Heart & Lung 50 (2021) 1–6

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

High-flow Nasal Cannula therapy: A feasible treatment for vulnerable elderly COVID-19 patients in the wards

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ARTICLE INFO

Article History:
Received 17 November 2020
Revised 22 April 2021
Accepted 26 April 2021
Available online 25 May 2021

Keywords:
COVID-19
Intensive care unit
High-flow Nasal Cannula
Frailty

ABSTRACT

Background: Invasive mechanical ventilation is the treatment of choice in COVID-19 patients when hypoxemia persists, despite maximum conventional oxygen administration. Some frail patients with severe hypoxemic respiratory failure are deemed not eligible for invasive mechanical ventilation.
Objectives: To investigate whether High-flow nasal cannula (HFNC) in the wards could serve as a rescue therapy in these frail patients.
Methods: This retrospective cohort study included frail COVID-19 patients admitted to the hospital between March 9th and May 1st 2020. HFNC therapy was started in the wards. The primary endpoint was the survival rate at hospital discharge.
Results: Thirty-two patients with a median age of 79.0 years (74.5–83.0) and a Clinical Frailty Score of 4 out of 9 (3–6) were included. Only 6% reported HFNC tolerability issues. The overall survival rate was 25% at hospital discharge.
Conclusions: This study suggests that, when preferred, HFNC in the wards could be a potential rescue therapy for respiratory failure in vulnerable COVID-19 patients.

Background

Approximately 80% of COVID-19 patients experience respiratory symptoms and roughly 20% of the patients develop severe symptoms requiring hospital admission.[1] With the lack of effective antiviral drugs, symptomatic treatment with oxygen administration remains the cornerstone of the treatment. As an intermediate step between conventional oxygen administration and invasive mechanical ventilation, High-flow Nasal Cannula (HFNC) is widely used to treat hypoxemic respiratory failure. HFNC is a form of non-invasive ventilation and contains high flow, pre-heated and humidified air delivering high concentrations of oxygen. In a recent large worldwide survey HFNC was used in the Intensive Care Unit (ICU) in 53% of the COVID-19 cases with initial flow settings between 30 and 45 liters per minute aiming for lower tidal volumes and higher positive end-expiratore pressure (PEEP) compared to conventional oxygen therapy.[2] Furthermore a recent study in the ICU has proven HFNC not to be beneficial in terms of fatality rate but has shown to reduce tintubation rates.[3] These findings are limited to the ICU and data specifically on the use of HFNC in frail COVID-19 patients in a hospital ward setting is limited. The aim of this study was to investigate whether HFNC therapy in the wards could serve as an appropriate rescue strategy for frail patients who failed on conventional oxygen administration but were considered not eligible for invasive mechanical ventilation in the ICU. The primary outcome was survival at hospital discharge. Subsequently, possible determinants of survival were studied.

Abbreviations: ACE, Angiotensine Converting Enzyme; ALAT, Allanine transaminase; ARDS, Acute Respiratory Distress Syndrome; ASAT, Aspartate transaminase (ASAT); BMI, Body Mass Index; CK, Creatine kinase; COPD, Chronic Obstructive Pulmonary Disease; COVID-19, Coronavirus disease 2019; CT, Computed tomography; eGFR, estimated Glomerular Filtration Rate; FFP-2, Filtering Facepiece Particles-2; FiO2, Fraction of inspired oxygen; HFNC, High-flow nasal cannula; ICU, Intensive Care Unit; LD, Lactate dehydrogenase; NIV, Noninvasive Ventilation; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SOFA, Sequential Organ Failure

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https://doi.org/10.1016/j.hrtlng.2021.04.008
0147-9563/

Methods

Study design and setting

This was retrospective cohort study in the Maasstad Medical center, the largest non-academic teaching hospital in the Rotterdam area, the Netherlands. The study was approved by the Hospitals Medical Ethical Committee (application number W20.081).

Inclusion criteria

COVID-19 patients aged 18 years and older who were hospitalised between 9th of March and 1st of May 2020 and experienced severe respiratory insufficiency but were not eligible for mechanical ventilation were included. Severe respiratory insufficiency was defined as persisting hypoxemia (e.g. saturation (SpO2) lower than 92%) despite administration of oxygen using a non-rebreating mask with a flow rate of 15 liters per minute. Patients were judged non-eligible for mechanical ventilation for several reasons, namely due to frailty, pre-existent comorbidities or because of their preference not to be mechanically ventilated. These patients were therefore treated with HFNC in the wards.

