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Title page

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Title

Development and validation of a mechanical power-oriented prediction model of weaning failure in mechanically ventilated patients: a retrospective cohort study

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ABSTRACT

Objective To develop and validate a mechanical power (MP)-oriented prediction model of weaning failure in mechanically ventilated patients.

Design A retrospective cohort study.

Setting Data were collected from the large US Medical Information Mart for Intensive Care-IV (MIMIC-IV) v1.0, which integrates comprehensive clinical data from 76,540 intensive care unit (ICU) admissions from 2008 to 2019.

Participants A total of 3,695 patients with invasive mechanical ventilation for more than 24 hours and weaned with T-tube ventilation strategies were enrolled from the MIMIC-IV database.

Primary and secondary outcome Weaning failure.

Results All eligible patients were randomized into development cohort (n=2,586, 70%) and validation cohorts (n=1,109, 30%). Multivariate logistic regression analysis of the development cohort showed that positive end-expiratory pressure, dynamic lung compliance, MP, inspired oxygen concentration, length of intensive care unit stay and invasive mechanical ventilation duration were independent predictors of weaning failure. Calibration curves showed good correlation between predicted and observed outcomes. The prediction model showed accurate discrimination in the development and validation cohorts, with area under the ROC curve (AUC) values of 0.828 (95%CI: 0.812–0.844) and 0.833 (95%CI: 0.809–0.857), respectively. Decision curve analysis indicated that the predictive model was clinically beneficial.

Conclusion The MP-oriented model of weaning failure accurately predicts the risk of

weaning failure in mechanical ventilation patients and provides valuable information for clinicians making decisions on weaning.

Strengths and limitations of this study

► This is the first study to develope and validate a mechanical power (MP)-oriented weaning failure prediction model through a retrospective analysis of the MIMIC-IV database.

► The area under the receiver operating characteristic curve, calibration curves, and decision curve analysis were enrolled to evaluate the performance of the prediction model in the development and validation cohort.

► Multiple imputation was used to impute variables with <15% missing data to minimize the bias caused by missing values.

► Continuous predictors with non-linear trends were transformed into categorical variables based on their distribution and clinical significance, increasing the utility of this prediction model.

► Some possible predictive variables, such as B-type natriuretic peptide and central veins pressure were not accessible in this study, and we could not compare the performance of MP-oriented model with existing model (e.g. Extubation Predictive Score and the Burns Wean Assessment Program scores).

Text

INTRODUCTION

Mechanical ventilation is an advanced respiratory support technique widely used in the intensive care unit (ICU) [1]. Both prolonged ventilation and premature weaning are associated with poor patient outcomes, resulting in an increased risk of ventilator-associated pneumonia, longer hospital stays, and higher mortality[2]. Therefore, it is important to accurately predict the risk of weaning failure in mechanically ventilated patients and optimize the weaning time[3]. The reasons for weaning failure are complicated, with airway and pulmonary dysfunction, and the imbalance of respiratory load and respiratory muscle function as main influencing factors[4-6]. Traditional weaning evaluation methods include shallow breathing index (RSBI) and spontaneous breathing test (SBT). However, the specificity of RSBI is affected by various factors such as ventilator settings, health state, and body position[7]. In addition, between 3% and 19% of patients who passed the SBT were re-intubated due to weaning failure[7 8], which may be related to the inaccuracy of short-term SBTs in reflecting airway and lung function, and the lack of objectivity in assessing the endurance of respiratory muscles to spontaneous breathing load.

Mechanical power (MP) is the energy delivered by the ventilator to the entire respiratory system per unit time[9]. MP can be used as a dynamic and objective measure of the energy load on the respiratory muscles before weaning, and accurately reflects the airway and lung function status. Based on multiple studies, Ghiani et al[10 11] concluded that MP can be used to assess the workload of the respiratory muscles before

SBT and to guide the weaning of patients with long-term mechanical ventilation. In clinical practice, the MP-oriented prediction model constructed by combining the respiratory system parameters and the overall condition of the patient can be used to improve the prediction of weaning failure. Due to their complexity and clinical feasibility, previous predictive scoring tools are difficult to be widely used in clinical practice. In this study, we aimed to further develop and validate a MP-oriented weaning failure prediction model through a retrospective analysis of the MIMIC-IV database and use nomograms to visualize the model for evaluation of weaning failure to assist clinicians in making decisions about weaning.

METHODS

Data source

We performed a retrospective analysis of data from the large US Medical Information Mart for Intensive Care-IV (MIMIC-IV) v1.0, which integrates comprehensive clinical data from 76,540 intensive care unit (ICU) admissions at Beth Israel Deaconess Medical Center in Boston, Massachusetts, USA, from 2008 to 2019. The use of the database for research purposes was approved by the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Since all patient identification information was de-identified, the requirement for informed consent was waived[12]. The researcher (YY) completed the NIH 'Protecting Human Research Participants' online course and obtained access to the database (Certification Number: 41699414).

Study cohort

After screening the MIMIC-IV database, a total of 3,695 patients with invasive mechanical ventilation for more than 24 hours and weaned with T-tube ventilation strategies were included in this study. The research cohort was randomly divided into a development and validation cohorts at a ratio of 7:3. The development cohort was used to build the predictive model, and the validation cohort was used for validation. Each cohort was further divided into weaning success and weaning failure groups according to the weaning outcome (figure 1).

Data extraction

Data extraction was performed using structured query language with the following analysis variables: (1) basic demographic data [age, sex, body mass index (BMI), smoking history, and Sequential Organ Failure Score (SOFA)]; (2) time-related data, time to first intubation, the start and end time of mechanical ventilation, the start time of the first SBT, the successful and aborted time of SBT, the time of the first extubation, the time of the second intubation, the time of the first non-invasive ventilation after extubation, the length of ICU stay and the duration of invasive mechanical ventilation (IMV) before SBT; (3) combined symptoms, extracting comorbidities [hypertension, diabetes, chronic obstructive pulmonary disease (COPD), congestive heart failure, chronic kidney disease, stroke] according to the ICD-9 codes recorded in the MIMIC-IV database; (4) the average value of respiratory mechanics parameters [tidal volume (V_T), respiratory rate (RR), peak inspiratory pressure (P_{peak}), plateau pressure (P_{plat}),

end-expiration positive pressure (PEEP), minute ventilation (MV), inspired oxygen concentration (FiO_2)] 4 hours before the first SBT; (5) laboratory indicators [white blood cell count (WBC), creatinine (SCr)] before SBT, and hourly urine output before SBT (uorate); and (6) vital signs [heart rate (HR), respiration (BF), mean arterial pressure (MAP), blood oxygen saturation (SPO_2); arterial blood gas analysis during SBT, including PH, arterial oxygen partial pressure (PO_2), arterial partial pressure of carbon dioxide (PCO_2), oxygenation index (PO_2/FiO_2, PF)] during SBT.

Calculation of MP

After excluding patients with missing variables required to calculate MP, including patients with missing P_{plat} (i.e., all patients in the study had P_{plat} measurements in volume control mode before SBT), we extracted data according to the simplified MP equation in the volume-controlled model proposed by Gattinoni[9] as follows:

$$MP(J/min) = 0.098 \times V_T \times RR \times (P_{peak} - 0.5 \times \Delta P)$$

where V_T represents tidal volume, RR represents respiratory rate, P_{peak} represents peak inspiratory pressure, and ΔP represents driving pressure.

Driving pressure (ΔP) in the ventilation mode was calculated using P_{plat} and PEEP:

$$\Delta P\ (cmH_2O) = P_{plat} - PEEP.$$

where P_{plat} represents plateau pressure, and PEEP represents end-expiration positive pressure.

Dynamic lung compliance (C_{dyn}) refers to the change in lung volume caused by a unit pressure change, reflecting the compliance of the overall respiratory system[11] and is

calculated as follows:

$$C_{dyn}\,(ml/cmH_2O) = V_T/(P_{peak} - PEEP).$$

where V_T represents tidal volume, P_{peak} represents peak inspiratory pressure, and PEEP represents end-expiration positive pressure.

Definition of weaning failure

Weaning failure was defined as failure of SBT (i.e., premature termination of SBT), or the need for re-intubation or non-invasive ventilation within 48 hours of cessation of mechanical ventilation, or death within 48 hours of extubation[13]. Early termination of SBT in the MIMIC-IV database was assigned as follows: respiratory rate >35 beats/min >5 min; heart rate >140 beats/min; blood pressure >180 or <90 mmHg; new-onset arrhythmia; pulse oximetry (SpO_2) <90% >2 minutes; with use of accessory respiratory muscles. SBT was discontinued when the clinicians at the bedside observed that the patient's vital signs exceeded the above indicators. Only patients on T-tube ventilation during weaning were included in this study to reduce the influence and bias of different SBT modalities on weaning outcomes[14].

Statistical analysis

Variables with >15% missing data in the study were excluded, and multiple imputation was used to impute variables with <15% missing data to minimize the bias caused by missing values[15]. A linear trend test was performed on continuous predictors[16]. Variables with non-linear trends in predictors and weaning outcomes were transformed

into categorical variables based on the distribution of the independent variables and their clinical significance. Normally distributed measurement data were expressed as the mean ± standard deviation (SD), and *t*-test was used for comparisons between groups. Non-normally distributed measurement data were expressed as the median and interquartile range (IQR) and compared using the Mann-Whitney U-test or the Kruskal-Wallis H-test. Enumeration data were expressed as numbers (percentages), and the χ^2 test was used for comparison between groups.

A logistic risk regression model was used to screen important predictors of weaning outcome, and the results were expressed as odds ratio (OR) with 95% confidence interval (95% CI). To limit the variables and increase the practicability of the final model, variables with $P < 0.05$ in the univariate analysis were included in the multivariate regression model for variable screening using the backward method. A nomogram was constructed based on the results of the multivariate analysis, and the discrimination and accuracy of the model were evaluated by receiver operating characteristic curve (ROC) and calibration curve[17]. The accuracy of the nomogram, MP, and C_{dyn} in predicting the outcome of weaning failure was further compared by area under the ROC (AUC). Decision curve analysis (DCA) was used to evaluate the clinical validity of the predictive model.

All tests were two-tailed, and $P < 0.05$ was set as the threshold for statistical significance. Data analysis was performed using Stata V16.0 (StataCorp LLC, Texas, USA) software and R software version 4.1.2 (2021-11-01) [18]. Graphs were drawn with the R package 'ggplot 2' version 3.3.5[19].

Patient and public involvement

Patients and/ or the public were not directly involved in this study.

RESULTS

Baseline characteristics of the development cohort and validation cohort

By screening data in the MIMIC-IV from 2008 to 2019, we identified 3,695 patients with IMV for more than 24 hours who were weaned by T-tube ventilation strategy. This cohort comprised 2,274 patients (61.5%) who were successfully weaned and 1,421 patients who failed weaning (38.5%) (figure 1). Weaning failure patients included 1,138 patients (80.1%) who failed SBT, and 283 patients (19.9%) who were re-intubated, received non-invasive ventilation or died 48 hours after weaning. Eligible patients were randomized into a development cohort (n = 2,586, 70%) and a validation cohort (n = 1,109, 30%). Table 1 summarizes the demographic and clinical baseline characteristics of the different weaning outcome groups in the development and validation cohorts. The baseline characteristics of the development and validation cohorts were balanced.

Table 1 Baseline characteristics of the development and validation cohorts

Variables	Development cohort				Validation cohort			
	Total (n=2586)	Weaning success (n=1591)	Weaning failure (n=995)	*P* value	Total (n=1109)	Weaning success (n=683)	Weaning failure (n=426)	*P* value
Age (years)				0.474				0.417
≤65	1170 (45.2)	711 (44.7)	459 (46.1)		514 (46.3)	310 (45.4)	204 (47.9)	
>65	1416 (54.8)	880 (55.3)	536 (53.9)		595 (53.7)	373 (54.6)	222 (52.1)	
Gender				0.664				0.097
Female	1121 (43.3)	695 (43.7)	426 (42.8)		472 (42.6)	304 (44.5)	168 (39.4)	
Male	1465 (56.7)	896 (56.3)	569 (57.2)		637 (57.4)	379 (55.5)	258 (60.6)	
BMI (kg/m²)	27.9 (24.5-32.4)	27.6 (24.4-31.6)	28.4 (24.7-34.0)	0.001	27.9 (24.3-32.7)	27.8 (24.2-32.3)	28.4 (24.6-33.2)	0.194
Smoking history				0.740				0.288
No	2353 (91.0)	1450 (91.1)	903 (90.8)		1027 (92.6)	637 (93.3)	390 (91.5)	

