Original Article

Use of high flow nasal cannula oxygen therapy for patients infected with SARS-CoV-2 outside intensive care setting

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Background: In early 2022, there was a sudden surge of patients infected by the Omicron variant of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in Hong Kong (HK), resulting in 9,163 deaths as of 29 May 2022. Many of the local population had not been vaccinated before this wave. The number of patients who developed coronavirus disease 2019 (COVID-19) related respiratory failure outnumbered the capacity of intensive care unit (ICU) beds. Some of these patients had to be supported with high flow nasal cannula (HFNC) therapy outside ICU setting. HK was in crisis situation. The primary objective of this study is to assess the 28-day mortality of this group of patients. The secondary objective is to explore any predictors of non-survivors to help clinical decision-making in future crisis.

Methods: This is a retrospective observational study of patients suffering from COVID-19 related respiratory failure who received HFNC therapy in general medical wards of two hospitals during the period of 17 Mar to 30 Apr 2022. Survival and risk factors were reviewed.

Results: Forty-nine patients were recruited. Twenty-six patients (53%) survived at 28-day after initiation of HFNC support. Three clinical parameters were found to be significantly associated with mortality at 28-day: (I) SpO_2/FiO_2 (SF) ratio <160 at 48 hours; (II) SF ratio <191 at 72 hours; (III) serial SF ratio at 48 or 72 hours showing no improvement over that at the time of initiation of HFNC therapy.

Conclusions: Use of HFNC outside ICU setting showed benefit to patients suffering from COVID-19 related acute hypoxemic respiratory failure (AHRF). Serial SF ratio monitoring at 48 and 72 hours after therapy initiation might serve as predictors of outcome and thus guide clinical decision-making for medical resource allocation in outbreak situation.

Keywords: Coronavirus disease 2019 (COVID-19); high flow nasal cannula therapy (HFNC therapy); SpO_2:FiO_2 ratio (SF ratio); outside intensive care unit setting (outside ICU setting); time-limited therapy

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Introduction

In November 2021, a new variant of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), named B1.1.529, was reported to the World Health Organization (WHO), which was subsequently named Omicron variant of SARS-CoV-2. The Omicron variant was found to be more infectious than the original SARS-CoV-2 virus (1). Since 31 Dec 2021, there had been an upsurge in the number of coronavirus disease 2019 (COVID-19) infected in Hong

Kong (HK). This wave of infection peaked on 4 Mar 2022. As of 29 May 2022, there were more than one million positive cases reported (2,3).

The very high transmissibility of the Omicron variant resulted in a sudden surge of healthcare demand in HK (4). Due to the low rate of vaccination among the elderly, more than 340,000 patients infected with the Omicron variant were >60 years old (2). They were at a much higher risk of severe infection including respiratory failure, especially for those with multiple comorbidities (3,5).

High flow nasal cannula (HFNC) therapy has been shown to improve oxygenation in patients with acute hypoxemic respiratory failure (AHRF) in the FLORALI Study (6), and it has been used in this group of patients since the last decade (7). HFNC has been shown to reduce intubation in patients with severe COVID-19 infection (8). WHO proposed the use of HFNC therapy as a treatment of mild acute respiratory distress syndrome (ARDS) in COVID-19 infected patients (9). The majority of the studies have been performed in the intensive care unit (ICU) settings. Studies investigating the efficacy of HFNC in improving oxygen saturation in patients with respiratory failure outside the ICU setting were limited (10,11).

During this wave of COVID-19 infection, HK faced a crisis situation. Many patients with COVID-19 associated AHRF were managed in general wards due to inadequate ICU beds. Many of these patients were frail with multiple comorbidities. Unlike practice in other countries (12), HFNC therapy had been rarely used outside the ICU setting in HK prior to 2022. To deal with the crisis, the use of HFNC therapy was implemented in the general wards in two hospitals under the authors' care. HFNC was given to patients who required >4 L/min O_2 via nasal cannula to maintain SpO_2 ≥92% (13).

The primary objective of this study is to assess the 28-day mortality of this group of patients. The secondary objective is to explore any predictors of non-survival to help clinical decision-making in future crisis. We present this article in accordance with the TREND reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1507/rc).

