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What can we Learn from Patients who Died from Covid-19 Following Escalation to a Respiratory High Dependency Unit for Trial of Non-Invasive Respiratory Support?

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Abstract

Background: Covid-19 infection is associated with significant risk of death, particularly in older, comorbid patients. Emerging evidence supports use of non-invasive respiratory support (CPAP and high-flow nasal oxygen [HFNO]) in this context, but little is known about its use in patients receiving end-of-life care. **Methods:** This was a retrospective study of 33 patients who died of Covid-19 on the Respiratory High Dependency Unit at the John Radcliffe Hospital, Oxford between 28/03/20 and 20/05/20. Data was sourced via retrospective review of electronic patient records and drug charts. **Results:** Patients dying from Covid-19 on the Respiratory HDU were comorbid with median Charlson Comorbidity Index 5 (IQR 4-6); median age 78 (IQR 72-85). Respiratory support was trialled in all but one case with CPAP being the most common form of first line respiratory support (84.8%) however, was only tolerated in 44.8% of patients. Median time to death was 10.7 days from symptom onset (IQR 7.5-14.6) and 4.9 days from hospital admission (IQR 3.1-8.3). 48.5% of patients remained on respiratory support at the time of death. **Conclusions:** End-of-life care for patients with Covid-19 remains a challenge. Patients tend to be frail and comorbid with a rapid disease trajectory. Non-Invasive Respiratory Support may play a key role in symptom management in select patients, however, further work is needed in order to identify patients who will most benefit from Respiratory Support and those for whom withdrawal may prevent unnecessary distress at the end of life or potential prolongation of suffering.

Keywords

Covid-19, palliative care, continuous positive airway pressure, high flow nasal oxygen, non invasive ventilation, respiratory medicine

Introduction

Managing patients with Covid-19 infection has created unprecedented challenges for healthcare systems around the world. With an estimated overall mortality of between 1% and 3%,[1] healthcare teams are gaining knowledge on which patients need admission to acute care, which patients require escalation to high dependency units (HDUs) and intensive care support; in which patients symptom management should be prioritised (in all settings) and when to de-escalate care and focus on symptom control at the end of life.[2]

Emerging evidence has supported the use of non-invasive respiratory therapies for patients with severe disease.[3] In the UK there is the capacity to support older and frailer patients in respiratory HDUs, who are not candidates for Intensive Care treatment. This will have unintended consequences, including the possibility of prolonging death in some patients in whom the disease is not survivable. In the case of a pandemic, it is likely that such patients will die without the support of those that are important to them and in a more frightening environment, as staff use extensive personal protective equipment.

While the experience of palliative care teams in the care of patients with Covid-19 has been described,[6] there is limited documentation of the experience of teams caring for awake patients requiring respiratory support at the end of life. It is imperative to learn from this experience in order to address and mitigate unintended consequences. We therefore conducted a retrospective study of patients who died from Covid-19 on the respiratory HDU at the John Radcliffe Hospital, Oxford, to identify potential lessons that may shape future practice.

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Methods

Study Design

Setting. This was a retrospective audit of patients who died on the Respiratory HDU of the John Radcliffe Hospital between 28/03/20 and 20/05/20 during the first wave of Covid-19 infection in the United Kingdom. This unit was established in order to provide specialised respiratory care and non-invasive respiratory support (most commonly High Flow Nasal Oxygen [HNFO] and Continuous Positive Airway Pressure [CPAP]) outside of an intensive care setting. It was closely supported by a seven day hospital Palliative Care service, providing both remote and in-person clinical reviews.

Patients were transferred from within the hospital, or other local hospitals, if they had increasing oxygen requirements or an absolute oxygen requirement of FiO2 >40% or >8L/min via face mask. This included patients who were for escalation to ICU and those in whom the ceiling of care was non-invasive ventilation on the high dependency unit. Treatment Escalation Plans (TEPs) were documented using a standardised trust-wide proforma, introduced as part of the Covid-19 response and were used to ensure patients received appropriate care while carefully defining ceilings of treatment early in admission.