Yes	233 (9.0)	141 (8.9)	92 (9.2)		82 (7.4)	46 (6.7)	36 (8.5)	
SOFA	7 (4-10)	6 (4-9)	8 (5-11)	0.000	7 (5-10)	7 (4-9)	8 (5-11)	0.000
Hypertension				0.543				0.917
No	1537 (59.4)	953 (59.9)	584 (58.7)		679 (61.2)	419 (61.3)	260 (61.0)	
Yes	1049 (40.6)	638 (40.1)	411 (41.3)		430 (38.8)	264 (38.7)	166 (39.0)	
Diabetes mellitus				0.839				0.702
No	1807 (69.9)	1130 (71.0)	677 (68.0)		750 (67.6)	459 (67.2)	291 (68.3)	
Yes	779 (30.1)	461 (29.0)	318 (32.0)		359 (32.4)	224 (32.8)	135 (31.7)	
COPD				0.108				0.888
No	2428 (93.9)	1495 (94.0)	933 (93.8)		1011 (91.2)	622 (91.1)	389 (91.3)	
Yes	158 (6.1)	96 (6.0)	62 (6.2)		98 (8.8)	61 (8.9)	37 (8.7)	
Congestive heart failure				0.286				0.455
No	1840 (71.2)	1144 (71.9)	696 (69.9)		748 (67.4)	455 (66.6)	293 (68.8)	
Yes	746 (28.8)	447 (28.1)	299 (30.1)		361 (32.6)	228 (33.4)	133 (31.2)	
Chronic kidney disease				0.336				0.308
No	2019 (78.1)	1252 (78.7)	767 (77.1)		838 (75.6)	509 (74.5)	329 (77.2)	
Yes	567 (21.9)	339 (21.3)	228 (22.9)		271 (24.4)	174 (25.5)	97 (22.8)	
Stroke				0.766				0.159
No	2079 (80.4)	1282 (80.6)	797 (80.1)		883 (79.6)	553 (81.0)	330 (77.5)	
Yes	507 (19.6)	309 (19.4)	198 (19.9)		226 (20.4)	130 (19.0)	96 (22.5)	
V_T (ml)	451 (394-510)	452 (392-519)	449 (397-505)	0.272	452 (396-515)	451 (391-520)	454 (401-512)	0.681
RR (bpm)				0.000				0.000
≤20	1621 (62.7)	1091 (68.6)	530 (53.3)		689 (62.1)	454 (66.5)	235 (55.2)	
>20	965 (37.3)	500 (31.4)	465 (46.7)		420 (37.9)	229 (33.5)	191 (44.8)	
PEEP (cmH_2O)				0.000				0.000
<5	312 (12.1)	268 (16.8)	44 (4.4)		146 (13.2)	122 (17.9)	24 (5.6)	
5-8	1575 (60.9)	1071 (67.3)	504 (50.7)		674 (60.8)	460 (67.3)	214 (50.2)	
≥8	699 (27.0)	252 (15.8)	447 (44.9)		289 (26.1)	101 (14.8)	188 (44.1)	
P_{plat} (cmH_2O)	17.5 (15.0-20.4)	17.0 (14.0-20.0)	19.0 (16.0-22.0)	0.000	17.5 (15.0-21.0)	17.0 (14.0-20.0)	19.0 (15.5-22.0)	0.000
P_{peak} (cmH_2O)				0.000				0.000
≤20	1325 (51.2)	1035 (65.1)	290 (29.1)		585 (52.8)	452 (66.2)	133 (31.2)	
20-25	699 (27.0)	362 (22.8)	337 (33.9)		283 (25.5)	142 (20.8)	141 (33.1)	
≥25	562 (21.7)	194 (12.2)	368 (37.0)		241 (21.7)	89 (13.0)	152 (35.7)	
MP (J/min)				0.000				0.000
≤5	303 (11.7)	285 (17.9)	18 (1.8)		144 (13.0)	136 (19.9)	8 (1.9)	
5-10	781 (30.2)	597 (37.5)	184 (18.5)		336 (30.3)	246 (36.0)	90 (21.1)	
10-15	743 (28.7)	418 (26.3)	325 (32.7)		307 (27.7)	181 (26.5)	126 (29.6)	
≥15	759 (29.4)	291 (18.3)	468 (47.0)		322 (29.0)	120 (17.6)	202 (47.4)	
C_{dyn} (ml/cmH_2O)				0.000				0.000
≥50	618 (23.9)	545 (34.3)	73 (7.3)		279 (25.2)	248 (36.3)	31 (7.3)	
40-50	321 (12.4)	214 (13.5)	107 (10.8)		141 (12.7)	89 (13.0)	52 (12.2)	
30-40	669 (25.9)	373 (23.4)	296 (29.7)		279 (25.2)	145 (21.2)	134 (31.5)	
≤30	978 (37.8)	459 (28.8)	519 (52.2)		410 (37.0)	210 (29.4)	209 (49.1)	
FiO_2 (%)				0.000				0.000
≤40	1552 (60.0)	1075 (67.6)	477 (47.9)		687 (61.9)	479 (70.1)	208 (48.8)	
>40	1034 (40.0)	516 (32.4)	518 (52.1)		422 (38.1)	204 (29.9)	218 (51.2)	
WBC (k/ul)	11.8 (8.8-15.8)	11.4 (8.5-15.3)	12.6 (9.3-16.8)	0.000	11.8 (9.0-15.2)	11.5 (8.9-14.7)	12.4 (9.3-15.8)	0.014
SCr (mg/dl)				0.000				0.276
≤1.1	1235 (47.8)	818 (51.4)	417 (41.9)		528 (47.6)	334 (48.9)	194 (45.5)	
>1.1	1351 (52.2)	773 (48.6)	578 (58.1)		581 (52.4)	349 (51.1)	232 (54.5)	
Uorate (ml/kg/h)				0.001				0.037
≤0.63	1281 (49.5)	747 (47.0)	534 (53.7)		521 (47.0)	304 (44.5)	217 (50.9)	
>0.63	1305 (50.5)	844 (53.0)	461 (46.3)		588 (53.0)	379 (55.5)	209 (49.1)	
HR (bpm)				0.036				0.001
≤90	1658 (64.1)	1045 (65.7)	613 (61.6)		729 (65.7)	474 (69.4)	255 (59.9)	
>90	928 (35.9)	546 (34.3)	382 (38.4)		380 (34.3)	209 (30.6)	171 (40.1)	
BF (bpm)	18.5 (16.0-22.0)	18.0 (15.0-21.0)	20.0 (16.5-24.0)	0.000	18.5 (15.5-22.0)	18.0 (15.0-21.5)	20.0 (16.0-23.8)	0.000
MBP (mmHg)	75 (68-84)	76 (68-86)	74 (67-82)	0.000	75 (68-84)	75 (68-85)	74 (68-84)	0.189
SPO_2 (%)	98 (97-100)	99 (97-100)	98 (96-100)	0.000	98 (96-100)	99 (97-100)	98 (96-100)	0.001
PH	7.39 (7.34-7.44)	7.40 (7.35-7.44)	7.38 (7.33-7.43)	0.003	7.40 (7.34-7.44)	7.40 (7.36-7.44)	7.38 (7.32-7.44)	0.006
PO_2 (mmHg)	106 (85-130)	108 (86-132)	104 (84-128)	0.336	105 (84-131)	104 (87-132)	107 (81-130)	0.755
PCO_2 (mmHg)	39 (34-44)	39 (34-44)	39 (34-45)	0.856	39 (34-45)	38 (34-44)	39 (34-46)	0.636

PF (mmHg)	242 (182-320)	254 (195-333)	228 (166-305)	0.000	238 (174-325)	248 (189-338)	226 (160-310)	0.012
ICU days				0.000				0.000
<7	1341 (51.9)	1047 (65.8)	294 (29.5)		564 (50.9)	447 (65.4)	117 (27.5)	
≥7	1245 (48.1)	544 (34.2)	701 (70.5)		545 (49.1)	236 (34.6)	309 (72.5)	
IMV duration				0.000				0.000
<3	1344 (52.0)	1057 (66.4)	287 (28.8)		570 (51.4)	453 (66.3)	117 (27.5)	
≥3	1242 (48.0)	534 (90.4)	708 (71.2)		539 (48.6)	230 (33.7)	309 (72.5)	

Data are median (interquartile range) or no./total (%).
Abbreviations: BMI, body mass index; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment; COPD, chronic obstructive pulmonary disease; V_T, tidal volume; RR, respiratory rate; PEEP, positive end expiratory pressure; P_{plat}, plateau pressure; P_{peak}, peak inspiratory pressure; MP, mechanical power; C_{dyn}, dynamic lung compliance; FiO_2, inspired oxygen concentration; WBC, white blood cell; SCr, serum creatinine; Uorate, urine output rate; HR, heart rate; BF, breathing frequency; MBP, mean blood pressure; SPO_2, pulse oximetry; PF, arterial partial pressure of oxygen (PaO_2) divided by the inspired oxygen concentration (FiO_2); ICU, intensive care unit; IMV, invasive mechanical ventilation.

Prognostic factors in the development cohort

Variables such as basic demographics, and respiratory mechanics, laboratory and clinical parameters in the development cohort were further tested by univariate regression analysis (table 2). BMI, SOFA, RR, PEEP, P_{plat}, P_{peak}, MP, C_{dyn}, FiO_2, WBC, SCr, Uorate, HR, BF, MBP, SPO_2, PH, PF, the length of ICU stay and duration of IMV at the first SBT were identified as potential predictors of weaning failure ($P < 0.05$). Incorporating these predictors into a multivariate logistic regression equation showed that PEEP, MP, C_{dyn}, FiO_2, the length of ICU stay and duration of IMV before the first SBT were independent predictors of weaning failure (table 2). Studies showed that higher PEEP is associated with an increased risk of weaning failure (<5 vs. 5–8, ≥8, OR = 1.34, 3.52, both $P < 0.05$), and patients with high MP had the highest risk of weaning failure (≤5 vs. 5-10, 10–15, ≥15, OR = 2.52, 3.90, 4.55, all $P < 0.001$), followed by patients with low C_{dyn} (≥50 vs. 40–50, 30–40, ≤30, OR = 3.02, 3.42, 4.44, all $P < 0.001$). The risk of weaning failure in patients with high FiO_2 was higher than that in patients with low FiO_2 (OR = 1.37, $P = 0.002$). Additionally, longer ICU days (<7 vs. ≥7, OR = 2.43, $P < 0.001$) and IMV duration (<3 vs. ≥3, OR = 2.33, P

< 0.001) were associated with a higher risk of higher weaning failure.

Table 2 Univariate and multivariable analyses for the relationship between weaning success and weaning failure in the development cohort

Variables	Univariate model			Multivariable model		
	OR	95%CI	*P* value	OR	95%CI	*P* value
BMI (kg/m²)	1.02	1.01-1.04	<0.001			
SOFA	1.07	1.05-1.09	<0.001			
RR (bpm)						
≤20	1 (reference)					
>20	1.91	1.63-2.25	<0.001			
PEEP (cmH_2O)						
<5	1 (reference)			1 (reference)		
5-8	1.15	0.82-1.48	<0.001	1.34	1.07-1.69	0.012
≥8	2.97	2.58-3.36	<0.001	3.52	2.56-4.86	<0.001
P_{plat} (cmH_2O)	1.14	1.12-1.16	<0.001			
P_{peak} (cmH_2O)						
≤20	1 (reference)					
20-25	1.20	1.00-1.40	<0.001			
≥25	1.91	1.70-2.13	<0.001			
MP (J/min)			<0.001			
≤5	1 (reference)			1 (reference)		
5-10	1.59	1.08-2.09	<0.001	2.52	1.51-4.41	<0.001
10-15	2.51	2.01-3.01	<0.001	3.90	2.33-6.87	<0.001
≥15	3.24	2.74-3.74	<0.001	4.55	2.66-8.17	<0.001
C_{dyn} (ml/cmH_2O)						
≥50	1 (reference)			1 (reference)		
40-50	1.32	0.98-1.65	<0.001	3.02	2.07-4.43	<0.001
30-40	1.78	1.49-2.07	<0.001	3.42	2.47-4.78	<0.001
≤30	2.13	1.86-2.41	<0.001	4.44	3.25-6.13	<0.001
FiO_2 (%)						
≤40	1 (reference)			1 (reference)		
>40	2.26	1.92-2.66	<0.001	1.37	1.12-1.68	0.002
WBC (k/ul)	1.04	1.02-1.05	<0.001			
SCr (mg/dl)						
≤1.1	1 (reference)					
>1.1	1.47	1.25-1.72	<0.001			
Uorate (ml/kg/h)						
≤0.63	1 (reference)					
>0.63	0.76	0.65-0.90	0.001			
HR (bpm)						
≤90	1 (reference)					
>90	1.19	1.01-1.41	0.036			
BF (bpm)	1.08	1.07-1.10	<0.001			
MBP (mmHg)	0.99	0.98-0.99	<0.001			
SPO_2 (%)	0.91	0.88-0.94	<0.001			
PH, per 10^{-1}	0.77	0.65-0.90	0.001			
PF (mmHg)	0.97	0.96-0.98	<0.001			
ICU days						
<7	1 (reference)			1 (reference)		
≥7	4.59	3.87-5.45	<0.001	2.43	1.96-3.02	<0.001
IMV duration				1 (reference)		
<3	1 (reference)			2.33	1.87-2.90	<0.001
≥3	4.88	4.11-5.80	<0.001			

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment; RR, respiratory rate; PEEP, positive end expiratory pressure; P_{plat}, plateau pressure; P_{peak}, peak inspiratory pressure; MP, mechanical power; C_{dyn}, dynamic lung compliance; FiO_2, inspired oxygen concentration; WBC, white blood cell; SCr, serum creatinine; Uorate, urine output rate; HR, heart rate; BF, breathing frequency; MBP, mean blood pressure; SPO_2, pulse oximetry; PF, arterial partial pressure of oxygen (PaO_2) divided by the inspired oxygen concentration (FiO_2); ICU, intensive care unit; IMV, invasive mechanical ventilation.

A prognostic nomogram of weaning failure

A predictive model of weaning failure in IMV patients was constructed based on the six independent predictors identified in the multivariate logistic regression model, and presented as a nomogram (figure 2). As shown in the nomogram, corresponding scores were assigned on the scale according to the OR value of each factor in these variables, with higher OR values corresponding to higher risk scores. The probability of weaning failure is predicted by summing the scores calculated for each prognostic factor in the nomogram. For instance, one IMV patient with a PEEP of 8 cmH_2O (83 points), a MP of 12 J/min (89 points), a C_{dyn} of 35 mL/cmH_2O (81 points), a FiO_2 of 45% (24 points), an ICU length of 7 days (59 points) and an IMV duration of 3 days (56 points) had a total score of 392 points, which corresponded to a weaning failure probability of approximately 86% in the nomogram.