Highlight box

Key findings

- Use of high flow nasal cannula therapy is feasible outside intensive care setting
- Monitoring of SpO_2:FiO_2 ratio is more practical and at specific therapeutic time points can predict 28-day survival under this setting

What is known and what is new?

- High flow nasal cannula has been used in patients with hypoxemic respiratory failure since the last decade. Majority of the studies has been performed in intensive care setting.
- At the time of infection outbreak when intensive care service is in short supply, the use of high flow nasal cannula therapy outside the intensive care setting for patients with acute hypoxemic respiratory failure should be considered.

What is the implication, and what should change now?

- Serial monitoring of SpO_2:FiO_2 ratio can be helpful to decide on therapy continuation in outbreak situations when medical resources are limited.

Methods

This retrospective cohort study was conducted in 6 COVID-19 general medical wards of the Princess Margaret Hospital (PMH), and 4 COVID-19 general wards of the North Lantau Hospital (NLTH) in HK. All patients admitted during the period of 17 March to 30 April 2022 with confirmed SARS-CoV-2 infection, who developed AHRF requiring HFNC support, were recruited. Those patients fulfilling these inclusion criteria but who used HFNC treatment for indications other than AHRF or were subsequently admitted to ICU were excluded.

The following data were retrieved from the clinical records for each recruited patient: demographic (age, sex, comorbidity), clinical (care plan decision, length of hospital stay, 28-day outcome), monitoring [baseline and serial oxygen saturation SpO_2/inspiratory oxygen ratio FiO_2 ratio (SF ratio) after HFNC therapy], and drug treatment.

Objective scores in describing patients' underlying illnesses and the severity of their COVID-19 infection were used. The Charlson Comorbidity Index (CCI) was calculated according to the comorbidities of patients. The Clinical Frailty Scale (CFS) was used to describe frailty of the patients. The modified chest X-ray (CXR) scoring system was used for objective comparison of CXR changes due to COVID-19 infection (14). The Comorbidity-Age-Lymphocyte count-Lactate dehydrogenase (CALL) score for prediction for progression risk in patients with COVID-19 pneumonia was calculated, which included data on defined comorbidities, age >60 years old, lymphocyte count $<1\times10^9$/L and lactate dehydrogenase (LDH) level >250 U/L (15). A CALL score of 4–6 points indicates <10% risk of progression of COVID-19 pneumonia while the risk was 10–40% and >50% for a CALL score 7–9 points and 10–13 points, respectively.

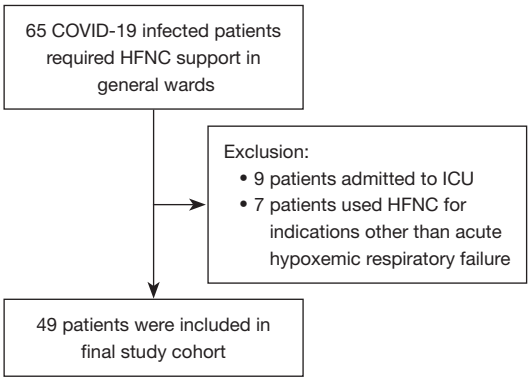

Figure 1 Study recruitment flow chart. COVID-19, coronavirus disease 2019; HFNC, high flow nasal cannula; ICU, intensive care unit.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Research Ethics Committee of the Kowloon West Cluster of the HK Hospital Authority (HA) [Reference No. KW/EX-22-046(172-02)], and individual consent for this retrospective analysis was waived.

Clinical setting and HFNC setup

The 6 COVID-19 general wards of PMH were in the Infectious Disease Centre (IDC) with standard airborne infection isolation room facility. The 4 COVID-19 wards of NLTH were converted from general wards; each equipped with high efficiency particulate air (HEPA) filters and strengthened ventilation. The HFNC device (Optiflow system) delivered up to 60 L/min of humidified gas admixture at 31, 34 or 37 ℃. FiO_2 was delivered in the range of 0.21–1.00 via a low resistance nasal cannula. HFNC was initiated by the in-charge physician if a patient required >4 L/min O_2 via nasal cannula to maintain SpO_2 ≥92%. A dedicated team of physicians with critical care training background then took over the management of the patient in the general wards as long as HFNC support was needed. The default settings of HFNC were 40 L/min flow and FiO_2 40%. Settings were adjusted according to SpO_2 and the respiratory status of patients. The patients were given anti-viral and anti-inflammatory drugs based on the prevailing guideline on the clinical management of adult patients with COVID-19 HK (13).

