

ORIGINAL



Distinct weaning phenotypes in patients unsuccessful in weaning from invasive mechanical ventilation: a secondary analysis of the WEAN SAFE cohort

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Abstract

Objective: To characterise the trajectories and outcomes of patients who enter the weaning process but fail to wean from invasive mechanical ventilation (MV).

Methods: In this secondary analysis of the Worldwide Assessment of Separation of pAtients From ventilatory assistancE (WEAN SAFE) cohort, we examined weaning duration and intensity, decisions to withdraw or withhold life-sustaining therapy (WLST), and clinical outcomes in patients not weaning from invasive ventilation. The primary outcome was ICU mortality.

Results: Of the 5664 patients in the study population, 1270 (22.4%) never underwent a separation attempt (SA), while 4394 (77.6%) had at least one SA; of these, 664 (15.1%) eventually failed weaning from invasive MV at day 90, while 3730 (65.9%) successfully weaned. Failed-Wean patients had the longest duration of invasive ventilation and longest ICU stay of all groups. Compared with Successful-Wean, Failed-Wean patients underwent more separation attempts, but fewer attempted extubations and more reintubations and tracheostomies. ICU mortality was 78% in Failed-Wean compared with 2% in Successful-Wean. Three clinically distinct Failed-Wean phenotypes were identified, distinguished by separation attempt count and WLST timing: Phenotype A (single SA + WLST), Phenotype B (single SA, no WLST), and Phenotype C (> 1 SA). A failed-first SA was strongly associated with WLST decisions. In this cohort, a WLST decision was associated with a higher hazard of ICU mortality and shorter median time to ICU death.

Conclusions: Three weaning failure phenotypes were identified with distinct clinical profiles, weaning trajectories, and outcomes. A strong relationship exists between failed first separation attempts, WLST decision, and the risk of death, which deserves further investigation.

Trial registration: ClinicalTrials.gov, NCT03255109.

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WEAN SAFE Investigators: A complete list of WEAN SAFE national coordinators, site investigators, and national societies endorsing the study can be found in the Online supplement.

Graphic abstract:

DISTINCT WEANING PHENOTYPES IN PATIENTS UNSUCCESSFUL IN WEANING FROM INVASIVE MECHANICAL VENTILATION: A SECONDARY ANALYSIS OF THE WEAN SAFE COHORT

Original Research

Background

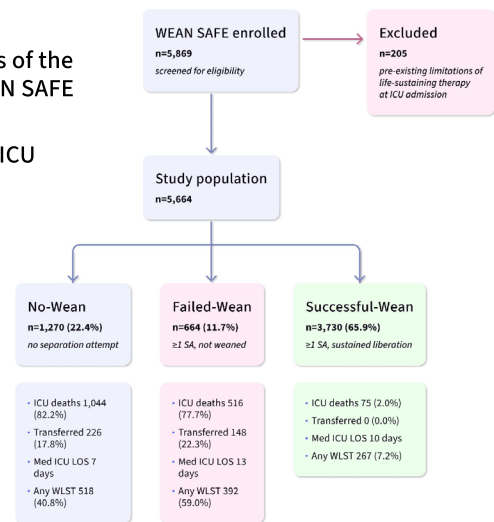
Failed weaning remains poorly characterized, despite being associated with prolonged ICU care and high mortality.

Study design

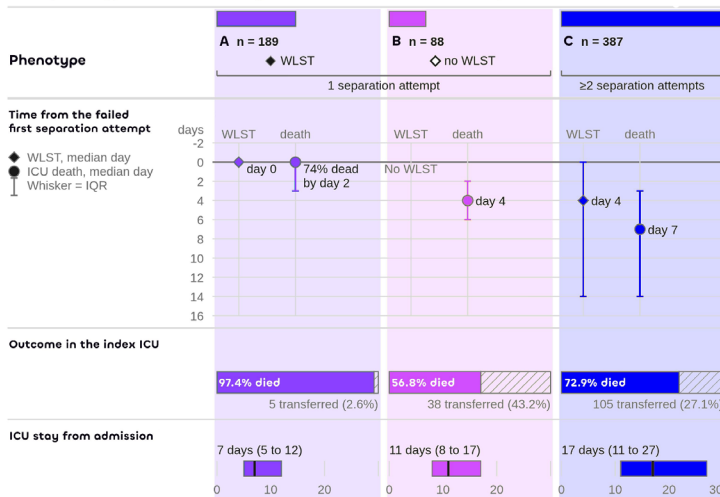
- Secondary analysis of the multinational WEAN SAFE cohort.
- Primary outcome: ICU mortality.

Results

- 15.1% of patients undergoing ≥ 1 separation attempt ultimately failed weaning by day 90.
- Failed weaning was associated with 78% ICU mortality, prolonged mechanical ventilation and ICU stay.
- Three distinct failed-weaning phenotypes with different mortality, WLST patterns and ICU trajectories were identified.



Three phenotypes of failed weaning: different reasons, different tempos



Findings

- A failed first separation attempt marked a critical turning point in subsequent clinical trajectory.
- WLST after a failed first separation attempt was associated with a 7-fold higher hazard of ICU mortality (HR 7.04).
- Failed weaning is not a single clinical entity and may warrant phenotype-specific prognostic assessment and individualized weaning strategies.

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Keywords: Weaning pattern, Weaning trajectory, Ventilator liberation, Invasive mechanical ventilation, Acute hypoxaemic respiratory failure, Failed Wean, WLST decisions

Introduction

Weaning failure, defined as the inability to achieve sustained liberation from invasive mechanical ventilation (MV), is a pivotal event leading to death from critical illness [1, 2]. Failed weaning has been associated with marked subsequent clinical deterioration [3], and can increase the risk for death, prolonged ICU stay, and need for transfer to a long-term care or rehabilitation facility [4]. Despite this, the weaning process and clinical trajectories in patients who experience weaning failure remain poorly understood. In addition, there is little consensus regarding what constitutes weaning failure. The international task force classification proposed by Boles and colleagues categorised weaning as simple, difficult, or prolonged, based on the number of spontaneous breathing trials and duration of weaning [5]. The WIND study subsequently proposed a refined classification based on duration from the first separation attempt (SA), demonstrating in a prospective European cohort of 2729 patients a stepwise increase in ICU mortality from 6% in short weaning to 17% in difficult weaning and 29% in prolonged weaning [2]. These frameworks have been valuable for epidemiological description; however, by classifying patients according to the trajectory towards successful liberation, they were not designed to characterise those who ultimately never achieve sustained independence from ventilatory support. Notably, the WIND classification grouped successfully weaned patients and those who ultimately failed within each duration tier and reported 29% ICU mortality among patients in its prolonged-weaning tier (Group 3), thus limiting its ability to characterise outcomes specific to weaning failure.

In the WEAN SAFE Study, the WIND definitions were expanded to include patients that failed to wean as a separate category, allowing for better understanding of this patient group [1]. In this secondary analysis of the WEAN SAFE cohort, we focused on patients who undergo an SA but fail to wean from invasive mechanical ventilation (i.e. 'Failed-Wean') patients. This group typically experiences a prolonged, resource-intensive clinical course and has poor overall outcomes. Our aim was to characterise the clinical course, weaning trajectories, and outcomes of Failed-Wean patients; compare them against patients who were successfully weaned, and against patients who never underwent an SA; determine whether clinically distinct phenotypes exist within the Failed-Wean group. ICU mortality and timing of death were expected to differ across weaning outcome groups, reflecting their differing illness trajectories. We hypothesised that within the Failed-Wean group, clinically distinct phenotypes would emerge based on separation attempt intensity and the use/timing of WLST decisions, and that a failed first

Take-home message:

Patients who enter the weaning process but fail to wean from invasive mechanical ventilation (MV) have an adverse ICU experience but are not well characterized. We show they comprise three distinct phenotypes, differentiated by the number of separation attempts and by the timing of any decision to withdraw or withhold life-sustaining therapy, and that a failed first separation attempt is strongly associated with both a subsequent WLST decision and a higher hazard of ICU death.

separation attempt would be independently associated with subsequent WLST decisions and mortality.

Methods

Study design and setting

This study is a secondary analysis of the Worldwide Assessment of Separation of pAtients From ventilatory assistance (WEAN SAFE) cohort. The primary WEAN SAFE Study protocol, data collection procedures, and participating centres have been described in detail previously [1]. Briefly, adult patients (>16 years) admitted to participating ICUs and receiving invasive mechanical ventilation were screened, and those still ventilated two calendar days after intubation were enrolled. Recruitment occurred during a pre-specified study week at each ICU. The study was registered (NCT03255109), and ethical approval and consent procedures were conducted in accordance with local regulations. From 5869 patients enrolled in the WEAN SAFE cohort, 205 with pre-existing limitations of life-sustaining therapy recorded at ICU admission were excluded, leaving 5664 patients in the study population.

