

# High-Flow Nasal Cannula therapy: A Feasible Treatment in Vulnerable Older COVID-19 Patients on the Wards

Job van Steenkiste (✉ [jobvansteenkiste@gmail.com](mailto:jobvansteenkiste@gmail.com))

Maasstad Ziekenhuis <https://orcid.org/0000-0002-5062-5397>

Michael C. van Herwerden

Maasstad Ziekenhuis

Dolf Weller

Maasstad Ziekenhuis

Christiaan J. van den Bout

Maasstad Ziekenhuis

Rikje Ruiter

Maasstad Ziekenhuis

Jan G. den Hollander

Maasstad Ziekenhuis

Rachida el Moussaoui

Maasstad Ziekenhuis

Gert T. Verhoeven

Maasstad Ziekenhuis

Charlotte van Noord

Maasstad Ziekenhuis

Marinus van den Dorpel

Maasstad Ziekenhuis

---

## Research article

**Keywords:** COVID-19, Intensive Care Unit, High-flow Nasal Cannula, Frailty

**Posted Date:** June 16th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-34470/v1>

**License:**   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

# Abstract

**Background:** In the midst of the COVID-19 crisis, many frail elderly were admitted to our hospital with COVID-19. We sought a treatment for those who had severe respiratory failure but were not eligible for invasive mechanical ventilation, due to frailty, functional status, comorbidity or wish of the patient. We started with applying High-flow nasal cannula (HFNC) treatment on the wards.

**Methods:** A retrospective cohort study amongst COVID-19 adult patients with respiratory failure defined as persisting hypoxemia despite maximum conventional oxygen administration requiring invasive mechanical ventilation at the Intensive Care Unit (ICU) but being treated with HFNC as they were non-eligible due to frailty or wish of the patient.

**Results:** We included 32 patients between March 9 and May 1, 2020. The median age was 79.0 years (74.5-83.0) with a median of three comorbidities (3-4) and a median Clinical Frailty Score of 4 out of 9 (3-6). The median SpO<sub>2</sub>/FiO<sub>2</sub> Ratio was 157.5 indicating moderate ARDS. Overall survival rate in the HFNC cohort was 25%. Age (80.5 (78.0-84.3) vs 69.5 (65.5-74.3) p=0.0040) and hypertension (92% vs 25%, p=0.0008) were associated with mortality.

**Conclusion:** HFNC can be used as a last resort respiratory management strategy in vulnerable elderly COVID-19 patients in respiratory failure on the wards who failed on conventional high dose oxygen supply and are not eligible for invasive mechanical ventilation.

## Background

At the end of December 2019 the province Hubei in China experienced an outbreak of multiple cases with unexplained low respiratory tract infections. The etiology of this illness is now attributed to the new coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Evidence indicates that SARS-CoV-2 was transmitted from wildlife animals to humans at the Huanan Seafood Market in Wuhan [1]. By the 14th of January 2020 human-to-human transmission of the coronavirus was reported. Following this outbreak in China, rapid worldwide spread occurred and by March 11, 2020, The World Health Organization has proclaimed Coronavirus disease 2019 (COVID-19), which is the infectious disease caused by the SARS-CoV-2 virus, to be a global pandemic [2]. By May 1th 2020, more than 4.893 proven COVID-19 patients in the Netherlands have died with total hospital admissions rising to 10.854 cases[3].

In approximately eighty percent of COVID-19 cases, respiratory symptoms occur [4]. Roughly twenty percent develop severe respiratory symptoms requiring hospital admission [5]. Of these, a quarter needs invasive respiratory support. Multiple case series and cohort studies have been published suggestion factors associated with poor clinical outcomes in COVID-19 disease including older age, hypertension and diabetes [4-7].

