Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-22-1507

Reviewer A

Comment 1: Utility of HFNO outside the ICU is already proven, and there is nothing unique or new in this.
Reply: Thank you for the comment. HFNO was newly introduced to Hong Kong just before year 2022, and was used in ICU setting. Use of HFNO outside ICU was new to the healthcare in Hong Kong during that time; furthermore, it was implemented within a very short period of time during the time of Omicron outbreak in Hong Kong. That's why the purpose of our study is to look at the use of HFNC outside ICU setting at the time of epidemic, which may add value to appropriate use of resources in crisis situation.

Comment 2: Again, the utility of HFNO in Covid-19 Pneumonia outside ICU or awaiting ICU bed availability or not for ICU is well proven and documented.
Reply 2: Thank you for the comment. Studies looking at use of HFNC outside ICU setting are limited currently. Furthermore, our study also looked at when HFNO would be considered futile.

Comment 3: Is ethical committee approval needed for a retrospective observational study?
Reply 3: Thank you for the comment. Ethical committee approval is needed in our institution and mentioned in L92-93.

Comment 4: English language still needs a bit of editing and refinement.
Reply 4: Thank you for the comment. English is refined.

Comment 5: Many abbreviations are used in the manuscript without mentioning full forms initially.
Reply 5: Thank you for the comment. Full forms of abbreviations are added.

Comment 6: In the method section you have mentioned X-ray scoring criteria, but in the result section I can see you have used CT scoring criteria. Both are not the same. Can I know which was used specifically?
Reply 6: Thank you for the comment. CT mentioned in the result section refers to Cycle Threshold (L130). I should have added the full form as mentioned in point 5 above.

Comment 7: Which frailty score have you used here?
Reply 7: Thank you for the comment. The frailty score used is the Clinical Frailty Score (L84) developed by Rockwood et al.

Comment 8: Were those patients with pre-recorded DNACPR and DNI orders eligible for escalation of medical care as well?
Reply 8: Thank you for your comment. Those patients with DNACPR and DNI orders are eligible for other organ supports unless specifically mentioned.

Comment 9: Can I know what positive bacterial growth did you see in your patients? Did you do colony counts and sensitivity tests? Did you also do viral counts as well?
Reply 9: Thank you for your comment. Colony counts and sensitivity tests were performed. Viral counts were performed and presented as cycle threshold.
Bacteria were isolated in sputum for some of the patients, included Klebsiella species, E. Coli, Pseudomonas species, Staphylococcus aureus (methicillin sensitive, methicillin resistant), Acinetobacter species.

Comment 10: Mortality in COVID-19 is multifactorial. Respiratory deterioration is one of them. Thus, only the SF ratio cannot determine all causes of mortality. Many COVID-19 patients in later waves had minimal respiratory involvement but other organ dysfunction especially the coagulation system. How did you predict those cases using the SF ratio?
Reply 10: Thank you for your comment. It is true that some of the patients developed other organ dysfunctions. As our sample size is small, we could not adjust the effect of other organ dysfunctions on mortality. This is one of the limitations of our study and added in the limitation section (L217-218).

Comment 11: I need a bit more details about conservative therapy apart from steroids and antivirals. Did you use any proning with HFNC or not? Did you use any mucolytics, or respiratory physiotherapy or not?
Reply 11: Thank you for your comment. The issue of prone positioning with HFNC was discussed in the department at that time, and was not performed as nurses were not confident to take care of patients on prone positioning. Mucolytics were routinely prescribed in oral forms. Respiratory physiotherapy was not performed to some patients infected with COVID-19, especially those on respiratory support, due to inadequate manpower.

Comment 12: Also, apart from respiratory failure, did you see any other organ dysfunction or not?
Reply 12: Thank you for your comment. Some of our patients had other organ dysfunction including – 60% had acute kidney injury (>80% stage 1), 20% required low dose vasopressor, 30% had mild thrombocytopenia.

