Weaning from mechanical ventilation in intensive care units across 50 countries (WEAN SAFE): a multicentre, prospective, observational cohort study

Tài Pham, Leo Heunks, Giacomo Bellani, Fabiana Madotto, Irene Aragao, Gaëtan Beduneau, Ewan C Goligher, Giacomo Grasselli, Jon Henrik Laake, Jordi Mancebo, Oscar Peñuelas, Lise Piquilloud, Antonio Pesenti, Hannah Wunsch, Frank van Haren, Laurent Brochard, John G Laffey*, for the WEAN SAFE Investigators†*

Summary

Background Current management practices and outcomes in weaning from invasive mechanical ventilation are poorly understood. We aimed to describe the epidemiology, management, timings, risk for failure, and outcomes of weaning in patients requiring at least 2 days of invasive mechanical ventilation.

Methods WEAN SAFE was an international, multicentre, prospective, observational cohort study done in 481 intensive care units in 50 countries. Eligible participants were older than 16 years, admitted to a participating intensive care unit, and receiving mechanical ventilation for 2 calendar days or longer. We defined weaning initiation as the first attempt to separate a patient from the ventilator, successful weaning as no reintubation or death within 7 days of extubation, and weaning eligibility criteria based on positive end-expiratory pressure, fractional concentration of oxygen in inspired air, and vasopressors. The primary outcome was the proportion of patients successfully weaned at 90 days. Key secondary outcomes included weaning duration, timing of weaning events, factors associated with weaning delay and weaning failure, and hospital outcomes. This study is registered with ClinicalTrials.gov, NCT03255109.

Findings Between Oct 4, 2017, and June 25, 2018, 10 232 patients were screened for eligibility, of whom 5869 were enrolled. 4523 (77·1%) patients underwent at least one separation attempt and 3817 (65·0%) patients were successfully weaned from ventilation at day 90. 237 (4·0%) patients were transferred before any separation attempt, 153 (2·6%) were transferred after at least one separation attempt and not successfully weaned, and 1662 (28·3%) died while invasively ventilated. The median time from fulfilling weaning eligibility criteria to first separation attempt was 1 day (IQR 0–4), and 1013 (22·4%) patients had a delay in initiating first separation of 5 or more days. Of the 4523 (77·1%) patients with separation attempts, 2927 (64·7%) had a short wean (≤1 day), 457 (10·1%) had intermediate weaning (2–6 days), 433 (9·6%) required prolonged weaning (≥7 days), and 706 (15·6%) had weaning failure. Higher sedation scores were independently associated with delayed initiation of weaning. Delayed initiation of weaning and higher sedation scores were independently associated with weaning failure. 1742 (31·8%) of 5479 patients died in the intensive care unit and 2095 (38·3%) of 5465 patients died in hospital.

Interpretation In critically ill patients receiving at least 2 days of invasive mechanical ventilation, only 65% were weaned at 90 days. A better understanding of factors that delay the weaning process, such as delays in weaning initiation or excessive sedation levels, might improve weaning success rates.

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Introduction

Successful separation of patients from invasive mechanical ventilation, referred to as weaning from mechanical ventilation, represents a crucial step in the recovery process following severe respiratory failure.[1–3] Many of the serious complications of invasive mechanical ventilation are directly related to the duration of ventilation.[4–6] Prolonged weaning of patients from invasive mechanical ventilation worsens patient outcomes, increases the risk of dying, and increases length of intensive care unit and hospital stay.[7,8] Together with age, duration of ventilation is the strongest predictor of 1-year functional outcome.[6] Weaning duration affects health-care resource use, whether direct financial cost or the opportunity for other patients of consumption of finite critical care capacity. A systematic approach to reduce the duration of ventilation is therefore crucial.[9–11]

Despite the importance of this period, neither the starting point nor the termination of the weaning process is rigorously defined,[12] with wide variations in definitions and practices of separating the patient from the ventilator.[12,13] Although weaning should start as soon as broad general criteria are present, an interval might exist between the time at which these criteria are present and

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*Equal contributors and joint senior authors

†A complete list of the WEAN SAFE investigators and endorsing societies is provided in the appendix (pp 22–49)

Service de Médecine Intensive-Réanimation, AP-HP, Hôpital de Bicêtre, DMU CORREVE, FHU SEPSIS, Groupe de Recherche CARMAS, Hôpitaux Universitaires Paris-Saclay, Le Kremlin-Bicêtre, France (T Pham PhD); **Université Paris-Saclay, UVSQ, Université Paris-Sud, Inserm U1018, Equipe d'Epidémiologie Respiratoire Intégrative, CESP, 94807, Villejuif, France** (T Pham); **Department of Intensive Care Medicine, Erasmus University Medical Centre, Rotterdam, The Netherlands** (Prof L Heunks MD); **School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy** (Prof G Bellani MD); **Department of Emergency and Intensive Care, University Hospital San Gerardo, Monza, Italy** (Prof G Bellani); **Department of Anaesthesia, Intensive Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy** (F Madotto PhD, Prof G Grasselli MD, Prof A Pesenti MD); **Department of Intensive Care Medicine, Centro Hospitalar Universitário do Porto, Porto, Portugal** (I Aragao MD); **Normandie University, UNIROUEN, UR 3830, CHU Rouen, Department of Medical Intensive Care, F-76000 Rouen, France** (G Beduneau MD);

Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada (E C Goligher MD, Prof H Wunsch MD, Prof L Brochard MD); **Department of Medicine, Division of Respirology, Toronto General Hospital Research Institute University Health Network, Toronto, Canada** (E C Goligher); **Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy** (Prof G Grasselli, Prof A Pesenti); **Department of Anaesthesiology and Department of Research and Development, Division of Critical Care and Emergencies, Oslo University Hospital, Oslo, Norway** (Prof J H Laake MD); **Department of Intensive Care Medicine, Hospital Universitari Sant Pau, Barcelona, Spain** (Prof J Mancebo MD*); **Intensive Care Unit, Hospital Universitario de Getafe, Madrid, Spain** (Prof O Peñuelas PhD); **Centro de Investigación Biomédica en Red, CIBER de Enfermedades Respiratorias, CIBERES, Madrid, Spain** (Prof O Peñuelas); **Adult Intensive Care Unit, University Hospital and University of Lausanne, Lausanne, Switzerland** (L Piquilloud MD); **Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada** (Prof H Wunsch); **College of Health and Medicine, Australian National University, Canberra, ACT, Australia** (Prof F v Haren PhD); **Intensive Care Unit, St George Hospital, Sydney, NSW, Australia** (Prof F v Haren); **Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St Michael's Hospital, Unity Health Toronto, Toronto, ON, Canada** (Prof L Brochard); **Anaesthesia and Intensive Care Medicine, School of Medicine, Clinical Sciences Institute, Galway University Hospitals, Galway, Ireland** (Prof J G Laffey MD); **School of Medicine, Regenerative Medicine Institute (REMEDI) at CÚRAM Centre for Research in Medical Devices, National University of Ireland Galway, Galway, Ireland** (Prof J G Laffey)

*Prof Mancebo is sadly deceased

Research in context

Evidence before this study

We searched PubMed on Dec 14, 2018, for articles published since Jan 1, 1990, with search terms relating to invasive mechanical ventilation and weaning or separation. Specific search terms used were "invasive mechanical ventilation" [MeSH Terms] OR ("invasive"[All Fields] AND "mechanical"[All Fields] AND "ventilation"[All Fields] AND "weaning"[All Fields]) OR "separation"[All Fields] OR "liberation"[All Fields]. Searches were not limited by language and were supplemented by review of reference lists. We found some studies reporting findings regarding weaning from ventilation from small geographical areas, such as individual countries or small groups of countries, but no study reporting data relating weaning practices to outcomes from invasive mechanical ventilation in a global cohort of patients at risk for prolonged weaning or weaning failure.

