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Authors' contributions :

MDr and LB designed the study. MD coordinated the study. MDr, TP, LS, WO, IT, DLG, MCS, DJ, LM, CS, LFD, LD, MDe and LB were responsible for patient screening, enrolment and follow-up. MD, TS, LB, AD and EG analyzed the data. MDr, AD and TS wrote the manuscript. All authors had full access to all of the study data, contributed to drafting the manuscript or critically revised it for important intellectual content, approved the final version of the manuscript, and took responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest Statements

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Abstract **(word=255)**

This study investigated dyspnea intensity and respiratory muscles ultrasound early after extubation to predict extubation failure.

It was conducted prospectively in two intensive care units in France and Canada. Patients intubated for at least 48 hours were studied within 2 hours after an extubation following a successful spontaneous breathing trial. Dyspnea was evaluated by the Dyspnea-Visual Analog Scale from 0 to 10 cm (VAS) and the Intensive Care - Respiratory Distress Observational Scale (range 0 – 10). The ultrasound thickening fraction of the parasternal intercostal and the diaphragm were measured; limb muscle strength was evaluated using the Medical Research Council score (MRC) (range 0 – 60).

Extubation failure occurred in 21 of the 122 enrolled patients (17%). Dyspnea-VAS and Intensive Care - Respiratory Distress Observational scale were higher in patients with extubation failure vs. success: 7 (5 – 9) cm versus 3 (1 – 5) cm respectively ($p<0.001$) and 4.4 (2.5 – 6.5) versus 2.4 (2.1 – 2.8) respectively ($p<0.001$). The ratio of intercostal muscle to diaphragm thickening fraction was significantly higher and MRC was lower in patients with failure (0.9 [0.4 – 3.0] vs. 0.3 [0.2 – 0.5], $p<0.001$, and 45 [36 – 50] versus 52 [44 – 60], $p=0.012$). The thickening fraction of the intercostal and its ratio to diaphragm thickening showed the highest area under the receiver operating characteristic curves for an early prediction of extubation failure (0.81). Areas under the receiver operating characteristic curves of Dyspnea-VAS and Intensive Care - Respiratory Distress Observational scale reached 0.78 and 0.74 respectively.

Respiratory muscle ultrasound and dyspnea measured within two hours after extubation predict subsequent extubation failure.

Keywords: extubation, diaphragm ultrasound, breathlessness, diaphragm, respiratory muscles

Introduction

Extubation failure occurs in 10% to 15% of the patients [1] and is associated with prolonged duration of mechanical ventilation and increased mortality [2]. The timing of reintubation is likely to influence the outcome: delayed reintubation is associated with a higher mortality rate [3]. Therefore, early identification of patients at high risk of reintubation is of great importance. In clinical practice, recognition of clinical worsening can be delayed because key elements of respiratory monitoring (e.g., tidal volume) are no longer available and respiratory rate alone is not a good indicator of inspiratory effort [4].

Dyspnea, a key feature of acute respiratory failure, could be a warning sign of extubation failure. For instance, in patients admitted to the intensive care unit (ICU) for acute respiratory failure, moderate to severe dyspnea is independently associated with non-invasive ventilation failure [5]. Therefore, assessing for dyspnea after extubation could help predict the risk of extubation failure. The intensity of dyspnea is strongly correlated with the activity of extradiaphragmatic inspiratory muscles such as parasternal intercostal and scalene [6–8]. These muscles are commonly activated together with the diaphragm in acute respiratory failure and weaning failure [9, 10]. Accordingly, the activity of the inspiratory muscles relative to the diaphragm could provide another early predictor of extubation failure. The activity of the parasternal intercostal [11] and the diaphragm [12, 13] can be easily quantified by ultrasound which could be useful during the weaning process. A recent study failed to identify differences in terms of diaphragm activity between patients who succeed and those who failed extubation in patients at high risk of extubation failure when ultrasound was performed during the spontaneous breathing trial [14]. Herein, we tested the hypothesis that, early after extubation, dyspnea, parasternal

intercostal muscle and diaphragm ultrasound can predict subsequent extubation failure in non selected patients separated from the ventilator after a successful spontaneous breathing trial.

Methods

This study complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. It was conducted between August 2016 and May 2018 in two sites: at the Medical and Surgical Intensive Care Unit, St. Michael Hospital, Toronto (August 2016 to November 2017) and at the Pulmonology and Intensive Care Department, Hôpital Pitié-Salpêtrière, Paris, France (August 2017 to May 2018). All patients or their next of kin provided informed consent. The study was approved by the Institutional Review Boards at both participating institutions (Comité de Protection des Personnes Ouest 17/048-3 – St Michael Hospital REB# 16-161) and has been performed in accordance with the ethical standards laid down in the 2008 Declaration of Helsinki.

Patients

Consecutive adult patients who were mechanically ventilated for at least 48 hours and who were extubated after a successful spontaneous breathing trial were eligible. Exclusion criteria were related to do not re-intubate orders, unplanned extubation, current use of extracorporeal membrane oxygenation, inability to perform ultrasound of the diaphragm and parasternal intercostal muscle (morbid obesity, thoracic dressings), tracheostomy, and pre-existing neuromuscular diseases or known diaphragm paralysis.

Patients were eligible for a spontaneous breathing trial as soon as they met predefined readiness to wean criteria: SpO_2 ≥90% on inspired oxygen fraction (FiO_2) ≤0.4 and positive end-expiratory pressure ≤8 cmH_2O, and low/no doses of vasopressors [15]. The spontaneous breathing trial was performed while patients were connected to the ventilator with no pressure assist of any kind (zero positive end-expiratory pressure and a pressure support level of zero) for 30 minutes. Success or failure of the spontaneous breathing trial and the decision to extubate were determined

by the physician in charge who had no role in the study (usual criteria for spontaneous breathing trial success and for extubation are listed in the online supplement). Prophylactic non-invasive ventilation or high flow nasal cannula could be applied in patients with pre-identified risk factors for extubation failure (chronic respiratory disease, chronic cardiac disease, age>65 years) [16]. The decision to use non-invasive ventilation or high flow nasal cannula was taken before the extubation by the physician in charge who has no role in the study.

Measurements

Dyspnea evaluation

Presence and severity of dyspnea were evaluated by using self-evaluation of dyspnea and dyspnea observation scales [17], depending on whether patients were communicative or non-communicative. Patients were considered as communicative when the Richmond Agitation-Sedation Scale (RASS) was between -1 and +1 and if they were able to consistently self-report dyspnea, attested by a dyspnea visual analog scale (Dyspnea-VAS) variation not exceeding 1 cm for three consecutive measures [18, 19]. In communicative patients only, self-evaluation was performed by the mean of Dyspnea-VAS that consisted in a 10-centimeter scale ranging from "no respiratory discomfort" to "intolerable respiratory discomfort". Hetero-evaluation was performed in communicative and non-communicative patients, by the mean of the Intensive Care Respiratory Distress Observational Scale (IC-RDOS) [17], which is based on respiratory, neurovegetative and behavioral signs and includes five observable items (heart rate, use of neck muscles during inspiration, abdominal paradox during inspiration, facial expression of fear and supplemental oxygen). IC-RDOS correlates strongly with Dyspnea-VAS [20] and has been previously validated in non-communicating ICU patients [21]. Clinically significant dyspnea was defined as a Dyspnea-VAS $\geq$4 [17] and IC-RDOS $\geq$2.4, since this latter predicts a Dyspnea-VAS $\geq$4 with equal sensitivity and specificity (72%) [20].

