9 Competing Risks Survival Analysis

D.G. Kleinbaum and M.Klein, *Survival Analysis: A Self-Learning Text, Third Edition,*
Statistics for Biology and Health, DOI 10.1007/978-1-4419-6646-9_9,

Introduction

This chapter considers survival data in which each subject can experience only one of several different types of events over follow-up. This situation contrasts with the topic of the preceding chapter in which subjects could experience more than one event of a given type. When only one of several different types of event can occur, we refer to the probabilities of these events as "competing risks," which explains the title of this chapter.

Modeling competing risks survival data can be carried out using a Cox model, a parametric survival model, or models that use the *cumulative incidence* (rather than survival). In this chapter, we mainly consider the Cox model because of its wide popularity and also because of the availability of computer programs that use the Cox model for analysis of competing risks.

The typical ("cause-specific") approach for analyzing competing risks data is to perform a survival analysis for each event type separately, where the other (competing) event types are treated as censored categories. There are two primary drawbacks to the above method. One problem is that the above method requires the assumption that competing risks are independent. The second problem is that the generalized Kaplan–Meier (KM)-based product-limit survival curve obtained from fitting separate Cox models for each event type has questionable interpretation when there are competing risks.

Unfortunately, if the independence assumption is incorrect, there is no direct methodology available for analyzing competing risks simultaneously. The only "indirect" method for addressing this problem involves carrying out a "sensitivity analysis" that treats subjects with events from competing risks as all being event-free or as all experiencing the event of interest. An example of this "sensitivity" approach is provided.

The primary alternative summary curve to the KM-based survival curve is the "cumulative incidence curve (CIC)," which estimates the "marginal probability" of an event (both terms are defined in this chapter). This CIC is not estimated using a product-limit formulation, and its computation is not included in mainstream statistical packages. Moreover, the independence of competing risks is still required when a proportional hazard model is used to obtain hazard ratio estimates for individual competing risks as an intermediate step in the computation of a CIC. Nevertheless, the CIC has a meaningful interpretation in terms of treatment utility regardless of whether competing risks are independent. A variation of the CIC, called the "conditional probability curve (CPC)," provides a risk probability conditional on an individual not experiencing any of the other competing risks by time t.

An equivalent approach to the cause-specific method for analyzing competing risks is called the Lunn–McNeil (LM) approach. The LM approach allows only one model to be fit rather than separate models for each event type and, moreover, allows flexibility to perform statistical inferences about simpler versions of the LM model. This approach has added appeal in that competing events are not considered as simply being censored. Nevertheless, as with the cause-specific approach, the LM method assumes the independence of competing risks.

Abbreviated Outline

The outline below gives the user a preview of the material covered by the presentation. A detailed outline for review purposes follows the presentation.

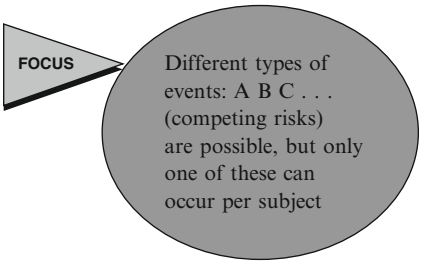
Objectives

Upon completing this chapter, the learner should be able to:

1. State or recognize examples of competing risks survival data.
2. Given competing risks data, outline the steps needed to analyze such data using separate Cox models.
3. Given computer output from the analysis of competing risk data, carry out an analysis to assess the effects of explanatory variables on one or more of the competing risks.
4. State or describe the independence assumption typically required in the analysis of competing risks data.
5. Describe how to carry out and/or interpret a "sensitivity analysis" to assess the independence assumption about competing risks.
6. State why a survival function obtained from competing risk data using the Cox model has a questionable interpretation.
7. State or describe the "cumulative incidence" approach for analyzing competing risks data.
8. Given competing risk data, describe how to calculate a CIC and/or a CPC curve.
9. Given competing risks data, outline the steps needed to analyze such data using the Lunn–McNeil method.
10. Given computer output from fitting either a LM or LM_{alt} model, carry out an analysis to assess the effect of explanatory variables on one or more of the competing risks.

Presentation

I. Overview



In this chapter, we consider survival data in which each subject can experience only one of different types of events over follow-up. The probabilities of these events are typically referred to as **competing risks**. We describe how to use the Cox PH model to analyze such data, the drawbacks to this approach, and some approaches for addressing these drawbacks.

II. Examples of Competing Risks Data

1. Dying from either lung cancer or stroke
2. Advanced cancer patients either dying from surgery or getting hospital infection
3. Soldiers dying in accident or in combat
4. Limb sarcoma patients developing local recurrence, lung metastasis, or other metastasis over follow-up

Competing risks occur when there are at least two possible ways that a person can fail, but only one such failure type can actually occur. For example,

1. A person can die from lung cancer or from a stroke, but not from both (although he can have both lung cancer and atherosclerosis before he dies);
2. Patients with advanced-stage cancer may die after surgery before their hospital stay is long enough for them to get a hospital infection;
3. Soldiers in war may die during combat or may die by (e.g., traffic) accident;
4. In a clinical trial, patients with nonmetastatic limb sarcoma undergoing chemotherapy and surgery might develop a local recurrence, lung metastasis, or other metastasis after follow-up.

Each example above allows only **one** event out of several possible events to occur per subject

If event not death, then recurrent events are possible

Competing risks + recurrent events beyond scope of this chapter

For each of the above examples, the possible events of interest differ, but only one such event can occur per subject. Note, however, if at least one of the possible event types does not involve death, it is also possible that such events can recur over follow-up. Thus, although the analysis of recurrent events that also involves competing risks may be required, this more complex topic is beyond the scope of this chapter (see Tai et al., 2001).

Objective: assess

$X_1, X_2, \ldots, X_p \Rightarrow$ Failure rate (survival probability)

for any one event allowing for competing risks from other possible events

A logical objective for competing risks data is to assess the relationship of relevant predictors to the failure rate or corresponding survival probability of any **one** of the possible events allowing for the competing risks of the other ways to fail.

Another objective

Compare hazard rate for event A with hazard rate for event B

We might also want to compare the failure rates (e.g., using a hazard ratio) for two or more possible events, controlling for relevant predictors.

Lung Cancer vs. Stroke (1)

HR_{LC}(E vs. not E) = 1? (allowing for competing risk from stroke)

In the lung cancer versus stroke example above, we might ask whether the lung cancer death rate in "exposed" persons is different from the lung cancer rate in "unexposed" persons, allowing for the possibility that subjects could have died from a stroke instead.

HR(LC vs. Stroke) = 1? (controlling for predictors)

We might also want to know if the lung cancer death rate differs from the stroke death rate controlling for predictors of interest.

Surgery Death vs. Hospital Infection (2)

$HR_{HOSPINF}$(E vs. not E) = 1? (allowing for competing risk from surgery)

Note: death from surgery reduces number of hospital infections to be treated

In the second example, the competing risks are death from surgery versus development of a hospital infection. For infection control investigators, the hospital infection event is of primary interest. Nevertheless, the occurrence of death from surgery reduces the burden of hospital infection control required. Thus, the estimation of hospital infection rates are complicated by the competing risk of death from surgery.

Accidental Death vs. Combat Death (3)

HR_{COMBAT} (E vs. not E) (allowing competing risk of accidental death)

Suppose entire company dies at accident time t before entering combat

$\Downarrow$

$S_{COMBAT}(t) = P(T_{COMBAT} > t) = 1$

where T_{COMBAT} = time to combat death

The third example involves competing risks of death from either combat or accident in a company of soldiers. Here, primary interest concerns the hazard ratio for combat death comparing two exposure groups. Suppose the entire company dies at time t in a helicopter accident on their way to a combat area. Because no one died in combat by time t, the survival probability of not dying in combat is one, even though no combat took place.

However,

T_{C+A} = combat or accidental death

$\Downarrow$

"event free" $S_{C+A}(t) = P(T_{C+A} > t) = 0$

However, if we define the outcome of interest as death from either combat or accident, the "event free" survival probability is zero after the accident occurred (at time t).

Moreover,

$$S_{KM}(T_{COMBAT} > t)$$

is undefined because the risk set is empty at time t

Moreover, the KM survival probability for combat death at time t is undefined because no one was at risk for a combat death at time t.

Competing Risks Data Survival Curve Interpretation?

This example points out that when there are competing risks, the interpretation of a survival curve may be difficult or questionable (more on this issue later).

Limb sarcoma patients (4)

In the fourth example involving limb sarcoma patients, the competing risks are the three failure types shown at the left.

Competing risks
1 = local recurrence, 2 = lung metastasis, or 3 = other metastasis

In this study, the investigators wanted hazard ratios for each failure type, allowing for competing risks from the other two failure types.

$HR_{\mathbf{c}}$(E vs. not E), $\mathbf{c} = 1, 2, 3$ (allowing for competing risk from other two failure types)

HR(Lung Metastasis vs. Local Recurrence)? Controlling for Predictors

It was also of interest to compare the failure rates for lung metastasis versus local recurrence (or any other two of the three failure types), controlling for relevant predictors.

No failure types involve death

$\Downarrow$

Recurrent events possible

Because none of the failure types involves death, recurrent events are possible for any of the three failure types. If, however, the information on only the first failure is targeted, the classical competing risk methodology described in this chapter can be applied.

But can use classical competing risk methods if focus on **only first failure**

III. Byar Data

- Randomized clinical trial
- Compare treatments for Stage III and IV prostate cancer
- Rx status: placebo or one of 3 dose levels of DES

We now introduce an example of competing risks survival analysis of data from a randomized clinical trial (Byar and Green, 1980) comparing treatments for prostate cancer. We henceforth refer to this as the **Byar data**. Patients with Stages III (local extension beyond the prostate gland) and IV (distant metastases, elevated acid phosphatase, or both) prostate cancer were randomized to receive either a placebo or one of three dose levels of the active treatment diethylstilbestrol (DES).

Competing risks: deaths from

Cancer (main focus)
CVD
Other

In this study, patients could die from prostate cancer, cardiovascular disease, or other causes. Covariate information was also collected to account for the possible influence of predictors on survival. These data have been analyzed extensively (Byar and Corle, 1977, Kay, 1986, and Lunn and McNeil, 1995). Some grouping of the predictors was considered to be clinically meaningful.

Covariate information collected

Some predictors grouped

Predictors	Value	Category
Treatment (Rx)	0	Placebo, 0.2 mg DES
	1	1.0,5 mg DES
Age at diagnosis Diagnosis (Age)	0	≤74 years
	1	75–79 years
	2	≥80 years
Standardized[a] weight (Wt)	0	≥100
	1	80–99
	2	>80
Performance status (PF)	0	Normal
	1	Limitation of activity
History of CVD (Hx)	0	No
	1	Yes
Hemoglobin (Hg)	0	≥ 12 g/100 ml
	1	9.0–11.9 g/100 ml
	2	<9 g/100 ml
Size of the primary lesion (SZ)	0	<30 cm^2
	1	≥30 cm^2
Gleeson Score[+](SG)	0	≤10
	1	>10

[a] weight (kg) – height (cm) + 200
[+] index of tumor invasiveness/ aggressiveness

Key risk factors related to the primary outcome of interest (cancer deaths) and the appropriate grouping is shown at the left.