Added value of this study

In this global prospective observational study, 5869 patients required invasive ventilation for at least 2 days. 4523 (77·1%) of these patients had at least one separation attempt, and only 3817 (65·0%) were successfully weaned from invasive ventilation. Overall, 1742 (31·8%) patients died in the intensive care unit and 2095 (38·3%) died in hospital. Of patients who had separation attempts, 2927 (64·7%) had a short wean (≤1 day), 457 (10·1%) had intermediate (2–6 days) weaning, 433 (9·6%) had a prolonged (≥7 days) weaning duration, and 706 (15·6%) had weaning failure (ie, they died, were transferred, or were still invasively ventilated at day 90). Higher sedation levels were independently associated with delays in initiating ventilator separation. Higher sedation levels and a delay in initiating ventilator separation were potentially modifiable factors independently associated with weaning failure.

Implications of all the available evidence

Weaning failure rates are high, with very poor outcomes in patients with weaning failure. Strategies to reduce delays in weaning initiation and to optimise sedation levels during weaning might improve weaning success rates, and enhance patient survival.

the first weaning attempt. This delay has not been rigorously measured and we wished to quantify this time interval and assess its association with the weaning outcome.

The aim of the WEAN SAFE (Worldwide Assessment of Separation of Patients from Ventilatory Assistance) study[14] was to understand the weaning process in a large, real world population of patients in intensive care units receiving invasive mechanical ventilation for at least 2 calendar days, and consequently at higher risk for prolonged weaning and weaning failure. Our overarching hypothesis was that there are variations and gaps in the weaning process and these factors might be associated with delayed and failed weaning.

Methods

Study design and participants

WEAN SAFE was an international, multicentre, prospective, observational cohort study, done in 481 intensive care units in 50 countries (appendix p 16). Each centre enrolled patients for 4 consecutive weeks during the enrolment period.

All patients older than 16 years who were admitted to a participating intensive care unit and were receiving invasive mechanical ventilation were screened for eligibility and a basic dataset collected. Patients were excluded in case of an absence of informed consent (where this was a requirement of the local ethics committee) or if they were already present in the intensive care unit at the beginning of the study. Patients still receiving invasive mechanical ventilation 2 calendar days after intubation had an extended dataset collected. Patients transferred to other facilities before successful weaning were deemed lost to follow-up and their intensive care unit and hospital outcomes were not collected. All participating intensive care units (appendix pp 22–33) obtained ethics committee approval, and either request for patient consent or waiver of consent. Participating intensive care units had to have enrolled and validated at least one patient to be included in the study. National coordinators and site investigators (appendix pp 34–49) were responsible for ensuring data integrity and validity. The study protocol and case report form are included in the appendix (pp 50–72).

Procedures

Spontaneous breathing was defined either (1) during mechanical ventilation, when the patient's total respiratory rate was higher than the set respiratory rate in assist-control mode (ie, the patient was triggering the ventilator) or when the mode of mechanical ventilation required patient's own spontaneous breathing;[15] or (2) breathing without invasive support.

Given the need to define a population potentially suitable to initiate the weaning process, we defined weaning eligibility criteria (modified from Boles et al[1]) as fractional concentration of oxygen in inspired air (FiO_2) less than 0·5, and positive end-expiratory pressure (PEEP) less than 10 cm H_2O and receiving no or low doses of vasopressors (<0·2 µg/kg per min of norepinephrine or equivalent), and not receiving paralysing agents. We decided against including the level of consciousness in weaning eligibility criteria as it is more an extubation criterion and because the management of sedation is potentially a modifiable factor regarding the duration of invasive mechanical ventilation.

Because the beginning of weaning is not easily identified, for the purpose of our analysis, a patient was considered to be formally in the weaning phase when a first attempt at separating a patient from the ventilator was performed.[16] In intubated patients, a separation attempt was defined as a spontaneous breathing trial (ie, a short period of decreased or absent ventilator support to predict extubation success), or a direct extubation without spontaneous breathing trial. For tracheostomised patients, a separation attempt was defined as a short period of either T-tube trial, low respiratory support (ie, continuous positive airway pressure of ≤5 cm H_2O, or pressure support ventilation with PEEP ≤5 cm H_2O and pressure support ≤7 cm H_2O), a short period of tracheostomy mask oxygenation, or a spontaneous breathing trial as declared by the investigator. A delay in attempting ventilator separation was defined as an interval of greater than 1 day between fulfilment of weaning eligibility criteria and the first separation attempt.

In intubated patients, weaning success was defined as extubation without death or reintubation within the next 7 days, or discharge from the study intensive care unit without invasive mechanical ventilation within 7 days, whichever came first.[16] For tracheostomised patients, weaning success was defined as spontaneous ventilation through tracheostomy without any mechanical ventilation during 7 consecutive days or discharged from the intensive care unit with unassisted breathing, whichever came first. Thus, we defined weaning duration as the number of days from the first separation attempt to weaning success.

We used a modified version of the WIND classification to define five groups of patients.[16] The no separation attempt group included patients who never had a separation attempt in the participating intensive care unit (patients who died or were transferred to another intensive care unit before the first separation attempt). The short wean group included patients who were successfully weaned within 1 day after the first separation attempt. The intermediate wean group included patients who were successfully weaned more than 1 day but less than 7 days following the first separation attempt. The prolonged wean group included patients who were successfully weaned at least 7 days after the first separation attempt (up to the follow-up limit of 90 days after intubation). The failed wean group included patients who underwent a separation attempt and had ongoing requirement for invasive ventilatory support at day 90 or at transfer out of the intensive care unit (if sooner), or death (without successful weaning).

We used the 2017 World Bank countries classification for gross national income per person to define three major geo-economic groups: high-income countries in Europe, high-income countries in the rest of the world, and middle-income countries. Frailty was assessed at admission to the intensive care unit, and was defined as a score of 5 or more on the clinical frailty scale, which corresponds to participants who are mildly, moderately, severely, or very severely frail.[17,18] Patients' level of consciousness at different stages of their course in the intensive care unit were classified in three groups: awake, moderate sedation, and deep sedation (for details, see appendix p 8). For all Sequential Organ Failure Assessment (SOFA) scores for which data points were missing, this value was omitted and the denominator adjusted accordingly. For computing the non-neurological SOFA score, the neurological component of the score was omitted and the denominator adjusted accordingly.

The site investigators were required to answer all queries raised by the electronic case report form before they could electronically finalise a patient dataset. Before analysis, all data were screened for potentially erroneous data and outliers; these data were verified or corrected by WEAN SAFE site investigators. Outlier data were carefully searched, and queries were sent to investigators to confirm or correct.

We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement guidelines for observational cohort studies (appendix pp 73–75).[19] Additional detailed definitions and descriptions of the procedures for data quality control are included in the appendix (pp 1–7).

Outcomes

The primary outcome was the proportion of patients requiring invasive mechanical ventilation for at least 2 days who successfully weaned from invasive ventilation at day 90. Secondary outcomes were the proportion of patients who underwent a separation attempt, the rate and timing of tracheostomy, identification of time intervals between meeting weaning eligibility criteria and the first separation attempt, risk factors for delayed weaning initiation and for weaning failure, intensive care unit and hospital mortality, and description of the population according to a modified WIND classification[16] based on weaning duration as described above.

Statistical analysis

To ensure a robust globally representative and geographically diverse patient cohort, we chose to enrol a convenience sample of approximately 5000 patients. On the basis of the LUNG SAFE study,[20] we estimated the enrolment of approximately 11 patients invasively ventilated on day 2 following intubation per participating intensive care unit in a 4 week period. We therefore targeted the enrolment of approximately 500 participating intensive care units (considering a 10% dropout).