Respiratory muscles ultrasound

All investigators involved in ultrasound measurements received a training program with a minimum of 15 ultrasounds supervised by an investigator experienced in respiratory muscles ultrasound imaging. Respiratory muscles measurements were performed by investigators who were independent of the clinical team. At the time of ultrasound, patients were breathing spontaneously without non-invasive ventilation nor high flow oxygen therapy. When indicated, non-invasive ventilation or high flow oxygen therapy were applied after ultrasound measurements. Ultrasound was performed by using two machines (Sparq ultrasound system, Phillips, Philips Healthcare, MA, USA and Fujifilm Sonosite, Bothell, WA, USA). The methods to evaluate diaphragm and parasternal intercostal thickness and thickening have been extensively detailed and validated elsewhere [11, 22] (see also the online supplement). Briefly, the parasternal intercostal muscle was evaluated by using a 10-15 MHz linear array transducer positioned at the level of the second right intercostal space. The second right parasternal intercostal muscle was identified as a three-layered biconcave structure: two linear hyperechoic membranes respectively running from the anterior and posterior aspects of the adjoining ribs, and a medial portion with muscle echotexture. Using M-mode, the thickness of the parasternal intercostal muscle was measured on frozen images at end-expiration and at peak inspiration. Change in thickness determined the thickening fraction of the parasternal intercostal muscle (TFic) as follows: TFic equals peak inspiration thickness minus end expiratory thickness divided by end expiratory thickness. Only the right parasternal intercostal muscle was evaluated for simplicity.

Diaphragm ultrasound was conducted using a 10-15 MHz linear array transducer. As for parasternal intercostal muscle, diaphragm thickness (including pleural and peritoneal membranes) was measured at end-expiration and at peak inspiration and thickening fraction (TFdi) was

calculated offline as follows: TFdi equals peak inspiration thickness minus end expiratory thickness divided by end expiratory thickness.

All ultrasound recordings were analyzed off-line by one single investigator (first author) who was blinded to the clinical outcomes. All ultrasound measurements were repeated on at least three separate breaths and their average was reported. Reproducibility of diaphragm and parasternal intercostal muscle ultrasound has been reported elsewhere and was not tested in the present study [11, 22].

Clinical data collection

Demographic data were collected from the electronic medical charts of the patients: age, gender, comorbidities (chronic hypertension, chronic pulmonary disease, diabetes, chronic renal failure, left heart dysfunction), sequential organ failure assessment and acute physiology and chronic health evaluation III, date of intensive care unit admission, date of intubation, main reason for intubation, weight and height at admission, number of spontaneous breathing trials before extubation and ventilation mode before extubation. At the time of dyspnea evaluation and respiratory muscle ultrasound, the following variables were collected: arterial blood pressure, heart rate, pulsed oxygen saturation (SpO_2), respiratory rate. We also evaluated limb muscle strength by the Medical Research Council (MRC) score in communicative patients [23]. ICU-acquired weakness was defined by an MRC score less than 48 [24]. Finally, cough strength was assessed by using a semi-quantitative categorical scale that classified cough strength as “weak”, “moderate” or “strong” [14].

Study protocol

Patients were enrolled in the study following extubation and ultrasound of the diaphragm and the parasternal intercostal muscle was made on the right side within two hours after extubation. Immediately before ultrasound measurements, dyspnea was assessed with the Dyspnea-VAS in

communicative patients and the items of IC-RDOS were collected in all patients and the sum was computed off line.

The primary endpoint was extubation failure defined as reintubation or death within the 7 days following planned extubation.

Statistical analyses

Variables are presented as median (interquartile range) or number (%). As, to our knowledge, no previous publications have evaluated the level of dyspnea nor respiratory muscles ultrasound after extubation, a formal sample size calculation was deemed not possible, and we estimated that a sample of 15 to 20 patients with extubation failure would be appropriate to make a relevant comparison between groups regarding their dyspnea scales and ultrasound respiratory muscles indices. Based on an estimate rate of extubation failure of 15% [25], we planned to enroll 120 patients.

Differences between patients with and without extubation failure were assessed using Mann-Whitney test or chi-square tests, where appropriate. Potential risk factors for extubation failure were assessed by univariate analysis and their predictive performances were computed with Receiver Operating Characteristic curves. Sensitivities, specificities, positive and negative predictive values, positive and negative likelihood ratios and areas under the Receiver Operating Characteristic curves were calculated. Areas under the receiver operating characteristic curves were performed to identify optimal cut-off values in predicting failure, and these estimates were obtained using bootstrapping with 1000 replications. The best threshold value for each index was determined as the value associated with the best Youden index for the prediction of failure.

The Spearman correlation was used to evaluate the relationship between ultrasound indices (TFic, TFdi, TFic/TFdi) and dyspnea scales (Dyspnea-VAS and IC-RDOS). In all cases, a p-value <0.05 was considered statistically significant and two-tailed testing was used to test hypothesis.

All analyses were performed using Prism (GraphPad 8, San Diego, CA, USA) and MedCalc Software (bvba, Ostend, Belgium).

Results

Population

Among the 470 patients eligible during the study period, 122 patients were enrolled in the study (see Flow Chart in Figure 1). The main characteristics of the patients are shown in Table 1. There were significant differences between both centres regarding some characteristics of the patients (see Table ESM1). The main reasons for intubation were hypoxemic acute respiratory failure and coma and the median [interquartile range] (IQR) duration of mechanical ventilation at the time of enrolment was 5 [3 – 8] days. Extubation failure occurred in 21 (17%) of the 122 patients. The median [IQR] duration between extubation and extubation failure was 1 [0 – 3] days (see Table ESM2). Of these 21 patients, one patient was not re-intubated because of a decision of "do not re-intubate" taken after extubation (see Table ESM2 for the detailed cause of extubation failure). Respiratory distress was the reason for extubation failure in 18 patients; three patients failed extubation for other reasons (one for coma, one for seizure and one for sepsis). No stridor occurred after extubation.

The 101 (83%) remaining patients were classified as extubation success. Of these 101 patients, two received rescue non-invasive ventilation not followed by a reintubation. Post extubation management and outcomes of the patients are reported in Table ESM3.

Post extubation assessment

Post extubation assessment was performed 23 [0 – 60] minutes after extubation; there was no difference in timing assessment between patients with extubation success and those with extubation failure (30 [5 – 59] minutes versus 22 [0 – 61] minutes, respectively, p=0.45). Median dyspnea-VAS was 4 [2 – 5] cm and was ≥4 (i.e., clinically important dyspnea) in 49 (52%) of the 95 patients with dyspnea-VAS measurements. Median IC-RDOS was 1.9 [1.6 – 3.5] and was ≥ 2.4

(i.e., clinically important) in 68/122 (56%) patients. Thirty-four patients (36%) had ICU-acquired weakness, defined by MRC <48. Cough strength was estimated as weak in 14 patients (13%), moderate in 72 patients (65%) and strong in 24 patients (22%).

Factors associated with extubation failure

Clinical features and arterial blood gases before and after the spontaneous breathing trial were not different in patients depending of the extubation outcome (Table ESM4). Except for the respiratory rate that was higher in patients with extubation failure, the rest of the clinical examination was not different between groups at the time of ultrasound and dyspnea evaluation (Table 2). The proportion of patients with weak, moderate and strong cough was not different between groups (Table 2). The MRC score was higher in patients with extubation success as compared to patients with extubation failure (Table 2). Clinically relevant dyspnea (≥4) was more frequent and dyspnea was more intense in patients who failed extubation (Table 2 and Figure 2). TFdi was significantly higher in patients who succeeded extubation whereas the TFic was significantly higher in patients who failed extubation (Figure 2, Table 2). The TFic/TFdi was higher in patients with extubation failure (Table 2). There was a moderate but significant correlation between TFic and IC-RDOS and between TFic and Dyspnea-VAS but there was no correlation between TFdi and IC-RDOS and between TFdi and Dyspnea-VAS (Table ESM5).