Statistical analysis

The Statistical Package for Social Sciences (Window version 22.0; SPSS Inc., Chicago, IL, USA) was used for analysis. Descriptive statistics were used to summarize patient demographics data. The Student's *t*-test was used to compare continuous variables between the two groups, while the Chi square test or Fisher's Exact test were used to compare categorical variables. A P value of less than 0.05 was considered statistically significant.

Results

During the study period, 460 SARS-CoV-2 infected patients were admitted to the IDC of PMH and to NLTH. Sixty-five patients required HFNC support in general wards. Nine were transferred to ICU for continuation of respiratory support. Fifty-six patients continued HFNC support in general wards. Seven patients who required HFNC for ventilator weaning or for humidification of airway were excluded. Forty-nine patients were treated for COVID-19 related respiratory failure and were included in the cohort study (*Figure 1*). There were no complications reported for the use of HFNC during the study period. The demographics, clinical characteristics, treatment and outcomes of the study population are summarized in *Table 1*. The mean age was 77.5. Thirty-four patients were male and 15 patients were female. Ten patients (20.4%) had received 2 doses of SARS-CoV-2 vaccine, and 24 patients (49%) did not receive any SARS-CoV-2 vaccination. Thirty-three patients (67.3%) received anti-viral treatment while 16 patients (32.7%) did not receive any anti-viral treatment due to delayed presentation. Forty-eight patients (98%) received dexamethasone treatment. Twenty-two patients (44.9%) had positive cytobacteriological growth in sputum culture.

The mean COVID-19 threshold cycle (CT) value of quantitative reverse transcriptase polymerase reaction of the cohort was 22.32. The mean CCI was 5.55. The mean CFS frailty score was 5.27. The mean CALL score was 11.3. The mean CXR score was 9.16. Thirty-six patients (73.5%) had a "Do-Not-Attempt-Cardiopulmonary-Resuscitation (DNACPR)" order, 34 patients (69.4%) had a "do not intubate (DNI)" order. The mean CFS was 5.42 for those patients with a DNACPR order.

Twenty-six patients (53.1%) survived at the 28-day after initiation of HFNC support. Twenty-three patients (46.9%) survived their index hospital admission. For the 36 patients with DNACPR order, 28-day mortality was 61.1% (22 patients) while 11 (30.6%) patients survived the index hospital admission.

Table 1 Patients' characteristics, treatments, laboratory results and outcomes of study population

Characteristics, treatments and laboratory results	Numbers (N=49)	28-day mortality		P value
		No (N=26)	Yes (N=23)	
Age (years), mean ± SD	77.5±11.9	75.9±12.1	79.2±11.6	0.343[a]
Sex (M:F)	34:15	17:9	17:6	0.518[b]
Source				0.130[b]
Home	31	19	12	
Old aged home	18	7	11	
Vaccination				0.469[b]
No	24	14	10	
Yes	25	12	13	
Completed vaccination				0.026[b]
No	42	25	17	
Yes	7	1	6	
COVID drug				0.357[b]
No	16	10	6	
Yes	33	16	17	
Remdesivir				0.539[b]
No	32	18	14	
Yes	17	8	9	
Molnupivir				0.947[b]
No	36	19	17	
Yes	13	7	6	
Paxlovid				0.626[b]
No	46	24	22	
Yes	3	2	1	
Dexamethasone				1.000[c]
No	1	1	0	
Yes	48	25	23	
Baricitinib				0.868[b]
No	40	21	19	
Yes	9	5	4	
Tocilizumab				0.480[b]
No	46	25	21	
Yes	3	1	2	
Low molecular weight heparin				0.124[b]
No	14	5	9	
Yes	35	21	14	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics, treatments and laboratory results	Numbers (N=49)	28-day mortality		P value
		No (N=26)	Yes (N=23)	
Vasopressor				0.189[b]
No	40	23	17	
Yes	9	3	6	
Abnormal troponin I*				0.321[b]
No	14	9	5	
Yes	33	16	17	
D-dimer*				0.622[b]
<1,000	12	7	5	
≥1,000	32	16	16	
C-reactive protein*				0.343[b]
<100	21	13	8	
≥100	27	13	14	
Procalcitonin*				0.238[b]
<0.5	18	13	5	
≥0.5	17	9	8	
Positive sputum culture*				0.154[b]
No	26	16	10	
Yes	22	9	13	

