Immortal Time Bias and Issues in Critical Care

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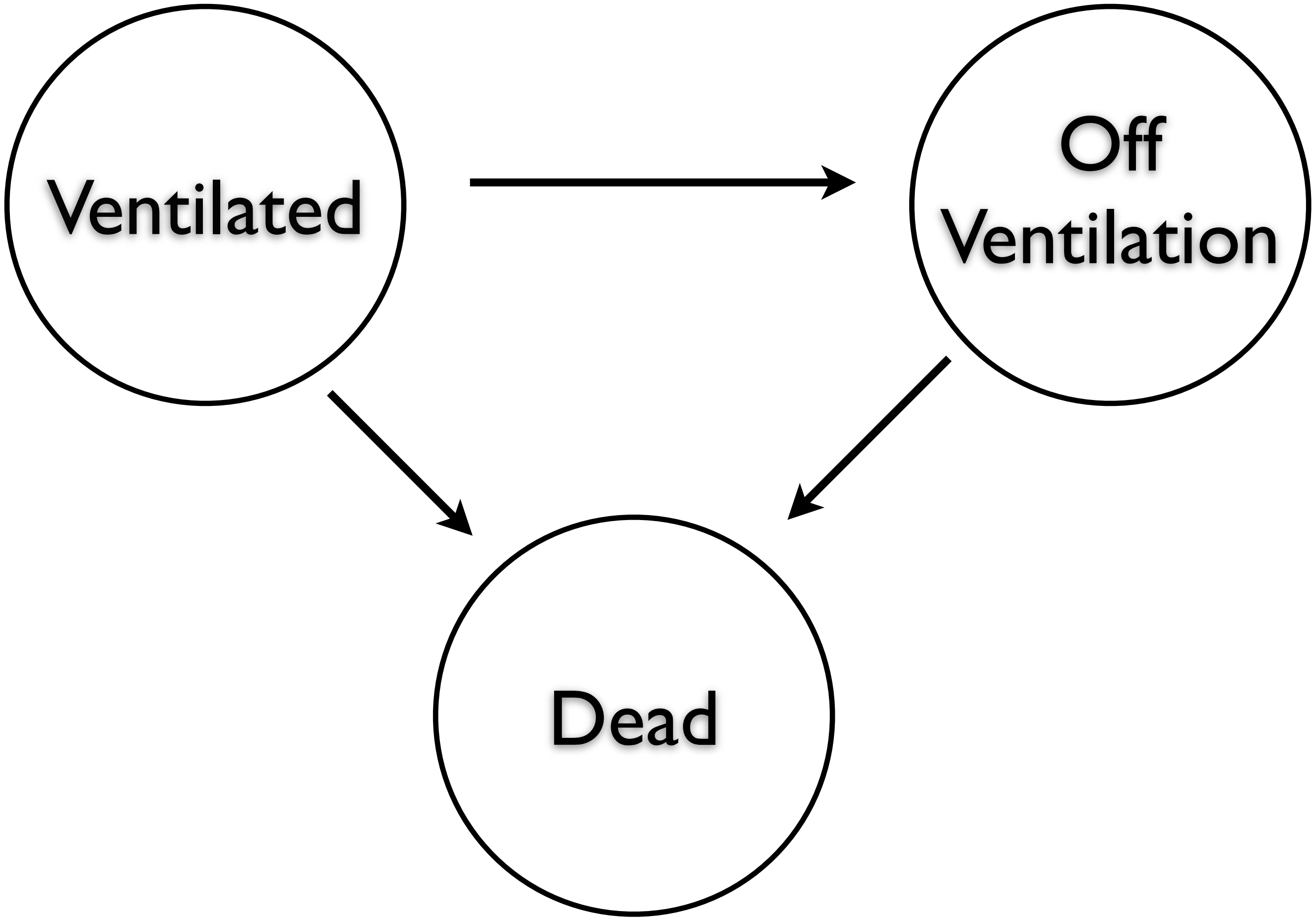
Critical Care

- Acute Respiratory Distress Syndrome
- Patients on ventilator
- Patients may recover or die
- Outcome: Ventilation/Death

