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# **Noninvasive ventilation on reintubation in patients with obesity and hypoxemic respiratory failure following abdominal surgery: a post hoc analysis of a randomized clinical trial**

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**Keywords:**

Acute respiratory failure; Intensive care unit; Noninvasive ventilation; Obesity; Weaning.

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# Abstract

## **Purpose:**

Although noninvasive ventilation (NIV) may reduce reintubation in patients with acute hypoxemic respiratory failure following abdominal surgery, this strategy has not been specifically assessed in patients with obesity.

## **Methods:**

We conducted a post hoc analysis of a multicenter randomized controlled trial comparing NIV delivered via facial mask to standard oxygen therapy among patients with obesity and acute hypoxemic respiratory failure within 7 days after abdominal surgery. The primary outcome was reintubation within 7 days. Secondary outcomes were invasive ventilation-free days at day 30, intensive care unit (ICU)-acquired pneumonia and 30-day survival.

## **Results:**

Among 293 patients with hypoxemic respiratory failure following abdominal surgery, 76 (26%) patients had obesity and were included in the intention-to-treat analysis. Reintubation rate was significantly lower with NIV (13/42, 31%) than with standard oxygen therapy (19/34, 56%) within 7 days (absolute difference: - 25%, 95% confidence interval (CI) - 49 to - 1%,  $p = 0.03$ ). NIV was associated with significantly more invasive ventilation-free days compared with standard oxygen therapy ( $27.1 \pm 8.6$  vs  $22.7 \pm 11.1$  days;  $p = 0.02$ ), while fewer patients developed ICU-acquired pneumonia (1/42, 2% vs 6/34, 18%;  $p = 0.04$ ). The 30-day survival was 98% in the NIV group (41/42) versus 85% in the standard oxygen therapy ( $p = 0.08$ ). In patients with body mass index (BMI)  $< 30 \text{ kg/m}^2$ , no significant difference was observed between NIV (36/105, 34%) and standard oxygen therapy (47/109, 43%,  $p = 0.03$ ). An interaction test showed no statistically significant difference between the two subsets (BMI  $\geq 30 \text{ kg/m}^2$  and BMI  $< 30 \text{ kg/m}^2$ ).

## **Conclusions:**

Among patients with obesity and hypoxemic respiratory failure following abdominal surgery, use of NIV compared with standard oxygen therapy reduced the risk of reintubation within 7 days, contrary to patients without obesity. However, no interaction was found according to the presence of obesity or not, suggesting either a lack of power to conclude in the non-obese subgroup despite existing differences, or that the statistical difference found in the overall sample was driven by a large effect in the obese subsets.

## **Trial registration:**

ClinicalTrials.gov NCT01971892.

# Introduction

The prevalence of obesity, defined by a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>, is increasing among patients admitted to intensive care units (ICUs) [1]. Physiological respiratory modifications are induced by obesity, and lead to atelectasis and gas exchange impairment: a decreased functional residual capacity, an increased abdominal pressure, lower pulmonary and chest wall compliance, a cephalic ascension of the diaphragm, and increased oxygen consumption and work of breathing [2, 3]. The postoperative period after abdominal surgery is associated with diaphragmatic dysfunction and a decrease in lung vital capacity, which leads to atelectasis and hypoxemia [4]. Dealing with postoperative acute hypoxemic respiratory failure frequently requires endotracheal reintubation and invasive mechanical ventilation [5–7]. Reintubation for acute respiratory failure is associated with higher mortality with a longer stay in ICU and in hospital [8, 9].

After major abdominal surgery, optimizing the management of patients with acute hypoxemic respiratory failure is challenging in this specific population of patients with obesity. The physiological effects of noninvasive ventilation (NIV) might be particularly beneficial in patients with obesity, since they experience reduction in lung volumes and are prone to obstructive sleep apneas [5, 10, 11]. Positive pressure improves oxygenation, reduces work of breathing and may prevent atelectasis [12, 13].

We performed a large multicenter randomized controlled trial (EXTUB-OBESE trial) [14] involving 981 patients with obesity compared post-extubation prophylactic NIV to oxygenation strategies (high-flow nasal oxygen or standard oxygen) to prevent extubation failure in ICU. This study [14] showed no significant difference in reintubation at day-3 in the intention-to-treat analysis but a significant lower rate of reintubation at day-3 in the NIV group in the per-protocol analysis.

