Homework2

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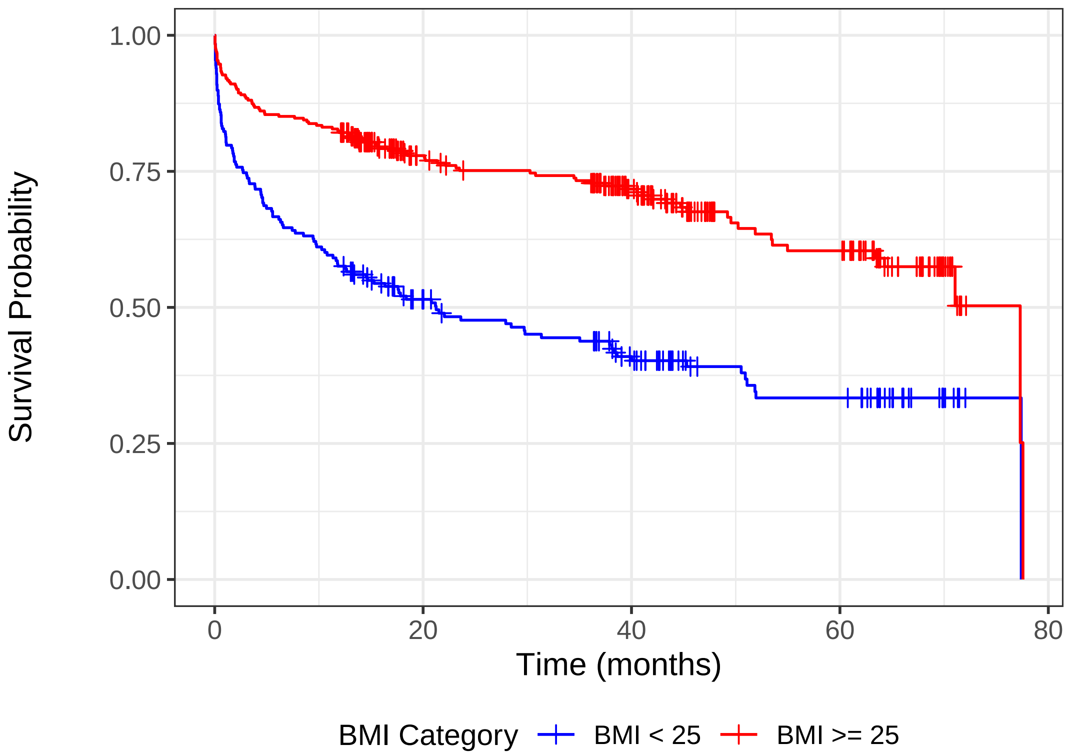
1. Logrank and Score Tests for MI Study

(a) Below is the plot of estimated Kaplan-Meier survival functions for the endpoint of death for those who are obese or overweight ($BMI \geq 25$) vs. those of normal weight (which we will define here as $BMI <$



df$obese_ovwt=0

At Risk	198	83	54	29	0
Censored	0	20	33	51	79
Events	0	95	111	118	119

df$obese_ovwt=1

At Risk	302	172	123	59	0
Censored	0	65	101	152	206
Events	0	65	78	91	96

25):

Difference in the censoring patterns between the two BMI groups:

- There is a higher frequency of censoring events throughout the study period in obese or overweight group.
- The censoring events appear to occur at similar time points for both groups, notably around 18 months, 40 months, and 67 months

```r
# the number of patients who are overweight or obese (BMI >= 25)
overweight_obese_count <- df |>
  filter(bmi >= 25) |>
  nrow()

# the percentage of overweight or obese patients out of 500
pct_overweight_obese <- (overweight_obese_count / 500) * 100
```

60.4% of the patients out of 500 are either overweight or obese.

(b) I will implement log-rank test and Wilcoxon test using CMH approach. Below is the output from SAS.

The LIFETEST Procedure

Testing Homogeneity of Survival Curves for dthtime over Strata

Rank Statistics		
obese_ovwt	Log-Rank	Wilcoxon
0	44.682	17295
1	-44.682	-17295

Covariance Matrix for the Log-Rank Statistics		
obese_ovwt	0	1
0	48.1884	-48.1884
1	-48.1884	48.1884

Covariance Matrix for the Wilcoxon Statistics		
obese_ovwt	0	1
0	6858079	-6858079
1	-6858079	6858079

Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	41.4301	1	<.0001
Wilcoxon	43.6153	1	<.0001
-2Log(LR)	47.4160	1	<.0001

$\chi^2_{MH} = 41.4301$ (p-value <0.0001)
$\chi^2_{W} = 43.6153$ (p-value <0.0001)

The both tests suggest that there is an association between whether being overweight/obese and death.
The log-rank test gives equal weight to all time points, while the Wilcoxon test gives more weight to early events. Given the KM curve, there is more differences in survival in early stage, so we can assume that Wilcoxon test would yield a larger test statistic.

