Critical Care

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Integrated comprehensive assessment for predicting weaning success in difficult-to-wean critically ill patients: the WEAN-US study

Alberto Fogagnolo[1†], Martin Dres[2†], Francesco Murgolo[3], Salvatore Grasso[3], Bianca Brazzoli[4], Gianluca Pasa[4], Mohd Rashid Khan[5], Danila Azzolina[6], Valentina Alvisi[1], Gaetano Scaramuzzo[1,4], Carlo Alberto Volta[1,4] and Savino Spadaro[1,4*]

Abstract

Background Liberation from mechanical ventilation (MV) remains challenging, particularly in difficult-to-wean patients. Weaning failure (i.e. inability to wean or post-extubation failure) and spontaneous breathing trial (SBT) failure are often grouped together despite distinct underlying mechanisms. Moreover, most studies have focused on a single physiological predictor of weaning success, although ventilator liberation is a complex, multiorgan process. We hypothesized that a multimodal, ultrasound-based assessment performed during SBT in difficult-to-wean patients would improve prediction of weaning outcomes compared with individual physiological parameters.

Methods In this single-center prospective observational study, adult difficult-to-wean patients (≥ 48 h of mechanical ventilation and failure of the first separation attempt) underwent a standardized SBT. A comprehensive assessment of diaphragmatic function, lung aeration, cardiac function, and peripheral muscle strength was performed. In addition, dyspnea assessment and clinical variables were recorded before and at the end of the SBT. An integrated predictive model was developed using clinical selection and Least Absolute Shrinkage and Selection Operator (LASSO) regression, and it was compared with individual predictors. The primary outcome was to predict weaning failure (inability to wean or post-extubation failure). SBT failure was evaluated as a secondary outcome and defined as the inability to successfully complete the SBT due to clinical signs of intolerance.

Results Weaning failure occurred in 27% of patients. Compared with successfully weaned patients, those with weaning failure had lower diaphragmatic contractile reserve (maximal diaphragm thickening fraction), reduced handgrip strength, higher prevalence of ICU-acquired weakness, greater dyspnea after SBT, and more pronounced loss of lung aeration during SBT. Cardiac parameters, including higher ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e') and ejection fraction, were associated with SBT failure, whereas neuromuscular impairment was more strongly associated with post-extubation failure. An integrated model

†Alberto Fogagnolo and Martin Dres equally contributed as first authors.

*Correspondence:
Savino Spadaro
spdsvn@unife.it

Full list of author information is available at the end of the article

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demonstrated good predictive performance (AUROC 0.88; 95% CI 0.78–0.95), outperforming individual predictors in predicting weaning failure.

Conclusions In difficult-to-wean patients, SBT failure and weaning failure are driven by several interacting physiological mechanisms. A multimodal, ultrasound-based approach integrating cardiac, pulmonary, diaphragmatic, and neuromuscular domains improves prediction of weaning outcomes and may enable more individualized ventilator liberation strategies.

Trial registration This study was prospectively registered in clinicaltrial.gov (NCT05539599; First Posted 2022–09-14).

Keywords Respiration, Artificial, Ventilator weaning, Diaphragm, Ultrasonography, Intensive care unit-acquired weakness, Predictive value of tests

Introduction

Mechanical ventilation (MV) is a cornerstone therapy for patients with acute respiratory failure; however, liberation from MV remains among the most challenging aspects in critical care practice [1, 2]. Failed weaning is associated with prolonged ventilation, increased ICU length of stay, and higher mortality [3–6]. Traditional weaning strategies primarily based on respiratory physiology have limited accuracy in predicting successful separation from the ventilator [7, 8]. Consequently, there is growing interest in more comprehensive assessment strategies that integrate multiple physiological domains involved in the weaning process [9].

A major source of inconsistency in existing literature is the heterogeneous definition of weaning failure. Numerous studies combine spontaneous breathing trial (SBT) failure and post-extubation failure, [10, 11] despite their distinct mechanisms and clinical implications, whereas others analyze them separately [12, 13] SBT failure typically reflects impaired heart–lung interactions, insufficient respiratory muscle reserve, or unresolved lung disease [14–17] whereas post-extubation failure is more frequently associated with ineffective cough, impaired secretion clearance, upper airway compromise, or frailty [18–20]. Considering these outcomes interchangeably may obscure important physiological differences and lead to conflicting studies results.

These issues are particularly relevant in difficult-to-wean patients, a high-risk subgroup defined by at least one failed separation attempt [21]. These patients exhibit higher mortality, greater healthcare resource use, and show a wider range of interacting mechanisms underlying weaning failure. Therefore, improved characterization of the determinants of weaning failure in this population is warranted.

Bedside ultrasound has emerged as a valuable tool for assessing key physiological domains relevant to weaning, as it allows real-time assessment of diaphragmatic function and lung aeration [22–25]. The Lung Ultrasound Score (LUS) has shown predictive value for weaning success by capturing dynamic changes in aeration and identifying patients at risk of increased post-extubation load [22]. Cardiac ultrasound is likewise crucial during the weaning process, particularly for detecting weaning-induced pulmonary edema, a frequent and often underrecognized mechanism of weaning failure [10, 26, 27]. Peripheral muscle dysfunction further contributes to extubation failure by impairing cough strength and is closely linked to frailty, an established risk factor for difficult weaning [28].

Integrating respiratory muscle function, lung aeration, cardiac performance, and global muscular strength may yield a more comprehensive evaluation of extubation readiness than conventional parameters alone. This integrated approach could be particularly useful in difficult-to-wean patients and could help distinguish predictors of SBT failure from those of post-extubation failure.

We hypothesized that a comprehensive assessment performed during SBT could more accurately predict weaning outcomes in patients with a prior failed separation attempt.

The aim of this study was to determine whether in difficult to wean patients an integrated, multidimensional model incorporating cardiac, pulmonary, and muscular variables provides greater predictive accuracy for both SBT and weaning failure compared with individual physiological parameters.

Methods

Study design and setting

This prospective, single-center, observational study was conducted in the intensive care unit (ICU) of Saint Anna Hospital (Ferrara, Italy), between October 2022 and March 2024. The study was approved by the local ethics committee (approval number 547/2022/Oss/AOUFe date 21/9/2022), and informed consent was obtained from all patients or their legal surrogates. This study was prospectively registered in clinicaltrials.gov (NCT05539599; First Posted 2022–09-14).

Patient population

Patients were eligible for inclusion if they were aged 18 years or older, classified as difficult to wean, and deemed ready for a new attempt to extubate after SBT.