Patient Population

Patients were included if they were over 18 years old and their primary cause of death was Covid-19. This included patients who tested negative on nasopharyngeal swab PCR but had clinical and radiological evidence of infection as determined by a respiratory consultant physician. Patients transferred to ICU prior to death were excluded.

Data Collection and Analysis

Data collected included: demographic and comorbidity data; timing of symptom onset and disease course; use of respiratory support; community and hospital Advance Care Planning; palliative care input, medication use and communication with families. Data was sourced via retrospective review of electronic patient records and drug charts. Each patient record was reviewed by one researcher and the data collected was analysed by two members of the team. Charlson Comorbidity Index[9] was calculated based on medical records and frailty was assessed using the Clinical Frailty Scale, CFS.[10] Tolerance of respiratory support was assessed based on nursing and medical documentation of compliance with wearing of facemasks or nasal cannulae; patient's expressed wishes and requirement for PRN medications.

Ethical Considerations

This was a study of departmental practice and was registered with the hospital's Quality Improvement department. No ethical approval or patient consent was required. Anonymised data collected for the purposes of the study was stored on secure hospital servers.

Results

In total, 84 patients were admitted to the Respiratory HDU between 28/03/20 and 20/05/20. 19 patients (22.6% of admissions) received no respiratory support aside from simple oxygen; of these 18 were discharged alive and 1 died on the unit. 65 patients (77.4% of admissions) received non-invasive respiratory support in the form of HFNO, CPAP or NIV. Of these, 16 were discharged from hospital alive and 17 required intubation and transfer to ICU (20.2% of total admissions). Of those intubated, 4 died on ICU and the remainder survived to discharge. 32 patients receiving respiratory support and 1 with no respiratory support died on the unit. In total 37 patients, (44% of admissions) died from Covid-19 on HDU or ICU during the specified time period (Figure 1).

Aside from 1 patient, who declined trial of non-invasive respiratory support on arrival to the unit, patients were escalated to non-invasive respiratory support based on oxygen requirements and disease trajectory. Those patients receiving respiratory support were found to have a significantly lower CFS[10] Score than those in whom respiratory support was not required (2 [IQR 2-3] vs. 4 [2-5], $p < 0.01$); otherwise no significant differences were found between the two groups (Table 1).

Of the 33 patients who died on the unit, 78.79% ($n = 26$) were PCR positive; the median age was 78 (IQR 72-85) and the majority were male (70%, $n = 23$) (Table 2). The most common comorbidities were hypertension (48.5%), chronic respiratory disease (39.4%) and cardiovascular disease (36.4%). Median Charlson Comorbidity Index[9] was 5 (IQR 4-6), associated with a 21% estimated 10-year-survival. Median CFS[10] score was 4 (IQR 3-6) equating to a 'vulnerable' state, with symptoms often limiting activities. The group of patients who died on the unit, were found to be significantly older than those who survived (median age 57 [IQR 48-69.5, $p < 0.01$] or were intubated [median age 57 [IQR 52-63], $p < 0.01$]; with significantly higher Charlson Comorbidity Index and CFS[10] scores [see Table 3].

The remainder of the results section will examine outcomes for the 33 patients who died from Covid-19 on the Respiratory HDU between the specified dates.

The median time from symptom onset to hospital admission was 3.9 days (IQR 2.8-6.8), while the median time from hospital to HDU admission was 1.3 days (IQR 0.2-2.4). Median time to death was 4.9 days from hospital admission (IQR 3.1-8.3) (see Figure 2).

12.1% ($n = 4$) had a Do Not Attempt Cardiopulmonary Resuscitation Decision (DNACPR) prior to hospital admission; of these 1 patient additionally had a formalised Advance Care Plan (ACP). In total, 72.7% of patients ($n = 24$) had a DNACPR and 84.85% of patients ($n = 28$) had a TEP prior to HDU admission. All patients had a DNACPR order prior to death.

Of those patients receiving respiratory support, CPAP was trialled first in 87.9% of cases ($n = 29$), but was only tolerated in 44.8% of cases ($n = 13$) (Table 4). Of those who did not tolerate CPAP, 100% ($n = 16$) were escalated to HFNO (Figure 2).

