High-flow nasal oxygen alone or alternating with non-invasive ventilation in critically ill immunocompromised patients with acute respiratory failure: a randomised controlled trial

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Summary

Background Although non-invasive ventilation (NIV) is recommended for immunocompromised patients with acute respiratory failure in the intensive care unit (ICU), it might have deleterious effects in the most severe patients. High-flow nasal oxygen (HFNO) alone might be an alternative method to reduce mortality. We aimed to determine whether HFNO alone could reduce the rate of mortality at day 28 compared with HFNO alternated with NIV.

Methods FLORALI-IM is a multicentre, open-label, randomised clinical trial conducted in 29 ICUs (28 in France and one in Italy). Adult immunocompromised patients with acute respiratory failure, defined as respiratory rate of 25 breaths per min or more and a partial pressure of arterial oxygen to inspired fraction of oxygen ratio of 300 mm Hg or lower, were randomly assigned (1:1) to HFNO alone (HFNO alone group) or NIV alternating with HFNO (NIV group). Key exclusion criteria were severe hypercapnia above 50 mm Hg, patients who could strongly benefit from NIV (ie, those with underlying chronic lung disease, with cardiogenic pulmonary oedema, or who were postoperative), severe shock, impaired consciousness defined as Glasgow coma score ≤12, urgent need for intubation, do not intubate order, and contraindication to NIV. Patients were assigned using computer-generated permuted blocks and were stratified according to centre and to the type of immunosuppression using a centralised web-based management system. In the HFNO alone group, patients were continuously treated by HFNO with a gas flow rate of 60 L/min or the highest tolerated. In the NIV group, patients were treated with NIV with a first session of at least 4 h, and then by sessions for a minimal duration of 12 h a day, with a dedicated ventilator, targeting a tidal volume below 8 mL/kg of predicted bodyweight, and with a positive end-expiratory level of at least 8 cm H_2O. NIV sessions were interspaced with HFNO delivered as in the HFNO alone group. The primary outcome was mortality at day 28 and was assessed in the intention-to-treat population. Secondary outcomes were mortality in the ICU, in hospital, at day 90 and at day 180, intubation at day 28, length of stay in the ICU and in hospital, number of ventilator-free days at day 28, number of oxygenation technique-free days at day 28, and efficacy and tolerance of oxygenation techniques. The trial is registered with ClinicalTrials.gov, NCT02978300, and is complete.

Findings Between Jan 21, 2017 to March 4, 2019, of 497 eligible patients, 300 were randomly assigned but one patient withdrew consent, leaving 299 patients included in the intention-to-treat analysis (154 assigned to the HFNO alone group and 145 assigned to NIV group). Mortality rate at day 28 was 36% (95% CI 29·2 to 44·2; 56 of 154 patients) in the HFNO alone group and 35% (27·9 to 43·2; 51 of 145 patients) in the NIV group (absolute difference 1·2% [95% CI –9·6 to 11·9]; p=0·83). None of the other prespecified secondary outcomes were different between groups except for greater decreased discomfort after initiation of HFNO than with NIV (–4 mm on visual analogic scale [IQR –18 to 4] *vs* 0 mm [–16 to 17]; p=0·040).

Interpretation In critically ill immunocompromised patients with acute respiratory failure, the mortality rate did not differ between HFNO alone and NIV alternating with HFNO. However, study power was limited, so results should be interpreted with caution.

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*Study group and research network listed in full in the appendix

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Research in context

Evidence before this study

We searched PubMed for papers published between Jan 1, 2000, and Nov 30, 2021, using the following search terms: "noninvasive ventilation" OR "non-invasive ventilation" AND "high flow" OR "high-flow" AND "immunocompromised" AND "random*". No language restrictions were used. Our search yielded three randomised trials, all of which included immunocomprosmised adult patients. The first trial found no differences between a 2-h treatment with high-flow nasal oxygen (HFNO) and conventional oxygen. Another trial found no differences between non-invasive ventilation (NIV) and conventional oxygen therapy or HFNO, the choice of which had been left at the discretion of the attending physician. The last trial also did not find any differences between conventional oxygen therapy and HFNO. Nevertheless, none of these trials compared NIV, the currently recommended treatment for immunocompromised patients, with acute respiratory failure, to HFNO alone.

Added value of this study

This multicentre, randomised, open-label, controlled trial (FLORALI-IM) showed that in immunocompromised patients with acute respiratory failure, the use of NIV alternating with HFNO or HFNO alone did not change the risk of mortality or of intubation at 28 days.

Implications of all the available evidence

The findings of the FLORALI-IM trial suggest that HFNO therapy could be an alternative to NIV for immunocompromised patients with acute respiratory failure. Adding our findings to the results of previous trials, NIV might not be recommended as firstline treatment for this particular patient population.