According to the WIND definition [21], patients were considered difficult to wean if they had received mechanical ventilation for at least 48 h and had experienced at least one prior failed separation attempt. The exclusion criteria were as follows: (a) age < 18 years; (b) pregnancy; (c) presence of thoracostomy, pneumothorax, pneumomediastinum; (d) presence of tracheostomy; (e) presence of flail chest or rib fractures; (f) use of muscle-paralyzing agents in continuous infusion within 48 h before the study (g) pre-existing neuromuscular diseases and (h) known diaphragmatic paralysis.

Readiness for SBT was determined according to standard ICU protocols, including adequate oxygenation (arterial oxygen partial pressure to inspiratory oxygen fraction (PaO2/FiO2) ≥ 150 mmHg, with positive end-expiratory pressure (PEEP) < 8 cmH2O, stable cardiovascular status (i.e., heart rate < 120 beats/min; systolic blood pressure, 90–160 mmHg; and no or minimal vasopressor use, i.e., dopamine or dobutamine < 5 μg/kg/min or noradrenaline < 0.05 μg/kg/min), Richmond Agitation and Sedation Scale (RASS) score ranging between −1 and + 1 and clinical improvement of the underlying acute cause of respiratory failure.

Study outcomes

The primary outcome was to assess the ability of an integrated, multidimensional ultrasound-based patient evaluation to predict weaning failure.

According to the WIND study, weaning success was defined if the patient remains free from invasive mechanical ventilation for at least 7 days after extubation. Weaning failure was defined as inability to wean (i.e. patients discharged with assisted ventilation) or as the need for reintubation within 7 days after extubation [21].

As a secondary outcome, we evaluate the impact of mechanical ventilation duration on all measured parameters in patients who did or did not experience weaning failure.

SBT failure was assessed as an additional outcome and defined as the inability to successfully complete the SBT due to clinical signs of intolerance.

Spontaneous breathing trial and comprehensive assessment during SBT

Following the first unsuccessful separation attempt, a spontaneous breathing trial (SBT) was determined by the physician in charge who had no role in the study. All patients were managed according to a standardized weaning and sedation protocol. Sedation was achieved using short-acting agents, targeting light sedation (RASS – 1 to 1) to ensure the patient remained calm and alert.

During the SBT, patients were ventilated in pressure-support ventilation (PSV) mode, with pressure support set at 4 cm H_2O and PEEP at 4 cm H_2O [29–31]. SBTs were conducted on the ventilator using minimal support to compensate for tube-related resistance, limit derecruitment, and provide a standardized and physiologically representative assessment of weaning readiness. After reaching a steady state, the first assessment (T1) was performed (Fig. 1).

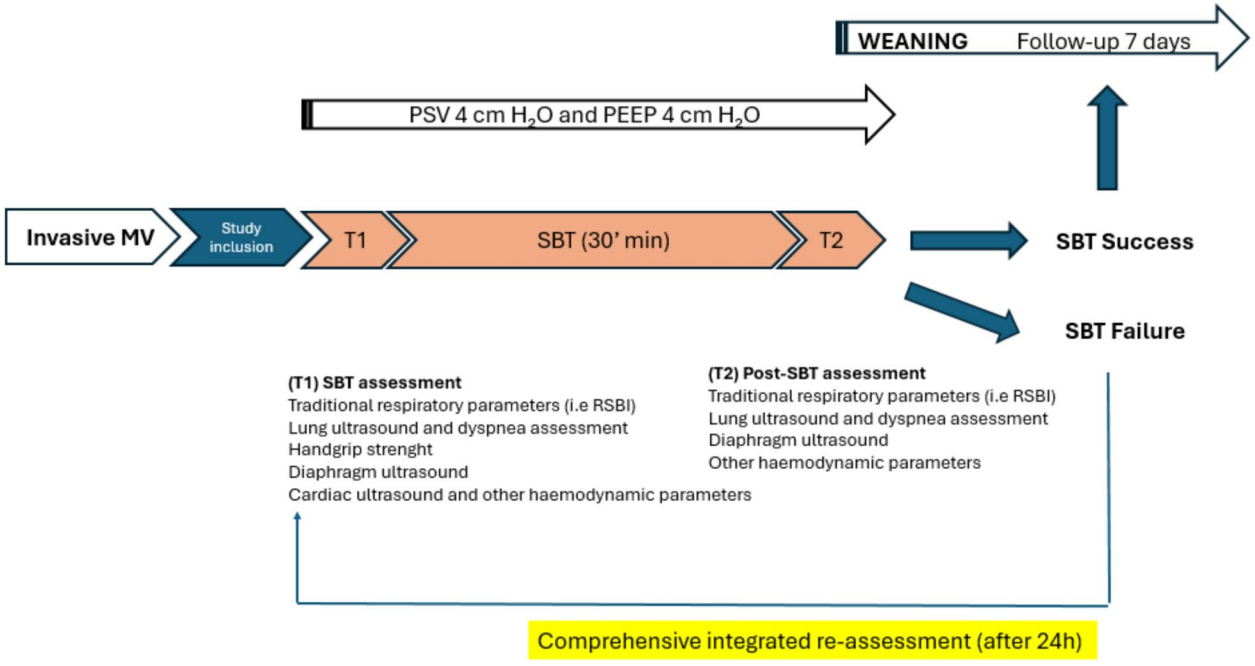


Fig. 1 Integrated Weaning Assessment Protocol

Physiological respiratory parameters, including tidal volume (VT), respiratory rate (RR), rapid shallow breathing index (RSBI calculated as RR/VT) and oxygenation were recorded. A comprehensive multimodal ultrasound assessment was then performed, integrating respiratory muscle, lung, and cardiac evaluations. Maximal inspiratory pressure (MIP) was measured as previously described [32] using a 25–30-s inspiratory occlusion; the highest pressure sustained for ≥ 1 s was retained. Dyspnoea self-evaluation was performed by means of the -visual analogue scale (VAS) which consisted of a 10-cm scale ranging from "no respiratory discomfort" to "intolerable respiratory discomfort".

After the first evaluation, a 30-min SBT was performed with unchanged ventilator parameters (setting pressure support level 4 cmH_2O and PEEP 4 cmH_2O) [29–31].

