



OPEN ACCESS

Original research

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

Cosmos L T Guo ^{1,2}, Sunny H Wong ^{1,2,3}, Louis H S Lau ^{1,2}, Rashid N S Lui,^{1,2}
Joyce W Y Mak,^{1,2} Raymond S Y Tang ^{1,2}, Terry C F Yip,^{1,2,4} William K K Wu ^{2,5},
Grace L H Wong,^{1,2,4} Francis K L Chan ^{1,2}, James Y W Lau ^{2,6},
Joseph J Y Sung ^{1,2,3}

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/gutjnl-2020-323054>).

For numbered affiliations see end of article.

Correspondence to

Professor Joseph J Y Sung, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore; josephsung@ntu.edu.sg
Dr Sunny H Wong; sunny.wong@ntu.edu.sg

CLTG and SHW are joint first authors.

Received 10 September 2020
Accepted 8 September 2021
Published Online First
21 September 2021

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 ($t \leq 6$), early ($6 < t \leq 24$) and late ($24 < t \leq 48$). 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.

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,

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.

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 groups⁴; 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}



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Guo CLT, Wong SH, Lau LHS, *et al*. *Gut* 2022;**71**:1544–1550.

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.

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](#).

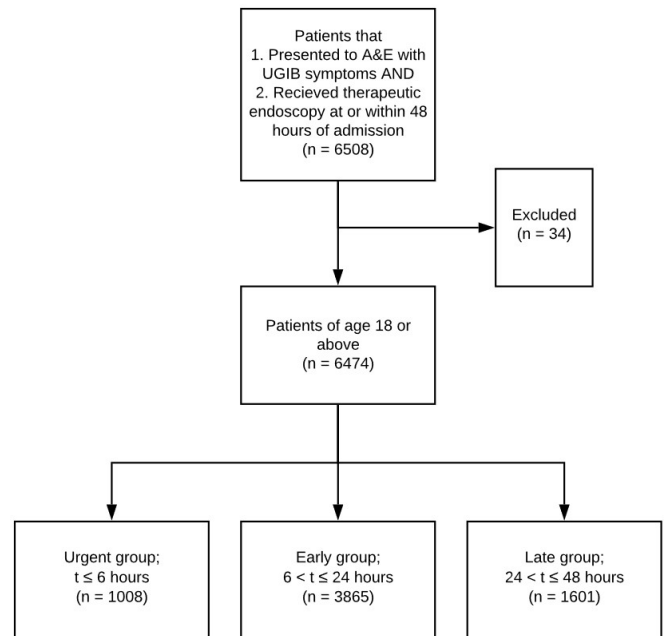


Figure 1 Patient inclusion criteria. A&E, accident & emergency department; UGIB, upper gastrointestinal bleeding.

