

Alternatives to Ventilator-Free Days in Critical Care Studies

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<http://www.biostat.ucsf.edu/dave/talks.html>

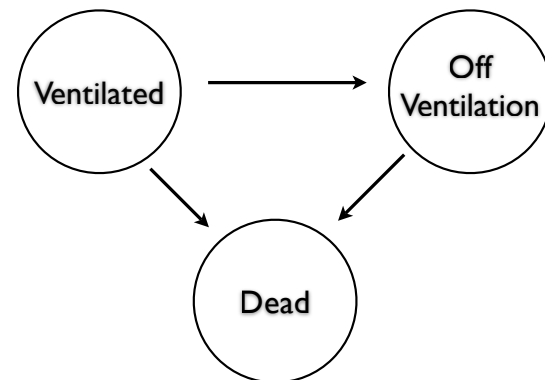
Example

- Collaboration with KD Liu
- Patients from FACTT trial
- Red blood cell transfusion (RBC)
- Does it increase time on the ventilator?
Does it increase risk of death?
- RBC given over clinical course in ICU

Critical Care Data

- Patients on ventilator
- Follow over 28 day period
- Patients may recover or die
- Outcome: Ventilation/Death
- Example of *multiple outcome data*

ALI Example



Considerations

Investigators have suggested...

- Not interested in when deaths occur
- Not interested in vent. duration if died
- Loss to follow-up: uncommon
- Some predictors change over time
time-dependent covariates

Notation

$$\Delta_i = \begin{cases} 1: \text{subject } i \text{ alive at 28 days} \\ 0: \text{subject } i \text{ dead at 28 days} \end{cases}$$

$$X_i = \text{number of days (up to 28) off ventilator}$$

Lots of ways to define “days off ventilator”

Two data components

Δ_i survival at 28 days

$X_i \mid \Delta_i = 1$ ventilator duration if person survives to day 28

Ignores when people died

Discards X_i if person died

Ventilator-Free Days

- Composite Outcome:
- Days off ventilator if person survives
- For subjects who die, VF days set to 0

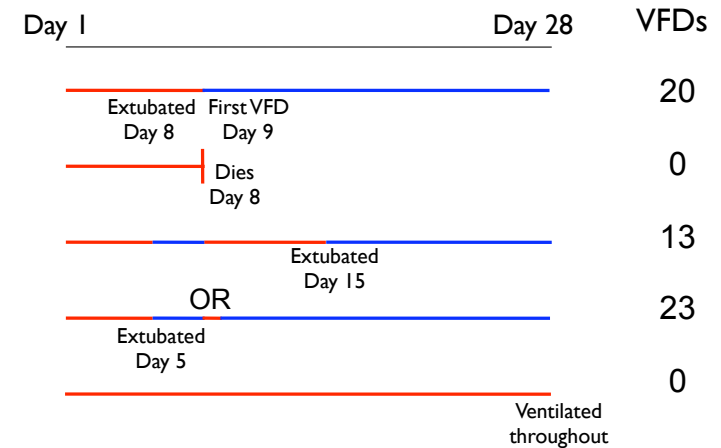
$$VFD_i = \begin{cases} X_i: \text{subject } i \text{ alive at 28 days} \\ 0: \text{subject } i \text{ dead at 28 days} \end{cases}$$

$$VFD_i = X_i * \Delta_i$$

FDA definition

- # days of unassisted breathing to day 28
 - Patient unassisted to day 28 (eg, if the patient is re-intubated, UAB starts at the time of successful extubation, unless re-intubated for a surgical procedure and period of UAB is < 24 hours)
 - If patient dies, VFD = 0
 - First VFD = first day patient achieves UAB from midnight to midnight

Ventilator Free Days



VFD Analysis

- Compare two groups
- Use Mann-Whitney U test
aka: Wilcoxon test
- Gives a p-value for effects on both outcomes
- VFD has important limitations

Critique of VFD

- Combines apples and oranges
- Isn't always most powerful
- Fails to parse effects on two outcomes
- Doesn't handle time-dependent covariates

Mean of VFD

$$E(\text{VFD}) = \text{Pr}(\text{Survival}) * E(X | \Delta = 1)$$

average of VFD fraction surviving to day 28 average time off vent for survivors

similar formula is true for the median

VFD Limitations

- Defines a composite outcome
- Puts death & vent. days on same scale
- Natural order but awkward scale
- What does avg.VFD of 11.9 days mean?