With the lack of high quality evidence for any specific antiviral drug, symptomatic treatment with oxygen and, in severe cases, invasive mechanical ventilation remains the cornerstone of the current treatment for COVID-19. As an intermediate step up between conventional oxygen therapy and invasive mechanical ventilation, High-flow Nasal Cannula (HFNC) is widely used to treat severe respiratory infections. It allows non-invasive ventilation in a relatively comfortable way using high flow with pre-heated, humidified air containing large oxygen concentrations. Rapidly after the outbreak of the virus, HFNC therapy was implemented on our hospital wards for patients who failed on conventional high dose oxygen administration and were considered not eligible for invasive mechanical ventilation in the Intensive Care Unit (ICU) due to frailty, functional status, comorbidity or following a specific wish of the patient. HFNC was the last available strategy of oxygen administration on the wards. Nurses and staff were properly trained, and surveillance was done by continuous remote monitoring systems measuring heart frequency and respiratory rate. So far, only two studies [8, 9] have described the clinical course of COVID-19 patients treated with HFNC. Large cohort studies assessing clinical outcomes are missing in this group.

Here, we describe the clinical course of a cohort of vulnerable elderly patients with respiratory failure despite conventional high dose oxygen administration, treated with HFNC for whom long standing invasive mechanical ventilation was not eligible due to functional status. The primary outcome was survival. Furthermore, we aimed to identify determinants associated with survival.

## Methods

### *Study design and population*

This was a retrospective, single center cohort study in the Maastad Medical Centre, which is the largest (600-bed) non-academic teaching hospital in the Rotterdam area, the Netherlands. This study was approved by the Hospitals Medical Ethical Committee, application number W20.081.

We conducted a study amongst patients older than 18 years who were admitted with a COVID-19 infection between the 9th of March 2020 and 1th of May 2020 and were admitted to the hospital with severe respiratory insufficiency. Laboratory confirmation of SARS-CoV-2 was done using PCR techniques on a nasopharyngeal swab with a Roche analyzer on admission.

Mechanical ventilation in the Intensive Care Unit was declined in a portion of the admitted patients because of clinical frailty status, performance status or history of disease (e.g. severe cardiopulmonary conditions). These decisions were made in accordance with the patient and his or her relatives and were discussed on a daily basis in a multidisciplinary team together with Critical Care, Internal Medicine, Pulmonology and Palliative Care Specialists. During these meetings, performance scores, comorbidities, cognitive functioning and frailty were used to make a considered decision. When there was unanimous agreement that patients were too frail for mechanical ventilation, HFNC was the only alternative treatment. We started HFNC with a flow of 60 liter per minute with a temperature of 37C and titrated oxygen fraction based on oxygen saturation ( $spO_2 >92\%$ ) and respiratory rate ( $<25$  per min).

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

### *Demographics, Medical history and Drug use*

Demographic data and medical history were extracted from the medical record. The following demographic data were extracted. Age, gender, date of admission, days of hospital stay, body mass index (BMI) and survival. Comorbidities that were scored, were hypertension (defined as the use of antihypertensives), 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 m<sup>2</sup>), malignancy (history of malignant neoplasm), occlusive peripheral arterial disease, ischemic heart disease (defined as obstructive coronary artery disease), non-ischemic heart disease, liver disease (radiological or pathological steatosis or cirrhosis) and the total number of comorbidities. Furthermore, out of hospital drug use (immunosuppressive drugs, ACE inhibitors and non-steroidal drugs) and in hospital drugs were scored (cefuroxime and azithromycin).

### *Signs and clinical parameters*

Clinical parameters were extracted from the medical record for every patient on admission, these include pulse rate, blood pressure, temperature, respiratory rate and oxygen saturation. Patients were asked if, and since when they had the following symptoms: cough, dyspnea, weight loss, diarrhea and nausea.

### *Frailty assessment*

For clinical frailty assessment we used the Clinical Frailty Score [10] ranging from 1 (very fit) to 9 (terminally ill). In addition WHO performance status score was extracted from the medical record ranging from 1 (fully active) to 4 (completely disabled) [11].

### *Laboratory values and Radiological findings*

For each patient 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. We choose for these specific laboratory measures as most of them have already proved to be discriminating between mild and severe clinical courses [5]. Chest X-ray was performed on admission in every patient. If there was a high clinical suspicion on pulmonary embolism with elevated d-dimer levels in absence of pulmonary infiltrates on chest x-ray, an additional computed tomography (CT) pulmonary angiogram was performed.

### *HFNC*

We registered days since admission before the start of HFNC. Furthermore, flow (liters per minute), fraction of inspired oxygen (FiO<sub>2</sub>) and reasons for failure of HFNC therapy were extracted from the medical record. FiO<sub>2</sub> increase of ten percent in the first 24 hours were scored separately.