Continuous variables are reported as mean (SD) or median (IQR) and categorical variables as count and proportion. Normality of the data distribution was visually assessed by means of histograms. Proportions were compared using χ^2 or Fisher exact tests and continuous variables were compared using Student's *t* test or Wilcoxon rank sum test when two groups were

Correspondence to:
Prof John G Laffey, Anaesthesia and Intensive Care Medicine, School of Medicine, Clinical Sciences Institute, University of Galway, Newcastle H91 TK33, Galway, Ireland
john.laffey@nuigalway.ie

See **Online** for appendix

compared; and one way analysis of variance or Kruskal-Wallis tests when more than two groups were compared, as appropriate. When the overall difference was statistically significant, Tukey's range tests were then used to compare all possible pairs of means within the groups. We assumed that patients discharged alive from hospital before 90 days were alive on day 90.

To determine variables associated with a delay in initiation of weaning in the patients who had at least one separation attempt, and due to the hierarchical structure of the data, we used a mixed effect logistic regression. This was a three-level random intercept binary logistic regression: level 1 comprised patient-related variables (eg, age, type of admission, comorbidities, and severity), level 2 comprised intensive-care-unit-level variables (number of beds and use of weaning protocols), and level 3 comprised a country-level variable (gross national income group). We selected variables a priori on the basis of their clinical relevance or their expected association with the outcomes of interest (appendix pp 6–7). Results are shown as odds ratios (ORs) with 95% CIs. We used the same approach to identify factors associated with weaning failure in the patients who had at least one separation attempt. For both models (delayed initiation of weaning and weaning failure), we performed post-hoc sensitivity analyses repeating the analyses first without patients with neurological impairment (after cardiac arrest, neurosurgery, or non-traumatic neurological event), and second adding the number of beds available as an intensive-care-unit-level covariate. For the model identifying the factors associated with weaning failure, we also did a sensitivity analysis excluding patients transferred out of the participating intensive care unit who were still receiving mechanical ventilation.

Patient trajectories in the intensive care unit were described graphically using a multistate model starting at intubation and transitioning over time to three different states: (1) successfully weaned, (2) transferred out of the participating intensive care unit and not weaned, and (3) deceased.[21,22]

No assumptions were made for missing data. Statistical analyses were done with R (version 4.1.0). All p values were two-sided, and values less than 0·05 were deemed statistically significant. This study is registered at ClinicalTrials.gov, NCT03255109.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Oct 4, 2017, and June 25, 2018, 10 232 patients were screened for eligibility. 5869 eligible patients admitted to the participating intensive care units who were still receiving invasive ventilation 2 calendar days after intubation were enrolled (figure 1). Median age of participants was 64 years (IQR 51–74), with 2242 (38·2%) women, 3627 (61·8%) men, and 3843 (65·5%) having at least one relevant comorbidity (table 1).

4523 (77·1%) patients underwent at least one separation attempt (figure 1) and 3817 (65·0%) patients were successfully weaned from ventilation at day 90 in the participating intensive care unit (figure 2A). Conversely, 237 (4·0%) patients were transferred before any separation attempt, 153 (2·6%) were transferred after at least one separation attempt and not successfully weaned, and 1662 (28·3%) died while invasively ventilated in the participating intensive care unit.

1742 (31·8%) of 5479 patients with complete follow-up in the participating intensive care units died in the intensive care unit (1109 [63·7%] of 1742 died before any separation attempt in the participating intensive care unit, 553 [31·7%] died in the participating intensive care unit after a separation attempt but were never weaned, and 80 [4·6%] did wean from ventilation but died in the intensive care unit). 2095 (38·3%) of 5465 patients with complete follow-up died in hospital, including 353 (16·8%) of 2095 patients who died in the hospital after discharge from intensive care (figure 1, table 1). Among the patients who died while still receiving