Primary interest was to assess the effect of treatment (Rx) adjusted for relevant risk factors in the presence of the competing risks. Notice from the table that the Rx variable is grouped into a binary variable by coding subjects receiving the placebo or 0.2 mg of DES as 0 and coding subjects receiving 1.0 or 5.0 mg of DES as 1.

Independence assumption (discussed later)

Next

Analysis of competing risks survival data

Assume independent competing risks

From a clinical perspective, these three competing risks can be considered to be **independent** (e.g., failure from heart disease and/or other causes of death is unrelated to risk of failure from prostate cancer). We discuss this "independence assumption" in more detail in a subsequent section of this chapter.

We now describe the approach typically used to analyze competing risks data. This approach assumes that competing risks are independent. We illustrate this approach using the Byar data.

IV. Method 1: Separate Models for Different Event Types

- Use Cox (PH) model
- Estimate separate hazards or HRs for each failure type
- Other (competing) failure types are treated as censored
- Persons lost to follow-up or withdrawal are also censored

The typical approach for analyzing competing risks data uses the Cox (PH) model to separately estimate hazards and corresponding hazard ratios for each failure type, treating the other (competing) failure types as censored in addition to those who are censored from loss to follow-up or withdrawal. We refer to this approach as **Method 1** because we later describe an alternative approach (Method 2) that requires only a single model to be fit.

If only one failure type of interest

$\Downarrow$

Estimate only one hazard or HR

If only one failure type is of primary interest, then the analysis might be restricted to estimating hazards or hazard ratios for that type only (but still treating the competing failure types as censored).

Cause-specific hazard function

$$h_c(t) = \lim_{\Delta t \to 0} P(t \le T_{\mathbf{c}} < t + \Delta t | T_{\mathbf{c}} \ge t)/\Delta t$$

where T_c = time-to-failure from event **c**

c = 1, 2, …, C (# of event types)

To describe this method mathematically, we define the **cause-specific hazard function** shown at the left. The random variable $T_{\mathbf{c}}$ denotes the time-to-failure from event type **c**. Thus, $h_{\mathbf{c}}(t)$ gives the instantaneous failure rate at time t for event type **c**, given not failing from event **c** by time t.

Cox PH cause-specific model (event-type **c**):

$$h_{\mathbf{c}}(t, \mathbf{X}) = h_{0\mathbf{c}}(t) \exp\left[\sum_{i=1}^{p} \beta_{ic} X_i\right], \quad \mathbf{c} = 1, \ldots, C$$

β_{ic} allows effect of X_i to differ by event-type

Using a Cox PH model that considers predictors $\mathbf{X} = (X_1, X_2, \ldots, X_p)$, the **cause-specific hazard model** for event type **c** has the form shown at the left. Note that $\beta_{\mathbf{ic}}$, the regression coefficient for the ith predictor, is subscripted by **c** to indicate that the effects of the predictors may be different for different event types.

Byar Data Example

Competing Risks: **Cancer, CVD, Other**

Cause-specific model: **Cancer**
No-interaction model:

$$h_{\mathbf{Ca}}(t, \mathbf{X}) = h_{0\mathbf{Ca}}(t)\exp[\beta_{1\mathbf{Ca}}Rx + \beta_{2\mathbf{Ca}}Age + \beta_{3\mathbf{Ca}}Wt + \beta_{4\mathbf{Ca}}PF + \beta_{5\mathbf{Ca}}Hx + \beta_{6\mathbf{Ca}}HG + \beta_{7\mathbf{Ca}}SZ + \beta_{8\mathbf{Ca}}SG]$$

$$HR_{\mathbf{Ca}}(RX = 1 \text{ vs. } RX = 0) = \exp[\beta_{1\mathbf{Ca}}]$$

CVD and **Other** deaths are censored

Cause-specific model: **CVD**

$$h_{\mathbf{CVD}}(t,\mathbf{X}) = h_{0\mathbf{CVD}}(t)\exp[\beta_{1\mathbf{CVD}}Rx + \beta_{2\mathbf{CVD}}Age + \beta_{3\mathbf{CVD}}Wt + \beta_{4\mathbf{CVD}}PF + \beta_{5\mathbf{CVD}}Hx + \beta_{6\mathbf{CVD}}HG + \beta_{7\mathbf{CVD}}SZ + \beta_{8\mathbf{CVD}}SG]$$

$$HR_{\mathbf{CVD}}(RX = 1 \text{ vs. } RX = 0) = \exp[\beta_{1\mathbf{CVD}}]$$

Cancer and **Other** are censored

Cause-specific model: **Other**

$$H_{\mathbf{OTH}}(t,\mathbf{X}) = h_{0\mathbf{OTH}}(t)\exp[\beta_{1\mathbf{OTH}}Rx + \beta_{2\mathbf{OTH}}Age + \beta_{3\mathbf{OTH}}Wt + \beta_{4\mathbf{OTH}}PF + \beta_{5\mathbf{OTH}}Hx + \beta_{6\mathbf{OTH}}HG + \beta_{7\mathbf{OTH}}SZ + \beta_{8\mathbf{OTH}}SG]$$

Cancer and **CVD** are censored

We illustrate the above model using the Byar data involving the three competing risks and the eight predictors.

A no-interaction cause-specific model for **Cancer** death (**Ca**) is shown at the left. From this model, the hazard ratio for the effect of Rx controlling for the other variables is $\exp[\beta_{1\mathbf{Ca}}]$.

Because **Cancer** is the event-type of interest, the two competing event-types, **CVD** and **Other**, need to be treated as censored in addition to usual censored observations (i.e., for persons who are either lost to follow-up or withdraw from the study).

Similarly, if **CVD** is the event-type of interest, the cause-specific no-interaction hazard model and the hazard ratio formula for the effect of treatment is shown at the left, and the event types **Cancer** and **Other** would be treated as censored.

And finally, if **Other** is the event-type of interest, the cause-specific no-interaction hazard model and the hazard ratio formula for the effect of treatment is shown at the left, and the event types **Cancer** and **CVD** would be treated as censored.

Edited output for each of the above three cause-specific models is now presented.

First, we show the results for the event type **Cancer**, treating **CVD** and **Other** as censored

Table 9.1. Edited Output for Cancer with **CVD** and **Other** Censored

Var	DF	Coef	Std. Err.	p > |z|	Haz. Ratio
Rx	1	−0.550	0.170	0.001	0.577
Age	1	0.005	0.142	0.970	1.005
Wt	1	0.187	0.138	0.173	1.206
PF	1	0.253	0.262	0.334	1.288
Hx	1	−0.094	0.179	0.599	0.910
HG	1	0.467	0.177	0.008	1.596
SZ	1	1.154	0.203	0.000	3.170
SG	1	1.343	0.202	0.000	3.830

Log likelihood = − 771.174

$\widehat{HR}_{\mathbf{Ca}}(\text{RX} = 1 \text{ vs. RX} = 0)$
$= \exp(-0.550) = 0.577$
Wald ChiSq $= (-.550/.170)^2$
$= 10.345$ (P $= 0.001$)
Signif. below .01 level

From this output, the adjusted $\widehat{HR}$ for the effect of Rx is 0.577 (=1/1.73).

The P-value for a two-tailed Wald test is 0.001; thus Rx has a significant positive effect on survival for **Cancer** death with competing risks from **CVD** and **Other** deaths.

95% CI for $\exp[\beta_{1\mathbf{Ca}}]$:
$\exp[-0.550 \pm 1.96(0.170)]$
$= (0.413, 0.807)$

Also, the 95% confidence interval for this HR is (0.413, 0.807) = (1/2.43, 1/1.24).

Table 9.2. Edited Output for **CVD** with **Cancer** and **Other** Censored

Var	DF	Coef	Std. Err.	p > |z|	Haz. Ratio
Rx	1	0.354	0.174	0.042	1.425
Age	1	0.337	0.134	0.012	1.401
Wt	1	0.041	0.150	0.783	1.042
PF	1	0.475	0.270	0.079	1.608
Hx	1	1.141	0.187	0.000	3.131
HG	1	0.018	0.202	0.929	1.018
SZ	1	−0.222	0.364	0.542	0.801
SG	1	−0.023	0.186	0.900	0.977

Log likelihood = −763.001

We next provide edited output when the event-type is **CVD**, treating **Cancer** and **Other** as censored.

$\widehat{HR}_{\mathbf{CVD}}(\text{RX} = 1 \text{ vs. RX} = 0)$
$= \exp(0.354) = 1.425$
Wald ChiSq $= (.354/.174)^2$
$= 4.220$ (P $= 0.042$)
Signif. at .05 level

Here, the adjusted $\widehat{HR}$ for the effect of Rx is 1.425.

The P-value for a two-tailed Wald test is 0.042; thus, Rx has a significant (P < .05) but negative effect on survival for **CVD** death with competing risks from **Cancer** and **Other** deaths.

95% CI for $\exp[\beta_{1\mathbf{CVD}}]$:
exp.$[0.354 \pm 1.96(0.174)]$
$= (1.013, 2.004)$

The 95% confidence interval for this HR is (1.013, 2.004).

Table 9.3. Edited Output for **Other** with **Cancer** and **CVD** Censored

Var	DF	Coef	Std. Err.	p > |z|	Haz. Ratio
Rx	1	−0.578	0.279	0.038	0.561
Age	1	0.770	0.204	0.000	2.159
Wt	1	0.532	0.227	0.019	1.702
PF	1	0.541	0.422	0.200	1.718
Hx	1	0.023	0.285	0.935	1.023
HG	1	0.357	0.296	0.228	1.428
SZ	1	0.715	0.423	0.091	2.045
SG	1	−0.454	0.298	0.127	0.635

Log likelihood = −297.741

Last, we provide edited output when the event-type is **Other**, treating **Cancer** and **CVD** as censored.

$\hat{HR}_{\mathbf{OTH}}(RX = 1 \text{ vs. } RX = 0) = \exp(-0.580) = 0.560$

Here. the adjusted $\hat{HR}$ for the effect of Rx is 0.561 (= 1/ 1.78).

Wald ChiSq = $(-.578/.279)^2$ =4.29 (P=0.038)
Signif. at .05 level

The P-value for a two-tailed Wald test is .038; thus, Rx has a significant ($P < .05$) protective effect on survival for **Other** deaths with competing risks from **Cancer** and **CVD** deaths.

95% CI for $\exp[\beta_{1\mathbf{OTH}})$:
$\exp[-0.578 +- 1.96(0.279)]$
=(0.325, 0.969)

The 95% confidence interval for this HR is (0.325,0.969), which is somewhat imprecise.

Not assessed in the above analysis:

PH assumption

Interaction of Rx with control variables

We have thus completed a competing risk analysis af the Byar data assuming that a no-interaction Cox PH model is appropriate. We haven't actually checked the PH assumption for any of the variables in the model nor have we assessed whether there is significant interaction between Rx and the other variables being controlled. Typically, these situations should be explored to ensure a more appropriate analysis.

V. The Independence Assumption

Censoring: a major concern in survival analysis

At the beginning of this text in Chapter 1, we introduced the concept of censoring as a major concern for the analysis of survival data. We distinguished between right- and left-censoring and indicated our focus in the text would be on right-censoring, which occurs more often.

