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Impact of comorbidities on management and outcomes of patients weaning from invasive mechanical ventilation: insights from the WEAN SAFE study

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Abstract

Background The impact of comorbidities on patients weaning from invasive ventilation is incompletely understood. We wished to understand the impact of the number and type of comorbidities on patients' weaning from invasive mechanical ventilation enrolled in the 'WorldwidE AssessmeNt of Separation of pAtients From ventilatory assistancE (WEAN SAFE) study.

Methods The study population consisted of patients enrolled in the WEAN SAFE study that commenced the weaning process. We categorized patients by the number of comorbidities (none, 1, 2, or 3 plus), and by specific comorbidity type. The primary outcome was the impact of comorbidities on delayed weaning and failed weaning from invasive MV. Secondary outcomes included the impact of comorbidities on ICU and hospital survival, and decisions to limit life-sustaining interventions.

Results Of 4523 patients in the study population, 1614 (35.7%) had one comorbidity, 889 (19.7%) had two comorbidities, 432 (9.6%) had three or more comorbidities, while 1562 (34.5%) had no comorbidities. The most frequently occurring comorbid conditions were respiratory (22%) and cardiovascular (11%). Patients with comorbidities were more likely to fail a separation attempt, more likely to receive an extubation attempt, and to require more than 1 extubation attempt. The proportion of patients with failed weaning from invasive MV increased progressively with increasing comorbidities. Neuromuscular comorbidities were associated with increased weaning duration. Weaning failure was increased with respiratory, hepatic, renal, neuromuscular, and immune dysfunction comorbidities. Hospital mortality rates increased progressively from 16% with no comorbidity to 34% with ≥ 3 comorbidities. Each specific comorbidity was independently associated with increased hospital mortality. The presence of comorbidities was associated with decisions to limit life sustaining interventions.

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Conclusions Most patients weaning from invasive ventilation have comorbidities, which are associated with higher weaning failure risk and worse outcomes. The adverse impact of comorbidities on the weaning outcomes and of the process are not explained by a less aggressive approach to weaning.

Keywords Comorbidities, Chronic respiratory impairment, Chronic renal failure, Chronic liver failure, Immune suppression, Congestive heart failure, Diabetes

Background

Prolonged and failed weaning of patients from invasive mechanical ventilation (MV) presents a significant clinical challenge that has profound impacts on patient outcomes. Patients who experience difficulties in being successfully weaned from IMV have a higher mortality risk, while survivors are faced with a longer intensive care unit (ICU) and hospital stay [1–4].

The impact of comorbidities on the duration and outcomes of weaning from invasive ventilation remains incompletely understood [5]. Our understanding of how comorbidities influence the weaning process, which is essential for optimizing patient care and improving outcomes, warrants further investigation. This is increasingly important as the demographics of critically ill patients has shifted with aging populations, contributing to growing numbers of patients in ICU with one or more comorbid conditions [6–8]. Multiple studies have demonstrated an association between the presence of comorbidities and poorer outcomes in critically ill patients [9–11]. Elucidating this relationship could provide valuable insights that might improve clinical management strategies and optimise patient outcomes.

Our primary aim, in this secondary WEAN SAFE analysis, was to determine the impact of comorbidities on the management and outcomes of the weaning process in patients receiving invasive ventilation. Secondary aims included determination of the frequency of specific comorbidities, and impact of comorbidities on survival, and on end-of-life care, and the risk factors for delayed and failed weaning these patients.

Methods

Study design and setting

This is a pre-defined sub-study of the WEAN-SAFE study, an international, multicentre, prospective cohort study of patients undergoing invasive or non-invasive ventilation, conducted during 4 consecutive weeks in the between October 2017 and June 2018 in a convenience sample of 481 Intensive Care Units (ICUs) from 50 countries, across 5 continents, that recruited 5859 patients that required at least 2 days of invasive MV [1]. The study, jointly supported by the European Society of Intensive Care Medicine (ESICM) and the European Respiratory Society (ERS), was endorsed by multiple national societies/networks (Appendix 1). National coordinators and site investigators (Appendix 1) were responsible for obtaining ethics committee approval and for ensuring data integrity and validity.

Participants and data collection

All patients admitted to a participating ICU aged > 16 years, receiving invasive MV two calendar days after intubation, and providing informed consent (where required), were included in the WEAN SAFE study. The study population for this analysis consisted of all patients undergoing at least 1 separation attempt (Fig. 1). Patients transferred to other facilities before successful weaning were deemed lost to follow-up and their ICU and hospital outcomes were not collected. All data were recorded for each patient at the same time each day within participating ICUs, normally as close as possible to 10 am each day.

Data definitions

Our data definitions have been previously reported [1]. Briefly, initiation of weaning from invasive MV is defined as the time that the first separation attempt (SA) from the ventilator was performed [12]. A separation attempt was defined as a short period of either T-tube trial, low respiratory support (i.e., 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. Delayed initiation of weaning is defined as a delay of > 1 day from meeting weaning eligibility criteria to the first SA [1]. Increased weaning duration is defined as requiring > 1 day to wean from invasive MV following the first SA. Successful weaning is defined as no reintubation within 7 days of extubation. Weaning success is defined as extubation without death or reintubation within the next 7 days, or discharge from the study ICU without invasive MV within 7 days, whichever came first. For tracheostomised patients, weaning success was defined as spontaneous ventilation through tracheostomy without any MV during 7 consecutive days or discharged from the intensive care unit with unassisted breathing, whichever came first. We defined weaning failure as those