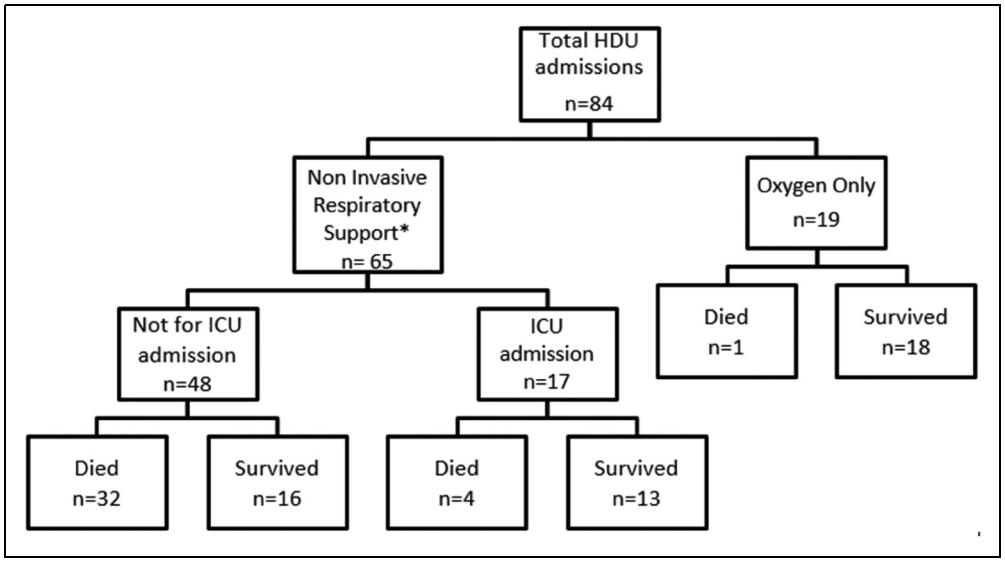

Figure 1. Outcome of patients admitted to respiratory HDU between 28/03/20 and 20/05/20.

Table 1. Demographics of Patients Receiving Respiratory Support on HDU Compared to Those Receiving Simple Oxygen Therapy Alone.

	Resp Support ($n=65$)	No Resp Support ($n=19$)	P value
Median age (IQR)	71 (56-80)	61 (57-79)	0.61
Male %	69.2 (45)	63.2 (12)	0.71
Clinical Frailty Scale[10] (median, IQR)	2 (2-3)	4 (2-5)	<0.01
Charlson Comorbidity Index (median, IQR)	3 (2-3.5)	3 (2-5)	0.226
Number of Comorbidities (median, IQR)	2 (1-2.5)	2 (1-4)	0.47
Hypertension %	47.7% ($n=31$)	47.4% ($n=9$)	>0.05
Chronic Lung Disease %	35.4% ($n=23$)	26.3% ($n=5$)	>0.05
Diabetes Mellitus %	30.8% ($n=20$)	21.1% ($n=4$)	>0.05
Cardiovascular Disease %	21.5% ($n=14$)	31.6% ($n=6$)	>0.05

Table 2. Demographics of 33 Patients who Died on Respiratory HDU Between 01/04/20 and 24/05/20.

	$N=33$
Median Age (IQR)	78 (72-85)
Male %	69.7 ($n=23$)
Number of Comorbidities median (IQR)	3 (1-4)
Hypertension %	48.5 ($n=16$)
Diabetes Mellitus %	27.3 ($n=9$)
Cardiovascular Disease %	36.4 ($n=12$)
Chronic Lung Disease %	39.4 ($n=13$)
Asthma %	9.1 ($n=3$)
Chronic Obstructive Pulmonary Disease %	15.2 ($n=5$)
Interstitial Lung Disease/ sarcoid %	12.1 ($n=4$)
Chronic Kidney Disease %	24.2 ($n=8$)
Immunosuppression %	12.1 ($n=4$)
Autoimmune disease %	3.0 ($n=1$)
Stroke %	12.1 ($n=4$)
Other %	30.3 ($n=10$)
Charlson Comorbidity Index median (IQR)	5 (4–6)
Clinical Frailty Scale[10] median (IQR)	4 (3–6)

Of note, of those patients who survived following trial of respiratory support on HDU, 29 were initially commenced on CPAP, of whom 69.0% ($n=20/29$) tolerated therapy. Successful proning, defined as >2 hours on 2 consecutive days, was achieved in one patient while 33.3% ($n=11/33$) tolerated semi-proning. Overall, 48.5% of patients ($n=16$) remained on respiratory support at the time of death: the reasons for this included ongoing active treatment ($n=8$), respiratory distress on weaning ($n=6$), awaiting further family discussions ($n=1$) and was undocumented in one case.