We conducted a multicenter randomized controlled trial (NIVAS trial) comparing curative NIV via facial mask to standard oxygen therapy among patients who developed acute hypoxemic respiratory failure within 7 days after abdominal surgery [16]. This NIVAS trial [16] showed that curative use of NIV after extubation significantly decreases the rate of reintubation within 7 days after abdominal surgery compared to standard oxygen therapy. To our knowledge, no multicenter randomized controlled trial has to date compared curative NIV for acute hypoxemic respiratory failure to standard oxygen therapy in patients with obesity after abdominal surgery. Since discrepancies have been found in preventive and curative NIV in postoperative patients [17] and in patients with obesity [14, 18], a confirmation of the NIVAS results is required in the peculiar subset of patients with obesity in the postoperative period.

Based on the NIVAS trial [16], we conducted a post hoc analysis aimed at comparing the effects of curative NIV vs. standard oxygen therapy on reintubation within 7 days in patients with obesity following abdominal surgery. We hypothesized that NIV decreases reintubation within 7 days in the subgroup of patients with obesity compared to standard oxygen therapy. We also evaluated invasive ventilation-free days at day 30, ICU-acquired pneumonia and 30-day survival.

# Materials and methods

## Study design and patients

We performed a post hoc analysis of a multicenter randomized controlled trial performed in 20 French ICUs (electronic supplementary material [ESM] 1.) comparing NIV to standard oxygen therapy following abdominal surgery [16]. Patients were eligible for participation in the trial if they were older than 18 years and had undergone laparoscopic or non-laparoscopic elective or non elective abdominal surgery under general anesthesia. Patients were included if they met the following criteria: a diagnosis of acute respiratory failure occurring within 7 days of the surgical procedure [19] defined as the presence and persistence for more than 30 min of hypoxemia (defined by a partial oxygen pressure  $< 60$  mmHg when breathing room air or  $< 80$  mmHg when breathing 15 L/min of oxygen or a peripheral oxygen saturation [ SpO<sub>2</sub>]  $\leq 90\%$  when breathing room air plus either [1] a respiratory rate higher than 30/min or [2] clinical signs suggestive of intense respiratory muscle work and/or labored breathing, such as use of accessory respiratory muscles, paradoxical motion of the abdomen, or intercostal retraction). Exclusion criteria were withholding of life-sustaining treatment [20], contraindications to NIV, sleep apnea syndrome, immediate tracheal intubation, requirement for an emergent surgical respiratory failure (Tables 1 and 2), and gas exchange (Table 2).

## Primary outcome: reintubation within 7 days after randomization

Table 3 shows the results on the primary outcome. At day 7 after randomization in patients with BMI  $\geq 30$  kg/m<sup>2</sup>, reintubation was significantly lower with NIV (13/42, 31%) than with standard oxygen therapy (19/34, 56%,  $p = 0.03$ ), with an absolute difference of  $- 25\%$  (95% confidence interval [CI]  $- 49$  to  $- 1\%$ ).

In patients with BMI  $< 30$  kg/m<sup>2</sup>, no significant difference was observed between NIV (36/105, 34%) and standard oxygen therapy (47/109, 43%,  $p = 0.03$ ), with an absolute difference of  $- 9\%$  (95% CI  $- 21$  to  $4\%$ ).

An interaction test showed no statistically significant difference between the two subsets (BMI  $\geq 30$  kg/m<sup>2</sup> and BMI  $< 30$  kg/m<sup>2</sup>, Fig. 1).

## Secondary outcomes

Table 3 shows the results on the secondary outcomes. At day 30 after randomization, reintubation was significantly lower with NIV (14/42, 33%) than with standard oxygen therapy (19/34, 56%,  $p = 0.049$ ), with an absolute difference of  $- 23\%$  (95% CI  $- 47$  to  $- 1\%$ ). Figure 2A shows the Kaplan–Meier curves for reintubation until day 30. Reintubation was significantly lower with NIV than with standard oxygen therapy ( $p = 0.02$ ) by the log-rank test.

