

Additional file 1

Beyond the ventilator-free days: review of several estimands.

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METHODS

Appendix 1. The LIVE Study [1]

The Lung Imaging for Ventilator Setting in Acute Respiratory Distress Syndrome (ARDS) (LIVE) study (NCT02149589, first posted on 29/05/2014) [1] was a randomized controlled trial that examined two ventilation strategies, which were allocated randomly in a 1:1 ratio. The intervention group received a personalised mechanical ventilation approach tailored to the “focal” or “non-focal” computed tomography scan subphenotype of lung aeration loss, while the control group was provided with a standard strategy consistent with traditional care, regardless of lung morphology. The primary outcome was the survival status at day 90. All patients had a follow-up of 90 days unless they died prior to day 90.

Patients were enrolled within 12 hours of onset of moderate-to-severe ARDS, as defined by the Berlin criteria [2]. Exclusion criteria of the LIVE study were:

- mechanical ventilation for more than 7 consecutive days in the past 30 days;
- a previous history of acute respiratory distress syndrome in the previous month;
- intracranial hypertension;
- a body-mass index higher than 40 kg/m²;
- chronic respiratory diseases requiring long-term oxygen therapy or respiratory assistance;
- allogeneic bone-marrow transplantation;
- metastatic cancer;
- extensive burns;
- liver cirrhosis with Child Pugh class C;
- bronchopleural fistula;
- pulmonary fibrosis;
- pregnant patients;
- patients who were moribund, or facing end of life;
- patients under tutelage;
- and patients already enrolled in another interventional acute respiratory distress syndrome study.

A post-hoc analysis performed after reclassification of subphenotypes (nearly 20% misclassification in the study) suggested a potential benefit of the personalised

strategy when the subphenotype was correctly identified. Consequently, the exclusion criteria applied in our study, in addition to those of the LIVE study, included the misclassification of patients based on lung morphology (i.e., focal vs. non-focal subphenotype) in the personalised group. Notably, misclassified patients of the control group (i.e., the standard strategy) were not misaligned with the mechanical ventilation strategy, which, by definition, was not influenced by lung morphology.

All data needed for our analyses were prospectively and previously collected through the LIVE study's electronic case report form.

Appendix 2. Data structure

To illustrate our point, we selected two different individuals from the dataset:

- Patient "056": he/she was in the control group (sometimes coded 0, format required for the function used), the first extubation was at day 6, the reintubation at day 7 (i.e., intubation 2), the second extubation at day 9, the reintubation at day 11 (i.e., intubation 3) and the last extubation at day 15; he/she did not die.
- Patient "095": he/she was in the personalised group (i.e., the experimental group, sometimes coded 1, format required for the function used), he/she was extubated at day 6 and died at day 25.

The data structure required for implementing each model is presented in supplemental tables 1 to 7.

For the multiple event framework, there were three states:

- 1: intubated,
- 2: extubated,
- 3: dead.

And four transitions:

- 1: *from* intubated *to* extubated,
- 2: *from* intubated *to* dead,
- 3: *from* extubated *to* intubated,
- 4: *from* extubated *to* dead.

The considered matrix was: (NA for not available)

From / To	Intubated	Extubated	Dead
Intubated	NA	1	2
Extubated	3	NA	4
Dead	NA	NA	NA

For the current ventilation-free survival, there were four states:

- 1: intubated,
- 2: extubated,
- 3: relapse (i.e., new intubation),
- 4: dead.

And six transitions:

- 1: *from* intubated *to* extubated,
- 2: *from* intubated *to* dead,
- 3: *from* extubated *to* relapse,
- 4: *from* extubated *to* dead,
- 5: *from* relapse *to* extubated,
- 6: *from* relapse *to* dead.

The considered matrix was:

From / To	Intubated	Extubated	Relapse	Dead
Intubated	NA	1	NA	2
Extubated	NA	NA	3	4
Relapse	NA	5	NA	6
Dead	NA	NA	NA	NA

Appendix 3. Software syntax and mathematical expression

All statistical analyses were conducted using R Core version 4.4.1 [3]. The syntax and the mathematical expression are organised by model following the principal manuscript. Furthermore, we encourage consulting the supplementary tables (Tables S1–S7) outlining the data structure for each model to ensure proper data formatting prior to conducting analyses.

We used the following expressions:

- β for the regression coefficient,
- Z for a specific covariable (e.g., the randomization group),
- λ for the hazard function,
- λ_0 for the baseline hazard function.

