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High flow nasal cannula oxygenation in COVID-19 related acute respiratory distress syndrome: a safe way to avoid endotracheal intubation?

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Abstarct

Backgrounds: High flow nasal cannula (HFNC) is an alternative therapy for acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19). This study aimed first to describe outcomes of patients suffering from COVID-19-related ARDS treated with HFNC; secondly to evaluate safety of HFNC (patients and healthcare workers) and compare patients according to respiratory outcome.

Methods: A retrospective cohort was conducted in French general hospital intensive care unit (ICU). Patients were included if receiving HFNC for hypoxemia (saturation pulse oxygen (SpO_2) <92% under oxygen ⩾6 L/min) associated with ARDS and positive SARS-CoV-2 polymerase chain reaction (PCR). Main clinical characteristics and outcomes are described in patients: (a) with do not intubate order (HFNC-DNIO); (b) who did not need intubation (HFNC-only); and (c) eventually intubated (HFNC-intubation). Medians are presented with (1st–3rd) interquartile range.

Results: From 26 February to 30 June 2020, 46 patients of median age 75 (70–79) years were included. In the HFNC-DNIO group ($n = 11$), partial arterial oxygen pressure (PaO_2)/inhaled fraction of oxygen (FiO_2) ratio median worst PaO_2/FiO_2 ratio was 109 (102–172) and hospital mortality was 54.5%. Except the HFNC-DNIO patients ($n = 35$), 20 patients (57%) were eventually intubated (HFNC-intubation group) and 15 were only treated by HFNC (HFNC-only). HFNC-intubation patients presented higher worst respiratory rates per minute in ICU [37 (34–41) *versus* 33 (24–34) min, $p < 0.05$] and worsened ICU admission PaO_2/FiO_2 ratios [121 (103–169) *versus* 191 (162–219), $p < 0.001$] compared with HFNC-only patients. Hospital mortality was 35% ($n = 7/20$) in HFNC-intubation group, 0% in HFNC-only group with a global mortality of these two groups of 20% ($n = 7/35$). Among tests performed in healthcare workers, 1/12 PCR in symptomatic healthcare workers and 1.8% serologies in asymptomatic healthcare workers were positive. After review of each case, COVID-19 was likely to be acquired outside hospital.

Conclusions: HFNC seems to be useful for COVID-19-related ARDS and safe for healthcare workers. ARDS severity with PaO_2/FiO_2 <150 associated with respiratory rate >35/min could be regarded as a predictor of intubation.

The reviews of this paper are available via the supplemental material section.

Keywords: ARDS, COVID-19, HFNC, intubation rate, SARS-Cov-2

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Introduction

The SARS CoV-2 coronavirus disease 2019 (COVID-19)[1–4] ranges from asymptomatic to acute respiratory distress syndrome (ARDS)[5–7] leading to 5–7.4% intensive care unit (ICU) admission.[1,3] Invasive mechanical ventilation concerns 42–71% of these patients.[8,9] Global ICU COVID-19 mortality rate ranges from 26%[10] to 65%.[9,11]

High flow nasal cannula (HFNC) oxygenation emerged to prevent intubation for mild to severe ARDS,[12–15] but is still subject to debate; in COVID-19-related ARDS due to potential HFNC induced viral aerosolization which may contaminate healthcare workers.[16–21] With regard to conventional pathophysiology of ARDS, COVID-19 has some particularities at the initial stage: a preserved compliance and high oxygen shunt which could sustain the hypothesis of loss of adapted hypoxic vasoconstriction[22] which would be in favor of preserving spontaneous breathing as far as possible. Early guidelines were either against[23] or in favor[24] of HFNC. Several small studies report that use of HFNC (17 patients,[11] 33 patients)[8] seems to limit the intubation rate (respectively, 41.1 and 42%) compared to 71.0–88.0%[9,10] in studies with no or limited HFNC use (<5%).