Data definitions

Our data definitions have been previously reported [1]. Patients were considered to have entered the weaning process if they underwent at least one separation attempt (SA), defined as any deliberate effort to discontinue invasive ventilation, including spontaneous breathing trials, direct extubation, or tracheostomy weaning [1]. Weaning eligibility criteria (adapted from Boles et al. [5]) included $\text{FiO}_2 < 0.5$, $\text{PEEP} < 10 \text{ cmH}_2\text{O}$, minimal or no vasopressor support ($< 0.2 \text{ } \mu\text{g/kg/min}$ norepinephrine or equivalent), and absence of neuromuscular blocking agents [1]. 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 Table S1).

Weaning success is defined as extubation without death or reintubation within the following 7 days, or discharge from the study ICU without invasive MV within 7 days, whichever came first. For tracheostomised patients,

weaning success is 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 define weaning failure as those patients that entered the weaning process, but who either died, were transferred, or were still invasively ventilated at day 90. Extubation failure was defined as the need for reintubation within 7 days of extubation. Palliative extubations were defined as the planned removal of the endotracheal tube with full comfort and/or palliative care.

Patient classification

Patients were classified into three mutually exclusive groups based on weaning outcomes. The 'No-Wean' group included patients who never underwent an SA, including those who died or were transferred before any attempt. Palliative extubations were not considered to constitute SAs, as these extubations are performed for end-of-life care. The 'Successful-Wean' group included patients who achieved sustained liberation from invasive ventilation, defined as ≥ 7 days free of invasive ventilation without reintubation, per the WEAN SAFE protocol [1]. The 'Failed-Wean' group included patients who underwent at least one attempt but did not achieve sustained liberation. For ICU and hospital discharge status, patients discharged to other facilities while receiving invasive ventilation ($n=374$ patients) were classified as a separate 'transferred' outcome category alongside dead and alive. Mortality timing analyses included only patients who died in the participating ICU. Duration of mechanical ventilation analyses excluded transferred patients for whom this data was unavailable.

Outcomes

The primary outcome was ICU mortality. Secondary outcomes included timing of death, in-hospital mortality, ICU and hospital length of stay, and decisions to withdraw or withhold life-sustaining therapy (WLST). WLST captures any formal in-ICU decision to withhold or withdraw life-sustaining therapy, including do-not-resuscitate orders, comfort-care directives, palliative extubation, and withdrawal of vasopressors, renal replacement, or other organ-support modalities, consistent with the original WEAN SAFE definition [1]. Weaning process variables included number of SAs, spontaneous breathing trials (SBTs), extubations, and reintubations.

Time-matched physiological comparison: *P/F* ratio and SOFA at first SA were used directly for the Successful-Wean and Failed-Wean groups; for the No-Wean group, day-5 values were used as a population-level

proxy. Detailed handling is provided in the online supplement.

Mortality timing: Cumulative ICU mortality curves were generated for the three main groups and for the Failed-Wean subgroups; transferred patients were excluded because their date of death is unknown.

Failed SA subgroups: Within the Failed-Wean group, subgroup analyses compared patients with one SA versus more than one SA on physiological trajectory and WLST timing; full detail is provided in the online supplement.

Statistical analysis

Patient characteristics are reported as mean (standard deviation) for normally distributed variables, median (interquartile range) for non-normally distributed variables, and counts (percentages) for categorical data. Between-group comparisons used the Kruskal–Wallis test (three cohorts) or the Mann–Whitney *U* test (two groups) for continuous variables and the Chi-squared test for categorical variables, including diagnostic distributions across groups and phenotypes. Reported group *p* values are omnibus, and pairwise orderings are presented descriptively without formal post hoc adjustment. Analyses of physiological change were conducted using the same tests applied to per-patient delta values. Complete case analysis was applied, with sample size and missingness reported in tables and figures.

Statistical analyses used Python (v3.12; pandas, scipy, statsmodels, matplotlib) and R (v4.5; matchit, survival). A two-sided $p < 0.05$ was nominally significant. Comparisons of baseline and clinical characteristics across groups are descriptive and hypothesis generating and are presented without correction for multiple testing; the pre-specified inferential analyses (the multivariable logistic regression for WLST and the propensity-matched survival analysis) were not adjusted, as they were limited in number and specified a priori. No formal sample size calculation was undertaken.

Logistic regression evaluated the association between first SA outcome and in-ICU WLST decisions in two cohorts: all patients undergoing ≥ 1 SA, and a restricted cohort of patients whose first SA failed. The failed-first SA model was adjusted for the case-mix and physiological covariates listed in Table S2; the ≥ 1 SA analysis (Table S3) was univariable. Exposure was anchored on first SA outcome to ensure temporal precedence; in the failed-first SA cohort, the first SA term is encoded by cohort definition and is not separately estimable.

A propensity-matched analysis was done in patients failing the first SA ($n=1816$), of whom 68 with a pre-existing limitation of life-sustaining therapy at ICU

admission were excluded leaving 1748, to understand the relationship between WLST decisions and outcomes after controlling for physiological characteristics and illness severity. We performed 1:1 nearest-neighbour propensity-score matching (caliper 0.2 SD) of patients with a WLST decision after failed-first SA to those without a WLST decision after failed-first SA.

Patients were matched on baseline characteristics at the time of separation attempt; matching of 1495 patients with complete data yielded 736 matched patients. Because 1:1 caliper matching restricts comparisons to patients with overlapping baseline characteristics, the resulting hazard ratio applies to the subset of failed-first SA patients for whom comparable matches exist, not to the full no-WLST population. The model included case-mix (age, diagnoses, frailty, paralysis) and physiological variables at first SA (respiratory rate, *P/F* ratio, sedation, SOFA without GCS). Outcomes were analysed using a Cox proportional-hazards model; robustness to unmeasured confounding was assessed via the *E*-value [6].

Results

Cohort characteristics

Of the 5664 patients in the study population, 4394 (77.6%) underwent a separation attempt. Of these, 664 (15.1%) patients that underwent ≥ 1 SA (664/5664, 11.7%, of full study population) experienced weaning failure at day 90 (the Failed-Wean group); 3730 (65.9%) weaned successfully and 1270 (22.4%) never underwent an SA (No-Wean group) (Fig. 1). Failed-Wean patients were the oldest, most frail, and most comorbid, with admission and diagnostic profiles differing across groups (Table 1). As expected, baseline illness severity was highest in No-Wean and lowest in Successful-Wean patients (Table 1). At the first SA, Failed-Wean patients had higher SOFA scores, lower $\text{PaO}_2/\text{FiO}_2$ ratios, higher respiratory rates and driving pressures, and deeper sedation (all $p < 0.001$) than the other groups (Table 2, Fig. 2A, B).

Clinical trajectory during weaning phase

Among patients with at least one SA, the change in physiological variables from study entry (days 3–4 from ICU admission) to usual timing of first SA (i.e. days 5–7) differed across the patient groups. $\text{PaO}_2/\text{FiO}_2$ ratio was unchanged in Failed-Wean [median +3.3 mmHg (–35.1 to +44.4)] and improved in Successful-Wean groups [median +6.7 mmHg (–34.8 to +45.7)]. In contrast, in the No-Wean group, $\text{PaO}_2/\text{FiO}_2$ significantly worsened [median change –6.5 mmHg (IQR –48.8 to +32.0; $p < 0.001$) (Fig. 2A, B). SOFA score remained unchanged in Failed-Wean [median +0.2 (–2.0 to +2.0)], and in Successful-Wean [median 0.0 (–2.2 to +1.7)], but worsened

in the No-Wean group [median change +0.7 (IQR –1.2 to +2.8; $p < 0.001$).

Weaning process and milestones

A higher proportion of Failed-Wean patients underwent ≥ 2 SAs and ≥ 2 SBTs than those who weaned successfully (Fig. 2C–F, Table 3), reflecting the clinical intensity of the weaning effort. Among 489 reintubated patients, reintubation occurred a median of 1 day after extubation (IQR 0–3), with 80% within 3 days (Figure S1). Reintubation after day 3 was associated with worse outcomes than early reintubation, and this association persisted after adjustment for baseline severity (Table S4). Tracheostomy was more common in Failed-Wean than Successful-Wean patients (34.2% vs 19.4%, $p < 0.001$). Failed-Wean patients had the longest duration of invasive MV and ICU stay of all groups (Table S5, Figure S1A).

