HW 3

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Parametric Survival Analysis

Question 1: Assuming ***Weibull*** distributed event times,

a) Write out the *general* expression, not substituting any estimated values, and clearly defining any parameters and distributions for any random terms, the log-hazard function, including the complete baseline hazard.

Assuming $T \sim$ Weibull, then the log-hazard function is expressed as:

$$log[h_0(t|\boldsymbol{x})] = log(p * t^{p-1}) + \beta_0 + \boldsymbol{x}\beta$$

where $log[h_0(t|\boldsymbol{x}]$ is the log-hazard function given the set of covariates, p is the shape parameter, $log(p*t^{p-1})+\beta_0$ is the log-baseline hazard, and $\boldsymbol{x}\beta$ is the vector of coefficients times the vector of covariate values. Each individual β within the β vector (in this case, the coefficients are on the following covariates: x_1 = underweight BMI (<18.5), x_2 = overweight BMI (25 - <30), x_3 = obese BMI (>30), x_4 = current smoking status, x_5 = age, and x_6 = sex) is the log hazard ratio for a one unit change in that variable, with Weibull distribution.

b) Repeat the above for the log-time function (in the accelerated failure time metric).

*Again assuming $T \sim$ Weibull, the log-**time** function is expressed as:*

$$log(T) = \alpha_0 + \boldsymbol{x}\alpha + \sigma \times \epsilon^*$$

where α_0 is the baseline time-to-event, $\boldsymbol{x}\alpha$ is the vector of covariate values multiplied by the vector of coefficients (with each individual coefficient representing the log-time ratio for a one unit change in each variable as listed in 1(a)), σ is the variance-type constant term (also known as p, unrestricted with Weibull specificiations), and ϵ^* is the error term, which with a Weibull model approximates a G distribution (0,1).

c) For an arbitrary covariate, show the expression of the hazard ratio from the proportional hazards Weibull model as a function of parameters from the accelerated failure time expression of the same model.

$$h^{AFT}(t|\boldsymbol{x}) = \frac{t^{\frac{1}{\sigma}} - 1}{\sigma} exp(-(\alpha_0 + \boldsymbol{x}\alpha)/\sigma)$$

Note that this hazard function will take the ratio of h^{AFT} but will not necessary be proportional as in the log-hazard function expressed in part (a).

Question 2: Complete the following table using the results from your analyses.

BMI	Cox HR (95% CI)	Cox SE_β	Exponential HR (95% CI)	Exp SE_β	Weibull HR (95% CI)	Weibull SE_β
<18.5	1.26 (0.79, 2.01)	0.24	1.21 (0.76, 1.93)	0.24	1.22 (0.79, 1.88)	0.22
18.5 - <25	*ref*	-	*ref*	-	*ref*	-
25 - <30	1.06 (0.95, 1.19)	0.06	1.07 (0.96, 1.2)	0.06	1.06 (0.95, 1.17)	0.05
$\geq$ 30	1.54 (1.32, 1.78)	0.08	1.46 (1.25, 1.69)	0.08	1.47 (1.28, 1.68)	0.07

Question 3: Answer the following questions

a) Which model estimates the relationships of interest most precisely? Justify your answer.

For these data, all three of the models provide a quite good fit. However, the Weibull model estimates the relations of interest most precisely, as evidenced by tighter CIs and smaller standard errors in the table from Question 2. Explanations for this slightly better fit are likely related to the basic definition of the models. As a parametric model the Weibull provides better statistical efficiency than the Cox model, when the assumptions are met. The Weibull also allows the baseline hazard to vary over the entire time period (the scale of the shape parameter p is allowed to vary), making it more flexible than the exponential model, which restricts $p = 1$.

b) Based on the likelihood ratio test, what parameter from the model you outlined in Q1 is being evaluated? Based on the results of this test, would you select the exponential or Weibull model? Justify your answer.

The likelihood ratio test is evaluating whether p, the shape parameter, is significantly different than 1. The test produces the following p-value: 1.8×10^{-89}. *From this we can see that the p-value for* $H_0 : p = 1$ *(exponential) vs.* $H_A : p \neq 1$ *is essentially zero; therefore we reject the exponential model and select the Weibull model.*

c) Using the output from the Weibull model, calculate the time ratio comparing individuals with BMI > 30 to those with BMI 18.5-<25 (no need for confidence interval). Interpret this parameter. Does this agree or not with the corresponding hazard ratio?

