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BS852 Course Project

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**Introduction**

The framdat4 dataset includes 2000 observations from a subsample of data from the Framingham Heart Study, which is a longitudinal study. Subjects had data measured at exam 4, including age (AGE4), total cholesterol (CHOL4), whether the subject smokes (SMOKE), number of cigarettes smoked per day (CIGS4), systolic and diastolic blood pressure (SPF4 and DPF4), weight in pounds (WGT4), pulmonary function (FVC4), BMI (BMI4), hypertension (HTN4), and menopause (MENO4). The incidence of CHD, type 2 diabetes, and death were recorded following 22 years of follow-up. We are interested in exploring the association between systolic blood pressure (SPF4) and overall survival.

**Methods**

Since this is a longitudinal study, survival analysis was used in all following analyses to account for time to death and censoring. First, variable selection techniques were used to create a final Cox Proportional Hazards (PH) model with SPF4 as the main predictor and including other relevant covariates. MENO4 was dropped due to its relevance only to females, while T2D and T2D\_SURV were removed due to irrelevance to the analysis. Univariate analyses with Spearman correlations and survival analyses identified collinear variables and variables significantly associated with mortality. Potential confounders to SPF4 were identified using bivariate survival analyses and the 10% rule. A full Cox PH model was made including all variables that were significantly associated with mortality and that were confounders to SPF4, and a Wald Test at a significance level of 0.15 determined which predictors were significant while adjusting for all other predictors. Non-significant variables were removed, and all remaining variables were tested for collinearity via a correlation test. The final Cox PH model included non-collinear variables that were significant in the Wald test. Results were validated with forward and stepwise automatic variable selection at a 0.15 significance level.

Once the final model was generated, a new dataset was created with just the final covariates, predictor of interest, and censoring and time to event variables. CHD and CHD\_SURV were included but not used, as CHD development over 22 years is a different outcome from death, which is the focus here. Rows with missing values for any covariates, DTH, or SURV variables were removed, resulting in 1,964 non-missing observations. The Schoenfeld residuals method tested the proportional hazards assumption on the final model. Continuous covariates that violated the PH assumption were converted to categorical variables, and all following survival analyses were stratified accordingly. Summary statistics were generated using a proc means procedure.

A crude, stratified survival analysis was used to assess the association between SPF4 and mortality. Analysis of Schoenfeld residuals showed no violation of the PH assumption. The null hypothesis states that SPF4 is not associated with mortality. Confounding by each covariate in the final model was assessed using bivariate Cox PH analysis applying the 10% rule to crude and adjusted hazard ratios for SPF4. We tested the null hypothesis that there is no interaction by sex to explore whether the association between SPF4 and mortality differs between males and females. An interaction term for SPF4 and SEX was added to the final Cox PH model and was tested for significance at a .05 significance level. Hazard ratios for SPF4’s effect on mortality, adjusted by all covariates, were calculated separately for males and females and compared.

Survival analysis was used to assess if CHD (coded as 1 if CHD occurred during the 22 years of follow up) is associated with total mortality, using exam 4 as the baseline. A Kaplan-Meier plot compared the survival functions of 2 groups classified by the dichotomous CHD variable, and the Log-Rank test formally tested the association between developing CHD and survival under the null hypothesis of no difference between survival curves. A limitation of this analysis is that CHD is a time-varying variable which may cause the proportional hazard assumption to fail. Therefore, results of the analysis testing the association between CHD and mortality may be biased.

