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Comparison of power between different recurrent events analysis methods using simulation

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ABSTRACT

Recent research in Cardiovascular diseases has resulted in significant advancements in statistical methodologies which have played crucial role to improve the understanding of CVD risk factors and treatment of CVD and to find out effective strategies to reduce burden of CVD. Although Cox proportional hazards regression models have traditionally been used to analyse CVD data, the chronic nature of the disease necessitates addressing complicated scenarios such as recurrent events which provides a more comprehensive picture of disease progression and quality of life. In RCT with recurrent events the power calculation methods are less straightforward and different approaches can be taken. Considering the assumptions simulation studies will be utilized to compare power calculation by time to first event analysis (Cox) with different recurrent events analysis methods such as semi-parametric proportional rates model (LWYY) and mean cumulative incidence function model “adjusted for death as terminal event” (Ghosh and Lin).

Keywords : Power, cardiovascular, recurrent events, time-to-first, win-ratio, LWYY, Ghosh-Lin, survival analysis.

INTRODUCTION

Cardiovascular disease(CVD) is the major cause of morbidity and mortality worldwide accounting to over 17 million deaths annually. Through research there has been rapid advances in technology, use of digital health. Advanced statistical methodologies have played crucial role to improve the understanding of CVD risk factors and treatment of CVD disease and to find out effective strategies to reduce burden of CVD.

In CVD clinical trials the time to first event analyses are widely used and have been the gold standard of survival analysis. But there are certain limitations of time to first event analyses such as there is substantial loss of information as no consideration of recurrent events and there is no differentiation between mortality and morbidity. Also, it avoids competing risks. On the other hand, there are several instances seen in recent guidance from EMA and FDA where they have acknowledged the use of recurrent events analysis methods. The guideline on developing treatments for chronic heart failure (CHF) issued by the Committee for Medicinal Products for Human Use (CHMP) in 2017 acknowledged the clinical significance of recurrent hospitalization for heart failure (HHF). However, it also acknowledged the substantial difficulties associated with analyzing recurrent event data in the presence of a terminal event. FDA (2019) guidance also had discussed on acceptable approaches of use of recurrent hospitalisations.

Also, as chronic diseases are characterised by “recurrent encounters” and hence the true burden of the disease can only be known by the participants’ journey. We, as biostatisticians care about recurrent events because it increases the statistical power and decreases the sample size. But, we need to also consider the economic burden of these chronic failures and in that sense, we should consider the efficacy of a therapy along with the cost. We should find whether the drug is having persistent effect or not or does the treatment’s efficacy extends beyond initial occurrence i.e. does it provide consistent benefits over preventing or manging subsequent events also? That is the reason we should evaluate the burden of the participants throughout the trial duration in these therapeutic area studies.

Recurrent events such as repeated falls among elderly and transient ischemic attacks and hospitalization due to CVD or progression of tumor being very common in these chronic diseases. Hence, it is important to consider looking at the participant’s journey not only for analysis but also to get more comprehensive picture of disease progression and quality of life.

METHODOLOGY

Suppose, we consider a study where we are interested in composite endpoints such as
(1) CV hospitalization and CV death or (2) CV hospitalization and all-cause death
In this case Death (CV or Non-CV) will both be competing events.

There are several models which can be used for analyzing such data, such as in terms of Rate models we can use Anderson-Gill model which provides cause specific hazard ratio. It is an extension of Cox proportional hazards model where events are considered to be independent.

Similarly there is Lin-Wei-Yang-Ying (LWYY) Or Anderson-Gill with robust variance estimator also where target of estimation is rate ratio. This method accounts for the dependence of recurrent events on same subjects. In this method we consider conditional rate (conditional on being alive and at risk) hence the subjects after death do not contribute to the likelihood function. Here, Non-CV death is taken out of the risk set and CV-death is considered as an event.

For an example,

	id	enum	t.start	t.stop	event	death	reason	AG/LWYY	Censoring/Removal from risk set
1	1	1	0	24	1	0		1	
2	1	2	24	457	1	0		1	
3	1	3	457	1037	0	0	lost-to-follow-up	0	Cens.
4	2	1	0	489	1	0		1	
5	2	2	489	1182	0	1	CV-death	1	
6	2	3	1182	1183				0	Remov.
7	3	1	0	15	1	0		1	
8	3	2	15	783	0	1	Non CV-death	0	Remov.

The essence of the problem is different, i.e. the terminology of censoring. Subject ID : 1, is censored as its lost to follow up but for the Subject ID : 2, the CV death is considered as a composite event and then its removed in the next step from the risk set. We must acknowledge, this is a technical trick, still competing risk is a problem here. At times, we assume non-CV death is non-dependent in analysis i.e. similar in two arms. But, we don't normally know that upfront.

