a. State the Cox PH model that allows for main effects of CHR and AGE as well as the interaction effect of CHR with AGE.

b. Carry out the test for significant interaction; i.e., state the null hypothesis, the test statistic, and its distribution under the null hypothesis. What are your conclusions about interaction?

c. Assuming no interaction, should AGE be controlled? Explain your answer on the basis of confounding and/or precision considerations.

d. If, when considering plots of various hazard functions over time, the hazard function for persons with CHR = 1 crosses the hazard function for persons with CHR = 0, what does this indicate about the use of any of the three models provided in the printout?

e. Using model 2, give an expression for the estimated survival curve for persons with CHR = 1, adjusted for AGE. Also, give an expression for the estimated survival curve for persons with CHR = 0, adjusted for AGE.

f. What is your overall conclusion about the effect of CHR on survival time based on the computer results provided from this study?

3. The data for this question contain remission times of 42 multiple leukemia patients in a clinical trial of a new treatment. The variables in the dataset are given below:

Variable 1: survival time (in weeks)
Variable 2: status (1 = in remission, 0 = relapse)
Variable 3: sex (1 = female, 0 = male)
Variable 4: log WBC
Variable 5: *Rx* status (1 = placebo, 0 = treatment)

Below, we provide computer results for several different Cox models that were fit to this dataset. A number of questions will be asked about these results starting below.

Model 1:

Variable	Coeff	S.E.	p-value	*HR*	0.95	CI	*P(PH)*
Rx	0.894	1.815	.622	2.446	0.070	85.812	0.391
Sex	−1.012	0.752	.178	0.363	0.083	1.585	0.058
log WBC	1.693	0.441	.000	5.437	2.292	12.897	0.482
Rx × Sex	1.952	0.907	.031	7.046	1.191	41.702	0.011
Rx × log WBC	−0.151	0.531	.776	0.860	0.304	2.433	0.443

−2 ln *L*: 139.029

Model 2:

Rx	0.405	0.561	.470	1.500	0.499	4.507	0.483
Sex	−1.070	0.725	.140	0.343	0.083	1.422	0.068
log WBC	1.610	0.332	.000	5.004	2.610	9.592	0.461
Rx × Sex	2.013	0.883	.023	7.483	1.325	42.261	0.016

−2 in *L*: 139.110

Model 3:

Rx	0.587	0.542	.279	1.798	0.621	5.202	0.340
Sex	−1.073	0.701	.126	0.342	0.087	1.353	0.003
Rx × Sex	1.906	0.815	.019	6.726	1.362	33.213	0.000

−2 ln *L*: 166.949

Model 4:

Rx	1.391	0.457	.002	4.018	1.642	9.834	0.935
Sex	0.263	0.449	.558	1.301	0.539	3.139	0.038
log WBC	1.594	0.330	.000	4.922	2.578	9.397	0.828

−2 ln *L*: 144.218

a. Use the above computer results to carry out a chunk test to evaluate whether the two interaction terms in model 1 are significant. What are your conclusions?

b. Evaluate whether you would prefer model 1 or model 2. Explain your answer.

c. Using model 2, give an expression for the hazard ratio for the effect of the *Rx* variable adjusted for SEX and log WBC.

d. Using your answer in part 3c, compute the hazard ratio for the effect of *Rx* for males and for females separately.

e. By considering the potential confounding of log WBC, determine which of models 2 and 3 you prefer. Explain.

f. Of the models provided which model do you consider to be best? Explain.

g. What does the information provided in the *P(PH)* column suggest about the analyses you have carried out? Explain.

Answers to Practice Exercises

1. a. $h(t,X) = h_0(t) \exp [\beta_1 \text{SNI} + \beta_2 \text{ AGE} + \beta_3 \text{ RACE} + \beta_4 \text{ SEX} + \beta_5 \text{SNI} \times \text{AGE} + \beta_6 \text{ SNI} \times \text{RACE} + \beta_7 \text{ SNI} \times \text{SEX}]$

   b. $HR = \exp [\, 2\beta_1 + 2(\text{AGE})\beta_5 + 2(\text{RACE})\beta_6 + 2(\text{SEX})\beta_7]$

   c. H_0: $\beta_5 = \beta_6 = \beta_7 = 0$

   Likelihood ratio test statistic: $-2 \ln \hat{L}_R - (-2 \ln \hat{L}_F)$, which is approximately χ^2_3 under H_0, where R denotes the reduced model (containing no product terms) under H_0, and F denotes the full model (given in part 1a above).

d. 95% CI for adjusted *HR*: $\exp\left[2\hat{\beta}_1 \pm 1.96 \times 2\sqrt{\text{var}(\hat{\beta}_1)}\right]$

e. $\hat{S}(t,\mathbf{X}) = \left[\hat{S}_0(t)\right]^{\exp[4\hat{\beta}_1+(\overline{\text{AGE}})\hat{\beta}_2+(\overline{\text{RACE}})\hat{\beta}_3+(\overline{\text{SEX}})\hat{\beta}_4]}$

f. The two survival curves will **not** cross, because both are computed using the same proportional hazards model, which has the property that the hazard functions, as well as their corresponding estimated survivor functions, will not cross.