ARDS Example



Ventilator-Free Days

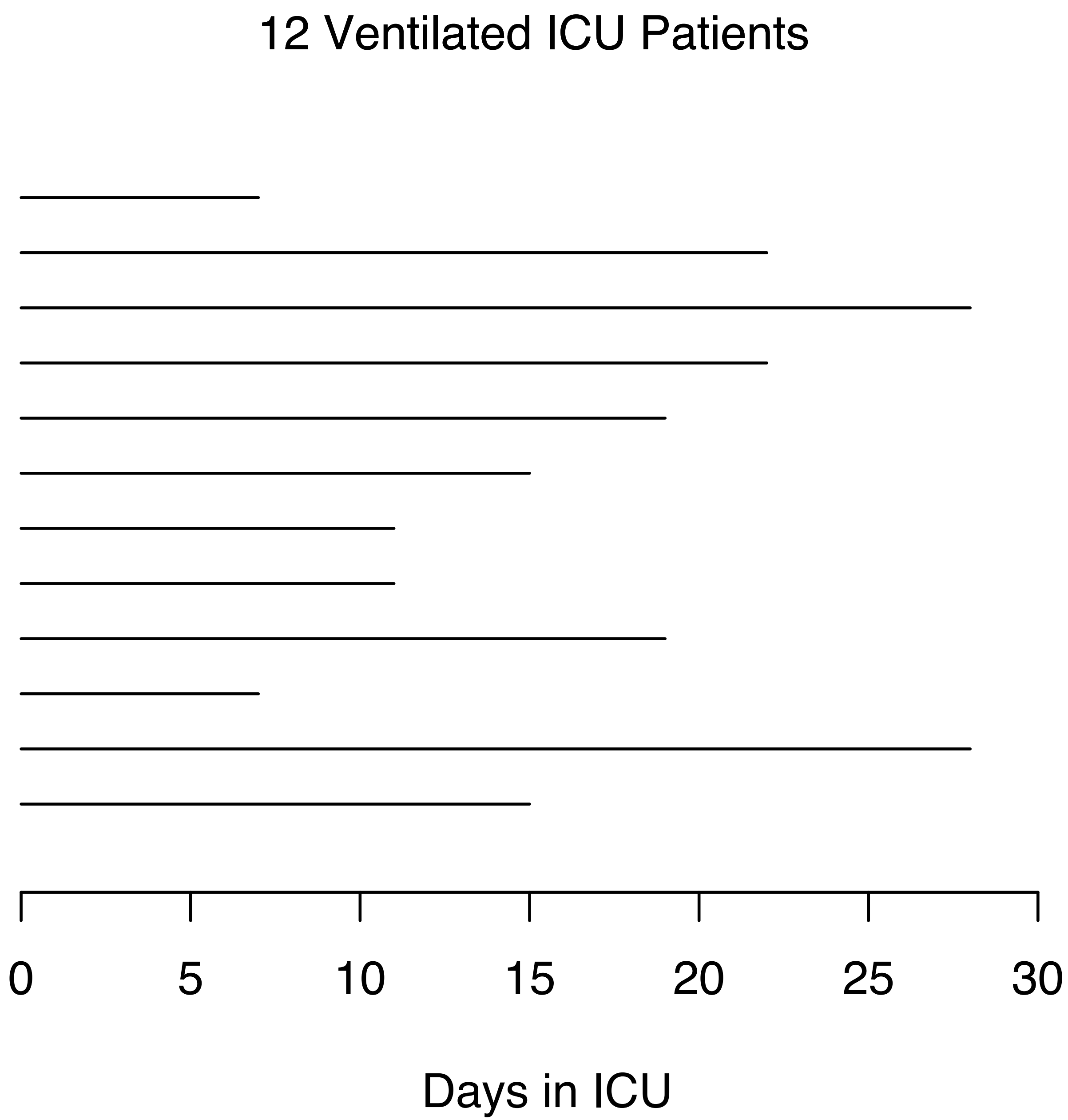
- Count days off ventilator (until day 28) ventilator-free days (VFD)
- For subjects who die, VF days set to 0
- Two-group: Mann-Whitney U-test
- Approach designed for clinical trial