Right-censoring vs. left-censoring
↓
- more often
- our focus

Typical assumption:
Censoring is Independent

- Required for all approaches/ models described to this point
- Relevant for competing risks

We also introduced in Chapter 1 an important assumption about censoring that is typically assumed for all approaches/models for analyzing survival data described up to this point, including data with competing risks. This assumption is often stated as follows: **censoring is independent**.

Two other (different) assumptions
Random censoring
Non-informative censoring

In addition, we distinguished (in Chapter 1) "independent" censoring from two other assumptions: "random" censoring and "non-informative" censoring, but emphasized the importance of the independence assumption.

Independent censoring:

Chapter 1 context: no competing risks

$h(t \mid G, Ce) = h(t \mid G, NCe)$ where

G denotes any subgroup of subjects at risk at time t
$h(t \mid G, Ce)$ denotes hazard for censored subjects in subgroup G
$h(t \mid G, NCe)$ denotes hazard for noncensored subjects in subgroup G

Bias possible:
$\hat{S}(t)$ may over-estimate $S(t)$
if
large proportion of subjects censored at time t actually fail after time t

In Chapter 1, we defined **independent censoring** in a context that assumed the absence of competing risks as follows:

Within any subgroup of interest, subjects who are censored at time t should be representative of all subjects in that subgroup who remained at risk at time t with respect to their survival experience.

Non-independent censoring unfortunately can lead to **biased results** in a survival analysis. A bias can result if people who get censored are more likely to fail than those not censored. Thus, the estimated survival probability at any time t may over-estimate the true survival probability at time t if a large proportion of those with unknown status (i.e., censored) actually failed.

Independent censoring with competing risks

⇓

Different types of censoring:

- failure from competing risks
- lost-to-follow-up
- withdrawal
- end of study

When the survival analysis problem involves competing risks, the requirement of **independent censoring** has the additional complication that there are different types of censoring that are possible. That is, when focusing on the cause-specific hazard for event-type **A**, say, competing risks other than **A** are also considered as censored in addition to standard censorship from lost-to-follow-up, withdrawal or ending of the study.

EXAMPLE (Byar data)

3 competing risks:
Cancer, CVD, or Other deaths
Independent censoring?

Suppose censoring is **independent** and Harry censored at time t

⇓

$h_{\mathbf{Ca}}(t \mid G, Ce) = h_{\mathbf{Ca}}(t \mid G, NCe)$

Suppose censoring is **not independent** and Harry died from **CVD** or **Other** Cause at time t

⇓

$h_{\mathbf{Ca}}(t \mid G, Ce) \neq h_{\mathbf{Ca}}(t \mid G, NCe)$

For example, in the Byar data set, there were three competing risks of interest, **Cancer, CVD,** or **Other** deaths. What, then, must we assume if censoring in this study were independent?

Suppose **censoring is independent** and we focus on cause-specific deaths for **Cancer**, then any subject (e.g., Harry) in the risk set at time t with a given set (G) of covariates who is censored at time t is presumed to have the same failure rate as any noncensored subject in the risk set with the same set of covariates regardless of whether the reason for censoring is either a **CVD** or **Other** death, withdrawal from study, or lost-to-follow-up.

On the other hand, suppose **censoring were not independent,** then if Harry was censored at time t because he died from **CVD** or **Other** causes at time t, Harry's (unknown) failure rate at time t for dying of **Cancer** would differ from the Cancer failure rate for noncensored subjects at time t (who didn't previously die of **Cancer, CVD**, or **Other** causes prior to time t).

Important assumption for competing risks

Censoring is independent regardless of different types of censoring possible

Synonym: **Competing risks are independent**

The important message at this point when analyzing competing risks survival data is that it is typically assumed that **censoring is independent** regardless of the different ways that censoring can occur, including failure from competing risks other than the cause-specific event-type of interest. A synonymous expression is to say that **competing risks are independent**, which we henceforth adopt in our remaining discussion of this topic.

Questions about independence assumption

1. How can we determine whether this assumption is satisfied?
2. How can we proceed with the analysis to consider the possibility that the assumption is not satisfied?

So, if we typically require that competing risks are independent, (1) how can we determine whether this assumption is satisfied and (2) how can we proceed with the analysis to consider the possibility that the assumption is not satisfied?

Answer to 1:
We can never explicitly prove the assumption is satisfied for given data.

For example, Byar data: **Cancer** death
Then can't determine would have died from **Cancer** if hadn't died from **CVD**.

Unfortunately, the answer to the first question is that we can never explicitly prove that competing risks are or are not independent for a given dataset. For example, in the Byar dataset, we cannot determine for certain whether a subject who died from, say, **CVD** at time t would have died from **Cancer** if he hadn't died from **CVD**.

CVD death
⇓
Cancer death unobservable

In general
Failure from competing risk A
⇓
Failure from competing risk B unobservable

In other words, dying from **Cancer** at time t is an unobservable outcome for a subject who died from **CVD** at or before time t. More generally, failure from a competing risk at time t is unobservable for a subject who has already failed from a different competing risk up to time t.

Answer to 2:
Alternative strategies available but no strategy is always best

Because we can never fully determine whether competing risks are independent, how can we proceed with the analysis of competing risks survival data? The answer is that there are several alternative strategies, but no one strategy that is always best.

Strategy 1
Decide assumption satisfied on clinical/biological/other grounds

One strategy is to decide on clinical/biological/other grounds without any data analysis that the independence assumption is satisfied and then carry out the analysis assuming independence.

EXAMPLE OF STRATEGY 1—CANCER VS. CVD

Decide independence if subjects who were censored because of **CVD** death were no more or less likely to have died from **Cancer**.

For example, suppose the two competing risks are **Cancer** deaths and **CVD** deaths. Then you may decide that the assumption of independent competing risks is reasonable if at any time t, subjects who were censored because of **CVD** death were no more or less likely to have died from **Cancer**.

Strategy 2
Include common risk factors for competing risks in survival model

A second strategy is to measure those variables that are common risk factors for competing risks being considered and then include those variables in the survival model. For example, with **Cancer** and **CVD**, perhaps including age and smoking status in the survival model might remove common effects on competing risks.

EXAMPLE OF STRATEGY 2—CANCER VS. CVD

Include age smoking in model to remove the common effects of these variables on competing risks.

Criticism of Strategies 1 and 2
Assumptions cannot be verified with observed data

A criticism of each of the above strategies is that they both rely on assumptions that cannot be verified with the observed data.

Strategy 3
Use a sensitivity analysis

- Considers "worst-case" violations of the independence assumption

Another strategy (3) that can be used is a sensitivity analysis. As with Strategies 1 and 2, a sensitivity analysis cannot explicitly demonstrate whether the independence assumption is satisfied. However, this strategy allows the estimation of parameters by considering "worst-case" violations of the independence assumption.

Sensitivity analysis

- Determines extreme ranges for estimated parameters of one's model

Thus, using a sensitivity analysis, the investigator can determine extreme ranges for the estimated parameters in one's model under violation of the independence assumption.

If "worst-case" not meaningfully different from independence
then
at most a small bias when assuming independence

If such "worst-case" results do not meaningfully differ from results obtained under the independence assumption, then the investigator may conclude that at most a small bias can result from an analysis that assumes independence.

If "worst-case" meaningfully
different from independence
then
only extreme of bias but not
actual bias is determined

If, on the other hand, the sensitivity analysis provides results that meaningfully differ from results obtained under the independence assumption, the investigator learns only the extremes to which the results could be biased without adjusting for the actual bias.

EXAMPLE BYAR DATA

Cause-specific focus: **Cancer**
Censored: **CVD** deaths. **Other** deaths, usual censoring

Worst-case situations:

1. **CVD** or **Other** deaths are assumed to die of cancer instead
2. **CVD** or **Other** deaths assumed to survive as long as the largest survival time observed in the study

We now illustrate how a sensitivity analysis can be carried out using the Byar data, where we focus on the cause-specific survival for **Cancer** deaths, treating **CVD** and **Other** deaths as censored in addition to usual censoring.

The following two worst-case situations are considered. (1) All subjects that are censored because of **CVD** or **Other** deaths are assumed to die of cancer instead. (2) All subjects that are censored because of **CVD** or **Other** deaths survive as long as the largest survival time observed in the study.

Table 9.4. Edited Output for Cancer Worst-Case (1)

var	DF	Coef	Std.Err.	p > |z|	Haz. Ratio
Rx	1	−0.185	0.110	0.092	0.831
Age	1	0.286	0.087	0.001	1.332
Wt	1	0.198	0.093	0.032	1.219
PF	1	0.402	0.170	0.018	1.495
Hx	1	0.437	0.112	0.000	1.548
HG	1	0.292	0.120	0.015	1.339
SZ	1	0.672	0.159	0.000	1.958
SG	1	0.399	0.115	0.001	1.491

Log likelihood = −1892.091

Table 9.5. Edited Output for Cancer Worst-Case (2)

Var	DF	Coef	Std.Err.	p > |z|	Haz. Ratio
Rx	1	−0.411	0.169	0.015	0.663
Age	1	−0.118	0.139	0.394	0.888
Wt	1	0.086	0.138	0.532	1.090
PF	1	0.125	0.254	0.622	1.133
Hx	1	−0.266	0.179	0.138	0.767
HG	1	0.314	0.169	0.063	1.369
SZ	1	0.825	0.197	0.000	2.282
SG	1	1.293	0.201	0.000	3.644

Log likelihood = −839.631

Table 9.4 and **Table 9.5** give edited output for the above two scenarios followed by a repeat of the output previously shown (**Table 9.1**) under the independence assumption.

To carry out worst-case scenario (1), the Status variable (indicating whether a subject failed or was censored) was changed in the dataset from 0 to 1 for each subject that had a **CVD** or **Other** death.

For worst-case scenario (2), the longest survival time observed in the study was 76 weeks. Thus, the survival time for each subject that had a **CVD** or **Other** death was changed in the dataset from the actual time of death to 76 weeks.

To evaluate the results of the sensitivity analysis, we need to compare the output in **Table 9.1**, which assumes that competing risks are independent, with output for worst-case situations provided in **Table 9.4** and **Table 9.5**. We focus this comparison on the estimated coefficient of the Rx variable.

Table 9.1 (Repeated). Edited Output for Cancer with **CVD** and Other censored (Assumes Competing Risks Independent)

Var	DF	Coef	Std.Err.	P>|z|	Haz. Ratio
Rx	1	−0.550	0.170	0.001	0.577
Age	1	0.005	0.142	0.970	1.005
Wt	1	0.187	0.138	0.173	1.206
PF	1	0.253	0.262	0.334	1.288
Hx	1	−0.094	0.179	0.599	0.910
HG	1	0.467	0.177	0.008	1.596
SZ	1	1.154	0.203	0.000	3.170
SG	1	1.343	0.202	0.000	3.830

Log likelihood = −771.174

Var	DF	Coef	Std. Err.	p > |z|	Haz. Ratio
Worst-Case (1):					
Rx	1	−0.185	0.110	0.092	0.831
Worst-Case (2):					
Rx	1	−0.411	0.169	0.015	0.663
Independent competing risks:					
Rx	1	−0.550	0.171	0.001	0.577

The first line of output corresponding to the Rx variable is shown at the left for both worst-case scenarios together with the output obtained from assuming independent competing risks.