(c)

The LIFETEST Procedure

Testing Homogeneity of Survival Curves for dthtime over Strata

Rank Statistics	
obese_ovwt	Fleming
0	44.682
1	-44.682

Covariance Matrix for the Fleming Statistics		
obese_ovwt	0	1
0	48.1884	-48.1884
1	-48.1884	48.1884

Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Fleming(0,0)	41.4301	1	<.0001

The LIFETEST Procedure

Testing Homogeneity of Survival Curves for dthtime over Strata

Rank Statistics	
obese_ovwt	Fleming
0	36.014
1	-36.014

Covariance Matrix for the Fleming Statistics		
obese_ovwt	0	1
0	30.4221	-30.4221
1	-30.4221	30.4221

Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Fleming(1,0)	42.6330	1	<.0001

The LIFETEST Procedure

Testing Homogeneity of Survival Curves for dthtime over Strata

Rank Statistics	
obese_ovwt	Fleming
0	6.399
1	-6.399

Covariance Matrix for the Fleming Statistics		
obese_ovwt	0	1
0	1.36298	-1.36298
1	-1.36298	1.36298

Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Fleming(1,1)	30.0436	1	<.0001

p=0, q=0: $\chi^2_{FH} = 41.4301$ (p-value <0.0001)
p=1, q=0: $\chi^2_{FH} = 42.6330$ (p-value <0.0001)
p=1, q=1: $\chi^2_{FH} = 30.0436$ (p-value <0.0001)

When p=0, q=0, the test statistic is equal to that of log-rank test. When p=1, q=0, the test is similar to the Peto-Prentice test and it is closer to the test statistic of Gehan's Wilcoxon test in (b). When p=1, q=1, the Fleming-Harrington test gives more weight to events happening around the median time. The smaller test statistic indicates fewer mid-term differences between two BMI groups.
If most events happen earlier, we expect p=1, q=0 to be more powerful than log-rank test, and if most events happen around the middle of the study period, we expect p=1, q=1 to be more powerful. Fleming-Harrington may be less powerful compared to log-rank test when most of the events occur later in the follow-up period.

(d) I will use a logistic regression model to test whether the proportions of deaths during follow-up differ for those who are over-weight/obese versus those of normal weight.

```
##
## Call:
## glm(formula = dthstat ~ obese_ovwt, family = binomial, data = df)
##
## Coefficients:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept)   0.4097     0.1451   2.823  0.00476 **
## obese_ovwt   -1.1732     0.1906  -6.155 7.51e-10 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 683.31  on 499  degrees of freedom
## Residual deviance: 644.01  on 498  degrees of freedom
## AIC: 648.01
##
## Number of Fisher Scoring iterations: 4
```

The result indicates that being over-weight/obese has approximately 69.06% lower odds of death compared to non-obese individuals when adjusting for no other variables, and this is statistically significant.
This conclusion (being over-weight/obese have somewhat positive effect on mortality) is similar to the results of survival analysis in (b) and (c). Survival analysis may become more powerful when there are considerable number of censoring in the study subject and the data is highly skewed.

2. Cox Model for Myocardial Infarction Study

(a) Below is the SAS output of Cox PH model and Wald, Score, and LR tests.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	2341.649	2302.583
AIC	2341.649	2304.583
SBC	2341.649	2307.954

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	39.0651	1	<.0001
Score	41.4301	1	<.0001
Wald	38.9804	1	<.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
obese_ovwt	1	-0.86184	0.13804	38.9804	<.0001	0.422	0.322	0.554

Given the results of MLE, over-weight/obese individuals have hazard ratio of 0.422 (p-value <0.0001). In other words, over-weight/obese individuals have a 57.8% lower risk of death compared to normal-weight individuals.

Wald test: $\chi^2 = 38.9804$ (p-value <0.0001)
Score test: $\chi^2 = 41.4301$ (p-value <0.0001)
LR test: $\chi^2 = 39.0651$ (p-value <0.0001)
The three test indicates that the model including covariate `obese_ovwt` is significant. The score test has

a test statistic that is exactly the same as the log-rank test from 1(b), because there is only one binary covariate in this model.