Vannes (Morbihan, France) was one of the first clusters of cases in France (first case 26 February), before national and international guidelines publication. In view of increased COVID-19 hospitalization (24 COVID-19 admissions within 15 days at the beginning of March 2020) and limited availability of ventilators (20 ICU beds), our ICU and pneumology department decided to use HFNC with strict protective measures after infectiologist agreement. We then conducted a retrospective analysis of the COVID-19-related ARDS patients treated with HFNC in order to assess the intubation rates, evaluate patients' outcomes and safety for healthcare workers. The originality of our study was the creation of a COVID-19 acute-HFNC-pneumology department in order to spare ICU beds; the study of patients prior limited to life sustaining therapy and the investigation of healthcare workers' exposition.

Materials and methods

Study design

This is a retrospective monocenter analysis conducted in a secondary hospital in Vannes, France between 26 February 2020 and 30 June 2020.

The primary end point was to describe outcomes of patients treated with HFNC for COVID-19-related ARDS (intubation rate, mortality, and hospital length of stay). The secondary end points were to evaluate safety of HFNC (for patients and healthcare workers) and to compare characteristics of patients according to respiratory outcome (intubation requirements).

Population

Inclusion criteria: all adult patients (over 18 years old) with a COVID-19-related ARDS diagnosis and treated by HFNC were eligible.

Berlin criteria diagnoses for ARDS were: acute respiratory symptoms with bilateral opacities on chest-X rays and a partial arterial oxygen pressure (PaO_2)/inhaled fraction of oxygen (FiO_2) ratio under 300.[25] According to PaO_2/FiO_2 ratio, ARDS was classified as mild (200–300), moderate (100–200) or severe (<100). The COVID-19 etiology was obtained with positive SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction (RT-PCR) (Laboratory of Rennes and Brest University Hospital or Quimper Hospital, France) tested on nasal and/or pharyngeal swab samples or broncho-alveolar lavage.

Patients were treated by HFNC when French-speaking resuscitation society (Société de Réanimation de Langue Française) criteria for theoretical endotracheal intubation[23] appear: saturation pulse oxygen (SpO_2) $\leqslant$92% on standard oxygen $\geqslant$6 L/min.

Exclusion criteria: pregnant women, patients under legal protection and refusal to participate.

Three groups were defined: patients with prior do not intubate order (HFNC-DNIO group), patients treated with HFNC who were not intubated (HFNC-only group, DNIO patients excluded) and HFNC-intubation group when requiring mechanical ventilation after HFNC use.

Patients were intubated depending on physician decision, based on the following: hypoxia with SpO_2 $\leqslant$90% despite FiO_2 $\geqslant$80% associated with one of the following: respiratory rate >35/min or use of accessory respiratory muscles or inability to clear tracheal secretions or deterioration of consciousness.

Data collection

We reviewed clinical electronic medical records, nursing records, laboratory findings, and radiological examinations for all patients.

We collected the following data: (a) demographic characteristics; (b) past medical histories; (c) decision to limit life-sustaining therapy, including DNIO; (d) symptoms onset, vital signs, and severity scores namely SOFA (sequential organ failure assessment) and APACHE II (acute physiology and chronic health evaluation) score[26,27] upon admission; (e) arterial blood gas analysis; (f) oxygenation, ventilation and organ supports (vasopressors).

Department organization

An acute-HFNC-pneumology department (without continuous monitoring) was created in the pneumology department for HFNC patients treated with FiO_2 40–60% and/or for patients with DNIO. Of note, HFNC was routinely used in the pneumology department since Frat *et al.*[12] study, especially for DNIO patients. The nurse ratio was increased compared to the traditional pneumology department. The 56 healthcare workers were, as possible in this sanitary crisis, dedicated to the HFNC beds. Patients with FiO_2 ⩾60% under HFNC were transferred to a conventional ICU. Non-invasive mechanical ventilation was not used in our cohort. In ICU departments, healthcare workers treated COVID-19 patients with either HFNC or invasive mechanical ventilation; and non-COVID-19 patients.

HFNC was delivered as recommended: 50–60 L/min, 34–37°C.[28] Once HFNC was started, the therapy was maintained 24 h/24 h until weaning seemed possible (when FiO_2 reached 30%). Awake prone position under HFNC was not performed during this study period.

Neither acute-HFNC-pneumology department nor ICU department are equipped with a negative pressure room. All intubated patients had closed circuit ventilation. Healthcare workers were protected with FFP2 (filtering face piece type 2) masks, overcoat gowns, glasses, hat and gloves. Patients did not wear surgical masks.

