average Units of Blood Transfused in 30 Days (mean (SD))	2.91 (3.95)	3.01 (3.64)	0.421	3.21 (4.11)	0.018

Supplementary Table 3. Cox regression on subgroups based on comorbidity burden. HR, hazard ratio. * Hazard ratios for mortality and OGD outcomes are given as average hazard ratios, calculated using weighted Cox regression for nonproportional hazards.

Outcome	Subgroup	Timing	HR (95% CI)*	*P*-value
30-Day All-Cause Mortality	With Significant Comorbidity			
		Early	Reference	NA
		Urgent	1.033 (0.780 - 1.368)	0.819
		Late	1.242 (0.957 - 1.611)	0.103
	Without Significant Comorbidity			
		Early	Reference	NA
		Urgent	1.694 (1.384 - 2.074)	<0.001
		Late	1.310 (1.058 - 1.622)	0.013
30-Day Repeat Therapeutic Endoscopy	With Significant Comorbidity			
		Early	Reference	NA
		Urgent	1.039 (0.789 - 1.368)	0.786
		Late	1.109 (0.855 - 1.438)	0.436
	Without Significant Comorbidity			
		Early	Reference	NA
		Urgent	1.294 (1.165 - 1.437)	<0.001
		Late	1.057 (0.947 - 1.180)	0.323
30-Day ICU Admission after Index Endoscopy	With Significant Comorbidity			
		Early	Reference	NA
		Urgent	0.829 (0.455 - 1.509)	0.539
		Late	0.701 (0.363 - 1.355)	0.291
	Without Significant Comorbidity			
		Early	Reference	NA
		Urgent	1.549 (1.282 - 1.873)	<0.001
		Late	0.769 (0.614 - 0.964)	0.023

Supplementary Table 4. Cox regression on subgroups based on variceal versus nonvariceal bleeding. HR, hazard ratio. * Hazard ratios for mortality and OGD outcomes are given as average hazard ratios, calculated using weighted Cox regression for nonproportional hazards.

Outcome	Subgroup	Timing	HR (95% CI)*	*P*-value
30-Day All-Cause Mortality	Nonvariceal			
		Early	Reference	NA
		Urgent	1.432 (1.232 - 1.666)	<0.001
		Late	1.270 (1.089 - 1.482)	0.002
	Variceal			
		Early	Reference	NA
		Urgent	1.425 (0.818 - 2.481)	0.211
		Late	1.376 (0.784 - 2.415)	0.266
30-Day Repeat Therapeutic Endoscopy	Nonvariceal			
		Early	Reference	NA
		Urgent	1.250 (1.135 - 1.377)	<0.001
		Late	0.994 (0.899 - 1.100)	0.912
	Variceal			
		Early	Reference	NA
		Urgent	0.877 (0.614 - 1.252)	0.470
		Late	1.732 (1.254 - 2.391)	0.001
30-Day ICU Admission after Index Endoscopy	Nonvariceal			
		Early	Reference	NA
		Urgent	1.417 (1.190 - 1.687)	<0.001
		Late	0.634 (0.511 - 0.787)	<0.001
	Variceal			
		Early	Reference	NA
		Urgent	1.359 (0.333 - 5.542)	0.669
		Late	6.607 (1.948 - 22.404)	0.002

Supplementary Table 5. Sensitivity analysis with univariate Cox regression. HR, hazard ratio. * Hazard ratios for mortality and OGD outcomes are given as average hazard ratios, calculated using weighted Cox regression for nonproportional hazards.

