P8108 Homework 11

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Since the events for right eye and left eye are not recurrent events, we cannot order which event come "first" and it is not proper to exclude subjects outside the risk set of the other eye even if the subject had a event before in another eye. Therefore it is better to use a marginal approach, which is the WLW methods.

Method 1: Wei -Lin-Weissfeld (WLW) method

- Events are ORDERED or CLASSIFIED INTO DIFFERENT TYPES
- The order/type is used as a stratification factor
  - Correlation among strata due to cluster effect - different types of events occurred in the same subjects
- Apply stratified Cox proportional hazard regression model
  - Time scale: Time from the study entry or randomization to the different types of events
  - Risk set - A marginal approach
    - Each stratum has its own risk set
    - All subjects are eligible in the risk set for the analysis of all stratums at the beginning
  - Regression:
    - Covariates can be stratum-specific
    - Effect parameter can be
      - Strata-specific
      - Common effect
- WLW Method Structure Data for analysis:
  - Structure data set for K types of events: Form K strata
  - Observations are in counting process style (start, stop):
    - Start – always study entry or randomization
      - Stop – the kth event time or censored
      - Id – cluster indicator
      - Strata indicator – for the K types of events
      - Censoring indicator
    - Each subject has K observations –> K strata

The dataset `Diabetic` from the `survival` package satisfies the structure for WLW method, therefore, I implement the WLW method analysing both stratum specific treatment effects and the common effects.

First, let's look at the stratum specific effect.

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	1520.452	1481.278
AIC	1520.452	1497.278
SBC	1520.452	1521.626

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	39.1741	8	<.0001
Score (Model-Based)	37.4002	8	<.0001
Score (Sandwich)	34.5127	8	<.0001
Wald (Model-Based)	34.0491	8	<.0001
Wald (Sandwich)	31.1894	8	0.0001

Analysis of Maximum Likelihood Estimates							
Parameter	DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio
laserL	1	0.62220	0.41026	0.896	2.3001	0.1294	1.863
laserR	1	-0.21277	0.37026	0.969	0.3302	0.5655	0.808
ageL	1	0.02832	0.01462	0.950	3.7487	0.0528	1.029
ageR	1	-0.00367	0.01246	0.971	0.0868	0.7682	0.996
trtL	1	-1.34765	0.32172	1.053	17.5473	<.0001	0.260
trtR	1	-0.51931	0.21746	0.998	5.7031	0.0169	0.595
riskL	1	0.15204	0.08436	0.993	3.2480	0.0715	1.164
riskR	1	0.11958	0.07406	1.000	2.6070	0.1064	1.127

Wei-Lin-Weissfeld Model

The PHREG Procedure

Linear Coefficients for Test TREATMENT			
Parameter	Row 1	Row 2	Average Effect
laserL	0	0	0.00000
laserR	0	0	0.00000
ageL	0	0	0.00000
ageR	0	0	0.00000
trtL	1	0	0.33111
trtR	0	1	0.66889
riskL	0	0	0.00000
riskR	0	0	0.00000
CONSTANT	0	0	0.00000

Test TREATMENT Results			
	Wald Chi-Square	DF	Pr > ChiSq
	25.8077	2	<.0001

Average Effect for Test TREATMENT			
Estimate	Standard Error	z-Score	Pr > |z|
-0.7936	0.1704	-4.6567	<.0001

From the above stratum specific analysis results, we found that the treatment effect to the Left eye (trtL) and Right eye (trtR) are both significant, and it seems that the effect is greater for left eye than the right eye (hazard ratio 0.260 vs. 0.595). The test results also shows that the treatment effects are significantly different.

Here are the analysis results for the common effect.

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	31.5619	4	<.0001
Score (Model-Based)	31.4211	4	<.0001
Score (Sandwich)	30.3609	4	<.0001
Wald (Model-Based)	30.1842	4	<.0001
Wald (Sandwich)	31.8039	4	<.0001

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
laser	1	0.2125	0.6448
age	1	0.6121	0.4340
trt	1	28.7542	<.0001
risk	1	6.1495	0.0131

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
laser	argon	1	-0.13722	0.29767	1.024	0.2125	0.6448	0.872	laser argon
age		1	0.00799	0.01021	1.054	0.6121	0.4340	1.008	
trt		1	-0.81738	0.15243	0.897	28.7542	<.0001	0.442	
risk		1	0.14525	0.05857	1.055	6.1495	0.0131	1.156	

From the above result, we can see that the hazard ratio for the common treatment effect is 0.442, and it's significant. That means patients with treatment reduces the risk of recurrence by a factor of 0.442 compared to patients without laser treatment, holding other effects.