	WC(1)	WC(2)	Independent
$\widehat{HRs}$	0.831	0.663	0.577
P-values	0.092	0.015	0.001
	(N.S.)	(<.05)	(< <.01)

These results for the RX variable show considerable differences among all three scenarios. In particular, the three estimated hazard ratios are 0.831 (= 1/1.20), 0.663 (=1/1.51), and .577 (=1/1.73). Also, the P-values for the significance of the effect of Rx (0.092, 0.015, .001) lead to different conclusions about the effect of Rx.

Independence Nonindependence
_____x_____ [_____] ___
.577 .663 .831

Note that the HR obtained from assuming independence does not lie between the HRs from the two worst-case scenarios. This should not be surprising because both worst-case scenarios assume non-independence.

If
competing risks not independent
then
conclusions about the effect of Rx could be very different

These results suggest that if the competing risks were not independent, then the conclusions about the effect of Rx could be somewhat different.

But,

- Have not demonstrated whether independence assumption satisfied
- Have not obtained correct results under violation of independence assumption

However, these results do not demonstrate whether the independence assumption is satisfied, nor do they provide estimates of the unbiased hazard ratios and corresponding Wald tests under violation of the independent assumption.

Worst-case (1)
More departure from independence
More realistic
More emphasis
than
Worst-case (2)

Worst-case (1) gives more departure from independence than worst-case (2). It can also be argued that worst-case (1) is more realistic and thus should be emphasized more than worst-case (2), because subjects who were censored because of **CVD** or **Other** deaths would not be expected to survive the entire study if they hadn't died.

Sensitivity analysis: approaches can vary for example,

- Randomly select subset of 50% (or 25%) of subjects censored with **CVD** or **Other** deaths
- Assume everyone in subset dies of **Cancer**

The previous observation suggests that the investigator can vary the approach used to either carry out or interpret such a sensitivity analysis. For example, an alternative approach would be to modify worst-case (1) by randomly selecting a subset of 50% (or 25%) of subjects censored with **CVD** or **Other** deaths and then assuming that everyone in this subset dies of **Cancer** instead.

Main point:

Sensitivity analysis is one of several strategies to address concern about independence assumption

Evaluates how badly biased the results can get if independence not satisfied

In any case, the main point here is that a sensitivity analysis of the type we have illustrated is one of several strategies that can be used to address concern about the independence assumption. Such a sensitivity analysis allows the investigator to evaluate how badly biased the results could get if the independence assumption is not satisfied.

Nevertheless

- No method to directly assess independence assumption
- Typical analysis assumes independence assumption is satisfied

Nevertheless, as mentioned earlier, there is no method currently available that can directly assess the independence assumption nor guarantee correct estimates when the independence assumption is violated. Consequently, the typical survival analysis assumes that the independence assumption is satisfied when there are competing risks, even if this is not the case.

VI. Cumulative Incidence Curves (CIC)

Survival curves S(t):
provide summary information over time of survival experience

KM: empirical approach for estimating survival curves

Adjusted survival curves: generalized version of KM using a regression model to adjust for covariates

Up to now: One event-type of interest (no competing risks)

We have previously discussed (Chapter I and beyond) the use of survival curves to provide summary information over time of the survival experience of (suh) groups of interest. The Kaplan-Meier (KM) approach (Chapter 2), also called the product-limit approach, is a widely used empirical method for estimating survival culves. A generalized version of KM can be used with a regression (e.g., Cox) model to estimate adjusted survival curves (Chapter 3) that account for covariates. Up to now, such survival curves have been described only for the situation when there is only one event- type of interest.

Competing risks: **KM** may not be as informative as when only one risk

When competing risks are being considered, the KM survival curve may not be as informative as with only one risk.

Hypothetical Study

- n = 100 subjects
- All subjects with prostate cancer

Survt (months)	# Died	Cause
3	99	CVD
5	1	Cancer

Consider the following hypothetical scenario: a 5-month follow-up of 100 subjects with (say, prostate) cancer. Suppose that at 3 months from start of follow-up, 99 of the 100 subjects die from CVD. And at 5 months, the 1 remaining subject dies from prostate cancer.

Study goal: cause-specific cancer survival
Censored: CVD deaths

The goal of the study is to determine the cause-specific survival experience for cancer mortality, where a CVD death is considered as censored.

Table 9.6. Hypothetical Survival Data

f	t_f	n_f	m_f	q_f	$S_{Ca}(t_f) \leftrightarrow$ KM
0	0	100	0	0	1
1	3	100	0	99	1
2	**5**	1	1	–	**0**

Table 9.6 summarizes the survival experience in this hypothetical study. The first five columns of this table show the ordered failure-time interval number (f), the time of failure (t_f), the number in the risk set (n_f), the number who fail (m_f), and the number who are censored at each failure time (q_f), assuming that a subject who died of CVD at a given time is censored at that time. The last column shows the KM survival probabilities $S_{Ca}(t_f)$ for cause-specific cancer at each failure time.

Risk set at $t_f = 5$: 1 subject

$\Pr(T > 5 \mid T \geq 5) = (1 - 1)/2 = 0$

$$\mathbf{KM_{Ca}}\text{: } \mathbf{S_{Ca}}\,(t = 5) = S(t = 4) \times \Pr(T > 5 | T \geq 5) = 1 \times 0 = \mathbf{0}$$

From this table, we see that there is only one subject in the risk set at 5 months, and that this subject fails at month 5. The conditional probability of surviving past 5 months given survival up to 5 months is $(1 - 1)/1 = 0$, so that the KM survival probability at 5 months is 0.

$$\mathbf{KM_{Ca}} = 0 \Rightarrow \text{Risk}_{\mathbf{Ca}}\,(T \leq 5) = 1 - 0 = \mathbf{1}$$

Thus, use of the $\mathbf{KM_{Ca}}$ curve in the presence of competing risks (for CVD), suggests that the 5-month risk for cancer death is 1; that is, $1 - \mathbf{S_{Ca}}\,(t = 5)$. Nevertheless, because 99 patients died of CVD instead of cancer, the proportion of the initial 100 subjects who died of cancer is .01, a very small "risk" in contrast to the KM-based "risk" of 1.

Nevertheless,

$$\frac{1 \text{ cancer death}}{100 \text{ initial subjects}} = 0.01 \quad \text{(small)}$$

Question:

How many of the 99 CVD deaths would have died of cancer at $t = 5$ if they hadn't died of CVD at $t = 3$?

A natural question at this point is, how many of the 99 patients who died of CVD at 3 months would have died of cancer by 5 months instead if they hadn't died of CVD?

Cannot answer: unobservable

Unfortunately, we cannot ever answer this question because those dying of CVD cannot be observed further once they have died.

Table 9.7. Hypothetical Survival Data Sensitivity Analysis A (99 **CVD** Deaths of Cancer at $t = 5$)

f	t_f	n_f	m_f	q_f	$S_{Ca}(t_f) \leftrightarrow KM$
0	0	100	0	0	1
1	3	100	0	0	1
2	5	100	100	0	**0**

But we can consider a sensitivity-type of analysis to see what might happen under certain alternative scenarios. Suppose, for example, that all 99 subjects who died of CVD at 3 months would have died of cancer at 5 months if they hadn't died of CVD. Also assume as before that the 100th subject survived up to 5 months but then immediately died. The survival experience for this situation is shown in **Table 9.7**. Notice that the KM survival probability at month 5 is 0, which is the same value as obtained in the original dataset.

KM method assumes non-informative (i.e., independent) censoring

⇓

Pr(T > 5|censored at month 3)

=

Pr(T > 5|survived to month 5) = 0

⇓

99 CVDs deaths would have been cancer deaths at month 5

The reason why **Tables 9.6** and **9.7** give the same 5-month survival probability (=0) is that the KM method assumes independent censoring. For the original data (**Table 9.6**), independent censoring requires that those who were censored at month 3 were as likely to have died from cancer at month 5 as those who were in the risk set at month 5. Because the one person in the risk set at month 5 actually died from cancer, then the KM method assumes that all 99 CVD deaths being viewed as censored would have been cancer deaths at month 5, which is what is represented in **Table 9.7**.

Table 9.8. Hypothetical Survival Data Sensitivity Analysis B (99 **CVD** Deaths of survive past t = 5)

f	t_f	n_f	m_f	q_f	$S_{Ca}(t_f) \leftrightarrow KM$
0	0	100	0	0	1
1	3	100	0	0	1
2	5	100	1	99	**0.99**

Now let's consider a different version (B) of a sensitivity analysis. Suppose that all 99 subjects who died of CVD at 3 months would **not** have died of cancer at 5 months if they hadn't died of CVD. Also assume as before that the 100th subject survived up to 5 months but then immediately died. The survival experience for this situation is shown in **Table 9.8**.

Table 9.8: $S_{Ca}(t = 5) = 0.99$ different from **Table 9.6:** $S_{Ca}(t = 5) = 0$

The KM survival probability at month 5 is 0.99 (i.e., close to 1), which is very different from the value of 0 obtained in the original dataset (**Table 9.6**).

Focus on 1 − S(t) = Risk:
$Risk_{Ca}(T \leq 5) = 1 - 0.99 = \mathbf{0.01}$

If we then focus on 1 − S(t) instead of S(t), sensitivity analysis B suggests that the 5-month risk for cancer death is 0.01 (i.e., 1 − 0.99).

Table 9.6: $Risk_{Ca}(T \leq 5) = \mathbf{1}$ derived from the data

Table 9.8: $Risk_{Ca}(T \leq 5) = \mathbf{0.01}$ derived from sensitivity analysis

but also derived directly from data as a **marginal probability**

We thus see that the KM-based risk of 1 computed from the actual data (**Table 9.6**) is quite different from the KM-based risk of .01 computed in **Table 9.8**, where the latter derives from a sensitivity analysis that does not use the actual data. Note, however, that a "risk" of .01 for cancer death can be derived directly from the actual data by treating the CVD deaths as cancer survivors. That is, .01 is the proportion of all subjects who actually developed cancer regardless of whether they died from CVD. This proportion is an example of what is called a **marginal probability**.

Which is more informative,

$\text{Risk}_{\mathbf{Ca}}(T \leq 5) = \mathbf{1}$ or $\mathbf{0.01}$?

So which of these two "risk" estimates (1 vs. 01) is more informative? Actually, they are both informative in different ways.

Answer: both informative

"Risk" of .01 considers treatment utility
for example, proportion of cancer patients needing treatment

The "risk" of .01 is informative from the standpoint of treatment utility for cancer because in these data, the proportion of cancer patients needing treatment is quite small when allowing for competing risks.

"Risk" of 1 considers etiology, providing competing risks are independent
for example, cancer survival is unlikely after 5 months

On the other hand, the "risk" of 1, corresponding to the survival probability of 0, is informative from an etiologic standpoint providing competing risks are independent; for example, cancer patients who don't die of CVD would be expected to die from their cancer by 5 months; that is, cancer survival is unlikely after 5 months.

Main point

KM survival curve may not be very informative

- Requires independence assumption about competing risks
- Independence assumption cannot be verified

The main point of the above illustration is that when there are competing risks, the KM survival curve may not be very informative because it is based on an independence assumption about competing risks that cannot be verified.