The performance of IC-RDOS, Dyspnea-VAS, MRC score, TFic, TFdi and TFic/TFdi to predict extubation failure were evaluated by computing their areas under the receiver operating characteristic curves (Figure 3, Table ESM6). The best thresholds to predict extubation failure were IC-RDOS >3.3, Dyspnea-VAS>4.0, MRC score<50, TFic>8.6%, TFdi<15.6% and TFic/TFdi >0.44 (Table ESM5). IC-RDOS was below 3.3 in 8/21 patients who failed extubation. Among these eight patients, five had a TFic/TFdi>0.44. Therefore, combining IC-RDOS and TFic/TFdi predicted extubation failure in 18/21 patients. A sensitivity analysis comparing patients with

extubation failure (reintubation and rescue non-invasive ventilation) and extubation success reached similar findings (Table ESM7).

Discussion

This study investigated the performance of dyspnea scales and respiratory muscle ultrasound following extubation after a successful spontaneous breathing trial to predict the risk of extubation failure. The main findings are the following: 1) patients who eventually failed extubation experienced higher self-reported dyspnea intensity and higher observational dyspnea scale after extubation, 2) there was a moderate but significant correlation between dyspnea and TFic and TFic/TFdi as evaluated by ultrasound, 3) TFic/TFdi predicted extubation outcome with a good performance, the higher the ratio, the higher the risk of subsequent reintubation.

Weaning failure occurs when respiratory loading (pulmonary edema, secretions, atelectasis, hyperinflation) exceeds the compensatory capacity of the respiratory muscles [26]. This load capacity imbalance stimulates the respiratory drive [27], which in turn induces the recruitment of accessory inspiratory muscles [9, 11], both well-established determinants of dyspnea. Dyspnea is a frequent but underestimated symptom that is encountered in approximatively 50% of ICU patients [5, 20, 28, 29]. Dyspnea is strongly associated with the recruitment of extra diaphragmatic respiratory muscles [6, 8, 30] and behaves as a reliable surrogate of the increase in respiratory drive that is subsequent to the load capacity imbalance. The correlation between dyspnea and extra diaphragmatic respiratory muscles activity has been already established with electromyogram [6, 30]. Our study confirms this physiological relationship with ultrasound. In contrast, there was no correlation between dyspnea and TFdi, a finding already highlighted in a previous study [30]. Therefore, the recruitment of extradiaphragmatic inspiratory muscles seems to be a better indicator of the respiratory load capacity imbalance than the diaphragm activity. This may explain why dyspnea, which is closely linked to respiratory drive, is better correlated with parasternal intercostal activity than with diaphragm activity alone.

While our patients had successfully passed a spontaneous breathing trial suggesting a relatively adequate load capacity balance, the prevalence of dyspnea was as high as 52% after extubation. Since dyspnea was not evaluated before extubation, it cannot be ruled out that some patients were dyspneic while they did not develop classical criteria of spontaneous breathing trial failure. Interestingly, the intensity of dyspnea predicted extubation outcome. Several studies already reported on the relationship between dyspnea – as a warning sign – and clinical outcomes. Dyspnea seems to be a proxy for the severity of a respiratory or cardiac disease [31]. For instance, there is an association between poor respiratory comfort and hospital mortality in patients with suspected acute myocardial infarction [32, 33], in those admitted for acute COPD exacerbation [34] and even in patients without previously diagnosed cardiopulmonary diseases [35]. Regarding the prediction of intubation, a recent study suggested that in patients receiving non-invasive ventilation for acute respiratory failure, moderate-to-severe dyspnea can predict non-invasive ventilation failure and subsequent intubation [5]. These findings and ours suggest that evaluation of dyspnea in non-intubated patients – before or after extubation – may be of clinical interest. Eventually, further studies will have to investigate whether preventive strategies of extubation failure could rely on dyspnea scales and timely application of non-invasive ventilatory supports.

It is of notice that the IC-RDOS, an observational scale that can evaluate dyspnea in non-communicative patients as opposed to D-VAS that required patient cooperation, performed as D-VAS to predict extubation failure. This is of great help since freshly extubated patients may show delirium and be unable to self-report dyspnea. Finally, it is important to remind that, with a median D-VAS of 4, dyspnea was present in a substantial proportion of patients. Similar pain intensity would have immediately trigger a medical response involving the administration of antalgic medication. The suffering that dyspnea induces in extubated patients should not be neglected as

dyspnea contributes to the dark recollections following an ICU stay [36]. For some authors, failing to address dyspnea breaches human rights [37, 38].

The present study shows that ultrasound of respiratory muscles could identify patients who further presented extubation failure. Indeed, patients who developed extubation failure had a lower TFdi and a higher TFic. The association between either increased TFic or decreased TFdi and weaning failure has been already well established [11, 39]. It is noticeable that, at the time of respiratory muscles ultrasound, patients who further developed extubation failure had similar clinical presentation as compared to their counterparts. Furthermore, the respiratory rate was associated with a poor receiver operating characteristic curve, suggesting that ultrasound was able to detect a subclinical impairment of the respiratory load/capacity balance.

Because diaphragm dysfunction is compensated by an increase in extradiaphragmatic inspiratory muscle activity [40–42], the relationship between TFic and TFdi is invert, the lower the TFdi, the higher the TFic [11]. The TFic/TFdi combines the evaluation of the diaphragm and the extradiaphragmatic inspiratory muscle. When the TFic/TFdi ratio increases, it indicates a recruitment of parasternal intercostal muscles (high TFic) because of a weak diaphragm (low TFdi). This ratio may appropriately reflect the respiratory load/capacity balance. Indeed, in case of increased respiratory drive, extradiaphragmatic respiratory muscles are activated more prematurely and more vigorously than the diaphragm [43]. In ICU patients, recruitment of scalene muscles predicts weaning failure [9] and recruitment of parasternal intercostal muscle predicts poor outcome in patients with chronic obstructive pulmonary disease exacerbation [44]. These data and ours raise the relevance of monitoring extradiaphragmatic inspiratory muscles, which seem to be a better indicator of the respiratory load capacity imbalance than diaphragm activity alone. However, combining TFdi with TFic did not offer predictive advantage for extubation failure probably because TFdi provides a lower performance than TFic to predict extubation failure as already

reported by others who observed similar values of TFdi in patients who succeeded and in those who failed extubation [14]. In this previous study, diaphragm ultrasound was performed while patients were still under mechanical ventilation while on T-piece and not after extubation (such as in our study). In addition, in this former study, patients were selected as being at high risk of extubation failure which was not particularly the case of our population. Our approach was to evaluate a strategy aiming to predict extubation outcome after and not before extubation ,which could be questionable. We reasoned that despite a successful spontaneous breathing trial, the risk of extubation failure still ranges between 10% and 20% [25, 45]. This is explained by the fact that the SBT behaves like any other diagnostic test and will never reach a perfect specificity (i.e. 100%) [46]. Accordingly, we believe that it is still relevant to evaluate the risk of extubation failure after extubation. The implications (not investigated in the present work) would be to personalize the management of these patients in order to prevent post extubation acute respiratory failure and subsequent re intubation (non-invasive ventilation, high flow nasal oxygen, physiotherapy, mobilization, delayed ICU discharge).

Strengths and limitations of the study

The study was conducted in two centers in two different countries and used a standardized weaning protocol. In addition, the inclusion criteria were broad, which might help generalizing our findings. However, this study has limitations. First, the number of patients is limited due the weak occurrence of extubation failure and there were significant differences between both centers regarding some characteristics of the patients; further studies will have to evaluate the extrinsic validity of our calculated cut-offs and to confirm the predictive thresholds identified in the present work in a validation cohort. Second, the reproducibility of D-VAS and IC-RDOS was not evaluated in our study although previous studies reported good reproducibility [20, 47]. Third, in order to standardize measurements, ultrasound was performed while patients were breathing spontaneously.