At the end of the SBT (T2), the same lung and diaphragmatic ultrasound evaluation, dyspnea assessment and respiratory parameters were reassessed. To capture dynamic physiological responses during the SBT trial, the following variables were reassessed at the end of the 30-min SBT: systolic and diastolic arterial pressure, heart rate, respiratory rate, tidal volume, end-tidal carbon dioxide ($ETCO_2$), lung ultrasound (LUS) score, central venous pressure (CVP), and central venous oxygen saturation ($ScvO_2$) (Fig. 1).

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. In case of SBT failure, readiness for a further separation attempt was assessed after every 24 h.

Measurements

Respiratory muscle assessment

All measurements were performed using a single ultrasound machine (Sonosite Edge II, Fujifilm, Bothell, United States). Diaphragmatic displacement (DD) and thickening fraction (TF%) were assessed according to previously published studies [25, 33].

TF was measured during both quiet breathing and deep breathing. For quiet breathing measurement, the mean value of three consecutive breaths was considered. Then, we recorded TF during deep breathing twice; the maximal value registered was used for the analysis.

$$\mathrm{TF}_{\mathrm{MAX\%}} \text{ was calculated as } \frac{\text{TF during deep breathing}}{\mathrm{TF}} * 100$$

In cooperative patients, handgrip strength was evaluated with a handheld dynamometer (Jamar®, Fred Sammons, Bolingbrook, Illinois) before SBT trial. The dominant hand of each subject was tested. With the shoulders in neutral rotation and elbow flexion of 90, subjects were asked to hold the dynamometer at their maximum strength for 2–3 s [34]. The handgrip value is expressed as an absolute value in Kilograms and as a relative value as a percentage [35]. Muscle weakness was diagnosed on the basis of the previously published handgrip strength-derived definition of ICU-acquired weakness (< 11 kg for men and < 7 kg for women) [36]

Lung ultrasound assessment

The ultrasound examination was conducted over six regions of each lung, specifically the superior and inferior segments of the anterior, lateral, and posterior zones, using the anterior and posterior axillary lines as anatomical landmarks. As clinical practice, linear probe was used for anterior zones whereas curve probe was used in posterior ones. In each region, lung aeration was classified into one of four patterns. In each region, lung aeration was classified into one of four patterns: (1) normal aeration (N, score 0), characterized by lung sliding with A-lines or fewer than two isolated B-line; (2) moderate loss of aeration: multiple, well-defined B1 lines (score 1); (3) severe loss of aeration: coalescent B2 lines (score 3); and (4) lung consolidation (C score 3), showing a tissue-like pattern. Points were assigned based on the most severe pattern observed in each region. The global LUS score was then calculated, ranging from 0 to 36.

Cardiac ultrasound assessment

At the beginning of the SBT, transthoracic echocardiography was performed using a Sonosite Edge II system (Fujifilm) by a single trained operator (FA) to ensure measurement consistency. Examinations were conducted according to current guideline recommendations [37], including acquisition of standard parasternal and apical views. Standard views were acquired, and cardiac function was assessed using conventional parameters, including left ventricular systolic and diastolic indices.

Cardiac assessments were performed using the apical four-chamber view [38]. Left ventricular (LV) systolic function was evaluated by estimating the ejection fraction. Diastolic function was assessed through transmitral flow analysis using pulsed Doppler, with the sample volume positioned at the tips of the mitral valve leaflets. Peak velocities during early (E) and late (A) diastolic filling were recorded. Additionally, tissue Doppler imaging (TDI) was used to measure mitral annular motion, with a 5-mm sample volume placed at the lateral mitral annulus. The early diastolic velocity (Ea) was obtained from the TDI recordings to assist in evaluating LV relaxation [38].

Tricuspid Annular Plane Systolic Excursion (TAPSE) as a measure of right ventricular (RV) base-to-apex shortening during systole was recorded on M-mode using the four-chamber view. The cursor was placed at the junction of tricuspid valve plan with the free wall of the RV,

whereas data were averaged over three beats. The echocardiographic assessment was revised within the same time frame (24 h) with another formal assessment by a blinded cardiologist to minimize bias.

Post-extubation care

After extubation, oxygen therapy was administered via high-flow nasal cannula (Airvo 2®, Fisher & Paykel, New Zealand). Flow was initiated at 60 L/min and decreased in case of patient intolerance. The humidifier was set in invasive mode (37 °C) but was switched to noninvasive mode (34 °C) if the patient felt excessive warmth.

Statistical analysis

The characteristics and outcomes of patients who weaned successfully (extubated and free from MV for at least 7 days) and those who failed were described using absolute frequencies and percentages. At the same time, continuous variables were summarized using the median and interquartile range (IQR). The Wilcoxon test has been considered for comparing the continuous variables, and the Chi-square test or Fisher's exact test was used whenever appropriate for the categorical variables. The patient assessment findings are also reported and described for patients who experienced success and failure during weaning. The univariable logistic regression Odds Ratio, along with its 95% Confidence Interval (CI) and p-value, has also been reported. Paired Effects for repeated measurements (SBT attempts) have been estimated via GLMM (Generalized Linear Mixed Model).

Integrated predictive assessment. A predictive model was developed to identify determinants of weaning success through a three-step process: 1) selection of relevant clinical and physiological variables, 2) evaluation of their individual predictive performance, and 3) construction of an integrated model whose accuracy was compared with that of single predictors.

The variable selection process begins with the clinical selection of baseline patient data, diaphragm assessment, respiratory muscle assessment, lung ultrasound, and other hemodynamic variables. This baseline variable set has been selected according to clinical judgment. A further model-based selection was performed on the defined variable set using LASSO penalization.

The analytical approach for evaluating the individual performance of the selected variables included a descriptive Receiver Operating Characteristic (ROC) curve analysis. This method allowed for the evaluation of each predictor's ability to discriminate between successful and unsuccessful weaning outcomes. For each predictor, the Area Under the Curve (AUC), along with sensitivity and specificity measures, and accuracy, were calculated to determine the optimal cut-off points that optimize the Youden index.

The final regularized model predicts weaning success in critically ill patients. The model was calibrated using a fivefold cross-validation technique to determine the best regularization parameter, optimizing the binomial deviance measure, balancing the trade-off between bias and variance. After selecting the best-fit model, selective inference techniques were applied to lasso coefficients to estimate confidence intervals and p-values.

The robustness and predictive performance of the final model were thoroughly evaluated using internal validation techniques. Bootstrap methods were utilized to estimate the stability and reliability of the model's predictions by reporting the AUC, the Sensitivity, Specificity, and Accuracy with 95% bootstrap CI within 1000 resamples. Additionally, the importance of each variable in the model was assessed and computed as the average change in log loss performance after randomly permuting each feature. The analyses were conducted by R 3.5.2.

