



# Analysing Factors Prolonging Hospital Stay After Excision of Choledochal Cyst—A Pathway Towards Enhanced Recovery After Surgery

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## Abstract

**Background** To evaluate factors affecting length of stay (LOS) after choledochal cyst resection in paediatric patients.

**Methods** This was a retrospective study on patients operated between 2004 and 2021. Associations between clinical factors and LOS were evaluated by bivariate analysis, multiple regression, and equivalence test.

**Results** Sixty-two patients were included. Twenty-four underwent hepaticoduodenostomy as biliary reconstruction. Five suffered from major complications. The median (25th–75th percentile) operation time was 279 (182–378) min. Median LOS, time to enteral feeding, and time to abdominal drain removal were 8(6–10), 2(1–3), and 5(4–7) days, respectively. Seven factors were found significantly associated with a shorter LOS in bivariate analysis and were included in multiple regression. It revealed that early abdominal drain removal ( $p < 0.001$ ), early enteral feeding ( $p = 0.042$ ), and the absence of major complications ( $p < 0.001$ ) were significantly associated with shorter LOS. Equivalence test suggested that age and preoperative cholangitis had no practical effect on LOS.

**Conclusions** Early enteral feeding, early drain removal, and avoidance of major complications are associated with a shorter LOS.

## Introduction

Choledochal cyst is a congenital cystic dilation involving the extrahepatic and/or intrahepatic biliary tree [1, 2], and surgical resection is the standard treatment to avoid complications including obstructive jaundice, cyst rupture, cholangitis, and malignancy [1, 3]. Enhanced recovery after surgery (ERAS) is an evidence-based, multidisciplinary, and perioperative approach designed to smoothen

postoperative recovery [4]. Since its introduction more than two decades ago, it has become more popular and brought significant benefits to patients and healthcare systems [5].

Several studies attempted to reduce postoperative length of stay (LOS) in choledochal cyst patients. Two recent meta-analysis suggested that laparoscopy and hepaticoduodenostomy (HD) reconstruction, compared to open surgery and hepaticojejunostomy (HJ), respectively, were associated with a shorter LOS and a non-inferior complication rate [6, 7]. A retrospective study suggested that robotic surgery had a similar LOS and complication rate compared to laparoscopic surgery [8].

Nevertheless, factors other than surgical approach may also reduce LOS of these patients. Therefore, we would like to perform a retrospective review of patients in our centre and establish the association between each potential ERAS factor and LOS. Furthermore, we would discuss

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important factors and give recommendations on choledochal-cyst-specific ERAS protocol.

## Materials and methods

To analyse the association between the clinical factors as shown in the supplementary table 1 (Online Resource 1) and the primary outcome—postoperative LOS, we conducted a single-centre retrospective cohort study for patients that underwent complete biliary resection for choledochal cyst between 2004 and 2021, by retrieving and analysing data from their clinical records. The patients were followed up from their initial presentation to discharge. Firstly, we described their demographics. Secondly, we conducted a bivariable analysis on the association between factors and LOS. For continuous factors, Spearman's correlation test would be conducted, after which the  $p$  value and the Spearman's rank correlation coefficient  $\rho$  would be reported. For categorical factors, Mann–Whitney  $U$  test or independent-samples Kruskal–Wallis test for factors with three categories would be used. To study the effect of advance in technique and laparoscopy, we divided the patients into group 1 (operated between 2004 and 2013) and group 2 (operated between 2014 and 2021) according to the year at which the operation was done and compared the LOS between the two groups using Mann–Whitney  $U$  test. Thirdly, we conducted a multiple regression on significant factors in bivariate analysis. In the regression analysis, we excluded patients with incomplete data, and confirmed compliance to assumptions of multiple regression by examining Cook's distance variance inflation factor (VIF), Durbin–Watson statistic, and multicollinearity.

Finally, as adjunct, we performed an equivalence test on clinical factors insignificant in the abovementioned tests [9, 10]. Ninety percentage confidence interval (CI) of effect size was evaluated for categorical factors, with  $(-0.5, 0.5)$  being the equivalence boundary [9, 10]. Similarly, for continuous factors, 90% CI of  $\rho$  was evaluated, with  $(-0.3, 0.3)$  being the equivalence boundary [9, 10].