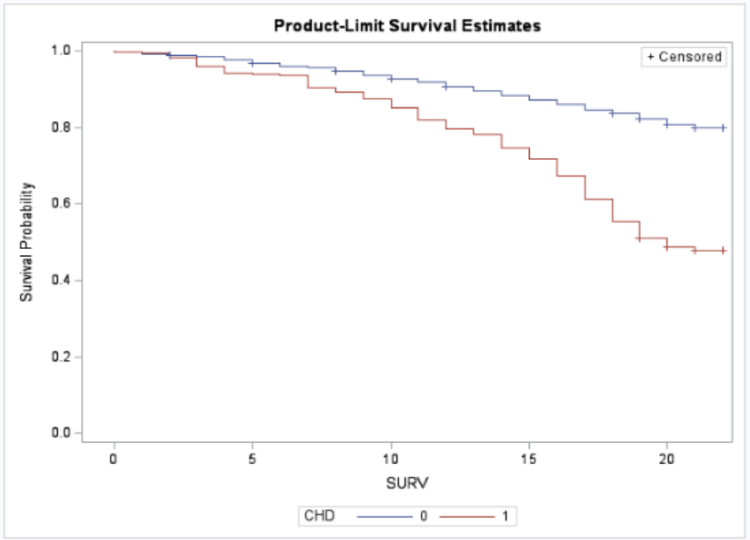
**Results**

Correlation analysis showed that BMI and WGT4 (Spearman correlation coefficient r = 0.79), CIGS4 and SMOKE (r = 0.95), and SPF4 and DPF4 (r = 0.76) were collinear. Univariate survival analysis showed that all variables (SEX, AGE4, CHOL4, CIGS4, WGT4, FVC4, BMI4, HTN4) were significantly associated with mortality except SMOKE. DPF4 was dropped due to collinearity with predictor of interest SPF4, and SMOKE was dropped due to collinearity and insignificance. Bivariate survival analyses showed that no variables confounded the association between SPF4 and mortality. Remaining variables were included in a Cox PH model and adjusted significance was determined via a Wald test for specific variables (Table 5). Significant predictors (SEX, AGE4, CIGS4, SPF4, FVC4) were retained, while insignificant ones (CHOL4, HTN4, WGT4, BMI4) were dropped. Correlation analysis between each of the final covariates showed that none of the predictors were collinear (no coefficient > .6). The final model was validated using forward and stepwise selection at a 0.15 significance level.

Analysis of Schoenfeld residuals on the final model indicated that AGE4 violated the Proportional Hazards assumption, so it was converted into a categorical variable based on age groups (Table 6). All remaining analyses were stratified by the age group variable. Results of the crude survival analysis showed that SPF4 is significantly associated with mortality (Likelihood Ratio Chi-Square = 73.49 on 1DF and p<.0001, Wald Chi-Square = 83.26 on 1DF and p<.0001), and that with every unit increase in SPF4, the hazard of death increases by 1.014 units within the same age stratum (Table 2). Note that we cannot compare hazard of death based on SPF4 for subjects in different age strata. Age group stratified bivariate survival analysis and the 10% rule applied to crude and adjusted hazard ratios showed no covariate confounded the relationship between SPF4 and mortality (Table 2). Analysis of the interaction term included in the final Cox PH model showed that there is no interaction by sex on the association between SPF4 and mortality (Wald Chi-Square = 0.0435 and p = 0.8347), and therefore that the association between SPF4 and mortality is the same in males and females (Table 3).

Survival analysis was used to determine whether CHD is associated with mortality. The Kaplan-Meier plot illustrates the difference in survival between individuals who developed CHD over 22 years of follow up and those who did not, and that the two groups seem to satisfy the PH assumption (Figure 1). Those who did not develop CHD over follow up appear more likely to survive longer than those who did. Results of the Log-Rank test are consistent with the results of the Kaplan-Meier curves and suggest that there is a significant association between CHD and mortality (Log-Rank Chi-Square = 170.17 on 1df and p<.0001), therefore we reject our null hypothesis (Table 7). To include time-to-event variables for CHD alongside time-to-death variables in our survival analysis with SPF4 as the main predictor, we could use a competing risk analysis. The Fine and Gray Subdistribution Hazard Model would calculate the hazard of death in the presence of CHD as a competing event.