The risk of death was recognised and documented in 100% of cases, while a decision to stop active treatment was documented in 72.7% of cases ($n=24$). The median time from documented decision to death was 21.5 hours (IQR 9.75-44.5). Assessment of physical symptoms in the dying phase was documented in 69.7% of cases ($n=23$), whereas emotional and psychological needs were assessed in 18.2% ($n=6$) and spiritual needs in 18.2% ($n=6$).

Anticipatory 'as required' (PRN) medications were prescribed in 93.9% of cases ($n=31$) and 60.6% ($n=20$) of

Table 3. Comparison of Patients Receiving Respiratory Support Based on HDU Admission Outcome.

	Survived ($n=16$)	Intubated ($n=17$)	Died ($n=32$)
Median age (IQR)	57 (48-69.5)	57 (52-63) $p=0.91$	78.5 (72-85.3) $p<0.01$
Male %	75 ($n=12$)	58.8 ($n=10$) $p=0.17$	68.8 ($n=22$) $p=0.33$
Clinical Frailty Scale median (IQR)	3 (2-4)	2 (2-3) $p=0.46$	4 (3-6) $p<0.01$
Charlson Comorbidity Index median(IQR)	2 (1-4)	2 (1-3) $p=0.64$	5 (4-6) $p<0.01$
Number of Comorbidities median (IQR)	2 (1.75-3.25)	2 (1-3) $p=0.54$	3 (1-4) $p=0.67$
Hypertension %	50 (n = 8)	47.1 ($n=8$) $p>0.05$	50 ($n=16$) $p>0.05$
Diabetes Mellitus %	43.8 (n = 7)	29.4 ($n=5$) $p>0.05$	34.4 ($n=11$) $p>0.05$
Chronic Lung Disease %	37.5 (n = 6)	29.4 ($n=5$) $p>0.05$	25 ($n=8$) $p>0.05$
Cardiovascular Disease %	12.5 (n = 2)	5.8 ($n=1$) $p>0.05$	40.6 ($n=13$) $p>0.05$

*Statistical analysis of groups who were intubated/ died as compared to those who survived.