This study was performed in line with the principles of the Declaration of Helsinki. Approval of the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 21–648) was obtained, and STROBE statement and checklist [11] were followed. Data were presented as median (25th percentile [Q1]—75th percentile [Q3]). SPSS version 27.0.0.0 (IBM) was used to analyse the data, and a  $p$  value less than 0.05 was considered significant for all tests.

## Results

The results are summarized in Tables 1–4. We identified 62 cases and included all of them. Fifty (80.6%) patients were female, and fifty-four (87.1%) of them had type 1 choledochal cyst. Thirty-eight patients were operated between 2004 and 2013 (group 1), while the rest were operated between 2014 and 2021 (group 2). The age and weight at operation was 23.00 (8.00–71.00) months and 10.60 (8.10–18.80) kg, respectively. Postoperatively, the time to enteral feeding, urinary drain removal, abdominal drain removal, and hospital discharge were 2.00 (1.00–3.00), 2.00 (1.00–3.00), 5.00 (4.00–7.00), and 8.00 (6.00–10.00) days, respectively. The operative time was 279.00 (182.00–378.25) min, and fifty-five (88.7%) patients had a surgery with blood loss less than 100 mL. Fifty-seven (91.9%) patients were discharged without major postoperative complications requiring intervention, i.e. Clavien–Dindo grade 3 or above complications.

The results of bivariate analysis, which aims to establish association between clinicopathological factors and LOS, are presented in Tables 2 and 3. For demographical data, patients operated between 2014 and 2021 have significantly shorter LOS than those operated between 2004 and 2013 ( $p = 0.001$ ), for which we further conducted additional analysis as described in the following paragraph. All other demographical factors and preoperative history, illustrated in tables 1.1 and 1.2, respectively, in Online Resource 1, were insignificantly associated with LOS (Tables 1, 2). In equivalence test, preoperative cholangitis, age at operation, and weight at surgery were found to have practically no important effect on LOS.

To find out why patients operated between 2014 and 2021 (group 2) have shorter LOS than those operated between 2004 and 2013 (group 1), we analysed characteristics of the two groups, as shown in the supplementary table 2 (Online Resource 2). The former group comprises more operations with asymptomatic presentation (33.3% vs. 18.4%), HD (58.3% vs. 26.3%), blood loss less than or equal to 100 mL (91.7% vs. 86.8%), non-opioid analgesic regimen (29.2% vs. 17.6%), and spared postoperative ICU stay (75.0% vs. 28.9%). The former group also demonstrated shorter median operative time (170.50 min vs. 336.00 min), time to enteral feeding (2.00 days vs. 3.00 days), and time to removal of abdominal drain (4.00 days vs. 7.00 days).

For surgical factors, a shorter operative time (Spearman's rank coefficient  $\rho = 0.446$ ,  $p < 0.001$ ) and HD as biliary reconstruction ( $p = 0.047$ ) were associated with a significant reduction of LOS. For postoperative factors, four factors were associated with a significant reduction of LOS: the absence of ICU stay ( $p = 0.004$ ), early enteral

**Table 1** Basic demographics and characteristics of patients, with comparison to recent series

| Characteristics ( <i>N</i> = 62, unless specified)  | Median (25th percentile–75th percentile), unless specified | Median in series 1, published in 2019 [15] | Median in series 2, published in 2020 [16] |
|---|--|--|--|
| Sex (M:F)   | 12:50  | 7:36                                       | 11:24                                      |
| Type (I:II:IV) ( <i>N</i> = 60)   | 54:1:5   | 33:1:9                                     | 36:3                                       |
| Group 1 (2004–2013): Group 2 (2014–2021)  | 38:24  | NR   | N/A  |
| Age at diagnosis (for patients without antenatal diagnosis/counselling) (months) ( <i>N</i> = 44) | 43.00 (8.75–82.50)   | NR   | N/A  |
| Age at operation (months)   | 23.00 (8.00–71.00)   | 13 days                                    | 3 (AN); 15.5 (PN)                          |
| Weight at surgery (kg) ( <i>N</i> = 59)   | 10.60 (8.10–18.80)   | 3.43                                       | 5.6 (AN); 10.5 (PN)                        |
| Operation time (min)  | 279.00 (182.00–378.25)                                     | 222.00                                     | 288 (AN); 315 (PN)                         |
| Duration to removal of abdominal drains (days) ( <i>N</i> = 51)                                   | 5.00 (4.00–7.00)   | NR   | NR   |
| Duration to removal of urinary drain (days) ( <i>N</i> = 41)                                      | 2.00 (1.00–3.00)   | NR   | NR   |
| Time to enteral feeding (days) ( <i>N</i> = 51)   | 2.00 (1.00–3.00)   | 4.30                                       | NR   |
| Length of stay (days)   | 8.00 (6.00–10.00)  | 10.50                                      | 8 (AN); 7.5 (PN)                           |