*Figure 1: Kaplan-Meier curves illustrating the difference in survival for those who developed CHD over follow up and those who did not.*



**Discussion**

We performed survival analysis to assess the association between systolic blood pressure (SPF4) at exam 4 and mortality over 22 years of follow up. Before analyses occurred, variable selection techniques were used to determine a final Cox PH model for the question of interest. No confounding was found between any of the chosen covariates and SPF4, and no interaction by sex on the association between SPF4 and mortality was found. Survival analysis was also used to show that CHD is significantly associated with mortality, though this analysis is likely biased due to the time-varying nature of the CHD variable. Finally, we found that competing risk analyses could account for the addition of more complex time-to-CHD variables as a competing risk in the survival analysis at hand.

**Continued Results– Additional Page of Figures and Tables**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ***SEX*** | ***Number of Observations*** | ***Variable Name*** | ***Minimum*** | ***Maximum*** | ***Median*** | ***Mean*** | ***Std Deviation*** |
| 1 = Male | 850 | AGE4 | 34.0 | 69.0 | 49.0 | 49.7 | 8.6 |
| CIGS4 | 0.0 | 43.0 | 9.0 | 12.5 | 13.3 |
| SPF4 | 90.0 | 252.0 | 130.0 | 133.0 | 21.7 |
| FVC4 | 227.0 | 833.0 | 539.0 | 542.5 | 93.4 |
| 2 = Female | 1114 | AGE4 | 34.0 | 68.0 | 49.0 | 49.9 | 8.4 |
| CIGS4 | 0.0 | 43.0 | 0.0 | 5.2 | 8.7 |
| SPF4 | 88.0 | 290.0 | 130.0 | 134.6 | 25.9 |
| FVC4 | 82.0 | 636.0 | 419.0 | 413.2 | 85.6 |

Table 1: summary of patient characteristics for all variables included in the final model (generated with PROC MEANS)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ***Analysis Type*** | ***Predictors Included*** | ***p-value of Association*** | ***Chi-Squared Value of Association*** | ***Effect (Beta) Coefficient of SPF4*** | ***HR for 1 unit increase of SPF4 within each age stratum*** | ***Confounding? (Y/N)*** |
| Crude Cox PH | SPF4 | <.0001 | 83.3 | 0.01424 | 1.014 | N/A |
| Adjusted Cox PH | SPF4 SEX | <.0001 | 104.7 | 0.01600 | 1.016 | N |
| Adjusted Cox PH | SPF4 AGE4 | <.0001 | 68.8 | 0.01311 | 1.013 | N |
| Adjusted Cox PH | SPF4 CIGS4 | <.0001 | 91.1 | 0.01509 | 1.015 | N |
| Adjusted Cox PH | SPF4 FVC4 | <.0001 | 81.8 | 0.01460 | 1.015 | N |
| Adjusted Cox PH | SPF4 SEX AGE4 CIGS4 FVC4 | <.0001 | 72.3 | 0.01384 | 1.014 | N |

Table 2: Measures of crude and adjusted associations between SPF4 and mortality within each age stratum, generated with bivariate Cox PH analyses with SPF4 as predictor of interest.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Parameter*** | ***Parameter Estimate*** | ***Standard Error*** | ***Chi-Square*** | ***p-value of Term*** |
| SPF4 | 0.01418 | 0.00230 | 38.1026 | <.0001 |
| SEX | -0.73051 | 0.45743 | 2.5504 | 0.1103 |
| SPF4\*SEX | -0.00063 | 0.00302 | 0.0435 | 0.8347 |
| AGE4 | 0.07397 | 0.01728 | 18.3349 | <.0001 |
| CIGS4 | 0.01722 | 0.00394 | 19.0606 | <.0001 |
| FVC4 | -0.00233 | 0.00055 | 16.9370 | <.0001 |

|  |  |  |  |
| --- | --- | --- | --- |
| **Hazard Ratios for SPF4** | | | |
| *Description* | *Point Estimate* | *95% Wald Confidence Limits* | |
| SPF4 at SEX = Male (1) | 1.014 | 1.010 | 1.019 |
| SPF4 at SEX = Female (2) | 1.014 | 1.009 | 1.018 |

Table 3: gender-specific associations between SPF4 and mortality, adjusting for all covariates. Results show that the interaction term is not significant, and that the hazard ratio for SPF4 is the same between males and females.