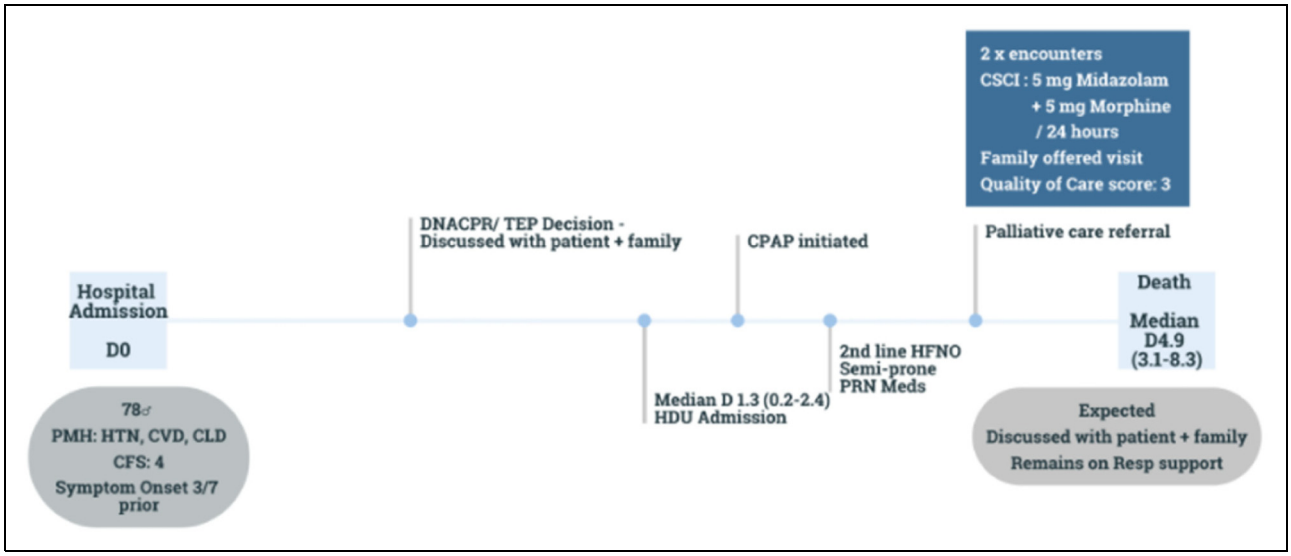

Figure 2. Average timeline of patients admitted to respiratory HDU between 28/03/20 and 20/05/20 (median [IQR]).

patients were commenced on a continuous subcutaneous infusion (CSCI). The most commonly prescribed CSCI medications were morphine (85%, $n=17$) and midazolam (85%, $n=17$). The median total dose of benzodiazepine (midazolam or lorazepam) in the 24 hours prior to death was 5mg (IQR 0-10; oral diazepam equivalent 10mg/24 hours) while median dose of opioid, subcutaneous morphine equivalent, was 5mg (IQR 2.03- 12.36; oral morphine equivalent 10mg/24 hours).

A referral to Palliative Care was made in 45.5% of cases ($n=15$), most commonly for 'support at the end of life' (66.7%, $n=10$). Of all palliative care referrals, 40% ($n=6$) were made within 24 hours of death. The median number of encounters with palliative care services per patient referred was 2 (IQR 1-3). 62.5% ($n=20$ out of a total of 32 encounters) were in person, either with a Clinical Nurse Specialist 59.4% ($n=19$) or a consultant palliative care physician.

Patients referred to the palliative care team were more likely to have a CSCI prescribed (80% $n=12$, vs. 44% $n=8$) although this did not reach clinical significance $p>0.05$); of these 66.7% ($n=8$), were prescribed after referral to the team. Those referred received significantly higher total doses of benzodiazepines in the 24 hours prior to death (9.17mg, IQR 4.18-10), versus 1.36 IQR 0–7.08mg $p<0.05$) and were significantly more likely to have unnecessary interventions discontinued (73.3% vs. 33.3%, $p<0.05$).

Family members were offered the opportunity to visit patients in 78.8% of cases ($n=26$), and half of relatives accepted (50%, $n=13$); however, of those who did not visit, 38.5% ($n=5$) were able to speak to the patient via Skype. Of those who accepted, 10 (76.9%) visited within 24 hours of death and 7 (53.8%) were present at the time of death.

Discussion

The Respiratory HDU at the John Radcliffe was developed in order to create a safe environment for administration of non-invasive respiratory support to patients both for full escalation and ward based ceilings of care. Over time, respiratory support has become standard practice for patients with high or escalating oxygen requirements in the context of Covid-19

Table 4. Use of Respiratory Support in Patients who Died on Respiratory HDU.

First Respiratory Support		%	Tolerated, %
	CPAP	87.9 ($n=29$, including 1 patient on wall CPAP)	44.8 ($n=13$)
	NIV [a]	6.1 ($n=2$)	50 ($n=1$)
	HFNO [b]	3.0 ($n=1$)	100 ($n=1$)
	None	3.0 ($n=1$)	N/A
Escalation to Second Respiratory Support %		66.7 ($n=22$)	
Indication	Poorly Tolerated	72.7 ($n=16$)	
	Hypoxia	13.6 ($n=3$)	
	Palliation	9.1 ($n=2$)	
	Mixed acidosis	4.5 ($n=1$)	
Second Respiratory Support %			
	HFNO [b]	81.8 ($n=18$)	
	Wall CPAP	13.6 ($n=3$)	
	NIV[1]	4.5 ($n=1$)	
Peak FiO2 (median, IQR)		90 (75, 95)	
Successful Proning % *		3.0 ($n=1$)	
Successful Semi-proning %		37.9 ($n=11$)	
Resp Support at Time of Death %		48.5% ($n=16$)	

* Defined as >2 hours on 2 consecutive days [a] Non Invasive Ventilation [b] High Flow Nasal Oxygen.

infection however, limited data currently exists to support decision making regarding its use at the end of life.