Symptomatic healthcare workers were tested by PCR at the onset of symptoms. A serological test was proposed to asymptomatic healthcare workers in June 2020 to evaluate the contamination rate. Serological testing used total antibodies (including IgG) directed toward SARS-CoV-2 nucleocapside, using electrochemiluminescence immunoassay (Roche).

Ethics

The study was approved by Rennes academic hospital ethics committee (no. 20.32) and National Commission for Data Protection (Commission Nationale de l'Informatique et des Libertés, CNIL, no. 2217312). All living patients received oral and written information and non-opposition was collected.

Statistical analysis

Continuous variables are presented as median (1st–3rd interquartile range) and categorical variables by frequencies. Continuous data were tested with Mann–Whitney test and nominal variables were compared with a chi-square test or Fisher's exact test, depending on sample size. The p value <0.05 in two-tailed test was considered significant. Statistical analysis was performed with StatView 5.0 software.

Results

Population

From 20 February 2020 to 30 June 2020, 378 patients were diagnosed with virologically confirmed COVID-19 (flow chart, Figure 1). Forty-six patients who received HFNC as first line therapy were included. No patient opposed enrolment. Fourteen patients (30.4%) only stayed in acute-HFNC-pneumology department without need for conventional ICU transfer.

Demographic characteristics

The baseline characteristics of the 46 patients are summarized in Table 1. Of note, after excluding DNIO patients 15/35 patients (42.9%) were ⩾75 years old, 19 (41.3%) and only two (5%) less than 50 years old. Sex ratio M/F was 3.2. Forty (86.9%) patients had co-morbidities. All patients had ARDS, with a mean PaO_2/FiO_2 of 227 (196–292).

Comparing demographic characteristic between HFNC-only and HFNC-intubation group, we especially note a difference regarding smoking habits (0% in HFNC-only group *versus* 50% in HFNC-intubation group).

Admission and ICU parameters

Median delay from SARS-CoV-2 symptoms onset to ICU admission (conventional and pneumology) was 8 days (7–9) and to intubation was 9

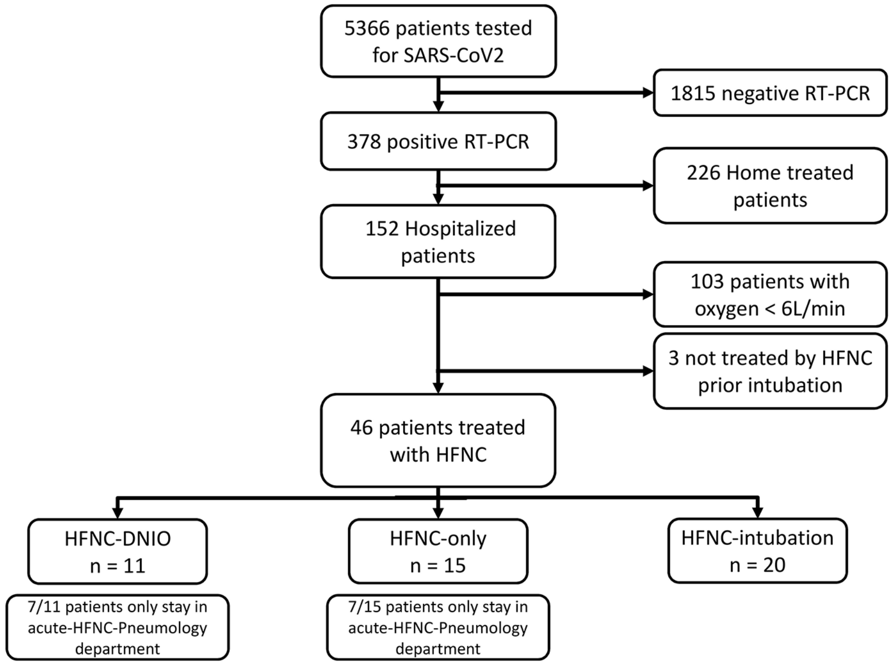

Figure 1. Flow chart.

days (9–11) (see Figure 2), with a peak of admission and intubation, respectively, of 8 and 9 days after symptoms onset (Table 1).

With the exception of the 11 HFNC-DNIO patients, 20/35 (57%) were eventually intubated.