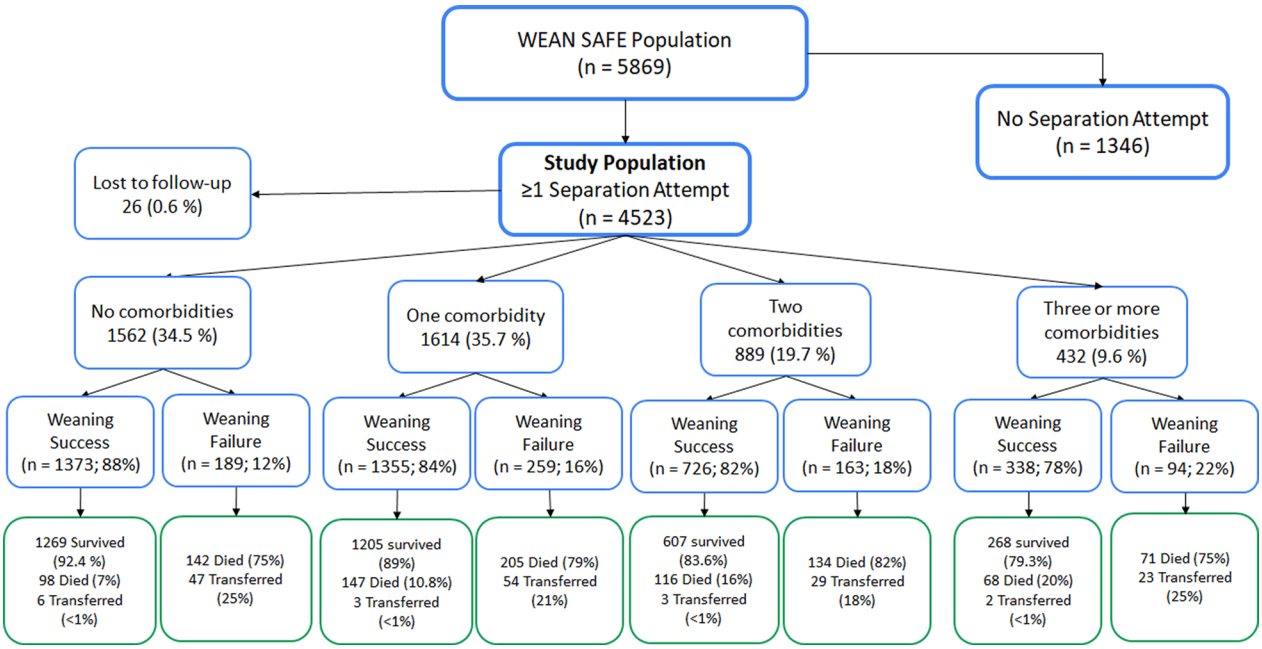


Fig. 1 Flow chart for impact of comorbidities on the Weaning process and outcomes. Of note, patients 'transferred' were transferred from the study ICU to another facility prior to discharge, and hence were lost to subsequent follow-up

Table 1 Definitions of comorbidities

Comorbidity	Specific disease/Condition	Severity assessment	Score
Respiratory	COPD	GOLD 1–2—Mild	+ 1 if one or more of these are present
		GOLD 3–4—Severe	
	Asthma	Requiring inhaled or oral medications	
	Other chronic lung disease		
	Kyphoscoliosis with respiratory dysfunction		
	Interstitial Lung Disease		
Cardiovascular	Heart failure	NYHA classes III-IV	+ 1 if one or more of these are present
	Pulmonary Hypertension		
Liver	Chronic Liver failure	Known or suspected	+ 1 if one or more of these are present
		Child Pugh score ≥ 10	
Kidney	Chronic Renal Failure	Creatinine Clearance < 30 mls per minute	+ 1 if one or more of these are present
		Chronic dialysis	
Neuromuscular	Dementia	Known or suspected	+ 1 if one or more of these are present
	Congenital/Acquired Myopathies/Neuropathies		
	Cognitive deterioration last 2/12		
	Alcohol misuse Disorder		
Immune 'Dysfunction'	Immune Compromised	Hematologic neoplasm	+ 1 if one or more of these are present
		Bone marrow transplant	
		Active Solid Organ Neoplasm	
	Immunosuppression		
Diabetes			+ 1 if present

patients that entered the weaning process, but who either died, were transferred, or were still invasively ventilated at day 90.

The pre-existing conditions that comprise each comorbidity were predefined and are reported in Table 1. We categorized patients by the number of comorbidities (none, 1, 2, or 3 plus), or by the specific type of comorbidity. Patients with more than one comorbidity appear in each relevant comorbidity category. Duration of invasive MV was calculated as the number of days between the date of intubation and the date of extubation in ICU (or death, if the patient died while receiving invasive MV). Survival was assessed at ICU discharge with follow-up extending up to 28 days, or at hospital discharge with follow-up extending up to 90 days. Information about the limitation of life-sustaining measures was also recorded.

Study outcomes

The primary outcome of the study was the impact of the number and specific type of comorbidities on delayed and failed weaning from invasive MV. Secondary outcomes included determination of the relationship between number and specific type of comorbidities on ICU and hospital survival, decisions to limit life-sustaining interventions, and the risk factors for delayed and failed weaning and for survival in these subgroups.

Statistical analysis

Descriptive statistics included proportions for categorical and mean (standard deviation) or median (interquartile range) for continuous variables. To compare the impact of the number of comorbidities on outcomes, patients were divided into four groups based on the number of comorbidities they had: no comorbidities, single comorbidity, 2 comorbidities, or 3 or more comorbidities. A Kaplan–Meier analysis was conducted to identify differences in time-to-event outcomes. To investigate the association of the number of comorbidities with outcomes, we used a logistic regression model. In all models, we accounted for patient age, and for admission reasons such as cardiac arrest, trauma, or non-traumatic neurological events. Furthermore, we adjusted for various weaning-related factors including decisions to limit life-sustaining interventions (not adjusted for when this was used as an outcome), the ratio of PaO_2 to FiO_2 (P/F ratio), dynamic driving pressure, respiratory rate, PEEP (Positive End-Expiratory Pressure), sedation levels, and sequential organ failure assessment (SOFA) score on the day of the first SA. Additionally, we examined whether the patient received paralyzing medication before the first weaning attempt. These variables were chosen in advance based on previous research on ICU weaning duration.

We report the Odds Ratios (OR) for the logistic regression models along with 95% confidence intervals and p values. All analyses were carried out in R software, version 4.4. (R Project for Statistical Computing, http://www.R-project.org).

Results

Of the 5869 patients admitted to the participating ICU from 481 centres across 50 countries worldwide that were still receiving invasive ventilation two calendar days after intubation, 4523 (80%) patients entered the weaning process (i.e. underwent a SA), and constitute the study sample (Fig. 1). Of these, 1614 (35.7%) had one comorbidity, 889 (35.7%) had two comorbidities, 432 (9.6%) had three or more comorbidities, while 1562 (34.5%) had no comorbidities (Table 2). The most frequently occurring comorbid conditions were neuromuscular (n = 1044, 23.3%, respiratory (n = 975, 21.6%), diabetes (n = 971, 21.5%) cardiovascular (n = 501, 11.1%), followed by immune dysfunction (n = 637, 14.1%), renal (n = 469, 10.4%), and hepatic (n = 199, 4.4%) (Fig. e1). Patients with higher comorbidity scores tended to be older and frailer than those without comorbidities (Table 2).