### *Outcome*

The primary end-point of our study was survival on the hospital ward in patients who used HFNC. Furthermore, we checked for determinants associated with mortality during HFNC use.

### *Definitions*

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

Respiratory failure was defined as persisting hypoxemia despite maximum conventional oxygen administration e.g. saturation (SpO<sub>2</sub>) lower than 92% despite maximum oxygen administration with a non-rebreathing mask (15 liters per minute). To assess the severity of Acute Respiratory Distress Syndrome (ARDS) SpO<sub>2</sub>/FiO<sub>2</sub> ratios were calculated, as it was impossible to collect PO<sub>2</sub>/FiO<sub>2</sub> ratios for all patients and because SpO<sub>2</sub>/FiO<sub>2</sub> can be considered equally sensitive and specific as compared to PO<sub>2</sub>/FiO<sub>2</sub> ratios [12].

### *Statistical analysis*

Baseline data is presented as median (IQR) or n (%) were appropriate. In order to compare differences between survivors and non-survivors, we used 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 R Studio version 3.6.3. Variables with clinical relevance and in between group differences were used in a univariate logistic regression model to calculate odds ratios in order to assess factors associated with in hospital mortality. No multivariate analysis was performed because of the size of cohort leading to high risk of overfitting the model.

## **Results**

### *Demographics, Medical history and Drug use*

Between 9th of March 2020 and 1th of May 2020, 297 COVID-19 positive patients were admitted to our hospital with a median age of 62.5 years (52.5-78.0), men being predominant (58%). Thirty-four (11%) COVID-19 patients received HFNC treatment. After excluding two patients that were still hospitalized during the analysis, 32 patients were included in the final cohort. There were no patients with missing baseline data. Baseline data is shown in table 1. In the total cohort the median age was 79.0 years (74.5-83.0) and more than half were male (69%). Median BMI was 27.1 (26.3-31.4) and a median of three comorbidities were reported (3-4). Hypertension was the most frequently reported comorbidity (75%)

followed by diabetes mellitus type 2 (44%). Sixteen percent of patients were current smokers and 19% had a history of tobacco use. With regards to medication use outside of the hospital, median number of drugs used for chronic purposes was seven (5-10).

### *Signs and clinical parameters*

The median time in days between onset of symptoms and hospital admission was six (4-14). Nearly all patients reported cough (91%) and dyspnea (84%) on admission. Thirty-four percent of the patients had fever and all patients were tachypneic during presentation in the emergency department. See table 2 for a complete overview.

### *Frailty assessment*

The overall Clinical Frailty score was 4 (categorized as vulnerable) out of 9 (3-6) compared to a WHO performance score of 2 out of 4 (2-4).

### *Laboratory values and Radiological findings*

For an overview of laboratory values on admission and during hospital stay, see table 3. Most of the patients had radiological findings on chest x-rays during admission. Out of these, bilateral pulmonary infiltrates were the most frequently found (72%). Only 12 (38%) patients underwent a CT-scan, pulmonary embolism was confirmed in 5 (45%).

### *HFNC settings*

Median admission duration before HFNC initiation was 2.0 days (1.0-4.3). The median FiO<sub>2</sub> at start was 0.60 (0.60-0.80) and the FiO<sub>2</sub> max was 0.95 (0.80-0.95). Air flow was set at 60 liters per minute in all patients. Two-third of patients (66%) required an increment in FiO<sub>2</sub> of at least 10% in the first 24 hours after initiating the HFNC therapy. The median SPO<sub>2</sub>/FiO<sub>2</sub> Ratio at start was 157.5 (150-163.3) which can be classified as a moderate ARDS. The most reported reason for failure in the non-survivors group on HFNC was persistent hypoxemia (92%). See table 4 for a complete overview.

### *Survival and between group differences*

Overall survival rate in the HFNC cohort was 25%. We found no statistically significant differences between survivors and non-survivors for BMI, comorbidities (including smoking), frailty and performance scores, medication use, HFNC settings, most of the laboratory values and radiological findings.