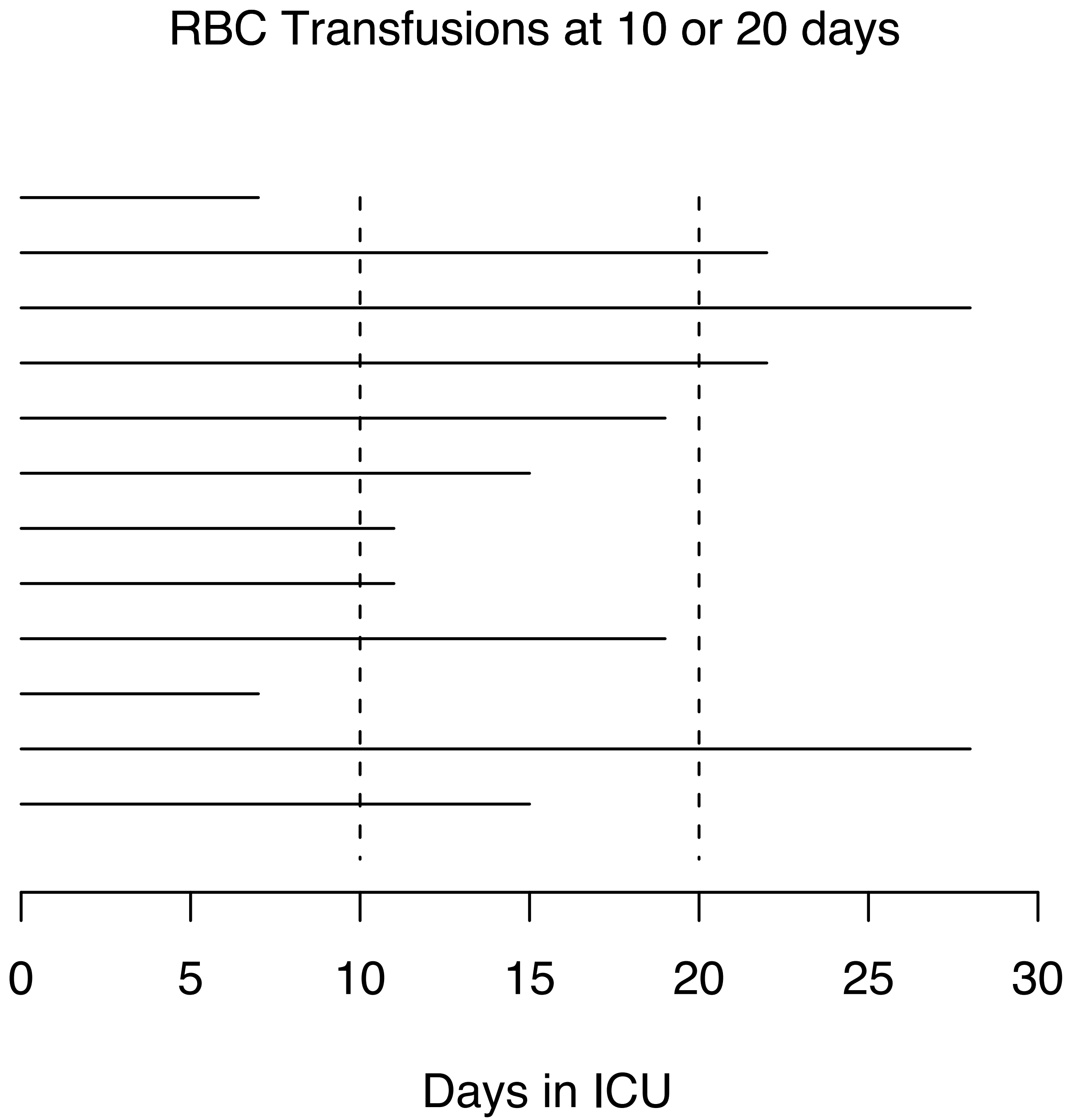
Data Example

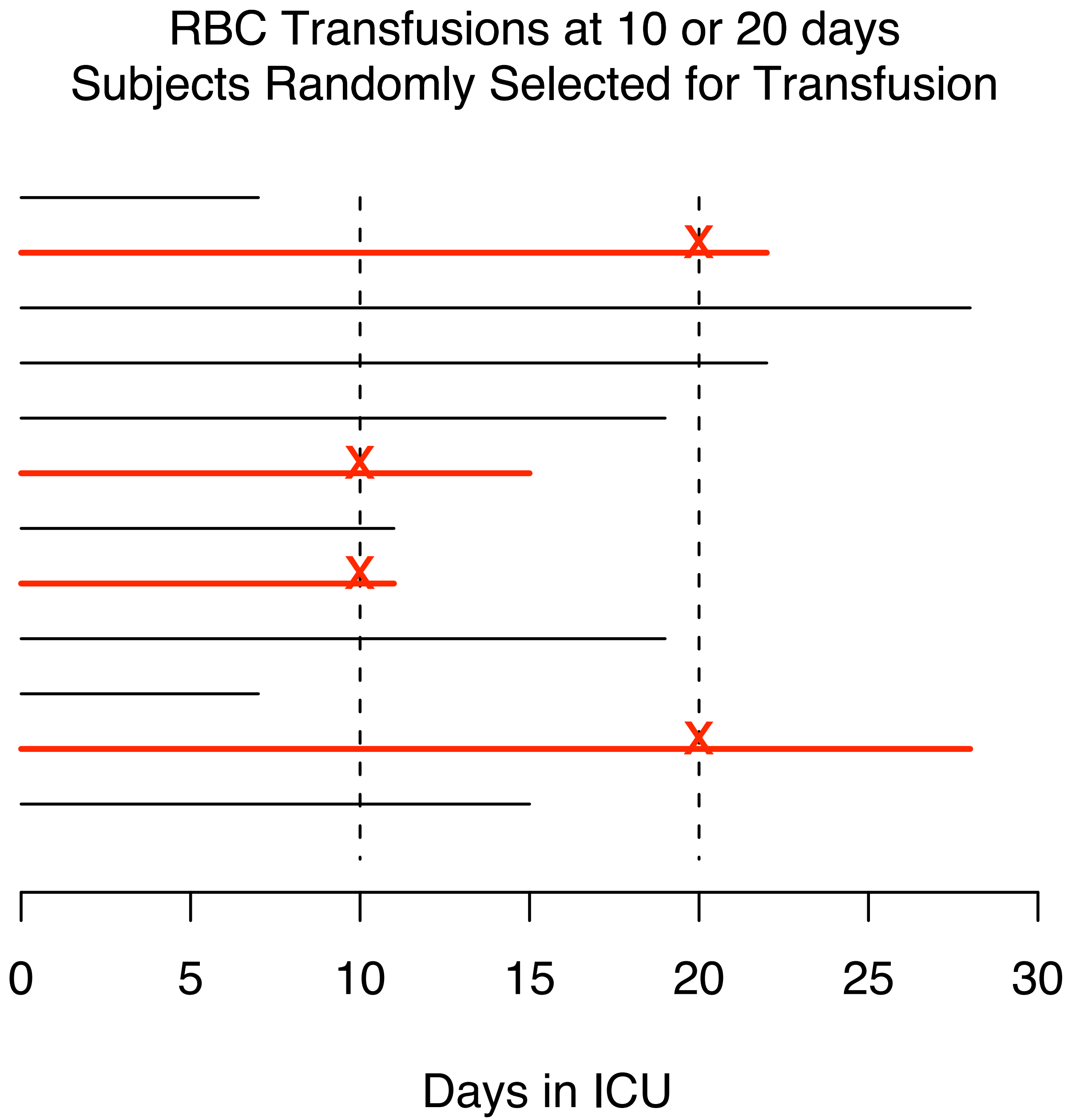
- Collaboration with ICU investigators
- Cohort of ventilated patients
- Red blood cell transfusion (RBC)
- Does it increase time on the ventilator? Does it increase risk of death?
- RBC given over clinical course in ICU