Introduction

The number of people who are immunocompromised has been increasing worldwide,[1,2] and they account for about 20% of intensive care unit (ICU) admissions.[3] Acute respiratory failure is the main reason for ICU admission in these patients,[4] with mortality exceeding 50% in cases where invasive mechanical ventilation is needed. Therefore, assessment of the most adequate oxygen strategy to avoid intubation in immunocompromised patients with acute respiratory failure deserves consideration.

Non-invasive ventilation (NIV) reduces the work of breathing in patients with acute hypoxaemic respiratory failure and improves oxygenation compared with conventional oxygen therapy.[5] The most recent international clinical practice guidelines suggest NIV as firstline therapy in immunocompromised patients with acute respiratory failure,[6] and they were reinforced by a network meta-analysis of all randomised trials.[7] However, in patients with vigorous breathing efforts, NIV might cause harm by increasing transpulmonary pressure and tidal volume,[8] resulting in worsened underlying lung injury[9,10] and leading to an increased risk of intubation.[8,11] Although the use of NIV was supported by two small randomised trials in immunocompromised patients conducted in the early 2000s,[12,13] this use has been challenged in a large-scale randomised trial, which did not find any benefit when compared with oxygen therapy,[14] suggesting that NIV may no longer be required as an oxygen strategy to avoid intubation. This discrepancy might be explained by the decreased risk of intubation and the decreased risk of mortality of intubated patients—possibly through more appropriate use of fluid, blood, and blood substitutes, avoidance of fluid overload, better infection management, or increased use of immunomodulating therapies—which led to decreased mortality over time in immunocompromised patients.[12–14]

High-flow nasal oxygen (HFNO) is now widely used to manage acute respiratory failure.[15,16] Like NIV, it relieves the work of breathing and improves oxygenation compared with conventional oxygen therapy.[17] Meta-analyses have suggested that HFNO might decrease intubation and mortality versus conventional oxygen therapy in patients with acute hypoxaemic respiratory failure,[18] and even versus NIV.[19] However, results from studies on immunocompetent patients might not be generalisable to immunocompromised patients insofar as immunocompromised patients are more severely ill,[20] are more likely to have bilateral infiltrates on chest x-ray,[21] have causes of respiratory failure that are difficult to identify,[22] are at increased risk of multidrug-resistant bacteria,[23] and have underlying malignancy, all of which can result in increased mortality rate after intubation. Moreover, the retrospective nature of the studies analysed in the meta-analyses meant that no firm conclusions could be made on the effectiveness of HFNO compared with NIV in immunocompromised patients.

We aimed to investigate whether NIV alternating with HFNO versus HFNO alone reduces mortality rate at day 28 in immunocompromised patients admitted to the ICU due to acute respiratory failure.

Methods

Study design and participants

FLORALI-IM is a multicentre, open-label, randomised clinical trial conducted in 29 ICUs (28 in France and one in Italy; appendix p 4). Adult immunocompromised patients admitted to participating ICUs for acute hypoxaemic (type 1) respiratory failure were considered eligible. Acute hypoxaemic respiratory failure was defined as a respiratory rate of at least 25 breaths per

min and partial pressure of arterial oxygen (PaO_2) to inspired fraction of oxygen (FiO_2) ratio equal to or below 300 mm Hg, while spontaneously breathing with standard oxygen (oxygen flow rate ≥10 L/min), with HFNO therapy, or with NIV. For patients on standard oxygen, FiO_2 was calculated according to the formula: $FiO_2 = 0{\cdot}21 + 0{\cdot}03$ per supplemental litre of oxygen.[24] Immunosuppression was defined by one of the following criteria: haematological malignancy (active or remitting <5 years), allogeneic stem cell transplantation within the last 5 years, active solid cancer, leucopenia <1 G/L or neutropenia ≤0·5 G/L induced by chemotherapy, solid organ transplantation, acquired immunodeficiency syndrome, systemic steroids ≥0·5 mg/kg per day of prednisone equivalent for at least 3 weeks, or immunosuppressive or immunomodulatory drugs.[25]

Exclusion criteria were partial pressure of carbon dioxide higher than 50 mm Hg; patients who could strongly benefit from NIV (ie, those with underlying chronic lung disease, with cardiogenic pulmonary oedema, or who were postoperative); those with severe shock, defined as a vasopressor dose of more than 0·3 µg/kg per min norepinephrine-equivalent to maintain systolic blood pressure at higher than 90 mm Hg; those with impaired consciousness with a Glasgow coma score of 12 or lower; those with an urgent need for intubation (ie, respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, severe hypoxaemia defined as pulse oximetry [SpO_2] lower than 90% despite maximum oxygen support); those with do-not-intubate order at time of inclusion; or those with contraindication to NIV according to the French consensus conference (ie, patient refusal, cardiorespiratory arrest, coma, non-drained pneumothorax, unresolved vomiting, upper airway obstruction, haematemesis, or severe facial trauma).[26]

The trial was overseen by a steering committee that presented information about the progression and monitoring of the study at Réseau Européen de Recherche en Ventilation Artificielle (REVA) Network meetings every 6 months. The accuracy of data recorded was checked regularly by research assistants. At each centre, an investigator was responsible for enrolling patients in the study, ensuring adherence to the protocol and completing the electronic case-report form according to Good Clinical Practice.