Initiation of weaning

The frequency of moderate and deep sedation at the time of fulfilling weaning eligibility criteria was lower in patients with comorbidities (Table 3). The effect of the type and number of comorbidities on the timing of weaning initiation was limited (Fig. 2A; Fig. e2A). In fact, the frequency of delayed weaning initiation was reduced in patients with comorbidities (Table 3; Fig. 2A; Fig. e2A). In multivariable analyses, the presence of respiratory (OR = 0.79, CI = 0.67, 0.94, $p = 0.01$) or cardiovascular (OR = 0.54, CI = 0.43, 0.66, $p < 0.01$) comorbidities were both independently associated with a reduced risk of delayed weaning initiation. There was no association between hepatic, renal, neuromuscular, immune dysfunction, and diabetes and timing of weaning initiation (Fig. 3A). The presence or number of comorbidities were not independently associated with timing of weaning initiation (eTable 1).

Weaning events and milestones

Patients with comorbidities had more separation attempts, and more failed separation attempts (Table 3). The type of separation attempt differed in patients with comorbidities, with more patients receiving SBTs compared to those with no comorbidities. The number of SBTs was increased in patients with 1 or more comorbidities (Table 3). The percentage of patients that underwent an extubation attempt, and the number extubation attempts, and the number of

Table 2 Demographics and outcome data in patients that entered the weaning process

	No comorbidities (n = 1562, 34.7%)	One comorbidity (n = 1614, 35.9%)	Two comorbidities (n = 889, 19.8%)	Three + comorbidities (n = 432, 9.6%)	Missing data N (%)	*p* value*
Sex: Female	600 (38%)	656 (41%)	332 (37%)	158 (37%)	26 (0.6%)	0.3
Age	56 ± 19	62 ± 17	66 ± 14	68 ± 12	26 (0.6%)	< 0.001
Body Mass Index	27 ± 6	27 ± 7	27 ± 7	28 ± 8	161 (3.6%)	0.038
ICU admission category						
Medical	839 (54%)	1,111 (69%)	705 (79%)	357 (83%)	26 (0.6%)	< 0.001
Planned Surgery	121 (8%)	171 (10%)	59 (7%)	26 (6%)		
Trauma	285 (18%)	76 (5%)	27 (3%)	12 (3%)		
Urgent Surgery	317 (20%)	256 (16%)	98 (11%)	37 (8%)		
Cause(s) for ICU admission						
Hypoxemic respiratory failure	370 (24%)	571 (35%)	362 (41%)	196 (45%)	26 (0.6%)	< 0.001
Sepsis	254 (16%)	394 (24%)	243 (27%)	112 (26%)	26 (0.6%)	< 0.001
Hypercapnic respiratory failure	92 (5.9%)	240 (15%)	205 (23%)	125 (29%)	26 (0.6%)	< 0.001
Non traumatic neurological event	284 (18%)	217 (13%)	111 (12%)	44 (10%)	26 (0.6%)	< 0.001
Emergency surgery	287 (18%)	225 (14%)	93 (10%)	35 (8.1%)	26 (0.6%)	< 0.001
Airway protection	190 (12%)	196 (12%)	119 (13%)	57 (13%)	26 (0.6%)	0.8
Cardiac arrest	140 (9.0%)	128 (7.9%)	66 (7.4%)	31 (7.2%)	26 (0.6%)	0.4
Comorbidities and risk factors						
Respiratory	0 (0%)	349 (22%)	367 (41%)	259 (60%)	26 (0.6%)	< 0.001
Cardiovascular	0 (0%)	126 (8%)	174 (20%)	201 (47%)	26 (0.6%)	< 0.001
Liver	0 (0%)	36 (2%)	89 (10%)	74 (17%)	26 (0.6%)	< 0.001
Kidney	0 (0%)	95 (6%)	176 (20%)	198 (46%)	26 (0.6%)	< 0.001
Neuromuscular	0 (0%)	412 (26%)	388 (44%)	244 (56%)	26 (0.6%)	< 0.001
Immune Dysfunction	0 (0%)	267 (17%)	213 (24%)	157 (36%)	26 (0.6%)	< 0.001
Diabetes	0 (0%)	329 (20%)	373 (42%)	269 (62%)	26 (0.6%)	< 0.001
Outcomes						
Total duration of invasive mechanical ventilation, days	7 (4, 12)	7 (4, 12)	6 (4, 11)	7 (4, 12)	179 (4.0%)	0.8
Length of ICU stay, days	11 (7, 18)	11 (7, 18)	10 (7, 17)	11 (7, 18)	180 (4.0%)[$§]	0.4
Length of hospital stay, days	23 (14, 39)	24 (14, 42)	21 (14, 37)	23 (14, 38)	239 (5.3%)[$§]	0.031
Limitation of life sustaining interventions	195 (12%)	285 (18%)	197 (22%)	108 (25%)	26 (0.6%)	< 0.001
ICU mortality, n (%)	156 (10%)	239 (15%)	154 (18%)	83 (20%)	179 (4.0%)[$]	< 0.001
Hospital mortality, n (%)	240 (16%)	352 (23%)	250 (29%)	139 (34%)	193(4.3%)[$§]	< 0.001

The data are n (%), mean ± SD, or median (IQR)

* *p* value comparison between the four groups. Kruskal–Wallis for continuous and F-test for categorical

$: For patients transferred to other institutions still receiving invasive mechanical ventilation (n = 150), follow-up stopped at transfer from participating ICU and mortality beyond this point was not collected

§: Among patients discharged alive from the participating ICU, 1 has missing data for ICU length of stay, 60 for hospital length of stay and 14 for hospital mortality

failed extubations, were all increased in patients with 1 or more comorbidities (Table 3). The percentage of patients that received tracheostomies was reduced in patients with comorbidities. In contrast, the use of tracheostomies was higher in patients that failed to wean who had comorbidities (Table 3).

