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Continued enteral nutrition until extubation compared to fasting prior to extubation in the intensive care unit: a cluster randomised trial

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Médecine Intensive Réanimation. CHRU de Tours. 2, Bd Tonnellé – 37044 Tours cedex 9, France. Tel : +33(0)247473855. Fax : +33(0)247396536. stephan.ehrmann@univ-tours.fr <u>Summary</u>

Background: Fasting is frequently imposed to patients before extubation in intensive care units with the aim to reduce risks of aspiration. This unevaluated practice may delay extubation, increase workload and reduce caloric intake. We hypothesized that continued enteral nutrition until extubation is a non-inferior alternative.

Methods: Multicentre, open-label, cluster-randomised, parallel group, non-inferiority trial including adult patients extubated in the intensive care unit. Centres were randomly allocated to continued enteral nutrition until extubation or six hours fasting with concomitant gastric suctioning prior to extubation. The primary outcome was extubation failure (composite criteria: reintubation or death within seven days), the non-inferiority margin was set at 10%. **Findings:** Extubation failure occurred in 106 out of 617 (17·2%) patients allocated to continued enteral nutrition until extubation versus 90 out of 513 patients (17·5%) allocated to fasting, meeting the *a priori* defined non-inferiority criterion in the intention to treat population (absolute difference -0·4%, 95% confidence interval -5·2% to 4·5%), and in the *per*-protocol population (101 out of 595 (17·0%) versus 74 out of 413 (17·9%), respectively, absolute difference 0·9%, 95% confidence interval -5·6% to 3·7%). Ten (1·6%) and 13 patients (2·5%), developed pneumonia within 14 days of extubation, respectively, rate ratio 0·77 (95% confidence interval: 0·22 to 2·69).

Interpretation: Continued enteral nutrition until extubation of critically ill patients in the intensive care unit was non inferior to a six hours fasting maximum gastric vacuity strategy comprising continuous gastric tube suctioning, in terms of extubation failure within seven days, a patient centred outcome, and thus represents a safe alternative, in the studied population.

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INTRODUCTION

Extubation in the intensive care unit is a key procedure in the course of critical illness recovery.^{1,2} As oropharyngeal dysfunction lasts several hours after removal of the tracheal tube protecting the airways, the procedure carries a risk of gastric content aspiration.³⁻⁵ Up to twenty percent of patients, despite meeting mechanical ventilation weaning criteria, experience extubation failure and are intubated again within a week,⁶⁻⁸ a procedure also associated with a risk of aspiration.⁹ A strong association is observed between extubation failure and occurrence of nosocomial pneumonia which may be favoured by aspiration of digestive secretions.^{10,11} To favour gastric vacuity, many practitioners impose an enteral fasting period to patients, interrupting enteral nutrition and sometimes suctioning the gastric content via the gastric tube, before extubation in the intensive care unit.¹² This practice is partly based on guidelines for scheduled surgery but has never been evaluated among intensive care unit patients extubated after critical illness requiring invasive mechanical ventilation.⁹ Fasting before extubation is not devoid of potential harms such as delayed extubation and reduced nutritional intake and associated metabolic disturbances as well as potential extra nursing workload.¹³

We designed this randomised non-inferiority trial to test the hypothesis that continued enteral nutrition until extubation is a non-inferior safe alternative to fasting prior to extubation in intensive care units.

<u>METHODS</u>

<u>Study design</u>

From April 2018 to October 2019, we conducted this pragmatic open label, clusterrandomised, parallel group, non-inferiority trial comparing continued enteral nutrition until extubation versus fasting prior to extubation in 22 intensive care units in France, each unit being a cluster. Implementing a cluster randomisation design was motivated by the fact that the assessed intervention was a care practice intervention, with a risk of group contamination which is highly deleterious in a non-inferiority trial, to further limit the risk of contamination, no crossover was implemented between clusters. The published study protocol,¹⁴ which is available with the full text of this article at thelancet.com, was approved by the relevant ethics committee (Comité de protection des personnes Sud Mediterranée No.2017.10.02 bis) for all centres and the study registered (www.clinicaltrials.gov NCT03335345). Informed consent was obtained from all the patients, or in case of impossibility, from their next of kin, or another surrogate decision maker according to French law. In all cases, the patient was informed, and patient consent obtained as soon as possible.

<u>Patients</u>

Adults were eligible for enrolment if they had undergone invasive mechanical ventilation for at least 48 hours in the intensive care unit and received prepyloric enteral nutrition for at least 24 hours at the time of extubation decision.

Exclusion criteria were pregnancy, breastfeeding, do-not-reintubate order, guardianship, trusteeship, lack of social security coverage, tracheostomy, post-pyloric enteral nutrition (jejunal tube), and prior inclusion in the trial.

Randomisation and blinding

Clusters were randomised all at once, before the first inclusion with stratification on whether the centre is university-affiliated and on predominant recruitment case-mix to reduce potential recruitment bias related to medical and surgical case mix. A statistician not involved in patient recruitment prepared a computer-generated 1:1 randomisation list. Each unit applied the strategy assigned by randomisation (continued enteral nutrition until extubation or fasting) to all the patients included within the unit during the entire trial. The very nature of the intervention assessed did not allow blinding.

Procedures

Prior to the decision to extubate, weaning of mechanical ventilation and performance of spontaneous breathing trials was left at the attending physician discretion. Patients were included once the decision to extubate was made.

In centres assigned to the continued enteral nutrition until extubation cluster, enteral nutrition was continued until extubation without changing the flow rate. No suctioning *via* the gastric tube was performed before, during or after extubation. Aspiration prevention measures such as head of bed elevation were left at the discretion of the attending physician, as well as the nutrition strategy prior to study inclusion.

Among patients included in centres assigned to the fasting prior to extubation cluster, a strategy of maximal gastric vacuity was implemented at least six hours prior to planned extubation comprising an interruption of enteral nutrition and concomitant continuous suctioning *via* the gastric tube when feasible (i.e. tube of sufficient diameter), as fasting alone may not guarantee gastric vacuity.

In both groups, after extubation, the choice to maintain the gastric tube, the conduct of nutrition *via* the gastric tube, parenteral or oral route was left to the discretion of the attending physician. In case of reintubation and subsequent extubation, patients were managed according to the initial allocation group.

<u>Outcomes</u>

The primary outcome was the rate of extubation failure defined as a composite criteria: reintubation or death within the seven days following extubation. The choice of a composite

outcome was made to take into account the minority of patients who may die without being reintubated. The decision of reintubation was left at the discretion of the attending physician. Key secondary outcomes were hypo- and hyperglycaemia, nursing workload (visual analogical scale from 0 to 100 with higher values indicating higher workload), duration between the first successful spontaneous breathing trial and extubation and intensive care unit discharge, and intensive care unit mortality. Nosocomial pneumonia diagnosis was adjudicated by a centralised independent blinded committee based on clinical, radiological and bacteriological data. The incidence of nosocomial pneumonia in the intensive care unit within the fourteen days following extubation, was compared between groups as well as the occurrence of respiratory failure within seven days of extubation (unplanned oxygen therapy or non-invasive ventilation, tachypnoea above 30 breath/min); total calorie intake the day before, the day of extubation and the following day; last, extubation failure within 48h and 72h was recorded as well as extubation failure attributable to aspiration at 7 days. Detailed secondary outcomes are provided in the Appendix.

Statistical analysis

Analyses were performed in accordance with the pre-established statistical analysis plan, according to both the intention-to-treat and *per*-protocol principles (detailed in the Appendix: no nutrition interruption of more than 30 minutes or nutrition flow rate reduction of more than 50%, no gastric tube suctioning interruption of more than 30 minutes). In both populations, the difference in extubation failure rates between the two groups was estimated and a two-tailed 95% confidence interval with corrected variances taking into account the cluster design was calculated. The upper limit of this confidence interval was then compared with the *a priori* defined 10% non-inferiority margin. The relative risk was also calculated (mixed effect log-binomial model). Time from the first successful spontaneous breathing trial

to extubation was represented by Kaplan Meier curves and the difference between groups was tested with a clustered Log-rank test. Time from the first successful spontaneous breathing to intensive care unit discharge was represented by cumulative incidence curves and compared between groups using a competing risk model, with death as the competing event. Quantitative outcomes were compared between groups using a linear mixed effects model. Count outcomes were compared between groups using a mixed effect Poisson regression with the duration in the intensive care unit as the offset (see details in the appendix). All estimates of the secondary outcomes were reported with a 95% confidence interval taking into account clustering with a random effect for each cluster in the mixed effects regressions (Appendix).^{15,16}

Absolute difference in the primary outcome between groups, adjusted on potential confounders (steroids use, respiratory physiotherapy, age, disease severity, number of spontaneous breathing trial failure, cough evaluation, tracheal secretion abundance, risk factors of extubation failure, comorbidities), was evaluated by post-hoc univariate and multivariate mixed linear model sensitivity analyses (see Appendix).

Based on an expected incidence of extubation failure of 16% in the control group, with a noninferiority margin of 10%, a one-sided type I error of 2.5% and a power of 80%, an intraclass correlation coefficient of 0.03, 1100 patients needed to be included in 22 clusters.¹⁷

Role of the funding source

The trial was funded with a grant from the French Ministry of Health (No. API16/A/063, Groupement Interrégional de Recherche Clinique et d'Innovation Grand Ouest), the funder had no role in study design, conduct, results interpretation, manuscript drafting and decision to submit.