Evaluation of the prognostic nomogram performance

Internal cross-validation of nomograms using the bootstrap method (bootstrap = 1,000 resampling) in the development cohort. As shown in figure 3A, the calibration plot yielded a straight line with a slope close to 1, indicating that the nomogram was well calibrated for predicting weaning failure. Using ROC curves, we evaluated the effectiveness of the nomogram in predicting weaning failure in both the development and validation cohorts, with an AUC of 0.828 (95% CI: 0.812–0.844) for the development cohort and 0.833 (95% CI: 0.809–0.857) for the validation cohort (figure 3C,D). In addition, by comparison, the accuracy of the nomogram in the development cohort and the validation cohort in the prediction of weaning failure was significantly

higher than that of the single indexes MP and C_{dyn} (development cohort AUC, 0.828 vs 0.746, 0.692, both $P < 0.001$; validation cohort AUC, 0.833 vs. 0.743, 0.682, both $P < 0.001$) (figure 3C,D). Based on DCA, we concluded that the nomogram was clinically valid in the validation cohort (figure 3B).

DISCUSSION

This study is the first to establish and validate a mechanical power-oriented prediction model for weaning outcome based on a large database. The model visualizes six simple and easily obtained variables through a nomogram, and can be used to evaluate the risk of weaning failure before the SBT, thereby assisting clinicians in making decisions related to weaning in critically ill mechanically ventilated patients.

Increased respiratory load and respiratory muscle work resulting from increased airway resistance combined with decreased respiratory system compliance are major causes of weaning failure[5 6]. MP integrates multiple factors of mechanical ventilation, and the total energy delivered by the ventilator to the lung parenchyma can be calculated by combining parameters such as V_T, PEEP, P_{plat}, P_{peak}, and RR[9 20]. The measurement of MP is simple and non-invasive, and the work load required to maintain optimal alveolar ventilation acting on the respiratory muscles per unit time can be obtained without disconnecting the ventilator at the bedside; consequently, MP has recently become a new guideline for clinical weaning [10 11 21]. The MP-oriented weaning outcome prediction model has certain advantages in the assessment of respiratory load before weaning and provides a comprehensive judgment of weaning decisions

combined with clinical feasibility.

Among the 3,695 mechanically ventilated patients in this study, 38.5% (1,421/3,695) failed weaning after the first SBT. Furthermore, 11.07% (283/2,557) of patients required re-intubation, non-invasive ventilation or died 48 hours after successful SBT weaning, which was consistent with the multicenter observational study by Jaber et al[22]. Among a total of 32 variables were assessed in the study, the following 20 key variables related to weaning outcomes were identified through screening: BMI, SOFA score, respiratory mechanics indicators (RR, PEEP, P_{plat}, P_{peak}, MP, C_{dyn}, FiO_2), inflammatory markers (WBC), organ function status (SCr), fluid management (uorate), physiological status at weaning (HR, BF, MBP, SPO_2, PH, PF), the length of ICU stay and duration of IMV (table 2). Our study and previous research shows that higher BMI[23] and SOFA score[24], abnormal vital signs[25], acid-base balance[26], degree of infection control[27], organ function, and fluid levels and management[23] are important predictors of weaning failure risk. However, after incorporating these potential predictors into a multivariate logistic regression model, only six predictors (PEEP, MP, C_{dyn}, FiO_2, the length of ICU stay and duration of IMV) were found to be independently associated with weaning failure. Four of these were respiratory mechanics-related indicators (table 2). These findings suggest that respiratory factors have greater weight in the prediction of weaning outcomes, which is consistent with the results reported by Heunks et al[4]. Although reversible factors leading to weaning failure are treated aggressively, objective assessment of airway and lung function is still an important aspect of avoiding weaning failure.

PEEP can prevent lung collapse and reduce intrapulmonary shunting, thereby maintaining alveolar recruitment and increasing arterial oxygenation[28]. The lower the level of PEEP required to achieve the therapeutic goal before weaning reflects a lower number of collapsed alveoli and better uniformity of lung ventilation[28]. Zhao et al. [8] also used PEEP as an independent risk indicator for predicting weaning failure. FiO_2 levels before weaning reflect the severity of hypoxia, as well as the state of circulatory function and oxygen transport capacity[29]. Our results are consistent with those of Yan Jia et al.[30], but differ from the findings of Savi et al. [31], showing that FiO_2 is a better predictor of the risk of weaning failure than PO_2/FiO_2. This discrepancy may be related to significant influence of FiO_2 and PEEP levels on PO_2/FiO_2[32]. PEEP and FiO_2 are also important indicators for weaning screening tests[26]. In accordance with the findings of Baptistella et al. [3], our research supported the conclusion that dynamic lung compliance is a respiratory mechanics parameter that can be used as a predictor of weaning outcome. C_{dyn} represents the pressure required to generate an appropriate volume to meet physiological needs, reflecting the ease with which the lung undergoes volume change under the action of external force[33]. C_{dyn} is affected by both lung tissue elasticity and airway resistance, with greater the lung compliance during weaning associated with lower the risk of weaning failure [3]. As a comprehensive respiratory mechanics index, MP is a quantitative measure of the energy required to overcome pulmonary resistance and maintain alveolar opening and optimal oxygenation during mechanical ventilation, and can reflect the severity of lung lesions[34]. In this study, we found that larger MP values before weaning were associated with a greater energy load that must be

overcome by the respiratory muscles during spontaneous breathing, and a higher the risk of weaning failure, which is consistent with the findings of Ghiani et al.[11].

In accordance with previous studies[3 35], the length of ICU stay and duration of IMV were also independent predictors of weaning failure. With a length of stay in ICU >7 days and duration of IMV >3 days, the OR values of the risk of weaning failure increased to 2.43 (95%CI 1.96–3.02) and 2.33 (95%CI 1.87–2.90), respectively (both $P < 0.001$) (table 2). This may be related to the increased risk of weaning failure due to prolonged mechanical ventilation and prolonged ICU stays leading to increased risk of diaphragmatic dysfunction, ventilator-related morbidity and mortality[2 36]. Although a single index such as MP and C_{dyn} can predict the weaning outcome to a certain extent, our ROC analysis provided evidence that the nomogram (AUC = 0.828) constructed using a combination of parameters is more accurate in predicting weaning failure than a single index, which is consistent with the conclusions reported by Torrini et al[37].

Several limitations of this study should be pointed out. First, we mainly extracted the data for patients with complete P_{plat} measurements and MP calculated in volume control mode before SBT. Since this study is a secondary analysis of the data set in the MIMIC-IV for clinical purposes, there is no guarantee that the parameters analyzed were collected under standard conditions without spontaneous breathing and adequate levels of sedation. Second, due to database limitations and missing data for some variables, we cannot rule out the possibility that other variables that were not included in our study, such as serological markers B-type natriuretic peptide (BNP)[38] and central veins pressure (CVP)[39], may also have predictive value for weaning outcomes. In

addition, we could not compare the performance of MP-oriented model with existing model (e.g. Extubation Predictive Score[3] and the Burns Wean Assessment Program scores[40]). Finally, although we randomly assigned a validation cohort of 30% of the total sample size to verify the superiority of our model, analysis of a large external cohort will further enhance the credibility and validity of our model.

In conclusion, this study is the first to establish and validate a MP-oriented prediction model for weaning failure based on a database and provides an intuitive and visualization of the model with a nomogram that predicts weaning failure with good accuracy and clinical validity. The model is simple to use and can be used with ease to provide information with clinical practicability. Moreover, this model can be used as a by clinicians as a decision support tool in the weaning process.

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Contributors YY and YX contributed equally to this work. YY: Study design, data extraction, data analysis, and drafting the manuscript. YX: Study design, data analysis, writing review and editing. XC: Data analysis and curation. SS: Data analysis and curation. ZD: Literature search and data interpretation. YW: Conceptualisation, writing review and editing. XL: Conceptualisation, writing review and editing, and data curation.

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Disclaimer The funders had no roles in study design, data collection, data analysis, interpretation and writing of the report.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval All the data presented in this study were extracted from an online database named 'MIMIC IV', which was approved by the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Thus, requirement for individual patient consent was waived because the study did not impact clinical care, and all protected health information was deidentified.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement The data set analysed to generate the findings for this study are available from the corresponding author on reasonable request.

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Figure Legend

Figure 1 Flow chart of the study.

Figure 2 Nomogram predicting the probability of weaning failure. PEEP: positive end expiratory pressure; MP: mechanical power; C_{dyn}: dynamic lung compliance; FiO_2: inspired oxygen concentration; ICU: intensive care unit; IMV: invasive mechanical ventilation.

Figure 3 Evaluation of the prognostic nomogram performance in the development and validation cohort. Calibration polt of the nomogram for the probalility of weaning failure within development (A). Decision curve for treatment failure within validation

cohort (B). Area under the receiver operation characteristic curve (95% CI) for nomogram, MP and C_{dyn} within development (C) and validation cohort (D). CI, confidence interval; MP, mechanical power; C_{dyn}, dynamic lung compliance.

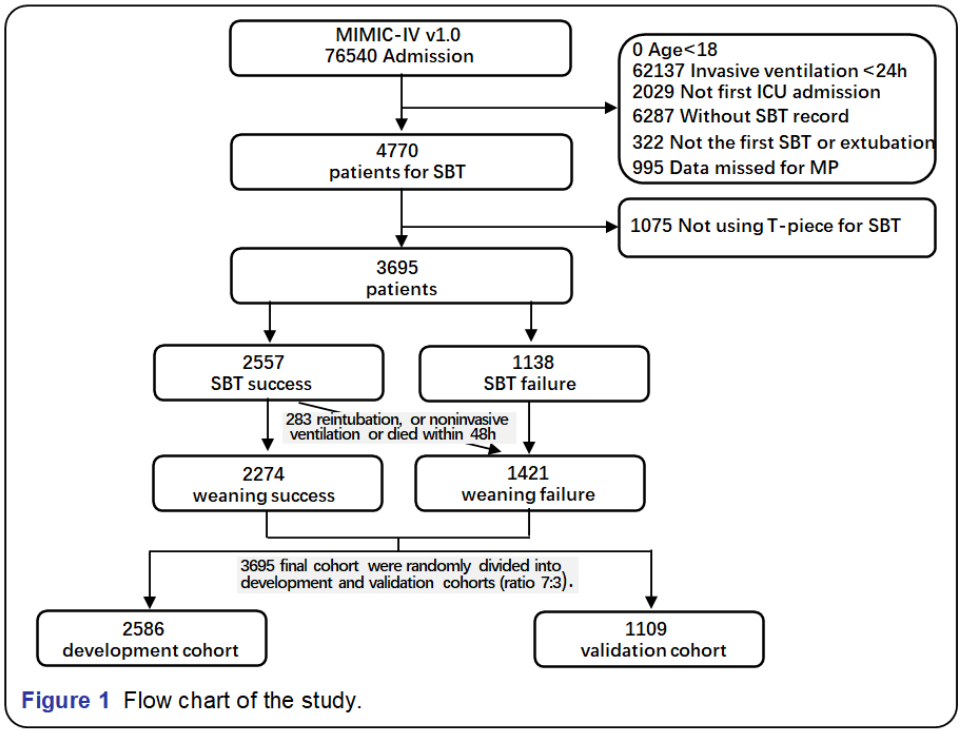

Figure 1 Flow chart of the study.

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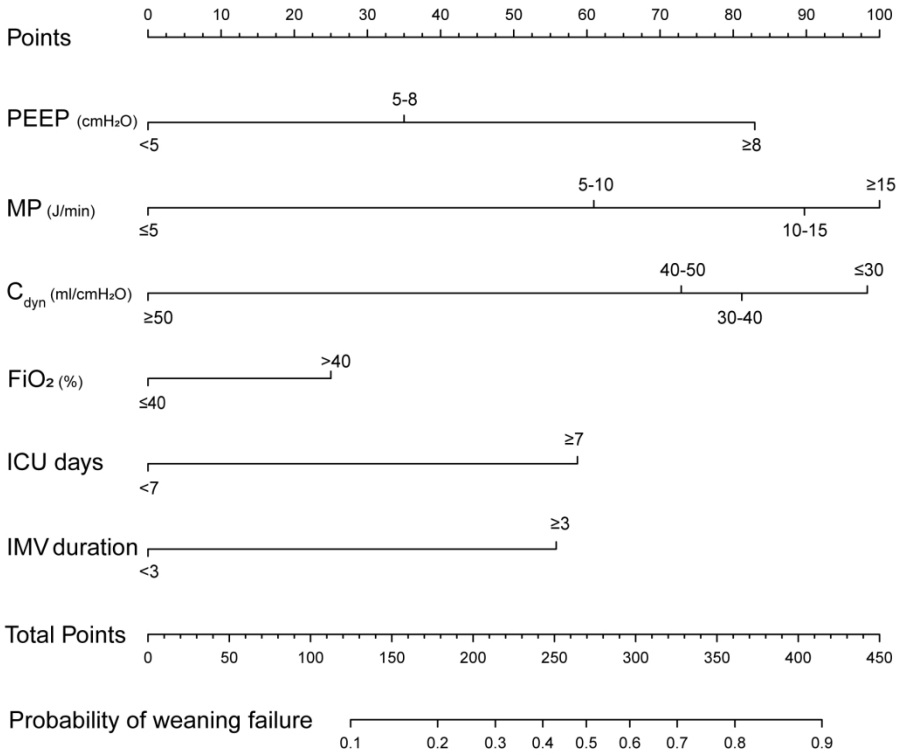

Figure 2 Nomogram predicting the probability of weaning failure. PEEP: positive end expiratory pressure; MP: mechanical power; C_{dyn}: dynamic lung compliance; FiO_2: inspired oxygen concentration; ICU: intensive care unit; IMV: invasive mechanical ventilation.