Simplistic Example

- Consider 12 ventilated patients
- RBC occurs at 10 or 20 days into ICU
- Do RBC patients have longer stay
- An example of immortal time bias


12 Ventilated ICU Patients
0
5
10
15
20
25
30
Days in ICU

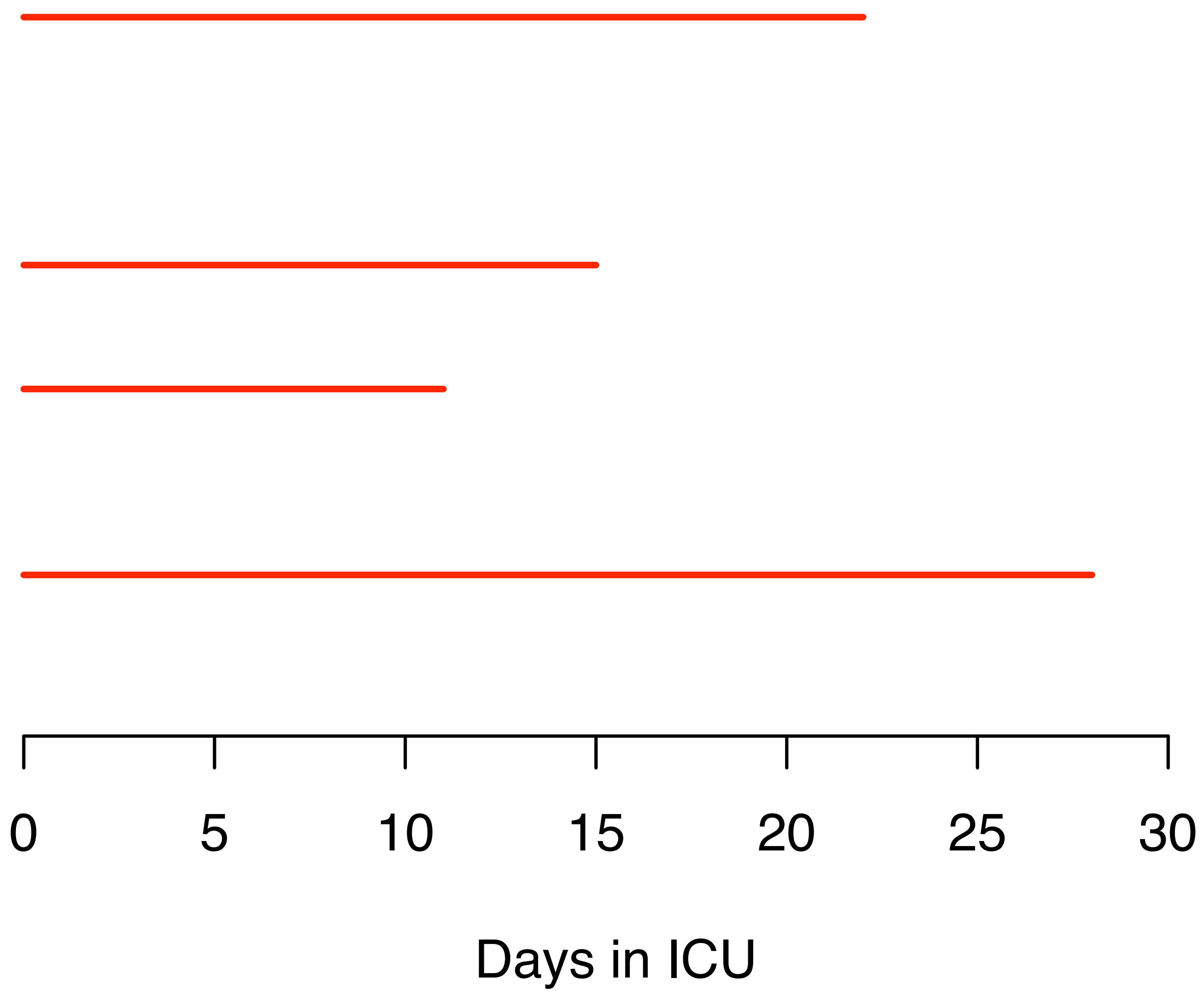