Comment 13: I can see possibly because of ward-level care you used SpO2 as a monitor of oxygenation. But this is very unreliable in critically ill patients with SpO2 below 85% and those with poor peripheral perfusion. Can I know why an arterial line was not inserted in moderate to severe cases especially those who were not improving with the initial plan of management?

Reply 13: Thank you for your comment. Nurses outside ICU do not care arterial line, which may pose risk to patients in general ward setting. When arterial blood gas is checked, arterial puncture is performed by doctor. At the time of Omicron outbreak in Hong Kong, there was not enough nurses and intensivists to convert general ward setting into critical care beds. This is added to the limitation section (L218-222).

Comment 14: Many repetitions are seen in basic demographics as well as hospitals' restructuring to deal with Omicron's surge. Limit them to a minimum in the introduction section.
Reply 14: Thank you for your comment. The introduction section is revised as suggested.

Comment 15: Start the discussion with the most positive and negative findings of your study than a general discussion of the covid surge.
Reply 15: Thank you for your comment. The discussion section is revised as suggested. Please see the discussion section.

Comment 16: Recruitment and exclusion part should be discussed in the result section, not in the discussion section.
Reply 16: Thank you for your comment. The result section is changed as suggested (118-121).

Comment 17: Discussion section should be more of comparative, argumentative, and scientific than a general descriptive one. You have to defend your findings with other similar or correlated studies. Refrain from personal expert comments unless essential in defending your findings.
Reply 17: Thank you for your comment. The discussion section is revised as suggested. Please see the discussion section.

Strengths:

Good initiative was taken to see the feasibility of using HFNC in caring for patients with COVID pneumonia. But is there anything new in this? I doubt.

Weakness:
1. Retrospective observational study with the obvious risk of bias.
2. I am confused here whether this can be called a study of just case series with posthoc group division between survivors and non-survivors.
Reply: Thank you for the comment. The study design of this study is to retrospectively review 28-days mortality of a group of patients with severe COVID-19 infection supported by HFNC out of ICU during the 5th wave of COVID-19. Statistical analysis is performed to evaluate the potential predictors for 28-days mortality. This is not a case series with simple description of the patients. Therefore, it is more appropriate to

describe our study as a retrospective cohort study instead of a case series.

3. Several details missing about conservative care.

Reply: Thank you for the comment. I am sorry that I could not find the part mentioned as “conservative care” in my manuscript

4. Few confusions about the use of risk stratification scores.

Reply: Thank you for the comment. Abbreviations of the scores are added and is no longer confusing.

5. Discussion section is the most poorly written.

Reply: Thank you for the comment. Discussion part is re-written.

Areas of improvement:

6. Avoidance of repetitions of basic and unnecessary details.

Reply: Thank you for the comment. Those details were re-written.

7. Refinement of English language.

Reply: Thank you for the comment. The article is refined by English fluent colleague

8. Discussion should be written in a more scientific, argumentative, and logical way to defend results.

Reply: Thank you for the comment. Discussion part is re-written.

9. Uniqueness of this study should be clarified.

Reply: Thank you for the comment. This study is unique in providing evidence to clinician that “Serial monitoring of SpO_2:FiO_2 ratio can be helpful to decide on therapy continuation in outbreak situations when medical resources are limited”

Reviewer B

We thank the author for this study which evaluated the high flow nasal canula (HFNC) outside intensive care units (ICU) in conventional wards for patients infected with SARS-CoV-2.

General comment:

The writing is not rigorous: not all results are presented using the mean AND the standard deviation, not all abbreviations are defined, and many sentences are starting with a number in a numeric format. Number below ten should be written in letter. Some formulation seems to not be “English standard”: did the authors asked an English language service to copyedit the manuscript?

Reply: Thank you for the comment. Table 1 is revised; mean and standard deviation of patients’ age are shown. Ages of the 2 groups are compared by student’s t-test and indicated in the table.