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

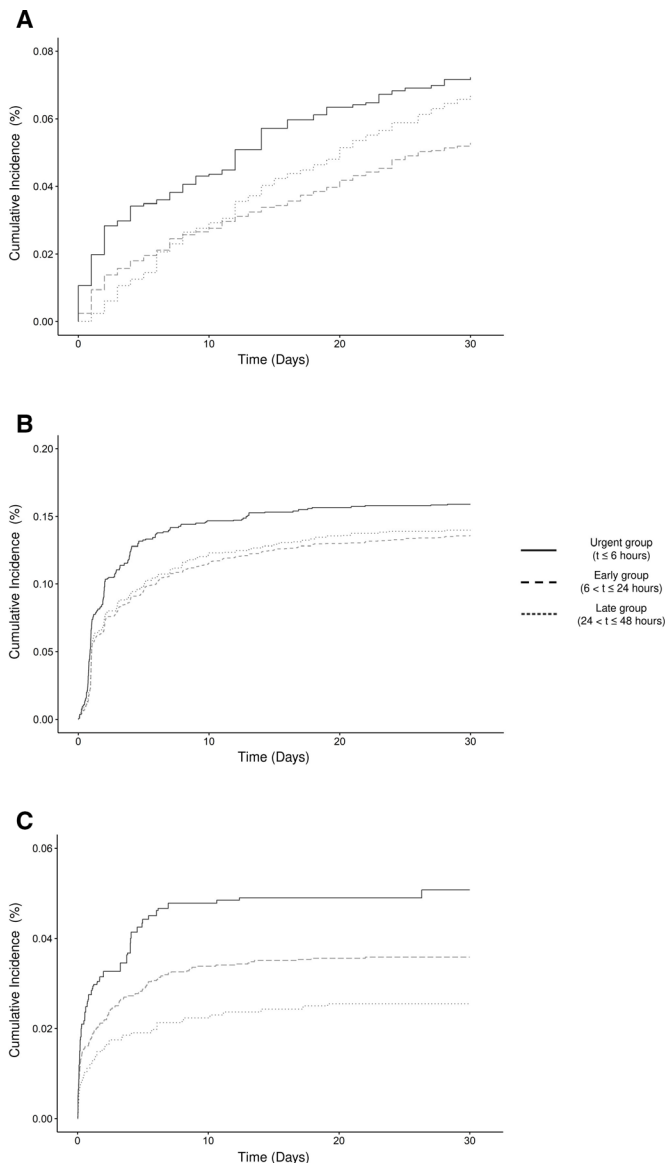


Figure 2 Kaplan-Meier plots for (A) 30-day mortality, (B) 30-day repeat therapeutic OGD, (C) 30-day ICU admission after index endoscopy. ICU, intensive care unit; OGD, oesophagogastroduodenoscopy.

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 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

Outcomes	Timing	Univariate		Multivariate	
		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 ($t \leq 6$ hours) has worse outcomes compared with early endoscopy ($6 < t \leq 24$ hours). In contrast, the outcomes for late timing ($24 < t \leq 48$ 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 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.

Author affiliations

¹Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong

²Institute of Digestive Disease, State Key Laboratory of Digestive Disease, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, Hong Kong

³Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

⁴Medical Data Analytics Centre, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong

⁵Department of Anaesthesia and Intensive Care, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong

⁶Department of Surgery, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong

Twitter Joyce W Y Mak @wingyanjoyce

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.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was conducted in accordance with the Declaration of Helsinki (2013 version) and approved by the Joint Clinical Research Ethics Committee of the Chinese University of Hong Kong and Hospital Authority New Territory East Cluster.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data will be available upon reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Cosmos L T Guo <http://orcid.org/0000-0001-5023-8226>

Sunny H Wong <http://orcid.org/0000-0002-3354-9310>

Louis H S Lau <http://orcid.org/0000-0002-4163-4531>

Raymond S Y Tang <http://orcid.org/0000-0002-2433-8036>

William K K Wu <http://orcid.org/0000-0002-5662-5240>

Francis K L Chan <http://orcid.org/0000-0001-7388-2436>

James Y W Lau <http://orcid.org/0000-0003-0122-4068>

Joseph J Y Sung <http://orcid.org/0000-0003-3125-5199>

REFERENCES

- 1 Weledji EP. Acute upper gastrointestinal bleeding: a review. *Surgery in Practice and Science* 2020;1:100004.
- 2 Abougergi MS, Travis AC, Saltzman JR. The in-hospital mortality rate for upper Gi hemorrhage has decreased over 2 decades in the United States: a nationwide analysis. *Gastrointest Endosc* 2015;81:882–8.
- 3 Sung JJ, Chiu PW, Chan FKL, et al. Asia-Pacific Working group consensus on non-variceal upper gastrointestinal bleeding: an update 2018. *Gut* 2018;67:1757–68.
- 4 Lau JYW, Yu Y, Tang RSY, et al. Timing of endoscopy for acute upper gastrointestinal bleeding. *N Engl J Med* 2020;382:1299–308.
- 5 Hwang JH, Fisher DA, Ben-Menachem T, et al. The role of endoscopy in the management of acute non-variceal upper Gi bleeding. *Gastrointest Endosc* 2012;75:1132–8.
- 6 Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012;107:345–60.
- 7 Barkun AN, Almadi M, Kuipers EJ, et al. Management of Nonvariceal upper gastrointestinal bleeding: guideline recommendations from the International consensus group. *Ann Intern Med* 2019;171:805–22.
- 8 Cho S-H, Lee Y-S, Kim Y-J, et al. Outcomes and role of urgent endoscopy in high-risk patients with acute Nonvariceal gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2018;16:370–7.
- 9 Laursen SB, Leontiadis GI, Stanley AJ, et al. Relationship between timing of endoscopy and mortality in patients with peptic ulcer bleeding: a nationwide cohort study. *Gastrointest Endosc* 2017;85:936–44.
- 10 Jairath V, Kahan BC, Logan RFA, et al. Outcomes following acute nonvariceal upper gastrointestinal bleeding in relation to time to endoscopy: results from a nationwide study. *Endoscopy* 2012;44:723–30.
- 11 Lin HJ, Wang K, Perng CL, et al. Early or delayed endoscopy for patients with peptic ulcer bleeding. A prospective randomized study. *J Clin Gastroenterol* 1996;22:267–71.
- 12 Saleem SA, Kudaravalli P, Riaz S, et al. Outcomes of upper gastrointestinal bleeding based on time to endoscopy: a retrospective study. *Cureus* 2020;12:e7325.
- 13 Lee JG, Turnipseed S, Romano PS, et al. Endoscopy-based triage significantly reduces hospitalization rates and costs of treating upper Gi bleeding: a randomized controlled trial. *Gastrointest Endosc* 1999;50:755–61.
- 14 Schacher GM, Lesbros-Pantoflickova D, Ortner MA, et al. Is early endoscopy in the emergency room beneficial in patients with bleeding peptic ulcer? A "fortuitously controlled" study. *Endoscopy* 2005;37:324–8.
- 15 Cheng DW, Lu YW, Teller T, et al. A modified Glasgow Blatchford score improves risk stratification in upper gastrointestinal bleed: a prospective comparison of scoring systems. *Aliment Pharmacol Ther* 2012;36:782–9.
- 16 Shahrami A, Ahmadi S, Safari S. Full and modified Glasgow-Blatchford bleeding score in predicting the outcome of patients with acute upper gastrointestinal bleeding; a diagnostic accuracy study. *Emerg* 2018;6:e31.
- 17 McCaffrey DF, Griffin BA, Almirall D, et al. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med* 2013;32:3388–414.
- 18 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424.