Decision on ventilation strategy

Decisions about the ventilation strategy were made in accordance with the patient and his or her relatives. Additionally, the patients were also discussed on a daily basis in a multidisciplinary team. This team includedd Critical Care, Internal Medicines, Pulmonology and Palliative Care specialists who collaborated together to achieve an unanimous decision. During these discussions functionality based on frailty scores, cognitive functioning and comorbidities were taken into account. When there was an unanimous agreement that a patient was too frail for mechanical ventilation, HFNC in the ward was considered as treatment. There was no disconcordance between the team and the patients about the treatment strategy.

Data collection

Data were collected using SQL Server Management Studio (version 18.3) from the electronic patient record (Chipsoft: Healthcare Information X-change). The hospital datamanager (GW) performed a first check after automatic extraction. A final check on the database was performed by the two principal investigators (JvS and MvH).

Demographics, Medical history and Drug use

Demographic data such as age, gender, date of admission, days of hospital stay, body mass index (BMI) and survival were extracted. The following comorbidities were scored: hypertension (defined as the use of antihypertensive drugs), diabetes mellitus type 2 (defined as fasting plasma glucose level $\geq$ 6.1 mmol/L), asthma (bronchodilator use and spirometry with reversibility), chronic obstructive pulmonary disease (COPD GOLD classification), smoking (current or former), chronic kidney disease (eGFR $<$60 ml/min/1,73 m2), malignancy (history of malignant neoplasm), occlusive peripheral arterial disease, a history of (non)-ischemic heart disease (ischemic defined as obstructive coronary artery disease), liver disease (radiological or pathological steatosis or cirrhosis) and the total number of comorbidities. Furthermore, medication administered at home (immunosuppressive drugs, ACE inhibitors and non-steroidal drugs) and during admission (cefuroxime and azithromycin) were reported.

Frailty assessment and clinical prediction scores

The Clinical Frailty Score ranging from 1 (very fit) to 9 (terminally ill) and WHO performance status scoreranging from 1 (fully active) to 4 (completely disabled) were extracted from the medical record.[4,5] Sequential organ failure assessment scores (SOFA) of the first 24 h of admission were collected.[6] HFNC was seen as a form of mechanical ventilation in the SOFA score, subsequently resulting in a higher score in the domain Respiratory system.

Signs and clinical parameters

The following clinical parameters were extracted from the medical record: pulse rate, blood pressure, temperature, respiratory rate and oxygen saturation. Patients were questioned about the presence and onset of the following symptoms: cough, dyspnea, weight loss, diarrhea and nausea.

Laboratory values and radiological findings

Blood examinations including hemoglobin, leukocyte count with differential count, platelet count, D-dimer, alanine transaminase (ALAT), aspartate transaminase (ASAT), creatine kinase (CK), lactate dehydrogenase (LDH), troponin T and ferritin levels were collected. A chest X-ray was performed upon admission. When there was a high clinical suspicion of pulmonary embolism a computed tomography pulmonary angiogram (CTPA) was performed.

High flow nasal cannula therapy

When deemed appropriate, HFNC was started at a flow rate of 60 liter per minute with a fraction of inspired oxygen (FiO2) of 60% and a temperature of 37 °Celsius. The inspired oxygen fraction was titrated based on oxygen saturation (target SpO2 $>$92%) and respiratory rate ($<$25 per min). The flow, FiO2 and reasons for a possbile failure of treatment were extracted from the medical record. An increment of 10% in the FiO2 in the first 24 h was scored separately. Hypoxemic respiratory failure on HFNC was defined as an SpO2 below 84% while receiving HFNC with a flow of 60 liter/min and a FiO2 of 100%.

Definitions

Fever was defined as a tympanic temperature lower than 36 or greater than 38 °Celsius. Patients were considered infected if they were proven positive for SARS-CoV-2 using a nasopharyngeal PCR test.