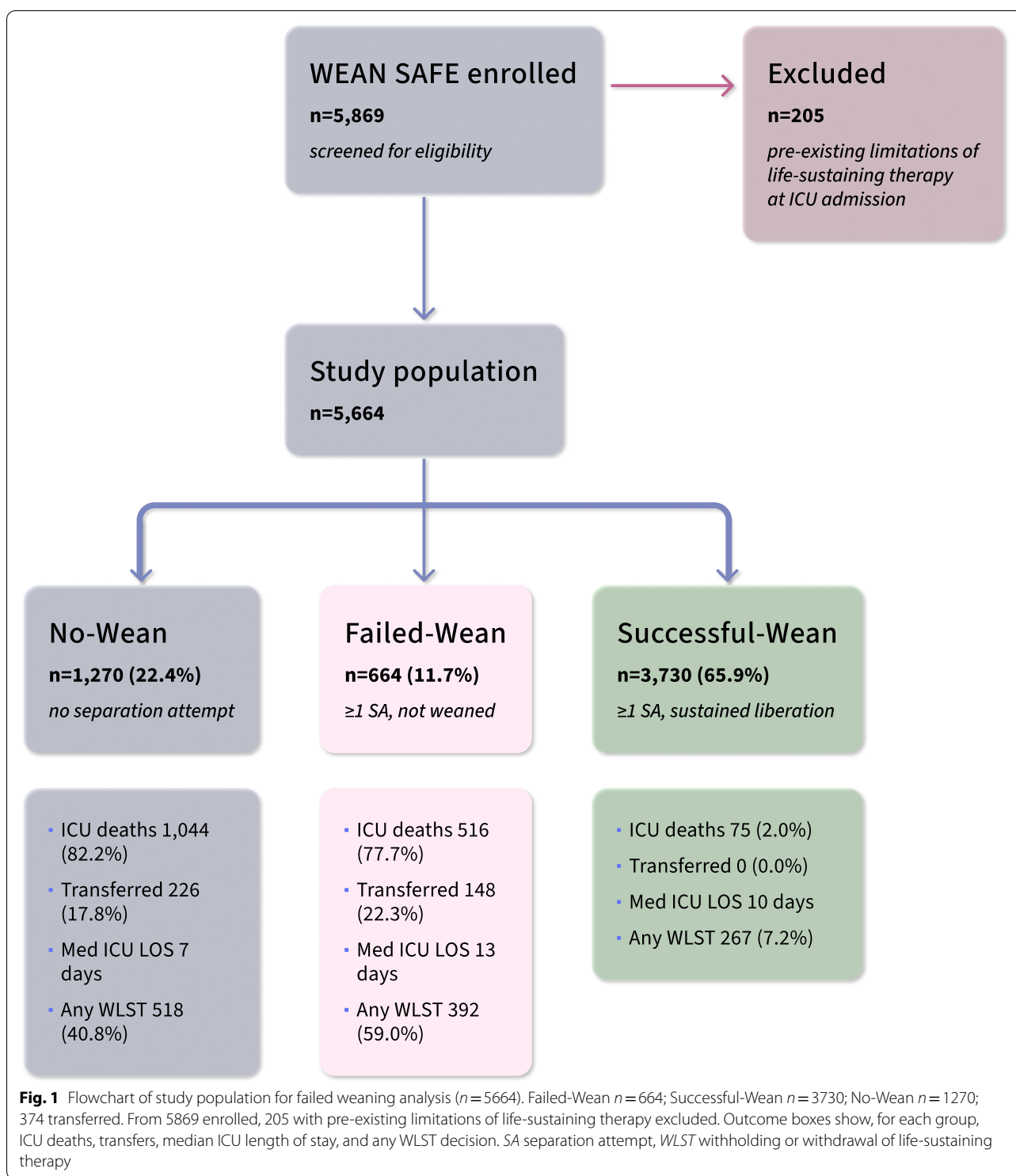
Clinical progress and outcomes

Among patients who remained in their original ICU, ICU mortality was 100% in the No-Wean and Failed-Wean groups and 2.0% in Successful-Wean patients; these figures are reported here principally to define the denominator for the mortality analyses that follow, since vital status was unknown for the 374 patients transferred to another care area. The median day of death was day 11 in Failed-Wean, day 6 in No-Wean and day 27 in Successful-Wean patients (Fig. 4A). WLST decisions occurred in 59.0% of Failed-Wean, 40.8% of No-Wean, and 7.2% of Successful-Wean patients, and weaning difficulty was a contributing reason in 34.2% of Failed-Wean patients with a WLST decision (Table 4).

Failed-Wean clinical phenotypes

Three clinical phenotypes were identified within the Failed-Wean group based on the number of SAs and the presence and timing of WLST (Table 4; Figs. 3–4). Phenotype A (single SA followed by WLST, $n = 189$) had very high ICU mortality (97.4%) and the shortest median ICU stay (7 days) (Fig. 4C). These patients typically had WLST initiated rapidly, with a median of 0 days after the failed SA (Fig. 4B). By day 2 post-failed SA, 82.0% had WLST decisions and 74% had died. These patients had low tracheostomy rates and minimal transfers, consistent with an early transition to comfort-focused care (Table 4).

Phenotype B (single SA, no WLST, $n = 88$) showed lower mortality (56.8%) and a longer ICU stay (11 days). These patients experienced a single failed SA but did not undergo WLST. About one-third received a tracheostomy, and many were transferred for ongoing care. Mortality occurred later (median 11 days from ICU admission; 4 days from failed SA), suggesting continued active treatment until death or transfer. Phenotype



C (> 1 SA, n = 387) had intermediate mortality (72.9%) and the longest ICU stay (17 days). Diagnostic profiles differed across phenotypes (Table S6). These patients underwent multiple SAs, with 52.5% eventually receiving WLST at a median of 4 days after the failed-first SA

(IQR 0–14) and median time to ICU death of 7 days (IQR 3–14). They had the highest tracheostomy rate (47.5%) and prolonged ICU stays, reflecting extended but unsuccessful weaning efforts prior to death or transfer. Weaning difficulty was a contributing reason

Table 1 Baseline characteristics by weaning outcome group (N = 5664)

Characteristic	Overall (N = 5664)	No-Wean (n = 1270)	Failed-Wean (n = 664)	Successful-Wean (n = 3730)	Missing	p-value
Demographics						
Male sex	3502 (61.8%)	810 (63.8%)	389 (58.6%)	2303 (61.7%)	0	0.081
Age, years	64 (51–74)	66 (54–75)	68 (59–76)	62 (49–73)	0	<0.001
Clinical Frailty Scale, median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	461	<0.001
CFS ≥ 4 (vulnerable/frail)	1701 (32.7%)	408 (35.6%)	268 (45.0%)	1025 (29.6%)	461	<0.001
BMI, kg/m ²	26 (23–30)	26 (23–29)	26 (23–29)	26 (23–30)	201	0.399
PaO ₂ /FiO ₂ ratio, day 3–4	226 (164–300)	192 (126–267)	224 (161–288)	237 (177–313)	717	<0.001
SOFA score, day 3–4 (non-neurological)	6 (4–8)	8 (5–10)	7 (4–9)	5 (3–8)	1627	<0.001
ICU admission category						
Medical	3798 (67.1%)	929 (73.1%)	501 (75.5%)	2368 (63.5%)		<0.001
Urgent surgery	853 (15.1%)	158 (12.4%)	75 (11.3%)	620 (16.6%)		
Planned surgery	429 (7.6%)	54 (4.3%)	37 (5.6%)	338 (9.1%)		
Trauma	512 (9.0%)	113 (8.9%)	43 (6.5%)	356 (9.5%)		
Reasons for ICU admission						
Hypoxaemic respiratory failure	1871 (33.0%)	425 (33.5%)	248 (37.3%)	1198 (32.1%)	0	0.029
Hypercapnic respiratory failure	798 (14.1%)	164 (12.9%)	101 (15.2%)	533 (14.3%)	0	0.322
Sepsis	1289 (22.8%)	312 (24.6%)	158 (23.8%)	819 (22.0%)	0	0.127
Cardiac arrest	569 (10.0%)	218 (17.2%)	107 (16.1%)	244 (6.5%)	0	<0.001
Non-traumatic neurological event	812 (14.3%)	174 (13.7%)	112 (16.9%)	526 (14.1%)	0	0.132
Emergency surgery	777 (13.7%)	150 (11.8%)	74 (11.1%)	553 (14.8%)	0	0.003
Airway protection	673 (11.9%)	130 (10.2%)	68 (10.2%)	475 (12.7%)	0	0.023
Non-septic shock	402 (7.1%)	109 (8.6%)	48 (7.2%)	245 (6.6%)	0	0.054
Trauma	426 (7.5%)	91 (7.2%)	37 (5.6%)	298 (8.0%)	0	0.081
Comorbidities						
Any pre-existing comorbidity	3697 (65.3%)	870 (68.5%)	478 (72.0%)	2349 (63.0%)	0	<0.001
Chronic obstructive pulmonary disease	761 (13.4%)	178 (14.0%)	116 (17.5%)	467 (12.5%)	0	0.002
Other respiratory disease	332 (5.9%)	102 (8.0%)	53 (8.0%)	177 (4.7%)	0	<0.001
Diabetes mellitus	1237 (21.8%)	299 (23.5%)	156 (23.5%)	782 (21.0%)	0	0.087
Chronic cardiac failure (NYHA >0)	477 (8.4%)	123 (9.7%)	52 (7.8%)	302 (8.1%)	0	0.179
Chronic renal failure	596 (10.5%)	147 (11.6%)	93 (14.0%)	356 (9.5%)	0	<0.001
Chronic liver disease	256 (4.5%)	65 (5.1%)	37 (5.6%)	154 (4.1%)	0	0.130
Immunocompromised	358 (6.3%)	89 (7.0%)	56 (8.4%)	213 (5.7%)	0	0.015
Active malignancy, solid	443 (7.8%)	112 (8.8%)	74 (11.1%)	257 (6.9%)	0	<0.001
Active malignancy, haematological	167 (2.9%)	67 (5.3%)	25 (3.8%)	75 (2.0%)	0	<0.001
Neuromuscular disease	144 (2.5%)	35 (2.8%)	26 (3.9%)	83 (2.2%)	0	0.033
Dementia/cognitive impairment	304 (5.4%)	73 (5.7%)	40 (6.0%)	191 (5.1%)	0	0.503
Current smoker	797 (14.1%)	160 (12.6%)	84 (12.7%)	553 (14.8%)	0	0.076
Geography, continent					0	<0.001
Europe	3015 (53.2%)	702 (55.3%)	372 (56.0%)	1941 (52.0%)		
Asia	998 (17.6%)	221 (17.4%)	82 (12.3%)	695 (18.6%)		
North America	786 (13.9%)	122 (9.6%)	127 (19.1%)	537 (14.4%)		
South America	564 (10.0%)	147 (11.6%)	49 (7.4%)	368 (9.9%)		
Oceania	189 (3.3%)	21 (1.7%)	18 (2.7%)	150 (4.0%)		
Africa	112 (2.0%)	57 (4.5%)	16 (2.4%)	39 (1.0%)		