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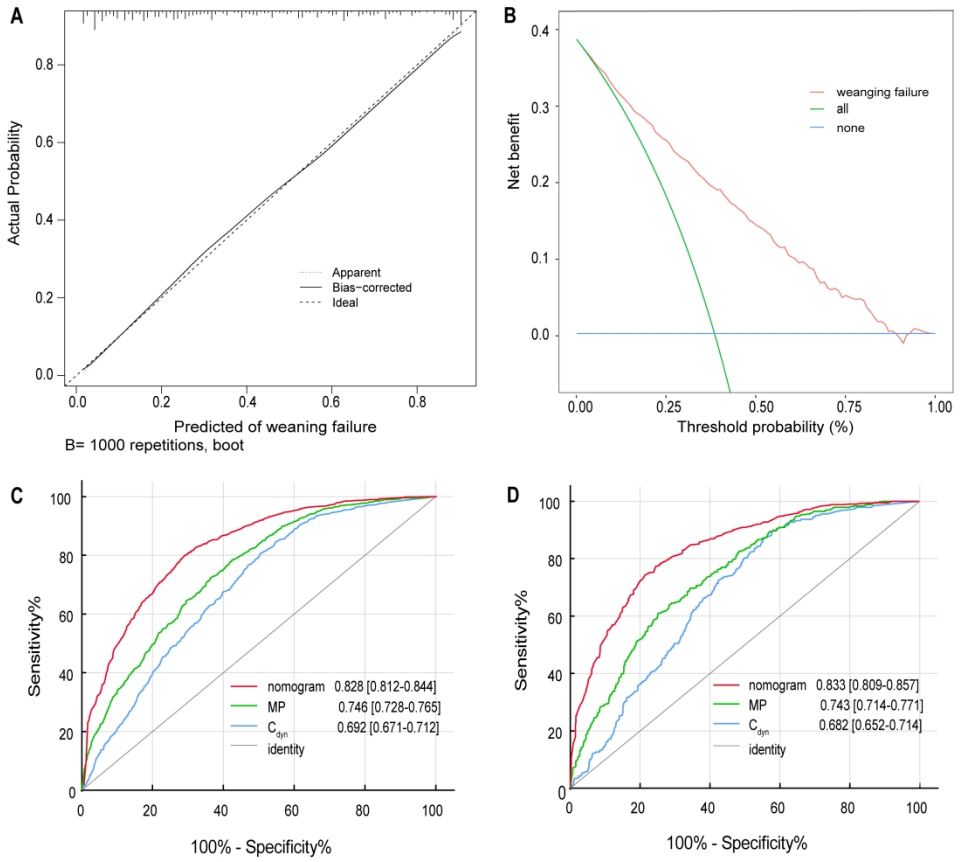

Figure 3 Evaluation of the prognostic nomogram performance in the development and validation cohort. Calibration plot of the nomogram for the probability of weaning failure within development cohort (A). Decision curve for treatment failure within validation cohort (B). Area under the receiver operating characteristic curve (95% CI) for nomogram, MP and C_{dyn} within development (C) and validation cohort (D). CI, confidence interval; MP, mechanical power; C_{dyn}, dynamic lung compliance.

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Supplementary Table 1. TRIPOD checklist for prediction model development and validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4-5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4-5
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6, 28
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	8
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6-7
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6-7
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	8
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	8-9
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	9
	10c	V	For validation, describe how the predictions were calculated.	NA
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	9
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	24-25
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	10, 28
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	24-25
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	24-25
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	24-25
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	26
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	26
	15b	D	Explain how to the use the prediction model.	11-12
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	12, 30
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	16
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	NA
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	16-17
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	16
Other information				
Supplementary	21	D;V	Provide information about the availability of supplementary resources, such as study	NA

information			protocol, Web calculator, and data sets.	
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	17

Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. Some of the items were not applicable (NA) to the current study.

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Development and validation of a mechanical power-oriented prediction model of weaning failure in mechanically ventilated patients: a retrospective cohort study

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Title page

Abstract: 221 words (max. 300 words)

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Title

Development and validation of a mechanical power-oriented prediction model of weaning failure in mechanically ventilated patients: a retrospective cohort study

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ABSTRACT

Objective To develop and validate a mechanical power (MP)-oriented prediction model of weaning failure in mechanically ventilated patients.

Design A retrospective cohort study.

Setting Data were collected from the large US Medical Information Mart for Intensive Care-IV (MIMIC-IV) v1.0, which integrates comprehensive clinical data from 76,540 intensive care unit (ICU) admissions from 2008 to 2019.

Participants A total of 3,695 patients with invasive mechanical ventilation for more than 24 hours and weaned with T-tube ventilation strategies were enrolled from the MIMIC-IV database.

Primary and secondary outcome Weaning failure.

Results All eligible patients were randomized into development cohort (n=2,586, 70%) and validation cohorts (n=1,109, 30%). Multivariate logistic regression analysis of the development cohort showed that positive end-expiratory pressure, dynamic lung compliance, MP, inspired oxygen concentration, length of intensive care unit stay and invasive mechanical ventilation duration were independent predictors of weaning failure. Calibration curves showed good correlation between predicted and observed outcomes. The prediction model showed accurate discrimination in the development and validation cohorts, with area under the ROC curve (AUC) values of 0.828 (95%CI: 0.812–0.844) and 0.833 (95%CI: 0.809–0.857), respectively. Decision curve analysis indicated that the predictive model was clinically beneficial.

Conclusion The MP-oriented model of weaning failure accurately predicts the risk of

weaning failure in mechanical ventilation patients and provides valuable information for clinicians making decisions on weaning.

Strengths and limitations of this study

► Multiple imputation was used to impute variables with <15% missing data to minimize the bias caused by missing values.

► Continuous predictors with non-linear trends were transformed into categorical variables based on their distribution and clinical significance, increasing the utility of this prediction model.

► The nomogram was constructed using the multivariable logistic regression analysis with the R package "rms".

► The area under the receiver operating characteristic curve, calibration curves, and decision curve analysis were enrolled to evaluate the performance of the prediction model in the development and validation cohort.

► We could not compare the performance of MP-oriented model with existing model (e.g. the modified Burns Wean Assessment Program scores).

Text

INTRODUCTION

Mechanical ventilation is an advanced respiratory support technique widely used in the intensive care unit (ICU) [1]. Both prolonged ventilation and premature weaning are associated with poor patient outcomes, resulting in an increased risk of ventilator-associated pneumonia, longer hospital stays, and higher mortality[2]. Therefore, it is important to accurately predict the risk of weaning failure in mechanically ventilated patients and optimize the weaning time[3]. The reasons for weaning failure are complicated, with airway and pulmonary dysfunction, and the imbalance of respiratory load and respiratory muscle function as main influencing factors[4-6]. Traditional weaning evaluation methods include shallow breathing index (RSBI) and spontaneous breathing test (SBT). However, the specificity of RSBI is affected by various factors such as ventilator settings, health state, and body position[7]. In addition, between 3% and 19% of patients who passed the SBT were re-intubated due to weaning failure[7 8], which may be related to the inaccuracy of short-term SBTs in reflecting airway and lung function, and the lack of objectivity in assessing the endurance of respiratory muscles to spontaneous breathing load.

Mechanical power (MP) is the energy delivered by the ventilator to the entire respiratory system per unit time[9]. MP can be used as a dynamic and objective measure of the energy load on the respiratory muscles before weaning, and accurately reflects the airway and lung function status. Based on multiple studies, Ghiani et al[10 11] concluded that MP can be used to assess the workload of the respiratory muscles before

SBT and to guide the weaning of patients with long-term mechanical ventilation. In this study, we aimed to further develop and validate a MP-oriented weaning failure prediction model through a retrospective analysis of the MIMIC-IV database and use nomograms to visualize the model for evaluation of weaning failure to assist clinicians in making decisions about weaning.

METHODS

Data source

We performed a retrospective analysis of data from the large US Medical Information Mart for Intensive Care-IV (MIMIC-IV) v1.0, which integrates comprehensive clinical data from 76,540 intensive care unit (ICU) admissions at Beth Israel Deaconess Medical Center in Boston, Massachusetts, USA, from 2008 to 2019. The use of the database for research purposes was approved by the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Since all patient identification information was de-identified, the requirement for informed consent was waived[12]. The researcher (YY) completed the NIH 'Protecting Human Research Participants' online course and obtained access to the database (Certification Number: 41699414).

Study cohort

After screening the MIMIC-IV database, a total of 3,695 patients with invasive mechanical ventilation for more than 24 hours and weaned with T-tube ventilation strategies were included in this study. The research cohort was randomly divided into

a development and validation cohorts at a ratio of 7:3. The development cohort was used to build the predictive model, and the validation cohort was used for validation. Each cohort was further divided into weaning success and weaning failure groups according to the weaning outcome (figure 1).

Data extraction

Data extraction was performed using structured query language with the following analysis variables: (1) basic demographic data [age, sex, body mass index (BMI), smoking history, and Sequential Organ Failure Score (SOFA)]; (2) time-related data, time to first intubation, the start and end time of mechanical ventilation, the start time of the first SBT, the successful and aborted time of SBT, the time of the first extubation, the time of the second intubation, the time of the first non-invasive ventilation after extubation, the length of ICU stay and the duration of invasive mechanical ventilation (IMV) before SBT; (3) combined symptoms, extracting comorbidities [hypertension, diabetes, chronic obstructive pulmonary disease (COPD), congestive heart failure, chronic kidney disease, stroke] according to the ICD-9 codes recorded in the MIMIC-IV database; (4) the average value of respiratory mechanics parameters [tidal volume (V_T), respiratory rate (RR), peak inspiratory pressure (P_{peak}), plateau pressure (P_{plat}), end-expiration positive pressure (PEEP), minute ventilation (MV), inspired oxygen concentration (FiO_2)] 4 hours before the first SBT; (5) laboratory indicators [white blood cell count (WBC), creatinine (SCr)] before SBT, and hourly urine output before SBT (uorate); and (6) vital signs [heart rate (HR), respiration (BF), mean arterial

pressure (MAP), blood oxygen saturation (SPO_2); arterial blood gas analysis during SBT, including PH, arterial oxygen partial pressure (PO_2), arterial partial pressure of carbon dioxide (PCO_2), oxygenation index (PO_2/FiO_2, PF)] during SBT.

Calculation of MP

After excluding patients with missing variables required to calculate MP, including patients with missing P_{plat} (i.e., all patients in the study had P_{plat} measurements in volume control mode before SBT), we extracted data according to the simplified MP equation in the volume-controlled model proposed by Gattinoni[9] as follows:

$$MP(J/min) = 0.098 \times V_T \times RR \times (P_{peak} - 0.5 \times \Delta P)$$

where V_T represents tidal volume, RR represents respiratory rate, P_{peak} represents peak inspiratory pressure, and ΔP represents driving pressure.

Driving pressure (ΔP) in the ventilation mode was calculated using P_{plat} and PEEP:

$$\Delta P\ (cmH_2O) = P_{plat} - PEEP.$$

where P_{plat} represents plateau pressure, and PEEP represents end-expiration positive pressure.

Dynamic lung compliance (C_{dyn}) refers to the change in lung volume caused by a unit pressure change, reflecting the compliance of the overall respiratory system[11] and is calculated as follows:

$$C_{dyn}\,(ml/cmH_2O) = V_T/(P_{peak} - PEEP).$$

where V_T represents tidal volume, P_{peak} represents peak inspiratory pressure, and PEEP represents end-expiration positive pressure.

Definition of weaning failure

Weaning failure was defined as failure of SBT (i.e., premature termination of SBT), or the need for re-intubation or non-invasive ventilation within 48 hours of cessation of mechanical ventilation, or death within 48 hours of extubation[13]. Early termination of SBT in the MIMIC-IV database was assigned as follows: respiratory rate >35 beats/min >5 min; heart rate >140 beats/min; blood pressure >180 or <90 mmHg; new-onset arrhythmia; pulse oximetry (SpO_2) <90% >2 minutes; with use of accessory respiratory muscles. SBT was discontinued when the clinicians at the bedside observed that the patient's vital signs exceeded the above indicators. Only patients on T-tube ventilation during weaning were included in this study to reduce the influence and bias of different SBT modalities on weaning outcomes[14].

Statistical analysis

Variables with >15% missing data in the study were excluded, and multiple imputation was used to impute variables with <15% missing data to minimize the bias caused by missing values[15]. A linear trend test was performed on continuous predictors[16]. Variables with non-linear trends in predictors and weaning outcomes were transformed into categorical variables based on the distribution of the independent variables and their clinical significance. Normally distributed measurement data were expressed as the mean ± standard deviation (SD), and *t*-test was used for comparisons between groups. Non-normally distributed measurement data were expressed as the median and interquartile range (IQR) and compared using the Mann-Whitney U-test or the Kruskal-

Wallis H-test. Enumeration data were expressed as numbers (percentages), and the χ^2 test was used for comparison between groups.

A logistic risk regression model was used to screen important predictors of weaning outcome, and the results were expressed as odds ratio (OR) with 95% confidence interval (95% CI). To limit the variables and increase the practicability of the final model, variables with $P < 0.05$ in the univariate analysis were included in the multivariate regression model for variable screening using the backward method. A nomogram was constructed based on the results of the multivariate analysis, and the discrimination and accuracy of the model were evaluated by receiver operating characteristic curve (ROC) and calibration curve[17]. The accuracy of the nomogram, MP, and C_{dyn} in predicting the outcome of weaning failure was further compared by area under the ROC (AUC). Decision curve analysis (DCA) was used to evaluate the clinical validity of the predictive model.

All tests were two-tailed, and $P < 0.05$ was set as the threshold for statistical significance. Data analysis was performed using Stata V16.0 (StataCorp LLC, Texas, USA) software and R software version 4.1.2 (2021-11-01) [18]. Graphs were drawn with the R package 'ggplot 2' version 3.3.5[19].

Patient and public involvement

Patients and/ or the public were not directly involved in this study.