To assess the severity of Acute Respiratory Distress Syndrome (ARDS) SpO2/FiO2 ratios were calculated at introduction of HFNC therapy, as it was impossible to collect pO2/FiO2 ratios for all patients. SpO2/FiO2 can be considered equally sensitive and specific as compared to PO2/FiO2 ratios.[7]

Statistical analysis

Baseline data is presented as median (IQR) or n (%). Differences between survivors and non-survivors were compared using Mann Whitney U test for continuous data and Fisher's exact test for categorical data. P-values $<$0.05 were considered to be statistically significant. All statistical analysis were performed using The R Project for Statistical Computing (version 4.0.3).[8] Variables with clinical relevance and in between group differences were used in an univariate logistic regression model to calculate odds ratios in order to assess factors associated with in-hospital mortality. No multivariate analysis were performed due to a risk of overfitting the model due to the small size of the present cohort.

Results

Demographics, medical history and drug use

A total of 297 COVID-19 patients were admitted to our hospital, of which a total of 69/297 (23.2%) were admitted to the ICU. The number of patients who received conventional oxygen therapy in the wards was 194 (65.3%) and a total of 34 (11.4%) patients were treated with HFNC in the wards. After excluding two patients that were still hospitalized during the analysis, 32 patients were included in the HFNC cohort (see Fig. 1). There were no patients with missing data. Baseline data is shown in Table 1. The median age was 79.0 years (74.5–83.0) and more than half of the patients were male (69%). The median Body Mass Index (BMI) was 27.1 (26.3–31.4). Hypertension was the most frequent reported comorbidity (75%), the median comorbidities per patient was three (3–4). Patients reported a median of seven medications in use at home (5–10).

Frailty assessment and clinical prediction scores

The overall Clinical Frailty score was four (3–6), categorized as vulnerable. The WHO performance score was two out of four (2–4). SOFA scores within 24 h of admission was 5 (4–6) for non-survivors and 3.5 (2–4.25) for survivors ($p = 0.06$) (Table 1).

Signs and clinical parameters

The median time in days between onset of symptoms and hospital admission was six (4–14). Nearly all patients reported coughing (91%) and dyspnea (84%) and 34% of the patients had fever. All patients were tachypneic at presentation (Table 2).

Laboratory values and radiological findings

The overview of laboratory values at admission are presented in Table 3. Most of the patients had bilateral pulmonary infiltrates (72%). Only 12 (38%) patients underwent a CT-scan, in five of these patients (16%) a pulmonary embolism was confirmed.

HFNC settings

The median duration of admission before HFNC was introduced, was 2.0 days (1.0–4.3). The median FiO2 at start was 0.60 (0.60–0.80) and the maximum FiO2 during treatment was 0.95 (0.80–0.95). Two-thirds of patients (66%) required an increment in FiO2 of at least 10% in the first 24 h. The initial median SPO2/FiO2 ratio was 157.5 (150–163.3), which is classified as a moderate ARDS. Reasons for failure were hypoxemic respiratory failure (69%) and tolerability issues (6%) (Table 4).