However, between non-survivors and survivors, admission duration, HFNC therapy duration, age, hypertension, white blood cell count and procalcitonin levels came out significantly different. 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=0.0006) 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 (78-84.3) and 69.5 years (65.5-74.3) in the survivor group (p= 0.0040). Furthermore, hypertension

was evidently more frequently reported as a comorbidity in the non-survivor group (92% vs 25%  $p=0.0008$ ). 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)  $p=0.0385$ ) as was procalcitonin (0.22 (0.16-0.51) vs 0.12 (0.10-0.16)  $p=0.0335$ ). Findings were confirmed for admission duration (OR 0.8: 95%CI 0.6-0.9  $p=0.0088$ ), hypertension (OR 33: 95%CI 4.6-392.3  $p=0.0015$ ) and age (OR 1.2: 95%CI 1.1-1.4  $p=0.0071$ ) in our univariate analyses but not for laboratory values and HFNC duration.

## Discussion

To the best of our knowledge this is the first observational cohort study which describes the clinical course of a cohort of older COVID-19 patients with multiple comorbidities and frailty scores indicating vulnerability, treated with HFNC on the hospital wards because of failure of conventional administration with high volumes of oxygen, resulting in a survival rate of 25%. This survival percentage is similar to patients with multiple comorbidities admitted to Dutch, European and Northern-American intensive care units in the same age group [13-15]. Thus, in our opinion this study describes an alternative respiratory treatment strategy on the wards for vulnerable elderly COVID-19 patients for whom long standing invasive mechanical ventilation is not eligible due to frailty.

We found an overall case rate survival much lower than most reported survival rates on the clinical wards [6, 16, 17]. However, our cohort is a selection of frail patients with severe respiratory failure and high ARDS scores. Recently two other studies were published describing the successful use of HFNC in COVID-19 patients [8, 9]. Contrary to these studies, we did not use HFNC therapy as an intermediate step-up between invasive mechanical ventilation and conventional oxygen therapy. Success rate of HFNC seems to be mostly dependent on the severity of pulmonary infection, with lower PaO<sub>2</sub>/FiO<sub>2</sub> ratios resulting in a higher chances of therapy failure. Wang et al. [9] described failure of HFNC in 63% when PaO<sub>2</sub>/FiO<sub>2</sub> was below 200 mmHg, comparable with our group. Previous studies have shown that vulnerability is associated with worse clinical outcomes including mortality and duration of hospitalization in non-COVID patients [18, 19]. In line with our results, increasing age [6, 16, 20] and hypertension [5, 6, 20] are independent risk factors for mortality in COVID-19 positive patient. The latter finding is paradoxical since hypertension in frail older people without COVID-19 is not associated with higher mortality [21].

Regarding factors associated with poor outcome we only found procalcitonin and leukocyte count to be associated with higher mortality, we think this is due to our small sample size. Earlier risk factor defining studies in COVID-19 patients found neutrophilia, raised lactate dehydrogenase, leukocyte counts and raised ASAT are all associated with higher disease burden [4].

The ease of application of HFNC in comparison with noninvasive ventilation (NIV) makes HFNC an excellent strategy of oxygen administration on the wards. In line with the small case series on HFNC in COVID-19 patients published by Geng et al. [8] we have experienced HFNC to work in both a patient and staff friendly way. Staff reported HFNC to be an easy to work with machine while patients reported relatively high comfort breathing humidified and preheated air. The benefit of patient tolerance and

assuring more reliable delivery of FiO<sub>2</sub> due to dead space flushing makes HFNC an excellent method of oxygen supply [22]. Furthermore, as described by Marini et al. early initiation of HFNC can reduce inspiratory effort resulting in lowering pulmonary trans-vascular pressures and can protect lungs from patient self-inflicted lung injury [23].

On initiation of HFNC in our hospital, a comment was raised about potential safety issues with regards to aerosol and viral spread with non-invasive mechanical ventilation like HFNC. Available literature did not reveal any evidence of increased risk of contamination while working with HFNC [24, 25]. 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%) [26]. Although we did not specifically investigate these potential safety hazards, we did not find a higher infection rate of staff who worked on the wards with HFNC patients during the study period. All of our staff operating HFNC machines used Filtering Facepiece Particles-2 masks and eye protection.