For the French participating centres, the study protocol (appendix p 24) was approved by the Ethics Committee Ouest III (Poitiers, France); for the Italian centre, the study protocol was approved by the local ethics committee. According to French law and the decision of the ethics committees, no safety committee was required given that the oxygenation strategies tested are frequently used in clinical practice. Written informed consent was obtained from all patients or next of kin before inclusion in the study.

Randomisation and masking

Patients were assigned in a 1:1 ratio to either HFNO alone (HFNO alone group) or NIV alternating with HFNO (NIV group) using computer-generated permuted blocks, and were stratified according to centre and to the type of immunosuppression (haematological malignancy or leucopenia <1 G/L or neutropenia ≤0·5 G/L *vs* others)—because patients with haematological malignancy or leucopenia <1 G/L or neutropenia ≤0·5 G/L might have poorer prognosis than the others[27]—using a centralised web-based management system. The trial was open label, so patients and investigators were aware of treatment.

Procedures

After randomisation, the strategy assigned to the patient was initiated immediately, within the first 6 h after meeting inclusion criteria. Patients assigned to the HFNO alone group were continuously treated with HFNO at a gas flow rate of 60 L/min, or the highest tolerated, through a heated humidifier (MR 850, Fisher & Paykel Healthcare, Auckland, New Zealand). Patients assigned to the NIV group were treated with NIV alternating with HFNO. NIV was initiated with a first session of at least 4 h until clinical improvement (assessed by the attending physician) and then applied by sessions for a minimum duration of 12 h a day in total. NIV was carried out with a dedicated ventilator (ICU ventilator after activation of non-invasive mode or non-invasive bi-level ventilator) in pressure-support mode with protective settings—ie, aiming for a tidal volume below 8 mL/kg of predicted bodyweight to avoid excessive inspiratory transpulmonary pressure by decreasing pressure support level or increasing positive end-expiratory pressure (the use of sedatives to decrease tidal volume was not encouraged),[28] and with a positive end-expiratory level of at least 8 cm H_2O to promote alveolar recruitment.[9,10] The interface was left to the discretion of the attending physician. NIV sessions were interspaced with HFNO delivered as in the HFNO alone group.

In both groups, FiO_2 was adjusted to obtain adequate oxygenation on SpO_2 (oxygen saturation of 92% or more) and the two strategies (HFNO alone and HFNO alternating with NIV) had to be applied for at least 48 h from randomisation. In the NIV group, NIV had to be used at least 12 h per day.

To minimise differences between centres, weaning of HFNO and NIV was standardised when respiratory rate was below 25 breaths per min and SpO_2 was at least 92% with FiO_2 of 0·50 (appendix p 5). As the cause of respiratory failure is a key factor associated with mortality, non-invasive and invasive diagnostic strategies were encouraged in both groups (appendix p 5).[29] To standardise intubation criteria among centres, intubation criteria were predetermined in both groups: neurological failure defined as agitation or altered

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See **Online** for appendix

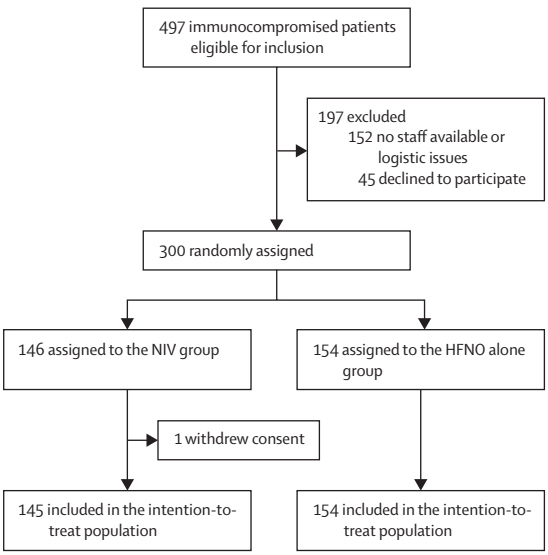

Figure 1: **Trial profile**
HFNO=high-flow nasal oxygen. NIV=non-invasive ventilation.

consciousness (Glasgow coma scale <12); haemodynamic failure defined as the need for a dose of norepinephrine of more than 0·3 µg/kg per min of norepinephrine-equivalent to maintain systolic blood pressure at 90 mm Hg; or persisting or worsening respiratory failure defined by the presence of at least two of the following criteria: respiratory rate more than 40 breaths per min, lack of improvement of high respiratory muscle workload (not defined but left at the physicians' discretion), severe hypoxaemia defined as a FiO_2 of 1·00 to maintain oxygen saturation of 92% or PaO_2/FiO_2 ratio of 100 mm Hg or less, or acidosis defined as pH less than 7·35 units.