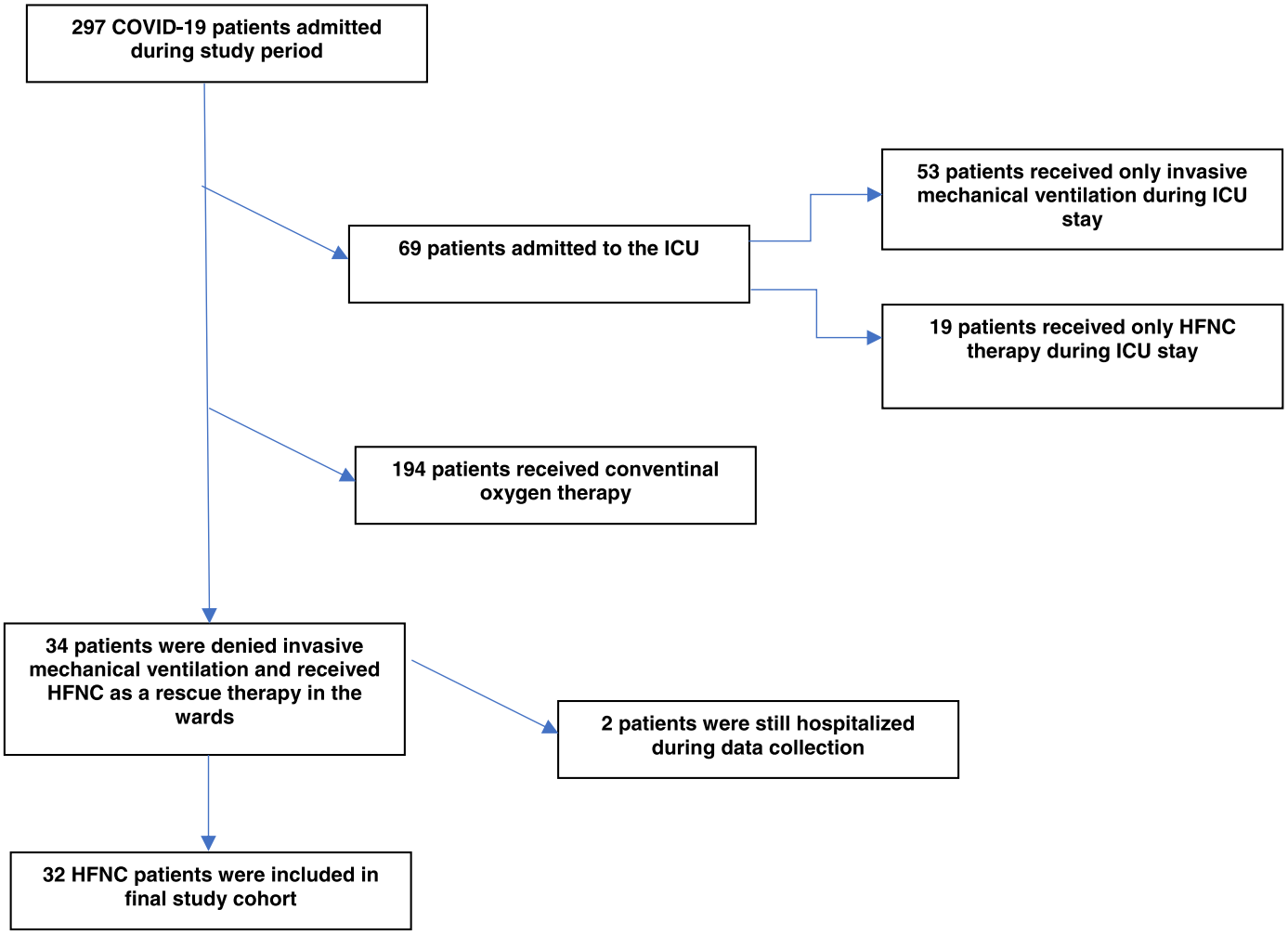

Fig. 1. Flowdiagram for included study patients receiving HFNC between 9th of March and 1st of May 2020.

Table 1
Baseline demographics, performance scores, clinical prediction score and medication use. Data are presented as n (%) or median (IQR).