Among the marginal models, there is Ghosh-Lin model where the target of estimation is mean ratio. This models marginal mean function but here death is included in competing risk acknowledging the fact that no recurrences can happen after death. The counting process continues after death and stays flat (no jumps) until the end of study. Here the model specification is same as LWYY. The estimating equations here are updated as to re-weight the data from subjects that have died. Next, terminal events are correctly handled by adjustment for death using IPCW or IPSW.

Here suppose, according to our clinical question of interest and objective of a study endpoint under consideration is : Number of occurrences of the composite endpoint consisting of – (1) All cause death and (2) Recurrent CV hospitalizations.

Our time frame of interest is : From baseline to end of study (up to 36 months)

Such studies, are event driven and there can be several ways in which we can design the study.

For example, Based on –

(i) The number of first occurrences (not recurrent) of the composite endpoint consisting of all-cause death and CV events

(ii) The number of first and second occurrence of event

(iii) The number of total occurrences of event

Here we have designed the study based on number of first occurrence (though we want to explore recurrent analysis methods). The reason behind this is, we want to ensure a minimum number of participants experience at least one event.

Next in cardiovascular studies being very long run studies, we always need to think rationally on the recruitment strategy also whether its feasible to ensure reach the study goal within a certain number of years as well as how many subjects can be recruited in a particular period.

SIMULATION STRATEGY AND DESCRIPTION

In this simulation study, we have certain assumptions such as :
Duration of the trial : 3 years, Accrual/ Recruitment rate : 40 participants each month i.e. 480 participants in 1 year
Yearly recurrent event rate : 0.22 and Yearly terminal event rate : 0.08
Effect of treatment on recurrent events and terminal events : 0.7

```
/* Using a recruitment rate of 40/month and 3 years duration */
/* HR=0.70 and 90% power and lost to follow up rate of 3% */
%let dur=3;
%let hr=0.70;
%let beta=0.10;

proc seqdesign boundaryscale=mle;
  design nstages=2 info=cum(2 3) alpha=0.025 beta=&beta.
  method=hp(pvalue=0.0005) stop=reject alt=upper;
  samplesize model=twosamplesurvival
    (nullhazard=0.25 hazardratio=&hr.
     loss=exp(hazard=0.03) accrate=%sysevalf(40*12) totaltime=&dur.)
;
ods output SampleSize=N;
run;
```

Sample Size Summary	
Test	Two-Sample Survival
Null Hazard Rate	0.25
Hazard Rate (Group A)	0.175
Hazard Rate (Group B)	0.25
Hazard Ratio	0.7
log(Hazard Ratio)	-0.35667
Reference Hazards	Alt Ref
Accrual	Uniform with Losses
Loss Hazard Rate	0.03
Accrual Rate	480
Accrual Time	2.167005
Follow-up Time	0.832995
Total Time	3
Max Number of Events	330.4256
Max Sample Size	1040.162
Expected Sample Size (Null Ref)	1040.162
Expected Sample Size (Alt Ref)	1040.162
Follow-up Time (Ceiling Time)	0.832995
Total Time (Ceiling Time)	3

According to above, we can observe required number of subjects 1040 and stopping rule : Stop after reaching first 331 composite events.

Next step, to simulate datasets and examining power for the primary recurrent number of occurances of the endpoint under the conditions mentioned above. Here we simulated from a model assuming Ghosh and Lin's proportional model for the recurrent CV events and Cox proportional hazard model for the terminal events of death. More details about the simulation strategy is available in : https://github.com/JulieKFurberg/simpowerrecurrent

One important note here is in our simulations the underlying recurrent events rate is same for all participants and hence its not heterogenous population such that some patients do not get more events compared to others, for this we should actually go for simulation using frailty models.

Steps in the approach :

Step 1 : Simulate the data, 5000 times each for different parameters according to below table for 5 years with accural time 2.2 years (1040 participants with rate of 480 participants each year)

Step 2 : Filter only first events for the subjects which had at least one composite event (death or recurrent event)

Step 3 : Define the 331st timepoint as the “study-stop” and keep all the events which had started before “study-stop”

Step 4 : Events having stoptime after the “study-stop” will be censored and will be imputed as stoptime=”Study-stop”

Step 5 : Define start_corrected as start time – randomisation time, and stop_corrected as stop time – randomisation

Step 6 : Perform the Cox analysis and store the Hazard rates and P values

Step 7 : Perform Ghosh Lin analysis on composite events and store the mean ratio and P values