Alternative to KM: **Cumulative Incidence Curve (CIC)** uses marginal probabilities

This has led to alternative approaches to KM for competing risk data. One such alternative, called the **Cumulative Incidence Curve (CIC)**, involves the use of marginal probabilities as introduced above. (Kalbfleisch and Prentice, 1980).

Only one risk: $\mathbf{CIC} = \mathbf{1} - \mathbf{KM}$

CIC with competing risk

- Derived from cause-specific hazard function
- Estimates **marginal probability** when competing risks are present
- Does not require independence assumption

In the simplest case, if there is only one risk, the **CIC** is (1 - KM). With competing risks, however, the **CIC** is derived from a cause-specific hazard function, provides estimates of the "marginal probability" of an event in the presence of competing events, and does not require the assumption that competing risks are independent.

Marginal probabilities:

- useful to assess treatment utility in cost-effectiveness analyses
- example: 0.01 = 5-month marginal probability for Cancer (**Table 9.6**)

Such marginal probabilities are relevant to clinicians in cost-effectiveness analyses in which risk probabilities are used to assess treatment utility. For example, the 0.01 (5-month) marginal probability for cancer derived from the hypothetical data in **Table 9.6** illustrates small treatment utility for cancer.

Steps to construct **CIC**:

1. Estimate hazard at ordered failure times t_f for event-type (**c**) of interest:

   $$\hat{h}_c(t_f) = m_{cf}/n_f$$

   where
   m_{cf} = # of events for event-type **c** at time t_f
   n_f = # of subjects at risk at time t_j

How does one construct a **CIC**? We first estimate the hazard at ordered time points t_f when the event of interest occurs. This hazard estimate is simply the number of events that occur at t_f divided by the number at risk at t_f (analogous to the KM estimate). We can write this as $\hat{h}_{\mathbf{c}}(t_f) = m_{\mathbf{cf}}/n_f$ where the $m_{\mathbf{cf}}$ denotes the number of events for risk **c** at time t_f and n_f is the number of subjects at that time. Thus, at any particular time, $m_{\mathbf{cf}}/n_f$ is the estimated proportion of subjects failing from risk **c**.

2. Estimate
   $S(t_{f-1})$ = **overall** survival probability of surviving previous time (t_{f-1})
   overall ⇒ subject survives all other competing events

To be able to fail at time t_f, the subject needs to be "around to fail", i.e., he must have survived the previous time when a failure occurred. The probability of surviving the previous time t_{f-1} is denoted $S(t_{f-1})$, where S(t) denotes the **overall survival curve** rather than the cause-specific survival curve $S_{\mathbf{c}}(t)$. We must consider "overall" survival here, since the subject must have survived all other competing events.

3. Compute estimated incidence of failing from event-type **c** at time t_f:

   $$\hat{I}_c(t_f) = \hat{S}(t_{f-1}) \times \hat{h}_c(t_f)$$

The probability (i.e., incidence) of failing from event-type **c** at time t_f is then simply the probability of surviving the previous time period multiplied by $\hat{h}_{\mathbf{c}}(t_f)$.

4.

$$\mathbf{CIC_c}(t_f) = \sum_{f'=1}^{f} \hat{I}_c(t_{f'}) = \sum_{f'=1}^{f} \hat{S}(t_{f'-1})\hat{h}_c(t_{f'})$$

The **cumulative incidence** ($\mathbf{CIC}_c$) for event-type **c** at time t_f is then the *cumulative* sum up to time t_f (i.e., from f′=1 to f′=f) of these incidence values over all event-type **c** failure times.

CIC = 1 − **KM** ↔ no competing risks
but
$\mathbf{CIC_c}(t_f) \neq 1 - \mathbf{KM_c}$ ↔ competing risks

Although, as previously mentioned, the **CIC** is equal to 1 − **KM** when there are no competing risks, formula 4 for $\mathbf{CIC}_c(t_f)$ differs from 1 - $\mathbf{KM}_c$ when there are competing risks. In particular, the **CIC** formula (4) uses the overall survival function S(t) that counts events from competing risks in addition to the event-type of interest as failures. In contrast, the formula for 1 − $\mathbf{KM}_c$ uses the event-type-specific survival function $S_{\mathbf{c}}(t)$, which treats failures from competing risks as censored observations; this formula has been called the *censor method* (Arriagada et al.,1992).

since

$$1 - \mathbf{KM_c} = \sum_{f'=1}^{f} \hat{S}_c(t_{f'-1})\hat{h}_c(t_{f'})$$

(censor method)

Example of **CIC** calculation

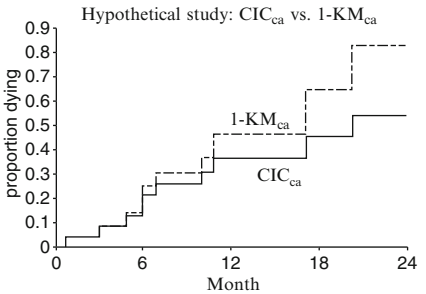
- n = 24 subjects
- all subjects receive treatment XRT for head and neck cancer

Survival time in (months)

Died of disease: 0.7, 3, 4.9, 6, 6, 6.9, 10, 10.8, 17.1, 20.3
Died of other causes: 1.5, 2.8, 3.8, 4.7, 7, 10, 10, 11.2
Censored: 3.2, 7.6, 10, 11, 15, 24.4

Table 9.9. CIC calculation Hypothetical data

t_f	n_f	m_f	$\hat{h}_{ca}(t_f)$	$\hat{S}(t_{f-1})$	$\hat{I}_{ca}(t_f)$	$CIC_{ca}(t_f)$
0	24	0	0	-	0	0
0.7	24	1	0.042	1.000	0.042	0.042
1.5	23	0	0	0.958	0	0.042
2.8	22	0	0	0.916	0	0.042
3.0	21	1	0.048	0.875	0.042	0.083
3.2	20	0	0	0.833	0	0.083
3.8	19	0	0	0.833	0	0.083
4.7	18	0	0	0.789	0	0.083
4.9	17	1	0.059	0.745	0.044	0.127
6	16	2	0.125	0.702	0.088	0.215
6.9	14	1	0.071	0.614	0.044	0.259
7.0	13	0	0	0.570	0	0.259
7.6	12	0	0	0.526	0	0.259
10	11	1	0.091	0.526	0.048	0.307
10.8	7	1	0.143	0.383	0.055	0.361
11.0	6	0	0	0.328	0	0.361
11.2	5	0	0	0.328	0	0.361
15	4	0	0	0.262	0	0.361
17.1	3	1	0.333	0.262	0.087	0.449
20.3	2	1	0.5	0.175	0.087	**0.536**
24.4	1	0	0	0.087	0	0.536



We illustrate the calculation of a **CIC** through an example.

Consider another hypothetical study involving 24 individuals receiving radiotherapy (XRT) for the treatment of head and neck cancer. Patients may either die of the disease (cancer), other causes or still be alive at the time of analysis.

The data are shown on the left.

The calculations required for the cumulative incidence curve $\mathbf{CIC_{ca}}$ for the event-type "death from cancer (i.e., **ca**)" are shown in **Table 9.9**.

From the table, we can see that the highest **CIC** probability of 0.536 is reached when t= 20.3 weeks when the last observed event occurred. Thus, the cumulative risk (i.e., marginal probability) for a Cancer death by week 20 is about 53.6% when allowing for the presence of competing risks for CVD and Other Deaths.

Because the **CIC** curve describes "cumulative incidence", a plot of the curve starts at 0 when t=0 and is a nondecreasing function up until the latest time of individual follow-up (t=24.4). We show on the left the graphs of both the $\mathbf{CIC_{ca}}$ and $1 - \mathbf{KM_{ca}}$. Notice that $1 - \mathbf{KM_{ca}}$ overestimates the probability of failure for the event-type "death from cancer (**ca**)."

CIC Summary

- Gives marginal probability.
- Does not use product limit formulation
- Not included in mainstream commercially avilable statistical packages (e.g., SAS, STATA, SPSS)

Thus, as the example illustrates, the "marginal probability" estimated by the **CIC** does not use a product-limit (i.e., KM) formulation. Moreover, the computation of a **CIC** is currently not included in mainstream commercially available statistical packages.

Independence of competing risks not required for **CIC** approach.

As mentioned earlier, the assumption of independent competing risks is not required for the calculation of the **CIC**, in contrast to the KM survival curve, which requires this assumption.

Nevertheless, **CIC** requires

$$h(t) = h_{\mathbf{c1}}(t) + h_{\mathbf{c2}}(t) + \ldots + h_{\mathbf{ck}}(t)$$

where

$h(t)$ = overall hazard

$h_{\mathbf{c}}(t)$ = hazard for event type **c**

Nevertheless, the **CIC** does require that the overall hazard is the sum of the individual hazards for all the risk types (Kalbfleisch and Prentice, 1980). The latter assumption will be satisfied, however, whenever competing risks are mutually exclusive and events are nonrecurrent, i.e., one and only one event can occur at any one time and only once over time.

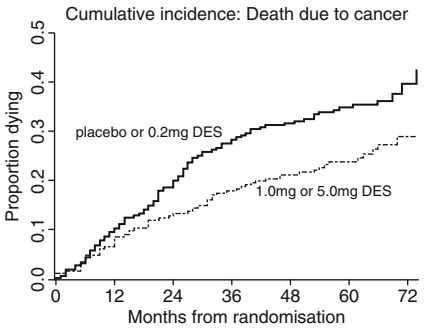
Note: Satisfied if

- Mutually exclusive event types
- Nonrecurrent events

Comparing **CIC**'s for two or more groups:

- Statistical test available (Gray, 1989)
- Analogous to log-rank test
- No independence assumption
- Does not adjust for covariates

Gray (1988) developed a test to compare two or more **CIC**s. This test is analogous to the log-rank test. The independence assumption is not required. However, this test does not adjust for covariates.



The plot shown on the left gives the **CIC**s for the two treatments for the Byar data that we originally introduced in Section III of this chapter.

Gray's test results: $\chi^2 = 6.6$, df = 1
P-value: 0.01

Using Gray's test to compare the two **CIC**s shown in the plot, we find the two curves to be significantly different (P=0.01).

PH model used to obtain **CIC**
⇓
Independence of competing risks required
(but **CIC** meaningful for treatment utility)

So far, we have described the **CIC** without considering (Cox PH) models that account for covariates. However, **when a PH model is used** to obtain hazard ratio estimates for individual competing risks as an intermediate step in the computation of a **CIC, the independence of competing risks is required.** In any case, the **CIC** has a meaningful interpretation in terms of treatment utility regardless of whether competing risks are independent.

Modeling **CIC** with covariates using PH model: Fine and Gray (1999)

(**CIC** also called **subdistribution** function)

Software available (Accord, 1997)

Fine and Gray (1999) provide methodology for modeling the **CIC** with covariates using a proportional hazards assumption. They refer to the **CIC** curves as **subdistribution** functions. Software is available that allows for such models to be fitted (Accord, 1997).