Respiratory Support

While breathlessness has been described as the most common symptom in advanced Covid-19,[7,11] it is unclear whether non-invasive respiratory support provides symptomatic relief at the end of life. CPAP was only tolerated in 44.8% of cases despite intensive physiotherapy and nursing support and pharmacological intervention. Comparable tolerance rates are not available for similar palliative populations, however, previous studies describing patient experience of non-invasive respiratory support have described mask discomfort and sensation of increased breathlessness due to high airflows as key factors in patient experience.[12] Poor tolerance may be exacerbated by agitation, described as the second most common symptom of advanced Covid-19[7,13,14] and likely to be prevalent in this frail, elderly population. While HFNO may be better tolerated, it is not thought to provide any treatment benefit over simple oxygen in the management of Covid-19[15] and was therefore used as second line therapy.

While we cannot comment fully on improvement in breathlessness in this population; non-invasive respiratory support appeared to provide symptomatic benefit in a proportion of patients as demonstrated by the fact that 6 patients remained on respiratory support at the time of death due to expressed wishes or increased distress on attempted weaning. While there is an emerging body of evidence supporting use of non-invasive respiratory support in the palliative management of several conditions,[16] including advanced cancer,[17,18] COPD[19] and neuromuscular disease;[20] use in the terminal phase of these illnesses has not been well described and therefore may not be directly applicable to patients experiencing the rapid trajectory seen in Covid-19. More objective evidence is needed in this area.

Lack of prognostic data and rapid trajectory from symptom onset to death in Covid-19 raises several challenges for treating teams. This was highlighted by the fact that 8 patients continued respiratory support as part of active treatment at the time of death, despite the fact that risk of death had been identified and discussed and anticipatory medications prescribed in all but one of these patients. Aside from use with potentially curative intent, additional benefits of continuing non-invasive respiratory support in certain patients included allowing relatives time to visit or aiding communication with families[21] which, as we have demonstrated was particularly challenging in the HDU setting with only 50% of relatives feeling able to visit relatives, even at the end of life.

Proning

There is a growing body of evidence which supports the use of awake proning outside of the ICU in reducing oxygen requirements and respiratory rate.[22,23] However, we found that very few of our patients were able to tolerate proning and in several cases it was documented to cause discomfort and increase patient distress suggesting careful consideration should be given before its use at the end of life. The nature of the relationship between inability to tolerate proning and poor prognosis is not yet clear and further work is needed in this area.

Advance Care Planning

Recommended Summary Plan for Emergency Care and Treatment (ReSPECT) is not yet used in Oxfordshire. Use of advance care plans has been highlighted as a key element of care in the COVID-19 pandemic[24] and TEPs were developed in the hospital at the start of the pandemic in order to ensure appropriate triage of patients with Covid-19 on admission to hospital. We found that both patients and families were generally receptive to treatment escalation discussions and formalisation of this process meant decisions were made by parent teams, relieving some of the burden of decision making on individual staff in a high turnover environment.

Despite this, we noted that there was limited exploration of patient's premorbid beliefs, wishes and spiritual needs prior to death. Rapid illness trajectory and limited prognostic information meant that patients were often in an advanced stage of disease when decision to withdraw active treatment or referral to palliative care team was made. Given the success of TEPs described above, more work is needed in order to consider how earlier discussions identifying holistic care needs could

be incorporated into this process, particularly as risk of dying is often recognised early in the admission.

Referral to Palliative Care Teams

Palliative Care teams were often involved in supporting management of patients with complex symptomatic needs, both pharmacologically and holistically, exploring patient and family wishes and expectations when possible. Beyond basic training in use of personal protective equipment; the rapidly evolving situation meant that no specific training was initially available in the adaptation of communication in this context. Given the high demand on the service, standardised Covid-19 specific 'End-of-Life' prescribing protocols were developed, meaning that referral was often reserved for more complex patients and is likely to explain the relatively late referral to services.