RESULTS

<u>Patients</u>

From April 2018 through October 2019 a total of 7056 patients with enteral nutrition and mechanical ventilation were admitted in the 22 participating intensive care units and 4,098 were eligible for inclusion in the study. Among them, 1,130 patients were included and analysed in the intention to treat population and 1,008 were included in the per-protocol population (Figure 1). The characteristics of the patients at baseline were similar in the two groups (Table 1 and Table S1 in the Appendix). Characteristics before extubation were similar except for the administration of steroids to prevent laryngeal oedema, which was more frequent in the fasting group, however no statistically significant interaction was observed (post hoc p-value for interaction = 0.882). Also, the proportion of patients with a weak or ineffective cough was higher in the fasting group (as compared to effective or very effective), concerning 112 (18.1%) versus 161 (31.4%) patients. The duration of mechanical ventilation prior to extubation was similar in both groups (Table 2 and Appendix Table S1). Two hundred seventeen out of 617 patients (35.2%) in the continued enteral nutrition until extubation and 197 out of 513 (38.4%) patients in the fasting group had one or more a priori defined risk factors for extubation failure such as stroke, neuromuscular disease, central nervous system infection, severe head trauma, diaphragmatic dysfunction, depressive disorder or delirium (Table 2 and Appendix Table S1). Three hundred ninety-five patients (64.9%) in the continued enteral nutrition until extubation group and 374 (74.5%) in the fasting group succeeded their first spontaneous breathing trial. The median volume of enteral intake six hours prior to extubation in the continued enteral nutrition until extubation group was 375 mL (interguartile range, 252 mL to 438 mL). The median volume of gastric contents suctioned six hours prior to extubation in the fasting group was 20 mL (interquartile range, 2 mL to 200 mL): Table 2.

Primary Outcome: extubation failure at day seven

In the intention to treat population, 106 out of 617 patients (17·2%) in the continued enteral nutrition until extubation group and 90 out of 513 patients (17·5%) in the fasting group experienced the composite outcome of extubation failure (absolute difference, -0·4%; 95% confidence interval -5·2% to 4·5%): Table 3. In the *per*-protocol population, 101 out of 595 patients (17·0%) in the continued enteral nutrition until extubation group and 74 out of 413 patients (17·9%) in the fasting group experienced extubation failure (absolute difference, -0·9%; 95% confidence interval, -5·6% to 3·7%). In both populations, the upper limit of the 95% confidence interval was within the *a priori* defined 10% non-inferiority margin, thus qualifying for non-inferiority (Figure 2). A minority of patients died without being re-intubated, representing less than 2% of the study population (11 patients in the continued enteral nutrition until extubation group).

Post-hoc sensitivity analysis, assessing absolute difference between groups in the primary outcome adjusted on various potential confounders, confirmed the non-inferiority results of the primary analysis (appendix).

Secondary Outcomes

There was no difference in occurrence of nosocomial pneumonia after extubation (10 patients, 1.6%, in the continued enteral nutrition until extubation group versus 13 patients, 2.5%, in the fasting group; rate ratio of 0.77 (95% confidence interval: 0.22 to 2.69) Table 3, Appendix Figure S2). The median duration from the first successful spontaneous breathing trial to extubation was significantly shorter in the continued enteral nutrition until extubation group (median of 2.0 hours, IQR 1.0-4.4) than in the fasting group (17.6 hours, IQR 3.4-26.8): Figure 3. The median duration from the first successful spontaneous breathing trial to alive discharge from the intensive care unit was shorter in the continued enteral nutrition until extubation until extubation group (4.0 days, IQR 2.0-8.0) than the fasting group (6.6 days, IQR 3.0-11.1), hazard

ratio 1.45 (95% confidence interval: 1.19 to 1.77): Figure 3. Death in the intensive care unit was significantly less frequent in the continued enteral nutrition until extubation group (3.9%, n=24) than in the fasting group (6.8%, n=35), relative risk of 0.56 (95% confidence interval: 0.32 to 0.99): Table 3.

Tachypnoea within seven days after extubation was more frequent in the continued enteral nutrition until extubation group (59%, n=364) than in the fasting group (54%, n=277): rate ratio of 1.41 (95% confidence interval 1.05 to 1.89). The use of unplanned oxygen therapy or unplanned non-invasive ventilation within the seven days after extubation did not differ significantly between groups. The extubation failure rates at 48 hours and 72 hours were higher in the continued enteral nutrition until extubation group (12.5%, n=77 and 14.7%, n=91, respectively) than in the fasting group (8.6%, n=44 and 10.5%, n=54, respectively): relative risk of 1.46 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 2.07), and relative risk of 1.40 (95% confidence interval 1.02 to 1.93), respectively (Table 3). Other pre-specified respiratory exploratory outcomes are detailed in the Appendix (Table S2).

Hypoglycaemia the day of extubation prior to extubation was significantly less frequent in the continued enteral nutrition until extubation group (0.3%, n=2) than in the fasting group (3.1%, n=16): relative risk of 0.11 (95% confidence interval 0.02 to 0.52): Table 3. There was no difference for hypoglycaemia at other timepoints. Hyperglycaemia the day before extubation was significantly less frequent in the continued enteral nutrition until extubation group (18.3%, n=113) than in the fasting group (26.5%, n=136): relative risk of 0.69, (95% confidence interval 0.53 to 0.89): Table 3. There was no difference concerning the occurrence of hyperglycaemia at other timepoints. Other pre-specified nutritional exploratory outcomes are detailed in the Appendix (Table S2).

Discussion

This pragmatic multicentre, open-label cluster-randomised parallel group non-inferiority trial showed that continued enteral nutrition until extubation compared to six hours fasting with concomitant gastric tube suctioning before planned extubation in the intensive care unit was non inferior in terms of extubation failure (i.e. composite outcome of reintubation or death within seven days). Patients with continued enteral nutrition until extubation were extubated earlier, had shorter intensive care unit stay and experienced less hypo- and hyperglycaemia episodes and even experienced improved survival. The early extubation failure rate (i.e. reintubation within 48 hours or 72 hours) was higher in the continued enteral nutrition until extubation failure rate is questionable given the similar extubation failure rate observed at seven days in both groups.

Overall, the low rate of aspiration prompting reintubation (8 patients (1·3%) in the continued enteral nutrition until extubation group and 15 patients (2.9%) in the fasting group, appendix), the low rate of nosocomial pneumonia after inclusion (10 patients, 1.6% and 13 patients, 2.5%, respectively), and the low caloric intake the day of extubation in both groups (880 Kcal (IQR 513-1539) and 700 kcal (IQR 241-1118) respectively) contributed to this result. The low calorie intake post extubation in both groups, represents an additional argument for avoiding fasting prior to extubation. The non-inferiority of continued enteral nutrition until extubation in terms of overall safety of extubation, as measured through extubation failure, needs to be put into perspective with the potential lack of efficacy of fasting. Indeed, a recent ultrasonographic study evaluating gastric vacuity prior to extubation of critically ill patients, showed that a quarter of patients had significant persisting gastric content despite fasting and observed a lack of association between fasting and decreasing gastric content volume²⁰. Furthermore, the secondary outcome of a significantly longer time interval between the first successful spontaneous breathing trial and extubation in the fasting group, raises concern of disbenefit for the patient, induced by the fasting strategy. Although the study included a broad population of critically ill patients, comprising 15% of scheduled and unscheduled surgical patients, results may not directly be generalizable to the specific context of major abdominal surgery.

The pathophysiology of hospital acquired pneumonia and particularly its relationship with extubation in the intensive care unit and the potential aspiration of oropharyngeal and digestive secretions remains debated.^{1,7-9,14,21,22} The present pragmatic trial demonstrates non-inferiority of the continued enteral nutrition until extubation strategy but does not enable to precisely decipher direct and indirect mechanisms linking fasting and nutrition to secondary outcomes such as time to extubation and incidence of pneumonia. Hospital acquired pneumonia occurred among 23 patients (2.0%) overall, thus, those pathophysiological hypotheses underpinning the rationale for a fasting period prior to extubation are associated with a very low event rate, of questionable clinical relevance compared to other mechanisms of extubation failure (Appendix Table S3).

The patients included in the study were at high risk of extubation failure with a significant proportion of patients aged more than 65 years, with significant respiratory and cardiovascular co-morbidities and a third of patients presenting one or more risk factors for extubation failure, 40% of patients presenting abundant or greatly abundant tracheal secretions and a quarter with ineffective or weak cough.⁶⁻⁸ The overall extubation failure rate of 17·3% observed in the present study, in the upper range of extubation failure rates reported in the literature is in accordance with studies evaluating high risk patients and the initial sample size calculation.^{1,6-8} This reinforces the external validity of the study. However, only 24·1% and 27·1% of patients received preventive post-extubation non-invasive ventilation, an

intervention proven to reduce extubation failure,²³ in the continued enteral nutrition until extubation and fasting groups, respectively. Conversely, respectively 14·4% and 19·5% of the patients in each group received unplanned curative non-invasive ventilation within seven days of extubation, a practice potentially associated with poor outcome.²⁴ Intensive care unit mortality was lower in the continued enteral nutrition until extubation group, this secondary outcome is only hypothesis generating, especially given the relatively small inter-group difference in overall nutritional intake. It is unlikely that continued enteral nutrition until extubation has a direct beneficial effect on patient survival, however as it hastened extubation and discharge from the intensive care unit, it may be indirectly beneficial, reducing the exposure to invasive, potentially deleterious, intensive care unit techniques.