Duration and outcomes of weaning

The effect of the type and number of comorbidities on the duration of weaning was limited (Fig. 2B). In multivariable analyses, only the presence of neuromuscular comorbidities was independently associated (OR = 1.24, CI = 1.01, 1.51, $p = 0.04$) with increased weaning duration

Table 3 Weaning management and outcomes

	No comorbidities (n = 1562, 34.7%)	One comorbidity (n = 1614, 35.9%)	Two comorbidities (n = 889, 19.8%)	Three + comorbidities (n = 432, 9.6%)	Missing data N (%)	*p* value*
Delayed initiation of weaning	785 (50.3%)	730 (45.2%)	409 (46.0%)	202 (46.8%)	26 (0.6%)	0.031
Sedation on the first day of fulfilling WEC						
Awake	344 (22.3%)	426 (26.9%)	227 (26.0%)	114 (26.6%)	61 (1.3%)	< 0.001
Moderate sedation	639 (41.3%)	667 (42.0%)	411 (47.1%)	221 (51.6%)		
Deep sedation	563 (36.4%)	494 (31.1%)	235 (26.9%)	93 (21.8%)		
Number separation attempts						
1	800 (51.2%)	771 (47.8%)	407 (45.8%)	183 (42.4%)	26 (0.6%)	0.017
2	424 (27.2%)	443 (27.4%)	265 (29.8%)	136 (31.5%)		
≥ 3	338 (21.6%)	400 (24.8%)	217 (24.4%)	113 (26.1%)		
First separation attempt type						
Direct Extubation	373 (23.9%)	314 (19.5%)	163 (18.3%)	65 (15.0%)	26 (0.6%)	< 0.001
SBT	926 (59.3%)	1091 (67.6%)	636 (71.5%)	308 (71.3%)		
PSV on trach	263 (16.8%)	209 (12.9%)	90 (10.1%)	59 (13.7%)		
Number of spontaneous breathing trials						
0	617 (39.5%)	491 (30.4%)	232 (26.1%)	114 (26.4%)		
1	717 (45.9%)	834 (51.7%)	479 (53.9%)	224 (51.9%)	26 (0.6%)	< 0.001
2	126 (8.1%)	133 (8.2%)	98 (11.0%)	50 (11.6%)		
≥ 3	102 (6.5%)	156 (9.7%)	80 (9.0%)	44 (10.2%)		
Number of extubations						
0	333 (21.3%)	318 (19.7%)	137 (15.4%)	80 (18.5%)		
1	1141 (73.1%)	1189 (73.7%)	691 (77.8%)	318 (73.6%)	26 (0.6%)	0.001
2	78 (5.0%)	94 (5.8%)	51 (5.7%)	25 (5.8%)		
≥ 3	10 (0.6%)	13 (0.8%)	10 (1.1%)	9 (2.1%)		
Tracheostomy (n, %)						
All patients	374 (23.9%)	338 (20.9%)	159 (17.9%)	94 (21.8%)	26 (0.6%)	0.005
Patients with weaning failure (n = 706)	57 (30.2%)	86 (33.2%)	49 (30.1%)	42 (44.7%)	1 (0.1%)	0.069
Weaning outcomes						
Failed weaned	189 (12.1%)	259 (16.0%)	163 (18.3%)	94 (21.8%)	26 (0.6%)	< 0.001
Successfully weaned	1373 (87.9%)	1355 (84.0%)	726 (81.7%)	338 (78.2%)		
Weaning Duration (successfully weaned)						
Short Wean (≤ 1 day)	1065 (77.6%)	1018 (75.1%)	561 (77.3%)	261 (77.2%)	26 (0.6%)	0.2
Intermediate Wean (2–7 day)	145 (10.6%)	173 (12.8%)	96 (13.2%)	41 (12.1%)		
Prolonged Wean (> 7 days)	163 (11.9%)	164 (12.1%)	69 (9.5%)	36 (10.7%)		

The data are n (%)

* *p* value comparison between the four groups. F-test for categorical

$: For patients transferred to other institutions still receiving invasive mechanical ventilation (n = 150), follow-up stopped at transfer from participating ICU and mortality beyond this point was not collected

§: Among patients discharged alive from the participating ICU, 1 has missing data for ICU length of stay, 60 for hospital length of stay and 14 for hospital mortality

(Fig. 3B). The presence or number of comorbidities were not associated with duration of weaning (eTable 2).

The proportion of patients with failed weaning from invasive MV increased progressively with an increasing number of comorbidities (Fig. 2C; Fig. e2B). The presence of respiratory (OR = 1.38, CI = 1.10, 1.74, $p = 0.01$), hepatic (OR = 1.76, CI = 1.19, 2.56, $p < 0.01$), renal (OR = 1.52, CI = 1.15, 2.01, $p < 0.01$), neuromuscular (OR = 1.32, CI = 1.06, 1.66, $p = 0.01$), and immune dysfunction (OR = 1.78, CI = 1.39, 2.27, $p < 0.01$)) comorbidities were each independently associated with increased weaning failure (Fig. 3C). The presence of any one or more comorbidities were associated with an increased risk of weaning failure (1 comorbidity:

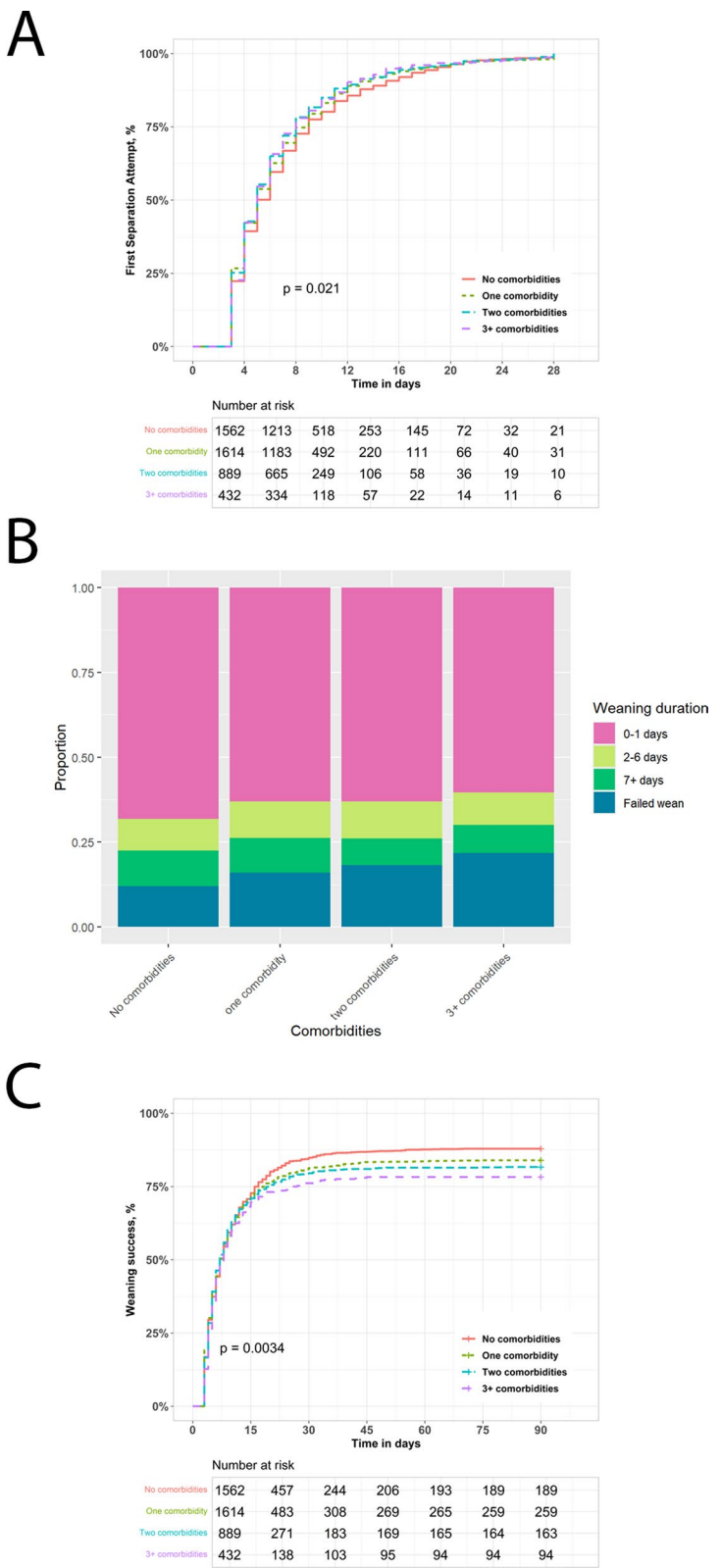


Fig. 2 Impact of comorbidities on weaning from invasive ventilation. Kaplan–Meier analysis of impact of comorbidities on likelihood of entering the weaning process (Panel A). Stacked bar chart of impact of comorbidities on weaning outcomes in the study population (Panel B). Kaplan–Meier analysis of impact of comorbidities on weaning success probability over time to Day 90 (Panel C)

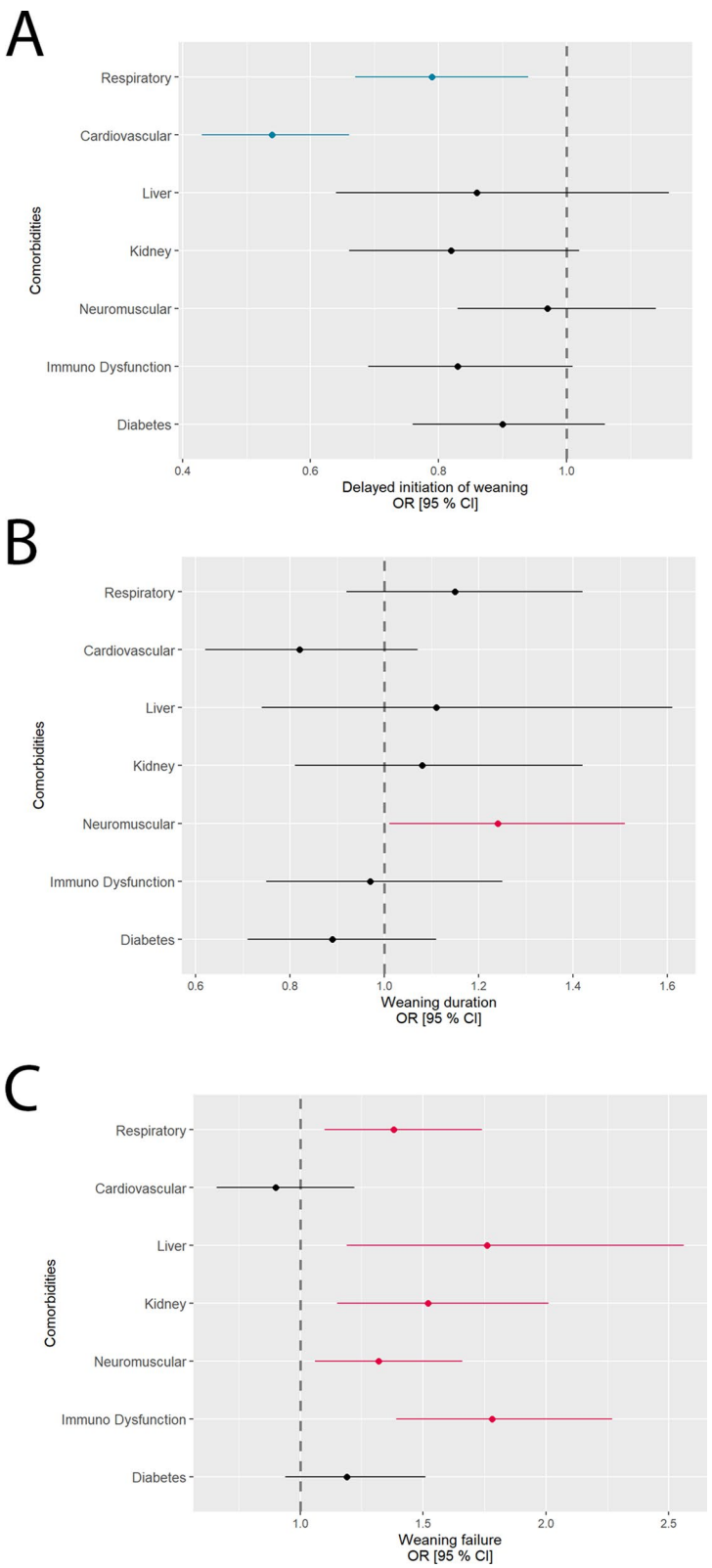
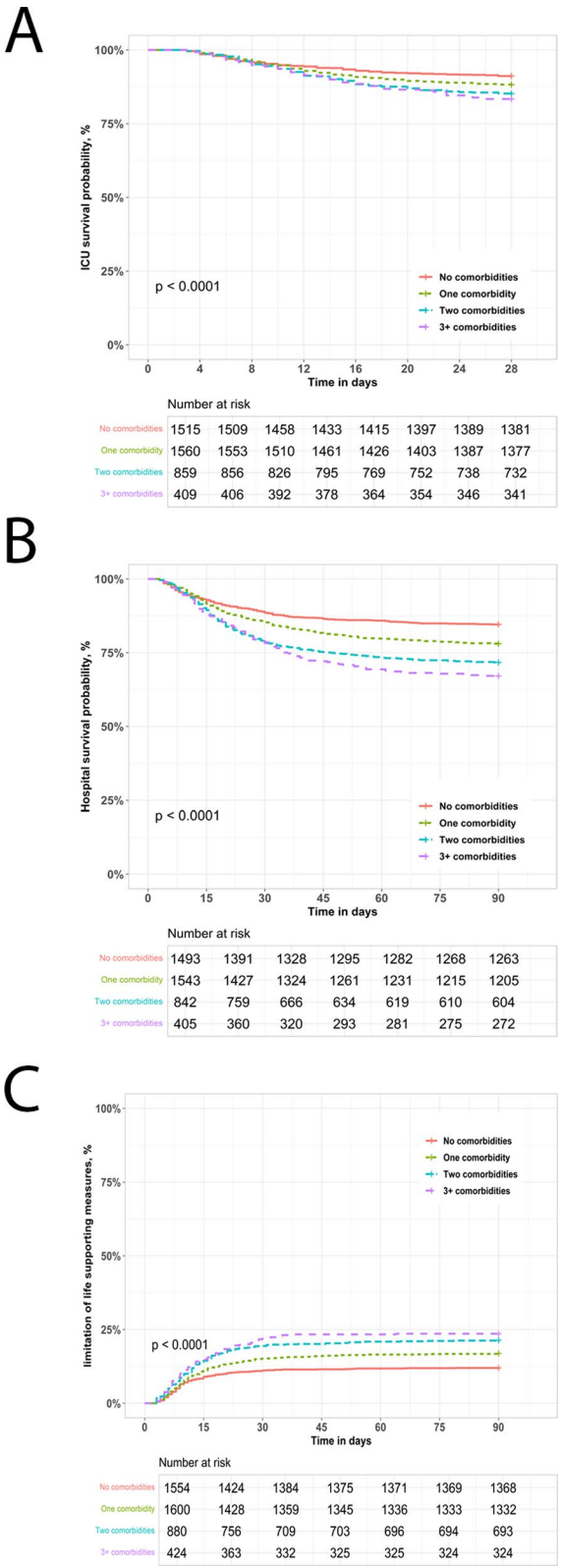