RESULTS

Baseline characteristics of the development cohort and validation cohort

By screening data in the MIMIC-IV from 2008 to 2019, we identified 3,695 patients with IMV for more than 24 hours who were weaned by T-tube ventilation strategy. This cohort comprised 2,274 patients (61.5%) who were successfully weaned and 1,421 patients who failed weaning (38.5%) (figure 1). Weaning failure patients included 1,138 patients (80.1%) who failed SBT, and 283 patients (19.9%) who were re-intubated, received non-invasive ventilation or died 48 hours after weaning. Eligible patients were randomized into a development cohort (n = 2,586, 70%) and a validation cohort (n = 1,109, 30%). Table 1 summarizes the demographic and clinical baseline characteristics of the different weaning outcome groups in the development and validation cohorts. See detailed comparison of continuous variables between groups in supplementary materials (Table S1-S2). The baseline characteristics of the development and validation cohorts were balanced.

Table 1 Baseline characteristics of the development and validation cohorts

Variables	Development cohort				Validation cohort			
	Total (n=2586)	Weaning success (n=1591)	Weaning failure (n=995)	*P* value	Total (n=1109)	Weaning success (n=683)	Weaning failure (n=426)	*P* value
Age (years)				0.474				0.417
≤65	1170 (45.2)	711 (44.7)	459 (46.1)		514 (46.3)	310 (45.4)	204 (47.9)	
>65	1416 (54.8)	880 (55.3)	536 (53.9)		595 (53.7)	373 (54.6)	222 (52.1)	
Gender				0.664				0.097
Female	1121 (43.3)	695 (43.7)	426 (42.8)		472 (42.6)	304 (44.5)	168 (39.4)	
Male	1465 (56.7)	896 (56.3)	569 (57.2)		637 (57.4)	379 (55.5)	258 (60.6)	
BMI (kg/m²)	27.9 (24.5-32.4)	27.6 (24.4-31.6)	28.4 (24.7-34.0)	0.001	27.9 (24.3-32.7)	27.8 (24.2-32.3)	28.4 (24.6-33.2)	0.194
Smoking history				0.740				0.288
No	2353 (91.0)	1450 (91.1)	903 (90.8)		1027 (92.6)	637 (93.3)	390 (91.5)	
Yes	233 (9.0)	141 (8.9)	92 (9.2)		82 (7.4)	46 (6.7)	36 (8.5)	
SOFA	7 (4-10)	6 (4-9)	8 (5-11)	<0.001	7 (5-10)	7 (4-9)	8 (5-11)	<0.001
Hypertension				0.543				0.917
No	1537 (59.4)	953 (59.9)	584 (58.7)		679 (61.2)	419 (61.3)	260 (61.0)	
Yes	1049 (40.6)	638 (40.1)	411 (41.3)		430 (38.8)	264 (38.7)	166 (39.0)	
Diabetes mellitus				0.108				0.702
No	1807 (69.9)	1130 (71.0)	677 (68.0)		750 (67.6)	459 (67.2)	291 (68.3)	
Yes	779 (30.1)	461 (29.0)	318 (32.0)		359 (32.4)	224 (32.8)	135 (31.7)	
COPD				0.839				0.888
No	2428 (93.9)	1495 (94.0)	933 (93.8)		1011 (91.2)	622 (91.1)	389 (91.3)	
Yes	158 (6.1)	96 (6.0)	62 (6.2)		98 (8.8)	61 (8.9)	37 (8.7)	
Congestive heart failure				0.286				0.455
No	1840 (71.2)	1144 (71.9)	696 (69.9)		748 (67.4)	455 (66.6)	293 (68.8)	
Yes	746 (28.8)	447 (28.1)	299 (30.1)		361 (32.6)	228 (33.4)	133 (31.2)	

Chronic kidney disease				0.336				0.308
No	2019 (78.1)	1252 (78.7)	767 (77.1)		838 (75.6)	509 (74.5)	329 (77.2)	
Yes	567 (21.9)	339 (21.3)	228 (22.9)		271 (24.4)	174 (25.5)	97 (22.8)	
Stroke				0.766				0.159
No	2079 (80.4)	1282 (80.6)	797 (80.1)		883 (79.6)	553 (81.0)	330 (77.5)	
Yes	507 (19.6)	309 (19.4)	198 (19.9)		226 (20.4)	130 (19.0)	96 (22.5)	
V_T (ml)	451 (394-510)	452 (392-519)	449 (397-505)	0.272	452 (396-515)	451 (391-520)	454 (401-512)	0.681
RR (bpm)				<0.001				<0.001
≤20	1621 (62.7)	1091 (68.6)	530 (53.3)		689 (62.1)	454 (66.5)	235 (55.2)	
>20	965 (37.3)	500 (31.4)	465 (46.7)		420 (37.9)	229 (33.5)	191 (44.8)	
PEEP (cmH_2O)				<0.001				<0.001
<5	312 (12.1)	268 (16.8)	44 (4.4)		146 (13.2)	122 (17.9)	24 (5.6)	
5-8	1575 (60.9)	1071 (67.3)	504 (50.7)		674 (60.8)	460 (67.3)	214 (50.2)	
≥8	699 (27.0)	252 (15.8)	447 (44.9)		289 (26.1)	101 (14.8)	188 (44.1)	
P_{plat} (cmH_2O)	17.5 (15.0-20.4)	17.0 (14.0-20.0)	19.0 (16.0-22.0)	<0.001	17.5 (15.0-21.0)	17.0 (14.0-20.0)	19.0 (15.5-22.0)	<0.001
P_{peak} (cmH_2O)				<0.001				<0.001
≤20	1325 (51.2)	1035 (65.1)	290 (29.1)		585 (52.8)	452 (66.2)	133 (31.2)	
20-25	699 (27.0)	362 (22.8)	337 (33.9)		283 (25.5)	142 (20.8)	141 (33.1)	
≥25	562 (21.7)	194 (12.2)	368 (37.0)		241 (21.7)	89 (13.0)	152 (35.7)	
MP (J/min)				<0.001				<0.001
≤5	303 (11.7)	285 (17.9)	18 (1.8)		144 (13.0)	136 (19.9)	8 (1.9)	
5-10	781 (30.2)	597 (37.5)	184 (18.5)		336 (30.3)	246 (36.0)	90 (21.1)	
10-15	743 (28.7)	418 (26.3)	325 (32.7)		307 (27.7)	181 (26.5)	126 (29.6)	
≥15	759 (29.4)	291 (18.3)	468 (47.0)		322 (29.0)	120 (17.6)	202 (47.4)	
C_{dyn} (ml/cmH_2O)				<0.001				<0.001
≥50	618 (23.9)	545 (34.3)	73 (7.3)		279 (25.2)	248 (36.3)	31 (7.3)	
40-50	321 (12.4)	214 (13.5)	107 (10.8)		141 (12.7)	89 (13.0)	52 (12.2)	
30-40	669 (25.9)	373 (23.4)	296 (29.7)		279 (25.2)	145 (21.2)	134 (31.5)	
≤30	978 (37.8)	459 (28.8)	519 (52.2)		410 (37.0)	210 (29.4)	209 (49.1)	
FiO_2 (%)				<0.001				<0.001
≤40	1552 (60.0)	1075 (67.6)	477 (47.9)		687 (61.9)	479 (70.1)	208 (48.8)	
>40	1034 (40.0)	516 (32.4)	518 (52.1)		422 (38.1)	204 (29.9)	218 (51.2)	
WBC (k/ul)	11.8 (8.8-15.8)	11.4 (8.5-15.3)	12.6 (9.3-16.8)	<0.001	11.8 (9.0-15.2)	11.5 (8.9-14.7)	12.4 (9.3-15.8)	0.014
SCr (mg/dl)				<0.001				0.276
≤1.1	1235 (47.8)	818 (51.4)	417 (41.9)		528 (47.6)	334 (48.9)	194 (45.5)	
>1.1	1351 (52.2)	773 (48.6)	578 (58.1)		581 (52.4)	349 (51.1)	232 (54.5)	
Uorate (ml/kg/h)				0.001				0.037
≤0.63	1281 (49.5)	747 (47.0)	534 (53.7)		521 (47.0)	304 (44.5)	217 (50.9)	
>0.63	1305 (50.5)	844 (53.0)	461 (46.3)		588 (53.0)	379 (55.5)	209 (49.1)	
HR (bpm)				0.036				0.001
≤90	1658 (64.1)	1045 (65.7)	613 (61.6)		729 (65.7)	474 (69.4)	255 (59.9)	
>90	928 (35.9)	546 (34.3)	382 (38.4)		380 (34.3)	209 (30.6)	171 (40.1)	
BF (bpm)	18.5 (16.0-22.0)	18.0 (15.0-21.0)	20.0 (16.5-24.0)	<0.001	18.5 (15.5-22.0)	18.0 (15.0-21.5)	20.0 (16.0-23.8)	<0.001
MBP (mmHg)	75 (68-84)	76 (68-86)	74 (67-82)	<0.001	75 (68-84)	75 (68-85)	74 (68-84)	0.189
SPO_2 (%)	98 (97-100)	99 (97-100)	98 (96-100)	<0.001	98 (96-100)	99 (97-100)	98 (96-100)	0.001
PH	7.39 (7.34-7.44)	7.40 (7.35-7.44)	7.38 (7.33-7.43)	0.003	7.40 (7.34-7.44)	7.40 (7.36-7.44)	7.38 (7.32-7.44)	0.006
PO_2 (mmHg)	106 (85-130)	108 (86-132)	104 (84-128)	0.336	105 (84-131)	104 (87-132)	107 (81-130)	0.755
PCO_2 (mmHg)	39 (34-44)	39 (34-44)	39 (34-45)	0.856	39 (34-45)	38 (34-44)	39 (34-46)	0.636
PF (mmHg)	242 (182-320)	254 (195-333)	228 (166-305)	<0.001	238 (174-325)	248 (189-338)	226 (160-310)	0.012
ICU days				<0.001				<0.001
<7	1341 (51.9)	1047 (65.8)	294 (29.5)		564 (50.9)	447 (65.4)	117 (27.5)	
≥7	1245 (48.1)	544 (34.2)	701 (70.5)		545 (49.1)	236 (34.6)	309 (72.5)	
IMV duration				<0.001				<0.001
<3	1344 (52.0)	1057 (66.4)	287 (28.8)		570 (51.4)	453 (66.3)	117 (27.5)	
≥3	1242 (48.0)	534 (90.4)	708 (71.2)		539 (48.6)	230 (33.7)	309 (72.5)	

Data are median (interquartile range) or no./total (%).

Abbreviations: BMI, body mass index; SOFA, sequential organ failure assessment; COPD, chronic obstructive pulmonary disease; V_T, tidal volume; RR, respiratory rate; PEEP, positive end expiratory pressure; P_{plat}, plateau pressure; P_{peak}, peak inspiratory pressure; MP, mechanical power; C_{dyn}, dynamic lung compliance; FiO_2, inspired oxygen concentration; WBC, white blood cell; SCr, serum creatinine; Uorate, urine output rate; HR, heart rate; BF, breathing frequency; MBP, mean blood pressure; SPO_2, pulse oximetry; PF, arterial partial pressure of oxygen (PaO_2) divided by the inspired oxygen concentration (FiO_2); ICU, intensive care unit; IMV, invasive mechanical ventilation.

Prognostic factors in the development cohort

Variables such as basic demographics, and respiratory mechanics, laboratory and clinical parameters in the development cohort were further tested by univariate regression analysis (table 2). BMI, SOFA, RR, PEEP, P_{plat}, P_{peak}, MP, C_{dyn}, FiO_2, WBC, SCr, Uorate, HR, BF, MBP, SPO_2, PH, PF, the length of ICU stay and duration of IMV at the first SBT were identified as potential predictors of weaning failure ($P < 0.05$). Incorporating these predictors into a multivariate logistic regression equation showed that PEEP, MP, C_{dyn}, FiO_2, the length of ICU stay and duration of IMV before the first SBT were independent predictors of weaning failure (table 2). Analyses showed that higher PEEP is associated with an increased risk of weaning failure (<5 vs. 5–8, ⩾8, OR = 1.34, 3.52, both $P < 0.05$), and patients with high MP had the highest risk of weaning failure (⩽5 vs. 5-10, 10–15, ⩾15, OR = 2.52, 3.90, 4.55, all $P < 0.001$), followed by patients with low C_{dyn} (⩾50 vs. 40–50, 30–40, ⩽30, OR = 3.02, 3.42, 4.44, all $P < 0.001$). The risk of weaning failure in patients with high FiO_2 was higher than that in patients with low FiO_2 (OR = 1.37, $P = 0.002$). Additionally, longer ICU days (<7 vs. ⩾7, OR = 2.43, $P < 0.001$) and IMV duration (<3 vs. ⩾3, OR = 2.33, $P < 0.001$) were associated with a higher risk of higher weaning failure.