Accordingly, ultrasound measurements may not reflect the patients' conditions under prophylactic measures (non invasive ventilation or high flow oxygen therapy). In addition, the use high flow oxygen therapy may have influenced the outcome of some patients. At the time of study, no evidences based guidelines were available on the use of high glow oxygen therapy. It was driven by the experience of physician in charge.

Conclusion

In patients who successfully passed a spontaneous breathing trial and were subsequently extubated, dyspnea as assessed by self-report or observational scales and respiratory muscles activity assessed with ultrasound predicted extubation failure. Although these results need to be confirm by a larger study, they suggest that monitoring dyspnea in every newly extubated patients may be useful to predict a future re-intubation. Our results pave the way of future studies evaluating whether monitoring dyspnea following extubation may tailoring the oxygenation and ventilation strategy in the post extubation period.

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Figures legends

Figure 1. Flow chart of the study

Figure 2. Dyspnea Visual Analogic Scale (Dyspnea-VAS) (Panel A), ICU-Respiratory Distress Observation Scale (IC-DROS) (Panel B), Medical Research Council (MRC) Score (Panel C), thickening fraction of the intercostal muscle (TFic) (Panel D) and diaphragm (TFdi) (Panel E), and TFic/TFdi (Panel F) in patients with extubation success and extubation failure. Box plots represent the median (min to max) of the distributions.

Figure 3. Receiver Operating Characteristic (ROC) curves of Dyspnea Visual Analogic Scale (Dyspnea-VAS) (Panel A), ICU-Respiratory Distress Observation Scale (IC-DROS) (Panel B), Medical Research Council (MRC) Score (Panel C), thickening fraction of the intercostal muscle (TFic) (Panel D) and diaphragm (TFdi) (Panel E), and TFic/TFdi (Panel F). AUC: area under the ROC curves.

Table 1. Characteristics of the patients

	Extubation Success N= 101	Extubation Failure N=21	*p*
Age, *years*	59 (46 – 66)	55 (48 – 72)	0.617
Male, *n (%)*	63 (62)	14 (67)	0.903
Body mass index, $kg.m^{-2}$	25 (22 – 31)	25 (23 – 29)	0.884
Conditions, *n (%)*			
Hypertension, *n (%)*	39 (39)	8 (40)	1.000
Chronic pulmonary disease, *n (%)*	17 (17)	1 (5)	0.310
Diabetes, *n (%)*	21 (21)	4 (20)	1.000
Chronic renal failure, *n (%)*	9 (9)	2 (10)	0.190
Left heart dysfunction, *n (%)*	11 (11)	1 (5)	0.150
Severity upon admission			
SOFA score	7 (5 – 10)	6 (5 – 9)	0.611
APACHE III score	26 (20 – 43)	46 (20 – 81)	0.104
Main cause of intubation			
Hypoxemic ARF, *n (%)*	38 (38)	8 (40)	1.000
Hypercapnic ARF, *n (%)*	6 (6)	1 (5)	1.000
Coma, *n (%)*	21 (21)	7 (35)	0.255
Shock, *n (%)*	10 (10)	0 (0)	0.208
Cardiac arrest, *n (%)*	4 (4)	1 (5)	1.000
Gastric bleeding, *n (%)*	6 (6)	0 (0)	0.588
Post-surgery, *n (%)*	16 (16)	4 (20)	0.898
Weaning			
Time since intubation, *days*	5 (3 – 7)	6 (4 – 11)	0.059
Number of Spontaneous breathing trials, *n*	2 (1 – 3)	1 (1 – 2)	0.491
Ventilation mode			
Pressure support, *n (%)*	96 (95)	20 (95)	0.688
Assist-control ventilation, *n (%)*	2 (2)	1 (5)	1.000
NAVA, *n (%)*	1 (1)	0	1.000
Pressure-control ventilation, *n (%)*	1 (1)	0	1.000
Proportional Assist Ventilation, *n (%)*	1 (1)	0	1.000

Quantitative variables are described as median (interquartile range) and qualitative variables are described as frequency (percentages).
SOFA, Sequential Organ Failure Assessment; APACHE III, Acute Physiology and Chronic Health Evaluation; ARF, Acute Respiratory Failure; NAVA, Neurally Adjusted Ventilatory Assist.

Table 2. Clinical evaluation and respiratory muscles ultrasound indices on enrollment

	Extubation Success N= 101	**Extubation Failure N=21**	***p***
Clinical evaluation			
Systolic blood pressure, *mmHg*	133 (120 – 147)	125 (110 – 151)	0.429
Diastolic blood pressure, *mmHg*	69 (61 – 76)	64 (57 – 80)	0.334
Heart rate, *beats.min^{-1}*	91 (76 – 103)	93 (84 – 117)	0.318
SpO2, *%*	98 (95 – 100)	98 (94 – 99)	0.358
Respiratory rate, cycles.*min^{-1}*	21 (17 – 24)	24 (21 – 28)	0.022
Dyspnea evaluation			
Patients with measurements, *n*	101	21	-
IC-RDOS	2.4 (2.1 – 2.8)	4.4 (2.5 – 6.5)	<0.001
IC-RDOS ≥ 2.4, *n (%)*	50 (49)	18 (86)	0.002
Patients with measurements, *n*	79	16	-
Dyspnea-VAS, cm	3 (1 – 5)	7 (5 – 9)	<0.001
Dyspnea-VAS ≥ 4, *n (%)*	35 (44)	14 (88)	0.002
Cough strength			0.236
Patients with measurements	91	19	-
Weak, *n (%)*	10 (11)	4 (21)	
Moderate, *n (%)*	60 (66)	12 (63)	
Strong, *n (%)*	21 (23)	3 (16)	
Limb muscles strength			
Patients with measurements	79	16	-
Medical Research Council	52 (44 – 60)	45 (36 – 50)	0.012
Medical Research Council <48, *n (%)*	24 (30)	10 (63)	0.031
Respiratory muscle Ultrasound indices			
Patients with measurements	88	19	
TFdi, *%*	21 (15 – 27)	11 (9 – 19)	0.001
TFic, *%*	7 (4 – 9)	13 (9 – 22)	<0.001
TFic/TFdi	0.3 (0.2 – 0.5)	0.9 (0.4 – 3.0)	<0.001

Quantitative variables are described as median (interquartile range) and qualitative variables are described as frequency (percentages).

SpO_2, pulsed oxygen saturation; VAS, Visual analogic scale; IC-RDOS, intensive care – respiratory distress observation scale; TFdi, diaphragm thickening fraction; TFic, parasternal intercostal thickening fraction

Dyspnea and respiratory muscles function to predict extubation failure

Online Supplement

Weaning protocol

A daily screening for readiness to wean criteria was performed in both centers. Readiness to wean criteria were the following: $SpO_2 \geq 90\%$ on inspired oxygen fraction (FiO_2) ≤ 0.4 or $PaO_2/FiO_2 > 150$ mmHg with and positive end-expiratory pressure ≤ 8 cmH_2O, patient awake with no continuous sedation and low/no doses of vasopressors [1].

Failure of spontaneous breathing trial was defined according to the criteria of the international conference consensus on weaning [1]. Specifically, they include the development during the spontaneous breathing trial of any of the following events: 1) respiratory rate > 35 breaths/min, 2) increased accessory muscle activity, 3) SpO_2 persistently below 90% (on $FiO_2<0.4$), 4) heart rate persistently above 140 beats / min, 5) systolic arterial blood pressure < 90 mmHg or > 180 mmHg, 6) appearance of cyanosis or mottling, 7) depressed mental status or agitation.

Decision of extubation was made by the clinician in charge of the patient based on the following criteria: 1) successful spontaneous breathing trial, 2) patient awake, calm and responsive to simple orders (squeeze the hand, knock the head, close the eyes), no agitation and 3) cough during suctioning.