Fig. 3 Multivariable analyses of association between specific comorbidities and weaning milestones and outcomes. Multivariable analysis odds ratios for specific comorbidities and delayed initiation of weaning (Panel A), longer duration of weaning (Panel B), and failed weaning (Panel C), in patients that entered the weaning process



◀ **Fig. 4** Impact of comorbidities on clinical outcomes in patients weaning from invasive ventilation. Kaplan–Meier analysis of impact of comorbidities on ICU survival probability over time to Day 28 (Panel A). Kaplan–Meier analysis of impact of comorbidities on hospital survival probability over time to Day 90 (Panel B). Kaplan–Meier plot of impact of comorbidities on probability of limitation of life supporting measures (Panel C)

HR = 1.30, CI = 1.06, 1.84, $p = 0.03$; two comorbidities: HR = 1.40, CI = 1.06, 1.84, $p = 0.02$; three or more comorbidities: HR = 1.79, CI = 1.27, 2.50, $p < 0.01$; eTable 3).

ICU and hospital survival

ICU and hospital survival rates decreased progressively (Fig. 4A, B), while limitation of life supporting measures increased progressively, with increasing number of comorbidities, (Fig. 4C). In multivariable analyses, the presence of comorbidities was associated with worse outcomes, but relationship between comorbidities and clinical outcomes again varied by the type (Fig. 5) and number (eTables 4–6) of comorbidities. The presence of respiratory (OR = 1.43, CI = 1.12, 1.82, $p < 0.01$), hepatic (OR = 2.20, CI = 1.48, 3.23, $p < 0.01$), renal (OR = 1.91, CI = 1.43, 2.54, $p < 0.01$), neuromuscular (OR = 1.44, CI = 1.13, 1.83, $p < 0.01$), immune-related (OR = 1.95, CI = 1.50, 2.53, $p < 0.01$) comorbidities and diabetes (OR = 1.31, CI = 1.02, 1.68, $p = 0.03$) were each independently associated with an increased risk of ICU mortality. Of interest, the presence of cardiovascular comorbidities was not associated with increased ICU mortality risk (Fig. 5A). The number of comorbidities was independently associated with an increased risk of ICU mortality (1 comorbidity: OR = 1.45, CI = 1.12, 1.87, $p < 0.01$; two comorbidities: OR = 1.61, CI = 1.21, 2.15, $p < 0.01$; three or more comorbidities: OR = 1.96, CI = 1.37, 2.79, $p < 0.01$; eTable 4).

The presence of each specific comorbidity was independently associated with an increased risk of hospital mortality (respiratory: OR = 1.36, CI = 1.10, 1.67, $p < 0.01$; cardiovascular: OR = 1.34, CI = 1.03, 1.73, $p = 0.03$; hepatic: OR = 2.58, CI = 1.83, 3.60, $p < 0.01$; renal: OR = 2.02, CI = 1.57, 2.59, $p < 0.01$; neuromuscular: OR = 1.63, CI = 1.33, 2.00, $p < 0.01$; immune dysfunction: OR = 2.05, CI = 1.63, 2.57, $p < 0.01$; diabetes: OR = 1.43, CI = 1.16, 1.76, $p < 0.01$; Fig. 5B). When grouped together, the any one or more comorbidities were significantly associated to the increased risk of hospital mortality (adjusted; 1 comorbidity: HR = 1.44, CI = 1.16, 1.79, $p < 0.01$; two comorbidities: HR = 1.76, CI = 1.38, 2.25, $p < 0.01$; three or more comorbidities: HR = 2.38, CI = 1.76, 3.23, $p < 0.01$; eTable 5).