To our knowledge, the present study is the largest randomised clinical trial evaluating continuation of nutrition as compared to fasting in the immediate time frame before extubation in the critical care setting. This study shows the overall safety of pursuing enteral nutrition until extubation given the non-inferior rate of extubation failure, a patients centred endpoint evaluating the overall safety of the procedure.²⁵ Those results support changes in clinical practice as extubation, as part of airway management, represents a very frequent cause of enteral nutrition interruption.^{12, 13, 26, 27}

This study has several limitations. The study was not blinded, due to the nature of the intervention and the pragmatic design with cluster randomisation at the level of the intensive care unit. The primary composite outcome of extubation failure is in part influenced by the physicians' decision to intubate a patient. However, the long observation period of seven days dampens potential bias. The primary composite outcome is to be considered as "objectively measured but potentially influenced by clinician judgement", which is associated with a low risk of bias.²⁸

The open-label clustered randomised design may not fully control all potential recruitment bias and confounding factors. Some potential confounders could have favoured extubation failure in the fasting group: e.g patients in the fasting group were two years older on average, more frequently presented with weak or ineffective cough. Conversely, patients in the continued enteral nutrition group were more severely ill, as measured by the simplified acute physiology score and had more frequently failed their first spontaneous breathing trial and received less frequently steroids to prevent laryngeal oedema which all may have favoured extubation failure in this group. More frequent steroid administration in the fasting group may be due to the available time, due to the 6h fasting duration, to administer the therapy prior to extubation²⁹ but one cannot formally exclude a patient or unit related bias given the potential heterogeneity in care in the peri-extubation period across centres. Those slight group imbalances, which in part counterbalance each other, should not distract from the pragmatic finding of the present large scale study showing an equal risk of extubation failure among 1130 patients whether they undergo fasting or not prior to extubation. Of note, posthoc sensitivity analysis of the primary composite outcome adjusted on potential confounders, including, among others, steroid administration and cough effectiveness, confirmed the noninferiority of the continued enteral nutrition until extubation strategy in all cases (Appendix). In conclusion, in the studied population, continued enteral nutrition until extubation in the intensive care unit was non inferior to a six hours fasting maximum gastric vacuity strategy comprising continuous gastric tube suctioning when feasible. The non-inferiority of continued enteral nutrition until extubation, in terms of extubation failure within seven days, a patient centred outcome, supports change in clinical practice towards this safe alternative.

Data sharing statement: study data including, individual participant data will be made available, on reasonable requests made to the corresponding author.

Authors' contributions: ML, MAN, JA, ET, SE conceived and coordinated the design and overall study conduct, data analysis and manuscript writing and vouch for the data analysis accuracy. NH participated in initial study design. ARe and ARo supervised methodology, study recruitment and data management. JR and AWT participated in study design and data interpretation and manuscript drafting, as nutrition and mechanical ventilation experts. ET and BG supervised methodology and carried out statistical analysis. All other authors participated in patient recruitment and study conduct. All authors revised the manuscript for important intellectual content and approved the final manuscript. ML, MAN, JA, ET, SE and BG had direct access to the data and are responsible for the decision to submit.

Conflict of interest statement: SE declars consultancies for Aerogen Ltd and research support, travel reimbursements and lecture fees from Aerogen Ltd and Fisher & Paykel Healthcare.

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Table 1. Patients' characteristics at randomisation		
	Continued enteral	Fasting (513
	nutrition until	patients)
	extubation (617	
	patients)	
Age - years	61·7 ± 13·5	64·1 ±13·3
Male sex – count (%)	418 (67·7)	322 (62·8)
Simplified acute physiology score 2 ^a	50·9 ± 17·2	49·9 ± 17·8
Height - cm	168·5 ± 9·2	168·8 ± 9·3
Weight - Kg	77·8 ± 19·5	79·1 ± 19·2
Body mass index ^b - Kg/m ²	27·4 ± 6·6	27·7 ± 6·3
Type of admission – count (%)		
 Unscheduled surgical 	69 (11·2)	63 (12·3)
 Scheduled surgical 	12 (1·9)	28 (5·5)
- Medical	536 (86·9)	422 (82·3)
Charlson comorbidity index ^c	4·4 ± 2·6	4·6 ± 2·7
Comorbidities – count (%)		
 Chronic obstructive pulmonary disease 	89 (14·4)	65 (12·7)
- Asthma	28 (4·5)	32 (6·2)
 Obesity hypoventilation syndrome 	24 (3·9)	19 (3·7)
 Obstructive sleep apnea syndrome requiring 	39 (6·3)	45 (8·8)
continuous positive pressure therapy		
 Long-term oxygen therapy 	6 (1)	12 (2·3)
 Noninvasive ventilation at home 	8 (1·3)	6 (1·2)
 Left ventricular dysfunction 	41 (7)	32 (7·1)
- Ischemic heart disease	85 (13·8)	69 (13·5)
- Atrial fibrillation	67 (10·9)	66 (12·9)
 History of cardiogenic pulmonary edema 	20 (3·2)	19 (3·7)
 Severe valvular heart disease 	13 (2·2)	34 (7·3)

Quantitative variables are reported as means ± standard deviation and qualitative variables as counts (%). Percentages may sum-up to more than 100 due to several conditions present in one patient and rounding. Additional baseline characteristics are provided in Table S1 in the Supplementary Appendix.

^a The simplified acute physiology score 2 was calculated from 17 variables at admission¹⁸. The score ranges from 0 to 163, with higher scores indicating more severe disease and higher mortality risk.

^b Calculated as weight in kilograms divided by height in meters squared.

^c Coexisting conditions were assessed according to the Charlson¹⁹ comorbidity index, in which 22 clinical conditions are scored with regard to the risk of death; the score ranges from 0 to 37, with higher scores indicating a higher risk of death.

	Continued enteral nutrition	Fasting
	until extubation (617 patients)	(513 patients)
Number of spontaneous breathing trial failure – count		
(%)		
- 0	395 (64·9)	374 (74·5)
- 1	117 (19·2)	77 (15.3)
- 2	48 (7.9)	26 (5.2)
- 3 or more	49 (8)	25 (5)
Systolic blood pressure - mmHg	135·1 ± 20·7	137·5 ± 22·9
Diastolic blood pressure - mmHg	72·2 ± 14·5	68·7 ± 14
Heart rate – beats per minute	93·8 ± 18·1	91·2 ± 16·7
Respiratory rate – beats per minute	23.9 ± 6.4	23·0 ± 6·2
Pulsed hemoglobin oxygen saturation - %	96·1 ± 2·9	96·1 ± 2·9
рН	7·45 ± 0·05	7·45 ± 0·05
Arterial partial pressure of oxygen – mmHg	75·5 ± 16·6	84·9 ± 36·7
Arterial partial pressure of carbone dioxide – mmHg	40.4 ± 9.3	40·3 ± 7·4
Hypercapnia ^a – count (%)	11 (30·6)	24 (21·4)
Administration of steroids before extubation – count	103 (16.7)	248 (48.3)
(%)		
- Prevention for laryngeal edema	17 (2·8)	161 (31·4)
- Other indication	86 (14)	87 (17)
Cough evaluation – count (%)		
- Ineffective	10 (1.7)	36 (7.5)
- Weak	102 (17)	125 (25·9)
- Effective	407 (67.7)	281 (58·2)
- Very effective	82 (13.6)	41 (8.5)
Tracheal secretion evaluation – count (%)		
- Absent	26 (4·3)	34 (6·8)
- Low abundance	321 (53·1)	247 (49·2)
- Abundant	219 (36·3)	190 (37·8)
- Great abundance	38 (6·3)	31 (6·2)
Respiratory physiotherapy – count (%)	201 (32·8)	137 (28·1)
Risk factors of extubation failure ^b – count (%)		
- None	400 (64·8)	316 (61·6)
- 1 or more	217 (35·2)	197 (38·4)
Median volume of enteral intake six hours prior to	375 (252 – 438)	0
extubation (interquartile range) – mL		
Median volume of gastric contents suctioned six hours	0	20 (2 – 200)
prior to extubation (interquartile range) – mL		
Median duration of invasive mechanical ventilation	8.4 [5.4;13.4]	8·3 [5·3;12·4]
prior to extubation ^c – days		

Quantitative variables are reported as means ± standard deviation and qualitative variables as counts (%) unless otherwise indicated. Percentages may sum-up to more than 100 due to several conditions present in one patient and rounding. Additional baseline characteristics are provided in Table S1 in the Supplementary Appendix.

^a Hypercapnia was defined by an arterial partial pressure of carbon dioxide > 45mmHg. Arterial blood gas analysis at the end of the spontaneous breathing trial was left at the discretion of the attending physician. ^b Predefined specific risk factors of extubation failure recorded in the study were stroke, neuromuscular disease, central nervous system infection, severe head trauma, diaphragmatic dysfunction and delirium¹⁴ ^c Time from intubation to extubation was analyzed with a mixed-effects Cox regression with a random effect for each cluster. The hazard ratio (95% confidence interval) was 0.93 (0.77 to 1.11).

Table 3. Primary and key secondary outcomes in the intention to tre	eat population			
	Continued enteral	Fasting (513	Difference ^a	Relative risk (95%
	nutrition until	patients)	(95%	confidence
	extubation (617		confidence	interval)
	patients)		interval)	
Primary outcome: extubation failure at day 7 – count (%) ^b	106 (17·2)	90 (17·5)	-0·4 (-5·2 to 4·5)	0·98 (0·74 to
				1.29)
Secondary outcomes				
Nosocomial pneumonia – count (%) ^c	10 (1.6)	13 (2·5)	Not applicable	0·77 (0·22 to 2·69)
Median and quartiles of duration from the first successful	2·0 (IQR 1·0 to 4·4)	17·6 (IQR 3·4 to	Not applicable	Not applicable
spontaneous breathing trial to extubation - hours ^d		26.8)		
Median and quartiles of duration from the first successful	4·0 (IQR 2·0 to 8·0)	6.6 (IQR 3.0 to 11.1)	Not applicable	Not applicable
spontaneous breathing trial to intensive care unit discharge - days ^e				
Median and quartiles of total nutritional intake (enteral and				
parenteral) – kilocalories				
The day before extubation	1775∙0 (1455∙0 to	1505∙0 (1065∙0 to	284·0 (132·0 to	Not applicable
	2150·0)	1876·0)	435·2)	
The day of extubation ^f . Before extubation	482·0 (260·0 to 890·0)	236·0 (26·0 to 823·0)	200 (-11·4 to	Not applicable
			411·5)	
The day of extubation ^f . After extubation	155·0 (48·0 to 575·0)	75·0 (13·0 to 321·0)	49.3 (-217·9 to	Not applicable
			314·9)	
The day after extubation	200·0 (50· to 996·0)	300·0 (93·0 to	-186·7 (-531·1	Not applicable
		1260.0)	to 155·4)	
Death in the intensive care unit – count (%)	24 (3·9)	35 (6·8)	-2·9% (-6·4% to	0·56 (0·32 to
			0.5%)	0.99)
Tachypnoea – count (%) ^g	364 (59)	277 (54)	Not applicable	1·41 (1·05 to
				1.89)