Diaphragm and parasternal intercostal ultrasound

For feasibility, ultrasound was performed on the right side only. For all measurement, at least three valid breathing cycles were recorded, and the average of the individual values was reported. All investigators involved in respiratory muscles ultrasound followed a training program consisting in theoretical and hand on sessions. They had to successfully performed at least 15 ultrasound examination on patients before to do it on their own. All images and measurements were checked by the first author.

Parasternal intercostal muscle ultrasound

Patients were studied in a semi-recumbent position and were breathing spontaneously without non-invasive ventilation nor high flow oxygen therapy at the time of the study. A 10-15 MHz linear array transducer (Sparq ultrasound system, Phillips, Philips Healthcare, Andover, MA, USA and HFL-38xe, FUJIFILM Sonosite, Bothell, WA, USA) was positioned perpendicular to the anterior thorax surface in the sagittal plane, at the level of the second right intercostal space, approximately 6-8 cm lateral to the sternal edge with a window visualising the 2nd and 3rd ribs. The second right parasternal intercostal muscle was identified as a three-layered biconcave structure. Using M-mode, the ultrasound beam was perpendicularly directed at the midsection of the muscle, where it is the thinnest at end-expiration. The thickness of the parasternal intercostal muscle was measured on frozen images at end-expiration (Tee) and at peak inspiration (Tei). TFic was defined as the percent change in muscle thickness between expiration and inspiration. This change in thickness determined the thickening fraction of the parasternal intercostal muscle (TFic = (Tei - Tee)/Tee). All measurements were repeated on at least three separate breaths and their average was reported.

Diaphragm ultrasound

Ultrasound assessment of the diaphragm was performed using a 4-12 MHz linear array transducer (Sparq ultrasound system, Phillips, Philips Healthcare, Andover, MA, USA and

HFL-38xe, FUJIFILM Sonosite, Bothell, WA, USA). The probe was placed perpendicular to the right chest wall, at the midaxillary line between the 9th and 10th right intercostal spaces (at the level of the zone of apposition) and the right diaphragm was identified as a three-layered structure comprising two hyperechoic lines representing the pleural and peritoneal membranes and a middle hypoechoic layer representing the diaphragmatic muscle fibers. Using M-mode at a sweep speed of 10 mm/s, at least three spontaneous quiet breathing cycles were recorded and the image was frozen. Diaphragm thickness (including pleural and peritoneal membranes) was measured at end-expiration (Tdi,ee) and end-inspiration (Tdi,ei) using electronic calipers. The thickening fraction of the diaphragm (TFdi) was calculated offline as (Tdi,ei – Tdi,ee)/ Tdi,ee. For all measurement, at least three valid breathing cycles were recorded, and the average of the individual values was reported.

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Table ESM1. Main characteristics of the patients, management and outcomes according to centres

	France n= 59	**Canada n=63**	***P***
Age, *years*	56 (44 – 64)	62 (53 – 70)	0.032
Male, *n (%)*	34 (58)	43 (68)	0.224
Body mass index, $kg.m^{-2}$	25 (22 – 28)	27 (22 – 31)	0.049
Severity upon admission			
SOFA score	6 (4 – 9)	8 (6 – 11)	0.008
Main cause of intubation			
Hypoxemic ARF, *n (%)*	28 (47)	18 (19)	0.041
Hypercapnic ARF, *n (%)*	5 (8)	2 (3)	0.208
Coma, *n (%)*	13 (22)	15 (24)	0.816
Shock, *n (%)*	4 (7)	6 (10)	0.581
Cardiac arrest, *n (%)*	2 (3)	3 (5)	0.702
Gastric bleeding, *n (%)*	2 (3)	4 (6)	0.450
Post-surgery, *n (%)*	5 (8)	15 (24)	0.022
Weaning			
Time since intubation, *days*	5 (3 – 7)	6 (3 – 8)	0.265
Cough strength			0.013
Patients with measurements	n=58	n=52	
Weak, *n (%)*	3 (5)	11 (21)	
Moderate, *n (%)*	38 (66)	34 (65)	
Strong, *n (%)*	17 (29)	7 (14)	
Dyspnea			
IC-RDOS	2.6 (2.1 – 4.7)	2.4 (2.1 – 2.6)	0.037
IC-RDOS ≥ 2.4, *n (%)*	40 (68)	28 (44)	0.009
Patients with VAS measurements	n=54	n=41	
Dyspnea-VAS, cm	3 (2 – 5)	4 (1 – 5)	0.857
Dyspnea-VAS ≥ 4, *n (%)*	26 (48)	23 (56)	0.442
Limb muscles strength			
Patients with measurements	N=58	N=37	
Medical Research Council	53 (47 – 60)	46 (36 – 54)	0.002
Medical Research Council <48, *n (%)*	15 (26)	19 (51)	0.012
Respiratory muscle Ultrasound indices			
Patients with measurements	n=49	n=58	
TFdi, *%*	22 (1 – 25)	18 (13 – 30)	0.346
TFic, *%*	8 (5 – 12)	7 (4 – 10)	0.097
Ratio	0.3 (0.2 – 0.6)	0.3 (0.2 – 0.6)	0.641
Outcomes			
Extubation failure, *n (%)*	12 (20)	9 (14)	0.376
Prophylactic NIV, *n (%)*	4 (7)	2 (3)	0.357
High Flow Nasal Oxygen, *n (%)*	18 (31)	8 (13)	0.016
ICU mortality, *n (%)*	6 (10)	2 (3)	0.119

Quantitative variables are described as median (interquartile range) and qualitative variables are described as frequency (percentages).
SOFA, Sequential Organ Failure Assessment; ARF, Acute Respiratory Failure, VAS, Visual analogic scale; IC-RDOS, intensive care – respiratory distress observation scale; TFdi, diaphragm thickening fraction; TFic, parasternal intercostal thickening fraction; ICU, Intensive Care Unit

Table ESM2. Causes of reintubation and delay between extubation and reintubation

Patients	Causes of reintubation	Delay of reintubation (days)
# 1	Increased work of breathing, atelectasis	3
# 2	Pleural effusion, pneumonia, increased work of breathing	1
# 3	Hypotension and decreased level of consciousness	3
# 4	Increased work of breathing	3
# 5	Respiratory distress	3
# 6	Increased work of breathing	<1
# 7	Decreased level of consciousness	2
# 8	Inability to cope with copious secretions, pulmonary edema	1
# 9	Inability to cope with copious secretions, respiratory acidosis	<1
# 10	Inability to cope with copious secretions, atelectasis	<1
# 11	Respiratory distress	1
# 12	Inability to cope with copious secretions, atelectasis	<1
# 13	Pulmonary edema	1
# 14	Coma	1
# 15	Increased work of breathing	1
# 16	Hypoxemia	2
# 17	Increased work of breathing, respiratory acidosis	3
# 18	Inability to cope with copious secretions	1
# 19	Respiratory distress, hypoxemia	1
# 20	Respiratory distress, hypoxemia	<1
# 21	Respiratory distress, patient deceased at day 3 after extubation	NA

Table ESM3. Post extubation management and outcomes

	Extubation Failure N=21	Extubation Success N= 101	*p*
Ventilation and oxygenation			
Ambient room air, n (%)	1 (5)	17 (17)	0.303
Standard oxygen, n (%)	19 (95)	83 (83)	0.303
Oxygen, L/min	7 (3 – 12)	4 (2 – 6)	0.012
Prophylactic Non-invasive Ventilation, n (%)	1 (5)	5 (5)	0.999
High Flow Nasal Oxygen, n (%)	8 (38)	13 (13)	0.010
Outcomes			
Intensive care unit mortality, n (%)	7 (33)	1 (1)	<0.001
Intensive care unit readmission, n (%)	3 (14)	9 (9)	0.432
Tracheotomy, n (%)	1 (5)	0 (0)	0.172

Table ESM4. Hemodynamic, respiratory characteristics and gases exchanges before and at the end of the spontaneous breathing trial