Outcomes	Timing	HR (95% CI)	*P*-value
Complete Case Analysis			
30-Day All-Cause Mortality			
	Early	Reference	NA
	Urgent	1.603 (1.287 - 1.998)	<0.001
	Late	1.251 (0.994 - 1.575)	0.057
30-Day Repeat Therapeutic Endoscopy			
	Early	Reference	NA
	Urgent	1.294 (1.133 - 1.477)	<0.001
	Late	0.971 (0.842 - 1.121)	0.691
30-Day ICU Admission after Index Endoscopy			
	Early	Reference	NA
	Urgent	1.198 (0.880 - 1.633)	0.251
	Late	0.824 (0.584 - 1.163)	0.272
No Baseline Characteristics Balancing			
30-Day All-Cause Mortality			
	Early	Reference	NA
	Urgent	1.694 (1.306 - 2.197)	<0.001
	Late	1.407 (1.112 - 1.781)	0.004
30-Day Repeat Therapeutic Endoscopy			
	Early	Reference	NA
	Urgent	1.411 (1.192 - 1.670)	<0.001
	Late	1.016 (0.867 - 1.190)	0.846
30-Day ICU Admission after Index Endoscopy			
	Early	Reference	NA
	Urgent	1.699 (1.251 - 2.307)	0.001
	Late	0.711 (0.500 - 1.012)	0.058
Effect of Weekend (versus Weekday)			
30-Day All-Cause Mortality			
	Early	Reference	NA
	Urgent	1.412 (1.222 - 1.632)	<0.001
	Late	1.252 (1.079 - 1.453)	0.003
	Weekend	1.064 (0.931 - 1.216)	0.361
30-Day Repeat Therapeutic OGD			
	Early	Reference	NA
	Urgent	1.410 (1.191 - 1.669)	<0.001
	Late	1.001 (0.854 - 1.175)	0.986
	Weekend	1.113 (0.960 - 1.292)	0.157
30-Day ICU Admission after Index Endoscopy			
	Early	Reference	NA
	Urgent	1.428 (1.201 - 1.699)	<0.001
	Late	0.709 (0.575 - 0.873)	0.001
	Weekend	0.970 (0.810 - 1.162)	0.742
Alternative Timing: 4-24-48			
30-Day All-Cause Mortality			
	Early	Reference	NA

	Urgent	1.427 (1.228 - 1.658)	<0.001
	Late	1.241 (1.072 - 1.438)	0.004
30-Day Repeat Therapeutic Endoscopy			
	Early	Reference	NA
	Urgent	1.294 (1.176 - 1.423)	<0.001
	Late	1.006 (0.914 - 1.107)	0.904
30-Day ICU Admission after Index Endoscopy			
	Early	Reference	NA
	Urgent	1.460 (1.224 - 1.740)	<0.001
	Late	0.667 (0.544 - 0.819)	<0.001
Alternative Timing: 8-24-48			
30-Day All-Cause Mortality			
	Early	Reference	NA
	Urgent	1.601 (1.368 - 1.875)	<0.001
	Late	1.396 (1.186 - 1.642)	<0.001
30-Day Repeat Therapeutic Endoscopy			
	Early	Reference	NA
	Urgent	1.300 (1.179 - 1.433)	<0.001
	Late	1.041 (0.940 - 1.153)	0.443
30-Day ICU Admission after Index Endoscopy			
	Early	Reference	NA
	Urgent	1.582 (1.315 - 1.903)	<0.001
	Late	0.736 (0.591 - 0.917)	0.006

Clinical Question

Does the timing of endoscopy affect clinical outcomes in patients presenting with acute upper gastrointestinal bleeding?

Methods

- Retrospective, territory-wide, adult cohort
- Baseline adjusted by inverse probability of treatment weighting (IPTW) method

Urgent (t ≤ 6 hr)	n = 1,008
Early (6 < t ≤ 24 hr)	n = 3,865
Late (24 < t ≤ 48 hr)	n = 1,601

Results

30-day all-cause mortality

Urgent (t ≤ 6)	1.43 (1.24 - 1.65)
Early (6 < t ≤ 24)	Reference
Late (24 < t ≤ 48)	1.25 (1.08 - 1.45)

30-day repeat endoscopic therapy

Urgent (t ≤ 6)	1.22 (1.11 - 1.33)
Early (6 < t ≤ 24)	Reference
Late (24 < t ≤ 48)	1.04 (0.94 - 1.15)