Curative oxygen therapy – count (%) ^h	208 (33.7)	249 (48.5)	Not applicable	0·82 (0·57 to 1·19)
Extubation failure at 48 hours – count (%)	77 (12.5)	44 (8.6)	3·9% (-0·1% to 7·9%)	1·46 (1·02 to 2·07)
Extubation failure at 72 hours – count (%)	91 (14·7)	54 (10·5)	4·2 (-0·1 to 8·6)	1·40 (1·02 to 1·93)
Hypoglycaemia – count (%) ⁱ				
- The day before extubation	18 (2·9)	17 (3·3)	-0·4 (-3·7 to 2·9)	0·86 (0·31 to 2·37)
- The day of extubation. Before extubation	2 (0·3)	16 (3·1)	-2·8 (-5·2 to - 0·4)	0·11 (0·02 to 0·52)
- The day of extubation. After extubation	16 (2·6)	11 (2·1)	0·4 (-1·5 to 2·4)	1·13 (0·62 to 2·04)
- The day after extubation	21 (3·4)	19 (3.7)	-0·3 (-2·6 to 2)	0·91 (0·47 to 1·75)
Hyperglycaemia – count (%) ^j				,
- The day before extubation	113 (18·3)	136 (26·5)	-8·2 (-15·3 to - 1·1)	0·69 (0·53 to 0·89)
- The day of extubation. Before extubation	69 (11·2)	78 (15·2)	-4 (-10·1 to 2·1)	0·75 (0·49 to 1·16)
- The day of extubation. After extubation	77 (12·5)	60 (11·7)	0·8 (-4·2 to 5·8)	1·02 (0·68 to 1·53)
- The day after extubation	85 (13·8)	98 (19·1)	-5·3 (-11·2 to 0·6)	0·72 (0·51 to 1·0)

^aThe difference is expressed as percentage points for binary variables, and mean difference for quantitative variables.

^b The primary outcome was assessed in the intention-to-treat population. The intraclass correlation coefficient was 0.002 (95% confidence interval 0 to 0.043) in the continued enteral nutrition until extubation group and 0.008 (95% confidence interval 0 to 0.066) in the fasting group.

^c Nosocomial pneumonia diagnosis was adjudicated by a centralized independent blinded committee based on clinical, radiological, and bacteriological data

^d The p-value associated with the clustered Log-rank test was <0.0001.

^e The median duration was analyzed with a competing risks model. The model was a population average regression taking into account the correlation across individuals within a cluster. The hazard ratio (95% confidence interval) was 1·39 (1·13 to 1·71).

^f Total total nutritional intake the day of extubation was 880 kcal (IQR 513-1539) in the continued enteral nutrition until extubation group and 700 kcal (241-1118) in the fasting group.


^g Tachypnea was defined by a respiratory rate greater than 30 breaths per minutes, that occurred during the first 7 days post extubation.

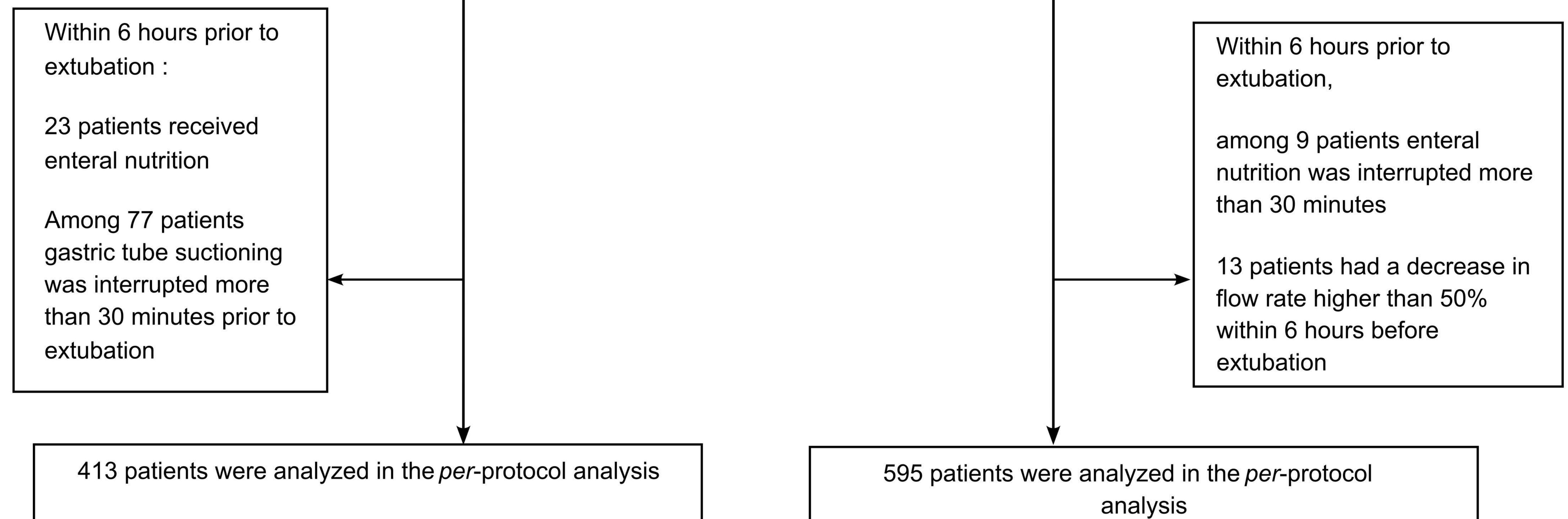
^h Curative oxygen therapy was defined as unplanned oxygen delivery with a flow rate ≥ 5 liters per minute or with high flow nasal cannula for respiratory failure, that occurred during the first 7 days post extubation.

ⁱ Curative noninvasive ventilation was defined as unplanned implementation in response to respiratory failure, that occurred during the first 7 days post extubation.

^j Presence of at least 1 episode during the period.

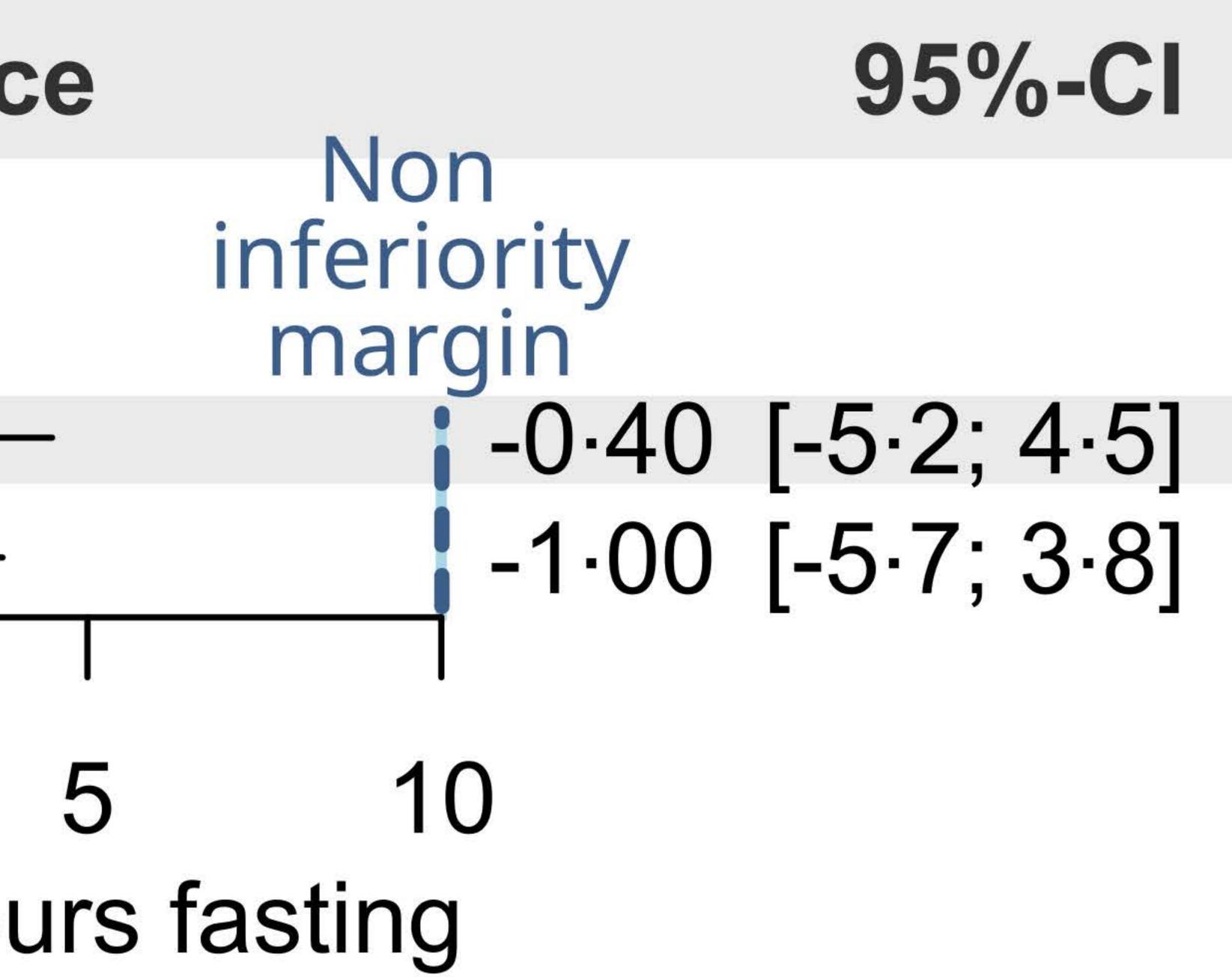
Risk differences were not reported, i.e. "not applicable", in cases where a Poisson model was used to analyse count data taking into account the exposure time (intensive care unit length of stay).