[a], Student's *t*-test; [b], Chi-square test; [c], Fisher's Exact test; *, detailed descriptions of missing date: 2 missing data of troponin I, 5 missing data of D-dimer, 1 missing data of C-reactive protein, 14 missing data of procalcitonin and 1 missing data of sputum culture. Listwise deletion for missing data is adopted in data analysis. SD, standard deviation; M, male; F, female.

The mean SF ratios for 28-day survivors and non-survivors were 175.89 and 136.70 at 2 hours, 189.01 and 134.32 at 24 hours, 228.43 and 157.86 at 48 hours, and 243.51 and 143.70 at 72 hours after initiation of HFNC respectively. Survivors had a statistically higher SF ratio at 2, 24, 48 and 72 hours as compared to non-survivors (P<0.05). Comparing with the SF ratio at the time of HFNC therapy initiation, if there was no significant improvement in SF ratio at 48 or 72 hours, the probability of 28-day mortality was higher (*Figure 2*).

Receiver operating characteristic (ROC) curve of SF ratio at 48 and 72 hours, which showed the greatest difference between survivors and non-survivors, were plotted respectively to identify threshold value to predict mortality. At 48 hours, an SF ratio of <160 had 92% sensitivity and 75% specificity in predicting mortality. The accuracy of using SF ratio at 48 hours to predict mortality was 79%. At 72 hours, an SF ratio of <191 had 83% sensitivity and 79% specificity in predicting mortality. The accuracy of using SF ratio at 72 hours to predict mortality is 86% (*Figure 3*).

There was no statistically significant difference in the CALL score, CXR score, CCI between survivors and non-survivors at 28-day.

Discussion

We assessed the effectiveness of HFNC therapy for use in COVID-19 related AHRF outside the ICU setting in two acute hospitals in HK. van Steenkiste *et al.* performed a retrospective cohort study on the hospital survival of 32 COVID-19 infected patients supported with HFNC therapy in general wards in a large non-academic hospital in the Netherlands (16). The overall CFS was 4 and 25% of patients survived at hospital discharge. Out of the