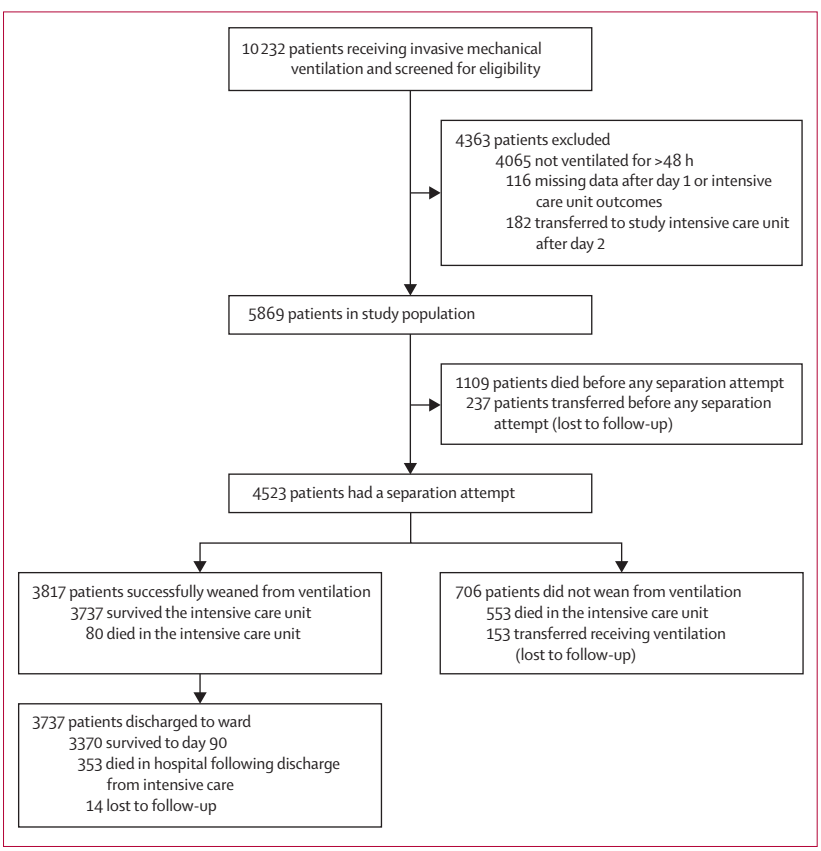

Figure 1: **Flow chart of patient screening and enrolment**

	Full patient population (n=5869)	Had at least one separation attempt		Never had a separation attempt because they died or transferred (n=1346)	p value*	Missing data
		Successfully weaned (n=3817)	Died or transferred without weaning success (n=706)			
Sex						
Female	2242 (38·2%)	1464 (38·4%)	290 (41·1%)	488 (36·3%)	0·010	0
Male	3627 (61·8%)	2353 (61·6%)	416 (58·9%)	858 (63·7%)	..	..
Age, years	64 (51–74)	62 (49–73)	66 (59–76)	66 (54–75)	<0·0001	0
Body-mass index, kg/m²	27·0 (6·9)	26·9 (7·0)	27·1 (7·5)	27·0 (6·5)	0·90	213 (3·6%)
Intensive care unit admission category	..	..	..	..	<0·0001	0
Medical	4035 (68·8%)	2488 (65·2%)	539 (76·3%)	1008 (74·9%)	..	..
Urgent surgery	881 (15·0%)	630 (16·5%)	82 (11·6%)	169 (12·6%)	..	..
Trauma	518 (8·8%)	357 (9·4%)	47 (6·7%)	114 (8·5%)	..	..
Planned surgery	435 (7·4%)	342 (9·0%)	38 (5·4%)	55 (4·1%)	..	..
Cause for intensive care unit admission						
Hypoxaemic respiratory failure	1954 (33·3%)	1238 (32·4%)	262 (37·1%)	454 (33·7%)	0·049	0
Sepsis	1335 (22·7%)	839 (22·0%)	164 (23·2%)	332 (24·7%)	0·12	0
Hypercapnic respiratory failure	837 (14·3%)	553 (14·5%)	109 (15·4%)	175 (13·0%)	0·26	0
Non-traumatic neurological event	845 (14·4%)	538 (14·1%)	118 (16·7%)	189 (14·0%)	0·17	0
Emergency surgery	796 (13·6%)	560 (14·7%)	81 (11·5%)	155 (11·5%)	0·0033	0
Airway protection	695 (11·8%)	486 (12·7%)	76 (10·8%)	133 (9·9%)	0·013	0
Cardiac arrest	593 (10·1%)	250 (6·5%)	116 (16·4%)	227 (16·9%)	<0·0001	0
Comorbidities and risk factors						
At least one comorbidity or risk factor	3843 (65·5%)	2415 (63·3%)	506 (71·7%)	922 (68·5%)	<0·0001	0
Diabetes	1283 (21·9%)	804 (21·1%)	167 (23·7%)	312 (23·2%)	0·13	0
Active smoker	824 (14·0%)	564 (14·8%)	90 (12·7%)	170 (12·6%)	0·86	0
COPD	801 (13·6%)	491 (12·9%)	124 (17·6%)	186 (13·8%)	0·0037	0
Chronic kidney disease	625 (10·6%)	369 (9·7%)	100 (14·2%)	156 (11·6%)	0·0008	0
With dialysis	162 (2·8%)	92 (2·4%)	25 (3·5%)	45 (3·3%)	0·080	0
Interstitial or other lung diseases (excluding asthma or COPD)	350 (6·0%)	186 (4·9%)	55 (7·8%)	109 (8·1%)	<0·0001	0
Chronic cardiac failure	505 (8·6%)	317 (8·3%)	57 (8·1%)	131 (9·7%)	0·24	0
Alcohol abuse	505 (8·6%)	334 (8·8%)	68 (9·6%)	103 (7·7%)	0·27	0
Solid neoplasm	466 (7·9%)	262 (6·9%)	79 (11·2%)	125 (9·3%)	<0·0001	0
Immunosuppressed	373 (6·4%)	217 (5·7%)	57 (8·1%)	99 (7·4%)	0·013	0
Dementia	323 (5·5%)	201 (5·3%)	41 (5·8%)	81 (6·0%)	0·54	0
Frail	1305 (22·4%)	736 (19·4%)	221 (31·4%)	348 (26·2%)	<0·0001	50 (0·9%)
Outcomes						
Total duration of invasive mechanical ventilation, days	7 (4–12)	6 (4–11)	11 (7–18)	6 (4–11)	<0·0001	390 (6·6%)
Length of intensive care unit stay, days	10 (6–16)	10 (7–18)	12 (7–19)	7 (5–12)	<0·0001	391 (6·6%)†‡
Length of hospital stay, days	20 (11–35)	24 (15–41)	14 (8–24)	9 (5–18)	<0·0001	452 (7·7%)†‡
Intensive care unit mortality	1742 (31·8%)	80 (2·1%)	..	..	..	390 (6·6%)†
Hospital mortality	2095 (38·3%)	433 (11·4%)	..	..	..	404 (6·9%)†‡

Data are n (%), median (IQR), or mean (SD). Where data are missing, percentages are calculated on actual denominator. COPD=chronic obstructive pulmonary disease. *Overall comparison between the three groups. †For patients transferred to other institutions still receiving invasive mechanical ventilation (n=390), follow-up stopped at transfer from participating intensive care unit and mortality beyond this point was not collected. ‡Among patients discharged alive from the participating intensive care unit, one had missing data for intensive care unit length of stay, 62 had missing data for hospital length of stay, and 14 had missing data for hospital mortality.

Table 1: **Demographics and outcome data in full study population**

invasive mechanical ventilation, 1109 (66·7%) of 1662 died before any separation attempt in the participating intensive care unit and 553 (33·3%) died while in the weaning phase (figure 1).

4523 patients had at least one separation attempt, 3817 (84·4%) of whom weaned successfully and 706 (15·6%) of whom died or were transferred after a separation attempt and not successfully weaned

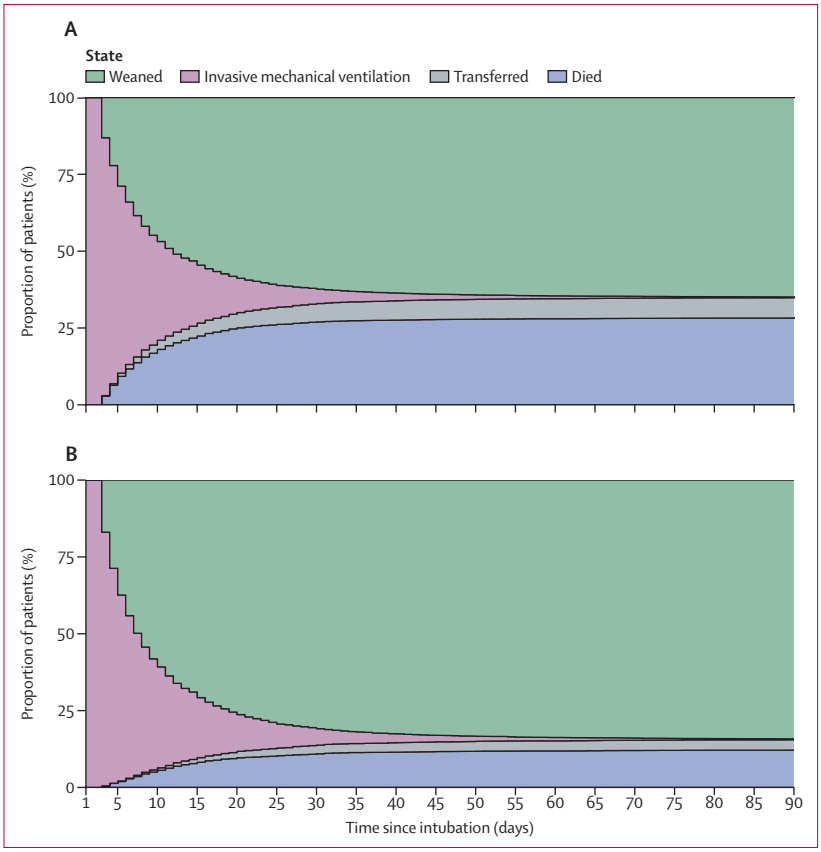

Figure 2: **Weaning process and outcomes in patients up to day 90**
(A) Weaning process and outcomes to day 90 in the full study population (n=5869). (B) Weaning process and outcomes to day 90 in the patients that underwent a separation attempt (n=4523).

(figure 2B; table 2). Of the 3817 patients successfully weaned from invasive mechanical ventilation in the participating intensive care unit, 433 (11·3%) died in the intensive care unit or in the hospital following discharge from intensive care (figure 1).

The timing of the different weaning events up to day 90 are shown in figure 3A, B (weaning events up to day 30 are shown in appendix pp 17–19). 5371 (91·5%) of 5869 patients met weaning eligibility criteria at a median of 3 days (IQR 3–4) following tracheal intubation. 5436 (92·6%) presented signs of spontaneous breathing activity at a median of 3 days (3–4) following tracheal intubation (figure 3A).

In the 4523 patients who had a separation attempt, the median time from weaning eligibility to first separation attempt was 1 day (IQR 0–4), and 1013 (22·4%) had a delay of 5 or more days from weaning eligibility to their first separation attempt (figure 3B, table 3, appendix p 18). The first separation attempt occurred a median of 5 days (4–8) after tracheal intubation (table 3). 2927 (64·7%) patients had a short weaning process (≤1 day), 457 (10·1%) had an intermediate (2–6 days) weaning process, and 433 (9·6%) had a prolonged (≥7 days) weaning process. The first separation attempt was a spontaneous breathing trial in 2986 (66·0%) patients, direct extubation in 925 (20·5%) patients, and a spontaneous breathing trial on a tracheostomy in 612 (13·5%) patients. The first spontaneous breathing trial occurred at a median of 5 days (IQR 3–7) after tracheal intubation.