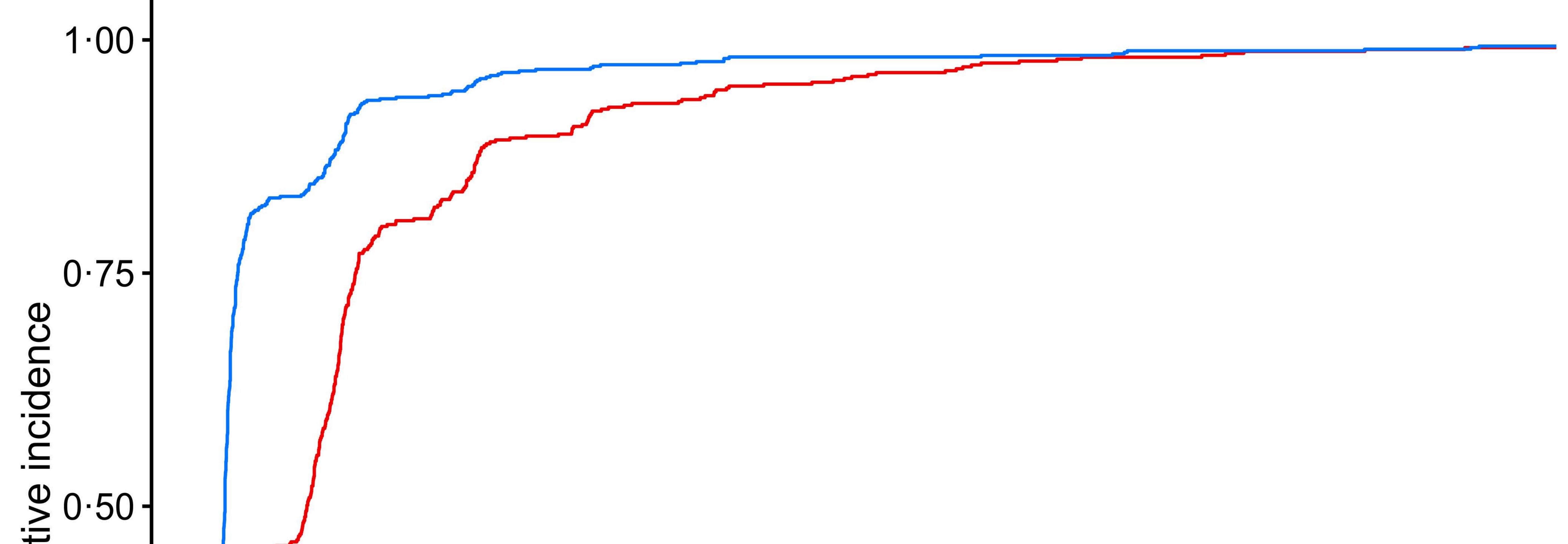


Intention to treat analysis Per protocol analysis

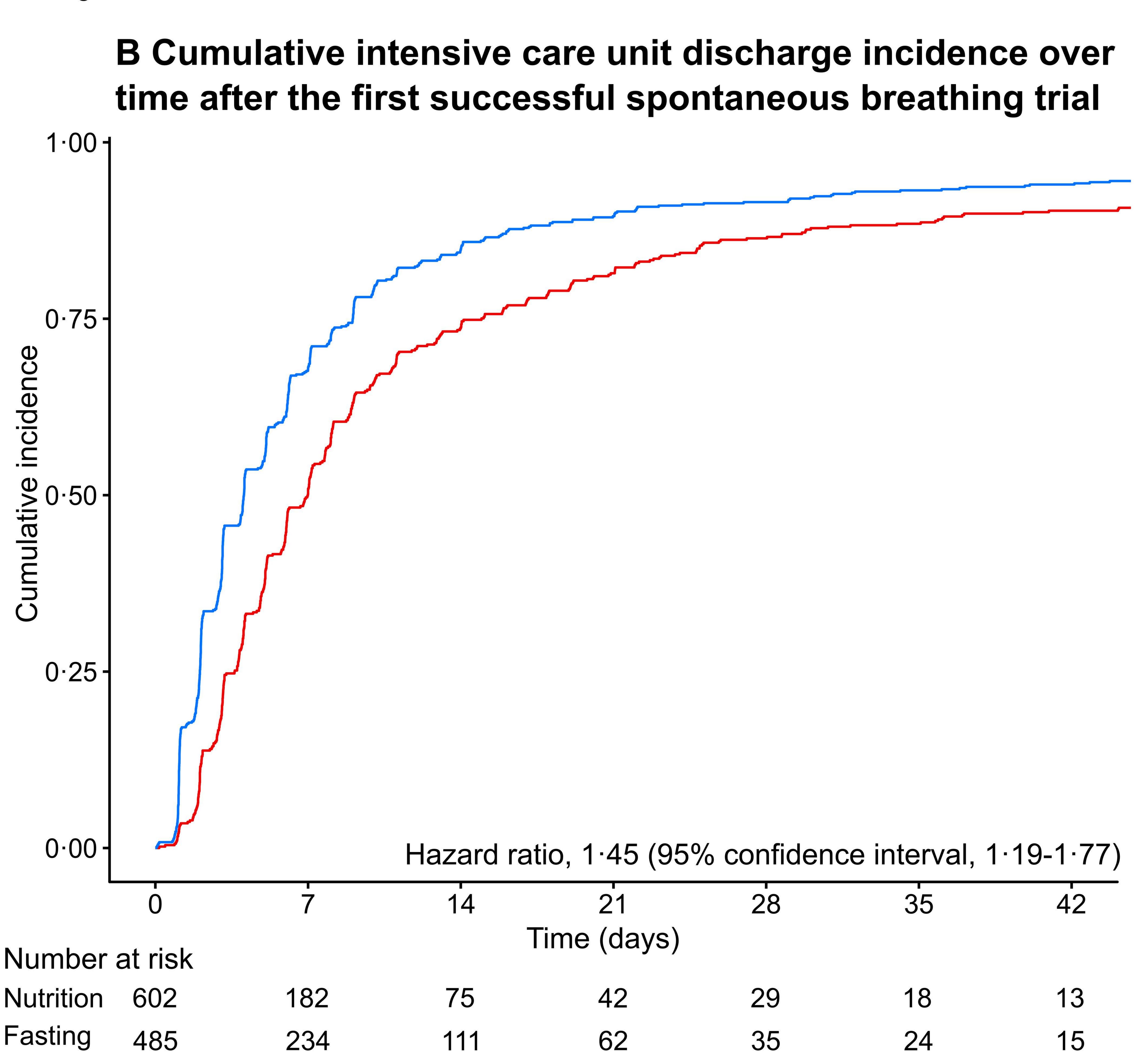
Continued enteral nutrition Fasting before extubation until extubation **Risk Difference** (%) (%) Events Events Extubation failure within the 7 days following extubation 106 (17.2%) 90 (17.5%)103 (16·9%) 74 (17·9%) -10 -5 Favours continued Favours fasting enteral nutrition



A Cumulative extubation incidence over time after the first successful spontaneous breathing trial



O·00 -					- Con	ting before tinued endowed by the second sec	enteral			extubati	on	
	0	24	48	72	96	120	144	168	192	216	240	
Number	at risk				Tin	ne (hou	Irs)					
Nutrition	602	67	32	18	14	11	11	10	7	7	5	
Fasting	485	161	76	37	26	20	14	9	8	6	4	



Continued enteral nutrition until extubation compared to fasting prior to extubation in the intensive care unit: a cluster randomized trial

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Supplementary Appendix

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3. ADDITONAL DETAILED METHODS:

1. Trial design and study oversight

From April 2018 to October 2019, we conducted this pragmatic open label, clusterrandomised, parallel group, non-inferiority trial comparing continued enteral nutrition until extubation versus fasting prior to extubation in 22 intensive care units in France, each unit being a cluster. Cluster randomisation design was motivated by the fact that the assessed intervention was a care practice, with a risk of group contamination which is highly deleterious in a non-inferiority trial, to further limit the risk of contamination, no crossover was implemented between clusters. The published study protocol (S1), which is available with the full text of this article at-thelancet.com, was approved by the relevant ethics committee (Comité de protection des personnes Sud Mediterranée No.2017.10.02 bis) and the study registered (NCT03335345). Informed consent was obtained from all patients, from their next of kin, or another surrogate decision maker according to French law. In all cases, the patient informed consent was obtained as soon as possible.

The trial was funded with a grant from the French Ministry of Health (No. API16/A/063, Groupement Interrégional de Recherche Clinique et d'Innovation Grand Ouest). All authors revised the manuscript, vouch for the accuracy of the data, and approved the decision to submit the manuscript for publication.

2. <u>Patients</u>

Adults (age \geq 18 years) were eligible for enrolment if they had undergone invasive mechanical ventilation for at least 48 hours in the intensive care unit and received prepyloric enteral nutrition for at least 24 hours at the time of extubation decision.

Exclusion criteria were pregnancy, breastfeeding, do-not-reintubate order, guardianship, trusteeship, lack of social security coverage, tracheostomy, post-pyloric enteral nutrition (jejunal tube), and prior inclusion in the trial.