NR not reported; AN antenatal diagnosis group (for series 2); PN postnatal diagnosis group (for series 2)

**Table 2** Association between continuous clinicopathological variables and length of stay (Spearman's rank correlation coefficient (two-tailed))

| Variables ( <i>N</i> = 62, unless specified)  | Spearman's rank correlation coefficient $\rho$ | <i>p</i> value      |
|---|--|---------------------|
| Age at diagnosis (excluded patients with antenatal counselling/diagnosis) (months) ( <i>N</i> = 44) | −0.062   | 0.687               |
| Age at operation (months)   | 0.003  | 0.982               |
| Weight at surgery (kg) ( <i>N</i> = 59)   | 0.008  | 0.950               |
| Operation time (h)  | 0.446  | <0.001 <sup>a</sup> |
| Time to removal of urinary drainage (days) ( <i>N</i> = 41)   | 0.141  | 0.378               |
| Time to removal of abdominal drainage (days) ( <i>N</i> = 51)                                       | 0.675  | <0.001 <sup>a</sup> |
| Time to enteral feedings (days) ( <i>N</i> = 51)  | 0.462  | 0.001 <sup>a</sup>  |

<sup>a</sup>*p* < .05

feeding ( $\rho = 0.462$ ,  $p = 0.001$ ), early abdominal drain removal ( $\rho = 0.675$ ,  $p < 0.001$ ), and a lack of complication ( $p < 0.001$ ). All other surgical and postoperative factors, as listed in parts 1.3 and 1.4 in Online Resource 1, were insignificant. The equivalence test on surgical or postoperative factors was unrevealing. In addition, via Chi-square test, we found that laparoscopy is associated with pain control without opioid, with  $X^2$  (1,  $N = 58$ ) = 11.827,  $p = 0.001$ .

In multiple regression (Table 4), factors including time period of operation (group 1 (2004–2013) vs. group 2 (2014–2021)), biliary reconstruction method (HD vs. HJ), operative time, postoperative ICU stay, time to enteral feeding, time to abdominal drain removal, and the presence of complication were included for analysis. There were 48 cases with complete data on these factors. On assumption checking, two influential cases with Cook's distance larger

than 1 were removed. Finally, we included 46 cases, and the factors significantly predicted LOS,  $F(7, 38) = 12.540$ ,  $p < 0.001$ ,  $R^2 = 0.698$ . Early abdominal drain removal ( $p < 0.001$ ), early enteral feeding ( $p = 0.042$ ), and lack of complication ( $p < 0.001$ ) were significantly associated with a shorter LOS. Although the contribution of other factors to the regression was statistically insignificant, the directions of each of their respective unstandardized coefficients were consistent with the suggested direction in bivariate analysis.

## Discussion

Since the introduction of ERAS, there have been many relevant publications and official ERAS protocols [12]. For paediatric patients, ERAS is safe and effective, but relevant

**Table 3** Association between discrete clinicopathological variables and length of stay, analysed by independent-sample Mann–Whitney *U* test (independent-sample Kruskal–Wallis test for “type of choledochal cyst”)