RBC Transfusions at 10 or 20 days
0
5
10
15
20
25
30
Days in ICU

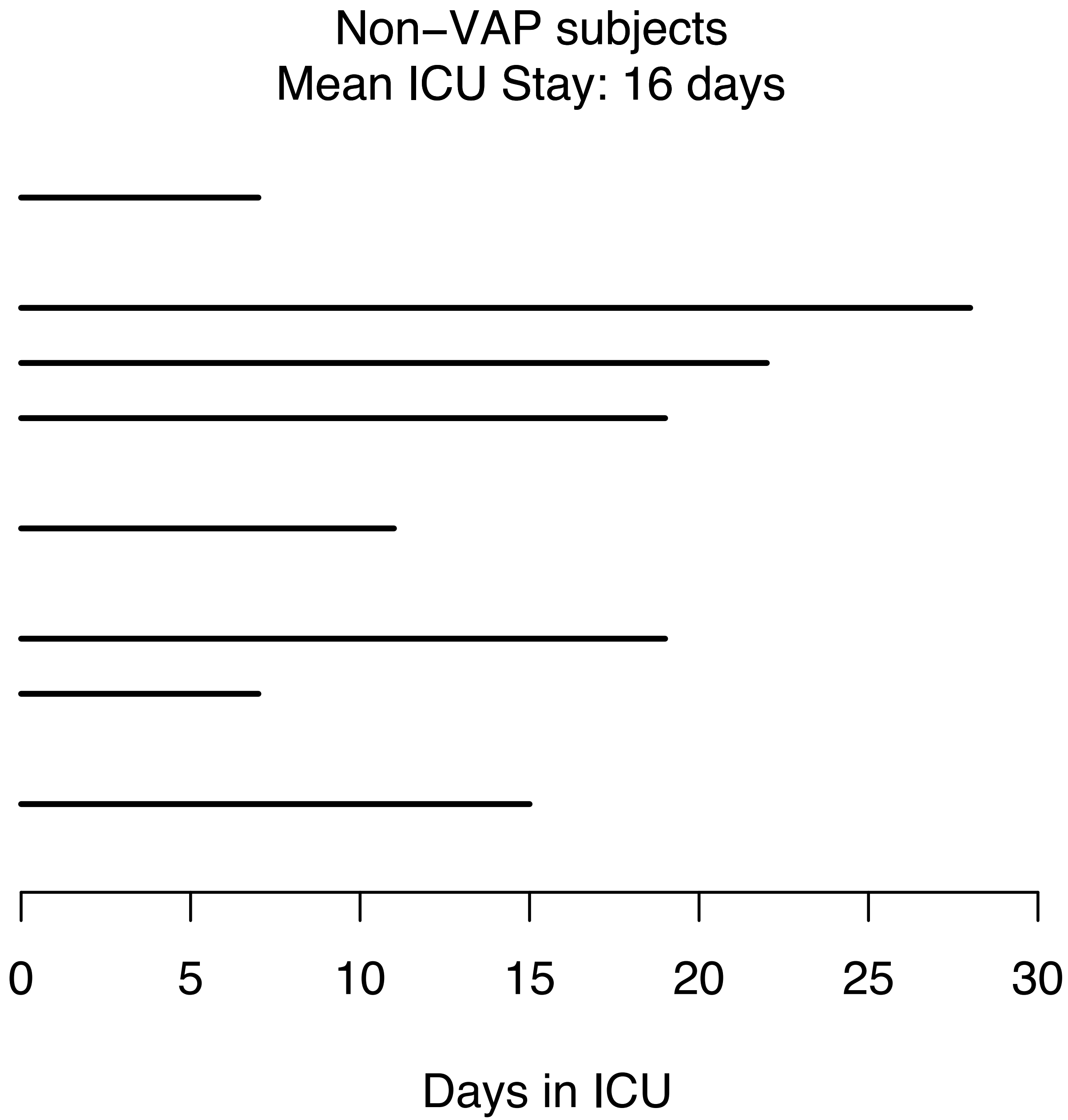


RBC Transfusions at 10 or 20 days
Subjects Randomly Selected for Transfusion
X
X
X
X
0
5
10
15
20
25
30
Days in ICU