		Total (n = 32)	non-survivor (n = 24)	survivor (n = 8)	p value
Age		79.0 (74.5–83.0)	80.5 (78.0–84.3)	69.5 (65.5–74.3)	<0.01
Gender (male)		22 (69%)	17 (71%)	5 (62%)	0.68
Body Mass Index		27.1 (26.3–31.4)	27.5 (26.4–31.3)	27.0 (26.2–30.7)	0.98
Comorbidities	*Hypertension*	24 (75%)	22 (92%)	2 (25%)	<0.01
	Diabetes	14 (44%)	9 (38%)	5 (62%)	0.25
	Chronic Obstructive Lung Disease	5 (16%)	5 (21%)	0	0.30
	Asthma	3 (9%)	1 (4%)	2 (25%)	0.15
	Chronic Kidney Disease	13 (41%)	12 (50%)	1 (12%)	0.11
	Malignancy	11 (34%)	9 (38%)	2 (25%)	0.68
	Occlusive Peripheral Arterial Disease	7 (22%)	4 (17%)	3 (38%)	0.33
	Non-ischemic Heart Disease	11 (34%)	9 (38%)	2 (25%)	0.68
	Ischemic Heart Disease	13 (41%)	10 (42%)	3 (38%)	1.00
	Neurovascular Disease	6 (19%)	6 (25%)	0	0.30
	Liver Disease	4 (12%)	2 (8%)	2 (25%)	0.25
	Total number of comorbidities	3 (3–4)	3 (3–4)	3 (3–3)	0.50
Smoking	*Current*	5 (16%)	4 (17%)	1 (12%)	1.00
	Former	6 (19%)	5 (21%)	1 (12%)	1.00
Performance scores	*Clinical Frailty score*	4 (3–6)	4 (4–6)	4(4–6)	0.44
	WHO Performance score	2 (2–4)	2 (2–4)	2 (2–3)	0.68
Clinical prediction score	*SOFA score within 24 h of admission*	5 (3–6)	5 (4–6)	3.5 (2 - 4,25)	0.06
In-hospital Medication	*Cefuroxim*	31 (97%)	23 (96%)	8 (100%)	1.00
	Azitromycin	32 (100%)	24 (100%)	8 (100%)	–
Out of hospital Medication	*Immunosuppressives*	3 (9%)	2 (8%)	1 (12%)	1.00
	NSAID's	2 (6%)	2 (8%)	0	1.00
	ACE-inhibitors	9 (28%)	7 (29%)	2 (25%)	1.00
	Total number of chronic medications	7 (5–10)	7 (6–9)	8 (4–12)	0.88

Table 2
Clinical symptoms and admission duration, Data are presented as n (%) or median (IQR).

		Total (n = 32)	non-survivor (n = 24)	survivor (n = 8)	p value
Clinical Symptoms	*Cough*	29 (91%)	22 (92%)	7 (88%)	1.00
	Dyspnea	27 (84%)	20 (83%)	7 (88%)	1.00
	Weight loss	2 (6%)	1 (4%)	1 (12%)	0.44
	Diarrhea	11 (34%)	8 (33%)	3 (38%)	1.00
	Nausea	5 (16%)	4 (17%)	1 (12%)	1.00
	Respiratory Rate	23 (20–26)	23 (20–25)	24 (16–26)	0.84
	Respiratory Rate >24	10 (31%)	6 (25%)	4 (50%)	0.22
	MAP >65	31 (97%)	23 (96%)	8 (100%)	1.00
	Heart rate	92 (77–102)	92 (77–102)	91 (78–99)	0.85
	Fever (>38 or <36 C)	11 (34%)	9 (38%)	2 (25%)	0.69
Time between symptom onset and admission (days)		6 (4–14)	5.5 (4–13)	7 (5–12)	0.80
Admission duration (days)		6 (3.8–12.8)	4.9 (3.5–8.1)	15.2 (12.3–25.9)	<0.01

Table 3
Laboratory markers and radiological findings,,Data are presented as n (%)or median (IQR).

		Total (n = 32)	non-survivor (n = 24)	survivor (n = 8)	p value
Laboratory Markers					
White Bloodcell Count (x10^9/L)		7.0 (5.2–10.7)	7.6 (6.2–10.9)	5.2 (5.0–6.3)	0.04
absolute lymfocyt count (x10^9/l)		1.0 (0.7–1.4)	0.9 (0.6–1.4)	1.1 (1.0–1.4)	0.27
hemoglobin (mmol/l)		8.1 (7.4–8.9)	8.1 (7.0–8.9)	8.5 (8.0–9.2)	0.27
Platelet Count (x10^9/L)		211 (180–281)	207 (182–279)	242 (182–335)	0.60
Alanine aminotransferase (U/L)		31 (25–40)	30 (25–39)	34 (29–40)	0.36
Aspartate aminotransferase (U/L)		59 (45–68)	54 (39–68)	60 (59–67)	0.28
Lactate dehydrogenase(U/L)		409 (296–528)	391 (280–581)	424 (395–517)	0.56
D-Dimer (mg/L)		1.4 (1.0–3.7)	1.34 (1.0–3.7)	1.3 (1.0–2.3)	0.77
Procalcitonin (μg/L)		0.17 (0.12–0.36)	0.22 (0.16–0.51)	0.12 (0.1–0.16)	0.03
Ferritin (μg/L)		695 (373–1313)	884 (397–1438)	498 (386–794)	0.32
C-reactive protein (mg/L)		111 (67–141)	111 (66–141)	119 (76–146)	0.84
Radiological findings					
Chest X-Ray	*Bilateral Pulmonary Infiltration*	23 (72%)	16 (67%)	7 (88%)	0.39
	Unilateral Pulmonary Infiltration	5 (16%)	5 (21%)	0 (0%)	0.30
	No Pulmonary Infiltration	4 (12%)	3 (12%)	1 (12%)	1.00
Computed Tomography scan		12 (38%)	8 (33%)	4 (50%)	0.43
Pulmonary embolism		5 (45%)	4 (57%)	1 (25%)	0.55