Among patients subsequently reintubated, patients who received NIV spent significantly less time under invasive mechanical ventilation than patients treated with standard oxygen therapy alone (Table 3). At 30 days, compared with standard oxygen therapy, NIV was associated with significantly more invasive ventilation-free days at day 30 (Table 3). Patients treated with NIV also experienced significantly less ICU-acquired pneumonia at day 7 (Table 3).

There was no significant difference of health care-associated infections neither to day 7 nor day 30 (Table 3). In the NIV group, the total duration of NIV use during ICU stay expressed in days median [IQR] was 4 [3–10].

**Table 1 Patient characteristics and biomechanical variables according to study group at randomization**

Characteristics	Standard oxygen therapy (n = 34)	Noninvasive ventilation (n = 42)
Age, years (mean ± SD)	64 (± 13)	65 (± 14)
Male, n (%)	22 (65)	37 (88)
BMI, kg/m <sup>2</sup>		
Mean (± SD)	35.7 (± 5.3)	34.4 (± 4.1)
Median (25%; 75%)	33.9 (31.9; 37.8)	33 (31.2; 37.3)
[Minimum; maximum]	[30; 52.7]	[30; 46.5]
SAPS II (mean ± SD)	33 (± 11)	36 (± 12)
SOFA (mean ± SD)	4 (± 3)	4 (± 3)
Preexisting conditions, n (%)		
Current smoker	7/32 (22)	9/40 (23)
Alcohol abuse	5/33 (15)	4/37 (11)
Psychotropic use	4/34 (12)	2/42 (5)
Chronic hypertension	24/34 (71)	26/42 (62)
Ischemic heart disease	3/34 (9)	8/41 (19)
Chronic heart failure	0/34 (0)	3/42 (7)
Chronic obstructive pulmonary disease	3/34 (9)	10/39 (26)
Chronic kidney disease	1/34 (3)	3/42 (7)
Cirrhosis	5/34 (15)	4/42 (10)
Cancer	15/34 (44)	19/39 (49)
Sepsis	8/33 (24)	7/39 (18)
Clinical variables		
Body temperature, °C (mean ± SD)	37.6 (± 0.6)	37.4 (± 0.8)
Heart rate, /min (mean ± SD)	103 (± 20)	99 (± 19)
Respiratory rate, /min (mean ± SD)	30.24 (± 8.46)	26.10 (± 8.14)
Blood pressure, mmHg		
Systolic (mean ± SD)	136 (± 23)	137 (± 23)
Diastolic (mean ± SD)	67 (± 11)	68 (± 13)
Biochemical variables		
Hemoglobin, g/dl. (mean ± SD)	10.7 (± 1.9)	11.1 (± 2.3)
Hematocrit, % (mean ± SD)	32 (± 5)	34 (± 7)
White blood cell count, × 10 <sup>3</sup> /μL (mean ± SD)	13 (± 8.4)	14.9 (± 6.1)

BMI body mass index, SD standard deviation, SAPS II Simplified Acute Physiology Score II, SOFA Sequential Organ Failure Assessment