Table 2 Univariate and multivariable analyses for the relationship between weaning success and weaning failure in the development cohort

Variables	Univariate model			Multivariable model		
	OR	95%CI	*P* value	OR	95%CI	*P* value
BMI (kg/m²)	1.02	1.01-1.04	<0.001			
SOFA	1.07	1.05-1.09	<0.001			
RR (bpm)						
≤20	1 (reference)					
>20	1.91	1.63-2.25	<0.001			
PEEP (cmH_2O)						
<5	1 (reference)			1 (reference)		
5-8	1.15	0.82-1.48	<0.001	1.34	1.07-1.69	0.012
≥8	2.97	2.58-3.36	<0.001	3.52	2.56-4.86	<0.001
P_{plat} (cmH_2O)	1.14	1.12-1.16	<0.001			
P_{peak} (cmH_2O)						
≤20	1 (reference)					
20-25	1.20	1.00-1.40	<0.001			
≥25	1.91	1.70-2.13	<0.001			
MP (J/min)			<0.001			
≤5	1 (reference)			1 (reference)		
5-10	1.59	1.08-2.09	<0.001	2.52	1.51-4.41	<0.001
10-15	2.51	2.01-3.01	<0.001	3.90	2.33-6.87	<0.001
≥15	3.24	2.74-3.74	<0.001	4.55	2.66-8.17	<0.001
C_{dyn} (ml/cmH_2O)						
≥50	1 (reference)			1 (reference)		
40-50	1.32	0.98-1.65	<0.001	3.02	2.07-4.43	<0.001
30-40	1.78	1.49-2.07	<0.001	3.42	2.47-4.78	<0.001
≤30	2.13	1.86-2.41	<0.001	4.44	3.25-6.13	<0.001
FiO_2 (%)						
≤40	1 (reference)			1 (reference)		
>40	2.26	1.92-2.66	<0.001	1.37	1.12-1.68	0.002
WBC (k/ul)	1.04	1.02-1.05	<0.001			
SCr (mg/dl)						
≤1.1	1 (reference)					
>1.1	1.47	1.25-1.72	<0.001			
Uorate (ml/kg/h)						
≤0.63	1 (reference)					
>0.63	0.76	0.65-0.90	0.001			
HR (bpm)						
≤90	1 (reference)					
>90	1.19	1.01-1.41	0.036			
BF (bpm)	1.08	1.07-1.10	<0.001			
MBP (mmHg)	0.99	0.98-0.99	<0.001			
SPO_2 (%)	0.91	0.88-0.94	<0.001			
PH, per 10^{-1}	0.77	0.65-0.90	0.001			
PF, per 10mmHg	0.97	0.96-0.98	<0.001			
ICU days						
<7	1 (reference)			1 (reference)		
≥7	4.59	3.87-5.45	<0.001	2.43	1.96-3.02	<0.001
IMV duration				1 (reference)		
<3	1 (reference)			2.33	1.87-2.90	<0.001
≥3	4.88	4.11-5.80	<0.001			

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment; RR, respiratory rate; PEEP, positive end expiratory pressure; P_{plat}, plateau pressure; P_{peak}, peak inspiratory pressure; MP, mechanical power; C_{dyn}, dynamic lung compliance; FiO_2, inspired oxygen concentration; WBC, white blood cell; SCr, serum creatinine; Uorate, urine output rate; HR, heart rate; BF, breathing frequency; MBP, mean blood pressure; SPO_2, pulse oximetry; PF, arterial partial pressure of oxygen (PaO_2) divided by the inspired oxygen concentration (FiO_2); ICU, intensive care unit; IMV, invasive mechanical ventilation.

A prognostic nomogram of weaning failure

A predictive model of weaning failure in IMV patients was constructed based on the

six independent predictors identified in the multivariate logistic regression model, and presented as a nomogram (figure 2). As shown in the nomogram, corresponding scores were assigned on the scale according to the OR value of each factor in these variables, with higher OR values corresponding to higher risk scores. The probability of weaning failure is predicted by summing the scores calculated for each prognostic factor in the nomogram. For instance, one IMV patient with a PEEP of 8 cmH_2O (83 points), a MP of 12 J/min (89 points), a C_{dyn} of 35 mL/cmH_2O (81 points), a FiO_2 of 45% (24 points), an ICU length of 7 days (59 points) and an IMV duration of 3 days (56 points) had a total score of 392 points, which corresponded to a weaning failure probability of approximately 86% in the nomogram.

Evaluation of the prognostic nomogram performance

Internal cross-validation of nomograms using the bootstrap method (bootstrap = 1,000 resampling) in the development cohort. As shown in figure 3A, the calibration plot yielded a straight line with a slope close to 1, indicating that the nomogram was well calibrated for predicting weaning failure. Using ROC curves, we evaluated the effectiveness of the nomogram in predicting weaning failure in both the development and validation cohorts, with an AUC of 0.828 (95% CI: 0.812–0.844) for the development cohort and 0.833 (95% CI: 0.809–0.857) for the validation cohort (figure 3C,D). In addition, by comparison, the accuracy of the nomogram in the development cohort and the validation cohort in the prediction of weaning failure was significantly higher than that of the single indexes MP and C_{dyn} (development cohort AUC, 0.828 vs

0.746, 0.692, both $P < 0.001$; validation cohort AUC, 0.833 vs. 0.743, 0.682, both $P < 0.001$) (figure 3C,D). Based on DCA, we concluded that the nomogram was clinically valid in the validation cohort (figure 3B).

DISCUSSION

This study is the first to establish and validate a mechanical power-oriented prediction model for weaning outcome based on a large database. The model visualizes six simple and easily obtained variables through a nomogram, and can be used to evaluate the risk of weaning failure before the SBT, thereby assisting clinicians in making decisions related to weaning in critically ill mechanically ventilated patients.

Increased respiratory load and respiratory muscle work resulting from increased airway resistance combined with decreased respiratory system compliance are major causes of weaning failure[5 6]. MP integrates multiple factors of mechanical ventilation, and the total energy delivered by the ventilator to the lung parenchyma can be calculated by combining parameters such as V_T, PEEP, $P_{plat,}$ P_{peak}, and RR[9 20]. The measurement of MP is simple and non-invasive, and the work load required to maintain optimal alveolar ventilation acting on the respiratory muscles per unit time can be obtained without disconnecting the ventilator at the bedside; consequently, MP has recently become a new guideline for clinical weaning [10 11 21]. The MP-oriented weaning outcome prediction model has certain advantages in the assessment of respiratory load before weaning and provides a comprehensive judgment of weaning decisions combined with clinical feasibility.

Among the 3,695 mechanically ventilated patients in this study, 38.5% (1,421/3,695) failed weaning after the first SBT. Furthermore, 11.07% (283/2,557) of patients required re-intubation, non-invasive ventilation or died 48 hours after successful SBT weaning, which was consistent with the multicenter observational study by Jaber et al[22]. Among a total of 32 variables were assessed in the study, the following 20 key variables related to weaning outcomes were identified through screening: BMI, SOFA score, respiratory mechanics indicators (RR, PEEP, P_{plat}, P_{peak}, MP, C_{dyn}, FiO_2), inflammatory markers (WBC), organ function status (SCr), fluid management (uorate), physiological status at weaning (HR, BF, MBP, SPO_2, PH, PF), the length of ICU stay and duration of IMV (table 2). Our study and previous research shows that higher BMI[23] and SOFA score[24], abnormal vital signs[25], acid-base balance[26], degree of infection control[27], organ function, and fluid levels and management[23] are important predictors of weaning failure risk. However, after incorporating these potential predictors into a multivariate logistic regression model, only six predictors (PEEP, MP, C_{dyn}, FiO_2, the length of ICU stay and duration of IMV) were found to be independently associated with weaning failure. Four of these were respiratory mechanics-related indicators (table 2). These findings suggest that respiratory factors have greater weight in the prediction of weaning outcomes, which is consistent with the results reported by Heunks et al[4]. Although reversible factors leading to weaning failure are treated aggressively, objective assessment of airway and lung function is still an important aspect of avoiding weaning failure.

PEEP can prevent lung collapse and reduce intrapulmonary shunting, thereby

maintaining alveolar recruitment and increasing arterial oxygenation[28]. The lower the level of PEEP required to achieve the therapeutic goal before weaning reflects a lower number of collapsed alveoli and better uniformity of lung ventilation[28]. Zhao et al. [8] also used PEEP as an independent risk indicator for predicting weaning failure. FiO_2 levels before weaning reflect the severity of hypoxia, as well as the state of circulatory function and oxygen transport capacity[29]. Our results are consistent with those of Yan Jia et al.[30], but differ from the findings of Savi et al. [31], showing that FiO_2 is a better predictor of the risk of weaning failure than PO_2/FiO_2. This discrepancy may be related to significant influence of FiO_2 and PEEP levels on PO_2/FiO_2[32]. PEEP and FiO_2 are also important indicators for weaning screening tests[26]. In accordance with the findings of Baptistella et al. [3], our research supported the conclusion that dynamic lung compliance is a respiratory mechanics parameter that can be used as a predictor of weaning outcome. C_{dyn} represents the pressure required to generate an appropriate volume to meet physiological needs, reflecting the ease with which the lung undergoes volume change under the action of external force[33]. C_{dyn} is affected by both lung tissue elasticity and airway resistance, with greater the lung compliance during weaning associated with lower the risk of weaning failure [3]. As a comprehensive respiratory mechanics index, MP is a quantitative measure of the energy required to overcome pulmonary resistance and maintain alveolar opening and optimal oxygenation during mechanical ventilation, and can reflect the severity of lung lesions[34]. In this study, we found that larger MP values before weaning were associated with a greater energy load that must be overcome by the respiratory muscles during spontaneous breathing, and a higher the

risk of weaning failure, which is consistent with the findings of Ghiani et al.[11].

In accordance with previous studies[3 35], the length of ICU stay and duration of IMV were also independent predictors of weaning failure. With a length of stay in ICU >7 days and duration of IMV >3 days, the OR values of the risk of weaning failure increased to 2.43 (95%CI 1.96–3.02) and 2.33 (95%CI 1.87–2.90), respectively (both $P < 0.001$) (table 2). This may be related to the increased risk of weaning failure due to prolonged mechanical ventilation and prolonged ICU stays leading to increased risk of diaphragmatic dysfunction, ventilator-related morbidity and mortality[2 36]. Although a single index such as MP and C_{dyn} can predict the weaning outcome to a certain extent, our ROC analysis provided evidence that the nomogram (AUC = 0.828) constructed using a combination of parameters is more accurate in predicting weaning failure than a single index, which is consistent with the conclusions reported by Torrini et al[37]. In clinical practice, the MP-oriented prediction model constructed by combining the respiratory system parameters and the overall condition of the patient can be used to improve the prediction of weaning failure. Given that there are no identified risk factors with the need for laboratory parameters and all variables in the final model are available at the bedside, the prediction model has better generalizability and simplicity than previous predictive scoring tools (e.g. Extubation Predictive Score[3]).

Several limitations of this study should be pointed out. First, we mainly extracted the data for patients with complete P_{plat} measurements and MP calculated in volume control mode before SBT. Since this study is a secondary analysis of the data set in the MIMIC-IV for clinical purposes, there is no guarantee that the parameters analyzed

were collected under standard conditions without spontaneous breathing and adequate levels of sedation. Second, due to database limitations and missing data for some variables, we cannot rule out the possibility that other variables that were not included in our study, such as serological markers B-type natriuretic peptide (BNP)[38] and central veins pressure (CVP)[39], may also have predictive value for weaning outcomes. In addition, we could not compare the performance of MP-oriented model with existing model (e.g. the modified Burns Wean Assessment Program scores[40]). Finally, although we randomly assigned a validation cohort of 30% of the total sample size to verify the superiority of our model, analysis of a large external cohort will further enhance the credibility and validity of our model.

In conclusion, this study is the first to establish and validate a MP-oriented prediction model for weaning failure based on a database and provides an intuitive and visualization of the model with a nomogram that predicts weaning failure with good accuracy and clinical validity. The model is simple to use and can be used with ease to provide information with clinical practicability. Moreover, this model can be used as a by clinicians as a decision support tool in the weaning process.

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Contributors YY: Study design, data extraction, data analysis, and drafting the manuscript. JL and YW: Conceptualisation, writing review and editing. XC: Data analysis and curation. ZD: Literature search and

data interpretation. YX: Study design, data analysis, writing review and editing. XL: Conceptualisation, writing review and editing, and data curation.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval All the data presented in this study were extracted from an online database named 'MIMIC IV', which was approved by the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Thus, requirement for individual patient consent was waived because the study did not impact clinical care, and all protected health information was deidentified.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement The data set analysed to generate the findings for this study are available from the corresponding author on reasonable request.

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Figure Legend

Figure 1 Flow chart of the study.

Figure 2 Nomogram predicting the probability of weaning failure. PEEP: positive end expiratory pressure; MP: mechanical power; C_{dyn}: dynamic lung compliance; FiO_2: inspired oxygen concentration; ICU: intensive care unit; IMV: invasive mechanical ventilation.

Figure 3 Evaluation of the prognostic nomogram performance in the development and validation cohort. Calibration polt of the nomogram for the probalility of weaning failure within development (A). Decision curve for treatment failure within validation cohort (B). Area under the receiver operation characteristic curve (95% CI) for nomogram, MP and C_{dyn} within development (C) and validation cohort (D). CI, confidence interval; MP, mechanical power; C_{dyn}, dynamic lung compliance.

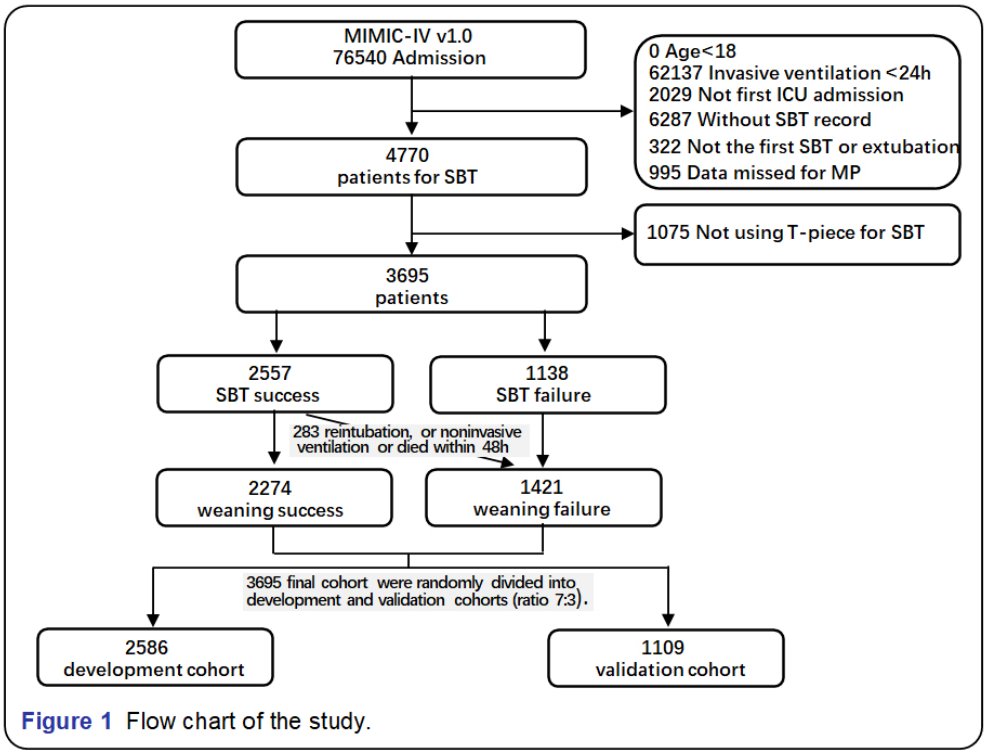

Figure 1 Flow chart of the study.

