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

Cosmos L T Guo, Sunny H Wong, Louis H S Lau, Rashid N S Lui, Joyce W Y Mak, Raymond S Y Tang, Terry C F Yip, William K K Wu, Grace L H Wong, Francis K L Chan, James Y W Lau, Joseph J Y Sung

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) presenting with acute upper gastrointestinal bleeding (AUGIB) 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.

INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) is a common medical emergency. In Western countries, its incidence was estimated to be over 100 cases per 100000 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.3 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.3–5 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.1 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.6 7
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). Other studies have also used different timings, such as before and after 12 hours, or before and after 2–3 hours.

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 0 hours or less, (2) early endoscopy group defined as a time difference 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. 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. Variables were considered well balanced if the SMD was less than 0.1. 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).

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.
burden. 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, V3.6.0. 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. 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. \( \chi^2 \) 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. 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.

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 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

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Table 1  Summarised table on patient characteristics before and after matching

<table>
<thead>
<tr>
<th></th>
<th>Before IPTW</th>
<th>After IPTW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Urgent</td>
</tr>
<tr>
<td>n</td>
<td>3865</td>
<td>1008</td>
</tr>
<tr>
<td>Male (%)</td>
<td>2700 (69.9)</td>
<td>729 (72.3)</td>
</tr>
<tr>
<td>Age (mean (SD))</td>
<td>67.11 (17.04)</td>
<td>66.37 (16.93)</td>
</tr>
<tr>
<td>Antithrombotic use (%)</td>
<td>463 (12.0)</td>
<td>127 (12.6)</td>
</tr>
<tr>
<td><strong>Bleeding severity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified GBS (mean (SD))</td>
<td>8.30 (3.21)</td>
<td>9.37 (2.81)</td>
</tr>
<tr>
<td>Pulse (mean (SD))</td>
<td>88.95 (17.14)</td>
<td>89.94 (17.95)</td>
</tr>
<tr>
<td>Systolic BP (mean (SD))</td>
<td>127.75 (22.63)</td>
<td>122.71 (22.77)</td>
</tr>
<tr>
<td>Haemoglobin (x10^12/L (mean (SD))</td>
<td>8.97 (2.79)</td>
<td>8.18 (2.64)</td>
</tr>
<tr>
<td>Urea (mmol/L (mean (SD))</td>
<td>13.83 (8.49)</td>
<td>15.50 (8.63)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer (%)</td>
<td>309 (8.0)</td>
<td>90 (8.9)</td>
</tr>
<tr>
<td>Cardiac diseases (%)</td>
<td>171 (4.4)</td>
<td>48 (4.8)</td>
</tr>
<tr>
<td>Hepatic diseases (%)</td>
<td>109 (2.8)</td>
<td>56 (5.6)</td>
</tr>
<tr>
<td>Renal diseases (%)</td>
<td>119 (3.1)</td>
<td>37 (3.7)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>323 (8.4)</td>
<td>120 (11.9)</td>
</tr>
<tr>
<td><strong>Bleeding aetiologies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasm (%)</td>
<td>107 (2.8)</td>
<td>29 (2.9)</td>
</tr>
<tr>
<td>Peptic ulcers (%)</td>
<td>3518 (91.0)</td>
<td>889 (88.2)</td>
</tr>
<tr>
<td>Varices (%)</td>
<td>160 (4.1)</td>
<td>66 (6.5)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>504 (13.0)</td>
<td>99 (9.8)</td>
</tr>
<tr>
<td><strong>Endoscopic therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection (%)</td>
<td>3405 (88.1)</td>
<td>903 (89.6)</td>
</tr>
<tr>
<td>Clipping (%)</td>
<td>890 (23.0)</td>
<td>267 (26.5)</td>
</tr>
<tr>
<td>Thermodissection (%)</td>
<td>2746 (71.0)</td>
<td>680 (67.5)</td>
</tr>
<tr>
<td>Banding (%)</td>
<td>92 (2.4)</td>
<td>44 (4.4)</td>
</tr>
<tr>
<td>Others (%)</td>
<td>245 (6.3)</td>
<td>59 (5.9)</td>
</tr>
</tbody>
</table>

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.
GI bleeding

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 1.63, 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, 95% CI 1.17 to 1.44, p<0.001)

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Timing</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>30-day all-cause mortality</td>
<td>Early Reference NA</td>
<td>1.412 (1.222 to 1.631)</td>
</tr>
<tr>
<td></td>
<td>Urgent</td>
<td>1.263 (1.090 to 1.464)</td>
</tr>
<tr>
<td>30-day repeat therapeutic endoscopy</td>
<td>Early Reference NA</td>
<td>1.221 (1.112 to 1.340)</td>
</tr>
<tr>
<td></td>
<td>Urgent</td>
<td>1.034 (0.939 to 1.139)</td>
</tr>
<tr>
<td>30-day ICU admission after index endoscopy</td>
<td>Early Reference NA</td>
<td>1.429 (1.202 to 1.699)</td>
</tr>
<tr>
<td></td>
<td>Urgent</td>
<td>0.706 (0.574 to 0.869)</td>
</tr>
</tbody>
</table>

aHR, adjusted HR; ICU, intensive care unit; NA, not available.
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 test 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. Gastric acid suppression, especially with the potent intravenous PPI infusion, has been demonstrated to improve outcomes in AUGIB patients. 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, previous study findings were conflicting over the precise timing of endoscopy: one study suggested that urgent endoscopy was superior, one suggested that early endoscopy was superior, while some suggested no significant difference, including our recently published RCT. 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. 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) and is associated with a poorer prognosis compared with non-variceal bleeding, contributing to the most to the mortality rate of AUGIB in the USA. 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 recognised factors and uncollected clinical data were inevitable and multiple patient characteristics on hospital admission, unrec-

worse outcomes with urgent endoscopy timings when compared of time while keeping other dependent variables constant

bleeding of moderate to high severity, which strongly suggests

able of time while keeping other dependent variables constant

Nonetheless, our study was able to isolate the independent vari-

these patients, the generalisability of this study may be limited,

were patients that required therapeutic endoscopy, who

Contributors SW conceived the study. CLG extracted the data, performed the analysis and drafted the manuscript. LHS, RNSL, WYMA, 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.

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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

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