Outcomes

The primary outcome was mortality at day 28 after randomisation. Secondary outcomes were mortality in the ICU, in hospital, at day 90, and at day 180; intubation within 28 days after randomisation; length of stay in the ICU and in hospital; number of ventilator-free days between randomisation and day 28; number of oxygenation technique-free days (without HFNO or NIV) between randomisation and day 28; and tolerance of oxygenation techniques. Efficacy of oxygenation techniques were assessed 1 h after randomisation (appendix p 5) using PaO_2/FiO_2, respiratory rate, and dyspnoea score (with a 5-point Likert scale indicating marked improvement [+2], slight improvement [+1], no change [0], slight deterioration [–1] and marked deterioration [–2]). Tolerance of oxygenation techniques was assessed using changes in the 100 mm visual analogue discomfort scale between randomisation and 1 h after randomisation, with decreased discomfort suggesting increased tolerance (appendix p 5).

	HFNO alone group (n=154)	NIV group (n=145)
Age, years	62 (13)	65 (12)
Sex		
Men	95 (62%)	97 (67%)
Women	59 (38%)	48 (33%)
Body-mass index, kg/m^2	25 (6)	25 (6)
SAPS II	46 (18)	45 (15)
SOFA score (excluding respiratory item)	2 (1–4)	3 (1–5)
Performance status 3 or 4	30 (20%)	19 (13%)
Charlson Comorbidity Index score	3·3 (2·3)	3·5 (2·5)
Underlying conditions		
Haematological malignancy	78 (51%)	73 (50%)
Solid cancer	35 (23%)	38 (26%)
AIDS	7 (5%)	5 (3%)
Solid organ transplant recipient	20 (13%)	15 (10%)
Other	14 (9%)	14 (10%)
Corticosteroids or immunosuppressive therapy	95 (62%)	95 (66%)
Leucopenia or neutropenia	26 (17%)	18 (12%)
Allogeneic stem cell transplant recipient	11 (7%)	12 (8%)
Autologous stem cell transplant recipient	14 (9%)	4 (3%)
Haematological malignancy or leucopenia or neutropenia (strata)	81 (53%)	75 (52%)
At time of randomisation		
Duration from ICU admission to randomisation, h	2·2 (1·1–5·9)	2·6 (1·0–7·6)
Duration from randomisation to start of treatments, h	0·1 (0·0–0·4)	0·4 (0·2–0·9)
Prior treatment with NIV	13 (8%)	23 (16%)
Respiratory rate, breaths per min	32 (6)	31 (5)
Arterial blood gases		
pH	7·44 (0·07)	7·44 (0·08)
PaO_2, mm Hg	85 (28)	84 (31)
FiO_2	0·61 (0·16)	0·61 (0·18)
PaO_2/FiO_2, mm Hg	148 (56)	147 (57)
$PaCO_2$, mm Hg	34 (6)	35 (6)
Bilateral infiltrates on chest x-ray	117 (76%)	106 (73%)
Vasopressors	8 (5)	10 (7)
Discomfort score, mm	50 (22–70)	43 (26–64)

Data are n (%), mean (SD), or median (IQR). HFNO=high-flow nasal oxygen. NIV=non-invasive ventilation. SAPS=Simplified Acute Physiology Score. SOFA=Sequential Organ Failure Assessment. ICU=intensive care unit. PaO_2=partial pressure of arterial oxygen. FiO_2=inspired fraction of oxygen. $PaCO_2$=partial pressure of arterial carbon dioxide. SAPS II was calculated from 17 variables at enrolment, information about previous health status, and information obtained at admission. Scores range from 0 to 163, with higher scores indicating more severe disease. SOFA score was based on the intensity of respiratory, coagulation, haemodynamic, neurological, liver, and kidney failure. Each organ was scored from 0 (no failure) to 4 (worse failure). FiO_2 was estimated for patients treated with standard oxygen therapy using the following formula: oxygen flow in L/min × 0·03 + 0·21. Discomfort score was assessed using a 100 mm visual analogue scale from no discomfort (0) to maximum imaginable discomfort (100).