Following death, a member of the bereavement team met with family members virtually and sign-posted additional services.

Prescribing Symptom Control Measures

Low doses of morphine and midazolam were required at the end of life. This has been reported by several other studies in COVID-19 infection.[6,7,13] However, the doses reported here (5mg of morphine and 5mg of midazolam) are significantly lower than those reported by Turner et al.[6] Furthermore, they are also lower than the average doses used throughout the hospital when both HDU and non-HDU deaths were included (10mg of morphine and 10mg of midazolam). Given that breathlessness has been well documented as the predominant symptom in the late stages of COVID-19 infection,[7,11,13] it is possible that low medication requirements in this group may at least be partially accounted for by the use of respiratory support, or at least that its use did not increase distress. However, without objective symptom assessment methods, the possibility of inadequate dosing cannot be excluded: further research on the use of medications alongside respiratory support to control symptoms in patients with Covid-19 is required.

Limitations

This work was derived from a retrospective dataset, meaning that conclusions cannot be drawn on the effect of Non-Invasive Respiratory Support on symptom burden. Further prospective studies using validated breathlessness scores would help differentiate this further.

Conclusions

End-of-life care for patients with Covid-19 remains a challenge. Patients tend to be frail and comorbid with a rapid disease trajectory. While there is a growing body of evidence supporting use on non-invasive respiratory support in severe infection, there is limited data regarding its use at the end of life. While it appears that in certain patients non-invasive respiratory support can provide symptomatic benefit, this work suggests that poor tolerance may itself be a poor prognostic sign. We would suggest that in those patients, who are not for escalation and who do not respond to simple pharmacological measures to improve tolerance, careful consideration should be given as to whether the benefits of prolonging life via non-invasive respiratory support may be outweighed by the potential increase in distress in the last hours or days of life. Where possible both patients and families should be involved in these discussions.

Author Contributions

SE, MH, WF and NR conceived the original project; SE, PE, AS, NK, MH, MM and RS designed the analysis; data collection by SE, PE, BP and RS; SE, PE and AS performed the analysis; SE and PE wrote the paper with contributions from RS, NK, WF, MH, NR and MM.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

Trial Registration

Not applicable, because this article does not contain any clinical trials.

References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA*. 2020;323-(13):1239. doi:10.1001/jama.2020.2648
2. Heath L , Yates S, Carey M, Miller M. Palliative care during COVID-19: data and visits from loved ones. *Am J Hosp Palliat Care*. Nov 2020;37(11):988-991. doi:10.1177/1049909120943577
3. Agarwal A, Basmaji J, Muttalib F, et al. High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. *Can J Anaesth*. Jun 15 2020.67(9):1-32. Les canules nasales à haut débit pour le traitement de l'insuffisance respiratoire hypoxémique aiguë chez les patients atteints de la COVID-19: comptes rendus systématiques de l'efficacité et des risques d'aérosolisation, de dispersion et de transmission de l'infection. doi:10.1007/s12630-020-01740-2.