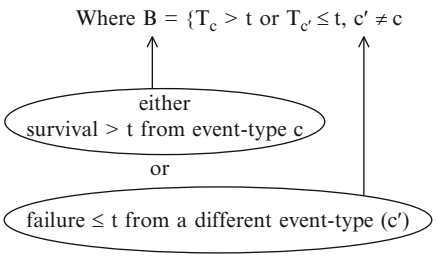
Fine and Gray model analogous to Cox PH model:

- use a hazard function defined from a CIC
- effects of predictors (e.g., HRs) have similar interpretation

The **CIC** models developed by Fine and Gray are analogous to the Cox PH model but, for any failure type, they model a hazard function (also called a **sub-distribution hazard**) derived from a **CIC**. The results from fitting these models have a similar interpretation regarding the effects of predictors in the model as can be derived from the (standard) Cox PH model approach for competing risks data.

Sub-distribution hazard function (for event-type c):

$$h_{\mathbf{c},CIC}(t) = \lim_{\Delta \to 0} \frac{\Pr(t < T_{\mathbf{c}} < t + \Delta t | B)}{\Delta t}$$



The (sub-distribution) hazard function for event-type **c** used in the Fine and Gray method is defined by $h_{\mathbf{c},CIC}(t)$ on the left. This function, based on the CIC, gives the hazard rate for a cause-specific event at time t based on the risk set that remains at time t after accounting for all previously occurring event-types (i.e., including competing risks).

In the above hazard formula, the expression defined by B to the right of the conditioning symbol (|) in the formula conditions on a subject's surviving from event-type **c** past time t or on a subject's failing from a different event-type (e.g., **c**′) at or before time t; this accounts for the occurrence of all event-types prior to time t.

Equivalent formula for $h_{\mathbf{c},CIC}(t)$:

$$h_{\mathbf{c},CIC}(t) = \frac{dCIC_{\mathbf{c}}(t)/dt}{1 - CIC_{\mathbf{c}}(t)}$$

analogous to

Hazard when no competing risks:

$$h(t) = \frac{f(t)}{S(t)}$$

where f(t) = probability density function

$$= \lim_{\Delta t \to 0} \frac{\Pr[t \leq T < t + \Delta t]}{\Delta t}$$

An equivalent mathematical expression for $h_{\mathbf{c},CIC}(t)$ is shown on the left, where $dCIC_{\mathbf{c}}(t)/dt$ is the derivative of the CIC function for event-type **c** at time t.

This expression for $h_{\mathbf{c},CIC}(t)$ is analogous to a similar expression shown on the left for the hazard function h(t) when there are no competing risks (see Chapter 7, Section II). In the latter case, h(t) is equal to the probability density function f(t) divided by the survival function S(t) shown on the left.

The analogy:

Competing Risks	No Competing Risks
$h_{\mathbf{c},CIC}(t)$	h(t)
$dCIC_{\mathbf{c}}(t)/dt$	f(t) = dF(t)/dt where F(t) = Pr(T ≤ t)
$1-CIC_{\mathbf{c}}(t)$	S(t) = 1 − F(t)

Note: $1 - CIC_{\mathbf{c}}(t)$ is not strictly a survival curve since the formula for $CIC_c(t)$ uses overall survival S(t) in its calculation rather than survival from event-type c, i.e., $S_{\mathbf{c}}(t)$

To clarify the analogy further, the term in $dCIC_{\mathbf{c}}(t)/dt$ in the numerator of the formula for $h_{\mathbf{c},CIC}(t)$ corresponds to the density function f(t) in the numerator of h(t). Note that f(t) is equal to dF(t)/dt, where F(t) is cumulative distribution function F(t); in other words, the derivative of $CIC_{\mathbf{c}}(t)$ in $h_{\mathbf{c},CIC}(t)$ corresponds to the derivative of F(t), which is f(t) in the expression for h(t).

Also, when there are no competing risks, S(t) equals 1 − F(t), which is analogous to the denominator $1 - CIC_{\mathbf{c}}(t)$ of $h_{\mathbf{c},CIC}(t)$. Strictly speaking, however, $1 - CIC_{\mathbf{c}}(t)$ is not directly equivalent to a survival curve for event-type c, since the formula $CIC_{\mathbf{c}}(t)$ treats the occurrence of events from other event-types as failures rather than as censored observations.

Fine and Gray's CIC model:

$$h_{\mathbf{c},CIC}(t) = h_{0\mathbf{c},CIC}(\exp)[\sum_{i=1}^{p} \gamma_i X_i]$$

The CIC model developed by Fine and Gray is shown on the left. This model is analogous to a Cox model, except that the model considers the subdistribution hazard function $h_{\mathbf{c},CIC}(t)$ instead of the hazard function h(t).

PH assumption satisfied in above model:

$$HR_{\mathbf{c},CIC}(\mathbf{X}^*, \mathbf{X}) = \exp[\sum_{i=1}^{p} \gamma_i (X_i^* - X_i)$$

analogous to

$$HR_{CoxPH}(\mathbf{X}^*, \mathbf{X}) = \exp[\sum_{i=1}^{p} \beta_i (X_i^* - X_i)$$

The model shown here satisfies the PH assumption for the subpopulation hazard being modeled, i.e., the general HR formula is essentially the same as for the Cox model, except that the β's in the Cox PH model are now replaced by γ's in the Fine and Gray model.

Can use "extended" Fine and Gray model to account for time-dependent variables.

The Fine and Gray model can be extended to allow for variables not satisfying the PH, including time-dependent variables.

Table 9.10. Edited Output for Cancer with CVD and Other censored Byar data (Fine and Gray CIC approach)

Var	DF	Coef	Std.Err.	P>|z|	Haz. Ratio
Rx	1	−0.414	0.171	0.008	0.661
Age	1	−0.112	0.145	0.221	0.894
Wt	1	0.088	0.146	0.274	1.092
PF	1	0.126	0.260	0.313	1.135
Hx	1	−0.256	0.182	0.080	0.774
HG	1	0.321	0.191	0.046	1.379
SZ	1	0.841	0.207	0.001	2.318
SG	1	1.299	0.198	0.001	3.665

−2 LOG L = 1662.766546

For the Byar data, the fitted Fine and Gray **CIC** model that focuses on cancer deaths as the event type of interest is shown in **Table 9.10** below which we have repeated in **Table 9.1**, which uses the standard competing risks Cox PH model approach.

Table 9.1. (Repeated). Edited Output for Cancer with **CVD** and Other Censored (Standard Cox PH approach)

Var	DF	Coef	Std.Err.	p > |z|	Haz. Ratio
Rx	1	−0.550	0.170	0.001	0.577
Age	1	0.005	0.142	0.970	1.005
Wt	1	0.187	0.138	0.173	1.206
PF	1	0.253	0.262	0.334	1.288
Hx	1	−0.094	0.179	0.599	0.910
HG	1	0.467	0.177	0.008	1.596
SZ	1	1.154	0.203	0.000	3.170
SG	1	1.343	0.202	0.000	3.830

Log likelihood = −771.174

Although corresponding coefficient estimates and standard errors are different in the two outputs, both outputs are reasonably similar.

Fine and Gray **CIC** (**Table 9.10**)	Standard Cox PH (**Table 9.1**)
$\hat{\beta}_{Rx}$: −0.414	−0.550
$\hat{HR}_{Rx}$: 0.661 $= (\frac{1}{1.513})$	0.577 $= (\frac{1}{1.733})$
P-value : 0.008	0.001

For example, the estimated coefficient of Rx is −0.414 in **Table 9.10** vs. −0.550 in **Table 9.1**. The corresponding hazard ratio estimates ($e^{\hat{\beta}}$) are 0.661 (=1/1.513) and 0.577 (=1/1.733), respectively, so that the strength of the association is slightly weaker using the Fine and Gray approach for these data, although both hazard ratios are highly significant.

VII. Conditional Probability Curves (CPC)

A third measure of failure risk: **CPC** (Other measures: **1-KM** and **CIC**)

$\mathbf{CPC_c} = \Pr(T_c \leq t \mid T \geq t)$

where T_c = time until event c occurs
T = time until any competing risk event occurs

Another approach to competing risks is called the **cumulative conditional probability** or **CPC**. CPCs provide a third summary measure, in addition to (1 - KM) and CIC, of the risk of failure of an event in the presence of competing risks. Put simply, the $\mathbf{CPC_c}$ is the probability of experiencing an event **c** by time t, *given that an individual has not experienced any of the other competing risks by time t*.

$\mathbf{CPC_c} = CIC_c/(1\text{-}CIC_{c'})$

where $\mathbf{CIC_{c'}}$ = CIC from risks other than **c**

Graphs of CPC's obtained from CIC's

Tests to compare CPC's:
Pepe and Mori (1993) −2 curves
Lunn (1998) −g curves

Example of **CPC** calculation

- n = 24 subjects
- all subjects receive treatment XRT for head and neck cancer
- CIC_{ca} previously calculated (Table 9.9)

For event-type **c**, the **CPC** is defined by $\mathbf{CIC_c}$ divided by (1 - $\mathbf{CIC_{c'}}$), where $\mathbf{CIC_{c'}}$ is the cumulative incidence of failure from risks other than risk **c** (i.e., all other risks considered together).

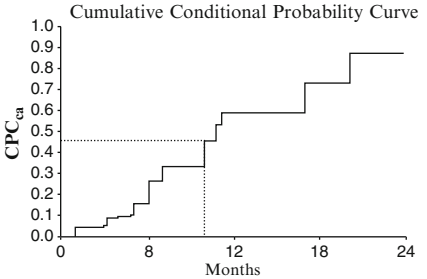
Graphs of **CPC** curves can be obtained from CIC curves and have been studied by Pepe-Mori (1993) and Lunn (1998). Pepe-Mori provide a test to compare two **CPC** curves. Lunn (1998) extended this test to g-groups and allow for strata.

We illustrate the calculation of a **CPC** using the previously described hypothetical study data involving 24 individuals receiving radiotherapy (XRT) for the treatment of head and neck cancer (**ca**). For these data, the calculations for the $\mathbf{CIC_{ca}}$ were given in previous **Table 9.9**, below which was shown the graph of the $\mathbf{CIC_{ca}}$ curve.

Table 9.11 CPC calculation—Hypothetical data

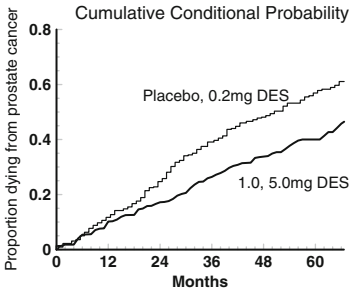
t_f	n_f	$CIC_{ca}(t_f)$	$CIC_{oth}(t_f)$	$CPC_c = CIC_c/(1-CIC_{c'})$
0	24	0	0	0
0.7	24	0.042	0	0.042
1.5	23	0.042	0.042	0.043
2.8	22	0.042	0.083	0.045
3.0	21	0.083	0.083	0.091
3.2	20	0.083	0.083	0.091
3.8	19	0.083	0.127	0.095
4.7	18	0.083	0.171	0.101
4.9	17	0.127	0.171	0.153
6	16	0.215	0.171	0.259
6.9	14	0.259	0.171	0.312
7.0	13	0.259	0.215	0.330
7.6	12	0.259	0.215	0.330
10	11	0.307	0.311	**0.445**
10.8	7	0.361	0.311	0.524
11.0	6	0.361	0.311	0.524
11.2	5	0.361	0.376	0.579
15	4	0.361	0.376	0.579
17.1	3	0.449	0.376	0.719
20.3	2	0.536	0.376	**0.860**
24.4	1	0.536	0.376	0.860

Table 9.11 on the left gives the calculation of the **CPC** for the event-type "death from cancer". A graph of the $\mathbf{CPC_{ca}}$ curve is shown below the table.