### *Limitations*

This study has several limitations. First, randomizing between HFNC and continuing standard oxygen supply, which is the only reasonable alternative active treatment on the wards, was considered to be ethically incorrect since there was failure on conventional oxygen supply. This means that no conclusions can be drawn with regards to survival and clinical performance between HFNC therapy and conventional oxygen administration in COVID-19 patients with similar characteristics. Secondary, no conclusion can be made about survival if our patients would be admitted to intensive care for invasive mechanical ventilation instead of receiving HFNC treatment on the ward. Due to our relatively small cohort, it was difficult to demonstrate differentiating factors between survivors and non-survivors in our population. Further studies are necessary to find factors for success or failure of HFNC therapy on the ward.

## **Conclusions**

Our retrospective cohort study shows that HFNC is a hopeful respiratory treatment strategy on the wards for vulnerable elderly COVID-19 patients for whom prolonged mechanical ventilation is beyond limits.

## **List Of Abbreviations**

HFNC: High-flow nasal cannula

ICU: Intensive Care Unit

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

COVID-19: Coronavirus disease 2019

BMI: Body Mass Index

COPD: Chronic Obstructive Pulmonary Disease

eGFR: estimated Glomerular Filtration Rate

ACE: Angiotensine Converting dnzyme

ALAT: alanine transaminase

ASAT: aspartate transaminase (ASAT)

CK: creatine kinase

LD: lactate dehydrogenase

CT: computed tomography

FiO2: fraction of inspired oxygen

ARDS: Acute Respiratory Distress Syndrome

NIV: Noninvasive Ventilation

## **Declarations**

### ***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.

### ***Consent for publication***

Not applicable.

### ***Availability of data and materials***

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

### ***Competing interests***

The authors declare that they have no competing interests.

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

### ***Acknowledgements***

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

### ***Author's information***

#### *Affiliations*

Department of Internal Medicine, Maastad Medical Centre, Rotterdam, Maastadweg 21, 3079DZ, Rotterdam, the Netherlands

Job van Steenkiste, Michael C. van Herwerden, Rikje Ruiten, Jan G. den Hollander, Rachida el Moussaoui, Charlotte. van Noord, Marinus A. van den Dorpel

Department of Intensive Care Medicine, Maastad Medical Centre, Rotterdam, Maastadweg 21, 3079DZ, Rotterdam, the Netherlands

Dolf Weller, Christiaan J. van den Bout

Department of Respiratory Medicine, Maastad Medical Centre, Rotterdam, Maastadweg 21, 3079DZ, Rotterdam, the Netherlands

Gert T. Verhoeven

#### *Corresponding Authors*

Job van Steenkiste

### **Ethics declarations**

#### *Ethics approval and consent to participate*

This study was approved by the Hospitals Medical Ethical Committee, application number W20.081.

## **References**

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R *et al*: **A Novel Coronavirus from Patients with Pneumonia in China, 2019**. *N Engl J Med* 2020, **382**(8):727-733.
2. **WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020** [<https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020>]
3. Environment NifPHat: **Current information about COVID-19 (novel coronavirus)**. In. Edited by Health Mo: Ministry of Health; 2020.
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y *et al*: **Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China**. *JAMA* 2020.
5. Cevik M, Bamford C, Ho A: **COVID-19 pandemic - A focused review for clinicians**. *Clin Microbiol Infect* 2020.
6. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, Guo GY, Du J, Zheng CL, Zhu Q *et al*: **Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study**. *Eur Respir J* 2020, **55**(5).
7. Tolksdorf K, Buda S, Schuler E, Wieler LH, Haas W: **Influenza-associated pneumonia as reference to assess seriousness of coronavirus disease (COVID-19)**. *Euro Surveill* 2020, **25**(11).
8. Geng S, Mei Q, Zhu C, Yang T, Yang Y, Fang X, Pan A: **High flow nasal cannula is a good treatment option for COVID-19**. *Heart Lung* 2020.
9. Wang K, Zhao W, Li J, Shu W, Duan J: **The experience of high-flow nasal cannula in hospitalized patients with 2019 novel coronavirus-infected pneumonia in two hospitals of Chongqing, China**. *Ann Intensive Care* 2020, **10**(1):37.
10. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A: **A global clinical measure of fitness and frailty in elderly people**. *CMAJ* 2005, **173**(5):489-495.
11. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: **Toxicity and response criteria of the Eastern Cooperative Oncology Group**. *Am J Clin Oncol* 1982, **5**(6):649-655.
12. Bilan N, Dastranji A, Ghalehgalab Behbahani A: **Comparison of the spo2/fio2 ratio and the pao2/fio2 ratio in patients with acute lung injury or acute respiratory distress syndrome**. *J Cardiovasc Thorac Res* 2015, **7**(1):28-31.
13. Evaluatie SNIC: **COVID-19 in Dutch Intensive Care Units; Patient characteristics and outcomes compared with pneumonia patients in the ICU from 2017-2019**. In.; 2020.
14. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R *et al*: **Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy**. *JAMA* 2020.
15. Auld SC, Caridi-Scheible M, Blum JM, Robichaux C, Kraft C, Jacob JT, Jabaley CS, Carpenter D, Kaplow R, Hernandez-Romieu AC *et al*: **ICU and Ventilator Mortality Among Critically Ill Adults With Coronavirus Disease 2019**. *Crit Care Med* 2020.

16. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X *et al*: **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.** *Lancet* 2020, **395**(10229):1054-1062.
17. Liang WH, Guan WJ, Li CC, Li YM, Liang HR, Zhao Y, Liu XQ, Sang L, Chen RC, Tang CL *et al*: **Clinical characteristics and outcomes of hospitalised patients with COVID-19 treated in Hubei (epicenter) and outside Hubei (non-epicenter): A Nationwide Analysis of China.** *Eur Respir J* 2020.
18. So RKL, Bannard-Smith J, Subbe CP, Jones DA, van Rosmalen J, Lighthall GK, investigators Ms: **The association of clinical frailty with outcomes of patients reviewed by rapid response teams: an international prospective observational cohort study.** *Crit Care* 2018, **22**(1):227.
19. Brummel NE, Bell SP, Girard TD, Pandharipande PP, Jackson JC, Morandi A, Thompson JL, Chandrasekhar R, Bernard GR, Dittus RS *et al*: **Frailty and Subsequent Disability and Mortality among Patients with Critical Illness.** *American journal of respiratory and critical care medicine* 2017, **196**(1):64-72.
20. Zangrillo A, Beretta L, Scandroglio AM, Monti G, Fominskiy E, Colombo S, Morselli F, Belletti A, Silvani P, Crivellari M *et al*: **Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy.** *Crit Care Resusc* 2020.
21. Todd OM, Wilkinson C, Hale M, Wong NL, Hall M, Sheppard JP, McManus RJ, Rockwood K, Young J, Gale CP *et al*: **Is the association between blood pressure and mortality in older adults different with frailty? A systematic review and meta-analysis.** *Age Ageing* 2019, **48**(5):627-635.
22. Spoletini G, Hill NS: **High-flow nasal oxygen versus noninvasive ventilation for hypoxemic respiratory failure: Do we know enough?** *Ann Thorac Med* 2016, **11**(3):163-166.
23. Marini JJ, Gattinoni L: **Management of COVID-19 Respiratory Distress.** *JAMA* 2020.
24. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J: **Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review.** *PLoS One* 2012, **7**(4):e35797.
25. Loh NW, Tan Y, Taculod J, Gorospe B, Teope AS, Somani J, Tan AYH: **The impact of high-flow nasal cannula (HFNC) on coughing distance: implications on its use during the novel coronavirus disease outbreak.** *Can J Anaesth* 2020.
26. Raboud J, Shigayeva A, McGeer A, Bontovics E, Chapman M, Gravel D, Henry B, Lapinsky S, Loeb M, McDonald LC *et al*: **Risk factors for SARS transmission from patients requiring intubation: a multicentre investigation in Toronto, Canada.** *PLoS One* 2010, **5**(5):e10717.

## Tables

Table 1 Demographics and medication use in COVID-19 patients.