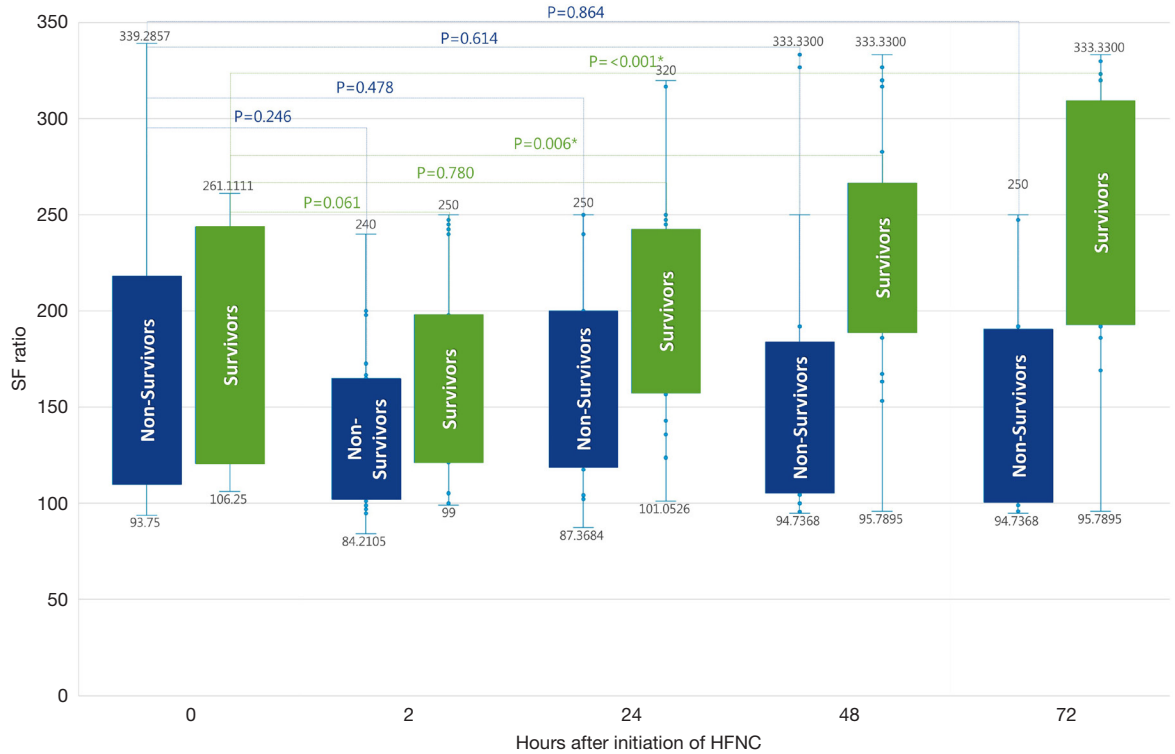

Figure 2 Box and whisker chart of SF ratio over time for non-survivors and survivors. SF ratios were compared by Student's *t*-test. The SF ratios at 2, 24 and 72 hours after initiation of HFNC treatment were compared with the baseline SF ratio at 0 hour in both non-survivors (blue line) and survivors (green line). There was no significant difference of the SF ratios at different time points compared with the baseline while the SF ratios were significantly higher than the baseline at 48 and 74 hours in the survivors. *, statistically significant. HFNC, high flow nasal cannula; SF, SpO_2:FiO_2.

49 patients in our cohort, the mean CFS was 5.27 and 28-day survival rate was 53.1%. van Steenkiste *et al.* concluded that HFNC in general wards could be a potential rescue therapy for respiratory failure in vulnerable COVID-19 infected patients. Result of our study shows similar findings and supported the use of HFNC therapy in general ward.

Issa *et al.* studied the use of HFNC for patents with COVID-19 outside ICU (17). Among the 41 patients included, the mortality rate was only 30%. In this cohort, 20 patients received HFNC therapy as a step-down measure from ICU and mortality was 9.5%. Mortality in the step-up group was 29% and more than half of the group was admitted to ICU. We had excluded patients using HFNC as a step-down measure in our cohort and patients who were subsequently admitted to ICU. As a result, it would not be appropriate to compare the mortality of our cohort with the study performed by Issa *et al.*

Wang *et al.* studied a cohort of 27 COVID-19 infected patients with severe acute respiratory failure (18). Among 17 patients who had received HFNC therapy, 11 patients (64%) with an PaO_2/FiO_2 (PF) ratio ≤200 mmHg at the time of HFNC initiation, required escalation in respiratory support while none of the 6 patients with PF ratio >200 mmHg required escalation in respiratory support. The mean SF ratio at the time of initiation of HFNC was <200 mmHg in our cohort, which would have been predicted by Wang's study to require escalation in respiratory support. Our cohort still managed to have 53.1% 28-day survival, which further suggested the clinical utility of HFNC therapy in this setting.

Ratio of oxygen saturation (ROX) index, defined as SF ratio to respiratory rate (RR) ratio, has been advocated as a monitoring tool for the detection of HFNC failure (19). However, Badawy *et al.* showed that RR was not recorded accurately by hospital personnel (20). There was rightward skew and a 'spot' estimate with values of 18 and 20 breaths per minute was frequently recorded. Since the SF ratio had also been found to be useful in monitoring patients