Table 1: **Baseline characteristics**

Statistical analysis

Enrolment of 280 patients was determined to provide a power of 80% and to show an absolute difference of 15% in the rate of mortality at day 28 between the NIV group (mortality rate of 35%)[30–32] and the HFNO alone group (mortality rate of 20%)[31,32] at a two-sided α level of 0·05. To allow for potential secondary exclusions and loss to follow-up, the number of patients to be enrolled was then inflated to 300 (increased by 20 patients, relative increase of 6%).

All the analyses were performed by the study statistician according to a predefined statistical analysis plan on an intention-to-treat basis. Kaplan-Meier curves were plotted to assess the time from randomisation to death or endotracheal intubation and were compared by means of the log-rank test at day 28. Ventilator-free days and oxygenation technique-free days at day 28 were calculated as the number of days alive and without mechanical ventilation or oxygenation techniques between randomisation and day 28, and were compared between groups using the non-parametric Mann-Whitney *U* test. Values were compared using student *t* test or Mann-Whitney *U* test for quantitative variables and Chi-squared (χ^2) test for qualitative variables. Post-hoc subgroup analyses were conducted according to the type of immunosuppression (stratification randomisation variable), because patients with leucopenia or haematological malignancy might benefit from NIV;[12] according to PaO_2/FiO_2 ratio at enrolment, because patients with PaO_2/FiO_2 ratio equal to or below 200 mm Hg might benefit from HFNO therapy;[33] and according to the cause of respiratory failure, because patients without an identifiable cause of respiratory failure had a worse prognosis.[29] In sensitivity analysis, the primary outcome was analysed with adjustment for baseline type of immunosuppression via logistic regression. Results were expressed as odds ratio with 95% CIs. No imputation for missing data was done. A two-tailed p value of less than 0·05 was considered to indicate statistical significance. All statistical analyses were performed with the R statistical software version 3.6.1. This trial is registered with ClinicalTrials.gov, NCT02978300.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and the final responsibility to submit for publication.

Results

From Jan 21, 2017 to March 4, 2019, 497 immunocompromised patients were admitted to the participating ICUs due to acute respiratory failure and were eligible for inclusion in the study; 300 underwent randomisation (figure 1). One patient was secondarily excluded because of withdrawn consent, leaving 299 patients included in the intention-to-treat analysis: 154 in the HFNO group and 145 in the NIV group.

	HFNO alone group (n=154)	NIV group (n=145)	Absolute or mean difference (95% CI)	p value
Primary outcome				
Mortality at day 28	56 (36%)	51 (35%)	1·2 (–9·6 to 11·9)	0·83
Secondary outcomes				
Intubation at day 28	78 (51%)	67 (46%)	4·4 (–6·8 to 15·5)	0·44
Mortality of intubated patients in the ICU	40/78 (51%)	43/67 (64%)	-	-
Mortality				
In the ICU	45 (29%)	49 (34%)	–4·6 (–15·0 to 5·9)	0·39
In hospital	63 (41%)	60 (41%)	–0·5 (–11·5 to 10·6)	0·93
At day 90	67 (44%)	63 (43%)	0·1 (–11·1 to 11·2)	0·99
At day 180	76 (49%)	70 (48%)	1·1 (–10·1 to 12·3)	0·85
Cause of death at day 28	..	..	..	0·95
Withdrawal or withholding of treatments	22/56 (39%)	21/51 (41%)	-	..
Denied intubation	3/22 (14%)	5/22 (23%)	..	..
Related to the underlying disease	9/56 (16%)	10/51 (20%)	-	..
Refractory shock	6/56 (11%)	5/51 (10%)	-	..
Refractory hypoxaemia	4/56 (7%)	4/51 (8%)	-	..
Sudden cardiac arrest	5/56 (9%)	2/51 (4%)	-	..
Other	10/56 (18%)	9/51 (18%)	-	..
Length of ICU stay, days	6 (4 to 13)	7 (4 to 14)	–2·0 (–3·5 to –0·6)	0·30
Length of hospital stay, days	14 (10 to 25)	16 (9 to 28)	–1·1 (–5·6 to 3·4)	0·39
Ventilator-free days at day 28, days	18 (0 to 28)	17 (0 to 28)	0·1 (–2·8 to 3·0)	0·92
Oxygenation technique-free days at day 28, days	4·5 (0 to 28)	4 (0 to 28)	0·0 (–3·1 to 3·1)	0·96
Respiratory parameters 1 h after treatment initiation				
PaO_2/FiO_2, mm Hg	143 (76)	199 (91)	–56 (–77 to –35)	<0·001
Respiratory rate, breaths per min	27 (7)	29 (8)	–1·6 (–3·4 to 0·1)	0·059
Change in discomfort scale, mm	–4 (–18 to 4)	0 (–16 to 17)	–8·5 (–16·2 to –0·8)	0·040
Time to intubation, h [n]	20 (5 to 58) [78]	29 (9 to 72) [67]	–2·3 (–23·4 to 18·8)	0·24

Data are n (%), mean (SD) or median (IQR), unless otherwise specified. HFNO=high-flow nasal oxygen. NIV=non-invasive ventilation. PaO_2/FiO_2=partial pressure of arterial oxygen to inspired fraction of oxygen ratio. ICU=intensive care unit.