| Clinicopathological variables ( <i>N</i> = 62, unless specified)              |                                       | Median LOS (25th percentile–75th percentile) | <i>p</i> value     |
|---|---------------------------------------|--|--------------------|
| Sex   | M ( <i>N</i> = 12)                    | 8.00 (6.25–10.00)                            | 0.781              |
|   | F ( <i>N</i> = 50)                    | 8.00 (6.00–10.00)                            |                    |
| Time period at which surgery was conducted                                    | Group 1 (2004–2013) ( <i>N</i> = 38)  | 8.00 (7.75–12.00)                            | 0.001 <sup>a</sup> |
|   | Group 2 (2014–2021) ( <i>N</i> = 24)  | 6.00 (5.00–8.75)                             |                    |
| Type of choledochal cyst ( <i>N</i> = 60)                                     | I ( <i>N</i> = 54)                    | 8.00 (6.00–10.50)                            | 0.842              |
|   | II ( <i>N</i> = 1)                    | N/A <sup>b</sup>                             |                    |
|   | IV ( <i>N</i> = 5)                    | 8.00 (6.50–9.50)                             |                    |
| Surgical approach   | Laparoscopy ( <i>N</i> = 37)          | 8.00 (6.50–9.00)                             | 0.401              |
|   | Open ( <i>N</i> = 25)                 | 8.00 (6.00–13.00)                            |                    |
| Biliary reconstruction  | Hepaticoduodenostomy ( <i>N</i> = 24) | 7.50 (6.00–8.00)                             | 0.047 <sup>a</sup> |
|   | Hepaticojejunostomy ( <i>N</i> = 38)  | 8.00 (7.00–12.50)                            |                    |
| Antenatal counselling   | Yes ( <i>N</i> = 18)                  | 7.00 (5.75–9.25)                             | 0.176              |
|   | No ( <i>N</i> = 44)                   | 8.00 (7.00–10.00)                            |                    |
| Preoperative jaundice/hyperbilirubinemia                                      | Yes ( <i>N</i> = 32)                  | 8.00 (7.00–10.00)                            | 0.191              |
|   | No ( <i>N</i> = 30)                   | 7.00 (6.00–10.75)                            |                    |
| Preoperative cholangitis  | Yes ( <i>N</i> = 19)                  | 8.00 (7.00–10.00)                            | 0.317              |
|   | No ( <i>N</i> = 43)                   | 8.00 (6.00–10.00)                            |                    |
| Preoperative pancreatitis   | Yes ( <i>N</i> = 13)                  | 9.00 (7.50–15.50)                            | 0.054              |
|   | No ( <i>N</i> = 49)                   | 8.00 (6.00–9.00)                             |                    |
| Preoperative cholecystostomy  | Yes ( <i>N</i> = 5)                   | 8.00 (5.50–11.00)                            | 0.960              |
|   | No ( <i>N</i> = 57)                   | 8.00 (6.00–10.00)                            |                    |
| Preoperative symptomatic presentation   | Yes ( <i>N</i> = 47)                  | 8.00 (7.00–10.00)                            | 0.202              |
|   | No ( <i>N</i> = 15)                   | 7.00 (6.00–9.00)                             |                    |
| Intraoperative blood loss   | > 100 mL ( <i>N</i> = 7)              | 9.00 (7.00–21.00)                            | 0.253              |
|   | ≤ 100 mL ( <i>N</i> = 55)             | 8.00 (6.00–10.00)                            |                    |
| Postoperative ICU stay  | Yes ( <i>N</i> = 33)                  | 9.00 (7.00–12.00)                            | 0.004 <sup>a</sup> |
|   | No ( <i>N</i> = 29)                   | 7.00 (5.50–8.00)                             |                    |
| Analgesia ( <i>N</i> = 58)  | Opioid sparing ( <i>N</i> = 13)       | 7.00 (6.00–9.00)                             | 0.319              |
|   | Opioid containing ( <i>N</i> = 45)    | 8.00 (6.50–10.00)                            |                    |
| Postoperative complications before discharge (Clavien–Dindo grade 3 or above) | Yes ( <i>N</i> = 5)                   | 21.00 (15.00–42.50)                          | <.001 <sup>a</sup> |
|   | No ( <i>N</i> = 57)                   | 8.00 (6.00–9.00)                             |                    |

<sup>a</sup>*p* < .05; <sup>b</sup>LOS data on items with sample size <5 are not disclosed due to privacy issue

research is still relatively limited [13, 14]. In this research, we proposed a perioperative approach to shorten LOS and suggested items to develop a tailor-made ERAS protocol for choledochal cyst patients based on the association between individual clinical factors and LOS.