		Extubation failure N = 21	Extubation success N=101	p
PEEP, cmH_2O	Before SBT	5 (5 – 8)	5 (5 – 8)	0.883
	End of SBT	0	0	-
FiO_2, %	Before SBT	40 (30 – 40)	30 (30 – 40)	0.122
	End of SBT	40 (30 – 50)	30 (30 – 40)	0.019
Tidal volume, mL/kg	Before SBT	6 (6 – 9)	6 (5 – 8)	0.256
	End of SBT	6 (5 – 8)	6 (5 – 7)	0.488
Respiratory rate, min^{-1}	Before SBT	22 (16 – 27)	18 (15 – 22)	0.120
	End of SBT	23 (20 – 28)	21 (16 – 26)	0.078
Heart rate, min^{-1}	Before SBT	93 (80 – 100)	91 (80 – 105)	0.861
	End of SBT	99 (86 – 108)	94 (79 – 104)	0.229
Systolic arterial pressure, mmHg	Before SBT	138 (120 – 147)	130 (118 – 140)	0.251
	End of SBT	141 (121 – 151)	131 (120 – 147)	0.115
Diastolic arterial pressure, mmHg	Before SBT	69 (60 – 77)	65 (59 – 76)	0.167
	End of SBT	67 (61 – 86)	69 (59 – 76)	0.395
pH	Before SBT	7.45 (7.41 – 7.48)	7.45 (7.40 – 7.48)	0.946
	End of SBT	7.46 (7.42 – 7.47)	7.46 (7.42 – 7.49)	0.671
PaO_2, mmHg	Before SBT	97 (78 – 118)	107 (86 – 130)	0.151
	End of SBT	83 (60 – 97)	84 (73 – 99)	0.537
$PaCO_2$, mmHg	Before SBT	43 (37 – 46)	40 (37 – 46)	0.709
	End of SBT	42 (34 – 49)	39 (36 – 47)	0.950
HCO_3^-, mmol/L	Before SBT	27 (24 – 34)	29 (25 – 32)	0.774
	End of SBT	28 (26 – 28)	30 (27 – 33)	0.114

SBT: spontaneous breathing trial; **PEEP**: positive end expiratory pressure; **FiO_2**: inspired fraction of oxygen

Table ESM5. Correlation between dyspnea and respiratory muscles thickening fraction

	IC-RDOS		**Dyspnea VAS**	
	Spearman coefficient	**p**	**Spearman coefficient**	**p**
TFic	0.226 (0.032 – 0.403)	0.019	0.285 (0.067 – 0.467)	0.009
TFdi	-0.176 (-0.358 – 0.017)	0.181	-0.084 (-0.298 – 0.137)	0.442
TFic/TFdi	0.250 (0.057 – 0.425)	0.009	0.269 (0.050 – 0.463)	0.014

IC-RDOS: intensive care – respiratory distress observation scale; **D-VAS**: Visual analogic scale; **TFdi**: diaphragm thickening fraction; **TFic**: parasternal intercostal thickening fraction

Table ESM6. Cut-offs, area under the receiver operating characteristics curves (AUC-ROC), sensitivity, specificity, positive and negative likelihood ratios and positive and negative predictive values of Intensive Care – Respiratory distress observation scale (IC-RDOS), Medical Research Council (MRC) score and diaphragm thickening fraction (TFdi) over parasternal intercostal muscle thickening fraction (TFic) ratio to predict extubation failure.

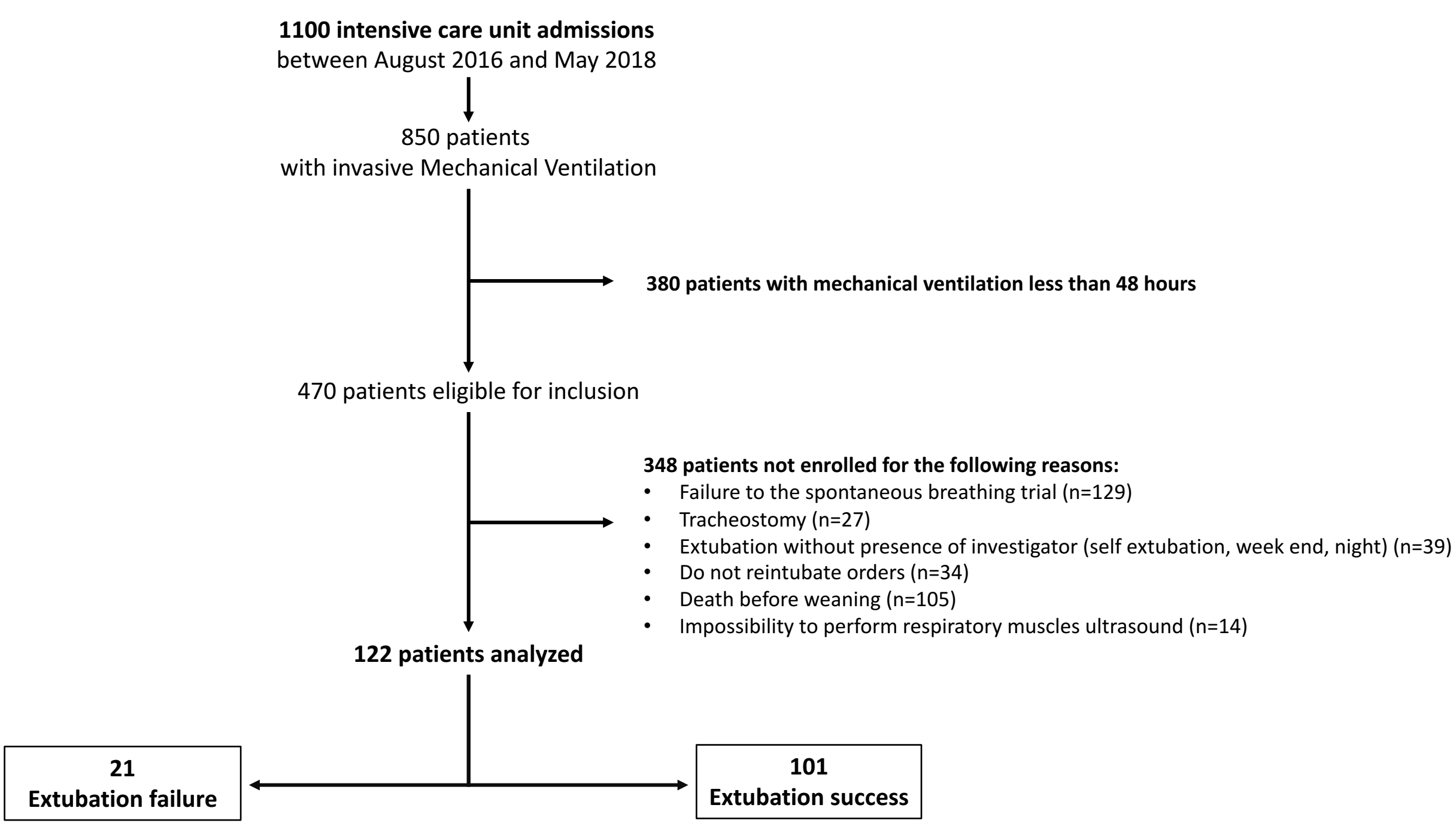
	Cut-offs	AUC-ROC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Likelihood ratios (95% CI)		Predictive Values (%) (95% CI)	
					Positive	Negative	Positive	Negative
Respiratory rate	>22	0.65 (0.57 to 0.74)	67 (43 to 85)	63 (52 to 72)	1.8 (1.2 to 2.6)	0.5 (0.3 to 1.0)	28 (20 to 36)	90 (83 to 94)
IC-RDOS	>3.3	0.74 (0.65 to 0.82)	62 (38 to 82)	82 (73 to 89)	3.5 (2.0 to 5.9)	0.5 (0.3 to 0.8)	42 (30 to 55)	91 (86 to 95)
Dyspnea-VAS	>4.0	0.78 (0.68 to 0.86)	75 (48 to 93)	72 (61 to 82)	2.7 (1.7 to 4.2)	0.4 (0.1 to 0.8)	35 (26 to 46)	93 (86 to 97)
MRC score	<50	0.69 (0.59 to 0.79)	81 (54 to 96)	57 (45 to 68)	1.9 (1.3 to 2.7)	0.3 (0.1 to 0.9)	28 (21 to 35)	94 (84 to 98)
TFic	>8.6	0.81 (0.72 to 0.88)	79 (54 to 94)	73 (62 to 82)	2.9 (1.9 to 4.4)	0.3 (0.1 to 0.7)	39 (29 to 49)	94 (87 to 98)
TFdi	<15.6	0.73 (0.63 to 0.81)	63 (38 to 84)	74 (64 to 83)	2.5 (1.5 to 4.0)	0.5 (0.3 to 0.9)	34 (24 to 46)	90 (84 to 95)
TFic/TFdi	>0.44	0.81 (0.72 to 0.88)	74 (49 to 91)	73 (62 to 82)	2.7 (1.7 to 4.2)	0.4 (0.2 to 0.8)	37 (27 to 47)	93 (86 to 96)