Values are median (IQR), mean (SD), or n (%). p values: Kruskal–Wallis (continuous), Pearson Chi-squared (categorical). Pairwise post hoc tests were not performed and group orderings should not be inferred from a global p-value

No-Wean includes 226 transferred patients; Failed-Wean includes 148 transferred patients; Successful-Wean includes no transfers. CFS = Clinical Frailty Scale.

P/F = PaO₂/FiO₂. SOFA Day 3–4 = SOFA score (non-neurological) at days 3–4 of ICU admission. Any pre-existing comorbidity = at least one of the comorbidity flags listed below

Table 2 AHRF severity and ventilator support by weaning outcome group (N = 5664)

Characteristic	Overall†	No weaning (n = 1270)	Failed-Wean (n = 664)	Successful-Wean (n = 3730)	Missing	p-value
At study inclusion (Day 3–4), all groups						
SOFA score (non-neurological)	6 (4–8)	8 (5–10)	7 (4–9)	5 (3–8)	1627	<0.001
PaO ₂ /FiO ₂ ratio	238.8 ± 102.2	204.0 ± 99.8	233.6 ± 98.4	252.2 ± 100.7	717	<0.001
Tidal volume (ml/kg PBW)	8.1 ± 2.1	7.9 ± 2.0	8.2 ± 2.2	8.2 ± 2.1	274	<0.001
PEEP (cmH ₂ O)	6 (5–8)	7 (5–10)	6 (5–8)	6 (5–8)	86	<0.001
Respiratory rate (breaths/min)	19.4 ± 5.2	20.2 ± 5.6	20.4 ± 5.3	19.0 ± 5.0	21	<0.001
Driving pressure (cmH ₂ O)	14 (10–18)	16 (12–21)	14 (11–20)	13 (10–17)	164	<0.001
Dynamic compliance (ml/kg/cmH ₂ O)	1 (0–1)	0 (0–1)	1 (0–1)	1 (0–1)	421	<0.001
At first weaning eligibility criteria, FW + SW only						
PaO ₂ /FiO ₂ ratio	280.1 ± 101.2	–	269.0 ± 104.4	282.1 ± 100.5	1314	0.004
Tidal volume (ml/kg PBW)	7.8 ± 2.0	–	7.8 ± 2.0	7.8 ± 2.0	751	0.836
PEEP (cmH ₂ O)	6 (5–8)	–	6 (5–8)	5 (5–8)	588	<0.001
Respiratory rate (breaths/min)	19.3 ± 9.4	–	20.5 ± 6.0	19.1 ± 9.9	504	<0.001
Driving pressure (cmH ₂ O)	13 (9–17)	–	14 (10–19)	13 (9–17)	740	<0.001
Dynamic compliance (ml/kg/cmH ₂ O)	1 (0–1)	–	1 (0–1)	1 (0–1)	944	<0.001
Ventilation mode	–	–	–	–	1038	<0.001
Controlled	2558 (65.8%)	–	445 (72.4%)	2113 (64.6%)		
Assisted	1327 (34.2%)	–	170 (27.6%)	1157 (35.4%)		
Sedation level	–	–	–	–	539	<0.001
Awake	1085 (25.0%)	–	134 (20.2%)	951 (25.9%)		
Moderate sedation	1899 (43.8%)	–	235 (35.4%)	1664 (45.3%)		
Deep sedation	1349 (31.1%)	–	294 (44.3%)	1055 (28.7%)		
NMBA use prior to WEC	338 (7.7%)	–	66 (9.9%)	272 (7.3%)	0	0.023
At first separation attempt, FW + SW only						
PaO ₂ /FiO ₂ ratio	287.7 ± 103.3	–	266.2 ± 104.1	291.5 ± 102.7	1940	<0.001
Tidal volume (ml/kg PBW)	7.8 ± 2.1	–	7.7 ± 2.1	7.8 ± 2.1	1503	0.008
PEEP (cmH ₂ O)	5 (5–7)	–	5 (5–8)	5 (5–7)	1333	<0.001
Respiratory rate (breaths/min)	20.0 ± 6.2	–	21.9 ± 6.6	19.7 ± 6.0	1295	<0.001
Driving pressure (cmH ₂ O)	11 (7–15)	–	12 (8–17)	10 (7–15)	1522	<0.001
Dynamic compliance (ml/kg/cmH ₂ O)	1 (0–1)	–	1 (0–1)	1 (1–1)	1694	<0.001
Type of first separation attempt	–	–	–	–	1270	<0.001
Spontaneous breathing trial	2893 (65.8%)	–	393 (59.2%)	2500 (67.0%)		
Extubation	894 (20.3%)	–	153 (23.0%)	741 (19.9%)		
Ventilatory support via tracheostomy	607 (13.8%)	–	118 (17.8%)	489 (13.1%)		

Values: mean (SD), median (IQR), or n (%). Between-group comparison by Kruskal-Wallis test. The first section reports all three groups at study inclusion; the second and third sections are restricted to Failed-Wean and Successful-Wean patients, since the No-Wean group has no weaning eligibility or separation attempt time point

†Overall includes all patients with data for that row: the full cohort (N = 5664) at study inclusion, and Failed-Wean plus Successful-Wean patients only (n = 4394) at the weaning eligibility and first separation attempt time points