1. Competing risks

Fine-Gray model [4]

$$\lambda_{ij}(t | Z) = \lambda_{0j} \times e^{\beta Z_i}$$

where e^{β} corresponds to the subdistribution hazard ratio of the event of interest j (i.e., extubation or death) and Z_i is the covariate value of individual i .

```
library(cmprsk)
fit.fg <- crr(ftime = mydata$competing_time,
             fstatus = mydata$competing_event,
             cov1 = I((mydata$groupe == "personalised")),
             failcode = 1)
```

2. Multistate models

Multiple events framework

$$E_j = \int_0^{28} P(X(u) = j) du$$

where E_j is the mean length of stay in a state j (i.e., intubated, extubated or dead) on day 28 and $P(X(u))$ is the probability of a state j being occupied over time.

```
library(mstate)
fit.msm <- coxph( Surv( time = Tstart, time2 = Tstop,
                      event = status) ~ groupe.1 + groupe.2 + groupe.3 +
                      groupe.4 + strata(trans) ,
                  data = mydata, method = "breslow")
```

Recurrent events framework

Andersen-Gill model [5]

$$\lambda_i(t) = Y_{ij}(t) \lambda_0(t) e^{\beta Z_i}$$

where $Y_{ij}(t)$ takes the value 1 if individual i is exposed to event j (i.e., extubation) at time t , and 0 otherwise.

```
library(survival)
fit.AG <- coxph( Surv( time = Tstart, time2 = Tstop,
                      event = status) ~ group + cluster(id),
                data = mydata)
```

Prentice-Williams-Peterson [6]

$$\lambda_{ij}(t) = Y_{ij}(t)\lambda_{0j}(t)e^{\beta_j Z_{ij}}$$

where $Y_{ij}(t)$ takes the value 1 if individual i is exposed to strata j (i.e., his/her past number of extubations) at time t , and 0 otherwise.

```
library(survival)
fit.PWP <- coxph( Surv( time = Tstart, time2 = Tstop,
                      event = status) ~ group + strata(enum) +
                  cluster(id),
                data = mydata)
```

3. Current ventilation-free survival

Markov multistate model [7]

$$E_j = \int_0^{28} P(X(u) = j) du$$

where E_j is the mean length of stay in a state j (i.e., intubated, extubated, reintubated or dead) on day 28 and $P(X(u))$ is the probability of a state j being occupied over time.

```
library(mstate)
fit.cvfs_msm <- coxph( Surv( time = Tstart, time2 = Tstop,
                      event = status) ~ group.1 + group.2 + group.3 +
                  group.4 + group.5 + group.6 + strata(trans),
                data = mydata, method = "breslow")
```

Three Kaplan-Meier estimators [8]

$$\widehat{CVFS}(t) = \widehat{S}_1^*(t) + \sum_{i=2}^r [\widehat{S}_i^*(t) - \widehat{S}_i(t)]$$

where $\widehat{CVFS}$ is the cumulative ventilation-free survival, $\widehat{S}_1^*(t)$ is the standard ventilation-free survival function, where the event of interest is death in the first extubation or the first loss of extubation (i.e., reintubation), $\widehat{S}_i^*(t)$ (with $i(t) = 2, \dots, r$) are the survival functions corresponding to the subsequent losses of extubation (i.e., reintubations), where the event of interest is death prior to the i th loss of reintubation or the i th loss of extubation, $\widehat{S}_i(t)$ (with $i(t) = 2, \dots, r$) are the survival functions corresponding to the i th achievement of extubation, and r is the maximum number of extubations.

```
library(currentSurvival)
fit.cvfs_km <- clfs(mydata,
                    com.est = F, conf.int = T, no.iter = 1000,
                    strat = T, pvals = T)
```

4. Mixture cure model

$$\lambda_i(t | Z) = \pi(Z_i) + [1 - \pi(Z_i)] \times \lambda_{i_{alive}}(t | Z_i)$$

where $\lambda_i(t | Z_i)$ is the hazard function for an individual i , $\pi(Z_i)$ is the probability of death modelled by logistic regression, and $\lambda_{i_{alive}}(t | x)$ is the conditional survival function for an individual i who did not die, modelled using a Cox model:

$$\pi(Z_i) = \frac{e^{\beta Z_i}}{1 + e^{\beta Z_i}}$$

$$\lambda_{i_{alive}}(t | Z_i) = \lambda_{i_0}(t) \times e^{\beta Z_i}$$

```
library(flexsurvcure)
fit.flex <- flexsurvcure( Surv(extub_time, extub_event) ~ group,
                        data = mydata,
                        dist = "gompertz", link = "logistic", mixture = T,
                        anc = list(rate = ~ group))
```

Appendix 4. Packages of R [3]

We used several packages:

`cmprsk` to the Fine-Gray model.

Gray B (2024). `_cmprsk`: Subdistribution Analysis of Competing Risks_. R package version 2.2-12, <https://CRAN.R-project.org/package=cmprsk>

`currentSurvival` to the current ventilation-free survival (three Kaplan-Meier estimators) [9].