3. <u>Randomisation</u>

Clusters were randomised all at once, before the start of the study and inclusion of the first patient, with stratification on whether the centre is university-affiliated and whether predominant recruitment is surgical, or mixed medical-surgical, to reduce potential recruitment bias related to medical and surgical case mix. A statistician not involved in patient recruitment prepared a computer-generated 1:1 randomisation list. Each unit applied the strategy assigned by randomisation (continued enteral nutrition until extubation or fasting) to all the patients included within the unit during the entire trial.

5

4. Intervention

Prior to the decision to extubate weaning of mechanical ventilation and performance of spontaneous breathing trials was left at the attending physician discretion. Patients were included once the decision to extubate was made.

In centres assigned to the continued enteral nutrition until extubation cluster, enteral nutrition was continued until extubation without changing the flow rate. No suctioning *via* the gastric tube was performed before, during or after extubation. Aspiration prevention measures such as head of bed elevation were left at the discretion of the attending physician, as well as the nutrition strategy prior to study inclusion.

Among patients included in centres assigned to the fasting prior to extubation cluster, a strategy of maximal gastric vacuity was implemented at least six hours prior to planned extubation comprising an interruption of enteral nutrition and concomitant continuous suctioning *via* the gastric tube when feasible (*i.e.* tube of sufficient diameter already in place), as fasting alone may not guarantee gastric vacuity.

In both groups, after extubation, the choice to maintain the gastric tube, the conduct of nutrition *via* the gastric tube, parenteral or oral route was left to the discretion of the attending physician. In case of reintubation and subsequent extubation, patients were managed according to the initial allocation group.

5. <u>Study outcomes</u>

1. <u>Primary outcome:</u>

The primary outcome was the rate of extubation failure defined as a composite criteria: reintubation or death within the seven days following extubation. The choice of a composite outcome was made to take into account the minority of patients who may die without being reintubated. The decision of reintubation was left at the discretion of the attending physician.

6

2. <u>Secondary outcomes were:</u>

- Total calorie intake (enteral and parenteral): the day before extubation, the day of extubation and the day after extubation;
- Proportion of patients with hypoglycaemia (venous or capillary glucose concentration < 0.7 g/L) and hyperglycaemia (venous or capillary glucose concentration > 2g/L) the day before extubation, on the day of extubation and during the day after extubation;
- Visual analogical scale measurement of the nursing workload during the six hours preceding extubation, during extubation and during the six hours following extubation (scale from 0 to 100 with higher values indicating higher workload);

Weaning from mechanical ventilation and intensive care unit outcome:

- Mechanical ventilation duration as evaluated by the duration of the episode of invasive mechanical ventilation before the extubation prompting study inclusion, defined by the time between extubation within the study and the last intubation or, for patients intubated outside of the participating intensive care unit, the time of admission in the participating intensive care unit.
- Duration between the first successful spontaneous breathing trial and extubation;
- Duration of the intensive care unit stay;
- Proportion of patients dying in the intensive care unit.
- Pulmonary aspiration and nosocomial pneumonia:
- Proportion of patients with extubation failure within seven days of extubation attributable to the aspiration of digestive secretions as determined by the investigator;
- Proportion of patients developing nosocomial pneumonia in the intensive care unit within the 14 days following extubation. Nosocomial pneumonia diagnosis was adjudicated by a centralized independent blinded committee based on clinical, radiological and

bacteriological data. Adjudication was based on original chest X-rays and a standardised form for the declaration of suspected pneumonia including a modified version of the Clinical Pulmonary Infection Score (CPIS) adapted for non-intubated patients (S3, S4). CPIS score is based on the abundance and appearance of bronchial secretions, temperature, hyperleukocytosis, hypoxemia, the presence of an infiltration on X ray and the culture of a pathogen from bronchial secretions. For reintubated patients, in addition to the chest X ray routinely performed following reintubation, a bacteriological sample was collected (modality of collection left to the discretion of the clinician: tracheal aspiration, protected distal sample, alveolar lavage).

Acute respiratory failure occurrence in the days following extubation:

- The proportion of patients undergoing unplanned oxygen therapy within seven days following extubation (*i.e.* for respiratory failure, not as implemented routinely in the post-extubation period);
- The proportion of patients undergoing unprogrammed non-invasive ventilation within seven days following extubation (*i.e.* for respiratory failure, not as a systematic prophylactic measure in the post-extubation period);
- The proportion of patients with at least one episode of tachypnoea exceeding 30 cycles per minute within seven days following extubation;
- The proportion of patients with extubation failure at 48 hours and 72 hours after extubation (same definition as the primary outcome);

6. <u>Blinding</u>

The very nature of the intervention assessed did not allow blinding. Nosocomial pneumonia diagnosis was adjudicated by a blinded committee.

7. <u>Statistical analysis</u>

All the analyses were performed by the study statistician (Elsa Tavernier, CIC INSERM 1415, CHRU Tours, France), in accordance with the International Conference on Harmonization and Good Clinical Practice guidelines, in accordance with the pre-established statistical analysis plan, using the software R (S2).

No intermediate analysis was performed, analysis and reporting are compliant with the CONSORT statement and the three extensions relating to this trial: cluster-randomised trials, non-pharmacological interventions and non-inferiority trials (S5). No data imputation was performed for missing data.

1. Definition of the populations for analysis:

Analyses of this non-inferiority trial have been performed according to both the intention-totreat and *per*-protocol principles.

Patients in the continued enteral nutrition until extubation group were included in the *per*protocol analysis if the enteral nutrition flow rate had been maintained until extubation without a decrease in flow rate higher than 50% within six hours before extubation, and enteral nutrition had not been completely interrupted more than 30 minutes within six hours before extubation.

Patients in the fasting group were included in the *per*-protocol analysis if no enteral nutrition had been administered during the six hours before extubation, and continuous suctioning was performed continuously with no interruption of more than 30 minutes during the six hours before extubation (among patients with a gastric tube of sufficient diameter for suctioning). Patients with unintentional extubation before six hours of continuous fasting and gastric tube suctioning were included in the *per*-protocol analysis as this may represent a side effect of the fasting strategy and not a protocol violation. Indeed, the 6h fasting period puts patients at risk of unintentional extubation for at least six more hours per design, during this time the patient may be uncomfortable and sometimes get agitated potentially favouring unintentional extubation. As, unintentional extubation is not a healthcare team decision, they were not considered as a protocol violation *per se*.

2. <u>Description of patient characteristics at inclusion:</u>

The groups resulting from randomisation were described with absolute numbers and percentages for qualitative variables, and, for quantitative variables, mean and standard deviation or median and interquartile range, depending on the data distribution. The characteristics of the patients at inclusion were reported at the patient level or at the cluster level when appropriate. No statistical tests were performed.

3. <u>Primary outcome analysis:</u>

The extubation failure rates were estimated in each group and the difference in extubation failure rates between the two groups estimated, a two-tailed 95% confidence interval with corrected variances to take into account the cluster design was calculated (S6). The upper limit of this confidence interval was then compared with the *a priori* defined 10% non-inferiority margin. The relative risk was also calculated using a mixed effect log-binomial model. The absolute numbers and percentages were calculated in each group. The principal analysis was completed by an estimation of the intraclass correlation coefficient performed independently within each of the two groups, with the Fleiss–Cuzick estimator (S7). Absolute difference in the primary outcome between groups, adjusted on potential confounders, was evaluated by post-hoc univariate and multivariate mixed linear model sensitivity analyses.

4. <u>Secondary outcomes analyses:</u>

All estimates were reported with a 95% confidence interval taking into account clustering.

- Total calorie intake: this quantitative endpoint was analysed with a linear mixed-effects model, with the group as a fixed effect and a random effect for each cluster.
- Proportion of patients with hyperglycaemia and hypoglycaemia: these binary endpoints were analysed according to the same principles as the primary outcome.
- Nursing workload scale: this quantitative endpoint was analysed with a linear mixed-effects
 model, with the group as a fixed effect and a random effect for each cluster.
 Weaning from mechanical ventilation, intensive care unit and hospital outcomes:
- Mechanical ventilation duration: this time-to-event endpoint was analysed with a mixedeffects Cox regression, with a random effect for each cluster (S8). The Schoenfeld residuals were verified to check for the proportional hazards assumption, which was met. The median durations and interquartile range were calculated in each group.
- Duration between the first successful spontaneous breathing trial and extubation: this timeto-event endpoint was analysed with Kaplan Meier curves and were compared with a clustered Log-rank test. The median durations and interquartile range were calculated in each group.
- Duration of the intensive care unit stay: this time to event endpoint was represented by cumulative incidence curves and was analysed with a competing risks model, with death as an event in competition with alive discharge from the intensive care unit. The model was a population average regression taking into account the correlation across individuals within a cluster with the group as a fixed effect (S9). The Schoenfeld residuals were verified to check for the proportional hazards assumption, which was met. The median durations and interquartile range were calculated in each group.

- Proportion of patients dying in the intensive care unit: this binary endpoint was analysed according to the same principles as the primary outcome.
- Proportion of patients with extubation failure attributable to the aspiration of digestive secretions: this binary endpoint was analyzed according to the same principles as the primary outcome.
- Proportion of patients developing nosocomial pneumonia: this endpoint is an integer count and was analysed with a mixed effect Poisson model, taking the duration of observation as an offset and considering the group as a fixed effect and a random effect of cluster.

Acute respiratory failure occurrence in the days following extubation:

- Respiratory events after extubation: unplanned use of oxygen therapy, unplanned noninvasive ventilation and occurrence of tachypnoea: these endpoints are integer count and were analysed with a mixed effect Poisson model, taking the duration of observation as an offset and considering the group as a fixed effect and a random effect of cluster.
- The proportion of patients with extubation failure at 48 hours and 72 hours after extubation:
 this binary endpoint was analysed according to the same principles as the primary outcome.
 For all mixed effect regression, a fixed effect was used on the group and a random effect on the centre.