In the 3817 patients who were weaned, 1198 (31·4%) never had a formal spontaneous breathing trial. The overall time from first separation attempt to weaning success was short at a median of 0 days (IQR 0–1), but varied considerably across the different groups with a median of 12 days (IQR 8–17) in the prolonged wean group (figure 3C, table 3).

1148 (19·6%) of 5869 patients had a tracheostomy at any point during the study period. Among the 4523 patients who had at least one separation attempt, weaning failure occurred in 706 (15·6%): 553 (12·2%) patients died during the weaning process at a median of 3 days (IQR 0–9) after their first separation attempt and 153 (3·4%) were transferred still ventilated at a median of 5 days (1–11) after the first separation attempt. Among the 3654 patients who had at least one extubation, 499 (13·7%) were reintubated; 147 (29·5%) of these patients did not survive the intensive care unit (table 3).

The factors independently associated with delayed initiation of the first separation attempt (>1 day after weaning eligibility) and weaning failure are shown in figure 4. Demographic factors associated with increased risk of delay in initiation included frailty, admission for trauma, and admission for non-trauma neurological events, whereas cardiac arrest was associated with decreased risk of delayed initiation (figure 4A, appendix p 9). Critical illness severity as measured by SOFA score was also associated with increased risk for delay in initiation (figure 4A). Among potentially modifiable factors, previous use of continuous neuromuscular blockade, and the presence of moderate or deep sedation levels on the first day of fulfilling weaning criteria were associated with delayed separation attempt (figure 4A). We performed two sensitivity analyses using the same approach, first including the number of intensive care unit beds in the analysis (appendix p 10); second, excluding patients with conditions that affect neurological status (post cardiac arrest, neurosurgery, or non-traumatic neurological event, appendix p 11) and sedation at time of weaning readiness remained strongly associated with weaning delays in both models.

We examined factors associated with weaning failure (ie, death while intubated or transfer out of the participating intensive care unit before weaning success, or still invasively ventilated at day 90) in patients who had at least one separation attempt (figure 4B, appendix p 12). Demographic factors independently associated with weaning failure were older age, being immunocompromised, and frailty. Critical illness-related factors associated with weaning failure were overall severity of critical illness as measured by (non-neurological) SOFA

	All patients with a separation attempt (n=4523)	Short wean <24 h (n=2927)	Intermediate wean (n=457)	Prolonged wean (n=433)	Died (n=553) or transferred (n=153) before weaning success	p value*	Missing data
Sex							
Female	1754 (38·8%)	1120 (38·3%)	171 (37·4%)	173 (40·0%)	290 (41·1%)	0·47	0
Male	2769 (61·2%)	1807 (61·7%)	286 (62·6%)	260 (60·0%)	416 (58·9%)	..	..
Age, years	60·9 (17·2)	59·7 (17·6)	60·8 (17·1)	60·3 (16·9)	66·4 (14·3)	<0·0001	0
Body-mass index, kg/m²	27·0 (7·1)	26·9 (7·1)	26·6 (6·0)	27·4 (7·3)	27·1 (7·5)	0·32	158 (3·5%)
Intensive care unit admission category	..	..	..	..	..	<0·0001	0
Medical	3027 (66·9%)	1899 (64·9%)	312 (68·3%)	277 (64·0%)	539 (76·3%)	..	..
Planned surgery	380 (8·4%)	287 (9·8%)	30 (6·6%)	25 (5·8%)	38 (5·4%)	..	..
Trauma	404 (8·9%)	250 (8·5%)	51 (11·2%)	56 (12·9%)	47 (6·7%)	..	..
Urgent surgery	712 (15·7%)	491 (16·8%)	64 (14·0%)	75 (17·3%)	82 (11·6%)	..	..
Cause for intensive care unit admission							
Hypoxaemic respiratory failure	1500 (33·2%)	921 (31·5%)	172 (37·6%)	145 (33·5%)	262 (37·1%)	<0·0001	0
Sepsis	1003 (22·2%)	635 (21·7%)	111 (24·3%)	93 (21·5%)	164 (23·2%)	0·54	0
Hypercapnic respiratory failure	662 (14·6%)	420 (14·3%)	71 (15·5%)	62 (14·3%)	109 (15·4%)	0·83	0
Non-traumatic neurological event	656 (14·5%)	385 (13·2%)	73 (16·0%)	80 (18·5%)	118 (16·7%)	0·0038	0
Emergency surgery	641 (14·2%)	425 (14·5%)	63 (13·8%)	72 (16·6%)	81 (11·5%)	0·081	0
Airway protection	562 (12·4%)	382 (13·1%)	53 (11·6%)	51 (11·8%)	76 (10·8%)	0·35	0
Cardiac arrest	366 (8·1%)	190 (6·5%)	27 (5·9%)	33 (7·6%)	116 (16·4%)	<0·0001	0
Comorbidities and risk factors							
At least one comorbidity or risk factor	2921 (64·6%)	1845 (63·0%)	301 (65·9%)	269 (62·1%)	506 (71·7%)	<0·0001	0
Diabetes	971 (21·5%)	635 (21·7%)	97 (21·2%)	72 (16·6%)	167 (23·7%)	0·044	0
Active smoker	654 (14·5%)	432 (14·8%)	67 (14·7%)	65 (15·0%)	90 (12·7%)	0·57	0
COPD	615 (13·6%)	381 (13·0%)	61 (13·3%)	49 (11·3%)	124 (17·6%)	0·0066	0
Chronic kidney disease	469 (10·4%)	278 (9·5%)	51 (11·2%)	40 (9·2%)	100 (14·2%)	0·0026	0
With dialysis	117 (2·6%)	75 (2·6%)	10 (2·2%)	7 (1·6%)	25 (3·5%)	0·22	0
Interstitial or other lung diseases (excluding asthma or COPD)	241 (5·3%)	137 (4·7%)	21 (4·6%)	28 (6·5%)	55 (7·8%)	0·0058	0
Chronic cardiac failure	374 (8·3%)	245 (8·4%)	38 (8·3%)	34 (7·9%)	57 (8·1%)	0·98	0
Alcohol abuse	402 (8·9%)	244 (8·3%)	43 (9·4%)	47 (10·9%)	68 (9·6%)	0·28	0
Solid neoplasm	341 (7·5%)	203 (6·9%)	30 (6·6%)	29 (6·7%)	79 (11·2%)	0·0011	0
Immunosuppressed	274 (6·1%)	172 (5·9%)	24 (5·3%)	21 (4·8%)	57 (8·1%)	0·077	0
Dementia	242 (5·4%)	145 (5·0%)	31 (6·8%)	25 (5·8%)	41 (5·8%)	0·36	0
Frail	957 (21·3%)	538 (18·5%)	97 (21·3%)	101 (23·4%)	221 (31·4%)	<0·0001	30 (0·7%)
Outcomes							
Total duration of invasive mechanical ventilation, days	7 (4–12)	5 (3–8)	10 (8–15)	20 (15–28)	11 (7–18)	<0·0001	153 (3·4%)
Length of intensive care unit stay, days	10 (7–18)	9 (6–13)	15 (11–22)	26 (19–37)	12 (7–19)	<0·0001	154 (3·4%)†‡
Length of hospital stay, days	23 (14–39)	21 (14–35)	32 (20–49)	47 (32–68)	14 (8–24)	<0·0001	213 (4·7%)†‡
Intensive care unit mortality	633 (14·5%)	52 (1·8%)	12 (2·6%)	16 (3·7%)	..	..	153 (3·4%)‡
Hospital mortality	986 (22·6%)	294 (10·1%)	62 (13·6%)	77 (17·9%)	..	..	167 (3·7%)†‡

Data are n (%), mean (SD), or median (IQR). Where data are missing, percentages are calculated on actual denominator. COPD=chronic obstructive pulmonary disease. *Overall comparison between the four groups. †For patients transferred to other institutions still receiving invasive mechanical ventilation (n=153), follow-up stopped at transfer from participating intensive care unit and mortality beyond this point was not collected. ‡Among patients discharged alive from the participating intensive care unit, one had missing data for intensive care unit length of stay, 60 for hospital length of stay, and 14 for hospital mortality.