As expected, intubated patients were more severe (see Figure 3): they presented higher worst respiratory rates per minute [37 (34–41) *versus* 33 (24–34) min, $p < 0.05$] and worsened admission PaO_2/FiO_2 ratios [121 (103–169) *versus* 191 (162–219), $p < 0.001$]. Severe ARDS concerned only patients in the HFNC-intubation group (75% of them) and none of them had mild ARDS. Most of HFNC-only patient had moderate ARDS (73%).

Outcomes

In the HFNC-DNIO group, hospital mortality was 54.5% (6/11) (Table 1). Death occurred in a median of 17 [10–17] days from onset of the symptoms, all related to refractory ARDS in ICU.

HFNC-DNIO patients excluded, mortality was 20.0% (7/35), of all deaths occurring in ICU. No patient in the HFNC-only group died. In the HFNC-intubation group, 7/20 patients died (35%), with a median time from onset of symptoms of 32 (26–39) days. No severe adverse effect occurred during intubation procedure. Six patients were intubated >48 h after HFNC initiation, of whom two died after extubation and ARDS resolution more than 3 weeks after admission. Concerning the remaining five deaths, medical staff decided to limit life-sustaining therapy while still intubated for five patients (all died). Mortality increases with the severity of ARDS with a mortality of 0% for mild, 12.5% for moderate and 38.5% for severe ARDS.

Healthcare workers

The cohort was cared for by 148 healthcare workers (30 physicians, 66 nurses, 3 physiotherapists, 2 psychologists, 2 dieticians and 45 other healthcare workers). Twelve healthcare workers presented mild COVID-19-like symptoms: fever, dry cough, throat pain. No one had pneumonia. Only one was PCR SARS-CoV-2 positive but physicians concluded certain home contamination by his relatives coming back from a bigger cluster in eastern France. Among the 74.3% asymptomatic healthcare workers tested by SARS-CoV-2 serology (110/148), two (1.8%) were positive (one nurse in acute pneumology-department and one

Table 1. Demographic characteristics and parameters upon hospital admission.

	Total ($n = 46$)	HFNC-DNIO ($n = 11$)	HFNC-only ($n = 15$)	HFNC-intubation ($n = 20$)[a]
Demographic data				
Age, years	75 [70–79]	80 [75–86]	73 [70–76]	74 [63–79]
Male, *n* (%)	35 (76)	8 (72)	11 (73)	16 (80)
Chronic heart disease, *n* (%)	13 (28)	4 (36)	6 (40)	3 (15)
Chronic renal disease, *n* (%)	7 (9)	3 (27)	0 (0)	1 (5)
Chronic respiratory disease, *n* (%)	8 (17)	3 (27)	2 (13)	3 (15)
Hypertension, *n* (%)	26 (57)	11 (100)	6 (40)	9 (45)
Diabetes, *n* (%)	15 (33)	4 (36)	3 (20)	8 (40)
Tobacco, *n* (%)	15 (35)	4 (36)	0 (0)	10 (50)*
BMI, kg/m² ($n = 42$)	26.9 [24.1–31.3]	25.6 [23.3–28.5]	26.5 [24.0–30.0]	28.5 [25.0–31.7]
Parameters upon hospital admission				
Delay from symptoms to hospital admission	7 [4–8]	5 [3–9]	7 [2–8]	7 [6–8]
SpO_2, %	90 [86–95]	94 [91–94]	89 [87–95]	90 [87–93]
Respiratory rate per minute ($n = 22$)	28 [24–31]	28 [21–29]	35 [30–40]	27 [24–31]
Temperature (C°)	38 [37.7–38.6]	38 [37.8–38.5]	38 [37.2–38.4]	38.5 [37.9–39]
Glasgow scale	15 [15–15]	15 [15–15]	15 [14–15]	15 [15–15]
PaO_2/FiO_2 ratio ($n = 41$)	227 [196–292]	226 [211–256]	248 [225–303]	207 [158–298]
Lactate level, mmol/L ($n = 30$)	1.3 [1–1.9]	1.2 [1–1.8]	1.7 [1.1–2.5]	1.1 [0.9–1.5]
Lymphocytes, G/L	0.81 [0.58–1.12]	1.03 [0.64–1.33]	0.86 [0.55–1.04]	0.72 [0.58–0.96]
Maximal FiO_2 before HFNC (%)	39 [36–47]	36 [36–39]	39 [39–39]	42 [39–57]*
Parameters on ICU admission				
Delay from symptoms to ICU admission	8 [6–11]	8 [5.5–12]	7 [6–11]	8 [7–9]
Admission PaO_2/FiO_2 ($n = 43$)	158 [117–191]	127 [117–208]	191 [162–219]	121 [103–169]***
Respiratory SOFA score	3 [2–3]	3 [2–3]	2 [2–3]	3 [3–3]**
SOFA score	3 [3–4]	3 [2–3]	3 [3–4]	4 [3–4]
APACHE II score	10 [8–13]	13 [9–15]	9 [8–11]	11 [7–12]
Parameters during ICU				
Worst respiratory rate per minute ($n = 28$)	34 [30–39]	34 [28–39]	33 [24–34]	37 [34–41]*
Worst PaO_2/FiO_2[b]	108 [87–158]	109 [102–172]	167 [140–190]	90 [76–105]**
Maximal FiO_2 under HFNC (%)	80 [60–80]	85 [73–90]	60 [50–60]	80 [80–80]***