Sample size

The sample size was determined using a precision-based approach to estimate the Area Under the Curve (AUC) with an acceptable level of confidence. Based on published evidence, multimodal ultrasound-based models for predicting weaning success typically report AUC values around 0.87 [30]. Assuming a true AUC of 0.87 and an expected weaning failure prevalence of 40%, a total sample size of approximately 89 patients was deemed sufficient to estimate the AUC with 95% precision (half-width) of ± 0.042. This level of precision aligns with recommended standards for the development and internal validation of prognostic models using ROC analysis.

Results

One hundred and forty patients undergoing mechanical ventilation (MV) for ≥ 48 h were screened (Fig. 2). A total of 89 patients failed the first SBT met the inclusion criteria. The main reasons for the failure of the first separation attempts were respiratory: inadequate ventilatory pattern, observed in 42 of 89 patients (47%), followed by impaired gas exchange in 20 patients (22%). Hemodynamic instability accounted for 13 cases (15%), while subjective clinical signs were reported in 12 cases (13%). The cause of failure was not documented in 2 patients (2%).

The overall occurrence of weaning failure was 27% (24/89), including 22 cases of post-extubation failure and 2 patients who had not been weaned by day 30 from study inclusion (Table 1, Fig. 2).

The groups (weaning success vs weaning failure) did not differ significantly in terms of age, comorbidities, ICU admission diagnosis, or baseline severity scores (SAPS II and SOFA), ventilator settings, blood gas parameters, and core physiological variables at study entry (Table 1).