**Table 2 Surgery and acute respiratory failure characteristics at randomization**

Characteristics	Standard oxygen therapy (n = 34)	Noninvasive ventilation (n = 42)
<b>Surgery</b>		
Recent surgical history, n (%)		
Elective	17/34 (50)	21/42 (50)
Emergency	17/34 (50)	21/42 (50)
Upper abdominal surgery, n (%)	21/34 (62)	26/42 (62)
Type of surgery, n (%)		
Esophagectomy	3/33 (9)	1/41 (2)
Gastrectomy	3/33 (9)	4/41 (10)
Colorectal resection	8/33 (24)	10/41 (24)
Liver resection	9/33 (27)	10/41 (24)
Pancreaticoduodenectomy	2/33 (6)	4/41 (10)
Other procedures	8/33 (24)	12/41 (29)
Laparotomy surgery, n (%)	29/34 (85)	37/40 (93)
Vertical midline incision	18/29 (62)	24/37 (65)
Transverse incision	10/29 (34)	12/37 (32)
Other	2/29 (7)	1/37 (3)
Laparoscopic surgery, n (%)	6/34 (18)	5/40 (13)
Thoracotomy/laparotomy, n (%)	1/34 (3)	0/40 (0)
Epidural analgesia, n (%)	5/34 (15)	3/42 (7)
Duration of surgical procedure, hours (mean ± SD)	5 (± 3)	4 (± 2)
Extubated < 6 h after end of surgery, n (%)	23/34 (68)	29/42 (69)
<b>Acute respiratory failure</b>		
Respiratory rate/min (mean ± SD)	30 (± 8)	27 (± 8)
Time from end of surgery to acute respiratory failure, days (mean ± SD)	2.6 (± 1.8)	2.5 (± 1.9)
Time from extubation to acute respiratory failure, days (mean ± SD)	2 (± 1.6)	2 (± 1.8)
Time from acute respiratory failure to inclusion in study, hours (mean ± SD)	5.9 (± 7.7)	6 (± 9.4)
Causes of acute respiratory failure, n (%)		
Atelectasis	20/33 (61)	27/41 (66)
Tracheal secretions	13/33 (39)	13/41 (32)
Pneumonia	5/32 (16)	5/41 (12)
Pulmonary edema	4/33 (12)	6/41 (15)
Pleural effusion	4/10 (40)	8/11 (73)
Pulmonary embolism	4/33 (12)	3/40 (8)
<b>Arterial blood gas at randomization</b>		
pH (mean ± SD)	7.4 (± 0.08)	7.41 (± 0.07)
PaO <sub>2</sub> /FIO <sub>2</sub> ratio, mmHg (mean ± SD)	189 (± 79)	182 (± 70)
PaCO <sub>2</sub> , mmHg (mean ± SD)	38 (± 7)	41 (± 8)
HCO <sub>3</sub> <sup>-</sup> , mmol/L (mean ± SD)	24 (± 4)	26 (± 4)

SD standard deviation

**Table 3 Primary and secondary outcomes according to study group**

Variables	Standard oxygen therapy (n = 34)	Noninvasive ventilation (n = 42)	Absolute difference (noninvasive ventilation-standard oxygen therapy), % (95% CI)	p value
<b>Outcomes, n/total (%)</b>				
Primary outcome: reintubation to day 7	19/34 (56)	13/42 (31)	- 25 (- 49; - 1)	0.03 <sup>1</sup>
<b>Secondary outcomes</b>				
Reintubation to day 30	19/34 (56)	14/42 (33)	- 23 (- 47; - 1)	0.049 <sup>2</sup>
Health care-associated infections to day 7	10/34 (29)	7/42 (17)	- 12 (- 34; 9)	0.19 <sup>1</sup>
ICU-acquired pneumonia to day 7	6/34 (18)	1/42 (2)	- 16 (- 32; - 1)	0.04 <sup>2</sup>
Health care-associated infections to day 30	14/34 (41)	12/42 (29)	- 12 (- 37; 12)	0.25 <sup>1</sup>
ICU-acquired pneumonia to day 30	6/34 (18)	2/42 (5)	- 13 (- 30; 4)	0.13 <sup>2</sup>
30-Day survival	29/34 (85)	41/42 (98)	13 (- 3; 28)	0.08 <sup>2</sup>
90-Day survival	28/34 (82)	37/42 (88)	6 (- 13; 25)	0.53 <sup>2</sup>
90-Day survival in intubated patients	13/19 (68)	10/14 (71)	3 (- 32; 38)	> 0.99 <sup>2</sup>
<b>Service utilization</b>				
Days of invasive mechanical ventilation over 30 days (median [IQR])	1 [0-6]	0 [0-2]	1	0.07 <sup>3</sup>
Invasive ventilation-free days to day 30 (median [IQR])	29.2 [1.9-30]	30 [28.4-30]	1	0.02 <sup>4</sup>
Days in ICU (median [IQR])	9 [5-14.8]	8 [5-15]	1	0.66 <sup>3</sup>
Days in hospital (median [IQR])	23 [16-43]	21 [14-40]	- 2	0.64 <sup>3</sup>
Time from inclusion to reintubation, hours (median [IQR])	24 [0-24]	48 [24-120]	24	0.02 <sup>3</sup>
Time from extubation to reintubation, days (median [IQR])	3 [2-4.5]	4 [2-8]	1	0.30 <sup>3</sup>
Time from acute respiratory failure to reintubation, days (median [IQR])	1 [0-1]	2 [1-5.8]	1	0.04 <sup>3</sup>

CI confidence interval, ICU intensive care unit, IQR interquartile range

<sup>1</sup> Pearson's Chi-squared test; <sup>2</sup> Fisher's exact test; <sup>3</sup> Wilcoxon rank sum test



At 30 days, 41 out of 42 patients (98%) in the NIV group and 29 out of 34 patients (85%) in the standard oxygen therapy group had survived (absolute difference, - 13%; 95% CI - 3 to 28%;  $p = 0.08$ ). Figure 2B shows the Kaplan–Meier curves for survival until day 30. There was no difference in survival at day 30 according to the log-rank test ( $p = 0.052$ ). There was no significant difference in survival at day 90 between the NIV group and the standard oxygen group (Table 3).

