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Short communication

Predictors of failure of high flow nasal cannula failure in acute hypoxemic respiratory failure due to COVID-19

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ABSTRACT

Hypoxemic respiratory failure is a common manifestation of COVID-19 pneumonia. Early in the COVID-19 pandemic, patients with hypoxemic respiratory failure were, at times, being intubated earlier than normal; in part because the options of heated humidified high flow nasal cannula (HFNC) and non-invasive ventilation (NIV) were considered potentially inadequate and to increase risk of virus aerosolization. To understand the benefits and factors that predict success and failure of HFNC in this population, we evaluated data from the first 30 sequential patients admitted with COVID-19 pneumonia to our center who were managed with HFNC. We conducted Cox Proportional Hazards regression models to evaluate the factors associated with high flow nasal cannula failure (outcome variable), using time to intubation (censoring variable), while adjusting for comorbidities and immunosuppression. In the majority of our patients (76.7%), the use of HFNC failed and the patients were ultimately placed on mechanical ventilation. Those at increased risk of failure had a higher sequential organ failure assessment score, and at least one comorbidity or history of immunosuppression. Our data suggest that high flow nasal cannula may have a role in some patients with COVID-19 presenting with hypoxemic respiratory failure, but careful patient selection is the likely key to its success.

1. Introduction

The coronavirus disease 2019 (COVID-19) has caused the death of millions of people worldwide [1]. SARS-CoV-2 mainly affects the respiratory system by attaching itself to the angiotensin converting enzyme 2 receptor (ACE2r) on pneumocytes and replicating within that cell population [2,3]. This may lead to acute severe hypoxemia without respiratory distress or to acute respiratory distress syndrome (ARDS) [4–6]. Early recommendations suggested intubation at the first sign of hypoxemia and avoiding non-invasive ventilation (NIV) or high flow nasal cannula (HFNC) due to the risk of viral aerosolization [6,7]. This placed pressure on healthcare systems due to the rapidly contagious nature of the virus and the scarcity of ventilators [8–10]. The controversy surrounding timing of intubation remains; and the deleterious effects of invasive mechanical ventilation (IMV) coupled with the heterogeneity of the pulmonary manifestations of COVID-19 have prompted a rethink of HFNC [11,12].

In a pre-COVID study, HFNC has proven to be non-inferior to NIV or nasal cannula, and may reduce ICU and 90 day mortality [13]. There have been reports of the utilization of HFNC as a maneuver to avoid intubation in COVID-19 and the need for IMV, but the predictors of failure and success remain unknown [14,15]. We examined a cohort of COVID-19 patients with hypoxemic respiratory failure in order to identify predictors of failure and success in those who were placed in HFNC.

2. Material and methods

We performed a single-center, observational study evaluating adult patients admitted to large medical center in Houston, Texas. We reviewed electronic medical records (EMR) of consecutive patients with COVID-19 pneumonia between March 1 and April 28, 2020 and

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included those who utilized HFNC as rescue therapy to avoid intubation.

HFNC was considered successful if the patients did not require intubation and were eventually completely weaned from this modality; whereas patients who were subsequently intubated were considered as failures. Time to intubation was calculated as the first date the HFNC order was placed until the date when the patient was intubated.

Relevant data was extracted from patients identified by EMR using the key words, "heated high flow nasal cannula", "high flow nasal cannula", "humidified high flow nasal cannula", "nasal cannula", "Vapotherm™". Medical records of patients identified to have needed HFNC therapy were examined utilizing other key words, "intubation", "anesthesia", "procedure note", "mechanical ventilation", "ventilation", "ventilator", "ETT", "endotracheal tube". The purpose of this second search was to identify if the patient had been on mechanical ventilation during any point of their hospitalization. The information collected from the patients' records included hospitalization characteristics and socio-demographics such as race/ethnicity, age, BMI and gender; co-morbidities, symptoms, immunosuppressive conditions (cancer, organ transplant, chronic steroid user and/or HIV/AIDS), lab results, oxygenation, ventilation and sequential organ failure (SOFA) scores [16]. The study was performed in accordance with Baylor College of Medicine's (BCM) and Baylor-St. Luke's Medical Center (BSLMC) institutional review board (IRB) requirements.

A bivariate analysis comparing socio-demographic, hospitalization characteristics and HFNC failure using Fisher's exact test was conducted. We also calculated the incidence of HFNC failure among each of the aforementioned characteristics. For comparing lab characteristics and the outcome of HFNC failure, we utilized Independent Samples T-test. Furthermore, after testing the proportionality assumption using Kaplan-Meier survival analyses, we conducted Cox Proportional Hazards regression models to evaluate the factors associated with HFNC failure (outcome variable), using time to intubation (censoring variable), while adjusting for comorbidities and immunosuppression. Type-I error rate was set at 5%. All data analyses were conducted using R (version 3·5·1), RStudio (Version 1·1·423) and NCSS (Version 12.0.4).