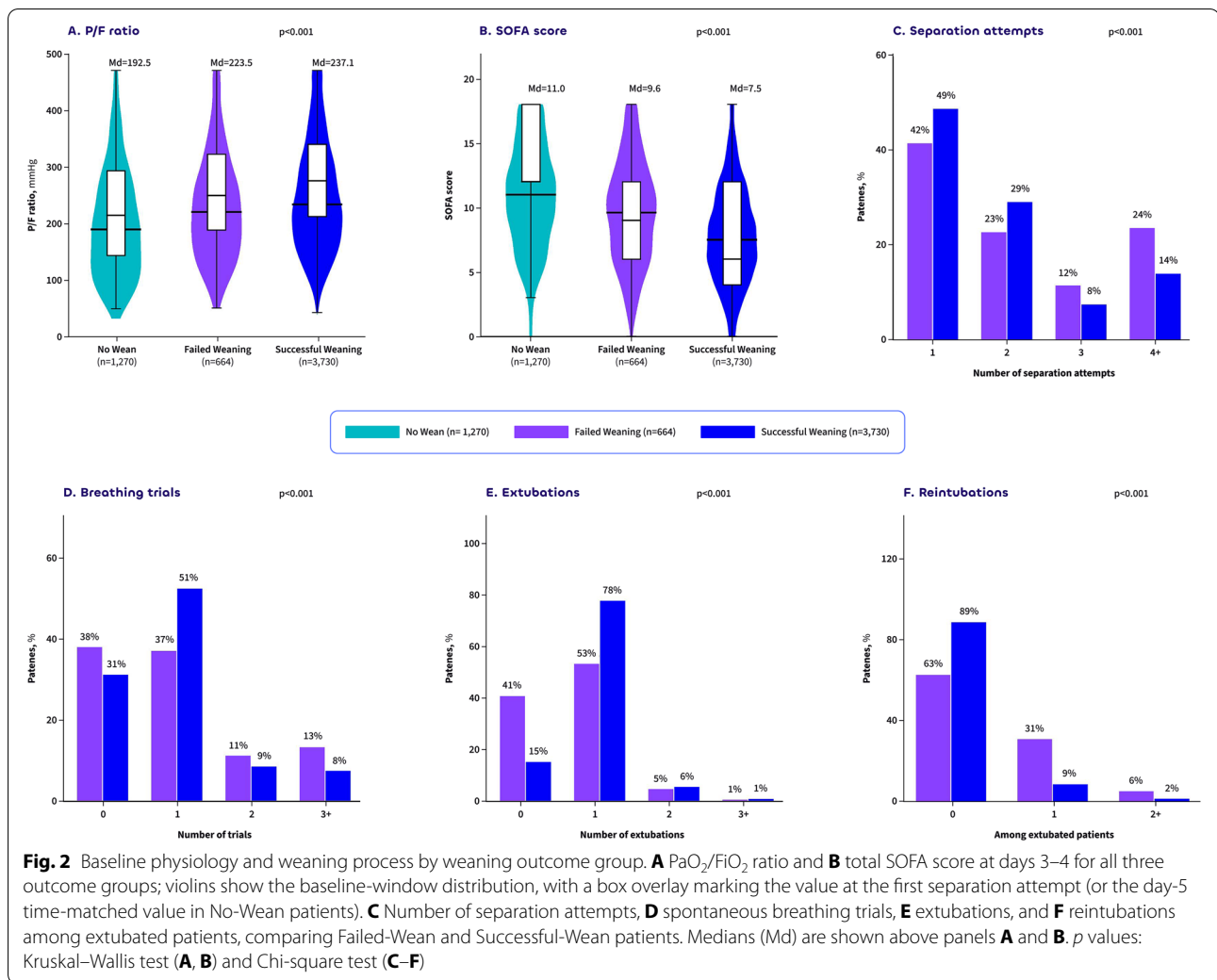
NMBA neuromuscular blocking agent

to WLST decisions in 43.8% of Phenotype C compared to 23.8% of Phenotype A patients (Table 4).

The underlying causes of respiratory failure varied significantly. Hypoxic respiratory failure was more frequent in Phenotypes B and C (42.1%) than in Phenotype A (25.4%). In contrast, cardiac arrest was a more frequent cause of admission in Phenotype A (29.1%) compared to B (10.2%) and C (11.1%).

Association between WLST decisions and outcomes

Among all patients undergoing ≥ 1 SA (n = 4394), a failed-first SA was strongly associated with a subsequent in-ICU WLST decision (OR 5.41, 95% CI 4.49–6.51, $p < 0.001$; Table S3). Within the failed-first SA cohort (n = 1748), in which the first SA term is not separately estimable, case-mix predictors of an in-ICU WLST decision included deep sedation at first SA (aOR 3.76, 95% CI



2.68–5.28) and frailty ($\text{CFS} > 4$; aOR 2.29, 95% CI 1.68–3.11) (Table 5). The association between deep sedation and subsequent WLST persisted after excluding patients with a primary acute brain injury (Table S7).

There was marked geographic variation in WLST decision rates across continents (Table S8), with WLST decisions in patients that fail to wean significantly lower in Asia (25%), Africa (12.5%), and South America (32%) compared to Europe (67%), with Oceania (77%) and North America (70%) not different from Europe (Tables 5 and S3).

In the propensity-score-matched cohort ($n=736$; 368 with WLST decision, 368 without), patients with a WLST decision had a substantially higher hazard of ICU mortality (HR 7.04, 95% CI 5.22–9.51, $p < 0.001$) (Fig. 5; Table S9). The matched cohorts were well balanced across baseline characteristics (Table S2). The median time to ICU death after a WLST decision was 2 days; in those without a WLST decision, the median time to sustained

weaning was 5 days. The robustness of this association to unmeasured confounding was assessed using the E -value: an unmeasured confounder would need to be associated with both WLST decision and ICU mortality by a risk ratio of at least 13.6-fold each, above and beyond the measured covariates, to fully explain away the observed HR of 7.0; even taking the lower bound of the 95% CI (HR 5.22), an unmeasured confounder of risk ratio 9.9 would be required, suggesting the association is unlikely to be explained by modest residual confounding alone.

Discussion

This secondary analysis of the WEAN SAFE cohort focuses on patients who entered the weaning process, but were not successfully liberated from invasive ventilation—a clinically important group distinct from both successfully weaned patients and those who never commenced weaning. Failed-Wean patients underwent a longer and more intensive weaning process, with more

Table 3 Weaning process by weaning outcome group (N = 4394)

Characteristic	Overall (N = 4394)	Failed-Wean (n = 664)	Successful-Wean (n = 3730)	Missing	p-value
Weaning initiation					
Day of first WEC met (from ICU admission)	3 (3–4)	3 (3–5)	3 (3–4)	0	<0.001
Day of first SA (from ICU admission)	5 (4–9)	6 (4–10)	5 (3–8)	0	<0.001
Delay from WEC to first SA (days)	1 (0–4)	2 (0–5)	1 (0–4)	0	<0.001
Delayed initiation (> 1 day from WEC to first SA)	2082 (47.4%)	371 (55.9%)	1711 (45.9%)	0	<0.001
Separation attempts					
Number of separation attempts				0	<0.001
1	2106 (47.9%)	277 (41.7%)	1829 (49.0%)		
2	1244 (28.3%)	152 (22.9%)	1092 (29.3%)		
≥ 3	1044 (23.8%)	235 (35.4%)	809 (21.7%)		
SBTs declared				0	<0.001
0	1420 (32.3%)	253 (38.1%)	1167 (31.3%)		
1	2207 (50.2%)	247 (37.2%)	1960 (52.5%)		
≥ 2	767 (17.5%)	164 (24.7%)	603 (16.2%)		
Type of first SA				0	<0.001
Spontaneous breathing trial	2893 (65.8%)	393 (59.2%)	2500 (67.0%)		
Extubation	894 (20.3%)	153 (23.0%)	741 (19.9%)		
Ventilatory support via tracheostomy	607 (13.8%)	118 (17.8%)	489 (13.1%)		
Extubation and reintubation					
Number of extubations				0	<0.001
0	847 (19.3%)	272 (41.0%)	575 (15.4%)		
1	3261 (74.2%)	355 (53.5%)	2906 (77.9%)		
2	244 (5.6%)	32 (4.8%)	212 (5.7%)		
≥ 3	42 (1.0%)	5 (0.8%)	37 (1.0%)		
Any reintubation	489 (13.8%)	145 (37.0%)	344 (10.9%)	847	<0.001
Tracheostomy					
Tracheostomy at any time	949 (21.6%)	227 (34.2%)	722 (19.4%)	0	<0.001
New tracheostomy after first SA (% of patients with tracheostomy)	342 (36.0%)	109 (48.0%)	233 (32.3%)	3445	<0.001
Weaning according to a New Definition category					
WIND category				0	<0.001
Group 1, Simple weaning	3034 (69.0%)	175 (26.4%)	2859 (76.6%)		
Group 2, Difficult weaning	611 (13.9%)	163 (24.5%)	448 (12.0%)		
Group 3A, Prolonged (no trach)	423 (9.6%)	0 (0.0%)	423 (11.3%)		
Group 3B, Prolonged (trach)	326 (7.4%)	326 (49.1%)	0 (0.0%)		
Respiratory support at ICU discharge*					
Still intubated at ICU discharge	2 (0.0%)	0 (0.0%)	2 (0.1%)	0	1.000
Tracheostomy at ICU discharge	472 (11.1%)	0 (0.0%)	472 (12.7%)	0	<0.001
Non-invasive ventilation at discharge	190 (4.5%)	0 (0.0%)	190 (5.1%)	0	<0.001
Supplemental oxygen at discharge	2033 (47.9%)	0 (0.0%)	2033 (54.5%)	0	<0.001
Room air (no supplemental oxygen)	1192 (28.1%)	0 (0.0%)	1192 (32.0%)	0	<0.001