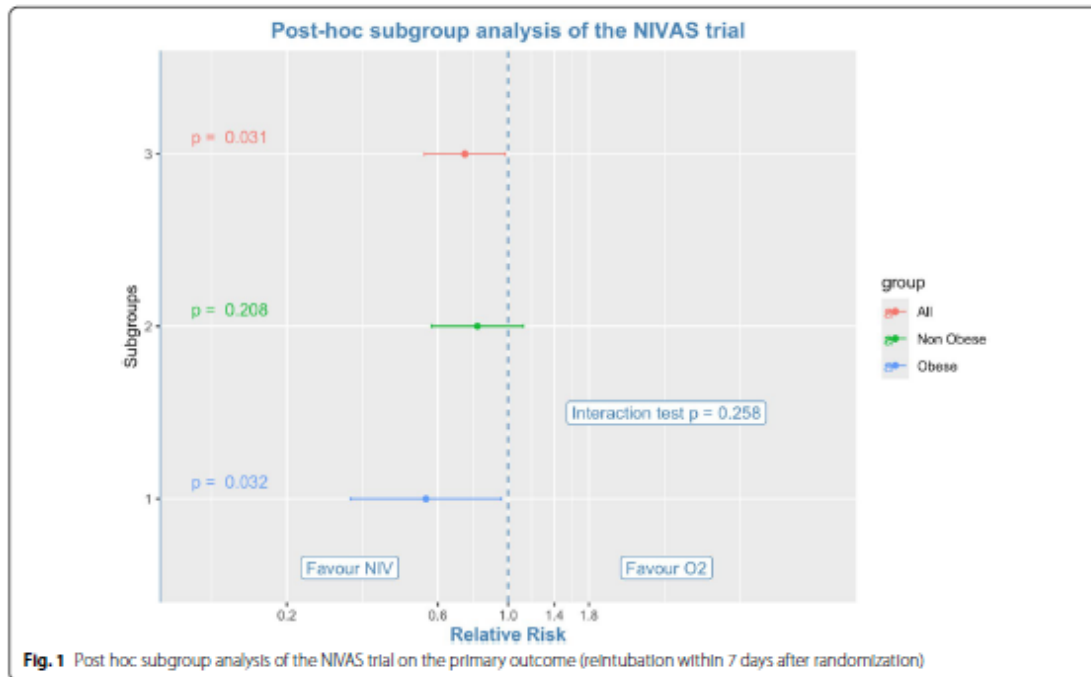
## Discussion

In this post hoc analysis of a multicenter randomized controlled trial, NIV significantly reduced reintubation within 7 days in patients with obesity who developed acute hypoxemic respiratory failure following abdominal surgery compared to standard oxygen therapy. NIV was also associated with significantly more invasive ventilation-free days at day 30 and with significantly lower ICU-acquired pneumonia at day-7 than standard oxygen therapy. However, there was no significant difference in cumulative 30-day survival between NIV and standard oxygen therapy (41/42 vs 29/34,  $p = 0.052$  by the log-rank test).

Hypoxemia develops in 30–50% of overall patients after abdominal surgery and may be well tolerated in some patients [4, 27, 28]. However, hypoxemia can lead to severe acute respiratory failure. The genesis of postoperative hypoxemic acute respiratory failure is multifactorial and partly related to atelectasis due to hypoventilation and collapsed alveoli, retained secretions, and diaphragmatic dysfunction [29–31]. These respiratory modifications are more marked in obese patients. In the present study, in obese patients, the reintubation rate within 7 days after inclusion is close to 10% better with NIV compared to general population (45.5 vs 56%). These results may suggest that obese patients may be those who benefit the most from curative NIV in case of postoperative hypoxemic failure. This could be explained in part by the fact that obese patients could more benefit from positive pressure (both PEEP and inspiratory support pressure) than in non-obese patients due to their mechanical respiratory characteristics [29–31]. Moreover, preventive and curative NIV might lead to different treatment effects in patients with obesity, since these patients are particularly prone to atelectasis and a decrease of lung volumes [14, 15].