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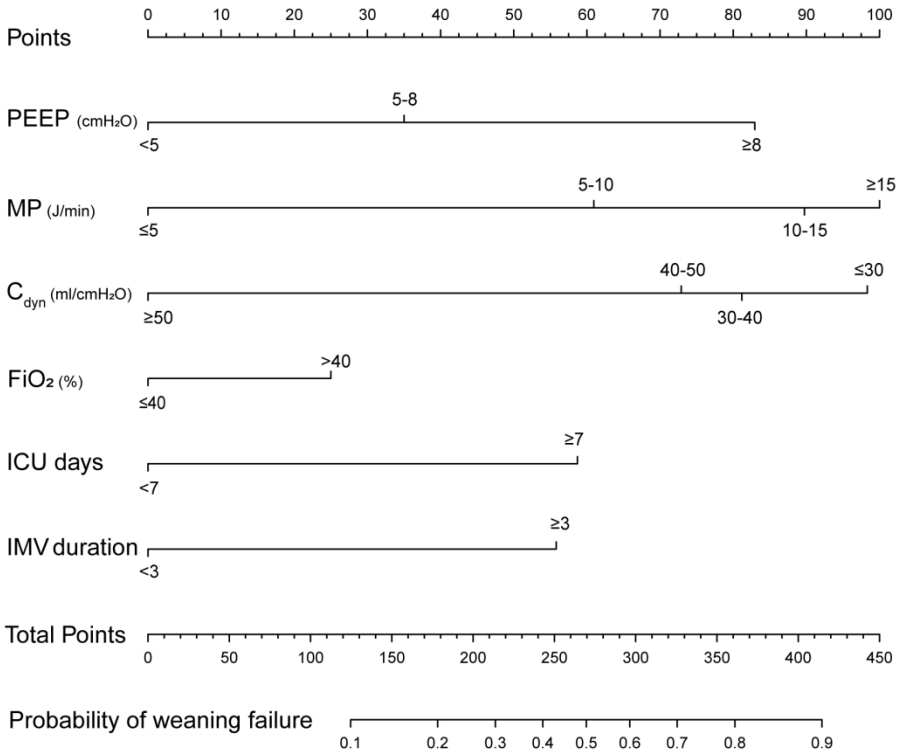

Figure 2 Nomogram predicting the probability of weaning failure. PEEP: positive end expiratory pressure; MP: mechanical power; C_{dyn}: dynamic lung compliance; FiO_2: inspired oxygen concentration; ICU: intensive care unit; IMV: invasive mechanical ventilation.

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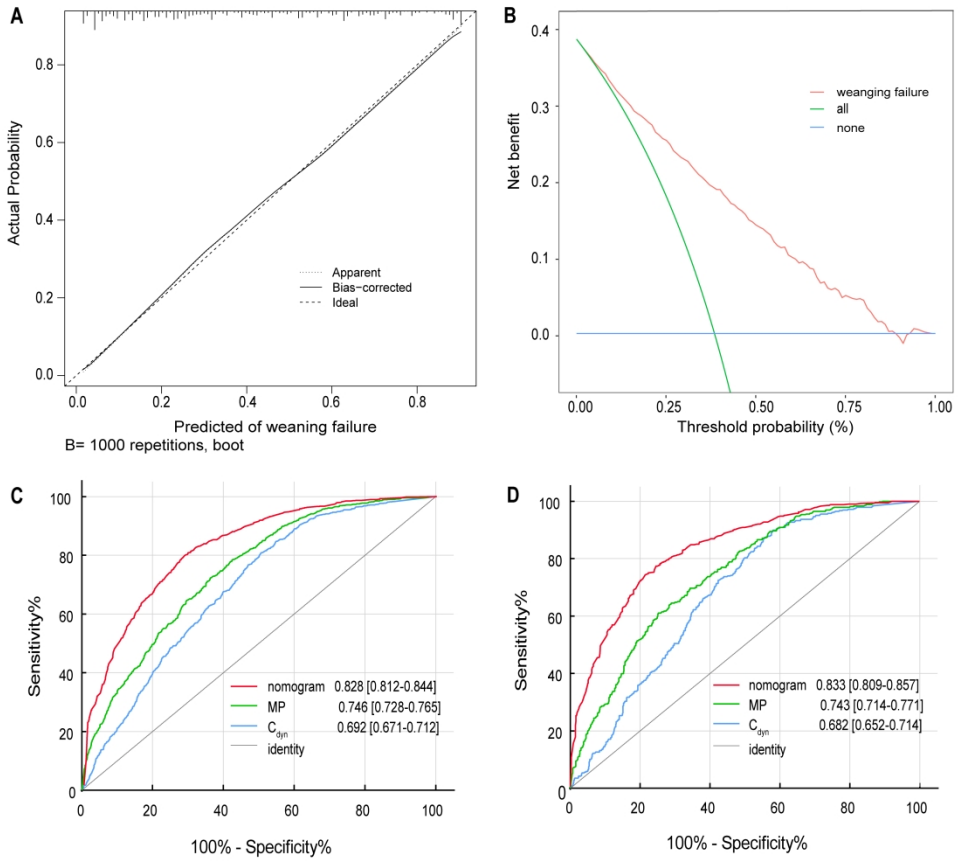

Figure 3 Evaluation of the prognostic nomogram performance in the development and validation cohort. Calibration plot of the nomogram for the probability of weaning failure within development cohort (A). Decision curve for treatment failure within validation cohort (B). Area under the receiver operating characteristic curve (95% CI) for nomogram, MP and C_{dyn} within development (C) and validation cohort (D). CI, confidence interval; MP, mechanical power; C_{dyn}, dynamic lung compliance.

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Development and validation of a mechanical power-oriented prediction model of weaning failure in mechanically ventilated patients: a retrospective cohort study

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Table

Table S1 Comparison of baseline characteristics between the weaning success and weaning failure group

Variables	All (n=3695)	Weaning success (n=2274)	Weaning failure (n=1421)	*p* value
Age(years)	66.8 (55.4-77.5)	67.3 (55.7-77.9)	66.5 (54.6-76.4)	0.052
Gender(male)	2102 (56.9)	1275 (56.1)	827 (58.2)	0.203
BMI(kg/m^2)	28.0 (24.2-33.3)	27.6 (24.1-32.5)	28.5 (24.5-34.0)	<0.001
Smoking history	315 (8.5)	187 (8.2)	128 (9.0)	0.406
SOFA	7 (4-10)	6 (4-9)	8 (5-11)	<0.001
Comorbidities				
Hypertension	1479 (40.0)	902 (39.7)	577 (40.6)	0.571
Diabetes mellitus	1138 (30.8)	685 (30.1)	453 (31.9)	0.261
COPD	256 (6.9)	157 (6.9)	99 (7.0)	0.942
Congestive heart failure	1107 (30.0)	675 (30.0)	432 (30.4)	0.643
Chronic kidney disease	838 (22.7)	513 (22.6)	325 (22.9)	0.826
Stroke	733 (19.8)	439 (19.3)	294 (20.7)	0.305
Parameters before SBT 4h				
V_T (ml)	451 (395-512)	452 (392-519)	451 (398-507)	0.498
RR (bpm)	19 (16-22)	18 (16-22)	20 (17-24)	<0.001
PEEP (cmH_2O)	5.0 (5.0-8.0)	5.0 (5.0-5.3)	6.0 (5.0-10.0)	<0.001
P_{plat} (cmH_2O)	17.5 (15.0-20.5)	17.0 (14.0-20.0)	19.0 (16.0-22.0)	<0.001
P_{peak} (cmH_2O)	19.0 (15.0-24.0)	17.0 (12.8-21.0)	23.0 (19.0-27.0)	<0.001
MP (J/min)	11.1 (7.4-16.2)	9.2 (6.0-13.2)	14.6 (10.6-20.2)	<0.001
C_{dyn} (ml/cmH_2O)	33.9 (26.2-49.2)	39.0 (28.5-62.0)	29.6 (24.2-36.7)	<0.001
FiO_2 (%)	40 (40-50)	40 (40-50)	40 (40-50)	<0.001
Laboratory data at the start of SBT				
WBC (k/ul)	11.5 (8.5-15.8)	11.2 (8.3-15.3)	11.9 (8.8-16.9)	<0.001
SCr (mg/dl)	1.1 (0.7-1.8)	1.0 (0.7-1.7)	1.2 (0.8-2.0)	<0.001
Uorate (ml/kg/h)	0.6 (0.4-1.1)	0.7 (0.4-1.2)	0.6 (0.3-1.1)	<0.001
Physiological variables during SBT				
HR (bpm)	83 (72-97)	82 (71-95)	86 (73-99)	<0.001
BF (bpm)	19 (16-22)	18 (15-21)	20 (17-24)	<0.001
MBP (mmHg)	75 (68-84)	76 (68-85)	74 (67-83)	<0.001
SPO_2 (%)	98 (97-100)	99 (97-100)	98 (96-100)	<0.001
PH (mmHg)	7.39 (7.34-7.44)	7.40 (7.35-7.44)	7.38 (7.33-7.43)	<0.001
PaO_2 (mmHg)	105 (84-130)	106 (86-132)	105 (83-129)	0.331
$PaCO_2$ (mmHg)	39 (34-45)	39 (34-44)	39 (34-45)	0.926
PF (mmHg)	240 (180-323)	253 (193-333)	226 (163-305)	<0.001
ICU days	6.2 (3.3-11.2)	4.5 (2.8-8.0)	9.5 (5.9-15.0)	<0.001
IMV duration	3.1 (1.1-7.4)	1.7 (0.8-4.1)	6.6 (3.4-11.1)	<0.001

Data are median (interquartile range) or no./total (%).

Abbreviations: BMI, body mass index; SOFA, sequential organ failure assessment; COPD, chronic obstructive pulmonary disease; V_T, tidal volume; RR, respiratory rate; PEEP, positive end expiratory pressure; P_{plat}, plateau pressure; P_{peak}, peak inspiratory pressure; MP, mechanical power; C_{dyn}, dynamic lung compliance; FiO_2, inspired oxygen concentration; WBC, white blood cell; SCr, serum creatinine; Uorate, urine output rate; HR, heart rate; BF, breathing frequency; MBP, mean blood pressure; SPO_2, pulse oximetry; PF, arterial partial pressure of oxygen (PaO_2) divided by the inspired oxygen concentration (FiO_2); ICU, intensive care unit; IMV, invasive mechanical ventilation.

Table S2 Comparison of baseline characteristics between the development and validation cohorts