In this series, LOS, operative time, time to enteral feeding, and complication rate, were comparable to results from two recent studies (Table 1) [15, 16]. However, with advances in medicine, there were a higher percentage of

successful laparoscopic surgery and antenatal diagnosis in this cohort [17]. Here, we identified that early abdominal drain removal, enteral feeding, and a lack of postoperative complication were the most significant factors leading to a shortened LOS. In bivariable analysis, shorter operative time, the use of HD, and the absence of ICU stay were significantly associated with shorter LOS, which were agreed by the signs of the coefficients in multiple regression. Hence, their insignificance in multiple regression may

**Table 4** Multiple regression on association between variables significant in bivariate tests and LOS

| Independent variables  | Standardized coefficient | <i>p</i> value     |
|--|--------------------------|--------------------|
| Time period at which surgery was conducted(Group 1: 2004–2013; Group 2: 2014–2021) | −0.104                   | 0.380              |
| Biliary reconstruction   | 0.218                    | 0.096              |
| Operative time (min)   | −0.016                   | 0.912              |
| Time to enteral feeding(days)  | 0.231                    | 0.042 <sup>a</sup> |
| Abdominal drainage (days)  | 0.406                    | 0.000 <sup>a</sup> |
| Postoperative ICU admission  | 0.046                    | 0.681              |
| Postoperative complication   | 0.497                    | 0.000 <sup>a</sup> |

<sup>a</sup>*p* < .05

**Table 5** Summary of significant findings and corresponding recommendations

| Factors significantly associated with shorter LOS | Recommendations  |
|---|--|
| Shorter operative time                            | Careful preoperative planning [18, 19]<br>Use of new technologies [18, 19]<br>Effective administration [18, 19]  |
| Hepaticoduodenostomy                              | Consider HD as an alternative, while also taking into account local expertise, experience, and outcome data  |
| The absence of postoperative ICU admission        | Involve more senior clinicians during triage<br>Collaborate closely with anaesthesiologist<br>Improve laparoscopic skill to reduce analgesic need and ICU care |
| Early abdominal drain removal                     | Remove abdominal drain early<br>Consider omission of abdominal drain under low leakage or haemorrhagic risk [4, 27]  |
| Early enteral feeding                             | Discontinue IV fluid early [4]<br>Consider avoiding or removing nasogastric tube early [4, 28, 29]<br>Initiates enteral feeding early                          |
| The absence of postoperative complications        | Early diagnosis and treatment<br>Preoperative health and weight optimization   |

merely stem from the small sample size. In the following, we will discuss these findings with reference to existing evidence and make recommendations to optimize these factors (Table 5).

For operative time, previous studies have already reported that in Roux-en-Y HJ, a longer operation was associated with a longer LOS [18]. Apart from indicating surgical difficulty, longer operations may lead to an increase in blood loss, fluid administration, period of tissue oxygen deprivation, and complication rate [18, 19]. To reduce operative time, meticulous preoperative planning, adaption of novel technologies, and effective administrative workflow should be encouraged [19]. HD was associated with shorter LOS, which was consistent with results from meta-analysis [7] and our centre's previous studies [20, 21]. It is also more physiological and technically manageable and provides better access for postoperative endoscopies [21]. However, recent meta-analysis also

suggested that HD was associated with higher gastritis and reflux rate [22], and there is still no uniform view on which reconstruction approach is better [23]. Individual centres should consider their skills, experience, and outcomes data when choosing the reconstruction method. In certain situations, postoperative ICU care to high-risk patients could minimize mortality and morbidity [24]. However, the other side of the coin is over-admission that delays the recovery [25]. The triage decision needs to be judicious and with an agreement between anaesthesiologist, intensivist, and surgeon. In our centre, the progression in laparoscopic skills has substantially reduced the analgesic need and hence the postoperative ICU care in the recent years, with three-fourth of our patients operated between 2014 and 2021 being spared from postoperative ICU stay. As expected, avoiding surgical complications would also reduce LOS. In general, complications have been associated with emergency surgery, poor functional status, and abnormal weight

[26]. Hence, early diagnosis and treatment, as well as preoperative health and weight optimization, maybe helpful in reducing complication rate.