(Continued)

Table 1. (Continued)

	Total ($n=46$)	HFNC-DNIO ($n=11$)	HFNC-only ($n=15$)	HFNC-intubation ($n=20$)[a]
HFNC duration, days	5 [2–8]	8 [5–10]	6 [4–8]	2 [1–5]**
Mechanical ventilation duration, day	ND	ND	ND	13 [9–20]
Neuromuscular blockers, *n* (%)	ND	ND	ND	19 (95)
Decubitus ventral session, *n* (%)	ND	ND	ND	12 (60)
Outcomes				
ICU length of stay, day	13 [8–18]	11 [7–14]	9 [7–13]	18 [14–25]**
Hospital length of stay,[c] median (day)	21 [14–33]	17 [10–43]	17 [10–23]	27 [19–41]**
Hospital mortality, *n* (%)	13 (28.2)	6 (54.5)	0 (0)	7 (35.0)

Continuous variables are presented as median (Q1–Q3) and categorical variables with *n* of patients (percentage). Continuous data were tested with Mann–Whitney test and nominal variables with a chi-square test or Fisher's exact test. FiO_2 equivalence with conventional oxygen therapy was calculated with the formula: oxygen flow $\times 0.03 + 0.21$.
[a]Statistical tests compare HFNC-only and HFNC-intubation group (not HFNC-DNIO), with *p* value as follows: *$p \leqslant 0.05$; **$0.001 \leqslant p < 0.05$; ***$p < 0.0001$.
[b]Worst PaO_2/FiO_2 ratio was calculated during HFNC if HFNC alone, and just before intubation in HFNC-intubation group.
[c]Hospital length of stay include rehabilitation care.
BMI, body mass index (kg/m²); DNIO, do-not-intubate order; FiO_2, inspired fraction oxygen; HFNC, high flow nasal cannula; ICU, intensive care unit; ND, not defined; *p*, *p*-value; PaO_2, partial pressure oxygen; Q1, 1st interquartile range; Q3, 3rd interquartile range; SpO_2, pulse saturation of oxygen.