Variables	Development cohort				Validation cohort			
	Total (n=2586)	Weaning success (n=1591)	Weaning failure (n=995)	*P* value	Total (n=1109)	Weaning success (n=683)	Weaning failure (n=426)	*P* value
Age (years)	67.0 (55.3-77.8)	67.4 (55.7-78.0)	66.5 (54.1-77.5)	0.105	66.7 (56.0-77.0)	67.1 (56.0-77.9)	66.2 (55.9-75.4)	0.220
Gender	1465 (56.7)	896 (56.3)	569 (57.2)	0.664	637 (57.4)	379 (55.5)	258 (60.6)	0.097
BMI (kg/m^2)	27.9 (24.5-32.4)	27.6 (24.4-31.6)	28.4 (24.7-34.0)	0.001	27.9 (24.3-32.7)	27.8 (24.2-32.3)	28.4 (24.6-33.2)	0.194
Smoking history	233 (9.0)	141 (8.9)	92 (9.2)	0.740	82 (7.4)	46 (6.7)	36 (8.5)	0.288
SOFA	7 (4-10)	6 (4-9)	8 (5-11)	<0.001	7 (5-10)	7 (4-9)	8 (5-11)	<0.001
Hypertension	1049 (40.6)	638 (40.1)	411 (41.3)	0.543	430 (38.8)	264 (38.7)	166 (39.0)	0.917
Diabetes mellitus	779 (30.1)	461 (29.0)	318 (32.0)	0.108	359 (32.4)	224 (32.8)	135 (31.7)	0.702
COPD	158 (6.1)	96 (6.0)	62 (6.2)	0.839	98 (8.8)	61 (8.9)	37 (8.7)	0.888
Congestive heart failure	746 (28.8)	447 (28.1)	299 (30.1)	0.286	361 (32.6)	228 (33.4)	133 (31.2)	0.455
Chronic kidney disease	567 (21.9)	339 (21.3)	228 (22.9)	0.336	271 (24.4)	174 (25.5)	97 (22.8)	0.308
Stroke	507 (19.6)	309 (19.4)	198 (19.9)	0.766	226 (20.4)	130 (19.0)	96 (22.5)	0.159
V_T (ml)	451 (394-510)	452 (392-519)	449 (397-505)	0.272	452 (396-515)	451 (391-520)	454 (401-512)	0.681
RR (bpm)	19 (16-22)	18 (16-22)	20 (17-24)	<0.001	19 (16-23)	18 (15-22)	20 (16-24)	<0.001
PEEP (cmH_2O)	5 (5-8)	6 (5-6)	6 (5-10)	<0.001	5 (5-8)	5 (5-5)	6 (5-10)	<0.001
P_{plat} (cmH_2O)	17.5 (15.0-20.4)	17.0 (14.0-20.0）	19.0 (16.0-22.0)	<0.001	17.5 (15.0-21.0)	17.0 (14.0-20.0)	19.0 (15.5-22.0)	<0.001
P_{peak} (cmH_2O)	19.0 (15.0-24.0)	17.0 (13.0-21.0)	23.0 (19.0-27.0)	<0.001	19.0 (14.5-24.0)	16.0 (12.0-21.0)	23.0 (19.0-26.0)	<0.001
MP (J/min)	11.2 (7.5-16.2)	9.2 (6.1-13.2)	14.5 (10.7-20.2)	<0.001	11.0 (7.3-16.1)	9.1 (5.7-13.3)	14.7 (10.5-19.7)	<0.001
C_{dyn} (ml/cmH_2O)	33.7 (26.1-48.9)	38.6 (28.8-61.1)	29.4 (23.9-36.3)	<0.001	34.9 (26.6-50.1)	39.8 (28.3-65.4)	30.1 (24.7-37.9)	<0.001
FiO_2 (%)	40 (40-50)	40 (40-50)	45 (40-50)	<0.001	40 (40-50)	40 (40-50)	45 (40-50)	<0.001
WBC (k/ul)	11.8 (8.8-15.8)	11.4 (8.5-15.3)	12.6 (9.3-16.8)	<0.001	11.8 (9.0-15.2)	11.5 (8.9-14.7)	12.4 (9.3-15.8)	0.014
SCr (mg/dl)	1.1 (0.8-1.8)	1.0 (0.7-1.7)	1.2 (0.8-1.9)	<0.001	1.1 (0.8-1.9)	1.1 (0.7-1.8)	1.1 (0.8-2.0)	0.095
Uorate (ml/kg/h)	0.6 (0.4-1.1)	0.7 (0.4-1.1)	0.6 (0.3-1.1)	<0.001	0.7 (0.4-1.1)	0.7 (0.4-1.2)	0.6 (0.3-1.0)	0.005
HR (bpm)	84 (72-97)	82 (72-96)	86 (73-98)	0.006	82 (71-96)	81 (70-94)	85 (73-99)	<0.001
BF (bpm)	18.5 (16.0-22.0)	18.0 (15.0-21.0)	20.0 (16.5-24.0)	<0.001	18.5 (15.5-22.0)	18.0 (15.0-21.5)	20.0 (16.0-23.8)	<0.001
MBP (mmHg)	75 (68-84)	76 (68-86)	74 (67-82)	<0.001	75 (68-84)	75 (68-85)	74 (68-84)	0.189
SPO_2(%)	98 (97-100)	99 (97-100)	98 (96-100)	<0.001	98 (96-100)	99 (97-100)	98 (96-100)	0.001
PH	7.39 (7.34-7.44)	7.40 (7.35-7.44)	7.38 (7.33-7.43)	0.003	7.40 (7.34-7.44)	7.40 (7.36-7.44)	7.38 (7.32-7.44)	0.006
PO_2(mmHg)	106 (85-130)	108 (86-132)	104 (84-128)	0.336	105 (84-131)	104 (87-132)	107 (81-130)	0.755
PCO_2 (mmHg)	39 (34-44)	39 (34-44)	39 (34-45)	0.856	39 (34-45)	38 (34-44)	39 (34-46)	0.636
PF (mmHg)	242 (182-320)	254 (195-333)	228 (166-305)	<0.001	238 (174-325)	248 (189-338)	226 (160-310)	0.012
ICU days	6.2 (3.3-11.1)	4.6 (2.7-8.2)	9.2 (6.0-14.4)	<0.001	6.0 (3.3-11.4)	4.4 (2.8-7.4)	10.2 (5.8-16.3)	<0.001
IMV duration	3.1 (1.2-7.3)	1.8 (0.9-4.1)	6.5 (3.5-10.9)	<0.001	3.0 (1.1-8.0)	1.7 (0.9-4.1)	7.1 (3.2-11.9)	<0.001

Data are median (interquartile range) or no./total (%).

Abbreviations: BMI, body mass index; SOFA, sequential organ failure assessment; COPD, chronic obstructive pulmonary disease; V_T, tidal volume; RR, respiratory rate; PEEP, positive end expiratory pressure; P_{plat}, plateau pressure; P_{peak}, peak inspiratory pressure; MP, mechanical power; C_{dyn}, dynamic lung compliance; FiO_2, inspired oxygen concentration; WBC, white blood cell; SCr, serum creatinine; Uorate, urine output rate; HR, heart rate; BF, breathing frequency; MBP, mean blood pressure; SPO_2, pulse oximetry; PF, arterial partial pressure of oxygen (PaO_2) divided by the inspired oxygen concentration (FiO_2); ICU, intensive care unit; IMV, invasive mechanical ventilation.

The construction of the nomogram

Preliminary univariate analyses were performed to identify potential risk factors, and multivariate analyses were subsequently performed using backward method to select a best-fit model (Table S3). Variables achieving $P < 0.05$ in univariate analysis were entered into multivariate mode 1. Variables achieving $P < 0.2$ in univariate analysis were entered into multivariate mode 2. Six variables were included in the final multivariable model 1: PEEP, MP, C_{dyn}, FiO_2, ICU LOS and IMV duration. The variables included in model 2 were those in model 1 plus V_T and WBC. We assessed the ability of the final models and model variables to discriminate patients at risk of weaning failure using C-statistics (Table S4). The 6-variable model (Multivariable model 1) showed superior weaning failure prediction performance compared to the 8-variable model (Multivariable model 2) (Table S4). The final multivariable logistic regression model 1 was converted to a nomogram for ease of use in clinical practice.

Table S3 Univariate and multivariable analyses for the relationship between weaning success and weaning failure in the the development cohort

Variables	Univariate model			Multivariable model 1			Multivariable model 2		
	OR	95%CI	*P* value	OR	95%CI	*P* value	OR	95%CI	*P* value
Age(years)									
≤65	1 (reference)								
>65	0.94	0.80-1.11	0.470						
Gender									
Female	1 (reference)								
Male	1.04	0.88-1.22	0.660						
BMI (kg/m²)	1.02	1.01-1.04	<0.001						
Smoking history									
No	1 (reference)								
Yes	1.05	0.80-1.38	0.740						
SOFA	1.07	1.05-1.09	<0.001						
Hypertension									
No	1 (reference)								
Yes	1.05	0.89-1.24	0.540						
Diabetes mellitus									
No	1 (reference)								
Yes	1.15	0.97-1.37	0.110						
COPD									
No	1 (reference)								
Yes	1.03	0.74-1.44	0.840						
Congestive heart failure									
No	1 (reference)								
Yes	1.10	0.92-1.31	0.290						
Chronic kidney disease									
No	1 (reference)								
Yes	1.10	0.91-1.33	0.340						
Stroke									
No	1 (reference)								
Yes	1.03	0.84-1.26	0.770						
V_T (ml)	1.00	1.00-1.00	0.100				1.00	1.00-1.00	<0.001
RR (bpm)									
≤20	1 (reference)								
>20	1.91	1.63-2.25	<0.001						
PEEP (cmH_2O)									

<5	1 (reference)			1 (reference)			1 (reference)		
5-8	1.15	0.82-1.48	<0.001	1.34	1.07-1.69	0.012	1.47	1.16-1.86	0.001
≥8	2.97	2.58-3.36	<0.001	3.52	2.56-4.86	<0.001	4.50	3.12-6.54	<0.001
P_{plat} (cmH_2O)	1.14	1.12-1.16	<0.001						
P_{peak} (cmH_2O)									
≤20	1 (reference)								
20-25	1.20	1.00-1.40	<0.001						
≥25	1.91	1.70-2.13	<0.001						
MP (J/min)			<0.001						
≤5	1 (reference)			1 (reference)			1 (reference)		
5-10	1.59	1.08-2.09	<0.001	2.20	1.32-3.86	0.004	2.10	1.25-3.72	0.007
10-15	2.51	2.01-3.01	<0.001	3.21	1.91-5.67	<0.001	2.85	1.66-5.13	<0.001
≥15	3.24	2.74-3.74	<0.001	3.70	2.15-6.70	<0.001	2.99	1.68-5.56	<0.001
C_{dyn} (ml/cmH_2O)									
≥50	1 (reference)			1 (reference)			1 (reference)		
40-50	1.32	0.98-1.65	<0.001	3.09	2.11-4.54	<0.001	3.68	2.47-5.50	<0.001
30-40	1.78	1.49-2.07	<0.001	3.49	2.52-4.88	<0.001	4.63	3.22-6.73	<0.001
≤30	2.13	1.86-2.41	<0.001	4.56	3.33-6.31	<0.001	7.35	4.88-11.20	<0.001
FiO_2 (%)									
≤40	1 (reference)			1 (reference)			1 (reference)		
>40	2.26	1.92-2.66	<0.001	1.36	1.11-1.66	0.003	1.35	1.10-1.66	0.004
WBC (k/ul)	1.04	1.02-1.05	<0.001				1.02	1.00-1.04	0.038
SCr (mg/dl)									
≤1.1	1 (reference)								
>1.1	1.47	1.25-1.72	<0.001						
Uorate (ml/kg/h)									
≤0.63	1 (reference)								
>0.63	0.76	0.65-0.90	0.001						
HR (bpm)									
>90	1 (reference)								
>90	1.19	1.01-1.41	0.036						
BF (bpm)	1.08	1.07-1.10	<0.001						
MBP (mmHg)	0.99	0.98-0.99	<0.001						
SPO_2 (%)	0.91	0.88-0.94	<0.001						
PH, per 10^{-1}	0.77	0.65-0.90	0.001						
PO_2 (mmHg)	1.00	1.00-1.00	0.680						
PCO_2 (mmHg)	1.00	0.99-1.02	0.710						
PF (mmHg)	0.97	0.96-0.98	<0.001						
ICU LOS (days)									
≤7	1 (reference)			1 (reference)			1 (reference)		
>7	4.59	3.87-5.45	<0.001	2.40	1.93-2.98	<0.001	2.44	1.97-3.03	<0.001
IMV duration (days)				1 (reference)			1 (reference)		
≤3	1 (reference)			2.31	1.86-2.88	<0.001	2.43	1.95-3.03	<0.001
>3	4.88	4.11-5.80	<0.001						

Multivariable model 1: Variables achieving $P < 0.05$ in univariate analysis were entered into multivariate analysis.
Multivariable model 2: Variables achieving $P < 0.2$ in univariate analysis were entered into multivariate analysis.
Abbreviations: OR: odds ratio; CI: confidence interval; BMI: body mass index; SAPS II: simplified acute physiology score II; SOFA: sequential organ failure assessment; COPD, chronic obstructive pulmonary disease; V_T, tidal volume; RR: respiratory rate; PEEP: positive end expiratory pressure; P_{plat}: plateau pressure; P_{peak}: peak inspiratory pressure; MP: mechanical power; C_{dyn}: dynamic lung compliance; FiO_2: inspired oxygen concentration; WBC: white blood cell; SCr: serum creatinine; Uorate: urine output rate; HR: heart rate; BF: breathing frequency; MBP: mean blood pressure; SPO_2: pulse oximetry; PF: arterial partial pressure of oxygen (PaO_2) divided by the inspired oxygen concentration (FiO_2); LOS: length of stay; IMV: invasive mechanical ventilation

Table S4 C-statistics for the multivariable model 1, multivariable model 2 and model variables in the development and validation cohorts

	Development cohort (n=2586)		Validation cohort (n=1109)	
	C-statistic (95% CI)	***P* value**	**C-statistic (95% CI)**	***P* value**
Multivariable model 1	0.828 (0.812-0.844)	-	0.833 (0.809-0.857)	-
Multivariable model 2	0.827 (0.815-0.846)	-	0.830 (0.813-0.860)	-
V_T (ml)	0.513 (0.490-0.535)	0.272	0.507 (0.473-0.542)	0.681
PEEP (cmH_2O)	0.712 (0.691-0.733)	<0.001	0.712 (0.680-0.744)	<0.001
MP (J/min)	0.746 (0.728-0.765)	<0.001	0.754 (0.724-0.784)	<0.001
C_{dyn} (ml/cmH_2O)	0.692 (0.671-0.712)	<0.001	0.683 (0.652-0.714)	<0.001
FiO_2 (%)	0.629 (0.606-0.650)	<0.001	0.622 (0.588-0.657)	<0.001
WBC (k/ul)	0.556 (0.533-0.579)	<0.001	0.544 (0.509-0.579)	0.014
ICU LOS (days)	0.737 (0.718-0.757)	<0.001	0.736 (0.706-0.766)	<0.001
IMV duration (days)	0.735 (0.715-0.755)	<0.001	0.743 (0.714-0.772)	<0.001

Abbreviations: V_T: tidal volume; PEEP: positive end expiratory pressure; MP: mechanical power; C_{dyn}: dynamic lung compliance; FiO_2: inspired oxygen concentration; WBC: white blood cell; LOS: length of stay; IMV: invasive mechanical ventilation

Supplementary Table 1. TRIPOD checklist for prediction model development and validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4-5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4-5
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6, 28
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	8
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6-7
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6-7
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	8
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	8-9
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	9
	10c	V	For validation, describe how the predictions were calculated.	NA
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	9
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	24-25
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	10, 28
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	24-25
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	24-25
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	24-25
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	26
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	26
	15b	D	Explain how to the use the prediction model.	11-12
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	12, 30
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	16
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	NA
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	16-17
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	16
Other information				
Supplementary	21	D;V	Provide information about the availability of supplementary resources, such as study	NA

information			protocol, Web calculator, and data sets.	
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	17

Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. Some of the items were not applicable (NA) to the current study.