Table 2: **Demographics and outcome data in patients with a separation attempt**

score, cardiac arrest, or non-traumatic neurological event as cause for intensive care unit admission, pre-existing limitations of care, and the degree of respiratory dysfunction (respiratory rate and lower partial pressure of arterial oxygen to FiO_2 ratio) and ventilatory assistance (dynamic driving pressure and PEEP) used at the time of first separation attempt. Among potentially modifiable factors, the presence of deep sedation levels at first separation attempt were associated with weaning failure; and the time interval from development of weaning eligibility criteria to the first separation attempt was independently associated with weaning failure.

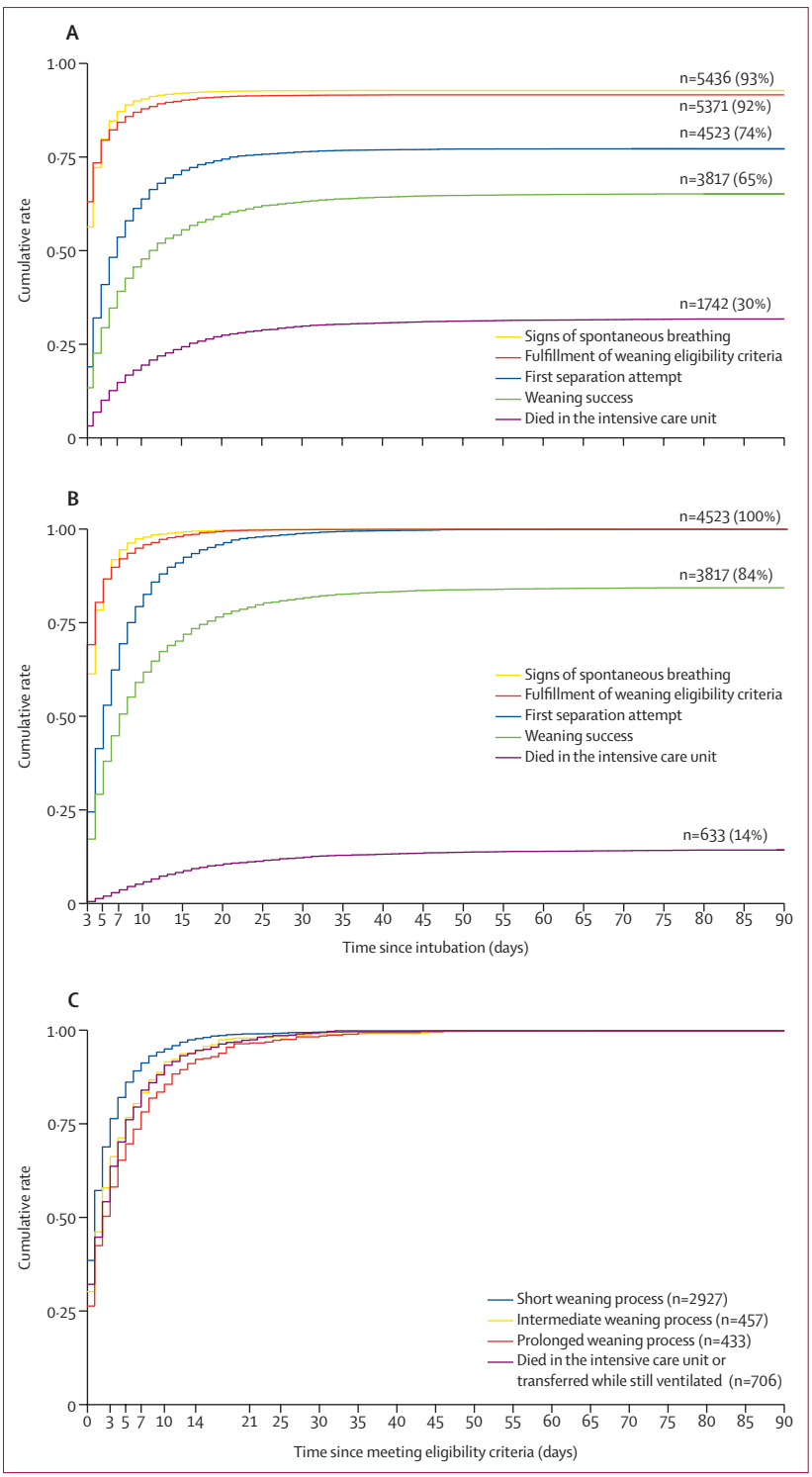

Figure 3: **Milestone events in the weaning process up to day 90**
(A) Cumulative frequency distributions of weaning related and outcome events in the full study population. (B) Cumulative frequency distributions of weaning related and outcome events in patients who entered the weaning process. (C) Cumulative frequency distributions of the delays between meeting weaning eligibility criteria and undergoing the first separation attempt.

Conversely, factors associated with weaning success included chronic cardiac failure as cause for admission.

We performed three sensitivity analyses using the same approach: first excluding patients transferred out of the participating intensive care unit still receiving invasive ventilation (appendix p 13); second including the number of intensive care unit beds in the analysis (appendix p 14); and third, excluding patients with conditions that affect neurological status (post-cardiac arrest, neurosurgery, and non-traumatic neurological event; appendix p 15), and found similar results each time. Particularly, sedation at time of weaning readiness remained strongly associated with weaning failure in all sensitivity analyses.

Discussion

In this large, prospective, international observational study, we report several novel and important findings. First, only 65·0% of patients receiving more than 2 days of invasive ventilation were successfully weaned at day 90 while in the participating intensive care unit. Second, a longer interval from meeting weaning eligibility criteria to the first separation attempt was independently associated with subsequent weaning failure. Third, we identified a key role of sedation at the time of weaning readiness in patients potentially ready to commence weaning in these delays. Reducing these delays by optimisation of sedation levels in patients during the recovery phase could potentially reduce the duration of invasive mechanical ventilation. Fourth, we identified significant patient-level variations in weaning practices, particularly in the use of spontaneous breathing trials. Fifth, we identified distinct patterns of weaning with very different outcomes across these patterns in this global dataset. In patients undergoing a separation attempt, 64·7% had a short wean, 10·1% had an intermediate wean, 9·6% had a prolonged wean, while 15·6% were not weaned from the ventilator, of whom 78·3% died in the study intensive care unit, highlighting the burden of delayed and failed weaning. Our findings therefore suggest that both variations in weaning practices and patients' physiological characteristics contribute to weaning failures.

Variations in weaning practices are an important concern[13,23] and differences exist in what should be considered the beginning of the weaning process. However, these differences are hard to study and interpret due to an absence of standardisation of definitions. The WIND classification is a recent approach to describe populations after they have received their first separation attempt, with regards to the difficulty of the weaning process and its influence on outcomes.[16] Several studies have used the WIND classification since its release, and showed its applicability.[13,23–25] The WIND classification includes patients entering the weaning process whose weaning process failed. We decided to modify this classification by identifying the group of patients who died after a separation attempt (without weaning success), and to apply this to our global weaning cohort.