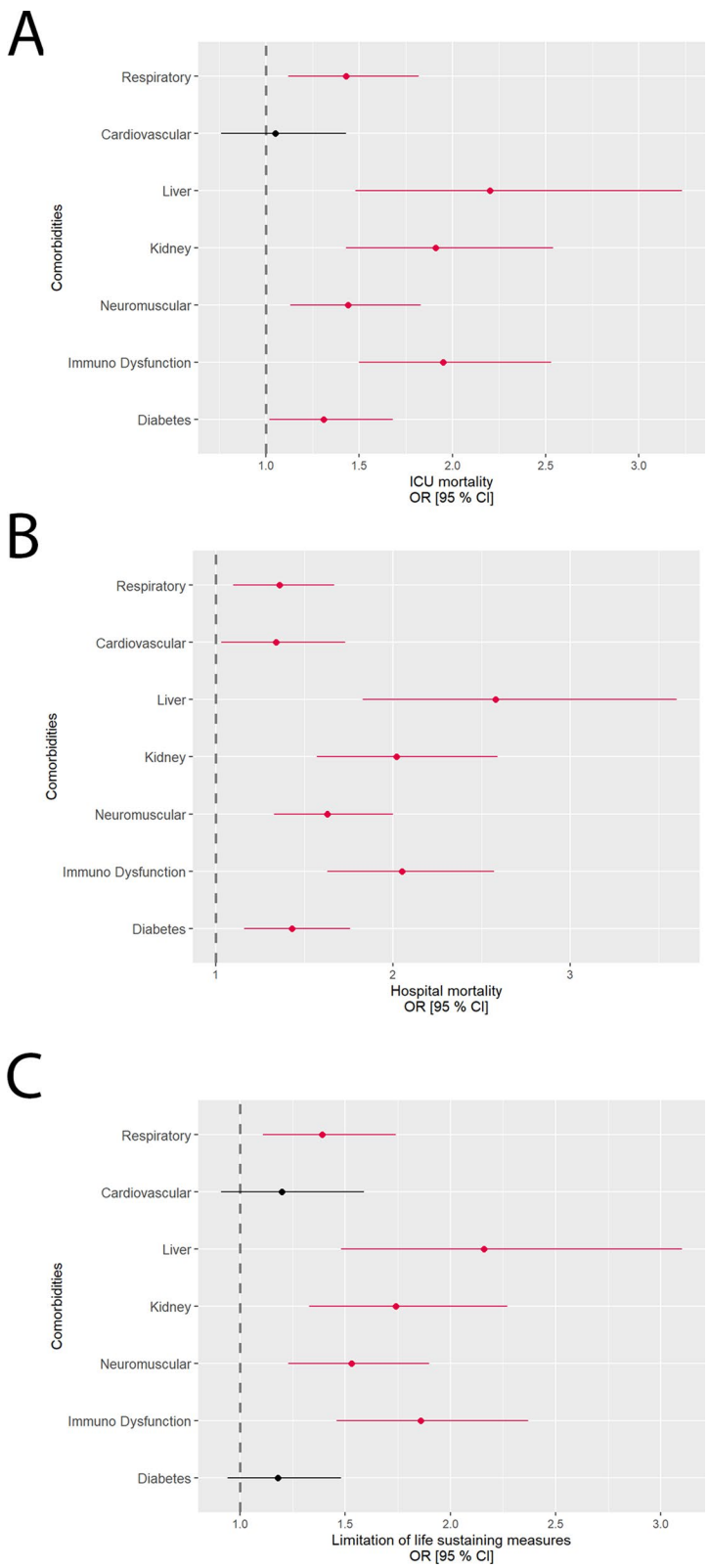


Fig. 5 Multivariable analyses of association between specific comorbidities and clinical outcomes. Multivariable analysis odds ratios for specific comorbidities and ICU mortality risk (Panel A), hospital mortality risk (Panel B), and likelihood of limitation of life sustaining measures (Panel C), in patients that entered the weaning process

Limitation of life supporting measures

The presence of any specific comorbidity, except for cardiovascular and diabetes comorbidities, was independently associated with an increased risk of limitations of life supporting measures (respiratory: OR = 1.39, CI = 1.11, 1.74, $p < 0.01$; hepatic: OR = 2.16, CI = 1.48, 3.10, $p < 0.01$; renal: OR = 1.74, CI = 1.33, 2.27, $p < 0.01$; neuromuscular: OR = 1.53, CI = 1.23, 1.90, $p < 0.01$; immune dysfunction: OR = 1.86, CI = 1.46, 2.37, $p < 0.01$; Fig. 5C). When grouped together, the presence of any one (or more) comorbidity was associated with an increased risk of limitations of life supporting measures (adjusted; 1 comorbidity: HR = 1.36, CI = 1.08, 1.73, $p = 0.01$; two comorbidities: HR = 1.52, CI = 1.16, 2.00, $p < 0.01$; three or more comorbidities: HR = 1.89, CI = 1.35, 2.62, $p < 0.01$; eTable 6).

Discussion

The potential for underlying comorbidities complicates the process of weaning from invasive MV, leading to prolonged mechanical ventilation (PMV) and increased rates of weaning failure, is increasingly recognised [5]. The mechanisms by which comorbidities may influence the process and outcomes from weaning are clear. Respiratory comorbidities may lead to increased work of breathing, while cardiovascular comorbidities may increase haemodynamic instability during weaning. Neuromuscular comorbidities include conditions that may either decrease level of consciousness or reduce muscle strength, while conditions like immune dysfunction and diabetes may increase coinfection risk [5, 13]. However, the impact of comorbidities on the key events within the weaning process, and the outcomes of weaning, remains incompletely understood.

We report that in the WEAN SAFE patient cohort, a large and geographically diverse cohort of 'real world' patients receiving invasive MV for at least 2 days, almost two thirds had at least one significant comorbidity. Patients with comorbidities were older and were more frequently admitted with acute medical conditions. Patients with comorbidities were less likely to enter the weaning process, illustrating the impact of comorbidities on outcomes from critical illnesses. They were more likely to fail to wean from invasive MV, with a stepwise increase in weaning failure rates with higher levels of comorbidity and were more likely to receive limitations in life-sustaining measures, and to die prior to ICU and hospital discharge.