3. Results

During the observation period, there were a total of 30 hospitalized patients who ultimately required HFNC, with 23 (76.7%) eventually failing HFNC, requiring MV. The highest proportion of HFNC utilization (failure and success) was in the 61–80 years age group. Among patients who failed HFNC, 60.9% (n = 14) were male, 60.9% obese (n = 14), 52.2% (n = 12) African American. A minority of those observed (34.8%, n = 8) received corticosteroids.

Patients who failed HFNC had a mean average lactate 1.29 mg/dL (SD = 1.42 mg/dL, p = 0.57), lactate dehydrogenase (LDH) 431.87 U/L (SD = 302.46 U/L, p = 0.27), C-reactive protein (CRP) 12.46 mg/L (SD = 10.14, p = 0.30), ferritin was 3,478.69 ng/mL (SD = 8,202.26 ng/mL, p = 0.17) and SOFA score of 6.

Successful HFNC patients were 57.1% female (n = 4, p = 0.39), 42.9% (n = 3, p = 0.41) overweight, were mostly African American (57.1%, n = 4, p = 0.59) and 28.6% (n = 2, p = 0.87) received corticosteroids. The also had a mean average lactate 0.97 mg/dL (SD = 0.72 mg/dL, p = 0.57), LDH 294.29 U/L (SD = 228.88 U/L, p = 0.27), CRP 8.10 mg/L (SD = 8.10, p = 0.30), ferritin was 1082 ng/mL (SD = 1317.55 ng/mL, p = 0.17) and SOFA score - 2.

A Cox proportional hazards regression to evaluate the association between socio-demographic characteristics and comorbidities (exposures) and MV (outcome) demonstrated that having any comorbidity or immunosuppression was associated with HFNC failure with a hazard ratio of 1.89 (CI = 1.59–2.36, p = 0.006) and hazard ratio of 1.22 (CI 1.14–1.77, p = 0.02) respectively (Table 1).

Table 1
Association between socio-demographic characteristics, comorbidities, immunosuppression and HFNC failure.

	HR	95%CI	p-value
Age	0.97	0.96–0.99	<0.001
Sex			
Female	reference		
Male	0.48	0.30–0.77	0.002
BMI category			
Normal	reference		
Underweight	0.94	0.04–8.16	0.96
Overweight	1.92	0.64–6.05	0.99
Obese	1.31	0.37–3.24	0.99
Race/ethnicity			
NH-White	reference		
NH-Black	0.21	0.11–0.39	<0.001
Hispanic	0.71	0.39–1.31	0.61
Any comorbidity			
No	reference		
Yes	1.89	1.59–2.36	0.006
Any immunosuppression			
No	reference		
Yes	1.22	1.14–1.77	0.02

p-values obtained from Cox proportional hazards regression model.

4. Discussion

In this cohort of 30 patients with COVID-19, those who failed HFNC were likely to be male, obese, with at least one comorbidity or immunosuppression, have higher inflammatory markers, SOFA scores and lactate levels. As previous literature has shown, our cohort was also mostly males and those belonging to racial/ethnic minorities [17].

Mellado-Artigas' et al., demonstrated that HFNC might decrease ventilator days, ICU length of days and all-cause-hospital mortality but their cohort had lower SOFA scores, BMIs and utilized higher flows [18]. A systematic review done found that HFNC may reduce the need for IMV but there was no difference in mortality or length of stay and the studies included did not pertain exclusively to COVID-19 [19].

Our data suggest that COVID-19 patients with higher SOFA scores, lactic acid levels, and at least one comorbidity or immunosuppression do not benefit from HFNC. To our knowledge this is the only study that aims to identify risk factors for success or failure of HFNC for patients with COVID-19 and is a glimpse of the impact of the therapy without concomitant steroids or interleukin-6 inhibitors (IL-6i). Limitations include small sample size based on convenience (since the study was conducted in the beginning of the pandemic), retrospective design, non-randomized enrollment. This cohort of patients was studied before IL-6i, remdesivir and steroids became standard of care with only a minority of patients receiving steroids. Our HFNC devices were limited to 40L flow, perhaps higher flow may have more impact.

5. Conclusion

HFNC remains an important part in the treatment for COVID-19 but patient selection seems to be key. We found that those with at least one comorbidity or immunosuppression, higher SOFA scores and lactate levels are more likely to fail HFNC.

Study performed in

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CRediT authorship contribution statement

Orlando Garner: Methodology, Investigation, Writing – original draft, Writing – review & editing, Resources, Data curation. **Deepa Dongarwar:** Formal analysis, Writing – original draft, Writing – review & editing. **Hamisu M. Salihu:** Formal analysis, Supervision. **Jairo H. Barrantes Perez:** Supervision. **Jocelyn Abraham:** Investigation. **Cameron McBride:** Investigation. **Sindhu Matthew:** Investigation. **Preethi Antony:** Investigation. **Keegan Collins:** Investigation. **Katherine L. Richards:** Investigation. **Christopher M. Howard:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

None of the authors have any conflict of interest.

References

[1] Coronavirus COVID-19 global cases by johns hopkins CSSE. https://www.arcgis.com/apps/opsdashboard/index.html#/85320e2ea5424dfaaa75ae62e5c06e61. (Accessed 31 August 2020).