Table 4
HFNC settings and use.,Data are presented as n (%) or median (IQR).

		Total (n = 32)	non-survivor (n = 24)	survivor (n = 8)	p value
HFNC Settings	*Fio2 Start%*	60 (60–80)	60 (60–83)	75 (60–80)	0.93
	Fio2 Max%	95 (80–95)	95 (88–95)	93 (78–95)	0.23
	Flow Start L/min	60 (60–60)	60 (60–60)	60 (60–60)	–
	Flow Max L/min	60 (60–60)	60 (60–60)	60 (60–60)	–
10% FiO2 increase in first 24 h		21 (66%)	16 (67%)	5 (62%)	1.00
SPO2/FiO2 Ratio start HFNC		157.5 (150.0–163.3)	157.5 (148.8–162.1)	157.5 (152.5–164.2)	0.56
HFNC Duration (days)		2.5 (1.0–4.3)	2.0 (1.0–3.0)	9.5 (4.8–17.5)	<0.01
Duration between admission and HFNC start (days)		2.0 (1.0–4.0)	2.0 (1.0–4.0)	3.5 (1.8–4.2)	0.29
Reasons for HFNC failure	*Persisting hypoxemia*	22 (69%)	22 (92%)	0	–
	Toleration issues	2 (6%)	2 (8%)	0	

Survival and between group differences

The overall survival rate in the HFNC cohort was 25%. Patients died because of a respiratory failure due to COVID-19. Median admission duration was 15.2 days (12.3–25.9) in the survivor group compared to 4.9 (3.5–8.1) days in the non-survivor group ($p < 0.01$) and median HFNC duration was 9.5 days (4.8–17.5) in the survivor group and 2.0 (1.0–3.0) in the non-survivor group ($p = 0.0012$). Median age in the non-survivor group was 80.5 years (78.0–84.3) and 69.5 years (65.5–74.3) in the survivor group ($p < 0.01$). Furthermore, hypertension was a more frequent comorbidity in the non-survivor group (92% vs 25% $p < 0.01$). Values of white blood cell count were significantly lower in the survivors (7.6 (6.2–10.9) vs 5.2 (5.0–6.3) $p = 0.039$) as was procalcitonin (0.22 (0.16–0.51) vs 0.12 (0.10–0.16) $p = 0.034$). Findings were confirmed for admission duration (OR 0.8: 95%CI 0.6–0.9 $p < 0.01$), hypertension (OR 33: 95%CI 4.6–392.3 $p < 0.01$) and age (OR 1.2: 95%CI 1.1–1.4 $p < 0.01$) in the univariate analyses but not for laboratory values and HFNC duration.

Discussion

This observational study describes the clinical course of a cohort of vulnerable COVID-19 patients treated with HFNC as a rescue therapy in the hospital wards. Overall survival at discharge was 25%, much lower than most reported survival rates in the clinical wards.[1,9,10] However, this cohort is a selection of frail patients with severe respiratory failure and high ARDS scores. Higher mortality rates are also reported in patients with multiple comorbidities admitted to Dutch, European and Northern-American intensive care units requiring invasive ventilation in the same age group.[11-13] Compared to a recent study by Calligaro et al.,[14] success rate of HFNC was reported to be 47% and therefore significantly higher compared to our study, however, in latter study, patients were much younger and HFNC was used in an ICU setting. Using HFNC in hypoxemic respiratory failure in COVID-19 has previously been described and advocated[15] but data on frail patients is missing. This is the first study to specifically describe HFNC as a ward based rescue therapy for frail elderly who are deemed not eligible for mechanical ventilation and comparion with previously published studies is therefore difficult.