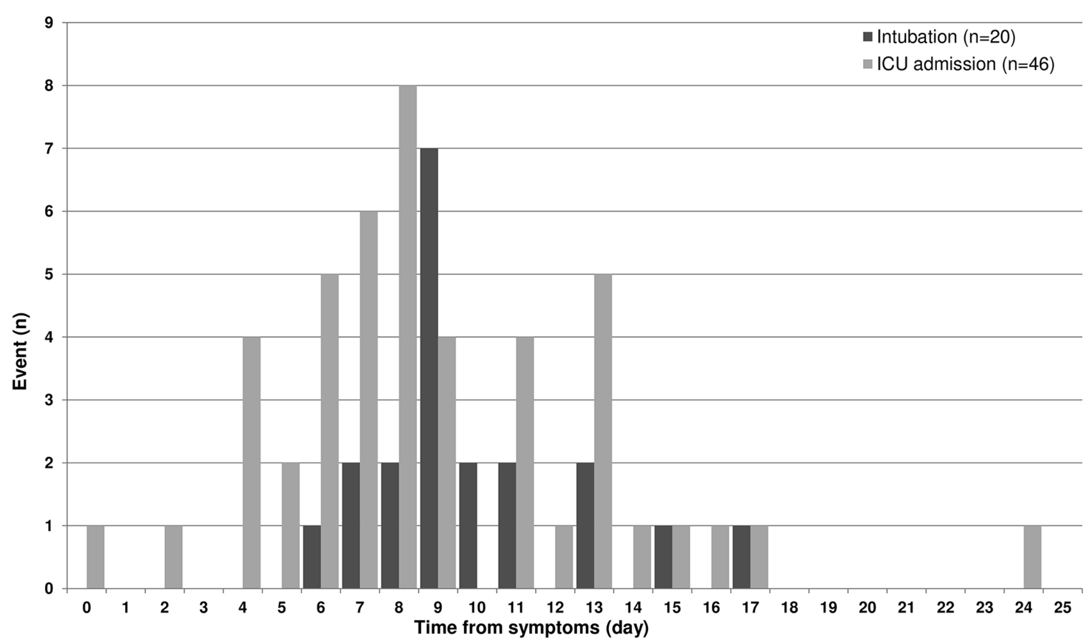

Figure 2. Delay from symptoms onset to intensive care unit (ICU) admission and intubation (for HFNC-intubation group). The delay from symptoms to ICU admission concerns first ICU admission (pneumology ICU or conventional ICU).
HFNC, high flow nasal canula.

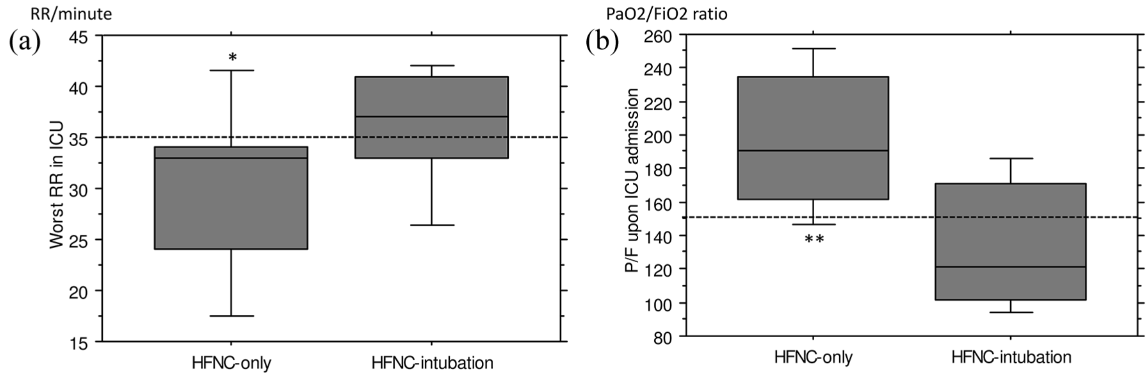

Figure 3. (a) Box plot representing PaO_2/FiO_2 ratio upon ICU admission in both HFNC-only and HFNC-intubation groups. (b) Box plot representing worst respiratory rate during ICU in both HFNC-only and HFNC-intubation groups. ICU includes conventional ICU and acute pneumology department.
**p* < 0.05; ***p* < 0.001.
HFNC, high flow nasal canula; P/F, PaO_2/FiO_2; RR; respiratory rate per minute.

caregiver in conventional ICU), without sufficient data for work-related infection.

Discussion

The first major point of this observational study is that our patients treated with HFNC for ARDS-related COVID-19 had a good outcome.