Step 8 : Perform LWYY analysis on composite events and store the mean ratio and P values

Step-9 : Find the Power of different methods by summarizing out of 5000 cases of each combination of parameters whether we get significant result or in-significant result (based on hazard rates/mean ratio as well as P-values)

Code snippets :

Step-3 and Step-4 :

```
maindata <- sim %>% filter(start≤studystop) %>%
  mutate(stop_c=ifelse(stop≥studystop,studystop,stop),
         composite_c=ifelse(stop≥studystop,0,composite),
         status_c=ifelse(stop≥studystop,0,status))
```

Step-6 :

```
# cox Model
cox_model <- coxph(Surv(start_corrected, stop_corrected, composite_c)~Z,data = final_cox)
```

Step-7 :

```
# Ghosh Lin Model
gl_model <- recreg(Event(start_corrected, stop_corrected, status_c) ~  Z + cluster(id),
                   data = for_GL_data, cause = 1, death.code = 2,
                   cens.code = 0)
```

Step-8 :

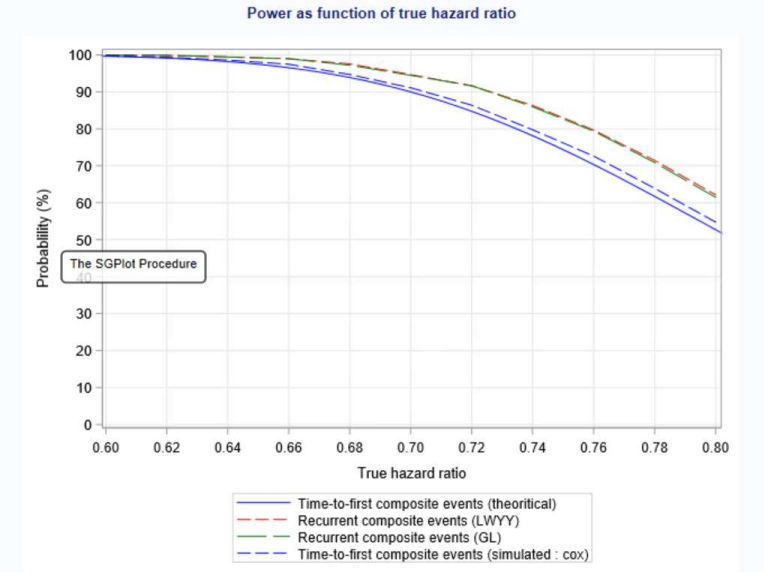
```
#LWYY model
lwyy_model <- coxph(Surv(start_corrected, stop_corrected, composite_c)~Z + cluster(id),data = final)
```

Results :