Absolute difference in the primary outcome between groups, adjusted on potential confounders (steroids use, respiratory physiotherapy, age, disease severity, number of spontaneous breathing trial failure, cough evaluation, tracheal secretion abundance, risk factors of extubation failure, comorbidities), was evaluated by post-hoc univariate and multivariate mixed linear model sensitivity analyses.

5. <u>Sample size:</u>

Based on the hypothesis of an incidence of extubation failure of 16% in the control group, with a non-inferiority margin of 10%, a one-sided type I error of 2.5% and a power of 80%, one would need to include 210 patients *per* group in an individual randomisation framework (S10). The cluster randomisation made it necessary to apply an inflation coefficient taking into account the correlation between patients from the same cluster. For this study, we assumed an intraclass correlation coefficient of 0.03 (S11). The principal endpoint is an "outcome" (*i.e.* it concerns the response of the patient to the management applied) rather than a "process" (*i.e.* dealing with the practices of the staff in the cluster). For endpoints of this type, Campbell and co-workers reported a median intraclass correlation coefficient of 0.03 (S11). We took into account differences in the sizes of the centres, using the approach of Eldridge and coworkers based on the coefficient of variation for cluster size (S12). In this regard, we used the number of beds per centre as a proxy estimating the number of patients eligible *per* centre. The coefficient of variation for the number of beds was 0.31. Finally, the planned number of clusters for this trial was 22. The mean number of patients per cluster was thus calculated with the following equation: $11*p = 210*[1+((0.31^2+1)p-1)*0.03)]$

Which gives p=49.8.

We therefore planned to include a mean of 50 patients per centre, resulting in a total of 1100 patients being required.

Role of the funding source

The trial was funded with a grant from the French Ministry of Health (No. API16/A/063, Groupement Interrégional de Recherche Clinique et d'Innovation Grand Ouest), the funder had no role in study design, conduct, results interpretation, manuscript drafting and decision to submit.

4. ADDITONAL RESULTS:

1. Table S1. Characteristics of the Patients before extubation

	Continued enteral nutrition (617 patients)	Fasting (513 patients)
Modalities of spontaneous breathing trial		
Fraction of inspired oxygen in case of spontaneous breathing trial with pressure support – %	31·1 ± 5·9	34·2 ± 13·4
Oxygen flow rate in case of spontaneous breathing trial with a T-piece – liter per minute	5·1 ± 1·7	4·1 ± 1·5
Specific predefined risk factors of extubation failure		
Stroke	57 (9·2)	78 (15·2)
Neuromuscular disease	52 (8·4)	73 (14·2)
Central nervous system infection	19 (3.1)	17 (3·3)
Severe Head trauma	19 (3·1)	11 (2·1)
Diaphragmatic dysfunction	4 (0·6)	10 (1·9)
Depressive disorder	83 (13·5)	81 (15·8)
Delirium	75 (12·2)	65 (12·7)
Number of risk factors		
None	400 (64·8)	316 (61.6)
1 or more	217 (35·2)	197 (38·4)
Richmond agitation sedation scale ^a		
Highest value		
-5	4 (0·8)	4 (1·1)
-4	1 (0·2)	4 (1·1)
-3	4 (0·8)	3 (0.8)
-2	3 (0.6)	4 (1·1)
-1	25 (5·1)	18 (4.8)
0	353 (72·3)	262 (70·1)
+1	56 (11·5)	53 (14·2)
+2	27 (5.5)	17 (4·5)
+3	14 (2·9)	8 (2·1)

+4	1 (0·2)	1 (0·3)
Lowest value		
-5	1 (0·2)	4 (1·1)
-4	12 (2·5)	10 (2·7)
-3	20 (4·1)	17 (4·5)
-2	27 (5·5)	28 (7·5)
-1	109 (22·3)	114 (30·5)
0	293 (60·0)	198 (52·9)
+1	18 (3·7)	2 (0·5)
+2	6 (1·2)	1 (0·3)
+3	2 (0·4)	0 (0·0)
+4	0 (0·0)	0 (0·0)

Quantitative variables are reported as means ± standard deviation and qualitative variables as counts (%). Percentages may sum-up to more than 100 due to several conditions present in one patient and rounding.

^a The Richmond agitation sedation scale is a 10 levels scale to evaluate sedation and agitated behaviour in patients in intensive care units. The scale ranges from -5 (unarousable patient) to +4 (combative patient). The highest and the lowest value were recorded within 6 hours before extubation for each patient (S13).

Of note, extubation failure was defined as a composite outcome of reintubation or death, however only a negligible minority of patients died without being re-intubated, representing less than 2% of the study population (11 patients in the continued enteral nutrition until extubation group and 9 in the fasting group), thus the primary endpoint was nearly exclusively driven by reintubation.

Unintentional extubation occurred among 8 patients in the continued enteral nutrition group

(1.3%) and among 7 patients (1.4%) in the fasting group.

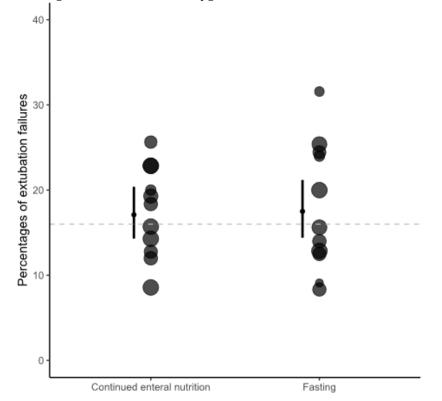
	Continued enteral nutrition	-		
	Events (%) Events (%)	Risk Ratio	95%-CI
I see a factor of a			1	
Hypoglycemia	10 (0.00()	47 (0.00()		0.00 [0.04 0.07]
The day before extubation	18 (2.9%)	· /		0.86 [0.31; 2.37]
The day of extubation, before extubation	2 (0.3%)	```		0.11 [0.02; 0.52]
The day of extubation, after extubation	16 (2·6%)	()		1.13 [0.62; 2.04]
The day after extubation	21 (3·4%)	19 (3·7%)		0.91 [0.47; 1.75]
Hyperglycemia				
The day before extubation	113 (18·3%) 136 (26·5%)	-	0.69 [0.53; 0.89]
The day of extubation, before extubation	69 (11·2%) 78 (15·2%)		0.75 [0.49; 1.16]
The day of extubation, after extubation	77 (12.5%) 60 (11.7%)	+	1.02 [0.68; 1.53]
The day after extubation	85 (13.8%) 98 (19.1%)	-	0.72 [0.51; 1.00]
	· ·			
Secondary outcomes				
Pneumonia at day 14	10 (1.6%)	13 (2·5%)		0.77 [0.22; 2.69]
Death in intensive care unit	24 (3.9%)	35 (6.8%)		0.56 [0.32; 0.99]
Extubation failure at hour 48	77 (12·5%	· ,	-=-	1.46 [1.02; 2.07]
Extubation failure at hour 72	91 (14.7%			1.40 [1.02; 1.93]
Tachypnea at day 7	364 (59%)	277 (54%)		1.41 [1.05; 1.89]
Curative oxygen therapy at day 7	208 (33.7%	· · ·	-++	0.82 [0.57; 1.19]
Curative non invasive ventilation therapy at day 7			_	0.93 [0.65; 1.32]
Reintubation for aspiration at day 7	8 (1.3%)			0.44 [0.18; 1.06]
	• (• • • • • • •	(_ 0,0)		[,]
			0.1 0.5 1 2 10	
		Favo	urs continued Favours fas	sting
		en	iteral nutrition	

2. Figures S2. Secondary outcomes

95%-CI: 95% confidence interval

By definition, secondary outcomes are only hypothesis generating and require further prospective confirmation.

Figure S3. Bubble plots of failure rates of individual hospitals relative to their group effects are shown. The size of the bubble indicates the number of patients contributing data in the hospital. The two vertical lines are the 95% confidence interval of the percentages of failures in each group. The horizontal dashed line corresponds to 16%, the hypothesised failure rate.



The intraclass correlation coefficients which estimate the proportion of the total variance of the outcome that can be explained by the variation between clusters were 0.002 (with 95% confidence interval 0 to 0.043) in the continued enteral nutrition and 0.008 (with 95% confidence interval 0 to 0.066) in the fasting group.

Continued enteral nutrition until extubation (617 patients)	Fasting (513 patients)
459 (74·5)	237 (48·7)
81 (13·1)	92 (17·9)
149 (24·1)	139 (27·1)
160 (25·9)	117 (22·8)
19 (3·1)	18 (3·5)
8 (1-3)	1 (0·2)
46·4 ± 14·2	48·8 ± 16·3
47·4 ± 14·2	48·2 ± 15·7
46·7 ± 15·8	48·7 ± 16·3
14·1 ± 11·3	17·6 ± 12·7
15·0 ± 11·4	16·8 ± 12·1
13·7 ± 11·1	11·8 ± 10·4
Not applicable	10·3 ± 7·2
Not applicable	22·7 ± 14·3
	$81 (13 \cdot 1)$ $149 (24 \cdot 1)$ $160 (25 \cdot 9)$ $19 (3 \cdot 1)$ $8 (1 \cdot 3)$ $8 (1 \cdot 3)$ $46 \cdot 4 \pm 14 \cdot 2$ $47 \cdot 4 \pm 14 \cdot 2$ $46 \cdot 7 \pm 15 \cdot 8$ $14 \cdot 1 \pm 11 \cdot 3$ $15 \cdot 0 \pm 11 \cdot 4$ $13 \cdot 7 \pm 11 \cdot 1$ Not applicable

3. Table S2. Respiratory and Nutritional exploratory outcomes.

Quantitative variables are reported as means ± standard deviation unless otherwise indicated and qualitative variables as counts (%). ^{*a*} Respiratory physiotherapy within 6 hours post extubation.