Atelectasis favors bacterial growth and increases lung permeability, leading to pneumonia [32]. In our study, NIV significantly decreased ICU-acquired pneumonia. NIV can reverse loss of pulmonary volume through the combined positive effects of PEEP and inspiratory pressure support, which increase lung ventilation, reopen atelectatic alveoli, and improve gas exchange [16]. The lower rate of endotracheal intubation was probably the main reason for the pneumonia reduction observed in patients treated with NIV [33, 34]. As the study is a post hoc analysis, it does not demonstrate the improvement in the subgroup of patients with obesity but only generates a hypothesis of efficacy.

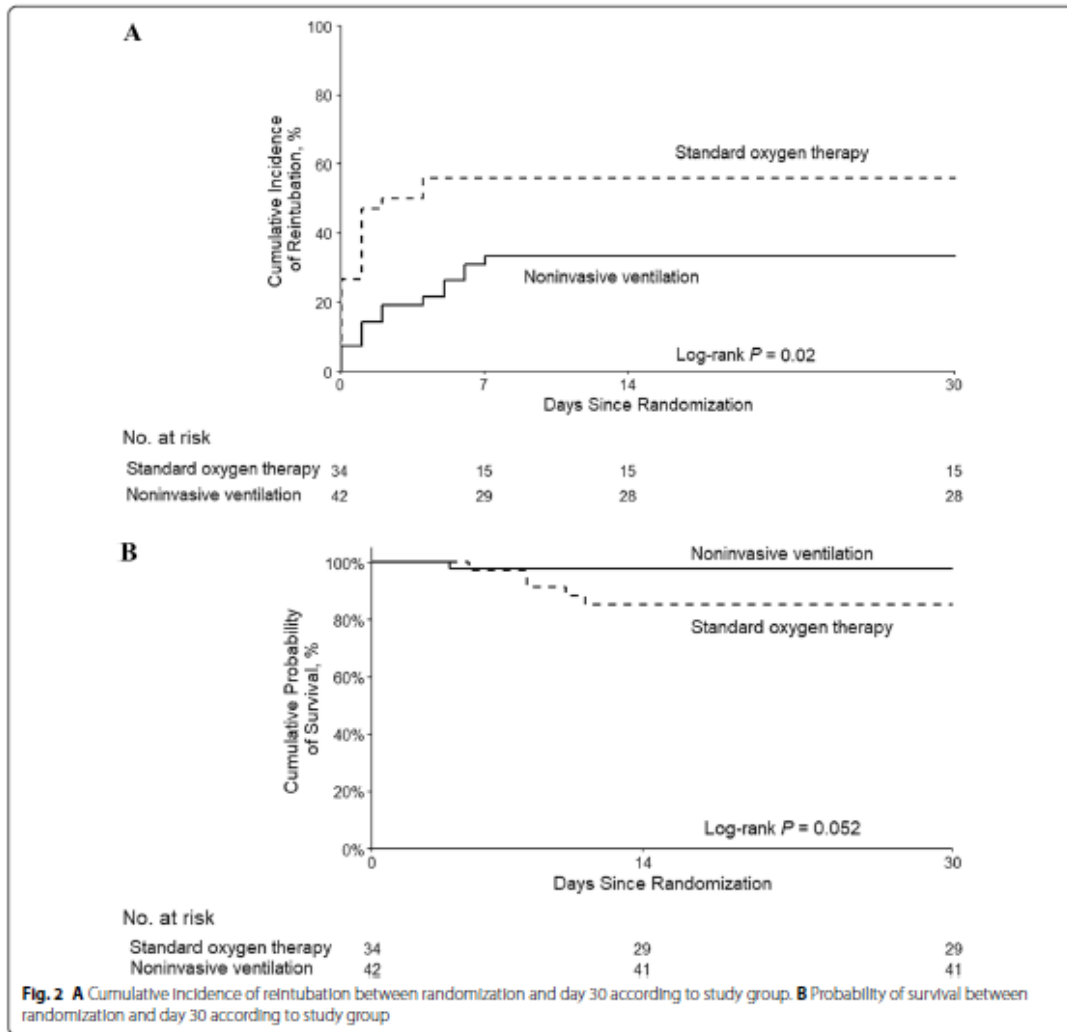
In the original study [16], an adjusted exploratory analysis was performed according to the age (younger or older than 60 years old), the surgery site (upper abdominal vs. lower abdominal surgery), and peridural analgesia. No post hoc analysis of the NIVAS trial [16] has been performed before this study.