**Appendix 1: Supplemental Materials**

|  |  |  |
| --- | --- | --- |
| **Spearman Correlation Coefficients** | | |
|  | ***BMI4*** | ***WGT4*** |
| ***BMI4*** | 1.0000 | 0.7905 |
| ***WGT4*** | 0.7905 | 1.0000 |
|  | ***CIGS4*** | ***SMOKE*** |
| ***CIGS4*** | 1.0000 | 0.9449 |
| ***SMOKE*** | 0.9449 | 1.0000 |
|  | ***SPF4*** | ***DPF4*** |
| ***SPF4*** | 1.0000 | 0.7586 |
| ***DPF4*** | 0.7586 | 1.0000 |

Table 4: Spearman Correlation Coefficients from correlated variables at exam 4 generated during univariate analysis portion of model selection.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Analysis of Maximum Likelihood Estimates** | | | | | | | | |
| *Parameter* | *DF* | *Parameter Estimate* | *Standard Error* | *Chi-Square* | *PR > ChiSq* | *Hazard Ratio* | *95% Hazard Ratio Confidence Limits* | |
| *SEX* | 1 | -0.793 | 0.128 | 38.293 | <.0001 | 0.453 | 0.352 | 0.582 |
| *AGE4* | 1 | 0.075 | 0.007 | 125.462 | <.0001 | 1.078 | 1.064 | 1.092 |
| *CHOL4* | 1 | 3.55E-5 | 0.001 | 0.001 | 0.975 | 1.000 | 0.998 | 1.002 |
| *CIGS4* | 1 | 0.018 | 0.004 | 18.199 | <.0001 | 1.018 | 1.010 | 1.026 |
| *SPF4* | 1 | 0.013 | 0.002 | 32.022 | <.0001 | 1.014 | 1.009 | 1.018 |
| *FVC4* | 1 | -0.002 | 5.884E-5 | 13.339 | 0.0003 | 0.998 | 0.998 | 0.999 |
| *BMI4* | 1 | -0.004 | 0.012 | 0.104 | 0.747 | 0.996 | 0.974 | 1.019 |
| *HTN4* | 1 | 0.039 | 0.129 | 0.089 | 0.765 | 1.039 | 0.806 | 1.340 |

Table 5: Results of Wald Test for specific variables from the Cox PH Model showing insignificance of BMI4, HTN4, CHOL4. Note WGT4 was not included since it is correlated with BMI4.

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| --- | --- | --- | --- | --- | --- | --- |
| **Zph Tests for Nonproportional Hazards** | | | | | | |
| *Transform* | *Predictor Variable* | *Correlation* | *Chi Square* | *Pr > ChiSquare* | *T Value* | *Pr > |t|* |
| RANK | SPF4 | -0.0194 | 0.2071 | 0.6490 | -0.44 | 0.6567 |
| RANK | SEX | 0.0593 | 1.9540 | 0.1622 | 1.36 | 0.1738 |
| RANK | AGE4 | 0.0866 | 4.1643 | 0.0413 | 1.99 | 0.0467 |
| RANK | CIGS4 | 0.0364 | 0.7382 | 0.3902 | 0.84 | 0.4036 |
| RANK | FVC4 | 0.0095 | 0.0570 | 0.8113 | 0.22 | 0.8272 |

Table 6: Results from Schoenfeld Residuals Analysis of final Cox PH Model with SPF4, SEX, AGE4, CIGS4, FVC4 illustrating AGE4’s departure from the proportional hazards assumption. These results showed that it was necessary to stratify the following survival analyses by age group.

|  |  |  |  |
| --- | --- | --- | --- |
| **Test of Equality over Strata** | | | |
| Test | Chi-Square | DF | Pr > Chi-Square |
| Log-Rank | 170.1727 | 1 | <.0001 |

Table 7: Result of the Log-Rank test testing the null hypothesis that there is no association between development of CHD over 22 years follow-up and risk of mortality. Results should be interpreted in tandem with Figure 1.