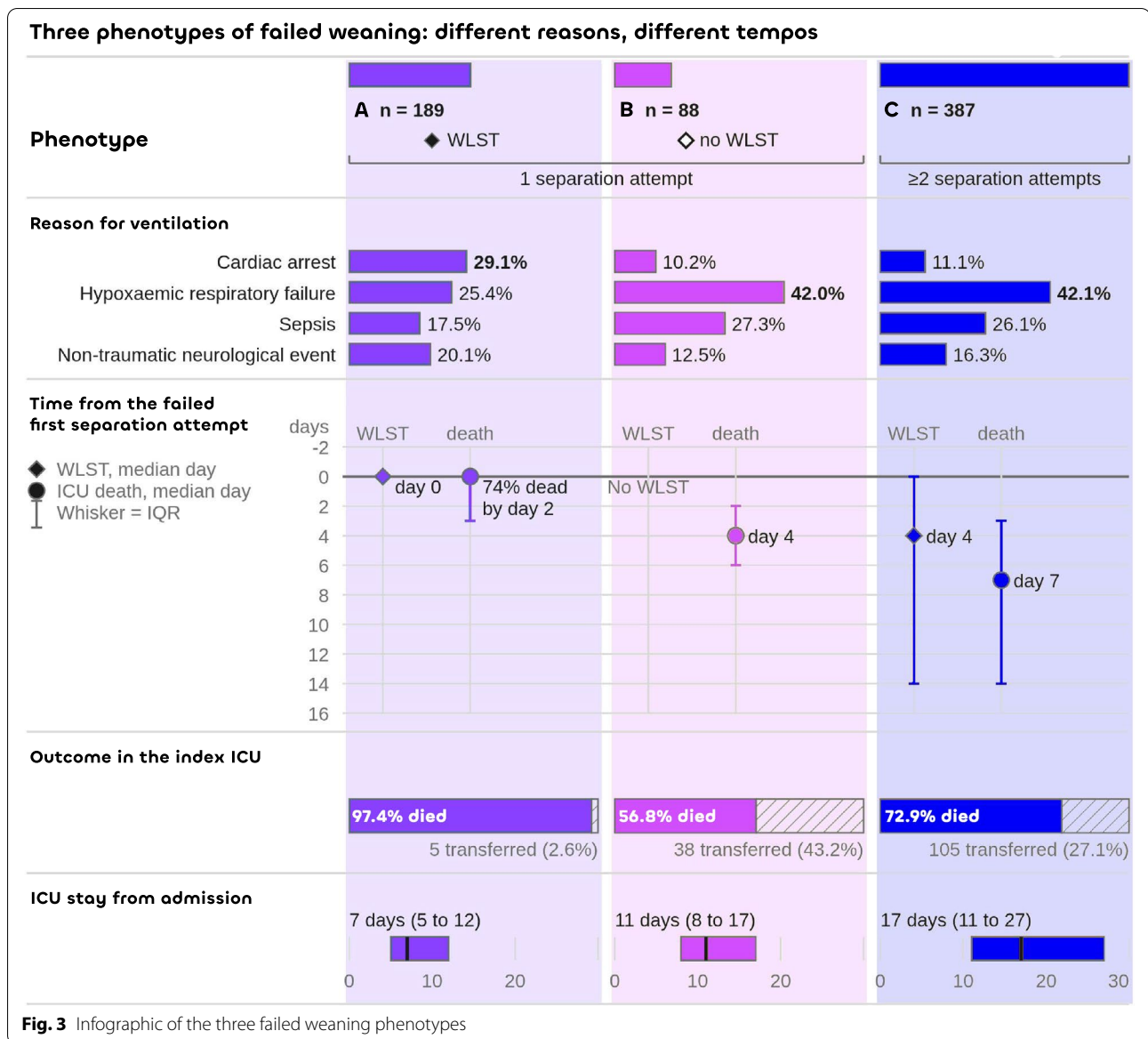
Failed-Wean (n = 664) vs Successful-Wean (n = 3730). Values: median (IQR) or n (%). p values: Mann–Whitney/Chi-squared

Starred (*) rows use non-transferred patients as the denominator: Failed Weaning n = 516 (148 of 664 transferred from study ICU), Successful Weaning n = 3730 (no transfers). New tracheostomy after first SA is expressed as % of the weaning-group total (not as % of patients who eventually received a tracheostomy)

WIND Weaning according to a New Definition, WLST Withdrawal/Withholding of Life-Sustaining Therapy

separation attempts, reintubations, and tracheostomies than those who weaned successfully. Failed-Wean patients experienced the longest durations of invasive

ventilation and had substantially higher in-ICU mortality. We identified three clinically distinct Failed-Wean phenotypes, based on the number of separation attempts



and the use and timing of WLST decisions. We found that a failed-first SA was strongly associated with the use of WLST decisions, and the use of a WLST decision was associated with a higher hazard of ICU mortality and a shorter median time to ICU death.

Clinical trajectories across weaning groups

The physiological trajectory analysis showed three distinct patterns evolving between study entry at day 3 and the time window within which the first SA occurred (in the patients that received one). The clinical status of the 'No-Wean' patients deteriorated, Failed-Wean patients remained unchanged, while Successful-Wean improved. The early severity and ongoing deterioration observed in No-Wean patients is consistent with the clinical decision

not to attempt separation in this group, despite the resulting relatively short ICU course and high mortality burden.

Failed-first SA as key adverse event

A substantial proportion of Failed-Wean patients underwent a single SA, and this subgroup had the highest mortality. WLST decisions in this single-attempt subgroup followed the failed-first SA at a median of 0 days, with 74% of these patients dying by day 2. The single and multiple SA subgroups appear similar at study entry and at the first SA and suggest clinicians may consider a failed-first SA as a prognostic test or indicator. Multivariable analyses indicated that a failed-first SA was a strong adjusted predictor of an in-ICU WLST decision. However, care is needed in this

Table 4 Failed weaning—three clinical phenotypes (*n* = 664; pre-existing limitations excluded)

Characteristic	Phenotype A (1 SA + WLST)	Phenotype B (1 SA, no WLST)	Phenotype C (> 1 SA)
<i>n</i>	189	88	387
ICU mortality	184 (97.4%)	50 (56.8%)	282 (72.9%)
Transferred	5 (2.6%)	38 (43.2%)	105 (27.1%)
Median ICU length of stay (Days, IQR)	7 (5–12)	11 (8–17)	17 (11–27)
Tracheostomy rate	7.9%	31.8%	47.5%
WLST timing	Median 0 days post-first SA; 82.0% by day 2	– (no WLST)	52.5% eventual WLST, median 4 days post-first SA (IQR 0–14)
Death timing	74% dead by day 2	Median 11 days from admission/4 days from failed SA	Median 7 days to ICU death (IQR 3–14)
Dominant cause of respiratory failure	Cardiac arrest enriched (29.1%)	Hypoxic resp. failure (part of 42.1% in B + C combined)	Hypoxic resp. failure (part of 42.1% in B + C combined)
Weaning difficulty cited as WLST reason	45 (23.8%)	–	89 (43.8%)

Failed-Wean cohort with pre-existing limitations excluded (*n* = 664). Three phenotypes: Single SA + WLST, Single SA without WLST, more than one SA. ICU outcome categories: died/transferred/alive

WLST = withdrawal/withholding of life-sustaining therapy decision after failed-first SA. Matched *n* = 368 in each stratum reflect the 368 1:1 caliper pairs

interpretation as a failed SA might simply be a marker of higher unmeasured illness severity or reflect discussions with the patient and family in parallel with and independent of the SA outcome. Temporal precedence supports, but does not establish causality. The single-event pattern observed in Phenotype A, where WLST followed a single failed SA within a median of 0 days, contrasts with the cumulative-burden pattern suggested in Phenotype C, where weaning difficulty was cited as a contributing reason for WLST in 43.8% of patients (versus 23.8% in Phenotype A). This suggests that in the multiple-attempt group, it is the accumulated experience of repeated failed attempts, rather than any single event that more often drives treatment limitation decisions.

Our finding that later reintubation was associated with worse outcomes than early reintubation, and that this association persisted after adjustment for baseline severity, suggests that the timing of extubation failure carries prognostic information rather than reflecting illness severity alone. Whether it is a modifiable target or a marker of an unfavourable trajectory requires prospective study.

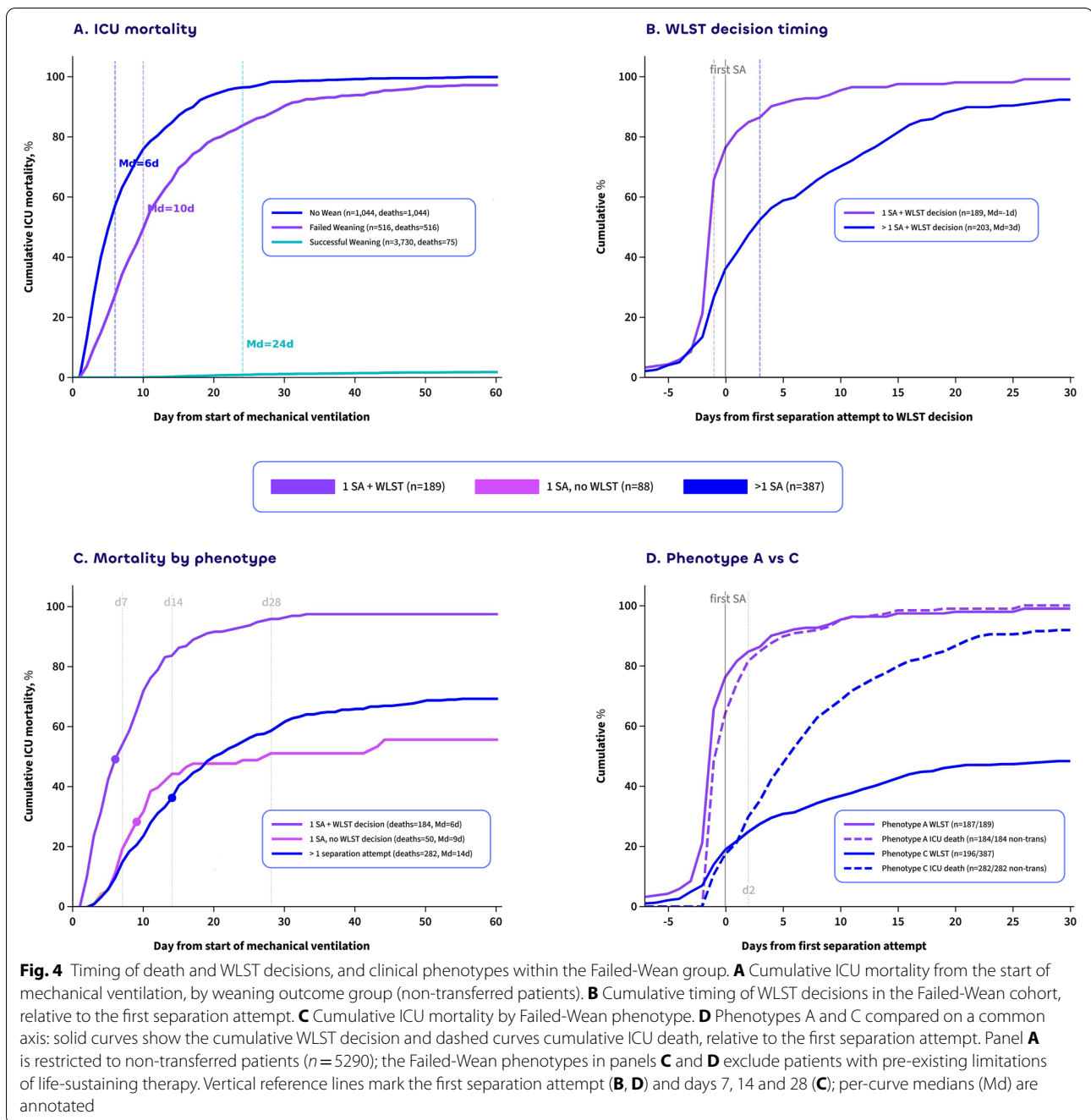
Failed-Wean phenotypes and WLST decisions