Using conventional criteria for intubation, we reported a 57% intubation rate. Wang *et al.*[11] reported a 42% intubation rate but the study included a limited number of patients ($n = 17$) and involved patients less severe: baseline ICU PaO_2/FiO_2 ratio in HFNC-only compared to HFNC-intubation groups was 223 and 159, respectively, *versus* 191 and 121 in our cohort. In Yang *et al.*[8] study, patients were younger, with a median age of 59.7 years old compared with 75 years old in our study, with a 41% intubation rate. Grasselli *et al.*[10] and Auld *et al.*[29] studies report, respectively, 88% and 76% invasive mechanical ventilation, in cohorts without HFNC use (non-invasive mechanical ventilation was applied for 11% patients in the Grasseli study). No randomized trial allows strong conclusion about preventing intubation in COVID-19 patients with HFNC.[30]

Mortality rate of the HFNC-intubation group was not higher than expected for neither ARDS patients nor COVID-19 patients in ICU. Indeed, overall hospital mortality rate of patients without DNIO was 20% (respectively, 0% and 35% in HFNC-only and HFNC-intubation groups). Our 0%, 12.5% and 38.5% hospital mortality rate in patients with mild, moderate or severe ARDS was lower if compared with 34.9%, 40.3% and 46.1% in general ARDS described in the LUNG SAFE study.[31] In COVID-19, a wide variation of mortality rates are reported in patients, ranging from 26%[10] (58% of the cohort still in the ICU at the time of publication), 30.9%,[29] 52.4%[9] or 61.5%[8] depending on studies. Mortality increased in patients >63 years old (36% *versus* 15%), the population largely represented in our cohort.[10]

There is still debate on whether timing and or clinico-biological parameters should guide physicians to decide upon intubation procedure.[32] Kang *et al.*[33] report that in patients with HFNC failure, ICU mortality of patients intubated after 48 h was higher (39.2 *versus* 66.7, $p = 0.001$). In our cohort, six patients were intubated after 48 h of HFNC therapy, the two deaths to deplore did not seem linked to delayed intubation. Considering that the HFNC-intubation group presented higher worst mean respiratory rates per minute [37 (34–41) *versus* 33 (24–34) min, $p < 0.05$] and worsened mean admission PaO_2/FiO_2 ratios [121 (103–169) *versus* 191 (162–219), $p < 0.001$], the association of a $PaO_2/FiO_2 < 150$ with a respiratory rate >35/min upon admission could help for intubation decision in COVID-19 patients. Indeed, an ICU (acute pneumology department or conventional ICU) PaO_2/FiO_2 ratio admission >150 and a worst respiratory rate <35/min seem to well classified patients who were not undergoing intubation.

In addition, HFNC could be considered as rescue therapy in DNIO patients: we currently report a 54.5% mortality rate. As previously described in Koyauchi *et al.*[34] HFNC ensures end of life comfort, allowing better communication and easier feeding for these patients.

The last major point is the fact that hospital-acquired COVID-19 was not observed in healthcare workers, which remains a serious concern for medical societies.[16,35] All symptomatic healthcare workers were tested with RT-PCR, with no positive test attributable to their professional activity. Only one nurse presented virologically confirmed COVID-19 but he was obviously infected at home by his parents. Among the 74.3% asymptomatic healthcare workers who accepted to be tested, 1.8% had positive SARS-CoV-2. Even at admission peak in early April, hospital influx did not reach total saturation, which enables us to respect optimal protection to healthcare workers.

Our study has several limitations. The retrospective design and sample size did not allow multivariate analysis. Due to retrospective analysis, time from symptoms to chest X-ray or computed tomography (CT) scan was too heterogeneous to be analyzed. Serological testing in healthcare workers was heterogeneous (only 110 healthcare workers tested on the 148 exposed) without precise timing, due to retrospective analysis, healthcare workers motivation (no obligation to perform the serology) and tests availability.

Conclusion

HFNC seems a safe therapy in order to avoid intubation in COVID-19-related ARDS patients, regarding the 20% hospital mortality rate (except HFNC-DNIO patients). ARDS severity with $PaO_2/FiO_2 < 150$ associated with respiratory rate > 35/min could be regarded as a predictor of intubation. Only one COVID-19 related to out-hospital acquisition and 1.8% of positive serologies in asymptomatic were observed in healthcare workers. Further studies with prospective and randomized design are needed.

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Authorship statement

AD, AF, FM, TG, and MG: have made the conception and design of the study, acquisition of data, analysis and interpretation of data; have drafted the article, revised it critically for important intellectual content and final approved of the version and to be submitted.

AD, AF, and MG: wrote the manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Informed consent

All living patients received oral and written information and non-opposition was collected.

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Supplemental material

The reviews of this paper are available *via* the supplemental material section.

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