	All patients with a separation attempt (n=4523)	Short wean <24 h (n=2927)	Intermediate wean (n=457)	Prolonged wean (n=433)	Died (n=553) or transferred (n=153) before successful weaning	p value*	Missing data
Weaning Milestones							
Number of extubations†							
0	869 (19·2%)	296 (10·1%)	124 (27·1%)	164 (37·9%)	285 (40·4%)	..	0
1	3363 (74·4%)	2592 (88·6%)	233 (51·0%)	155 (35·8%)	383 (54·2%)	..	0
2	249 (5·5%)	33 (1·1%)	95 (20·8%)	88 (20·3%)	33 (4·7%)	..	0
3	34 (0·8%)	5 (0·2%)	5 (1·1%)	19 (4·4%)	5 (0·7%)	..	0
4	8 (0·2%)	1 (0%)	0	7 (1·6%)	0	..	0
Reintubations	499 (13·7%)	48 (1·8%)	108 (32·4%)	193 (71·7%)	150 (35·6%)	<0·0001	0
Tracheostomy	967 (21·4%)	315 (10·8%)	144 (31·5%)	274 (63·3%)	234 (33·1%)	<0·0001	0
Tracheostomy already present at study day 3	137 (14·9%)	83 (29·1%)	21 (15·0%)	15 (5·6%)	18 (7·9%)	<0·0001	47 (0·5%)
Tracheostomy performed after at least one separation attempt	346 (35·8%)	19 (6·0%)	43 (29·9%)	174 (63·5%)	110 (47·0%)	<0·0001	0
Time intervals							
Intubation to weaning eligibility criteria, days	3 (3–4)	3 (3–4)	3 (3–4)	3 (3–5)	3 (3–5)	<0·0001	0
Intubation to signs of spontaneous breathing, days	3 (3–4)	3 (3–4)	3 (3–5)	4 (3–5)	3 (3–4)	<0·0001	0
Intubation to first separation attempt, days	5 (4–8)	5 (3–8)	6 (4–10)	7 (4–11)	6 (4–10)	<0·0001	0
Time from weaning eligibility criteria to first separation attempt, days	1 (0–4)	1 (0–3)	2 (0–5)	2 (0–7)	2 (0–5)	<0·0001	0
Time from intubation to first spontaneous breathing trial, days‡	5 (3–7)	4 (3–7)	5 (4–8)	6 (4–9)	6 (4–8)	<0·0001	0
Intubation to tracheostomy, days§	10 (6–15)	7 (3–12)	8 (6–12)	13 (9–18)	12 (8–16)	<0·0001	47 (0·5%)
Intubation to weaning success, days¶	6 (4–11)	5 (3–8)	10 (8–15)	20 (15–28)	NA	<0·0001	0
First separation attempt to weaning success, days¶	0 (0–1)	0 (0–0)	4 (2–5)	12 (8–17)	NA	<0·0001	0

Data are n (%) or median (IQR). Where data are missing, percentages are calculated on actual denominator. NA=not applicable. *Overall comparison between the four groups. †Some patients had tracheostomy before extubation, thus some patients had successful weaning without any extubation. ‡Among 3059 patients with at least one extubation. §Among 967 patients with a tracheostomy. ¶Among 3817 patients with a weaning success.

Table 3: **Weaning milestones and time intervals in patients with a separation attempt**

There is evidence of substantial variations in weaning practices in our global cohort. Although spontaneous breathing trials were used in more than two thirds of all patients during the weaning process, more than 30% of those who were successfully weaned never had a spontaneous breathing trial declared by the investigator. The distribution of direct extubation without spontaneous breathing trial, with initial spontaneous breathing trial, and with direct tracheostomy before any other separation attempt in WEAN SAFE compares well with findings from two other large international observational studies,[13,16] reinforcing the external validity of our results.

We identified variability in timings of key steps in the weaning process. Successful weaning occurred at the first separation attempt in nearly two thirds of patients. Although this high proportion might reflect good practices, it does not suggest how many patients could have had a separation attempt and been successfully weaned earlier. Conversely, clinical reasons other than sedation might explain why at least some patients had an interval of 5 or more days from meeting weaning eligibility criteria to having their first separation attempt.

Reintubation occurred in 13·7% of patients and their mortality was high at 29·5%. These figures are similar to previous findings of reintubation rates of 10–19% and mortality of 26–50% in reintubated patients.[26–28]

Multivariable analysis of factors associated with delayed first separation attempt showed that higher frailty scores and greater severity of critical illness were independently associated with delayed initiation of weaning. Multivariable analysis of factors associated with weaning failure showed that the time interval between meeting weaning eligibility criteria to the first separation attempt was independently associated with weaning failure. Interestingly, the amount of ventilatory support required at the time of the first attempt was also associated with failure. This might either reflect that these patients had a greater severity of critical illness or that the attempts were made sooner. In the latter case, daily assessment of weaning eligibility criteria should identify the optimal window to start the first separation attempt.

Of particular concern is the strong association between moderate and deep sedation levels and the risk of delayed weaning, and of weaning failure for deep sedation. We decided a priori not to include sedation levels in our eligibility criteria because this is a clinician modifiable factor, and this enabled an examination of its effect on the weaning process. Recent data, including from several