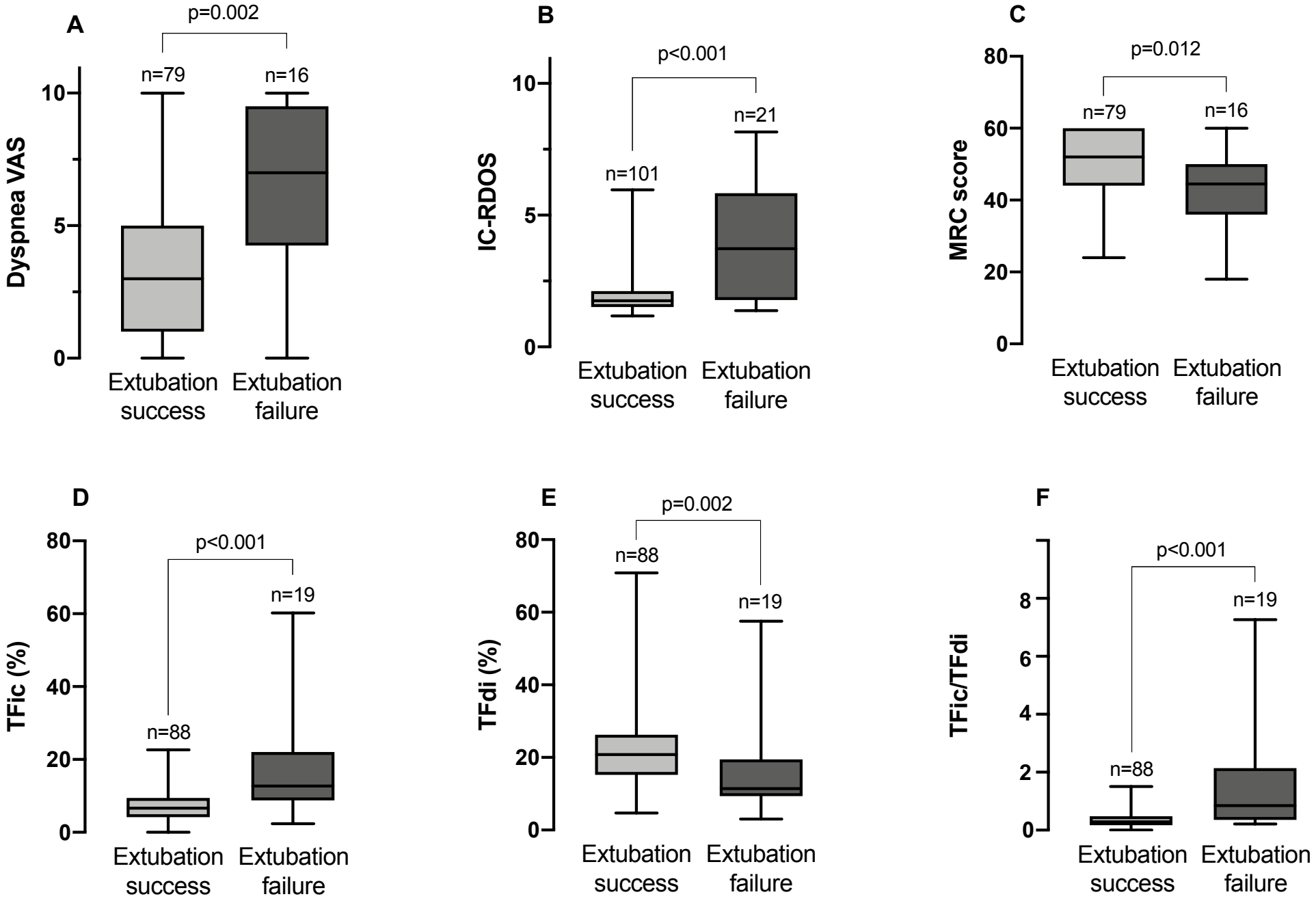
IC-RDOS: intensive care – respiratory distress observation scale; D-VAS: Dyspnea Visual Analogic Scale; MRC: medical research score; TFdi: diaphragm thickening fraction; TFic: parasternal intercostal thickening fraction; CI: Confidence interval.

Table ESM7. Cut-offs, area under the receiver operating characteristics curves (AUC-ROC), sensitivity, specificity, positive and negative likelihood ratios and positive and negative predictive values of Intensive Care – Respiratory distress observation scale (IC-RDOS), Medical Research Council (MRC) score and diaphragm thickening fraction (TFdi) over parasternal intercostal muscle thickening fraction (TFic) ratio to predict extubation failure (reintubation and rescue non-invasive ventilation).

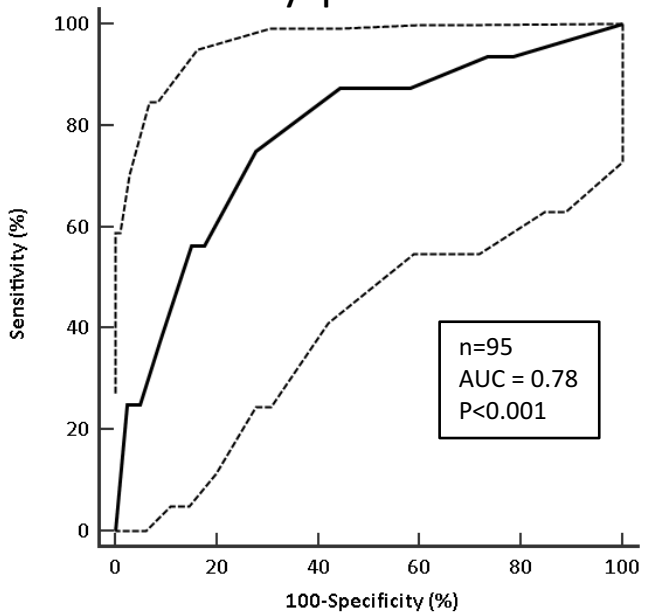
	Cut-offs	AUC-ROC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Likelihood ratios (95% CI)	
					Positive	Negative
Respiratory rate	>22	0.64 (0.55 to 0.73)	61 (39 to 80)	62 (51 to 72)	1.6 (1.1 to 2.4)	0.6 (0.4 to 1.1)
IC-RDOS	>3.3	0.78 (0.70 to 0.85)	61 (38 to 80)	83 (74 to 90)	3.5 (2.1 to 6.1)	0.5 (0.3 to 0.8)
Dyspnea-VAS	>4.0	0.75 (0.65 to 0.83)	72 (47 to 90)	73 (61 to 82)	2.7 (1.7 to 4.2)	0.4 (0.1 to 0.8)
MRC score	<50	0.66 (0.56 to 0.76)	72 (47 to 90)	56 (44 to 67)	1.6 (1.1 to 2.4)	0.5 (0.2 to 1.1)
TFic	>8.6	0.75 (0.65 to 0.83)	71 (48 to 89)	72 (61 to 81)	2.7 (1.7 to 4.0)	0.4 (0.2 to 0.8)
TFdi	<15.6	0.70 (0.61 to 0.79)	52 (30 to 74)	74 (63 to 83)	2.0 (1.2 to 3.4)	0.6 (0.4 to 1.0)
TFic/TFdi	>0.44	0.76 (0.66 to 0.83)	67 (43 to 85)	71 (60 to 80)	2.3 (1.4 to 3.5)	0.5 (0.3 to 0.9)

IC-RDOS: intensive care – respiratory distress observation scale; D-VAS: Dyspnea Visual Analogic Scale; MRC: medical research score; TFdi: diaphragm thickening fraction; TFic: parasternal intercostal thickening fraction; CI: Confidence interval.