Koritakova E, Pavlik T, Mayer J, Dusek L (2022). `_currentSurvival`: Estimation of CCI and CLFS Functions_. R package version 1.1, <https://CRAN.R-project.org/package=currentSurvival>

`flexsurvcure` to the mixture cure model.

Amdahl J (2025). `_flexsurvcure`: Flexible Parametric Cure Models_. R package version 1.3.3, <https://CRAN.R-project.org/package=flexsurvcure>

`mstate` to the multistate models [10] (multiple events framework and current ventilation free-survival).

Liesbeth C. de Wreede, Marta Fiocco, Hein Putter (2011). `mstate`: An R Package for the Analysis of Competing Risks and Multi-State Models. *Journal of Statistical Software*, 38(7), 1-30. URL <https://www.jstatsoft.org/v38/i07/>

Liesbeth C. de Wreede, Marta Fiocco, Hein Putter (2010) The `{mstate}` Package for Estimation and Prediction in Non- and Semi-Parametric Multi-State and Competing Risks Models. *Computer Methods and Programs in Biomedicine*, 99, 261-274.

Hein Putter, Marta Fiocco, and Ronald B. Geskus (2007) Tutorial in Biostatistics: Competing Risks and Multi-State Models. *Statistics in Medicine*, 26, 2389-2340.

`survival` to the cause-specific Cox model and the recurrent events framework models (i.e., the Andersen-Gill model and Prentice-Williams-Peterson model).

Therneau T (2024). _A Package for Survival Analysis in R_. R package version 3.8-3, <https://CRAN.R-project.org/package=survival>

ABBREVIATIONS

ARDS: acute respiratory distress syndrome;

LIVE: Lung Imaging for Ventilator Setting in Acute Respiratory Distress Syndrome study;

NA: not available.

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TABLES

Table S1. Data structure for competing risks

id	competing_time	competing_event	group
056	6	1	control
095	5	1	personalised

This data structure can be used for both cause-specific Cox model and Fine-Gray model.

Patients (*id*, character variable) were randomly assigned to two groups (*group*, factor variable): control or personalised groups (i.e., experimental).

The time of the event (*competing_time*, numeric variable) is measured in days. The event (*competing_event*, numeric variable) may have three possible values: 0 if the patient was censored, 1 if the patient was extubated (i.e., the event of interest) and 2 if the patient died (i.e., the competing event).

Definition of abbreviations: id: identifier.

Table S2. Data structure for multiple events framework

id	from	to	Tstart	Tstop	trans	status	group	group.1	group.2	group.3	group.4
056	1	2	0	6	1	1	control	0	0	0	0
056	1	3	0	6	2	0	control	0	0	0	0
056	2	1	6	7	3	1	control	0	0	0	0
056	2	3	6	7	4	0	control	0	0	0	0
056	1	2	7	9	1	1	control	0	0	0	0
056	1	3	7	9	2	0	control	0	0	0	0
056	2	1	9	11	3	1	control	0	0	0	0
056	2	3	9	11	4	0	control	0	0	0	0
056	1	2	11	15	1	1	control	0	0	0	0
056	1	3	11	15	2	0	control	0	0	0	0
056	2	3	15	99	4	0	control	0	0	0	0
056	2	1	15	99	3	0	control	0	0	0	0
095	1	2	0	5	1	1	personalised	1	0	0	0
095	1	3	0	5	2	0	personalised	0	1	0	0
095	2	3	5	25	4	1	personalised	0	0	0	1
095	2	1	5	25	3	0	personalised	0	0	1	0

Patients (id, character variable) were randomly assigned to two groups (group, factor variable): control or personalised groups (i.e., experimental).

Patients could present three states: intubated (1), extubated (2) and death (3). They may transit from one state (*from*, numeric variable) to another (*to*, numeric variable). There were four possible transitions (*trans*, numeric variable): 1 (from intubated to extubated), 2 (from intubated to death), 3 (from extubated to intubated, again) and 4 (from extubated to death). For each transition, they were two possible status (*status*, numeric variable): 0 if the patient was censored, 1 if the patient presented the state. Finally, the group was split into 4 variables (*group.1*, *group.2*, *group.3* and *group.4*, all numeric variables) according to the transition.

Definition of abbreviations: id: identifier.

Table S3. Data structure for recurrent events framework: Andersen-Gill model

id	Tstart	Tstop	status	group
056	0	6	1	control
056	6	9	1	control
056	9	15	1	control
095	0	5	1	personalised
095	5	25	0	personalised

Patients (*id*, character variable) were randomly assigned to two groups (*group*, factor variable): control or personalised groups (i.e., experimental).