Success rate of HFNC seems to be dependent on the severity of pulmonary infection, with lower PaO2/FiO2 ratios resulting in a higher therapy failure. Wang et al.[16] described failure of HFNC in 63% of the patients, when PaO2/FiO2 was below 200 mmHg, comparable with our cohort. Vulnerability is associated with a worse clinical outcome including mortality and duration of hospitalization in non-COVID patients.[17,18] In line with our results, increasing age[1,9,19] and hypertension[1,19,20] are independent risk factors for mortality in COVID-19 positive patients. The latter finding is paradoxical since hypertension in frail older people without COVID-19 is not associated with higher mortality.[21]

Furthermore, the small case series on HFNC in COVID-19 patients reported by Geng et al.[22] showed that HFNC therapy was patient friendly. Additionally, the medical staff reported that HFNC machines were easy to use while patients reported relatively high comfort breathing humidified and preheated air. The benefits of patients' tolerance combined with more reliable delivery of FiO2 due to dead space flushing, makes HFNC an excellent method of oxygen supply.[23] Furthermore, as described by Marini et al. early initiation of HFNC can reduce inspiratory effort resulting in lowering pulmonary transvascular pressures and can protect lungs from patient self-inflicted lung injury.[24]

The current study applied HFNC therapy, instead of CPAP or BiPAP, due to several benefits, namely the combination of tolerability for long ventilation duration, the reduced nursing workload and previous literature describing significantly lower 90-day mortality in favor of HFNC in acute hypoxemic respiratory failure as compared to other forms of NIV like Continuous Positive Airway Pressure (CPAP) or Bilevel Positive Airway Pressure (BiPAP).[25]

When HFNC was introduced in our hospital, concerns were raised about potential safety issues regarding to aerosol and viral spread with non-invasive mechanical ventilation like HFNC. The medical staff operating HFNC machines used Filtering Facepiece Particles-2 (FFP-2) masks, gowns, gloves and eye protection. Available literature did not reveal any evidence of increased risk infection while working with HFNC.[26,27] Only one retrospective study is available describing the infection rates of SARS-CoV-1 in hospital workers operating HFNC machines. As compared to tracheal intubation (35%) and NIV (38%), HFNC seems to be the safest option with a lower risk of infection (8%).[28] This study was not designed to address these potential safety hazards but based on the infection rates amongst hospital staff no concerns about using HFNC was reported which supports its deployment in future practice.

Limitations

This study has several limitations. First, randomizing between HFNC and continuing standard oxygen supply, which is the only reasonable alternative active treatment in the wards, was considered to be ethically inappropriate since failure occurred on conventional oxygen supply. This means that no conclusions can be drawn about the benefit of HFNC therapy over conventional oxygen administration.

Second, we did not study the survival rate of these patients, when they would be admitted to the ICU for invasive mechanical ventilation instead of receiving HFNC treatment in the ward. Finally, due to our small study cohort, it was difficult to demonstrate predictors between survivors and non-survivors in the study population. This risk was minimized by including all of the frail COVID-19 patients that received HFNC in the wards. A large multicenter prospective study could further improve generalizability, confirm our results, and identify predictors for success or failure of HFNC therapy in frail patients in the wards. Furthermore, future research should focus on the safe application of HFNC in the wards to allow deployment on a larger scale, for example during future pandemics.

Conclusions and implications for practice

This study suggests that in future practice, when deemed appropriate, HFNC in the wards could be a potential rescue therapy for respiratory failure in vulnerable COVID-19 patients and can be deployed both safely and satisfactorily for staff and patients.

Declaration of Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This study was approved by the Hospitals Medical Ethical Committee (Medical Research Ethics Committees United, reference L2019023), application number W20.081.

Availability of data and materials

The datasets that were used and/or analysed during the current study, are available from the corresponding author by a reasonable request.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

JS and MvH invented the study and were responsible for the integrity of the database. All authors were responsible for the treatment of patients, collecting clinical and additional data and for writing the manuscript. All authors approved the final version after reviewing

Acknowledgments

We thank Geeke van Waverijn for data extraction and preparation. We thank Evelien Oostdijk and Rob Zwinkels for the critical reading of the manuscript.

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