2. a. $h(t,\mathbf{X}) = h_0(t) \exp[\beta_1 X_1 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_7 X_7 + \ldots + \beta_{10} X_{10}]$

b. Adeno cell type: $\mathbf{X}^*$ = (treatment, 1, 0, 0, perfstat, disdur, age, prther)

Large cell type: $\mathbf{X}$ = (treatment, 0, 0, 0, perfstat, disdur, age, prther)

$$HR = \frac{h(t,\mathbf{X}^*)}{h(t,\mathbf{X})} = \exp\left[\sum_{i=1}^{k}\beta_i(\mathbf{X}^* - X_i)\right] = \exp\left[0 + \hat{\beta}_3(1-0) + \hat{\beta}_4(0-0) + \hat{\beta}_5(0-0) + 0 + \cdots + 0\right]$$
$$= \exp\left[\hat{\beta}_3\right] = \exp[0.789] = 2.20$$

c. Adeno cell type: $\mathbf{X}^*$ = (treatment, 1, 0, 0, perfstat, disdur, age, prther)

Squamous cell type: $\mathbf{X}$ = (treatment, 0, 0, 1, perfstat, disdur, age, prther)

$$HR = \frac{h(t,\mathbf{X}^*)}{h(t,\mathbf{X})} = \exp\left[\sum_{i=1}^{k}\beta_i(\mathbf{X}^* - X_i)\right] = \exp\left[0 + \hat{\beta}_3(1-0) + \hat{\beta}_4(0-0) + \hat{\beta}_5(0-1) + 0 + \cdots + 0\right]$$
$$= \exp\left[\hat{\beta}_3 - \hat{\beta}_5\right] = \exp[0.789 - (-0.400)] = \exp[1.189] = 3.28$$

d. There does not appear to be an effect of treatment on survival time, adjusted for the other variables in the model. The hazard ratio is 1.3, which is close to the null value of one, the p-value of 0.162 for the Wald test for treatment is not significant, and the 95% confidence interval for the treatment effect correspondingly includes the null value.

e. $\hat{S}(t,\mathbf{X}) = \left[\hat{S}_0(t)\right]^{\exp[\hat{\beta}_1+\hat{\beta}_5+(\overline{\text{perfstat}})\hat{\beta}_7+(\overline{\text{disdur}})\hat{\beta}_8+(\overline{\text{age}})\hat{\beta}_9+(\overline{\text{prther}})\hat{\beta}_9]}$

f. The *P(PH)* values for the variables "adeno cell," "small cell," "squamous cell," and "perf. status" are all below 0.05, suggesting that the PH assumption may not be satisfied for some or all of these variables. Moreover, "perf. status" has *P(PH)* = 0.000.

g. $HR = \dfrac{h(t,\mathbf{X}^*)}{h(t,\mathbf{X})} = \exp[\beta_1 + (\text{perfstat})\beta_{11} + (\text{disdur})\beta_{12} + (\text{age})\beta_{13} + (\text{prther})\beta_{14}]$

where β_1 is the coefficient of the treatment variable and β_{11}, β_{12}, β_{13}, and β_{14} are the coefficients of product terms involving treatment with the four variables indicated.

3. a. None of the *P(PH)* values for any variable in any of the models fitted is approaching statistical significance. Thus, there is no evidence from the results provided that the PH assumption is not satisfied.

b. $\widehat{HR} = \exp[0.470 + (-0.008)\text{age} + (-0.503)\text{sex}]$

c. 40-year-old male: $\widehat{HR} = \exp[0.470 + (-0.008)40 + (-0.503)1] = 0.70$

50-year-old female: $\widehat{HR} = \exp[0.470 + (-0.008)50 + (-0.503)2] = 0.39$

d. The LR (chunk) test for the significance of both interaction terms simultaneously yields the following likelihood ratio statistic which compares models 1 and 2:

$LR = 306.505 - 306.080 = 0.425$

This statistic is approximately chi-square with 2 degrees of freedom under the null hypothesis of no interaction. This LR statistic is highly nonsignificant. Thus, we conclude that there is no significant interaction in the model (1).

e. The gold-standard hazard ratio is 0.484, which is obtained for model 2. Note that model 2 contains no interaction terms and controls for both covariates of interest. When either age or sex or both are dropped from the model, the hazard ratio (for platelets) does not change appreciably. Therefore, it appears that neither age nor sex need to be controlled for confounding.

f. Models 2–5 are all more or less equivalent, since they all give essentially the same hazards ratio and confidence interval for the effect of the platelet variable. A political choice for best model would be the gold-standard model (2), because the critical reviewer can see both age and sex being controlled in model 2.

g.
- The point estimate of the hazard ratio for normal versus abnormal platelet count is .484 = 1/2.07, so that the hazard for an abnormal count is twice that for a normal count.
- There is no significant effect of platelet count on survival adjusted for age and sex ($P = .863$).
- The 95% CI for the hazard ratio is given by $0.221 < HR < 1.063$, which is quite wide and therefore shows a very imprecise estimate.