Table 2: **Primary and secondary outcomes in the intention-to-treat population**

Patient characteristics at enrolment were similar in the two groups (table 1). Median time from ICU admission to randomisation was 2 h (IQR 1–7). The mean values of respiratory rate and PaO_2/FiO_2 were 32 breaths per min (SD 6) and 147 mm Hg (57), respectively. Lung infiltrates were bilateral in 79% of cases (223 of 284 patients who had chest x-ray on admission). Diagnostic strategies included chest CT in 67% of patients (200 of 299 patients) and bronchoalveolar lavage in 50% (150 patients) (appendix p 6). Microbiological infection was documented in 49% of patients (147 patients). The median time interval between randomisation and initiation of treatment was 14 min (IQR 2–38).

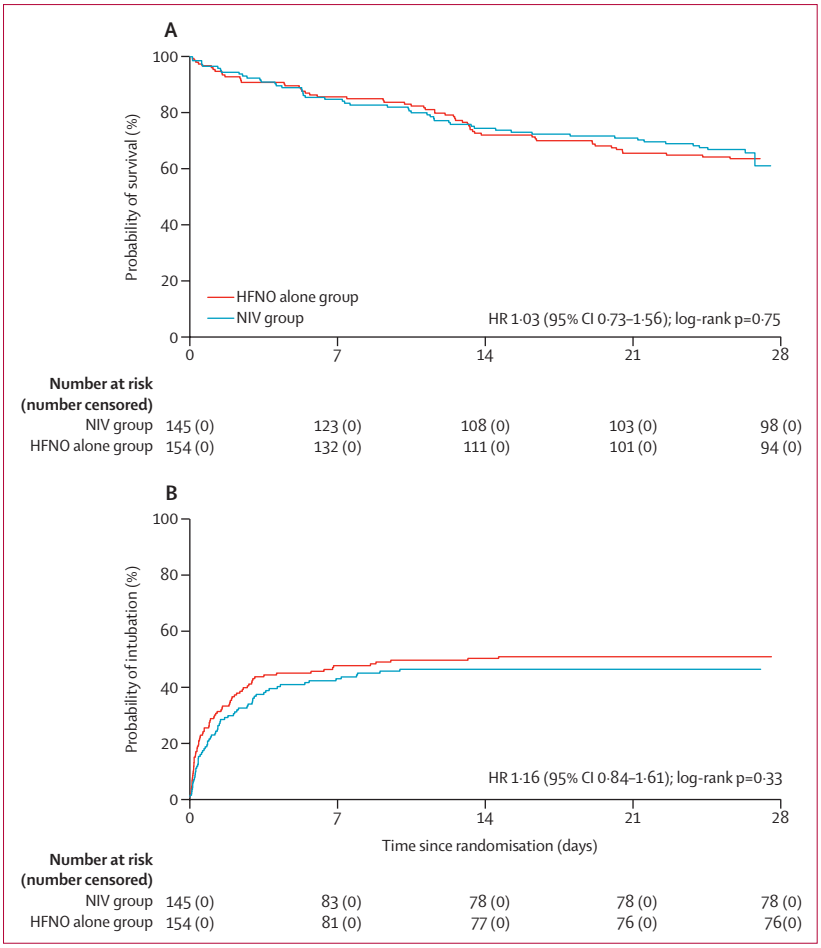

Figure 2: **Kaplan-Meier curves of the cumulative probability of survival (A) and of intubation (B) from randomisation to day 28**
HFNO=high-flow nasal oxygen. HR=hazard ratio. NIV=non-invasive ventilation.