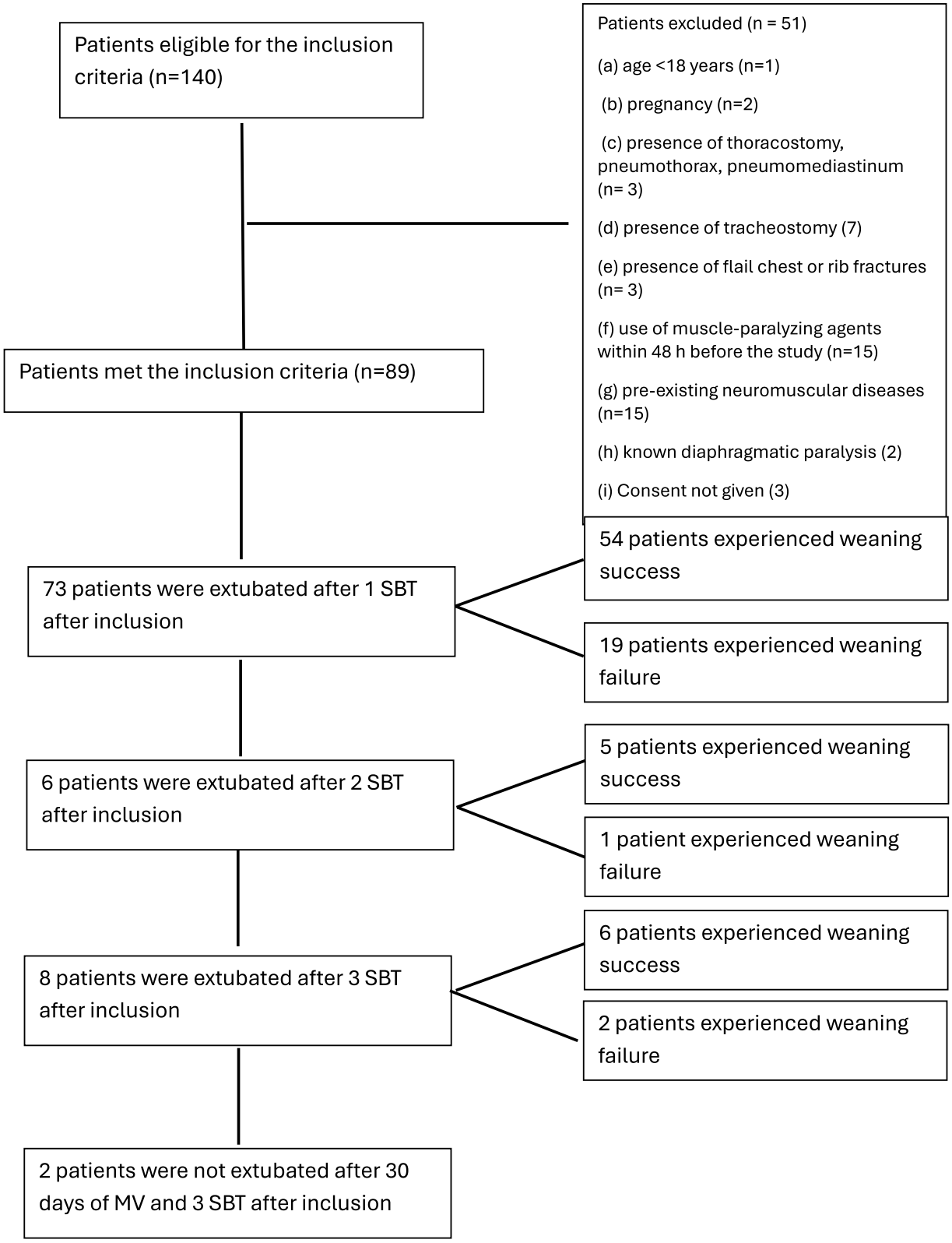


Fig. 2 Study flowchart

Table 1 Patients' characteristics and outcomes of weaning success and failure

	All Patients (n = 89)	Weaning success (n = 65)	Weaning failure (n = 24)	P-value
Sex, Female n (%)	52 (58.4%)	29 (44.6%)	17 (71%)	
Age (yrs)	71.0 [61.0;76.0]	71.0 [62.0;77.0]	68.5 [59.0;73.2]	0.224
Smokers, n (%)	14 (15.7%)	8 (12.3%)	6 (25.0%)	0.190
BMI (kg/m^2)	26.2 [23.7;30.1]	26.3 [23.7;30.1]	26.0 [24.7;30.1]	0.592
Use of corticosteroids n (%)	5 (5.62%)	5 (7.69%)	0 (0.00%)	0.318
Type of ICU admission n %				
Medical	29 (33.7%)	22 (35.5%)	7 (29.2%)	
Emergency surgery	42 (48.8%)	28 (45.2%)	14 (58.3%)	
Scheduled surgery	15 (17.4%)	12 (19.4%)	3 (12.5%)	
Reasons for ICU admission n (%)				
Sepsis/septic shock	40 (45)	31 (48)	9 (37)	
Acute Respiratory Failure	37 (42)	28 (43)	9 (37)	
Trauma	5 (6)	3 (5)	2 (8)	
Cardiogenic shock	7 (8)	3 (5)	4 (16)	
Clinical Variables				
Length of MV at inclusion	6.00 [3.00;10.0]	5.00 [3.00;10.0]	7 [4;11]	0.146
SAPS II score	41.0 [34.0;47.2]	41.0 [33.8;48.2]	39.5 [35.0;42.5]	0.473
SOFA score	5.00 [4.00;7.00]	5.00 [4.00;7.00]	5.00 [3.00;8.00]	0.611
Comorbidities n (%)				
Hypertension	45 (50.6%)	32 (49.2%)	13 (54.2%)	0.862
Diabetes	17 (19.1%)	11 (16.9%)	6 (25.0%)	0.381
COPD	8 (8.99%)	5 (7.69%)	3 (12.5%)	0.677
Ischemic cardiomyopathy	10 (11.2%)	8 (12.3%)	2 (8.33%	0.723
Chronic renal failure	9 (10.1%)	6 (9.23%)	3 (12.5%)	0.698
Ventilator settings at inclusion				
PSV level, cmH_2O	6.00 [5.00;8.00]	6.00 [5.00;8.00]	7.00 [5.00;8.00]	0.185
PEEP, cmH_2O	6.00 [5.00;7.00]	6.00 [5.00;7.00]	6.00 [5.00;8.00]	0.336
Tidal volume, mL	496 [410;600]	488 [416;615]	500 [400;565]	0.611
Respiratory rate, min-1	17.0 [14.0;20.0]	16.5 [14.0;20.0]	17.0 [14.0;19.5]	0.873
Blood gas analysis variables at inclusion				
PaO_2/F_iO_2 ratio	236 [179;285]	236 [190;276]	228 [160;294]	0.379
$PaCO_2$ mmHg	44.0 [40.7;50.2]	44.0 [40.0;48.0]	44.0 [41.0;51.1]	0.917
Bicarbonates, mmol/L	29.4 [27.0;32.6]	28.5 [26.5;32.1]	30.3 [27.2;36.9]	0.128
Hb, g/dL	9.80 [9.00;11.2]	9.65 [9.00;11.2]	10.0 [9.05;11.2]	0.887
Lactate, mmol	0.95 [0.80;1.30]	0.90 [0.80;1.20]	1.10 [0.80;1.30]	0.340
BE,mEq/L	5.80 [3.24;9.40]	5.50 [3.00;9.40]	6.20 [3.28;10.6]	0.486
Physiological variables at inclusion				
Heart rate, bpm	86.5 [77.0;95.8]	86.0 [77.0;95.0]	88.0 [78.0;96.0]	0.616
Cumulative fluid balance during the previous 24 h (ml)	1000 [180;2030]	1050 [200;2000]	840 [-190;2170]	0.554
Mean arterial pressure, mmHg	90.7 [78.7;100]	90.0 [79.7;100]	93.3 [76.7;100]	0.878
Respiratory rate, min^{-1}	17.0 [14.0;20.0]	16.5 [14.0;20.0]	17.0 [14.0;19.5]	0.873
SpO2, %	99.0 [97.0;100]	99.0 [97.0;100]	98.0 [97.0;99.0]	0.211
Outcomes				
Length of MV, days	6 [3;10]	5.50 [3;10]	7 [4;11]	0.006
180-days mortality, n (%)	20 (22)	11 (17)	10 (42)	0.015

Categorical variables were described using absolute frequencies (n) and percentages (%), while continuous variables were summarized using the median and interquartile range (IQR)

Table 2 First assessement of patients' variables in weaning success and failure patients

	Overall sample (n = 89)	Weaning success (n = 65)	Weaning failure (n = 24)	Odds ratio	P value (OR)	P value (Overall)
Diaphragm assessment						
Thickening fraction (%)	0.29 [0.15;0.45]	0.29 [0.15;0.41]	0.26 [0.15;0.49]	3.11 [0.50;19.5]	0.226	0.821
Thickening fraction $_{MAX\%}$	370 [242;513]	393 [278;519]	282 [200;383]	1.00 [0.99;1.00]	0.077	0.035
Diaphragmatic dysplacement, mm	1.40 [1.10;1.90]	1.40 [1.10;1.80]	1.40 [1.17;1.65]	1.01 [0.56;1.84]	0.97	0.678
Respiratory muscle assessment						
Maximum inspiratory pressure (cmH_2O)	28.0 [22.0;37.0]	30.0 [22.0;36.5]	26.0 [23.5;38.0]	1.01 [0.96;1.06]	0.697	0.913
Hand grip strength (Kg)	12.0 [8.00;18.0]	12.0 [9.00;18.0]	10.0 [5.2;16.2]	0.92 [0.86;1.00]	0.07	0.005
Hand grip strength (%)	69 [46 – 92]	74 [52 – 95]	48 [27 – 79]	0.98 [0.96;0.99]	0.007	0.003
ICUAW (n, %)						0.002
Yes	31 (34.8%)	16 (24.6%)	15 (62.5%)	5.80 [2.13;15.8]	< 0.001	
No	58 (65.2%)	49 (75.4%)	9 (37.5%)	Ref	Ref	
Dyspnea self-reported score	2.00 [1.00;3.00]	1.00 [1.00;2.00]	2.00 [1.00;2.00]	1.13 [0.79;1.16]	0.496	0.254
Rapid shallow breathing index	35.7 [22.6;44.9]	31.2 [21.7;44.3]	39.0 [26.0,45.0]	1.01 [0.98;1.04]	0.2	0.291
Echocardiography						
E/e' lateral (cm/sec)	7.00 [5.40;10.8]	6.20 [5.28;9.20]	7.50 [6.00;13.3]	1.13 [0.99;1.29]	0.062	0.110
TAPSE (mm)	20.0 [17.0;23.0]	20.0 [17.0;23.0]	21.0 [18.0;23.2]	0.99 [0.89;1.11]	0.876	0.889
Ejection fraction (%)	0.55 [0.50;0.60]	0.53 [0.50;0.60]	0.60 [0.53;0.60]	1.06 [0.99; 1.13]	0.063	0.040

Categorical variables were described using absolute frequencies (n) and percentages (%), while continuous variables were summarized using the median and interquartile range (IQR). The Univariable Odds Ratio with 95% Confidence Interval has also been reported

Table 3 Patients' assessment variables of weaning success and failure patients.