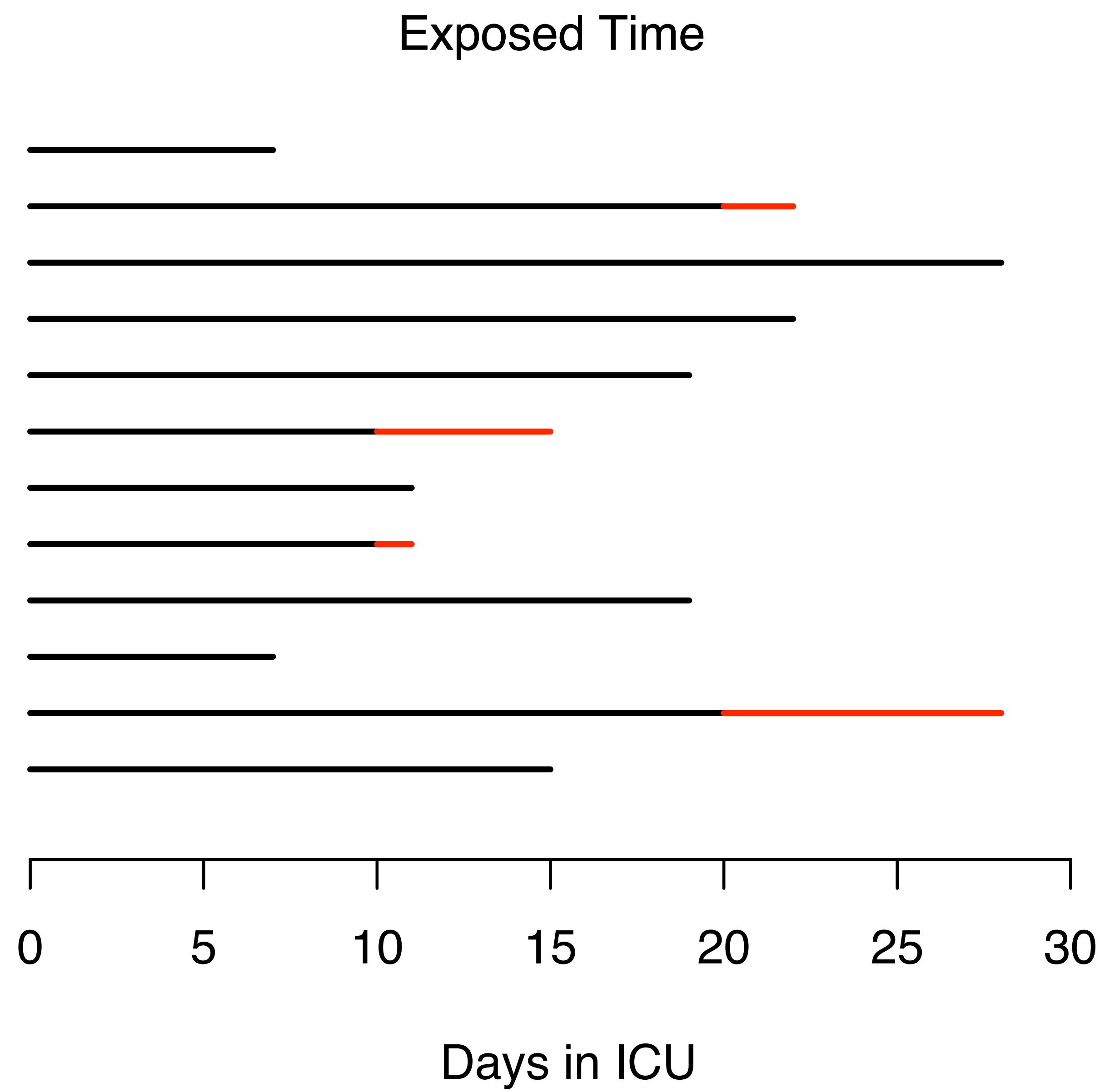
Transfused Subjects

Mean ICU Stay: 19 days

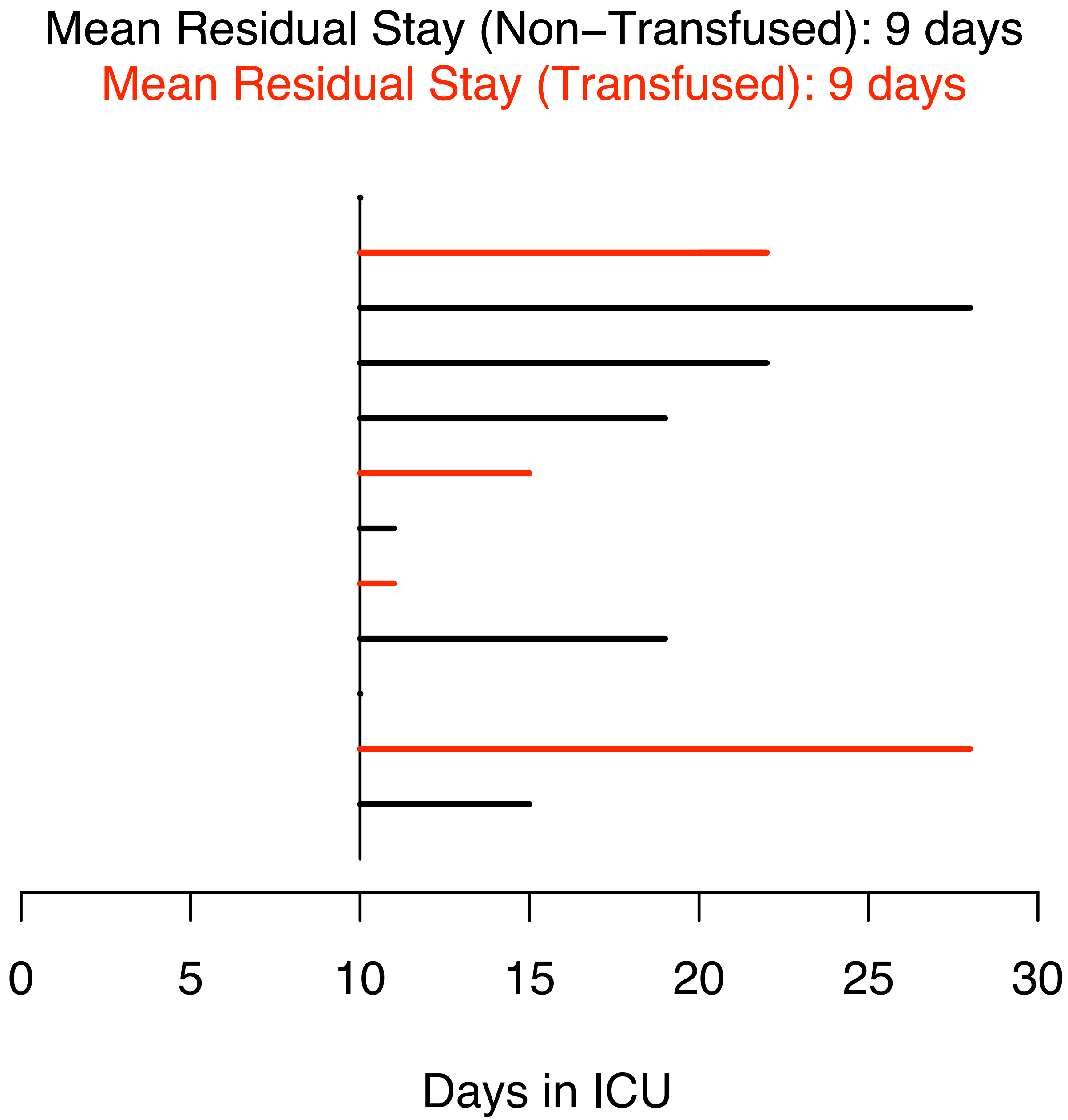


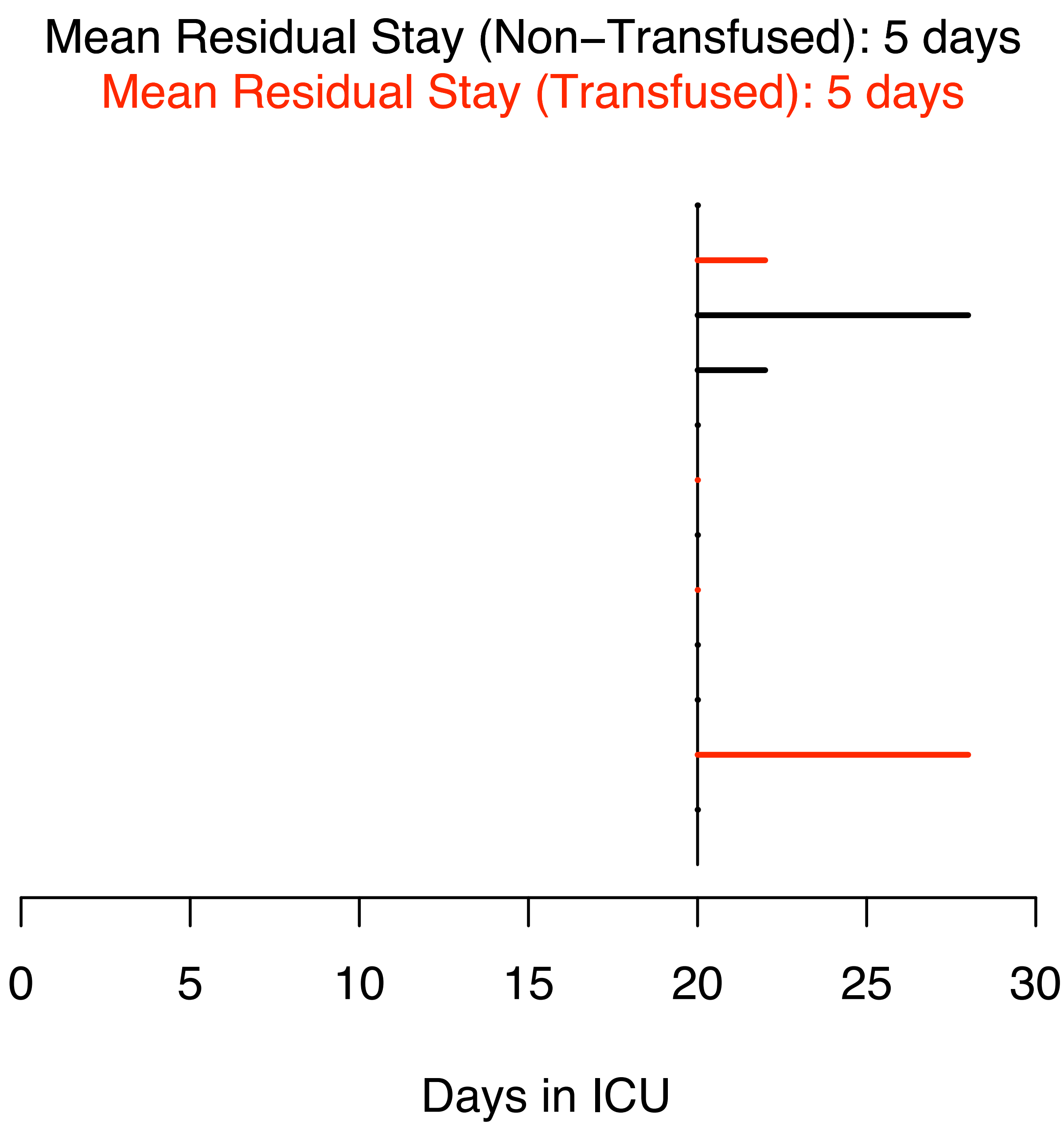


Non−VAP subjects
Mean ICU Stay: 16 days
0
5
10
15
20
25
30
Days in ICU



Exposed Time
0
5
10
15
20
25
30
Days in ICU


Mean Residual Stay (Non−Transfused): 9 days
Mean Residual Stay (Transfused): 9 days
0
5
10
15
20
25
30
Days in ICU