Total (n= 32)	non-survivor (n= 24)	survivor (n= 8)	p value		
<b>Age</b>	79.0 (74.5-83.0)	80.5(78.0-84.3)	69.5 (65.5-74.3)	0.0040	
<b>Gender (male)</b>	22 (69%)	17 (71%)	5 (62%)	0.6808	
<b>Body Mass Index</b>	27.1 (26.3-31.4)	27.5 (26.4-31.3)	27.0(26.2-30.7)	0.9764	
<b>Comorbidities</b>	<i>Hypertension</i>	24 (75%)	22 (92%)	2 (25%)	0.0008
<i>Diabetes</i>	14 (44%)	9 (38%)	5 (62%)	0.2517	
<i>Chronic Obstructive Lung Disease</i>	5 (16%)	5 (21%)	0 (0%)	0.2964	
<i>Asthma</i>	3 (9%)	1 (4%)	2 (25%)	0.1468	
<i>Chronic Kidney Disease</i>	13 (41%)	12 (50%)	1 (12%)	0.1006	
<i>Malignancy</i>	11 (34%)	9 (38%)	2 (25%)	0.6808	
<i>Occlusive Peripheral Arterial Disease</i>	7 (22%)	4 (17%)	3 (38%)	0.3265	
<i>Non-ischemic Heart Disease</i>	11 (34%)	9 (38%)	2 (25%)	0.6808	
<i>Ischemic Heart Disease</i>	13 (41%)	10 (42%)	3 (38%)	1.000	
<i>Neurovascular Disease</i>	6 (19%)	6 (25%)	0 (0%)	0.2964	
<i>Liver Disease</i>	4 (12%)	2 (8%)	2 (25%)	0.2542	
<i>Total number of comorbidities</i>	3 (3-4)	3 (3-4)	3 (3-3)	0.5035	
<b>Smoking</b>	<i>Current</i>	5 (16%)	4 (17%)	1 (12%)	1.000
<i>Former</i>	6 (19%)	5 (21%)	1 (12%)	1.000	
<b>Performance scores</b>	<i>Clinical Frailty score</i>	4 (3-6)	4 (4-6)	4(4-6)	0.4350
<i>WHO Performance score</i>	2 (2-4)	2 (2-4)	2 (2-3)	0.6773	
<i>Medication</i>					
<b>In-hospital Medication</b>	<i>Cefuroxim</i>	31 (97%)	23 (96%)	8 (100%)	1.000
<i>Azitromycin</i>	32 (100%)	24 (100%)	8 (100%)	-	
<b>Out of hospital Medication</b>	<i>Immunosuppressives</i>	3 (9%)	2 (8%)	1 (12%)	1.000

<i>NSAID's</i>	2 (6%)	2 (8%)	0 (0%)	1.000
<i>ACE-inhibitors</i>	9 (28%)	7 (29%)	2 (25%)	1.000
<i>Total number of chronic medications</i>	7 (5-10)	7 (6-9)	8 (4-12)	0.8781

Data are presented as n (%) or median (IQR).

Table 2 Clinical symptoms and admission duration in COVID-19 patients.

<b>Total (n= 32)</b>	<b>non-survivor (n= 24)</b>	<b>survivor (n= 8)</b>	<b>p value</b>		
<b>Clinical Symptoms</b>	<i>Cough</i>	29 (91%)	22 (92%)	7 (88%)	1.000
<i>Dyspnea</i>	27 (84%)	20 (83%)	7 (88%)	1.000	
<i>Weight loss</i>	2 (6%)	1(4%)	1(12%)	0.4435	
<i>Diarrhea</i>	11 (34%)	8(33%)	3(38%)	1.000	
<i>Nausea</i>	5 (16%)	4(17%)	1(12%)	1.000	
<i>Respiratory Rate</i>	23 (20-26)	23 (20-25)	24 (16-26)	0.8428	
<i>Respiratory Rate &gt;24</i>	10 (31%)	6 (25%)	4 (50%)	0.2182	
<i>MAP &gt;65</i>	31 (97%)	23 (96%)	8 (100%)	1.000	
<i>Heart rate</i>	92 (77-102)	92 (77-102)	91(78-99)	0.8446	
<i>Fever (&gt;38 or &lt;36 C)</i>	11 (34%)	9 (38%)	2 (25%)	0.6808	
<b>Time between symptom onset and admission (days)</b>	6 (4-14)	5.5 (4-13)	7 (5-12)	0.7967	
<b>Admission duration (days)</b>	6 (3.8-12.8)	4.9 (3.5-8.1)	15.2 (12.3-25.9)	0.0006	

Data are presented as n (%) or median (IQR).