Variables	Overall sample	Weaning success (n = 65)				Weaning failure (n = 24)				P value For interaction
	n = 89	(n = 65)				(n = 24)				
		T1	*T2*	*T2-T1*	*P-value*	*T1*	*T2*	*T2-T1*	*P-value*	
Diaphragm displacement (mm)	1.40 [1.10;1.90]	1.40 [1.10;1.80]	1.45 [1.10;1.90]	0.0 [0.0;0.5]	0.068	1.40 [1.17;1.65]	1.50 [1.20;2.38]	0.0 [0.0;0.07]	0.058	0.502
Lung ultrasound Score	10.0 [6.00;13.0]	8.00 [6.00;12.0]	9.50 [6.00;14.0]	0.0 [0.0 – 1.0]	0.000	10.0 [8.0;13.0]	12.0 [9.75;13.8]	1.0 [0.0; 2.0]	0.001	0.006
ScvO2 (mmHg)	71.0 [66.7;75.0]	71.2 [67.0;74.8]	71.8 [67.3;75.0]	1.0 [2.0; 1.0]	0.090	69.6 [67.3;74.5]	69.1 [65.2;74.4]	1.5 [2.7; 1.0]	0.203	0.172
CVP (%)	8.0 [6.0;10.0]	9.0 [6.75;11.0]	9.00 [6.00;11.0]	0.0 [0.0 – 0.7]	0.827	8.0 [6.0;9.0]	7.5 [6.0;9.0]	0.0 [1.0; 0.7]	0.724	0.081
Dyspnea self-reported score	2.0 [1.0;3.0]	1.0 [1.00;2.00]	2.00 [1.0;3.0]	0.0 [0.0; 1.0]	0.002	2.00 [1.00;2.00]	4.0 [2.75;4.0]	2.0 [0.0;3.0]	0.000	0.002

Categorical variables are presented as number (n) and percentage (%). Continuous variables are reported as median [IQR]. P-values refer to within-group comparisons (pre- vs post-SBT). Interaction p-values refer to group × time effects derived from mixed-effects models

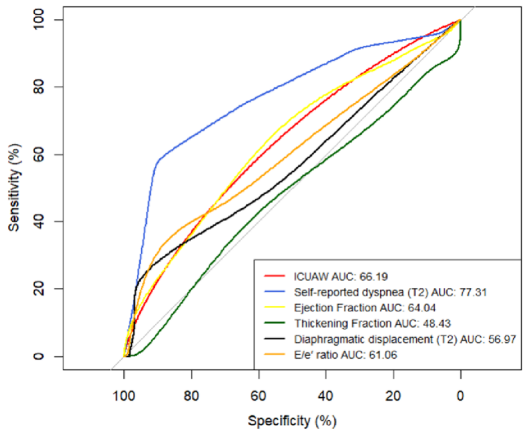
In contrast, clinical outcomes varied significantly between the groups. Patients who experienced weaning failure required a longer duration of mechanical ventilation than those with successful weaning (7 [4–11] vs 5.5 [3–10] days, p = 0.006). Additionally, 180-day mortality was significantly higher in the weaning failure group (42% vs 17%, p = 0.015).

Clinical predictors of weaning failure

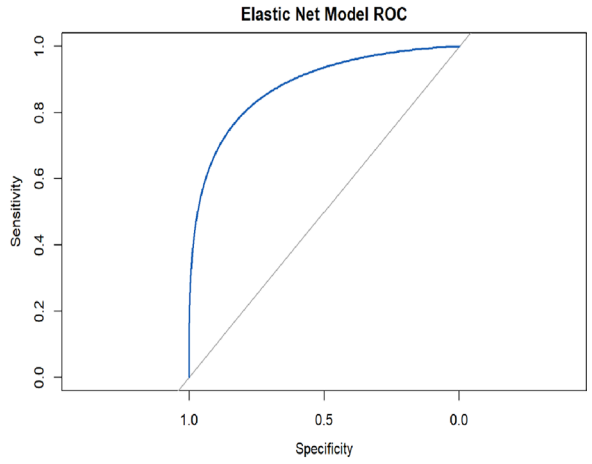
The weaning success group showed significantly higher TFmax% values compared with the failure group (393 [278–519] vs 282 [200–383] %, p = 0.035). Similarly, handgrip strength was greater among successfully weaned patients (12.0 [9.00;18.0] vs 10.0 [5.2;16.2], p = 0.005); accordingly, ICU-acquired weakness was more prevalent among patients with weaning failure (74% vs 48%, p = 0.003). Among the measures of cardiac function, ejection fraction (EF) differed significantly between the groups. In particular, weaning failure was associated with a slight increase in EF (Table 2). Diaphragmatic displacement, MIP, and TF during tidal breathing did not differ significantly between groups (Table 2).

Table 3 shows relevant cardiorespiratory parameters recorded at the beginning and the end of the study SBT (T1 and T2). Self-reported dyspnea did not differ between groups before SBT (T1) but was significantly higher after SBT (T2) among patients with weaning failure (2.00 [1.00–3.00] vs 4.00 [2.75–4.00], p < 0.001).

Panel A: Single predictors included in the model ROC



Panel B Integrated model ROC
AUROC = 0.88 (95% CI: 0.78–0.95)



Panel C Integrated model OR

Variable	Odds Ratio (OR)	95% CI	p-value
ICU-acquired weakness (ICUAW)	0.22	0.02 – 0.68	0.019
Self-reported dyspnea after SBT	2.67	1.52 – 3.86	0.005
Ejection Fraction (%)	1.88	0.58 – 3.73	0.183
Diaphragm Thickening Fraction (TF, %)	4.68	0.00 – 12.78	0.720
Diaphragmatic displacement after SBT	1.62	0.12 – 2.51	0.481
E/e′ ratio	1.08	0.56 – 1.24	0.606

Fig. 3 Receiver operating characteristic (ROC) analysis of individual predictors and the integrated model, together with multivariable model estimates. **Panel A.** ROC curves for each individual predictor included in the model: ICU-acquired weakness (ICUAW), self-reported dyspnea after spontaneous breathing trial (SBT), ejection fraction, diaphragm thickening fraction, diaphragmatic displacement after SBT, and E/e′ ratio. **Panel B.** ROC curve of the integrated elastic net model. The diagonal line represents the line of no discrimination. **Panel C.** Multivariable model results presented as odds ratios (OR) with corresponding 95% confidence intervals (CI) and p-values for all variables included in the integrated model

The global Lung Ultrasound Score (LUS) before SBT (T1) was comparable between groups (8.00 [6.00–12.0] vs 10.0 [8.00–13.0], p = 0.09). LUS values increased during SBT in both groups (Table 3). Notably, LUS scores were more pronounced in weaning failure group during SBT (Table 3). Violin-plot comparing weaning success and failure for every single variable pre (T1) and post (T2) SBT are shown in Figure S1.