Abstract:

Comment 1: To me, the introduction is too long. I’d prefer more methodology details.

Reply 1: Thank you for the comment. Method section and introduction section are changed as suggested. The study design of retrospective cohort study and exclusion criteria are added in the method section (L70-75).

Comment 2: L7+8: could be reformulated to better understand that the fifth wave in Hong-Kong (HK) was starting at 2022.
Reply 2: Thank you for your comment. The statement is revised (L5-7).

Comment 3: L14: 2 in letter, HA not defined
Reply 3: Thank you for your comment. HA is defined (L93).

Comment 4: L18: sentence starting with a number
Reply 4: Thank you for your comment. L15 is revised.

Introduction:
Comment 5: L48: needs some referend to the high transmissibility of Omicron variant
Reply 5: Thank you for the comment. Reference (4) is added.

Comment 6: L53: outcome? or survival or (survival and comfort of care)
Reply 6: Thank you for your comment. The outcome is 28-days mortality and L65 is revised.

Comment 7: L52-56: I would reformulate: because the WHO proposed the HFNC as a treatment of ARDS, HK provided some HFNC to hospitals.
Reply 7: Thank you for your comment. L52 is revised.

Comment 8: L59: you should better justify why you did this: 1) you have not enough ICU beds, 2) the HFNC outside ICU or outside the hospital has been evaluated (several references exist), 3) but only a few studies with a few patients. That is why you conducted your study.
Reply 8: Thank you for your comment. L53-63 is revised.

Methods:
Comment 9: The primary outcome to answer the primary objective is not defined, as well as the inclusion/exclusion criterions. Missing data are not evaluated, even in appendix.
Reply 9: Thank you for your comment. Primary outcome refers to 28-days mortality. All patients suffered from COVID-19 received HFNC support outside the ICU during the study period were recruited. Patients received HFNC support for acute hypoxemic respiratory failure were included. Patients received HFNC support for other reasons, e.g. weaning from invasive ventilator support, were excluded.
Missing data is handled by listwise deletion in data analysis and this is added in footnote of Table 1.

Comment 10: L77: You defined lower which patients required HFNC, but you did not define the AHRF. We need summary of clinical criterions for a patient to be considered as in AHRF.
Reply 10: Thank you for the comment. HFNC was indicated when patient

required >4L/min oxygen to maintain SpO2 ≥92%. It is mentioned in L62-63.

Comment 11: L79: You did not mention the ROX index. Even if you say later that the RR was not enough reported, if you planned to study it: you should mention it. Then calculate the number of missing variables and do not conclude on there were too much missing data.
Reply 11: Thank you for the comment. We did not intend to capture ROX index when we design the study. It is discussed in L184-190 and L218-222.

Results:
Comment 12: L119-122: I do not know if patients are excluded or not (same in figure 1). Should be specified.
Reply 12: Thank you for your comment. L117-121 and Figure 1 are revised.

Comment 13: L125: I would prefer the sex-ratio. Continue variables should be presented with mean (standard deviation).
Reply 13: Thank you for your comment. Table 1 are revised.

Comment 14: L126: CT not defined. Beginning the sentence with a number make it not understandable.
Reply 14: Thank you for the comment. L117 and CT (L130) are defined.

Comment 15: L129-130: to me DNI order implies DNACPR order, maybe only the DNI category is necessary.
Reply 15: Thank you for your comment. For our corporate guideline on end-of-life care, do-not-intubate order and do-not-attempt cardiopulmonary resuscitation order are different and thus both are included in our data.

Comment 16: L134: CXR not defined
Reply 16: Thank you for the comment. CXR (L85) is defined.

Comment 17: L138: cytobacteriological examination of sputum
Reply 17: Thank you for your comment. The term (L128) is revised.

Comment 18: L142: I do not understand what the “index hospital admission” is. Should be defined above.
Reply 18: Thank you for your comment. The index admission refers to the hospital admission episode when patient received HFNC support for the COVID-19 infection.