The only event of interest was the extubation (*status*, numeric variable): 0 if the patient was censored, 1 if the patient was extubated. Patients could present several recurrences of extubation, where (*Tstart*, numeric variable) (*Tstop*, numeric variable) is used to define the time interval of risk.

Definition of abbreviations: id: identifier.

Table S4. Data structure for recurrent events framework: Prentice-Williams-Peterson model

id	Tstart	Tstop	status	enum	group
056	0	6	1	1	control
056	6	9	1	2	control
056	9	15	1	3	control
095	0	5	1	1	personalised
095	5	25	0	2	personalised

Patients (*id*, character variable) were randomly assigned to two groups (*group*, factor variable): control or personalised groups (i.e., experimental).

The only event of interest was the extubation (*status*, numeric variable): 0 if the patient was censored, 1 if the patient was extubated. Patients may have experienced multiple extubation episodes, with each episode defined by the time interval from (*Tstart*, numeric variable) to (*Tstop*, numeric variable) indicating the risk period.

For each recurrence, the event was recorded as an occurrence count (*enum*, numeric variable), representing the sequence number of the extubation.

Definition of abbreviations: id: identifier.

Table S5. Data structure for current ventilation-free survival (multistate)

id	from	to	Tstart	Tstop	trans	status	group	group.1	group.2	group.3	group.4	group.5	group.6
056	1	2	0	6	1	1	control	0	0	0	0	0	0
056	1	4	0	6	2	0	control	0	0	0	0	0	0
056	2	3	6	7	3	1	control	0	0	0	0	0	0
056	2	4	6	7	4	0	control	0	0	0	0	0	0
056	3	2	7	9	5	1	control	0	0	0	0	0	0
056	3	4	7	9	6	0	control	0	0	0	0	0	0
056	2	3	9	11	3	1	control	0	0	0	0	0	0
056	2	4	9	11	4	0	control	0	0	0	0	0	0
056	3	2	11	15	5	1	control	0	0	0	0	0	0
056	3	4	11	15	6	0	control	0	0	0	0	0	0
056	2	4	15	99	4	0	control	0	0	0	0	0	0
056	2	3	15	99	3	0	control	0	0	0	0	0	0
095	1	2	0	5	1	1	personalised	1	0	0	0	0	0
095	1	4	0	5	2	0	personalised	0	1	0	0	0	0
095	2	4	5	25	4	1	personalised	0	0	0	1	0	0
095	2	3	5	25	3	0	personalised	0	0	1	0	0	0

Patients (id, character variable) were randomly assigned to two groups (group, factor variable): control or personalised groups (i.e., experimental).

Patients could present three states: first intubation (1), extubated (2), relapse intubation (3) and death (4). They may transit from one state (from, numeric variable) to another (to, numeric variable). There were six possible transitions (trans, numeric variable): 1 (from intubated to extubated), 2 (from intubated to death), 3 (from extubated to intubated again, i.e., relapse intubation), 4 (from extubated to death), 5 (from relapse intubation to extubated) and 6 (from relapse intubation to death). For each transition, they were two possible status (status, numeric variable): 0 if the patient was censored, 1 if the patient presented the state. Finally, the group was split into 6 variables (group.1, group.2, group.3, group.4, group.5 and group.6, all numeric variables) according to the transition.

Definition of abbreviations: id: identifier.

Table S6. Data structure for current ventilation-free survival (Kaplan-Meier)

extub_1	intub_2	extub_2	intub_3	extub_3	follow_up	dc	group
6	7	9	11	15	99	0	0
5	NA	NA	NA	NA	25	1	1

Patients were randomly assigned to two groups (`group`, numeric variable): 0 (i.e., control group) or 1 (i.e., personalised group). The first line corresponds to patient 056 and the second line to the patient 095. Please ensure that the data is presented in this order when using the `currentSurvival` package [9] and that the table class is a `dataframe`.

Patients may have experienced multiple intubation episodes (`intub_2` and `intub_3`, numeric variables) and extubation (`extub_1`, `extub_2` and `extub_3`, numeric variables) episodes. Additionally patient mortality is recorded (`dc`, numeric variable), and follow-up data (`follow_up`, numeric variables) are collected until the time of death or the last recorded follow-up.

Definition of abbreviations: NA: not available.

Table S7. Data structure for mixture cure model

id	extub_time	extub_event	group
056	15	1	0
095	99	0	1

Patients (*id*, character variable) were randomly assigned to two groups (*group*, numeric variable): 0 (i.e., control group) or 1 (i.e., personalised group).

The time-to-extubation (*extub_time*, numeric variable) is measured in days. The extubation (*extub_event*, numeric variable) may have two possible values: 0 if the patient was censored (due to death or remained intubation), 1 if the patient was extubated.

Definition of abbreviations: id: identifier.