Single Predictors and Integrated predictive model. A predictive model was developed to identify determinants of weaning success. The variable-selection process is summarized in Figure S2, which depicts a two-step approach that combines clinical expertise with statistical regularization to build an interpretable model. Of a set of 18 predictors, it has been considered to train the weaning failure model. The LASSO algorithm selected 6 predictors. The final integrated model included ICUAW, self-reported dyspnea after SBT, EF%, TF, diaphragmatic displacement after SBT, and E/e'.

Most ultrasound, respiratory, hemodynamic, cardiac, and neuromuscular predictors showed limited to moderate ability to discriminate weaning success, with the post-intervention dyspnea score performing best overall. (see Supplementary Table S1 for details).

The final integrated included ICUAW, self-reported dyspnea after SBT, EF%, TF, diaphragmatic displacement after SBT, and E/e'. The integrated model achieved an AUROC of 0.88 (95% CI: 0.78–0.95), outperforming individual predictors (Fig. 3). ICU-acquired weakness (ICUAW) and higher self-reported dyspnea after the spontaneous breathing trial (SBT) were both associated with a lower likelihood of weaning success. Comparative ROC curves for the integrated model and individual variables are shown in Fig. 3.

Clinical predictors of SBT failure

Among the patients included, 16 experienced at least one failed separation attempts after study inclusion, resulting in a total of 115 SBTs for analysis (87 successful and 28 failed). Among individual predictors, E/e′ showed the best discriminative performance (Table S2).

Clinical variables associated with failure of SBT failure included determinants of cardiac function (TAPSE, E/e'), respiratory muscle reserve (TFmax%, MIP%), and self-reported dyspnea before SBT. Univariate and multivariate relationship between clinical variables and SBT failure are reported in Table S2. The integrated model

yielded an AUROC of 0.86 (0.78–0.93), with a specificity of 74% and a sensitivity of 72%.

Discussion

This prospective study demonstrates that a multimodal ultrasound-based assessment improves prediction of weaning outcomes compared with individual physiological parameters, reinforcing the concept that ventilator liberation is a multiorgan challenge. As hypothesized, the integrated predictive model showed substantially better discriminative performance than any single clinical variable. Integrating diaphragmatic performance, lung aeration, cardiac function, and peripheral muscle strength aligns with emerging paradigms in critical care that emphasize the interplay between organ systems [9, 26, 39]. Consistent with this, traditional single predictors such as the RSBI showed limited discriminative ability in our cohort, whereas the integrated model provided superior performance by capturing the multifactorial nature of weaning failure. While the model's complexity may limit immediate bedside use, it was developed in a high-risk population where comprehensive assessment is justified, appears feasible within routine SBT in experienced settings, and can be simplified to a small set of key variables with preserved predictive performance.

When comparing weaning failure with SBT failure, we found that self-reported dyspnea, reduced diaphragmatic reserve ($TF_{max\%}$), and ICU-acquired weakness (ICUAW) were more prominent in predicting post-extubation failure, whereas markers of heart–lung interactions specifically E/e′ and TAPSE, were more predictive of SBT failure.

Cardiac function emerged as a key determinant of both SBT and post-extubation, albeit with different phenotypic expressions. During SBT, indices of fluid intolerance, particularly elevated E/e′ and reduced TAPSE, were the main cardiac predictors of failure. These findings support the established role of altered filling pressures and right ventricular dysfunction in the pathophysiology of weaning-induced pulmonary edema (WIPO) [10, 40], which may account for nearly one third of weaning failures [10]. In contrast, post-extubation failure was linked to elevated E/e′ alongside a hyperdynamic ejection fraction, highlighting the role of altered loading conditions and increased sympathetic activation rather than primary systolic dysfunction.

After extubation, cardiac factors remain relevant but are increasingly context dependent and should be interpreted in relation to diaphragmatic and systemic reserve. Consequently, determinants of failure appear to shift from mechanisms related to acute cardiopulmonary tolerance to those reflecting sustained respiratory and systemic endurance. This may explain the closer association of TFmax%, handgrip strength, and ICU-acquired weakness with post-extubation failure. Notably, markers of endurance, such as ICU-acquired weakness and post-SBT dyspnoea, were the variables most strongly associated with weaning failure.

Our findings indicate that maximal thickening fraction (TFmax %), rather than tidal TF, differentiates outcomes, underscoring the relevance of diaphragmatic contractile reserve assessment under stress. Diaphragmatic function has been widely studied in tidal breathing [41], whereas less evidence exists on the thickening fraction during maximal breathing ($TF_{MAX\%}$) [42]. In our patient's population, the differences between $TF_{MAX\%}$ and TF were remarkable, suggesting that mechanical ventilation-induced impairment of diaphragm contraction could be overestimated when considering only tidal TF. TFmax% may provide a more accurate measure of force generation under stress, which is critical for maintaining spontaneous breathing after extubation and its stronger association with post-extubation failure supports its link to diaphragmatic endurance [43, 44].

Notably, LUS score assessed before SBT did not differ significantly between SBT failure and success, but LUS score after SBT was higher in patients who failed, consistent with dynamic derecruitment [45] or evolving pulmonary edema under spontaneous breathing. These results confirmed previous results reported in literature, particularly in patients with limited cardiac reserve or elevated filling pressures [22, 39].

Furthermore, handgrip strength and ICU-acquired weakness strongly predicted weaning failure, supporting evidence that global muscle function, rather than respiratory strength alone, influences extubation success [34]. Patients with systemic weakness may lack the endurance required to tolerate increased respiratory load, airway clearance, and post-extubation mobilization [19].

Consistently, we observed an inverse relationship between duration of mechanical ventilation and TFmax%, MIP, handgrip strength in the weaning-failure group, but not in successfully weaned patients. This suggests that ventilator-induced deconditioning disproportionately affects patients with limited baseline reserve, and that repeated or stress-based physiological assessments may help identify patients at risk for delayed or failed liberation.