^b Preventive high flow nasal oxygen or non-invasive ventilation therapy (used each alone or alternatively) was defined as planned use implemented after extubation to prevent extubation failure.

^c An episode of post extubation respiratory failure was defined by the presence of at least 2 criteria among the following: a respiratory rate greater than 25 breaths per minute, clinical signs suggesting respiratory distress, respiratory acidosis defined as a pH level less than 7.35 units and a PaCO2 level greater than 45 mmHg, hypoxemia defined as a need for oxygen to maintain an SpO2 level of at least 92%. ^d Occurrence within 1 hour after extubation.

^e Nursing workload was evaluated with a visual analogical scale from 0 to 100 mm with higher values indicating higher workload, 50 mm corresponding to the usual workload.

^f In the continued enteral nutrition until extubation group, 230 (37·3%) patients continued feeding by gastric tube at the time of extubation.

5. Table S3. Predefined causes of extubation failure.

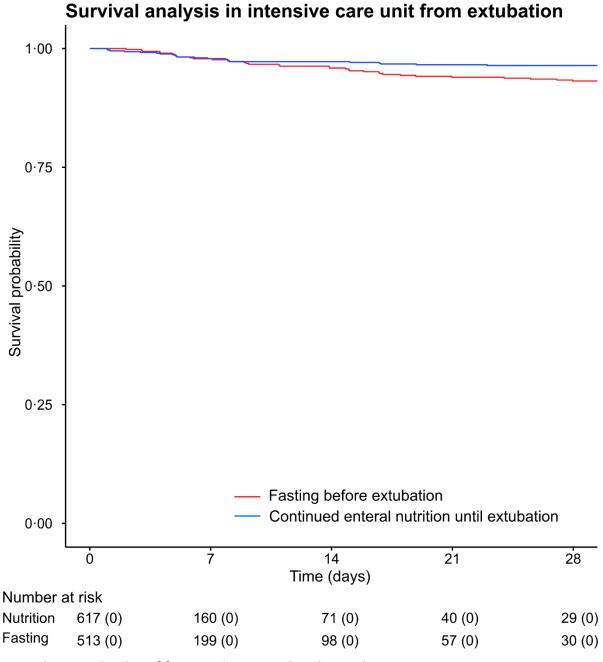
Percentages may sum-up to more than 100 due to several conditions present in one patient and rounding.

	Extubation	ibation to 48 hours 48 to 72 hours 72 hours to day 7		Extubation to Day 7				
	Continued enteral nutrition (n=77)	Fasting (n=44)	Continued enteral nutrition (=14)	Fasting (n=10)	Continued enteral nutrition (n=15)	Fasting (n=36)	Continued enteral nutrition (n=106)	Fasting (n=90)
Acute pulmonary edema	2 (2.6)	0 (0)	1 (7·1)	0 (0)	3 (20)	1 (2·8)	6 (5·7)	1 (1·1)
Obstruction/Oedema of upper airways	18 (23·4)	9 (20·5)	1 (7·1)	2 (20)	0 (0)	3 (8·3)	19 (17·9)	14 (15·6)
Pneumonia	2 (2·6)	3 (6·8)	3 (21·4)	1 (10)	4 (26·7)	8 (22·2)	9 (8·5)	12 (13·3)
Atelectasis	5 (6·5)	0 (0)	2 (14·3)	1 (10)	2 (13·3)	3 (8·3)	9 (8·5)	4 (4·4)
Pleurisy	2 (2·6)	0 (0)	1 (7·1)	0 (0)	1 (6·7)	3 (8·3)	4 (3·8)	3 (3·3)
Pneumothorax	0 (0)	2 (4·5)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	3 (3·3)
Bronchial congestion	20 (26)	16 (36·4)	6 (42·9)	4 (40)	6 (40)	15 (41·7)	32 (30·2)	35 (38·9)
Ineffective cough	19 (24·7)	9 (20·5)	2 (14·3)	2 (20)	3 (20)	13 (36·1)	24 (22·6)	24 (26·7)
Respiratory muscles weakness	15 (19·5)	10 (22·7)	4 (28·6)	3 (30)	3 (20)	11 (30·6)	22 (20·8)	24 (26·7)
Alveolar hypoventilation	9 (11·7)	3 (6·8)	0 (0)	1 (10)	2 (13·3)	7 (19·4)	11 (10·4)	11 (12-2)
Hypercapnic coma	6 (7·8)	5 (11·4)	1 (7·1)	1 (10)	3 (20)	3 (8·3)	10 (9·4)	9 (10)
Septic shock	2 (2.6)	1 (2·3)	0 (0)	0 (0)	2 (13·3)	3 (8·3)	4 (3·8)	4 (4·4)
Cardiogenic shock	1 (1·3)	1 (2·3)	0 (0)	0 (0)	0 (0)	2 (5·6)	1 (0·9)	3 (3·3)
Hemorrhagic shock	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neurological cause	11 (14·3)	1 (2·3)	0 (0)	4 (40)	3 (20)	4 (11·1)	14 (13·2)	9 (10)
Surgical intervention	1 (1·3)	1 (2·3)	1 (7·1)	0 (0)	3 (20)	9 (25)	5 (4·7)	10 (11·1)

Aspiration	5 (6·5)	5 (11·4)	1 (7·1)	2 (20)	2 (13·3)	8 (22·2)	8 (7.5)	15 (16·7)
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5. Post-hoc analyses:

- 1. Intensive care unit survival analysis:
 - 2. Figure S4. Survival after extubation



Day 0 denotes the day of first extubation within the study.

3. <u>Analysis of potential confounders:</u>

Analysis was performed in the intention to treat population. The following variables were considered as confounders : steroids administration prior to extubation to prevent laryngeal oedema, age, simplified acute physiology score II, at least failure of one spontaneous breathing trial failure (vs. success of the first spontaneous breathing trial), cough evaluation at extubation, tracheal secretion evaluation at extubation, 1 or more predetermined risk factors for extubation failure (vs. none), respiratory physiotherapy 6h prior to extubation, respiratory physiotherapy 6h post-extubation, presence of at least 1 cardio-pulmonary comorbidity (vs. none).

1. <u>Univariate adjusted sensitivity analysis:</u>

To evaluate the impact of confounders on treatment effect and the non inferiority hypothesis, a mixed effect linear model with the group and the confounder as fixed effects and the cluster as a random effect was estimated for each confounder (Table S4).

Variable	Absolute risk difference of extubation failure between groups	95% CI
Analyses of the primary outcome adjusted on treatment standa	rds	
Intervention effect adjusted on steroids	-0·5%	-4·1% to 3·2%
Intervention effect adjusted on respiratory physiotherapy 6h before extubation	-0·1%	-3·9% to 3·7%
Intervention effect adjusted on respiratory physiotherapy 6h after extubation	0.1%	-3·8% to 3·9%
Analyses of the primary outcome adjusted on baseline character	ristics	
Intervention effect adjusted on age > 65 years	0.0%	-3·5% to 3·5%
Intervention effect adjusted on age > 65 years Intervention effect adjusted on SAPS II	0·0% -0·3%	-3·5% to 3·5% -3·9% to 3·2%
Intervention effect adjusted on SAPS II Intervention effect adjusted on at least 1 spontaneous ventilation breathing trial failure	-0·3%	-3·9% to 3·2%
Intervention effect adjusted on SAPS II Intervention effect adjusted on at least 1 spontaneous ventilation-breathing trial failure Intervention effect adjusted on cough	-0·3% -0·1%	-3·9% to 3·2% -3·5% to 3·2%
Intervention effect adjusted on SAPS II Intervention effect adjusted on at least 1 spontaneous	-0·3% -0·1% 1·3%	-3·9% to 3·2% -3·5% to 3·2% -2·2% to 4·9%

5. Table S4 : Univariate adjusted sensitivity analysis

with the group and the variable of adjustment as fixed effects and the cluster as a random effect. The

reported difference of percentage represents the effect of continued enteral nutrition as compared to fasting on the primary outcome, taking into account the effect of the confounders

For all potential confounders, the sensitivity analysis confirmed the non-inferiority result of the main primary analysis of the primary outcome.

1. <u>Multivariate adjusted analysis:</u>

A final adjusted model was estimated on the main confounders. In order to select adjustment variables for this model, each confounder was analysed in a mixed effect linear model with the confounder as a fixed effect and the cluster as a random effect. Variables associated with a p-value below 0.1 were then included in a multivariate mixed effect linear model with the group and the selected confounders as fixed effects and the cluster as a random effect to calculate the adjusted risk difference of extubation failure between groups and its 95% confidence interval.

7. Table S5. Association between extubation failure and confounders

	p-value
Association between extubation failure and preventive or therapeutic interventions	
Steroids	0.74
Respiratory physiotherapy 6h before extubation	0.22
Respiratory physiotherapy 6h after extubation	0·11
Association between extubation failure and baseline characteristics	
Age > 65 years	0·11
SAPS II	0·11
At least 1 spontaneous ventilation failure	0·26
Cough evaluation	
Absent cough	reference
Weak cough	<0·37
Efficient cough	<0.01
Very efficient cough	<0.01
Tracheal secretion evaluation	
No tracheal secretions	reference
Low abundance secretions	<0.01

Abundant secretions	0.01
Great abundance secretions	0.58
At least 1 risk factor for extubation failure	0.05
At least 1 cardiopulmonary comorbidity	0.03

Final multivariate adjusted analysis: In the final multivariate adjusted model, including evaluation of cough strengths and tracheal secretions, presence of risk factors of extubation failure and cardio-pulmonary comorbidities the <u>adjusted absolute risk difference between</u> the continued enteral nutrition until extubation group and the fasting group was 1.7% with an 95% confidence interval of -1.5% to 4.9%, meeting the a priori defined non inferiority criterion.

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