Method 2: Frailty Model

Another way to deal with the correlation of different types of events for the same subject is to treat it as random effect: either left eye or right eye getting vision loss from the same subjects may share similar risk, thus subjects are considered as random effect by applying frailty model. There are j = 197 subjects in this study, so values r_1, r_2, ..., r_{197} represent the frailty of developing events. The shared frailty model for the ith events in the jth group:

$$h_{ij}\left(t \mid Z_{ij}\right) = \xi_j h_0(t) e^{\beta' Z_{ij}}$$

Here, I assume $\xi_j = e^{r_j}$ follows log-normal distribution with mean 0.

Testing Global Null Hypothesis			
Test	Chi-Square	Adjusted DF	Pr > ChiSq
Likelihood Ratio	203.9117	75.01	<.0001
Wald	131.0757	75.01	<.0001

Covariance Parameter Estimates		
Cov Parm	REML Estimate	Standard Error
id	0.7865	0.2110

Type 3 Tests					
Effect	Wald Chi-Square	DF	Pr > ChiSq	Adjusted DF	Adjusted Pr > ChiSq
laser	0.3174	1	0.5732	0.6011	0.3816
age	0.9207	1	0.3373	0.6011	0.2003
trt	26.9421	1	<.0001	0.9592	<.0001
risk	6.0213	1	0.0141	0.7501	0.0089
id	103.8895	.	.	71.0137	0.0067

Analysis of Maximum Likelihood Estimates								
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
laser	argon	1	-0.21417	0.38014	0.3174	0.5732	0.807	laser argon
age		1	0.01221	0.01272	0.9207	0.3373	1.012	
trt		1	-0.90896	0.17512	26.9421	<.0001	0.403	
risk		1	0.16472	0.06713	6.0213	0.0141	1.179	

Frailty Model Analysis: Hazard Ratios for trt			
Description	Point Estimate	95% Wald Confidence Limits	
trt Unit=1	0.403	0.286	0.568

From the frailty model, we can see that the hazard ratio for the common treatment effect is 0.403, and it's significant. That means patients with treatment reduces the risk of recurrence by a factor of 0.403 compared to patients without laser treatment, holding other effects.

Appendix: Code for this report

```
knitr::opts_chunk$set(echo = FALSE, message = FALSE, warning = FALSE)
library(tidyverse)
library(knitr)
library(kableExtra)
library(survival)
library(flexsurv)
library(survminer)
library(survMisc)
library(MASS)
diabetic = survival::diabetic
# For WLW method
diabetic_WLW = diabetic %>% mutate(
  eye_ind = ifelse(eye == "left", 1,2),
  laser_ind = ifelse(laser == "argon", 0, 1)
) %>%
  select(-eye,-laser)
write_csv(diabetic_WLW,"diabetic_WLW.csv")

knitr::include_graphics("./hw11_WLW_strata.png")
knitr::include_graphics("./hw11_WLW_strata_test.png")
knitr::include_graphics("./hw11_WLW_common.png")
proc import out = diabetic_WLW
    datafile="/home/u62725158/diabetic_WLW.csv"
    dbms=csv
    replace;
    GETNAMES=yes;
run;

proc import out = diabetic
    datafile="/home/u62725158/Diabetic.csv"
    dbms=csv
    replace;
    GETNAMES=yes;
run;


title'Wei-Lin-Weissfeld Model';
proc phreg data=diabetic_WLW covs(aggregate);
    /*class laser;*/
    model time*status(0)=laserL laserR ageL ageR trtL trtR riskL riskR;
    laserL = laser_ind * (eye_ind = 1);
    laserR = laser_ind * (eye_ind = 2);
    ageL = age * (eye_ind = 1);
    ageR = age * (eye_ind = 2);
    trtL = trt * (eye_ind = 1);
    trtR = trt * (eye_ind = 2);
    riskL = risk * (eye_ind = 1);
    riskR = risk * (eye_ind = 2);
    strata eye_ind;
    id id;
    TREATMENT: test trtL,trtR/average e;
```

```
run;

title'Wei-Lin-Weissfeld Model for
Common Effect';
proc phreg data=diabetic
    covs(aggregate);
    class laser eye;
    model time*status(0)=laser age trt risk;
    strata eye;
    id id;
run;


title'Frailty Model for Common Effect';
proc phreg data=diabetic ;
class id laser eye;
model time*status(0)=laser age trt risk;
random id;
hazardratio'Frailty Model Analysis' trt;
run;
knitr::include_graphics("./hw11_WLW_frailty.png")
```