We identified three Failed-Wean phenotypes that differed in clinical course and in apparent aetiology and weaning trajectory (Fig. 3—infographic). Phenotype A (single SA + WLST) resembled the No-Wean group physiologically, with relatively short ICU stays (median 7 days), very high mortality, and early end-of-life transitions. This cohort was enriched with post-cardiac arrest patients, where ventilator dependence may reflect severe

neurological injury and a poor prognosis. Phenotypes B (single SA, no WLST) and C (> 1 SA) were dominated by hypoxic respiratory failure (42%), consistent with prolonged pulmonary disease requiring continued ventilatory support. Palliative extubation was performed in over half of Failed-Wean patients with a WLST decision, compared with approximately 10% in the No-Wean and Successful-Wean groups. This suggests that active withdrawal of support, on a background of failed-weaning attempts, is an important pathway to death in these patients.

Phenotype B's intermediate mortality (56.8%) appears to reflect a clinically heterogeneous course. In the absence of a recorded WLST decision, later death in this subgroup may represent either delayed physiological recovery that ultimately led to weaning failure, or an unresolved trajectory in the one-third of this subgroup that were transferred for ongoing care elsewhere. This contrasts with the more clearly defined trajectories of Phenotypes A and C and underscores the need for individualised assessment in this group.

The contrasting predominance of cardiac arrest and neurologic injury in Phenotype A (29%) versus hypoxic respiratory failure in Phenotypes B and C (42%) is consistent with two distinct pathophysiological pathways to weaning failure: a neurologic/cardiac arrest-driven pathway, in which ventilator dependence reflects the primary brain injury and prognostic certainty is often reached rapidly, and a pulmonary/respiratory load-driven pathway, in which prolonged ventilatory support is required because of ongoing gas-exchange



impairment and increased respiratory load. This distinction reinforces the clinical rationale for phenotyping Failed-Wean patients beyond duration or attempt count alone. Despite the markedly higher tracheostomy rate in Phenotype C (47.5%) than Phenotype A (8%), ICU mortality in Phenotype C remained substantial (73%), suggesting that, while tracheostomy facilitated a more prolonged weaning trial, its potential to improve

the probability of survival in patients with refractory respiratory failure is unclear.

The relationship between WLST and subsequent mortality is already quite well established in the literature, especially in patients with neurologic injuries [7–9]. We wished to understand the relationship between WLST decisions and outcomes in patients failing their first SA after controlling for physiological characteristics and illness severity. In the propensity-matched

Table 5 Multivariable logistic regression of factors associated with in-ICU WLST decision in the failed-first SA cohort (n = 1748)

Characteristic	Adjusted OR	95% CI	p-value
Patient demographics and frailty			
Age (per year)	1.02	1.02, 1.03	< 0.001
Frailty CFS 0–3	–	–	
Frailty CFS 4	2.54	1.81, 3.58	< 0.001
Frailty CFS > 4	2.29	1.68, 3.11	< 0.001
Physiology and ventilation at first SA			
Prior Continuous paralysis	1.46	1.02, 2.10	0.039
Respiratory rate (per breath/min)	1.02	1.00, 1.04	0.047
PaO ₂ /FiO ₂	1.00	1.00, 1.00	0.020
Sedation: awake	–	–	
Sedation: deep	3.76	2.68, 5.28	< 0.001
Sedation: moderate	1.25	0.92, 1.69	0.152
Indication for ventilation			
Cardiac arrest	3.57	2.42, 5.27	< 0.001
Trauma	0.43	0.22, 0.81	0.009
Non-traumatic neurological	1.01	0.71, 1.45	0.944
Continent (vs Europe)			
Europe	–	–	
Asia	0.31	0.19, 0.52	< 0.001
Africa	0.16	0.02, 1.32	0.089
Oceania	1.94	0.93, 4.05	0.077
South America	0.45	0.27, 0.76	0.003
North America	1.47	1.03, 2.09	0.034

Patients with pre-existing limitations excluded (n = 1748; complete cases n = 1502). Covariates: continent, age, frailty (CFS category), continuous paralysis, respiratory rate at first SA, PaO₂/FiO₂ at first SA, sedation level at first SA, cardiac arrest, trauma, non-traumatic neurological

Adjusted OR = adjusted odds ratio from multivariable logistic regression. 95% CI = 95% confidence interval. Reference levels are shown as en dashes. CFS = Clinical Frailty Scale. WLST = withdrawal/withholding of life-sustaining therapy decision after failed-first SA

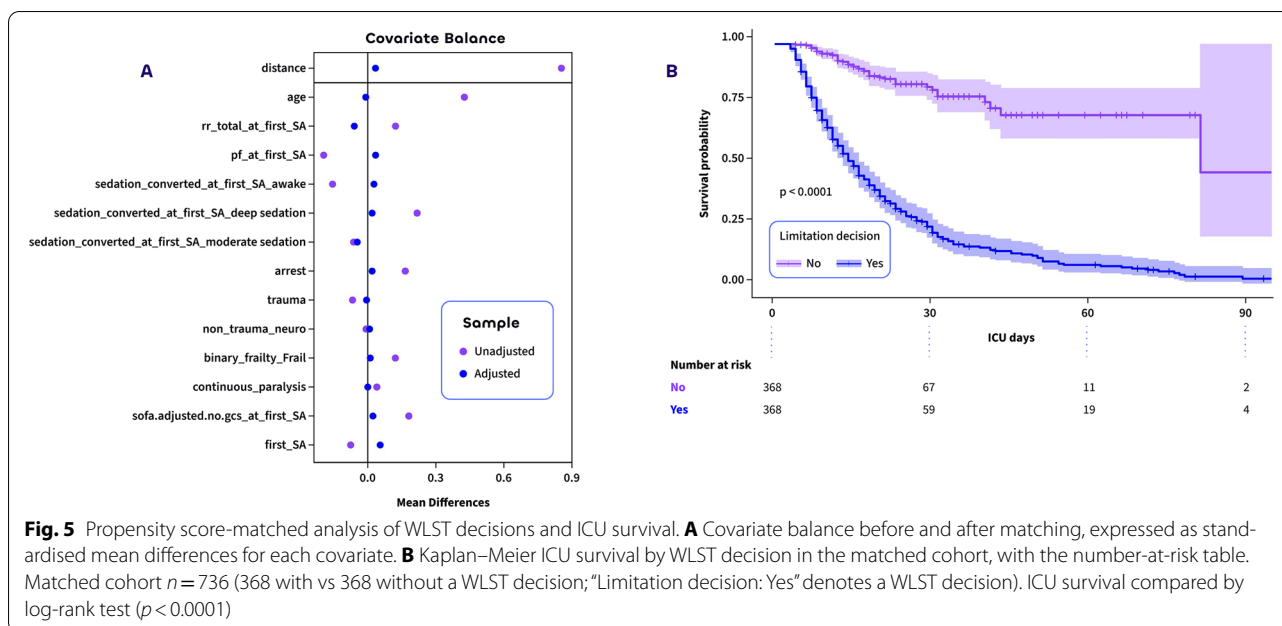
analysis, WLST after a failed-first SA was associated with a seven-fold higher hazard of ICU mortality. This hazard ratio should be interpreted as reflecting both the direct effect of the WLST decision itself and the underlying illness severity that prompted it; while propensity matching balances measured baseline severity between groups, it cannot fully separate these two contributors. The E-value analysis (13.5, lower 95% CI bound 9.9) indicates that only a strong unmeasured confounder could account for the observed association, suggesting residual confounding by indication alone is an unlikely full explanation. We also note that WLST decisions occurred a median of 0 days after the failed-first SA in Phenotype A, suggesting that in some patients, particularly those with post-cardiac arrest/neurologic injury, the first separation attempt may

function partly as a prognostic litmus test rather than solely a physiological trial. This finding of a relationship between WLST decisions and outcome in patients failing their first SA is novel. The extent to which earlier decision points reflect genuine prognostic certainty and a desire to minimise patient suffering, versus premature limitation in patients who might otherwise have recovered warrants further study.