From the $\mathbf{CPC_{ca}}$ curve, we can see, for example, that at 10 months, the probability of dying from cancer given that no other type of event has occurred is 0.455. Similarly, at 20.3 months, the probability of dying of cancer given that no other type of event has occurred is 0.860.

Example: Byar Data



Test for equality: p-value = .01 (Pepe-Mori)

Returning to the Byar dataset originally introduced in Section III of this chapter, the plot shown here gives the **CPC** curves comparing the two DES treatments. These curves give the probability of an event (death) from prostate cancer at any particular time *given* that the patient is alive at this time to experience the event.

(Note: the Fine and Gray approach has not been extended to model the **CPC**s in a regression framework.)

The Pepe-Mori test shows a significant difference between these two CPC curves.

VIII. Method 2—The Lunn-McNeil (LM) Approach

Method I: separate estimates for each failure type, treating the competing failure types as censored

Method 2: **LM** Approach

- Uses a single Cox (PH) model
- Gives identical results as obtained from Method 1
- Allows flexibility to perform statistical inferences not available from Method 1

We have previously (Section IV) described an approach (called Method 1) for analyzing competing risks data that uses the Cox (PH) model to separatelyestimate hazards and corresponding hazard ratios for each failure type, treating the other(competing) failure types as censored in addition?to those not failing from any event-type.

We now describe Method 2, called the **Lunn-McNeil (LM)** approach, that allows only one Cox PH model to be fit rather than separate models for each event-type (i,e., Method I above). This approach, depending on the variables put in the model, can give identical results to those obtained from separate models. Moreover, the **LM** approach allows flexihility to perform statistical inferences about various features of the competing risk models that can not be conveniently assessed using Method 1.

Table 9.12. Augmented Data for ith Subject at Time t_i Using LM Approach

Subj	Stime	Status	D_1	D_2	$D_3 \ldots D_C$	$X_1 \ldots X_p$
i	t_i	e_1	1	0	0 … 0	$X_{i1} \ldots X_{ip}$
i	t_i	e_2	0	1	0 … 0	$X_{i1} \ldots X_{ip}$
i	t_i	e_3	0	0	1 … 0	$X_{i1} \ldots X_{ip}$
.	.	.	.	.	…	…
.	.	.	.	.	…	…
.	.	.	.	.	…	…
i	t_i	e_C	0	0	0 … 1	$X_{i1} \ldots X_{ip}$

D_1, D_2, D_3,. . ., D_C: indicators for event-types

To carry out the LM approach, the data layout must be augmented. If there are C competing risks, the original data must be duplicated C times, one row for each failure type as shown in **Table 9.12** for the ith subject with survival time t_i in the table. Also, C dummy variables D_1, D_2, D_3,. . ., D_C are created as shown in the table. The value of the status variable $e_{\mathbf{c}}$, with **c** going from 1 to C, equals 1 if event type **c** occurs at time **c**, and equals 0 if otherwise. The Xs in the table denote the predictors of interest and, as shown in the table, are identical in each row of the table.

The dummy variables D_1, D_2, D_3,. . .,D_C are indicators that distinguish the C competing risks (i.e., event-types).

Definition

$D_{\mathbf{c}}$ equals 1 for event-type **c** and 0 otherwise, $\mathbf{c} = 1, 2, \ldots, C$

Thus, the dummy variable $D_{\mathbf{c}}$ equals 1 for event-type **c** and 0 otherwise.

for example,

Event-type 1: $D_1 = 1$, $D_2 = 0$, $D_3 = 0, \ldots, D_C = 0$
Event-type 2: $D_1 = 0$, $D_2 = 1$, $D_3 = 0, \ldots, D_C = 0$
Event-type 3: $D_1 = 0$, $D_2 = 0$, $D_3 = 1, \ldots, D_C = 0$

For example, for event type 1, the Ds are $D_1 = 1$, $D_2 = 0$, $D_3 = 0, \ldots, D_C = 0$; for event-type 2, the Ds are $D_1 = 0$, $D_2 = 1$, $D_3 = 0, \ldots, D_C = 0$; and for event-type 3, the Ds are $D_1 = 0$, $D_2 = 0$, $D_3 = 1, \ldots, D_C = 0$.

Table 9.13. Augmented Data for Subjects 1, 14, 16, and 503 from Byar Data Using LM Approach

Subj	Stime	Status	**CA**	**CVD**	**OTH**	**Rx**	**Age**	**Wt**
1	72	0	1	0	0	0	1	2
1	72	0	0	1	0	0	1	2
1	72	0	0	0	1	0	1	2
14	49	1	1	0	0	0	0	0
14	49	0	0	1	0	0	0	0
14	49	0	0	0	1	0	0	0
16	3	0	1	0	0	1	2	1
16	3	1	0	1	0	1	2	1
16	3	0	0	0	1	1	2	1
503	41	0	1	0	0	0	1	0
503	41	0	0	1	0	0	1	0
503	41	1	0	0	1	0	1	0

Table 9.13 shows observations for subject #s 1, 14, 16, and 503 from the Byar dataset. The **CA, CVD**, and **OTH** columns denote the C = 3 dummy variables D_1, D_2, and D_3, respectively. The last three columns, labeled **Rx, Age**, and **Wt** give values for three of the eight predictors.

In this table, there are three lines of data for each subject, which correspond to the three competing risks, **Cancer** death, **CVD** death, and **Other** death, respectively. The survival time (**Stime**) for subject 1 is 72, for subject 14 is 49, for subject 16 is 3, and for subject 503 is 41.

Subject 1: Censored
Subject 14: died of Cancer
Subject 16: died of CVD
Subject 503: died from OTH

From the Status and Event (i.e., **CA, CVD, OTH**) columns, we can see that subject 1 was censored, subject 14 died of **Cancer**, subject 16 died of **CVD**, and subject 503 died from **Other** causes.

	Rx	Age	Wt
Subject 1	0	1	2
Subject 16	1	2	1

For subject 1, the values for the predictors Rx, Age, and Wt, were 0, 1, and 2, respectively. These values appear identically in the last three columns of the three rows for this subject. Similarly, for subject 16, the predictor values for Rx, Age, and Wt, are 1, 2, and 1, respectively.

General Stratified Cox LM Model

$$g = 1, 2, \ldots, C$$

$$\begin{aligned} h_g^*(t, \mathbf{X}) &= h_{0g}^*(t) \\ &\times \exp\left[\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p \right. \\ &+ \delta_{21} D_2 X_1 + \delta_{22} D_2 X_2 + \cdots + \delta_{2p} D_2 X_p \\ &+ \delta_{31} D_3 X_1 + \delta_{32} D_3 X_2 + \cdots + \delta_{3p} D_3 X_p \\ &+ \cdots \\ &\left. + \delta_{C1} D_C X_1 + \delta_{C2} D_C X_2 + \cdots + \delta_{Cp} D_C X_p \right] \end{aligned}$$

1st row: predictors $X_1, X_2, \ldots, X_p$
2nd row: product terms
$D_2X_1, D_2X_2, \ldots, D_2X_p$

Cth row: product terms
$D_CX_1, D_CX_2, \ldots, D_CX_p$

To use the **LM** approach with augmented data to obtain identical results from fitting separate models (Method 1), an interaction version of a stratified Cox PH model is required. A general form for this model based on the notation used for the column heading variables in **Table 9.12** is shown at the left.

Recall that the $X_1, X_2, \ldots, X_p$ denote the p predictors of interest. $D_2, D_3, \ldots, D_C$ are $C - 1$ dummy variables that distinguish the C event-types. Note that event-type 1 ($g = 1$) is the referent group, so variable D_1 is omitted from the model. Thus, the first row in the exponential formula contains the Xs, the second row contains product terms involving D_2 with each of the Xs, and so on, with the last (Cth) row containing product terms of D_C with each of the Xs. The strata ($g = 1, \ldots, C$) are the C event-types.

LM Hazard Model for Event–Type 1

$$\begin{aligned} h_1^*(t, \mathbf{X}) &= h_{01}^*(t) \\ &\times \exp\left[\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p\right] \\ &(D_2 = D_3 = \cdots = D_C = 0) \end{aligned}$$

For event-type 1 ($g = 1$), the above stratified Cox model simplifies to the expression shown at the left. Note that because $g = 1$, the values of the dummy variables $D_2, D_3, \ldots, D_C$ are all 0.

No product terms in model:

$$HR_{g=1}(X_1 = 1 \text{ vs. } X_1 = 0) = \exp[\beta_1]$$

Product terms X_jX_1 in model:

$$HR_{g=1}(X_1 = 1 \text{ vs. } X_1 = 0) = \exp[\beta_1 + \Sigma\beta_jX_j]$$

Thus, for g = 1, if X_1 is a (0,1) variable, the other Xs are covariates, and there are no product terms X_jX_1 in the model, the formula for the HR for the effect of X_1 adjusted for the covariates is $\exp[\beta_1]$. The more general exponential formula described in Chapter 3 would need to be used instead to obtain adjusted HRs if there are interaction terms in the model of the form X_jX_1.

LM Hazard Model for Event-Type g (> 1)

$$\begin{aligned} h_g^*(t, \mathbf{X}) &= h_{0g}^*(t) \\ &\quad \times \exp\Big[\beta_1X_1 + \beta_2X_2 + \cdots + \beta_pX_p \\ &\qquad + \delta_{g1}X_1 + \delta_{g2}X_2 + \cdots + \delta_{gp}X_p\Big] \\ &= h_{0g}^*(t) \exp\big[(\beta_1 + \delta_{g1})X_1 + (\beta_2 + \delta_{g2})X_2 \\ &\qquad + \cdots + \big(\beta_p + \delta_{gp}\big)X_p\big] \end{aligned}$$

For any g greater than 1, the general hazard model simplifies to a hazard function formula that contains only those product terms involving the subscript g, because $D_g = 1$ and $D_{g'} = 0$ for g′ not equal to g.

With a little algebra we can combine coefficients of the same predictor to rewrite this hazard model as shown here.

No product terms X_jX_1 in the model and g > 1:

$$HR_g(X_1 = 1 \text{ vs. } X_1 = 0) = \exp[(\beta_1 + \delta_{g1})]$$

Thus, for g > 1, if X_1 is a (0,1) variable, the other Xs are covariates, and there are no product terms X_jX_1 in the model, the formula for the HR for the effect of X_1 adjusted for the covariates is $\mathbf{exp}[\beta_1 + \delta_{g1}]$. This HR expression would again need to be modified if the model contains product terms of the form X_jX_1.

Product terms X_jX_1 in the model and g > 1:

$$HR_g(X_1 = 1 \text{ vs. } X_1 = 0) = \exp[(\beta_1 + \delta_{g1}) + \Sigma(\beta_j + \delta_{gj}X_j)]$$

EXAMPLE OF LM MODEL FOR BYAR DATA

We now illustrate the above general **LM** model formation using the Byar data.

Separate models approach (Method 1): Cause-specific model: **Cancer** **CVD** and **Other** deaths censored

Recall that using Method 1, the separate models approach, the Cox hazard formula used to fit a separate model for **Cancer** deaths, treating **CVD** and **Other** deaths as censored is repeated here.