Early abdominal drain removal is a well-established ERAS factor [4]. A study on choledochal cyst excision with HJ further suggested that the low leakage and haemorrhagic risk of modern laparoscopy made abdominal drains harmful for these patients, since it would be associated with more pain, slower activity resumption, and increased complication rate, without bringing any additional benefits [27]. Hence, they recommended that drains are needed only in case of severe infection, stricture in common, left or right hepatic duct, or a cyst deep inside the pancreas [27]. Therefore, centres with mature laparoscopy techniques might consider omission of abdominal drains in cases without any adverse factor. Feeding optimization is necessary for early discharge [4], and early enteral feeding and avoidance of nasogastric tube should be considered. While early enteral feeding is associated with shorter LOS in our study, ERAS guideline has also advocated for avoidance or early removal of nasogastric tube and an early discontinuation of intravenous fluid [4]. A recent systematic review suggested that early enteral feeding after abdominal surgery was safe and effective in children and one included study initiated feeding as early as 6 h postoperatively, but all evidences were derived from gastrointestinal surgery [28]. Unfortunately, the relevant evidence for paediatric biliary surgeries is under reported [28]. However, in adults, patients undergoing hepatobiliary surgery would be offered clear liquids on the day of surgery and then escalate to solid diet the next day, while prophylactic nasogastric tube insertions are avoided [29]. Combining with the result of this study, an early establishment of full enteral feeding without stomach tube should be the future direction.

Clinical experience is also an important factor allowing the use of ERAS factors and shortening LOS. Patients operated between 2014 and 2021 have significantly shorter LOS than those operated between 2004 and 2013. An increased surgical and clinical experience, as well as technical maturity and surgical skill improvement, are likely direct contributors, as reflected by a less blood loss, shorter operation, less pain control needed, and less postoperative ICU admission in the former group. Also, although we have not developed an ERAS protocol, with improvement in local experience and more ERAS literature, we have been able to gradually increase the use of LOS-reducing elements, including early enteral feeding, earlier removal of abdominal drain, and avoidance of overtriage to postoperative ICU.

In meta-analysis, laparoscopy shortens LOS in choledochal cyst patients [6]. However, this was not demonstrated in our centre. It was expected because of a conservative approach towards early feeding during the early years, when laparoscopic biliary reconstruction in children was still an emerging approach without much evidence about anastomotic leakage. In recent years, with more experience and evidence, we began to initiate the enteral feeding early. Despite this, our early adoption of laparoscopy had its benefits. The first is less use of opioid, implying less pain, easier pain control, and less risk of opioid side effects. Moreover, a smaller scar provides a better cosmetic and functional outcome, leading to better quality of life and satisfaction.

In equivalence test, age and weight at surgery had no considerable association with LOS, which were consistent with a previous study [30]. This may be attributable to the high availability of tertiary centre services and timely treatment of symptomatic patients. Despite this, choledochal cyst needs to be treated early to avoid malignancy and complications [1, 3]. More importantly, the equivalence test showed that non-significant factors, especially laparoscopy, early urinary drain removal, and non-opioid analgesia, are not genuinely unimportant, and they are worth further investigation for the true significance.

The strength of this study lies on its comprehensive evaluation of individual effects of clinical factors, as well as the use of multiple regression and equivalence test. Moreover, a single-centre setting means a uniform practice, less surgeon or centre factors, and a similar discharge standard, ensuring the data reliability. However, this setting also limited our sample size, and the uniformity of practice made it impossible to analyse some factors, including bowel preparation, avoidance of drains and tubes, intraoperative temperature control, and correction of anaemia. In the future, apart from cooperation with other centres to increase the statistical power and analyse on more factors, we may use the study result to develop an ERAS protocol for choledochal cyst, which may be further validated in a multi-centred randomized control study. We may also investigate on preoperative length of stay and association between clinical factors and other outcomes such as complication rate, readmission in 30 days, and pain score.

In conclusion, avoidance of complications, early abdominal drains removal and enteral feeding are associated with an enhanced recovery after choledochal cyst surgery. In addition, HD as biliary construction, shorter operative time and minimized postoperative ICU admission are other potential factors that may shorten LOS. These recommendations should be considered in ERAS protocol for choledochal cyst.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00268-023-07206-y>.

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**Author contributions** We describe contributions of the authors to the paper using CRediT taxonomy [31]: all authors equally contributed to conceptualization, methodology, writing—reviewing and editing, and project administration; P.H.Y.C., F.Y., and K.K.Y.W. were involved in the supervision; M.K.I.M.\*, P.H.Y.C., F.Y., and K.K.Y.W. conducted the investigation and statistical analysis; M.K.I.M. contributed to the writing—original draft. An asterisk is used to denote a ‘lead’ degree of contribution in a specific role. Otherwise, it can be assumed that all authors listed contribute to that role equally.

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#### Declarations

**Conflict of interest** There is no conflict of interest to be declared for all authors.

**Ethical approval** Approval of the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 21–648) was obtained.

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