Impact on weaning initiation

An important issue is whether the weaning process in patients with comorbidities is different, and whether there is potential to improve outcomes by optimizing our weaning approaches in these patients. Interestingly, the frequency of moderate and deep sedation at the time of fulfilling weaning eligibility criteria, an independent risk factor for failed weaning in the WEAN SAFE patient cohort [1], was lower in patients with comorbidities. Furthermore, the frequency of delayed weaning initiation was reduced in patients with comorbidities. The presence of respiratory or cardiovascular comorbidities, the 2 most frequently encountered comorbidities, were both independently associated with a reduced risk of delayed weaning initiation. This data suggests that clinicians, if anything, take steps to optimize sedation and to expedite the start of the weaning process in patients with comorbidities, perhaps because of an awareness of the potential for these comorbidities to impact on weaning success rates.

Impact on weaning events and milestones

Our data demonstrates that patients with comorbidities were more likely to undergo an SBT and were more likely to fail an SBTs as evidenced by the fact that more of them received multiple SBTs. These patients were also more likely to undergo an extubation attempt, and were more likely to fail an extubation attempt, as evidenced by the greater numbers of extubation attempts in these patients. The percentage of patients that received tracheostomies was reduced in patients with comorbidities. However, in patients that ultimately failed to wean, the percentage of tracheostomized was higher in those with 1 or more comorbidities. These data suggest that, in general, patients with comorbidities did not receive a less aggressive weaning approach when compared to the non-comorbid patient population.

Impact on weaning duration and outcomes

In patients that successfully weaned from invasive MV, the impact of comorbidities on the duration of weaning from invasive MV were limited. Only the presence of neuromuscular comorbidities was associated with increased weaning duration.

In contrast, the adverse impact of comorbidities on likelihood of successfully weaning from invasive MV were clear. The proportion of patients with failed weaning from invasive MV increased in a stepwise fashion, almost doubling from 12% with no comorbidity to 22% in patients with 3 or more comorbidities. When the relationship between specific comorbidity types weaning outcomes were examined, the presence of respiratory, hepatic, renal, neuromuscular, and immune dysfunction comorbidities were each independently associated with increased weaning failure risk.

Taken together, our findings suggest that the impact of comorbidities on the outcomes of the weaning process

are not explained by clinician use of a less aggressive approach to weaning in these patients.

Impact on clinical outcomes

The adverse effect of comorbidities on ICU and hospital survival rates in critically ill patients, including those with COVID-19, sepsis and ARDS, has previously been described [14, 15]. Patients with ARDS with comorbidities were less likely to receive invasive MV, neuromuscular blockade, prone positioning or ECMO [16]. They were more likely to receive limitations of life sustaining measures and had correspondingly worse ICU and hospital survival rates [16]. The potential for comorbidities to increase long term mortality post discharge has also been demonstrated [17].

In the WEAN SAFE cohort, the relationship between comorbidities and survival in patients weaning from invasive MV was marked. ICU and hospital mortality rates increased progressively with increasing number of comorbidities, with both rates doubled in patients with 3 or more comorbidities compared to those with no comorbidities. The presence of respiratory, hepatic, renal, neuromuscular, immune-related comorbidities and diabetes were each independently associated with an increased risk of ICU mortality. Of interest, the presence of cardiovascular comorbidities was not associated with ICU mortality risk. The presence of each specific comorbidity was independently associated with an increased risk of hospital mortality. Patients with comorbidities were more likely to more likely to have limitations in life-sustaining measures.

Taken together, given our findings that patients with comorbidities receive an aggressive approach to weaning, the effects of comorbidities on clinical outcomes may result instead from direct effects of these comorbid conditions on patient physiological reserves.

Strengths and limitations

Our study examines the impact of comorbidities in patients weaning from invasive MV, performed in a large, and globally diverse, patient cohort. Nevertheless, there are important limitations to consider. While all raw data was entered directly into the electronic case report form, the interpretation of source data was performed by on-site clinicians, which potentially increased variability. To ensure data quality, we instituted a robust data quality control program as previously described [1]. Participating hospitals were representative of different levels of care and geography but despite enrolling many ICUs from around the world, our convenience sample may be prone to selection biases. Our definition of weaning success and failure do not clearly distinguish between weaning failure and extubation failure. Our assumption that patients discharged from the hospital before day 90 were alive at that time point is a further limitation. Lastly, a small proportion of patients (4%) were lost to follow-up because they were transferred prior to the first separation attempt.

Conclusions

Almost two thirds of patients weaning from invasive MV had at least one significant comorbidity, with many having multiple comorbidities. Patients with comorbidities were older and were more frequently admitted with acute medical condition. The impact of comorbidities on the weaning process, on key events during the weaning period, and on the duration of weaning from invasive MV was limited. Despite this, patients with comorbidities were more likely to fail to wean from invasive MV, to receive limitations in life-sustaining measures, and to die prior to ICU and hospital discharge. In conclusion, it appears that the adverse impact of comorbidities on the weaning outcomes and of the process are not explained by clinician use of a less aggressive approach to weaning in these patients but may result from limitations in physiological reserve induced by their comorbid conditions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05341-7.

Additional file 1.

Additional file 2.

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Author contributions

OK, CL, RS, AS, BM, and JL conceived of and designed this study, interpreted the data, drafted the manuscript, and revised the manuscript for important intellectual content. LH, GB, TP, and LB contributed to the acquisition of data, conducted data cleaning, analyzed the data, interpreted the data, and revised the manuscript for important intellectual content. All authors interpreted the data and revised the manuscript for important intellectual content, and reviewed, discussed, and approved the final manuscript.

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Availability of data and material

The data in this manuscript are owned by the individual contributing institutions of the WEAN SAFE investigators. 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.

Declarations

Ethics approval and consent to participate
All participating ICUs obtained ethics committee approval and obtained either patient consent or ethics committee waiver of consent in the WEAN SAFE study. The WEAN SAFE study was registered at Clinicaltrials.gov, number NCT03255109.

Consent for publication
Not Applicable.

Competing Interests
CL, RS, OK, BM, and AS have no conflicts of interest to report. GB reports a grant from Drager to his institution, consulting fees from Flowmeter, payments/honoraria from Drager and Getinge, and stock options in Dico technologies. LH reports funding from the European Respiratory Society to his institution support the study; grants from Liberate Medical and InflaRx to his institution, honoraria from Getinge and American Thoracic Society and reimbursement from European Respiratory Society. LB reports grants from Medtronic, Drager and Stimity to his institution, honoraria and equipment received from Fisher Paykel. JGL reports grants from Science Foundation Ireland and Health Research Board Ireland to his institution, and consulting fees from Cellenkos.

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