Over half of Failed-Wean patients with a WLST decision underwent palliative extubation, with a median time from WLST to death of 1 day in Phenotype A. This raises an important question: to what extent does a WLST decision predict an already-inevitable death, versus actively precipitating it? Our design cannot fully separate these possibilities, and we are cautious not to over-interpret our observational data in this regard. We suggest an HR of 7.04 for WLST-associated mortality is best understood as reflecting a composite of prognostic accuracy (correctly identifying patients who would have died regardless) and the direct effect of treatment limitation, rather than implying a single causal mechanism; this distinction carries ethical significance. Related to this, the very rapid transition from failed-first SA to WLST observed in some patients, particularly in the post-cardiac arrest/neurologic subgroup enriched in Phenotype A, raises the possibility that the separation attempt itself may, in some cases, function partly as a prognostic test rather than solely as a genuine weaning trial. We believe this warrants further prospective study.

Clinical implications and future directions

Our Failed-Wean cohort showed an ICU mortality of 78%, substantially exceeding the 29% reported for WIND Group 3 (prolonged weaning ≥ 7 days from first separation attempt) [2] and the 42.4% (92/217) replicated in the independent WIND-validation cohort of Jeong et al. [10]. Single-centre validations of the Boles classification report 32–37% hospital mortality in the prolonged-weaning category [11–13]. By contrast, the 88% ICU mortality observed in the independent WIND-validation cohort of patients who never attempted separation [10] approaches our 82.2% No-Wean figure, suggesting Failed-Wean identifies a population whose physiological trajectory lies between WIND Group 3 and the no-attempt group. The trajectory persists beyond the index admission: pooled meta-analytic data report 1-year mortality of 59% in patients treated with prolonged mechanical ventilation, rising to 73% in post-acute US cohorts [14], indicating that survivors of the acute phase remain at high long-term risk of death. The Boles/ERS classification categorises weaning difficulty by duration and SBT count but does not specifically address patients who never achieve



sustained liberation [5]. The 78% Failed-Wean signal also exceeds the worst-prognosis demographic subgroup within the WEAN SAFE parent cohort, where frail and elderly patients reached 46% hospital mortality [15] indicating that physiological failure to liberate, not demographic risk alone, is the dominant determinant. These findings reinforce our central argument that separating out a distinct Failed-Wean group, rather than classifying by SBT failure or duration alone, better highlights the substantial mortality burden of failed weaning.

Mortality and its timing in Failed-Wean patients is shaped not only by physiological trajectory but by goals-of-care decisions, consistent with prior work demonstrating that withdrawal of mechanical ventilation reflects clinician prognostication and patient preferences as much as underlying pathophysiology [16]. Previous WEAN SAFE secondary analyses identified comorbidity, frailty, and sex as key determinants of weaning outcomes [15, 17, 18]; our phenotype-based analysis extends this by showing that within the Failed-Wean stratum, process-related factors and WLST timing further define clinically meaningful subgroups whose mortality exceeds that captured by any of these demographic axes alone.

Prolonged weaning carries substantial human and resource burdens for patients, families, and care teams [19]. Cohort data demonstrates that prolonged weaning (>7 days) is associated with increased ICU mortality and that mortality risk rises after the first week of the weaning process [20]. The association between deep sedation at first weaning readiness and subsequent failure, though potentially confounded by indication, raises the

possibility that earlier sedation lightening could improve outcomes [21] and warrants prospective study.

Phenotype-specific strategies may be warranted, with protocolised weaning and specialised weaning units for the multiple-attempt phenotype patients, an approach supported by evidence from European weaning-centre networks demonstrating that approximately 50% of patients with initial weaning failure can be liberated from MV in specialised weaning centres through protocolised, multidisciplinary care [22]. Earlier prognostic discussion in patients at elevated risk of failure (frail, deeply sedated at SA, post-cardiac arrest) may be warranted, recognising that the outcome of any given SA is not predictable in advance, and structured reassessment frameworks for those with persistent uncertainty after a single failed attempt, but without a WLST decision. In practice, a failed-first SA should prompt a structured prognostic discussion with the patient's family, particularly in high-risk populations; however, the intermediate 56.8% mortality observed in Phenotype B demonstrates that some patients recover despite an initial failed attempt, underscoring that this prognostic assessment must remain individualised rather than applied as a uniform rule.

Limitations

This study has several limitations. The three-group classification was applied post hoc, though based on prospectively collected variables, and they are founded on the outcomes of the first SA, a clearly identifiable event in real time during the wean process. The Failed-Wean group is heterogeneous, including patients who died

during weaning and those undergoing withdrawal of life-sustaining therapy (WLST), which may dilute associations. Subgroup analyses are influenced by survival bias: patients in the multiple SA subgroup had to survive long enough to undergo repeated attempts, inherently selecting for longer ICU stays—more precisely, a form of immortal time bias. In contrast, longer hospital stays in the Successful-Wean group likely reflect survivor bias due to early deaths in other groups.

Outcomes for 374 patients transferred before ICU discharge are unknown. Although analysed separately, mortality in No-Wean (82.2%) and Failed-Wean (77.7%) groups may be underestimated if transferred patients later died; among non-transferred patients, ICU mortality reached 100%. Physiological trajectory analyses are also subject to survivor bias, as patients who died early were excluded. While WEAN SAFE recorded whether weaning difficulty was a contributing reason for WLST (as reported for Phenotypes A/C) the extent of any contribution was not assessed. The propensity-matched analysis restricts inference to the subset of patients with comparable baselines; unmatched no-WLST patients tended to be younger and less frail, and the hazard estimate does not generalise to this group. Critically unwell cardiac arrest WLST patients also frequently had no matchable no-WLST control, reflecting clinical practice rather than residual confounding. WLST practices vary across countries due to cultural and legal factors, limiting generalisability. Analyses did not account for clustering across 481 ICUs, and *p* values should be interpreted as descriptive. Diagnostic categories were non-mutually exclusive, allowing overlap.

Conclusions

Failure to wean from invasive mechanical ventilation is a sentinel event associated with very high ICU mortality. Three distinct clinical phenotypes exist within the Failed-Wean population, driven by the interplay between separation attempt intensity and WLST decision-making. A failed-first SA is a key event, heralding a poor outcome, and triggering rapid transitions in goals-of-care in a substantial proportion of patients. Despite this, a substantial proportion of patients die despite a prolonged active weaning process with multiple components and unsuccessful attempts to wean, including failed extubations, a distressing clinical course. The relationship between failed first separation attempts, WLST decision making and the timing and risk of death is important and deserves further investigation.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s00134-026-08592-2>.

Abbreviations

AHRF: Acute hypoxic respiratory failure; CFS: Clinical Frailty Scale; CI: Confidence interval; CPR: Cardiopulmonary resuscitation; eCRF: Electronic case report form; ESICM: European Society of Intensive Care Medicine; ERS: European Respiratory Society; FiO₂: Fraction of inspired oxygen; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; IQR: Interquartile range; LOS: Length of stay; MV: Mechanical ventilation; NMBA: Neuromuscular blocking agent; PaO₂: Partial pressure of arterial oxygen; PEEP: Positive end-expiratory pressure; P/F: PaO₂/FiO₂ ratio; SA: Separation attempt (any deliberate attempt to discontinue invasive mechanical ventilation); SBT: Spontaneous breathing trial; SD: Standard deviation; SOFA: Sequential Organ Failure Assessment; TBI: Traumatic brain injury; WEAN SAFE: Worldwide Assessment of Separation of pAtients From ventilatory assistance; WIND: Weaning according to a New Definition (Beduneau et al. [2]); WLST: Withdrawal/withholding of life-sustaining therapy; 1SA/> 1SA: Single separation attempt/more than one separation attempt.

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Concept and design: AS, JGL. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: RC, BM, ER, AS, JGL. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: RC, YZ, AS, JGL. Administrative, technical, or material support: N/A. Supervision: AS, JGL.

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Data availability

The WEAN SAFE dataset is available from the corresponding author upon reasonable request, subject to approval from the WEAN SAFE steering committee.

Declarations

Conflicts of interest

The authors declare no conflicts of interest.

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