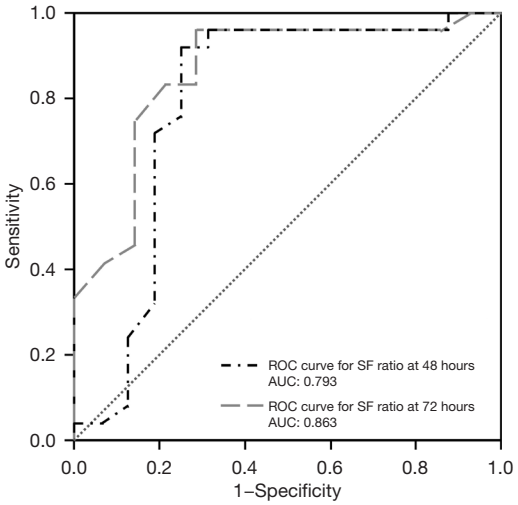

Figure 3 ROC curves for predicting 28-day mortality using SF ratio at 48 and 72 hours. For SF ratio at 48 hours, using a cutoff of SF ratio of <160 has 92% sensitivity and 75% specificity in predicting mortality. The accuracy of using SF ratio at 48 hours to predict mortality is 79%. For SF ratio at 72 hours, using a cutoff of SF ratio of <191 has 83% sensitivity and 79% specificity in predicting mortality. The accuracy of using SF ratio at 72 hours to predict mortality is 86%. ROC, receiver operating characteristic; AUC, area under curve; SF, SpO_2:FiO_2.

on HFNC support (21) and the RR parameter was not documented for many of our patients accurately, the ROX index was not used in our study.

There was a statistically significant correlation between lower SF ratio at 2, 24, 48 and 72 hours after starting HFNC and 28-day mortality of COVID-19 infected patients. SF ratio <160 at 48 hours and SF ratio <191 at 72 hours of HFNC initiation were most predictive of mortality in our cohort. Applying these clinical indicators may help to identify patients who are unlikely to benefit from continuing respiratory support, without jeopardizing those who may potentially benefit. This is well illustrated by the notable 28-day mortality rate of 30.6% in the group of patients with DNACPR order in our cohort who might have been excluded from this treatment otherwise. This result is comparable with the result of the study performed by Peters *et al.* (22). However, our study is not designed to evaluate whether those patients may survive without HFNC support.

When there is no improvement in SF ratio at 48 or 72 hours as compared to the baseline ratio, the life-sustaining treatment should be considered futile. At this point, the health care team should consider discussing and reviewing the care plan with the patient, family or guardian work out a well-defined set of therapeutic goals and end points, which will include withdrawal of treatment (23). A time-limited trial, which usually lasts for a few days, can be used to assess the response to the treatment. If at the end of this trial, no progress is made towards the agreed therapeutic goals, futility is established, and resolution can then be jointly reached to withdraw the life-sustaining treatment (24). This approach may avoid unnecessarily prolonged use of HFNC support and possibly other life-sustaining therapy in medically futile patients, especially in the resource limited outbreak setting.

Limitations

Our study presents several limitations. Due to the retrospective nature of the study, there might be issues of patient selection at initiation of HFNC support. When the HFNC machines were available, the number of COVID-19 AHRF patients started to decrease. As a result, the number of enrolled patients was limited. Furthermore, there was no control group in our study and thus effect of HFNC on 28-day mortality could not be fully ascertained. It would not be possible to examine the effect of organ dysfunction other than respiratory failure on mortality. Not all patients receiving HFNC support were connected to a physiological monitor with measurement of RR or had their arterial blood gas checked. We were not able to obtain accurate RR data and PaO_2 results. As a result, ROX index could not be calculated and captured in our study. SpO_2 measured by pulse oximeter might not be reliable when patient became very ill which might affect the SpO_2:FiO_2 ratio.

Conclusions

Use of HFNC oxygen therapy outside the ICU setting for COVID-19 related AHRF is feasible and useful. If standard ICU management is not available, HFNC outside the ICU setting can be considered. Our study showed a statistically significant correlation between lower SF ratio at 2, 24, 48 and 72 hours after starting HFNC and increased 28-day mortality of COVID-19 infected patients. Monitoring with SF ratio thus helps to identify patients who may not benefit from prolonged HFNC support, especially in patients with DNACPR order. Such information can guide clinical decision-making for medical

resource allocation in outbreak situations.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1507/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1507/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1507/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Research Ethics Committee of the Kowloon West Cluster of the HK Hospital Authority (HA) [Reference No. KW/EX-22-046(172-02)], and individual consent for this retrospective analysis was waived.

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