4. Zheng Y, Sun LJ, Xu M, et al. Clinical characteristics of 34 COVID-19 patients admitted to intensive care unit in Hangzhou, China. *J Zhejiang Univ Sci B*. May 2020;21(5):378-387. doi:10.1631/jzus.B2000174
5. Oranger M, Gonzalez-Bermejo J, Dacosta-Noble P, et al. Continuous positive airway pressure to avoid intubation in COVID-19 pneumonia: a two-period retrospective case-control study. *Eur Respir J*. 2020;56(2):2001692. doi:10.1183/13993003.01692-2020
6. Turner J, Eliot Hodgson L, Leckie T, Eade L, Ford-Dunn S. A dual-center observational review of hospital-based palliative care in patients dying with COVID-19. *J Pain Symptom Manage*. 2020;60(2):e75–e78. doi:10.1016/j.jpainsymman.2020.04.031
7. Lovell N, Maddocks M, Etkind SN, et al. Characteristics, symptom management, and outcomes of 101 patients with COVID-19 referred for hospital palliative care. *J Pain Symptom Manage*. 2020;60(1):e77-e81. doi:10.1016/j.jpainsymman.2020.04.015
8. Haydar A, Lo KB, Goyal A, et al. Palliative care utilization among patients with COVID-19 in an underserved population: a single-center retrospective study. *J Pain Symptom Manage*. 2020;60(2):e18-e21. doi:10.1016/j.jpainsymman.2020.05.022
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8
10. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489. doi:10.1503/cmaj.050051
11. Keeley P, Buchanan D, Carolan C, Pivodic L, Tavabie S, Noble S. Symptom burden and clinical profile of COVID-19 deaths: a rapid systematic review and evidence summary. *BMJ Support Palliat Care*. Dec 2020;10(4):381-384. doi:10.1136/bmjspcare-2020-002368
12. Beckert L, Wiseman R, Pitama S, Landers A. What can we learn from patients to improve their non-invasive ventilation experience? 'It was unpleasant; if I was offered it again, I would do what I was told'. *BMJ Support Palliat Care*. Mar 2020;10(1):e7. doi:10.1136/bmjspcare-2016-001151
13. Sun H, Lee J, Meyer BJ, et al. Characteristics and palliative care needs of COVID-19 patients receiving comfort-directed care. *J Am Geriatr Soc*. 2020;68(6):1162-1164. doi:10.1111/jgs.16507
14. Hetherington L, Johnston B, Kotronoulas G, Finlay F, Keeley P, McKeown A. COVID-19 and Hospital Palliative Care - A service evaluation exploring the symptoms and outcomes of 186 patients and the impact of the pandemic on specialist Hospital Palliative Care. *Palliat Med*. Oct 2020;34(9):1256-1262. doi:10.1177/0269216320949786
15. Perkins GD, Ji C, Connolly BA, et al. An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19. 2021.medRxiv. :2021.08.02.21261379. doi:10.1101/2021.08.02.21261379
16. Davies JD. Noninvasive respiratory support at the end of life. *Respir Care*. 2019;64(6):701. doi:10.4187/respcare.06618
17. Hui D , Morgado M, Chisholm G, et al. High-flow oxygen and bilevel positive airway pressure for persistent dyspnea in patients with advanced cancer: a phase II randomized trial. *J Pain Symptom Manage*. Oct 2013;46(4):463-473. doi:10.1016/j.jpainsymman.2012.10.284
18. Nava S, Ferrer M, Esquinas A, et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. *Lancet Oncol*. Mar 2013;14(3):219-227. doi:10.1016/s1470-2045(13)70009-3
19. Diaz de Teran T, Barbagelata E, Cilloniz C, et al. Non-invasive ventilation in palliative care: a systematic review. *Minerva Med*. Dec 2019;110(6):555-563. doi:10.23736/s0026-4806.19.06273-6
20. Andersen PM, Abrahams S, Borasio GD, et al. EFNS Guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force. *Eur J Neurol*. Mar 2012;19(3):360-375. doi:10.1111/j.1468-1331.2011.03501.x
21. Koyauchi T, Hasegawa H, Kanata K, et al. Efficacy and tolerability of high-flow nasal cannula oxygen therapy for hypoxemic respiratory failure in patients with interstitial lung disease with do-not-intubate orders: a retrospective single-center study. *Respiration*. 2018;96(4):323-329. doi:10.1159/000489890
22. Chad T, Sampson C. Prone positioning in conscious patients on medical wards: a review of the evidence and its relevance to patients with COVID-19 infection. *Clin Med*. 2020;20(4):e97–e103. doi:10.7861/clinmed.2020-0179
23. Sartini C, Tresoldi M, Scarpellini P, et al. Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. *JAMA*. 2020;323(22):2338. doi:10.1001/jama.2020.7861
24. Curtis JR, Kross EK, Stapleton RD. The importance of addressing advance care planning and decisions about do-not-resuscitate orders during novel coronavirus 2019 (COVID-19). *JAMA*. 2020;323(18):1771. doi:10.1001/jama.2020.4894