Taken together, our findings support a shift from single-parameter weaning predictors toward physiology-driven, multimodal assessment strategies that better reflect the complex and dynamic nature of ventilator liberation.

Strengths and limitations

The key strengths of our study include a prospective design with standardized ultrasound and weaning protocols. We performed a multimodal assessment, capturing

cardiac, pulmonary, diaphragmatic, and peripheral muscular domains. Clinically, distinguishing predictors of SBT failure from predictors of post-extubation failure may enable more personalized weaning strategies, such as preload optimization or diastolic unloading before SBT, versus inspiratory muscle training, early mobilization, or delayed extubation in patients with limited diaphragmatic or systemic reserve. A robust predictive model (AUROC 0.88) showing clear incremental value over single markers.

Although the integrated model demonstrated high discriminative performance, its complexity may limit immediate bedside applicability. The selected variables were chosen for their clinical availability and physiological relevance, and simplified models retaining key predictors showed acceptable performance, supporting the potential for clinical translation. In this context, a reduced model combining ICU-acquired weakness and post-SBT dyspnea provided good discrimination. A web-based tool described in Figure S3 further illustrates the feasibility of implementing the full model. Overall, this approach should be considered a proof of concept highlighting the value of multimodal integration, while further validation and simplification are required before routine clinical use, particularly given that high-risk patients may benefit from a more comprehensive physiological assessment.

This study has several limitations. First, its single-center design and relatively small sample size may limit the generalizability of the findings, as local practices, expertise in ultrasound, and patient characteristics may differ across ICUs. Although the predictive model showed strong performance, external validation in larger, multicenter cohorts is essential to confirm its clinical utility. Furthermore, penalization techniques and internal validation were employed to mitigate overfitting, the relatively small sample size may still limit the stability and generalizability of the model. Second, ultrasound assessments were performed by a single experienced operator, and interobserver variability was not evaluated. Even if most of the measurements included are well-established in previous studies, this may limit reproducibility and applicability in centers with different levels of expertise.

Third, handgrip strength was used as a proxy for global muscle function. While this method is a simple and reproducible measure; however, it requires patient cooperation and may not be feasible in all ICU patients. In our cohort, patients with severe neurological impairment were not included, and all enrolled patients were able to perform the test, supporting its feasibility in this context. Importantly, its use is consistent with clinical practice, as patient cooperation is a prerequisite for weaning according to international guidelines, which recommend that patients be awake and able to follow simple commands prior to extubation. Also, while our model incorporated several established predictors of weaning success, it did not include certain ultrasound-based measures, such as assessment of non-diaphragmatic respiratory or expiratory muscles, which could enhance the comprehensiveness and precision of future predictive tools [46, 47]. Finally, the absence of post-extubation measurements limits a more comprehensive mechanistic interpretation of post-extubation failure. While our study focused on early assessment during the spontaneous breathing trial as a clinically relevant decision point, future studies are warranted to determine whether the addition of post-extubation evaluations could further refine physiological understanding and improve patient risk stratification.

Conclusion

A multimodal ultrasound-based approach integrating cardiac, pulmonary, diaphragmatic, and peripheral muscle assessment improves prediction of weaning outcomes and clarifies the distinct mechanisms underlying SBT failure and post-extubation failure. This physiology-driven strategy may support more individualized and accurate decisions during ventilator liberation in high-risk, difficult-to-wean patients.

Abbreviations

AUC	Area under the curve
CVP	Central venous pressure
DD	Diaphragmatic displacement
$ETCO_2$	End-tidal carbon dioxide
LUS	Lung ultrasound score
MIP	Maximal inspiratory pressure
MV	Mechanical ventilation
PEEP	Positive end-expiratory pressure
PSV	Pressure-support ventilation
RASS	Richmond agitation and sedation scale
SBT	Spontaneous breathing trial
$ScvO_2$	Central venous oxygen saturation
SOFA	Sequential organ failure score
TDI	Tissue doppler imaging
TF%	Thickening fraction
EF	Ejection fraction
LASSO	Least absolute shrinkage and selection operator
ICU	Intensive care unit
VT	Tidal volume
RR	Respiratory rate
RSBI	Rapid shallow breathing index
VAS	Visual analogue scale
LV	Left ventricular
RV	Right ventricular
TAPSE	Tricuspid annular plane systolic excursion
IQR	Interquartile range
GLMM	Generalized linear mixed model
CI	Confidence interval
ROC	Receiver operating characteristic
WIPO	Weaning-induced pulmonary edemas

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-026-06113-7.

Additional file 1.

Additional file 2.

Additional file 3.

Additional file 4.

Acknowledgements
The authors thank the medical and nursing staff of all participating centers for their invaluable support throughout the study.

Author contributions
AF and SS conceived the study, supervised the study project, provided clinical data, analyzed data, interpreted data and wrote the manuscript;; MD, CAV and GS analyzed data, interpreted data, and revised the manuscript; FM and SG revised the manuscript; BB, VA and GP collected data and revised the paper; MRK and DA provided input on the methodology of the statistical analysis, interpreted data and revised the manuscript.

Funding
This study was supported by European Union – Next Generation EU – PNRR M6C2- Investment 2.1 Enhancement and strengthening of biomedical research within the national Health Service "PNRR-MCNT2-2023–12377245—Advanced bedside lung imaging and respiratory muscle monitoring for respiratory support managing in chronic ill patients with acute respiratory failure: From hospital to home.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the local ethics committee (approval number 547/2022/Oss/AOUFe date 21/9/2022), and informed consent was obtained from all patients or their legal surrogates.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Emergency, Azienda Ospedaliera-Universitaria Di Ferrara, Ferrara, Italy
[2]Service de Médecine Intensive - Réanimation (Département "R3S"), AP-HP, Sorbonne Université, Hôpital Pitié-Salpêtrière, Paris, France
[3]Department of Precision-Regenerative Medicine and Jonic Area (DiMePRe-J), University of Bari "Aldo Moro", Bari, Italy
[4]Department of Translational Medicine, University of Ferrara, 8, Aldo Moro, 44123 Ferrara, Italy
[5]Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy
[6]Department of Translational Medical Science, Biostatistics and Clinical Trial Methodology Unit, Clinical Research Center DEMeTra, University of Naples Federico II, Naples, Italy

Received: 30 March 2026 / Accepted: 25 May 2026
Published online: 04 June 2026

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