[2] I. Hamming, W. Timens, M.L. Bulthuis, A.T. Lely, G. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, J. Pathol. 203 (2) (2004) 631–637, https://doi.org/10.1002/path.1570.

[3] X. Li, M. Geng, Y. Peng, L. Meng, S. Lu, Molecular immune pathogenesis and diagnosis of COVID-19, J Pharm Anal 10 (2) (2020 Apr) 102–108, https://doi.org/10.1016/j.jpha.2020.03.001. Epub 2020 Mar 5. PMID: 32282863; PMCID: PMC7104082.

[4] The Ards Definition Task Force*, Acute respiratory distress syndrome: the berlin definition, JAMA 307 (23) (2012) 2526–2533, https://doi.org/10.1001/jama.2012.5669.

[5] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. Zhu, Y. Tai, Pathological findings of COVID-19 associated with acute respiratory distress syndrome, The Lancet respiratory medicine 8 (4) (2020) 420–422.

[6] N.D. Caputo, R.J. Strayer, R. Levitan, Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic [published online ahead of print, 2020 apr 22], Acad. Emerg. Med. (2020), https://doi.org/10.1111/acem.13994, 10.1111/acem.13994.

[7] J. Li, J.B. Fink, S. Ehrmann, High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion [published online ahead of print, 2020 Apr 16], Eur. Respir. J. (2020) 2000892, https://doi.org/10.1183/13993003.00892-2020.

[8] E. Chuang, P.A. Cuartas, T. Powell, M.N. Gong, We're not ready, but I don't think you're ever ready." clinician perspectives on implementation of crisis standards of care [published online ahead of print, 2020 may 5], AJOB Empir Bioeth 1-12 (2020), https://doi.org/10.1080/23294515.2020.1759731.

[9] N.A. Halpern, K.S. Tan, U.S. ICU resource availability for COVID-19, Updated: 03/19/2020, https://sccm.org/Blog/March-2020/United-States-Resource-Availability-for-COVID-19. (Accessed 8 May 2020).

[10] Shortage of ICU providers who operate ventilators would severely limit care during COVID-19 outbreak, Updated: 03/25/2020, https://sccm.org/getattachment/About-SCCM/Media-Relations/Final-Covid19-Press-Release.pdf?lang=en-US. (Accessed 8 May 2020).

[11] M.J. Tobin, Basing respiratory management of coronavirus on physiological principles [published online ahead of print, 2020 apr 13], Am. J. Respir. Crit. Care Med. (2020), https://doi.org/10.1164/rccm.202004-1076ED, 10.1164/rccm.202004-1076ED.

[12] L. Gattinoni, D. Chiumello, S. Rossi, COVID-19 pneumonia: ARDS or not? Crit. Care 24 (1) (2020) 154, https://doi.org/10.1186/s13054-020-02880-z. Published 2020 Apr 16.

[13] J.P. Frat, A.W. Thille, A. Mercat, et al., High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure, N. Engl. J. Med. 372 (23) (2015) 2185–2196, https://doi.org/10.1056/NEJMoa1503326.

[14] Q. Sun, H. Qiu, M. Huang, Y. Yang, Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province, Ann. Intensive Care 10 (1) (2020) 33, https://doi.org/10.1186/s13613-020-00650-2. Published 2020 Mar 18.

[15] F. Zhou, T. Yu, R. Du, et al., Clinical Course and Risk Factors for Mortality of Adult Inpatients with COVID-19 in Wuhan, China: a Retrospective Cohort Study [published Correction Appears in Lancet, vol. 395, 2020 Mar 28, p. 1038, https://doi.org/10.1016/S0140-6736(20)30566-3, 10229, [published correction appears in Lancet. 2020 Mar 28;395(10229):1038]. Lancet. 2020;395(10229):1054-1062.

[16] S. Lambden, P.F. Laterre, M.M. Levy, B. Francois, The SOFA score-development, utility and challenges of accurate assessment in clinical trials, Crit. Care 23 (1) (2019) 374, https://doi.org/10.1186/s13054-019-2663-7. Published 2019 Nov 27.

[17] S. Richardson, J.S. Hirsch, M. Narasimhan, et al., Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area [published correction appears in, JAMA 323 (20) (2020) 2052–2059, https://doi.org/10.1001/jama.2020.7681.

[18] R. Mellado-Artigas, B.L. Ferreyro, F. Angriman, et al., High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure, Crit. Care 25 (2021) 58, https://doi.org/10.1186/s13054-021-03469-w.

[19] A. Agarwal, J. Basmaji, F. Muttalib, D. Granton, D. Chaudhuri, D. Chetan, M. Hu, S. M. Fernando, K. Honarmand, L. Bakaa, S. Brar, B. Rochwerg, N.K. Adhikari, F. Lamontagne, S. Murthy, D.S.C. Hui, C. Gomersall, S. Mubareka, J.V. Diaz, K.E. A. Burns, R. Couban, Q. Ibrahim, G.H. Guyatt, P.O. Vandvik, 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. 67 (9) (2020 Sep) 1217–1248, https://doi.org/10.1007/s12630-020-01740-2. Epub 2020 Jun 15. PMID: 32542464; PMCID: PMC7294988.