Assumption				**Power of analysis methods**		
Effect of treatment on recurrent events and terminal events	Yearly recurrent event rate	Yearly terminal event rate	Censoring rate	Time to first event analysis (Cox)	Ghosh Lin analysis	LWYY analysis
0.7	0.22	0.08	0.03	91.1	94.5	94.7
0.74	0.22	0.08	0.03	79.74	85.9	86.3
0.8	0.22	0.08	0.03	54.8	61.5	62.1

```
/*********************************************************************;
*Description : Power calculation with theoritical time to first composite
*              from SAS and results of time to first composite (simulated),
*              recurrent composite events from R to combine and present
*              power as a function of true hazard ratio
*********************************************************************/

/* Use a recruitment rate of 40/month and 3.5 years duration */
/* HR=0.70 and 90% power*/
%let dur=3;
%let hr=0.70;
%let beta=0.10;

/*****************************************************************************/
/*
 Power curves using a one-sided 2.5% (blue solid) significance level
*/
/*****************************************************************************/

ods exclude all;
proc seqdesign boundaryscale=pvalue  stopprob(cref=0.1 to 4 by 0.02) ;
  design nstages=2 info=cum(2 3) alpha=0.025 beta=&beta.
  method=hp(pvalue=0.0005) stop=reject alt=upper;
  samplesize model=twosamplesurvival
    (nullhazard=0.25 hazardratio=&hr.
     loss=exp(hazard=0.03) accrate=%sysevalf(40*12) totaltime=&dur.)
;
   ods output stopprob=_prob25;
run;
proc seqdesign boundaryscale=pvalue  stopprob(cref=0.1 to 4 by 0.02);
  design nstages=2 info=cum(2 3) alpha=0.005 beta=0.2547
  method=hp(pvalue=0.0005) stop=reject alt=upper;
  samplesize model=twosamplesurvival
    (nullhazard=0.25 hazardratio=&hr.
     loss=exp(hazard=0.03) accrate=%sysevalf(40*12) totaltime=&dur.)
;
   ods output stopprob=_prob05;
run;

proc sql;
create table _prob as
select a.*, b.stage_1 as stage_1_05, b.stage_2 as stage_2_05
from _prob25 as a left join _prob05 as b
on a.cref=b.cref
;
quit;

data prob;
  set _prob;
  pStage_1=100*Stage_1;
  pStage_2=100*Stage_2;
  pStage_1_05=100*Stage_1_05;
  pStage_2_05=100*Stage_2_05;
  HR = exp(cref*log(&hr.));
run;
ods exclude none;
proc sort;
by HR;
run;
```

```
/* Importing power calculation by R : For simulated time to first composite and
recurrent composite analysis : final_power_plot consists of data of HR consideration
of 0.6 to 0.8 with difference of 0.2 */
proc import datafile = '~/final_power_plot.csv'
 out = work.pwr2
 dbms = CSV
 ;
run;

data prob1;
set pwr2;
HR = HR_death;
cox = cox_power;
lwyy = LWYY_power;
run;

data final;
merge prob(in=a) prob1(in=b);
if a or b;
by HR;
run;

/* Plot of power as a function of true hazard ratio */
title "Power as function of true hazard ratio";
ods graphics / noborder;
proc sgplot data=final;
  series x=hr y=pStage_2 / lineattrs=(color=blue pattern=1) legendlabel="Time-to-first
composite events (theoritical)" name="f25";
  series x=hr y=lwyy / lineattrs=(color=red pattern=4) legendlabel="Recurrent
composite events" name="f3";
  series x=hr y=cox / lineattrs=(color=blue pattern=4) legendlabel="Time-to-first
composite events (simulated)" name="f26";
  xaxis label="True hazard ratio" grid values=(0.60 to 0.80 by 0.02);
  yaxis label="Probablility (%)" grid values=(0 to 100 by 10);
keylegend "f25" "f3" "f26" / position=bottom;
run;
ods graphics off;
```



CONCLUSION

The simulation studies show that Ghosh Lin or LWYY analysis for recurrent event with terminal event models increases power of the clinical trial design and the difference increases with the increase in effect of treatment on recurrent events/terminal events. Further, as Ghosh and Lin assume no recurrences can happen after death hence it should be more reasonable to use when analysing recurrent events data with higher rate of deaths.
There are several controversial uses of recurrent event analyses such as – whether the recurrents events are actually independent of each other or not (ex: a case where same subjects having multiple events), how much should few participants influence the results of a study? , how to give more weightage to death compared to recurrent hospitalisations ?, Is it really worth to include the information of recurrent events with the cost of increase in the trial duration? , Some recurrent events can actually terminate the process itself (ex : a subject getting hospitalised and in the hospitalisation duration the subject dies), In case of time to first composite events we are only interested in the first event (hence even if treatment discontinuation occur at a later phase it would not necessiate loss of treatment effect) but in case of recurrent events analysis (in between treatment discontinuation will increase chance of loosing effect of subsequent events)

In clinical trials design related decision making does not depend only on power but also whether the analysis method is in line with the clinical question of interest or not. Here we have simulated the trial with some assumptions to explore an actual trial kind of scenario where we have limitation in terms of number of subjects to be included in the trial as well as how longer duration the study could be ran. For instance, we have not explored frailty models which is also promising. However, in more complex scenarios and applications future research and discussions are necessary to be extended.

REFERENCES

- Efficiency Comparison of Analysis Methods for Recurrent Event and Time-to-First Event Endpoints in the Presence of Terminal Events—Application to Clinical Trials in Chronic Heart Failure https://doi.org/10.1080/19466315.2021.1945488
- Anker, S. D., and McMurray, J. J. V. (2012), “Time to Move on From Time-to-First: Should All Events Be Included in the Analysis of Clinical Trials?” European Heart Journal, 33, 2764–2765. DOI: 10.1093/eurheartj/ehs277.
- Brian Claggett , Stuart Pocock, L J Wei , Marc A Pfeffer , John J V McMurray , Scott D Solomon,Comparison of Time-to-First Event and Recurrent-Event Methods in Randomized Clinical Trials, DOI 10.1161/CIRCULATIONAHA.117.033065
- Julie Kjærulff Furberg, Søren Rasmussen, Per Kragh Andersen, Henrik Ravn , Methodological challenges in the analysis of recurrent events for randomised controlled trials with application to cardiovascular events in LEADER
- Overview of Recurrent Events in Clinical Trials, ASA presentation by Brian Claggett

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