Mean Residual Stay (Non−Transfused): 5 days
Mean Residual Stay (Transfused): 5 days
0
5
10
15
20
25
30
Days in ICU

Example

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

Other Examples

- PTLD increase risk of death in kidney tx?
- Does heart tx extend life in listed patients?
- Do OSCAR winners live longer?
- Common thread: exposure occurs sometime after follow-up
- PTLD, transplants, awards occur over time

Immortal Time Bias

Recent study

- Statin subjects develop BCC after starting statins: FU time before statins is immortal
- Adds time to statin+ group
- Will underestimate BCC rate in statin
- How can we handle this?

Steroids in COPD
A more subtle example

- Cohort patients discharged after COPD-related illness
- Exposure: inhaled corticosteroids (ICS)
- Outcome: death or hospitalization in 1 yr
- Exposed if filled ICS prescription in 90 days
- That 90 days leads to the bias

Two Classic Approaches

- Matching
- Regression

Matching

- Identifies cases of BCC
  Case #156: BCC at 6 years, no statins
- Has matched control(s)
  Cont. #156-1: BCC- at 6 years,
  2 years statin use (years 8-10)
- Control is unexposed! Only count statin exposure up to year 6
- Fair: don't count statin exposure after BCC

Careful Matching

- Matched controls can become cases
- Control for case #156 selected at random from those with no BCC after 8 years
- Choosing from no BCC after 10 years induces slight bias
- If disease is rare, bias is negligible

Analysis

- Matched design requires matched analysis
- Conditional logistic regression (binary)
- Stratified Cox model (time-to-event)
- Makes comparisons within pairs only

Time Dependent Covariates

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

....and measured during the study

Regression Approach

- Creates exposure variable:
  1: statins   0: no statins
- Acknowledges that exposure changes
- Time prior to exposure, statin=0
- Time after exposure: statin=1
- Time-dependent covariate!

Time dependent covariate

Treat statin as a time-dependent covariate

$$\text{statin} = \begin{cases} 0 & \text{before initiating statins} \\ 1 & \text{after initiating statins} \end{cases}$$

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

two groups but membership changes

Two patients

- Case #156: BCC at 6 years, no statins
- Cont. #156-1: BCC- at 10 years,
  2 years statin use (years 8-10)
- Can code as time-dependent covariates

Data

	idno	t_from	t_to	statin	bcc
219.	156	0	6	0	1
200.	156-1	0	8	0	0
221.	156-1	8	10	1	0

idno: indicates subjects

t_from: start of interval

t_to: end of interval

statin: statins in interval

bcc: bcc in interval

Time-Dependent Covs

- Can be incorporated into Cox regression
- Use all the FU data
  doesn't discard FU just for matching
- Takes duration into account
- Some delicate modeling issues
- Doesn't work for all outcomes
  e.g., *ventilator free days*

Bad News

- Survival of OSCAR winners
  reanalysis show 1 year survival advantage
  not significant
- Inhaled steroids in COPD
  extensively studied and debated
  appears advantage due to immortal time
- Suissa (2007) documents 20 studies with this possible bias

TD Covs in Vent-Free Days

- X_i: Number of Ventilator-Free Days
- Δ_i: Alive at 28 days (1=yes, 0=no)
- VDF = $X_i \Delta_i$
  - Model 1: $pr(\Delta_i = 1)$
  - Model 2: $f(X_i \mid \Delta_i = 1)$

Model #1

- Cox model for survival
- Predictors entered as TD Covs
- Builds a model for pr(Δ_i = 1)
  = 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
                                                   LR chi2(1)      =      5.32
Log likelihood  =   -541.89494                     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
------------------------------------------------------------------------------
```

Model #2

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

Time on Ventilator

```
No. of subjects      =          720                Number of obs   =       4974
No. of failures      =          972
Time at risk         =         4974
                                                   Wald chi2(1)    =      25.32
Log pseudolikelihood =   -6023.2217                Prob > chi2     =     0.0000

                                (Std. Err. adjusted for 720 clusters in patno)
------------------------------------------------------------------------------
             |               Robust
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        prbc |   .2844534    .071075    -5.03   0.000     .1743112    .4641911
------------------------------------------------------------------------------
```

Model for VFD

- $E(VFD \mid Z) = pr(\Delta=1|Z)\ E(X|\Delta=1,Z)$
- First part from model 1
- Second term from model 2
- Other combinations are possible as well

Results

- Possible to model td cov but requires survival analysis methods
- Even in the absence of censoring
- Survival analysis keep track of time carefully *essential for avoid immortal time bias*