(b) The adjusted Cox PH model (age, gender, systolic blood pressure, type of MI) is shown below:

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	2341.649	2182.512
AIC	2341.649	2192.512
SBC	2341.649	2209.365

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	159.1363	5	<.0001
Score	148.1797	5	<.0001
Wald	139.0436	5	<.0001

Analysis of Maximum Likelihood Estimates								
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
obese_ovwt	1	-0.44895	0.14657	9.3827	0.0022	0.638	0.479	0.851
age	1	0.05972	0.00638	87.5696	<.0001	1.062	1.048	1.075
gender	1	-0.12025	0.14244	0.7128	0.3985	0.887	0.671	1.172
sysbp	1	-0.00354	0.00219	2.6086	0.1063	0.996	0.992	1.001
mitype	1	-0.33522	0.17214	3.7923	0.0515	0.715	0.510	1.002

Summary of findings

Unadjusted HR: `obese_ovwt` 0.422 (95% CI: 0.322-0.544)
Adjusted HR: `obese_ovwt` 0.638 (95% CI: 0.479-0.851)
`age` 1.062 (95% CI: 1.048-1.075)
`gender` 0.887 (95% CI: 0.671-1.172)
`sysbp` 0.996 (95% CI: 0.992-1.001)
`mitype` 0.715 (95% CI: 0.510-1.002)

The unadjusted HR of overweight/obesity for mortality was 0.422 (95% CI: 0.322-0.544), indicating a significant protective effect. Adjusting for other covariates reduces the protective effect, but the HR remains significant at 0.638 (95% CI: 0.479-0.851), suggesting that adjustment for factors such as age and blood pressure slightly reduces but does not eliminate the association.

(c)

i. Test for `obese_ovwt` from Cox PH model, stratifying by gender

Summary of the Number of Event and Censored Values					
Stratum	gender	Total	Event	Censored	Percent Censored
1	0	300	111	189	63.00
2	1	200	104	96	48.00
Total		500	215	285	57.00

Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	2154.653	2120.837
AIC	2154.653	2122.837
SBC	2154.653	2126.208

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	33.8160	1	<.0001
Score	35.3698	1	<.0001
Wald	33.6880	1	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
obese_ovwt	1	-0.81574	0.14054	33.6880	<.0001	0.442

Score test statistic: $\chi^2 = 35.3698$ (p-value <0.001)
HR for `obese_ovwt`: 0.442 (p-value <0.001)

ii. Test for `obese_ovwt` from Cox PH model, controlling for gender

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	2455.158	2413.734
AIC	2455.158	2417.734
SBC	2455.158	2424.475

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	41.4239	2	<.0001
Score	43.8816	2	<.0001
Wald	41.3908	2	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
obese_ovwt	1	-0.81648	0.14066	33.6933	<.0001	0.442
gender	1	0.22053	0.14035	2.4689	0.1161	1.247

Score test statistic: $\chi^2 = 43.8816$ (p-value <0.001)
HR for `obese_ovwt`: 0.442 (p-value <0.001)
HR for `gender`: 1.247 (p-value 0.1161)

iii. Log-rank test (linear rank) for `obese_ovwt`, stratifying by gender

Univariate Chi-Squares for the Log-Rank Test				
Variable	Test Statistic	Standard Error	Chi-Square	Pr > Chi-Square
obese_ovwt	41.0282	6.8987	35.3698	<.0001

Covariance Matrix for the Log-Rank Statistics	
Variable	obese_ovwt
obese_ovwt	47.5918

Forward Stepwise Sequence of Chi-Squares for the Log-Rank Test					
Variable	DF	Chi-Square	Pr > Chi-Square	Chi-Square Increment	Pr > Increment
obese_ovwt	1	35.3698	<.0001	35.3698	<.0001

Log-rank (linear rank) $\chi^2 = 35.3698$ (p-value <0.0001)

Log-rank (linear rank) test statistic is equivalent to score test statistic in (i).
In Cox PH model, by controlling for gender, the score test statistics increased from 35.3698 to 43.8816, indicating a better fit with the data. This suggests that controlling for gender has a higher power than stratifying by it.

(d) Stratification allows the baseline hazard to vary by gender, which is beneficial when gender is a strong confounder for the outcome and the proportional hazards assumption does not hold across genders. One of the disadvantages is the potential loss of power, as seen in (c), due to the smaller size within each stratum. To further examine whether stratification is appropriate, I would suggest testing the proportional hazards assumption, such as using the Schoenfeld residual test.