The time ratio (TR) for individuals with BMI > 30 compared to those with BMI 18.5-<25 is `0.781`. *This means that in the adjusted model, the time to death for those with BMI > 30 is* `0.781` *times the time to death for those in the normal weight category, conditional on age, sex and smoking status. This implies that those with a BMI >30 have an accelerated time until death. The corresponding hazard ratio from the Weibull model was* `1.47` *meaning that in the adjusted model, the hazard of death for those with BMI > 30 is* `1.47` *times the hazard of death for those in the normal weight category, conditional on age, sex and smoking status. A hazard ratio greater than one, as in this case, corresponds to a failure time ratio of less than one; so yes, the time ratio and hazard ratio agree.*

Competing Risks

Question 4: Conceptually, what is the difference between the KM failure estimate for CVD death and the estimated CIF for CVD death? What does the comparison of these curves tell you about the risk of the competing event?

The KM failure estimate for CVD death is the risk of all-cause mortality at time t, for people with CVD (compared to those without). The estimated CIF for CVD death represents the joint probability of mortality ***from CVD****, by time t. (Stated differently, this is the joint probability of both having death by time t, and it being the result of CVD). Comparison of the curves tells you that around 50 days of follow-up, subjects begin to die from causes other than CVD in higher proportion. The curves begin to diverge, with the KM failure function demonstrating greater probability of mortality than the CIF for the remainder of follow-up, implying that another cause is contributing to the higher mortality in the KM failure function.*

Question 5: In a competing risks analysis, briefly (in 1-2 sentences) define in words the following terms:

Cause-specific hazard

A cause-specific hazard is the instantaneous (very short-term) rate of failure ***for event*** *j among those who have not yet experienced either the event of interest* ***or*** *a competing event prior to t.*

Subdistribution hazard

The subdistribution hazard is the instantaneous (very short-term) rate of failure for event j among those alive at time t or who experienced a competing event before time t.

Question 6: Complete the following table for the cause-specific hazard ratios (csHRs) and subdistribution HRs (sHRs) you estimated.

BMI	CVD csHR (95% CI)	Oth csHR (95% CI)	CVD sHR (95% CI)	Oth sHR (95% CI)
18.5 - <25	*ref*	*ref*	*ref*	*ref*
25 - <30	0.89 (0.31, 2.53)	0.54 (0.19, 1.51)	1.17 (0.40, 3.47)	0.41 (0.15, 1.11)
$\geq$ 30	2.36 (0.79, 7.02)	0.25 (0.06, 0.96)	3.3 (1.22, 8.94)	0.18 (0.07, 0.45)

Question 7: From the above table, explain how the pattern you observe in the csHRs is consistent with the pattern in the sHRs. (Consider the relationship between the csHR and sHRs.)

The pattern in the csHRs shows that hazard of CVD-related death appears lower in people who are overweight (BMI 25 - <30) compared to those who are normal weight (BMI 18.5 - <25) but increases considerably for people who are obese (BMI >30) (hazard of mortality from CVD more than doubles). Note that both of these csHRs have very wide confidence intervals, making these results not statistically significant. These cause-specific hazards from the cox model approximate rates of the outcome.

As would be expected, then, the csHR for non-CVD-related mortality is lower among people who are obese compared to people who are overweight, since the rate of ***CVD-related*** *death has substantially increased for people who are obese, swamping out other causes.*

Comparing the csHR for the overweight category to the sHR it is notable that this changes from less than one to greater than one (though again both of these have confidence intervals that cross one). This implies that those in the overweight category who died of other causes would have been likely to die from CVD had they not been censored, increasing the subdistribution hazard of CVD mortality in the overweight group above one. Thus, even though the rate of CVD mortality in the overweight group is less than in the normal group, the risk is higher for the overweight group. (Though again, these are not statistically significant differences).

Regarding the relationship comparing weight categories, we see a similar pattern in the sHRs compared to the csHRs: risk of death from CVD is just slightly elevated (1.17 times the risk) in people who are overweight compared to those who are normal weight ; however, for people who are obese the risk of death from CVD is more than triple that of people who are normal weight (this increase in risk is in fact statistically significant).

As with the csHRs, with the sHRs we see a corresponding decrease in risk of mortality from non-CVD causes as BMI increases; risk of death from non-CVD causes is substantially lower for people who are obese compared to people of normal weight, since their risk of death from CVD has tripled.

Simply put, while ***rate*** *of failure (death) from an event of interest and/or competing events cannot be easily translated to* ***risk*** *of failure from that same event of interest and/or competing risks, we would expect the patterns to remain roughly the same - i.e. as cause-specific mortality rate increases, risk of failure from that cause also increases, and rate/risk of failure from other causes likely decreases.*