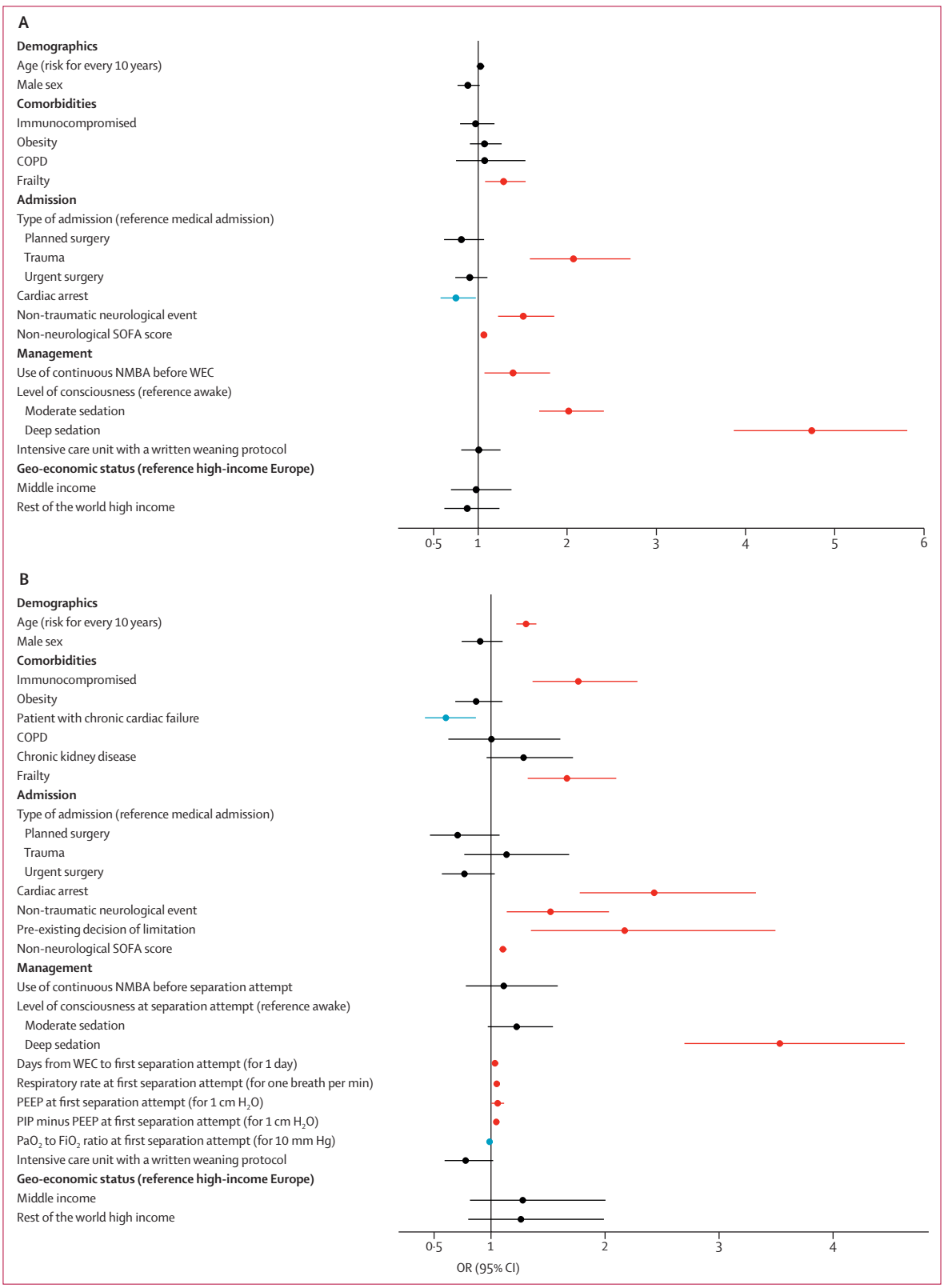

Figure 4: **Risk factors for weaning delays and weaning failure**

(A) Multilevel multivariable analyses showing the association between variables retained in the models and delayed initiation of weaning (ORs [95% CIs]). Blue dots and whiskers show variables significantly associated with lower risk of delayed initiation of weaning. Red dots and whiskers show variables associated with increased risk of delayed initiation of weaning. Black dots and whiskers show non-statistically significant ORs and 95% CIs. (B) Multilevel multivariable analyses showing the association between variables retained in the models and failed weaning. Blue dots and whiskers show variables significantly associated with lower risk of failed weaning (ORs [95% CIs]). Red dots and whiskers show variables associated with increased risk of failed weaning. Black dots and whiskers show non-statistically significant ORs and 95% CIs. COPD=chronic obstructive pulmonary disease. NMBA=neuromuscular blocking agents. OR=odds ratio. PEEP=positive end-expiratory pressure. PIP=peak inspiratory pressure. SOFA=Sequential Organ Failure Assessment. Pre-existing decision of limitation=decision to withhold or withdraw life sustaining treatments before intensive care unit admission. WEC=weaning eligibility criteria.

recent large randomised clinical trials, did not identify sedation as being associated with duration of mechanical ventilation or outcome.[29–31] Olsen and colleagues[29] analysed 700 patients who were randomly assigned to no sedation or light sedation and did not find any difference in ventilator-free days or mortality. In the SLEAP study, Mehta and colleagues[30] did not find any difference in duration of ventilation or mortality with daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol, despite the fact that a lower cumulative dose of sedatives was used in the sedation interruption group. Shehabi and colleagues[31] did not show a clinical benefit with the use of dexmedetomidine versus standard of care in critically ill patients. Our data show that the degree of sedation at the time of fulfilling weaning eligibility criteria and the degree of sedation at the moment of the first separation attempt have a strong influence on weaning delays and on weaning success rates, respectively. A greater degree of sedation delays the first assessment for separation of mechanical ventilation and increases the risk of weaning failure, which has a strong negative effect on patient outcome.

These data emphasise the need for greater attention to the modifiable factor of sedation level in patients before and during the weaning process to enhance the likelihood of weaning success. The feasibility of modifying sedation management has been shown in several randomised clinical trials,[11,29,32] including the ROSE trial in patients with acute respiratory distress syndrome, where light sedation could be achieved in a majority of patients after 72 h.[33] Our data confirm that sedation management is a major driver of delays in the subsequent weaning process. Our findings further suggest that incorporating sedation scores in weaning eligibility criteria in guidelines is not a good idea because it might impede the recognition of an important and modifiable cause of delay in weaning initiation and then weaning failure.

A strength of our study is that it was substantially larger in terms of number of patients enrolled, number of participating centres, and geographical spread than any previous weaning study. We focused on a higher risk population for weaning difficulties, namely patients requiring invasive ventilation for at least 2 full days, as evidenced by their need for longer durations of invasive mechanical ventilation and higher mortality compared with previous study populations.[13,16] We followed up patients for longer timeframes than previous studies, with our outcomes recorded up to day 90. We also used a more conservative definition of weaning success—ie, no reintubation within 7 days of extubation—than in previous studies, ensuring we captured events for longer timeframes after extubation. We consider this approach to be more rigorous than other weaning studies that used shorter periods,[13,16] as it minimises the potential for false positives for weaning success where patients are reintubated after 48 h.

This study has several limitations. Although all raw data were entered directly into the electronic case report form, the interpretation of source data (eg, radiographs) was done by on-site clinicians, which potentially increased variability. To ensure data quality, we instituted a robust data quality control programme in which all centres were requested to verify data that appeared inconsistent or erroneous. All data presented have been checked and verified. Due to the need to have a common definition across both tracheally intubated as well as tracheotomised patients, our definitions for weaning success did not distinguish between weaning and extubation, which is a potentially important distinction.[12]

Participating hospitals were representative of different levels of care and geography but, despite enrolling a large number of intensive care units from around the world, our convenience sample might be prone to selection biases. Our assumption that patients discharged from the hospital before day 90 were alive at that timepoint is a further limitation. Last, a small proportion of patients were lost to follow-up because they were transferred before the first separation attempt.

In this prospective observational study, 65% of patients who required invasive ventilation for at least 2 days were successfully weaned from invasive ventilation at day 90. Potentially important practice variations across patients were identified in the weaning process, with increased intervals from meeting weaning criteria to their first separation attempt independently related to weaning failure. Optimising sedation levels during weaning was identified as a key potentially modifiable variable to enhance weaning success rates. A better understanding of the reasons for these variations in weaning practice will be important in the future.

Contributors

GBel, JGL, TP, LH, and LB were responsible for study conception and design. TP, JGL, LB, GBel, and LH were responsible for the data cleaning and analysis. TP and JGL accessed and verified all the data in the study. TP, LH, GBel, JGL, and LB were responsible for the decision to submit for publication. All authors were responsible for data collection or clinical adjudication, and all authors had full access to all the data. GBel, JGL, TP, LH, and LB developed the first draft of the manuscript. All authors reviewed and edited the final version of the manuscript.

Declaration of interests

GBel reports a grant from Drager to his institution, consulting fees from Flowmeter, payments or honoraria from Drager and Getinge, and stock options in Dico technologies. LH reports funding from the European Respiratory Society to his institution in support of the study, grants from Liberate Medical and InflaRx to his institution, honoraria from Getinge and the American Thoracic Society, and reimbursement from the European Respiratory Society. ECG reports a grant from the Canadian Institutes of Health Research to his institution, payment or honoraria from Getinge, and travel support from Lungpacer. GG reports a grant from Fisher & Paykel, and payments or honoraria from Getinge, Drager Medical, Fisher & Paykel, and Cook Medical. LP reports fees received for participation as speaker to scientific conferences organised by Getinge, Fisher and Paykel, and Air Liquid System. AP reports receiving consulting fees from Baxter, Getinge, Boehringer Ingelheim, and Xenios, and payments or honoraria from Xenios and Getinge. LB reports grants from Medtronic, Drager, and Stimit to his institution, and honoraria and equipment received from Fisher Paykel. JGL reports funding from the European Society of

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Data sharing

The data in this manuscript are owned by the individual contributing institutions of the WEAN SAFE investigators, and the WEAN SAFE investigators have priority for a period of 6 months in regard to performing analyses on the dataset. Requests for data should be made to the WEAN SAFE Executive Committee, by way of email to the corresponding author. Any data provided will consist of de-identified participant with data dictionary, be restricted to the data presented in this paper, and be subject to a data sharing agreement.

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