Apples and Oranges

Rx 1: 70% Survival,
Avg. time off vent (survivors): 17 days
mean VFD = 11.9 days

Rx 2: 50% Survival,
Avg. time off vent (survivors): 23.8 days
mean VFD = 11.9 days

20% survival = 6.8 days of ventilator

Implied numerical equivalence

My concern

- 20% survival = 6.8 days of ventilator
- Equivalent is implicit and not explicit
- Can't control/vary the correspondence!

Power

Testing for Effects

- Wilcoxon for VFD: uses composite outcome
- Alternative: test for two components pooled
- Can choose arbitrary weight for pooling
- More control over relative emphasis
- Easy to find tests with excellent power

Example

- Z_1 : Wilcoxon test for $X|\Delta = 1$
- Z_2 : Z-test for survival
- Two tests “independent”
- $Z_1^2 + Z_2^2$: pooled test, follows a chi-square

Simulation

- Generated data from hypothetical trials
- 500 trials
- 250 patients/group
- Control: survival 70%, vent 18d (survivors)
- Considered different treatment effects

Equal Survival

- Control: 70% surv. $E(X|\Delta=1) = 18$
- Treat: 70% surv. $E(X|\Delta=1) = 20$
- Power (VFD Wilcoxon): 0.45
- Power (pooled chi-squared): 0.79

Equal Vent Time

- Control: 70% surv. $E(X|\Delta=1) = 18$
- Treat: 88% surv. $E(X|\Delta=1) = 18$
- Power (VFD Wilcoxon): 0.69
- Power (pooled chi-squared): 0.88

Discordant Effects

- Control: 70% surv. $E(X|\Delta=1) = 18$
- Treat: 60% surv. $E(X|\Delta=1) = 20$
- Power (VFD Wilcoxon): 0.09
- Power (pooled chi-squared): 0.94

Concordant Effects

- Control: 70% surv. $E(X|\Delta=1) = 18$
- Treat: 80% surv. $E(X|\Delta=1) = 20$
- Power (VFD Wilcoxon): 0.98
- Power (pooled chi-squared): 0.96

Pooled Test

- Alternative to test of VFD
- Combines two natural tests
- More flexible (can control weights)
- Excellent power

Regression

Regression

- Summarizes predictor effects
- Relates outcome mean to predictors
- Mean VFD is awkward
- VFD: no time-dependent predictors

FACCT Trial

	Conserv.	Liberal
mean VFD	14.6 d	11.2 d

Difference in survival? time off vent?

FACCT Trial

	Conserv.	Liberal
$E(X \Delta=1)$	19.6 d	16.9 d
Survival	74%	72%
mean VFD	14.6 d	11.2 d

Regression Strategy

- Separate regression for data components
 - $X|\Delta=1$ (continuous): linear regression
 - Δ (binary): logistic regression
- Accommodates various predictors
 - Multiple, continuous, time-dependent

Time Dependent Covariates

Time Dependent Covariates

A time-dependent covariate is a predictor whose values may vary with time

...and measured during the study

Example: RBC transfusion in FACTT

RBC Transfusion

- Not defined at baseline
- Some get transfused, others not (over time)
- Simple approach: ever v. never transfused
- Can be greatly misleading!

Example

- Patients ever exposed to RBC vented longer
- Transfused patients: two kinds of vent time
- Time before Trx: longer than non-Trx
- Time after trans: same as Trans- subjects
- Should time before Trans count for Trans+?

Time dependent covariate

Treat tranf. as a time-dependent covariate

$$\text{transf.} = \begin{cases} 0 & \text{before transfusion} \\ 1 & \text{after transfusion} \end{cases}$$

$$\text{risk} = \begin{cases} \text{baseline risk before transfusion} \\ \text{RR} * \text{baseline risk after transfusion} \end{cases}$$

two groups but membership changes

Model #1

- Cox model for survival
- Predictors entered as td covariates
- Builds a model for pr(survive to 28 days)

Survival Time

Cox regression -- Breslow method for ties

```
No. of subjects =      973      Number of obs =      6530
No. of failures =       81
Time at risk    =     6530
Log likelihood   = -541.89494      LR chi2(1)    =      5.32
                                      Prob > chi2    =     0.0210
```

_t	Haz. Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
prbc	2.153839	6572039	2.51	0.012	1.184363 3.916892

transfusions double risk of death

Model #2

- Ventilator-Free Days
- Repeated events among survivors
- Each day off vent is repeated event
- Model rate of new days off ventilator

Summary

- Death and vent. time both of interest
- VFD composite outcome
- Better to treat outcomes separately
- Can pool tests with flexible weight
- Separate approach gives fuller picture