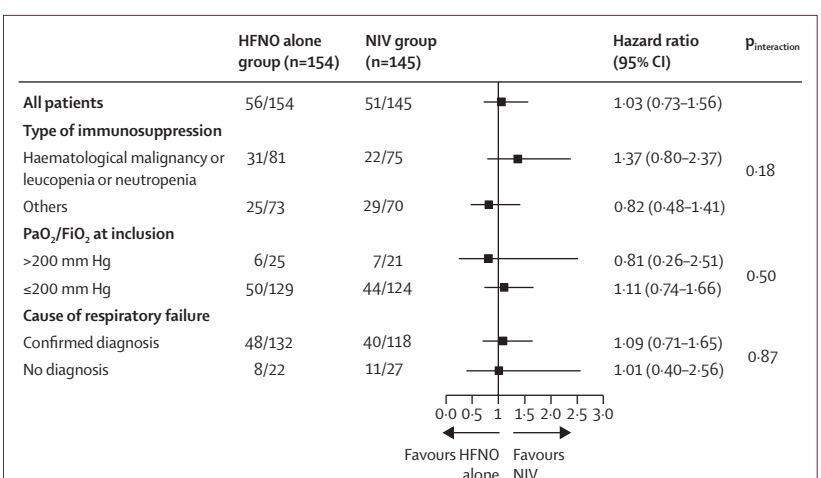

Figure 3: **Mortality at day 28 (primary outcome), overall and in predetermined subgroups**
HFNO=high-flow nasal oxygen. NIV=non-invasive ventilation.

Initial mean settings were: in the HFNO alone group, gas flow was 58 L/min (SD 5) with FiO_2 of 0·71 (0·22); in the NIV group, pressure-support level was 7 cm H_2O (3), positive end-expiratory pressure was 7 cm H_2O (2), and FiO_2 was 0·64 (0·22), resulting in a tidal volume of 9·6 mL/kg of predicted bodyweight (2·9). NIV was delivered for a median of 11 h (IQR 5–14) within the first 24 h, through a face mask in 99% of cases (141 of 143 patients) and using an ICU ventilator in 81% (116 of 144 patients). Duration of NIV during the first 48 h after randomisation and evolution of tidal volumes over time are reported in the appendix (p 7). Six (4%) patients in the HFNO alone group received NIV as a rescue therapy within the first 24 h after enrolment.

The mortality rate at day 28 was 36% (95% CI 29·2 to 44·2; 56 of 154 patients) in the HFNO alone group and 35% (27·9 to 43·2; 51 of 145 patients) in the NIV group (absolute difference 1·2% [95% CI –9·6 to 11·9]; χ^2 p=0·83; log-rank p=0·75; table 2; figure 2). After adjustment for the type of immunosuppression, mortality at day 28 remained similar between the two groups (adjusted odds ratio 1·05 [95% CI 0·66 to 1·69]; p=0·8552). No statistical interaction was found between the type of immunosuppression and the treatment group with respect to the primary outcome (p=0·15).

Mortality in ICU, at day 90, and at day 180, did not differ between the two groups (table 2). Intubation rate at day 28 after randomisation was 51% (95% CI 42·8 to 58·4; 78 of 154 patients) in the HFNO alone group and 46% (38·3 to 54·3; 67 of 145 patients) in the NIV group (absolute difference 4·4% [95% CI –6·8 to 15·5]; χ^2 p=0·44; log rank p=0·33; table 2; figure 2; appendix p 8). In a post-hoc analysis, there was no difference in tidal volume after 1 h of NIV between patients who required intubation (9·7 mL/kg of predicted bodyweight [SD 2·7]) and those who were not intubated (9·5 mL/kg of predicted bodyweight [3·0]; p=0·63). Mortality of intubated patients in the ICU was 51% (40·2 to 62·4; 40 of 78 patients) in the HFNO alone group, and 64% (52·7 to 75·7; 43 of 67 patients) in the NIV group (no statistical comparison made because patients' sampling was no longer randomised). Length of ICU and hospital stay, as well as number of ventilator-free days and number of non-invasive oxygenation technique-free days at day 28 did not differ between the two groups. 1 h after treatment initiation, oxygenation was better in the NIV group than in the HFNO alone group (PaO_2/FiO_2 was 199 mm Hg [SD 91] *vs* 143 mm Hg [76]; p<0·001). Conversely, discomfort in the HFNO alone group decreased significantly more than in the NIV group 1 h after randomisation (–4 mm on visual analogue scale [IQR –18 to 4] *vs* 0 mm [–16 to 17], p=0·040; table 2; appendix p 9).

Mortality at day 28 after enrolment (the primary outcome) did not differ according to the oxygenation strategy in any of the preplanned subgroup analyses: cause of immunosuppression, PaO_2/FiO_2 at enrolment,

or cause of respiratory failure with no heterogeneity of the treatment effect (figure 3).

Discussion

In this multicentre, randomised trial, there were no differences in mortality, intubation rates, or ventilation-free days at day 28 between the HFNO alone group and the NIV group for the treatment of acute respiratory failure in immunocompromised patients.