3. Model Interpretation - Myocardial Infarction Study

Variable Name	Estimate	s.e.	P-value
Age	0.0500	0.0066	< 0.0001
Heart rate	0.0112	0.0029	0.0001
Diastolic BP	-0.0107	0.0035	0.0024
Sex (0=male, 1=female)	-0.2732	0.1442	0.0581
Congestive heart failure	0.7816	0.1469	< 0.0001
BMI	-0.0453	0.0163	0.0055

(a) Given the coefficient estimate table, the estimated hazard for death is:
$\lambda(t, Z) = \lambda_0(t)exp(\beta_1 \cdot Age + \beta_2 \cdot HR + \beta_3 \cdot dBP + \beta_4 \cdot Sex + \beta_5 \cdot CHF + \beta_6 \cdot BMI)$
$= \lambda_0(t)exp(0.05 \cdot Age + 0.0112 \cdot HR - 0.0107 \cdot dBP - 0.2732 \cdot Sex + 0.7816 \cdot CHF - 0.0453 \cdot BMI)$

(b) "Baseline" group is defined as a model with the following values:
Age: `age` $= 0$
Heart rate: `hr` $= 0$
Diastolic BP: `diasp` $= 0$
Sex: `gender` $= 0$ (male)
Congestive heart failure: `chf` $= 0$ (no)
BMI: `bmi` $= 0$
There are no observations that fall into such a group.

(c) The estimated HR for death associated with `bmi` $= 30$ vs. `bmi` $= 24$, holding all other covariates constant:

$HR = \frac{exp(0.05 \cdot Age + 0.0112 \cdot HR - 0.0107 \cdot dBP - 0.2732 \cdot Sex + 0.7816 \cdot CHF - 0.0453 \times 30)}{exp(0.05 \cdot Age + 0.0112 \cdot HR - 0.0107 \cdot dBP - 0.2732 \cdot Sex + 0.7816 \cdot CHF - 0.0453 \times 24)}$
$= exp(0.0453 \times 30 - 0.0453 \times 24) = 0.76$

The 95% CI for this estimate can be obtained by calculating the following:
$L = exp(-0.0453 \times 6 - 1.96 \times 0.0163 \times 6) = 0.63$
$U = exp(-0.0453 \times 6 + 1.96 \times 0.0163 \times 6) = 0.92$

The estimated HR 0.76 indicates that individuals with a BMI of 30 have a 24% lower hazard of death compared to individuals with a BMI of 24, all else being equal. The 95% CI is (0.63, 0.92), suggesting that this HR estimate is statistically significant.

(d) The estimated HR of death for a subject aged 60 years vs. 50 years, holding all other covariates constant:
$HR = \frac{exp(0.05 \times 60 + 0.0112 \cdot HR - 0.0107 \cdot dBP - 0.2732 \cdot Sex + 0.7816 \cdot CHF - 0.0453 \cdot BMI)}{exp(0.05 \times 50 + 0.0112 \cdot HR - 0.0107 \cdot dBP - 0.2732 \cdot Sex + 0.7816 \cdot CHF - 0.0453 \cdot BMI)}$
$= exp(0.05 \times 60 - 0.05 \times 50) = 1.65$

The 95% CI for this estimate can be obtained by calculating the following:
$L = exp(0.05 \times 10 - 1.96 \times 0.0066 \times 10) = 1.45$
$U = exp(0.05 \times 10 + 1.96 \times 0.0066 \times 10) = 1.88$

The estimated HR 1.65 indicates that individuals aged 60 years have a 65% higher hazard of death compared to individuals aged 50 years, all else being equal. The 95% CI is (1.45, 1.88), suggesting that this HR estimate is statistically significant.

(e) The estimated HR of death for a female subject aged 60 years with BMI of 24 vs. male sugject aged 50 years with BMI of 30, holding all other covariates constant:
$HR = \frac{exp(0.05 \times 60 + 0.0112 \cdot HR - 0.0107 \cdot dBP - 0.2732 \times 1 + 0.7816 \cdot CHF - 0.0453 \times 24)}{exp(0.05 \times 50 + 0.0112 \cdot HR - 0.0107 \cdot dBP - 0.2732 \times 0 + 0.7816 \cdot CHF - 0.0453 \times 30)}$
$= exp(0.05 \times 60 - 0.2732 \times 1 - 0.0453 \times 24 - 0.05 \times 50 + 0.2732 \times 0 + 0.0453 \times 30) = 1.65$

(f) Hazard ratio of female vs. male, holding all other variables constant: $HR = exp(-0.2732) = 0.76$
95% CI for this:
$L = exp(-0.2732 - 1.96 \times 0.1442) = 0.57$
$U = exp(-0.2732 + 1.96 \times 0.1442) = 1.01$

The HR implies that, all else being equal, female is associated with 24% lower risk of death compared to male. However, the 95% CI includes 1 and suggests that this is not statistically significant.

4. Impact of Ties on Cox Model Estimation and Testing