- 19 Sundararajan V, Henderson T, Perry C, *et al.* New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol* 2004;57:1288–94.
- 20 Taha AS, Saffouri E, McCloskey C, *et al.* Falling mortality when adjusted for comorbidity in upper gastrointestinal bleeding: relevance of multi-disciplinary care. *Frontline Gastroenterol* 2014;5:243–8.
- 21 Lehr S, Schemper M. Parsimonious analysis of time-dependent effects in the COX model. *Stat Med* 2007;26:2686–98.
- 22 Schemper M. Cox analysis of survival data with non-proportional hazard functions. *Journal of the Royal Statistical Society: Series D* 1992;41:455–65.
- 23 Schemper M, Wakounig S, Heinze G. The estimation of average hazard ratios by weighted COX regression. *Stat Med* 2009;28:2473–89.
- 24 Sv B. *Flexible imputation of missing data*. Boca Raton, FL: CRC Press, 2012.
- 25 Madley-Dowd P, Hughes R, Tilling K, *et al.* The proportion of missing data should not be used to guide decisions on multiple imputation. *J Clin Epidemiol* 2019;110:63–73.
- 26 Jin Hyuk L, John H, Jr. *Multiple imputation with large proportions of missing data: How much is too much?* : Stata Users Group, 2011.
- 27 Targownik LE, Murthy S, Keyvani L, *et al.* The role of rapid endoscopy for high-risk patients with acute nonvariceal upper gastrointestinal bleeding. *Can J Gastroenterol* 2007;21:425–9.
- 28 Lau JY, Leung WK, Wu JCY, *et al.* Omeprazole before endoscopy in patients with gastrointestinal bleeding. *N Engl J Med* 2007;356:1631–40.
- 29 Tai C-M, Huang S-P, Wang H-P, *et al.* High-Risk ED patients with nonvariceal upper gastrointestinal hemorrhage undergoing emergency or urgent endoscopy: a retrospective analysis. *Am J Emerg Med* 2007;25:273–8.
- 30 Bjorkman DJ, Zaman A, Fennerty MB, *et al.* Urgent vs. elective endoscopy for acute non-variceal upper-GI bleeding: an effectiveness study. *Gastrointest Endosc* 2004;60:1–8.
- 31 Theocharis GJ, Arvaniti V, Assimakopoulos SF, *et al.* Acute upper gastrointestinal bleeding in octogenarians: clinical outcome and factors related to mortality. *World J Gastroenterol* 2008;14:4047–53.
- 32 Yavorski RT, Wong RK, Maydonovitch C, *et al.* Analysis of 3,294 cases of upper gastrointestinal bleeding in military medical facilities. *Am J Gastroenterol* 1995;90:568–73.
- 33 Alam MK. Factors affecting hospital mortality in acute upper gastrointestinal bleeding. *Saudi J Gastroenterol* 2000;6:87–91.
- 34 Hearnshaw SA, Logan RFA, Lowe D, *et al.* Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut* 2011;60:1327–35.
- 35 Jung DH, Huh CW, Kim NJ, *et al.* Optimal endoscopy timing in patients with acute variceal bleeding: a systematic review and meta-analysis. *Sci Rep* 2020;10:4046.
- 36 Wuerth BA, Rockey DC. Changing epidemiology of upper gastrointestinal hemorrhage in the last decade: a nationwide analysis. *Dig Dis Sci* 2018;63:1286–93.
- 37 Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. *Lancet* 2000;356:1318–21.