Table 3 Laboratory markers and radiological findings in COVID-19 patients.

Total (n= 32)	non-survivor (n= 24)	survivor (n= 8)	p value		
<i>Laboratory Markers</i>					
<b>White Bloodcell Count</b> (x10 <sup>9</sup> /L)	7.0(5.2-10.7)	7.6 (6.2-10.9)	5.2 (5.0-6.3)	0.0385	
<b>Absolute Lymfocyt Count</b> (x10 <sup>9</sup> /L)	1.0 (0.7-1.4)	0.9 (0.6-1.4)	1.1 (1.0-1.4)	0.2696	
<b>Haemoglobin</b> (mmol/L)	8.1 (7.4-8.9)	8.1 (7.0-8.9)	8.5 (8.0-9.2)	0.2667	
<b>Platelet Count</b> (x10 <sup>9</sup> /L)	211 (180-281)	207 (182-279)	242 (182-335)	0.6037	
<b>Alanine aminotransferase</b> (U/L)	31 (25-40)	30 (25-39)	34 (29-40)	0.3602	
<b>Aspartate aminotransferase</b> (U/L)	59 (45-68)	54 (39-68)	60 (59-67)	0.2759	
<b>Lactate dehydrogenase</b> (U/L)	409(296-528)	391 (280-581)	424 (395-517)	0.5568	
<b>D-Dimer</b> (mg/L)	1.4 (1.0-3.7)	1.34(1.0-3.7)	1.3 (1.0-2.3)	0.7696	
<b>Procalcitonin</b> (µg/L)	0.17 (0.12-0.36)	0.22 (0.16-0.51)	0.12 (0.1-0.16)	0.0335	
<b>Ferritin</b> (µg/L)	695 (373-1313)	884 (397-1438)	498 (386-794)	0.3165	
<b>C-reactive protein</b> (mg/L)	111 (67-141)	111 (66-141)	119 (76-146)	0.8447	
<i>Radiological findings</i>					
<b>Chest X-Ray</b>	<i>Bilateral Pulmonary Infiltration</i>	23 (72%)	16 (67%)	7 (88%)	0.3858
	<i>Unilateral Pulmonary Infiltration</i>	5 (16%)	5 (21%)	0 (0%)	0.2964
	<i>No Pulmonary Infiltration</i>	4 (12%)	3 (12%)	1 (12%)	1.000
<b>Computed Tomography scan</b>	12 (38%)	8 (33%)	4 (50%)	0.4325	
<b>Pulmonary embolism</b>	5 (45%)	4 (57%)	1 (25%)	0.5455	

Data are presented as n (%) or median (IQR).

Table 4 HFNC settings and use in COVID-19 patients.

Total (n= 32)	non-survivor (n= 24)	survivor (n= 8)	p value		
<b>HFNC Settings</b>	<i>Fio2 Start%</i>	60 (60-80)	60 (60-83)	75 (60-80)	0.9272
<i>Fio2 Max%</i>	95 (80-95)	95 (88-95)	93 (78-95)	0.2276	
<i>Flow Start L/min</i>	60 (60-60)	60 (60-60)	60 (60-60)	-	
<i>Flow Max L/min</i>	60 (60-60)	60 (60-60)	60 (60-60)	-	
<b>10% FiO2 increase in first 24 hours</b>	21 (66%)	16 (67%)	5 (62%)	1.000	
<b>SPO2/FiO2 Ratio start HFNC</b>	157.5 (150.0-163.3)	157.5 (148.8-162.1)	157.5 (152.5-164.2)	0.5560	
<b>HFNC Duration (days)</b>	2.5 (1.0-4.3)	2.0 (1.0-3.0)	9.5 (4.8-17.5)	0.0012	
<b>Duration between admission and HFNC start (days)</b>	2.0 (1.0-4.0)	2.0 (1.0-4.0)	3.5 (1.8-4.2)	0.2893	
<b>Reasons for HFNC failure</b>	<i>Persisting hypoxemia</i>	22 (69%)	22 (92%)	0	-
<i>Toleratation issues</i>	2(6%)	2 (8%)	0	-	

Data are presented as n (%) or median (IQR).