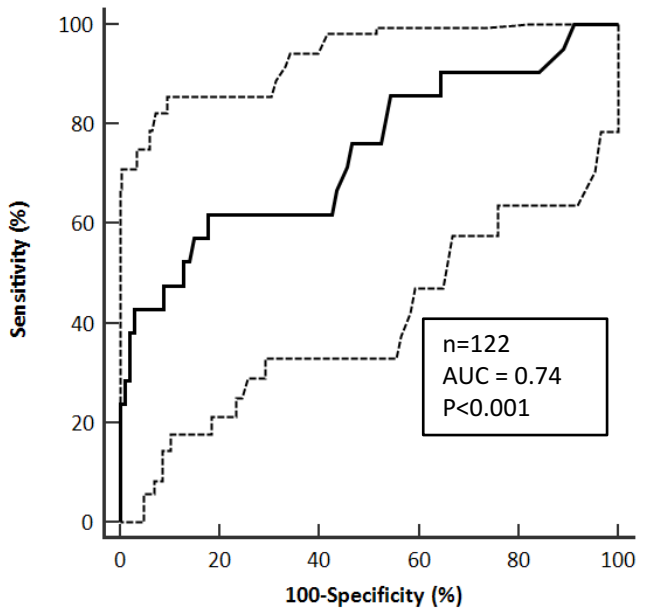

1100 intensive care unit admissions
between August 2016 and May 2018
850 patients
with invasive Mechanical Ventilation
380 patients with mechanical ventilation less than 48 hours
470 patients eligible for inclusion
348 patients not enrolled for the following reasons:
• Failure to the spontaneous breathing trial (n=129)
• Tracheostomy (n=27)
• Extubation without presence of investigator (self extubation, week end, night) (n=39)
• Do not reintubate orders (n=34)
• Death before weaning (n=105)
• Impossibility to perform respiratory muscles ultrasound (n=14)
122 patients analyzed
21
Extubation failure
101
Extubation success


A
p=0.002
n=79
n=16
Dyspnea VAS
10
5
0
Extubation success
Extubation failure
B
p<0.001
n=101
n=21
IC-RDOS
10
5
0
Extubation success
Extubation failure
C
p=0.012
n=79
n=16
MRC score
80
60
40
20
0
Extubation success
Extubation failure
D
p<0.001
n=88
n=19
TFic (%)
80
60
40
20
0
Extubation success
Extubation failure
E
p=0.002
n=88
n=19
TFdi (%)
80
60
40
20
0
Extubation success
Extubation failure
F
p<0.001
n=88
n=19
TFic/TFdi
8
6
4
2
0
Extubation success
Extubation failure

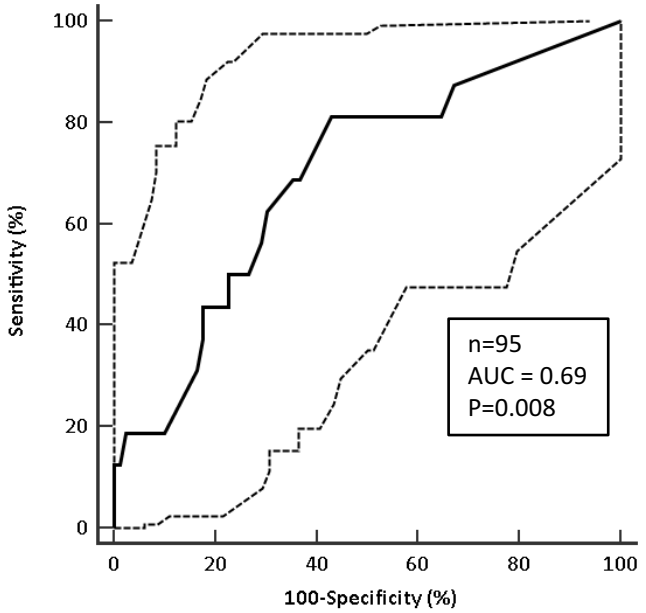
Dyspnea VAS



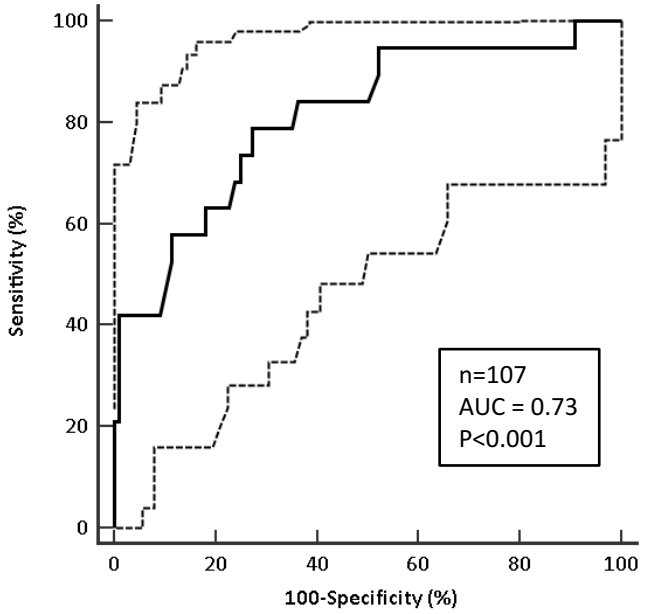
IC-RDOS



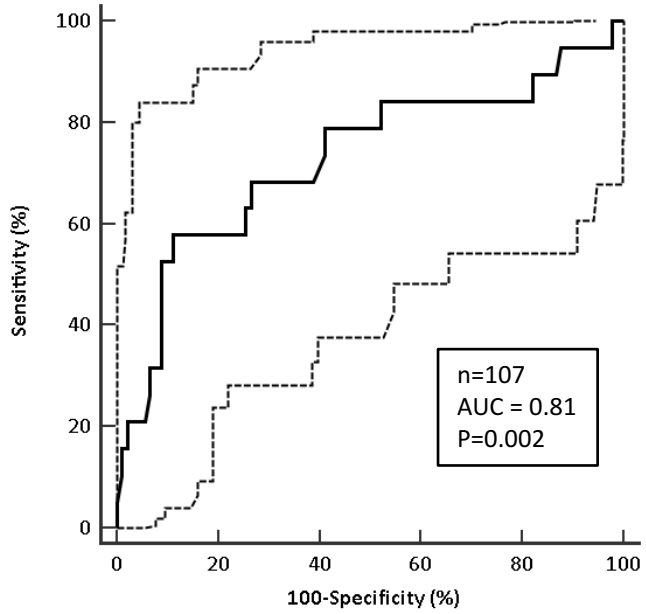
MRC score



TFdi



TFic



TFic/TFdi