To our knowledge, this study is the first to compare NIV alternating with HFNO and HFNO alone in immunocompromised patients. In the NIV group, the mortality rate observed at day 28 was 35%—ie, exactly as planned in the sample size calculation.[34] Although the largest clinical trial conducted up until now in immunocompromised patients with acute respiratory failure had reported a slightly lower mortality rate with NIV (27% at day 28), their criteria for respiratory failure were less severe than ours.[14] Additionally, in that trial, HFNO was more frequent in the NIV group than in the oxygen group, potentially masking the beneficial or deleterious effects of NIV.[14] By contrast, in our study, the 36% mortality rate observed in the HFNO alone group was much higher than the 20% rate we had estimated based on previous studies.[31,32] This discrepancy might be explained by the retrospective design,[32] the low sample size of the HFNO groups,[31,32] and the exclusion of patients with severe neutropenia[31] in these studies used for estimating mortality rate in the HFNO groups. As a consequence, the expected effect of HFNO alone was substantially overestimated. However, the 36% mortality rate observed at day 28 is exactly what was reported in a more recent clinical trial published after our study was designed in immunocompromised patients with acute respiratory failure treated with HFNO.[35]

There were no differences in intubation or mortality between HFNO alone and NIV groups. When added to the results of the trial by Lemiale and colleagues,[14] which did not show any difference between NIV and oxygen therapy, our results suggest that compared with other non-invasive oxygenation strategies, NIV does not benefit immunocompromised patients with acute respiratory failure. In fact, NIV for respiratory failure of immunocompromised patients is supported by previous, single-centre trials with small sample sizes.[12,13,36] However, whereas NIV has been suggested to be potentially harmful, causing patient self-inflicted lung injury in patients whose vigorous breathing efforts generate large tidal volumes,[8,11] we did not observe an increased risk of intubation or death with NIV. In addition, among patients who received NIV, we found no difference in expired tidal volume between patients who required intubation and those who did not.

From a clinical standpoint, and due to the complexity of ensuring adequate ventilator settings,[37] HFNO seems to be simpler to use compared with NIV, which requires a high intensity of nursing care.[38] As a consequence, in the absence of strong benefit in terms of intubation, survival, or comfort, our results and those of a previous large-scale clinical trial[14] suggest that NIV is not appropriate in the management of respiratory failure in immunocompromised patients in whom protective ventilation (ie, low tidal volumes) cannot be achieved due to high respiratory drive.

This study has several limitations. First, we cannot exclude potential selection bias given the number of eligible patients not enrolled due to the short time frame from eligibility to randomisation. However, characteristics and outcomes of patients included are similar to those of previous large, randomised trials,[14,35] reinforcing the external validity of our findings. Second, NIV was not as protective as expected, given that most patients had large tidal volumes, leading to potential ventilator-induced lung injury and subsequent increased risk of intubation.[8,11] Indeed, any potential benefit from NIV in some patients might have been offset by harm in others. It is possible that a different interface would have allowed increased positive end-expiratory pressure and decreased pressure-support levels, enabling beneficial effects of NIV without harm.[7] In a prematurely stopped, single-centre trial, helmet NIV was associated with better outcomes than NIV delivered by face mask.[39] However, positive end-expiratory pressure and pressure-support levels were very close to ours, which suggests that the interface has a greater impact on outcome than the settings. Moreover, in a recent multicentre trial including patients with COVID-19 pneumonia, helmet NIV was associated with a lower intubation rate than HFNO and could be promising, albeit not in reducing mortality.[40] Nevertheless, helmet NIV might be a better interface to achieve desired recruitment of patients and minimise leaks, and should be considered in future studies for this population. Third, given the nature of the interventions, masking was not feasible. However, the use of clinically important and objective outcomes such as mortality and intubation, according to predetermined criteria, might have reduced this bias. Fourth, among recent large, randomised trials testing NIV, HFNO, and conventional oxygen, no method was more effective than the others in reducing mortality of immunocompromised patients with acute respiratory failure, suggesting that there might not be a one-size-fits-all oxygenation strategy in this setting.[14,35] Whether a personalised approach would result in different outcomes remains to be tested.[41]

In conclusion, among immunocompromised patients admitted to the ICU for acute respiratory failure, intubation and mortality rates at day 28 did not differ between patients treated with HFNO alone and those treated with NIV alternating with HFNO.

Contributors

RC, J-PF, and AWT, in collaboration with all the authors and the REVA Research Network, designed the study and wrote the manuscript.
SR provided substantial contributions to the conception and design of the study, wrote the statistical analysis plan, and estimated the sample size

with RC. All authors contributed to drafting of the manuscript, revising it critically for important intellectual content, and approved the final version for publication. All authors give their agreement to be accountable for all aspects of the work and ensure the accuracy and integrity of any part of the work. RC, J-PF, AWT, and SR accessed and verified the data, and were responsible for the decision to submit the manuscript.

Declaration of interests

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Data sharing statement

No further data are available.

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