To our knowledge, this is the first study to assess curative NIV in patients with obesity in postoperative of abdominal surgery [14, 34]. The strengths of the present study are its multicenter design, the explicit criteria for reintubation, and a complete postoperative follow-up. The criteria for health care-associated infection diagnosis are validated and robust. The trial excluded patients who underwent another immediate surgical procedure.

The first limit of this study is the post hoc nature of the analysis, which was not prespecified [35]. Then, a lack of power is possible given the number of patients with obesity included in the original trial [16]. The lack of significance for higher survival observed in the NIV group could be due to an underpowered design. Third, although we applied predefined criteria for reintubation, bias could not be completely ruled out because blinding with NIV was not feasible. Fourth, since it is a post hoc analysis, slight imbalances in the demographic data might have an impact on the outcome. However, more patients with chronic heart failure and chronic obstructive pulmonary disease were present in the intervention group, associated with a higher risk of reintubation than the overall population [36, 37]. Finally, most of the patients underwent surgery by laparotomy, while laparoscopic surgery has now become more frequent.

In the overall critical care population, high-flow nasal oxygenation has led to guidelines in a post-extubation preventive setting and in medical patients with acute hypoxemic respiratory failure [37–39]. Future research should investigate whether high-flow nasal oxygenation and/or continuous positive airway pressure (CPAP) have a place, either on curative or prophylactic strategies after abdominal surgery in patients with obesity [14, 17, 27, 37, 38]. Our group started the large international multicenter KISS trial (clinicaltrials.gov number: NCT05812911) to assess the relative place of standard oxygen therapy, high flow nasal oxygenation and NIV for acute hypoxemic respiratory failure in both medical and postoperative populations.



## Conclusions

This post hoc analysis of a multicenter randomized controlled trial suggests that NIV may reduce reintubation and ICU-acquired pneumonia, and increase ventilator-free days in patients with obesity with acute respiratory failure following abdominal surgery, compared to standard oxygen therapy. Given the lack of significance on the primary outcome in the subset of non-obese patients, and the lack of interaction between the two subsets (obese and non-obese), two hypotheses can be made. The first one is that there is no difference between the two subgroups, but more power is needed to reject the null hypothesis of absence of effect of NIV in the non-obese subgroup. The second one is that the statistical difference found in the overall sample was driven by a large effect in the obese subsets, while NIV is uninfluential in the non-obese subset. These findings should be confirmed by further randomized controlled trials.

### Author contributions

SJ, JP, GC, ADJ and NM designed the study. NM analyzed the data. All the authors were involved in the data interpretation. SJ, JP, GC, ADJ and NM wrote the manuscript. All the authors read and approved the manuscript.

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## **Availability of data and materials**

Research data and other material (e.g., study protocol and statistical analysis plan) will be made available to the scientific community, immediately on publication, with as few restrictions as possible. All requests should be submitted to the corresponding author who will review with the other investigators for consideration. A data use agreement will be required before the release of participant data and institutional review board approval as appropriate.

## **Declarations**

### **Conflicts of interest**

SJ reports receiving consulting fees from Drager, Medtronic, Baxter, Fresenius- Xenios, Mindray, and Fisher & Paykel. ADJ reports receiving consulting fees from Medtronic, Drager, Viatrix and Fisher & Paykel. No conflict of interests is reported for other authors.

### **Ethics approval, consent to participate**

This original study was approved by a central ethics committee in accordance with French law and was registered at [http:// www. clini caltr ials. gov](http://www.clinicaltrials.gov) with the trial registration number NCT01971892. The trial was conducted in accordance with the Declaration of Helsinki. Written informed consent from the patient or consent from a relative was obtained on study inclusion.

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