Discussion:
Comment 19: L190: this result is not presented in the result section; therefore, it shouldn’t be discussed. I suggest describing it above as I find this interesting.
Reply 19: Thank you for your comment. The serial changes in SF ratios of survivors and non-survivors were mentioned in L141-146.

Comment 20: L207: the ROX section should be inserted in this section
Reply 20: Thank you for your comment. ROX is discussed in L184-190.

Conclusion:
Comment 21: L216: I would propose "If excluded from standard ICU management, the HFNC could be proposed. Our study showed a statistically significant correlation between lower SF ratio at 2, 24, 48 and 72 hours after starting HFNC and increased 28 days mortality of COVID-19 patients. Monitoring the SF ratio helps to identify patients who may not benefit prolonged HFNC support: decreasing SF is significantly correlated to a higher mortality."
Reply 21: Thank you for your comment. L225-231 is added.

Comment 22: Table 1: Contrary to your plans described in methods, the continuous variables are discretized and compared using a Chi-2 test instead of using the mean comparison with a Student t-test (or a Mann-Whitney considering the size of groups). I really would prefer the mean (standard deviation) and t-test.
Reply 22: Thank you for your comment. Table 1 is revised as suggested. Means and standard deviations of the age of the whole cohort, non-survivors and survivors are added. Ages of the 2 groups were compared by student's t test.

Comment 23: Figure 1: the exclusion should me specified
Reply 23: Thank you for your comment. Figure 1 is revised.

Comment 24: Figure 2: we do not understand the figure as there is no Y label, we do not understand what the numbers are.
Reply 24: Thank you for your comment. Y axis is labelled as the SF ratio.

Comment 25: Figure 3a+b: they should be concatenated on the same figure : 1 figure 2 curves.
Reply 25: Thank you for your comment. Figure 3a and 3 b are combined.

Reviewer C

Major comments
Abstract
Comment 1: P1L13: The authors stated that "this study is to assess the effectiveness of HNFC". But, this study did not set up a control respiratory management group and did not examine vital signs before and after HFNC, I think it is better to note correctly that assess the feasibility, not effectiveness.
Reply 1: Thank you for your comment. After discussion in our group, we agree replacing effectiveness with feasibility as depicted in L25 and L225.

Comment 2: P1L32: "Use of HFNC therapy benefits patients". How did you come to this conclusion?

Reply 2: Thank you for your comment. The aims of the study are to evaluate the feasibility of using HFNC treatment for COVID-19 patients with AHRF in non-COVID-19 settings and explore the potential predictors of mortality in our cohort. If frail patients are excluded from standard ICU management, then HFNC could be proposed. Our study showed a statistically significant correlation between lower SF ratio at 2, 24, 48 and 72 hours after starting HFNC and increased 28 days mortality of COVID-19 patients. Monitoring the SF ratio helps to identify patients who may not benefit prolonged HFNC support. It allows time for observation of the prognosis of the patient by monitoring simple bedside physiological monitoring, i.e. SF ratio. Therefore, we conclude that use of HFNC therapy benefit the patients. However, further study is need to evaluate the mortality benefit by comparing the effectiveness of HFNC therapy and conventional treatment.

Comment 3: P1L36: "HFNC therapy is futile and withdrawal may be considered". The palliative effect of HFNC has been indicated in several studies. We believe that stepping down from HFNC to conventional oxygen therapy is a courageous decision in patients who are predicted to fail HFNC. Were there any patients who made that choice in the cohort in this study? If not, we do not favor this conclusion.
Reply 3: Thank you for your comment. Patients in our cohort were frail and many of them were cared in elderly home. For some of them, there were discussions of care plan with family before hospitalization. Consensus with family were made for a few patients and HFNC was withdrawn when they continued to deteriorate with HFNC support.

Method
Comment 4: What is the definition of HFNC failure in this study? Did any patients in this cohort step up from HFNC to NIV or IMV? Are patients who die from other organ causes after respiratory failure improves and weaning from HFNC classified as HFNC failure? Please clarify the definition of HFNC failure.
Reply 4: Thank you for your comment. The term HFNC failure is changed to non-survival, which is more specific as our secondary outcome. It is revised in L66.

Results
Comment 5: Table1: I think that providing characteristics of patients of the whole population will help us to understand the characteristics of the cohort. Please add.
Reply 6: Thank you for your comment. Table 1 is revised and characteristics of the whole group of patients are shown.

Comment 6: I cannot understand the meaning of Figure2 well. Does this really mean "if there is no significant improvement in SF ratio at 48 hours or 72 hours, the patient would most likely die"? I think this figure is just saying that the SF ratio of the failure group is significantly lower than that of the success group, not a test that patients without improvement are more likely to die. Also, does this adjust for the p-value? I am concerned about multiple testing.

Reply 6: Thank you for your comment. Figure 2 is a Box and whisker chart showing the SF ratio over time for non-survivors and survivors. The SF ratios at 2 hours, 24 hours, 48 hours 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) by student's t-test. This is comparison of SF ratio between 2 different time points instead of multiple setting. Therefore, no adjustment of the p-value is needed. The results showed for non-survivors, there is no significant difference of the SF ratios at different time points compared with the baseline while SF ratios were signficiantly higher than the baseline at 48 hours and 72 hours in the survivors.

Comment 7: Were any healthcare workers involved in the care of HFNC patients infected with COVID-19? Transmission of SARS-CoV-2 infection by HFNC is a major concern, please add any information if you have it.
Reply 7: Thank you for your comment. As HFNC was implemented during fifth wave, some healthcare workers contracted SARS-CoV-2 infection, including those looking after patients with or without HFNC support. It would be difficult to differential whether their infections were related to their work, as contact tracing was not able to be carried out then.

Comment 8: Please provide odds ratios as well as p-values for the association between SF ratio and HFNC failure. This will assist the reader in understanding the performance of the SF ratio as a predictor.
Reply 8: Thank you for your comment. This is an observation of difference in the change of the SF ratios in the non-survivors and the survivors. Therefore, the changes in the 2 group are compared using the student's t-test. The performance of this observation is better evaluated by using a ROC curve instead of an odds ratio at a particular cut off of a SF ratio.

Comment 9: Please also add the area under ROC for the presented ROC curves.
Reply 9: Thank you for your comment. The areas under ROC curve (AUC) are added (Fig. 3).

Discussion
Comment 10: The lack of respiratory rate and the inability to use the ROX index is a major weakness of this study. However, I think the feasibility of SF ratio as a predictive tool could be strengthened by noting that respiratory rate is sometime inaccurately recorded by health care providers (BMJ Quality & Safety 2017;26:832-836.) and that a previous study has examined the performance of the SF ratio as a predictor of HFNC failure (Ther Adv Respir Dis. 2020 Jan-Dec;14:1753466620906327.) in the discussion section.
Reply 10: Thank you for your comment. The discussion section is revised as suggested (L185-190).

Comment 11: A major weakness of this study is the lack of a validation cohort; please

include this in the main text as a limitation.
Reply 11: Thank you for your comment. The limitation section is revised as suggested (L216-217)

Minor comments
Comment 12: P1L7: “COVID-infected patients”. I think that “COVID-19 infected patients” is correct.
Reply 12: Thank you for your comment. The term is revised as suggested (L8).

Comment 13: P1L8: “the HK population”. What is HK? Please give the full name of the abbreviation for the first time.
Reply 13: Thank you for your comment. HK is defined (L6).

Comment 14: P1L14: “2 hospital of HA”. What is HA?
Reply 14: Thank you for your comment. HA is defined (L93).

Comment 15: In main text, the 2 in SpO2 should be a subscript. SpO2.
Reply 15: Thank you for your comment. Revision is made.