No-interaction model

$$\begin{aligned} h_{\mathbf{Ca}}(t,\mathbf{X}) &= h_{0\mathbf{Ca}}(t)\exp[\beta_{1\mathbf{Ca}}Rx \\ &\quad + \beta_{2\mathbf{Ca}}Age + \beta_{3\mathbf{Ca}}Wt + \\ &\quad \beta_{4\mathbf{Ca}}PF + \beta_{5\mathbf{Ca}}Hx + \beta_{6\mathbf{Ca}}HG \\ &\quad + \beta_{7\mathbf{Ca}}SZ + \beta_{8\mathbf{Ca}}SG] \end{aligned}$$

$$HR_{\mathbf{Ca}}(RX = 1 \text{ vs. } RX = 0) = \exp[\beta_{1\mathbf{Ca}}]$$

Also shown is the formula for the hazard ratio for the effect of the Rx variable, adjusted for other variables in the model.

LM SC Model for Byar Data

$g = 1, 2, 3$

$$h_g^*(t, \mathbf{X}) = h_{0g}(t) \times \exp[\beta_1 RX + \beta_2 Age + \cdots + \beta_8 SG + \delta_{21} D_2 Rx + \delta_{22} D_2 Age + \cdots + \delta_{28} D_2 SG + \delta_{31} D_3 Rx + \delta_{32} D_3 Age + \cdots + \delta_{38} D_3 SG]$$

1st row: predictors
Rx, Age, Wt, PF,. . ., SG
2nd row: products
D_2Rx, D_2Age, . . ., D_2SG
3rd row: products
D_3Rx, D_2Age, . . ., D_3SG
D_2 = CVD and D_3 = OTH are (0,1) dummy variables that distinguish the 3 event-types

Using the general **LM** data layout given in Table 9.11, the stratified Cox **LM** model for the Byar data that incorporates C = 3 event-types is shown at the left. The strata, denoted by g = 1, 2, 3, identify the three event-types as **Cancer, CVD**, and **Other**, respectively.

Notice that in the exponential part of the model, there are 3 rows of terms that correspond to the 3 event-types of interest. The first row contains p = 8 predictors Rx, Age, Wt, PF, HX, HG, SZ, SG. The second row contains product terms of the dummy variable D_2 (the **CVD** indicator) with each of the 8 predictors. Similarly, the third row contains product terms of D_3 (the **Other** indicator) with each of the predictors.

$HR_{\mathbf{Ca}}(Rx = 1 \text{ vs. } Rx = 0) = \exp[\beta_1]$
$HR_{\mathbf{CVD}}(Rx = 1 \text{ vs. } Rx = 0) = \exp[(\beta_1 + \delta_{21})]$
$HR_{\mathbf{OTH}}(Rx = 1 \text{ vs. } Rx = 0) = \exp[(\beta_1 + \delta_{31})]$

From the above model, it follows that the hazard ratio formulas for the effects of Rx corresponding to each event-type are as shown at the left. Notice that for **CVD** and **Other** deaths, the coefficient δ_{g1} of the product term D_gRx, g = 2, 3, is added to the coefficient β_1 of Rx in the exponential term.

Table 9.14. Edited Output for LM Model (Interaction SC)-Byar Data

Var	DF	Coef	Std. Err.	p > |z|	Haz. Ratio
Rx	1	−0.550	0.170	0.001	0.577
Age	1	0.005	0.142	0.970	1.005
Wt	1	0.187	0.138	0.173	1.206
PF	1	0.253	0.262	0.334	1.288
Hx	1	−0.094	0.179	0.599	0.910
HG	1	0.467	0.177	0.008	1.596
SZ	1	1.154	0.203	0.000	3.170
SG	1	1.343	0.202	0.000	3.830
RxCVD	1	0.905	0.244	0.000	2.471
AgeCVD	1	0.332	0.196	0.089	1.394
WtCVD	1	−0.146	0.203	0.472	0.864
PFCVD	1	0.222	0.377	0.556	1.248
HxCVD	1	1.236	0.259	0.000	3.441
HGCVD	1	−0.449	0.268	0.094	0.638
SZCVD	1	−1.375	0.417	0.001	0.253
SGCVD	1	−1.366	0.275	0.000	0.255
RxOth	1	−0.028	0.327	0.932	0.972
AgeOth	1	0.764	0.248	0.002	2.147
WtOth	1	0.344	0.265	0.194	1.411
PFOth	1	0.288	0.497	0.562	1.334
HxOth	1	0.117	0.337	0.727	1.125
HGOth	1	−0.111	0.345	0.748	0.895
SZOth	1	−0.439	0.470	0.350	0.645
SGOth	1	−1.797	0.360	0.000	0.166

log likelihood = −1831.92

Table 9.14 shows edited output obtained from fitting the above **LM** model.

The first eight rows of output in this table are identical to the corresponding eight rows of output in the previously shown **Table 9.1** obtained from Method 1, which fits a separate model for **Cancer** deaths only. This equivalence results because the first eight rows of the **LM** output correspond to the reduced version of the **LM** model when $D_2 = D_3 = 0$, which identifies **Cancer** as the event of interest.

However, the remaining 16 rows of **LM** output are **not** identical to the corresponding 8 rows of **Table 9.2** (for **CVD**) and 8 rows of **Table 9.3** (for **Other**). Note that the remaining 16 coefficients in the **LM** output identify the δ_{gj} coefficients in the **LM** model rather than the sum $(\beta_1 + \delta_{gj})$ required for computing the HR when g = 2 and 3.

$\widehat{HR}_{\mathbf{Ca}}(\text{Rx} = 1 \text{ vs. Rx} = 0)$
$= \exp[-0.550] = 0.577$
$= (1/1.733)$
Wald ChiSq $= (-.550/.171)^2$
$= 10.345(\text{P} = 0.001)$

95% CI for $\exp[\beta_{1\mathbf{Ca}}]$:
$\exp[-0.550 \pm 1.96(0.171)]$
$= (0.413, 0.807)$

From **Table 9.14**, the adjusted $\widehat{HR}$ for the effect of Rx when the event-type is **Cancer** can be read directly off the output as 0.577. Also, the Wald statistic for testing H_0: $\beta_1 = 0$ is highly significant (P = .001). The corresponding 95% confidence interval for this HR has the limits (0.413, 0.807).

LM results for **Cancer** identical to Method 1 results for **Cancer**

These results are identical to those obtained for the adjusted $\widehat{HR}$, the Wald test, and interval estimate obtained in **Table 9.1** using Method 1 to assess the effect of Rx on survival for cancer death.

$\widehat{HR}_{CVD}(\text{Rx} = 1 \text{ vs. Rx} = 0)$
$= \exp\left(\hat{\beta}_1 + \hat{\delta}_{11}\right)$
$= \exp(-0.550 + 0.905)$
$= \exp(0.355) = 1.426$
$\widehat{HR}_{OTH}(\text{Rx} = 1 \text{ vs. Rx} = 0)$
$= \exp\left(\hat{\beta}_1 + \hat{\delta}_{21}\right)$
$= \exp(-0.550 - 0.028)$
$= \exp(-0.578) = 0.561$

Using **Table 9.14** to obtain adjusted $\widehat{HR}$ for the Rx effect when the event-type is **CVD** or **Other**, we must exponentiate the sum $(\hat{\beta}_1 + \hat{\delta}_{g1})$ for g = 2 and 3, respectively.

LM results for **CVD** and **Other** identical to Method 1 results for **CVD** and **Other**

These results are shown at the left, and they are identical to those obtained in **Tables 9.2 and 9.3** using Method 1.

Wald test statistics for **CVD** and **Other**

$$\text{Wald}_{\text{CVD}} = \left[\frac{\hat{\beta}_1 + \hat{\delta}_{11}}{\text{SE}_{\hat{\beta}_1 + \hat{\delta}_{21}}}\right]^2$$

$$\text{Wald}_{\text{OTH}} = \left[\frac{\hat{\beta}_1 + \hat{\delta}_{11}}{\text{SE}_{\hat{\beta}_1 + \hat{\delta}_{21}}}\right]^2$$

Note, however, that using the **LM** model to obtain Wald test statistics and 95% confidence intervals for the HRs for **CVD** and **Other**, the mathematical formulas (shown at left for the Wald tests) require obtaining **standard errors of the sums** $(\hat{\beta}_1 + \hat{\delta}_{g1})$ for g = 2 and 3, whereas the output in Table 9.14 gives only **individual standard errors** of $\hat{\beta}_1, \hat{\delta}_{11}$ and $\hat{\delta}_{21}$.

Computer packages provide for computation of the above formulas

SAS: **Contrast** statement

STATA: **lincom** command

SAS ans STATA provide special syntax to specify the computer code for such computations: SAS's PHREG allows a "Contrast" statement; STATA allows a "lincom" command.

Alternative **LM** formulation (**LM_{alt}** model)

Output identical to Method 1 (**Tables 9.1, 9.2, 9.3**)

Nevertheless, there is an alternative version of the **LM** model that avoids the need for special syntax. This alternative formulation, which we call the **LM_{alt}** model, results in output that is identical to the output from the separate models (Method 1) approach for analyzing competing risk data as given in **Tables 9.1** through **9.3**.

IX. Method 2a: Alternative Lunn–McNeil (LM_{alt}) Approach

- Uses same data layout as **Table 9.12**
- Column headings:
  - Dummy variables $D_1, D_2, \ldots, D_C$
  - Predictor variables $X_1, X_2, \ldots, X_p$
- Above variables are transformed into product terms

The data layout required to fit the **LM_{alt}** model is the same as shown earlier in **Table 9.12**. However, the variables listed in the columns of this table, namely, the dummy variables $D_1, D_2, \ldots, D_C$ and the predictor variables $X_1, X_2, \ldots, X_p$, serve as basic variables that are transformed into product terms that define the **LM_{alt}** model.

1st row of **LM_{alt}** model:
product terms
$D_1 X_1, D_1 X_2, \ldots, D_1X_p$
coefficients $\delta'_{11}, \ldots, \delta'_{1p}$

1st row of **LM** model
predictors $X_1, X_2, \ldots, X_p$
coefficients $\beta_1, \ldots, \beta_p$

The primary difference in the two formulas is that the first row of the exponential term in the **LM_{alt}** model contains product terms D_1X_1, $D_1X_2, \ldots, D_1X_p$ with coefficients denoted $\delta'_{11}, \ldots, \delta'_{1p}$ whereas the first row in the **LM** model contains the predictors $X_1, X_2, \ldots, X_p$ without product terms and coefficients denoted $\beta_1, \ldots, \beta_p$.

General Stratified Cox **LM_{alt}** *Model*

$$g = 1, \ldots, C$$

$$\begin{aligned} h'_g(t, \mathbf{X}) &= h'_{0g}(t) \\ &\times \exp\big[\delta'_{11}D_1X_1 + \delta'_{12}D_1X_2 + \cdots + \delta'_{1p}D_1X_p \\ &+ \delta'_{21}D_2X_1 + \delta'_{22}D_2X_2 + \cdots + \delta'_{2p}D_2X_p \\ &+ \delta'_{31}D_3X_1 + \delta'_{32}D_3X_2 + \cdots + \delta'_{3p}D_3X_p \\ &+ \cdots \\ &+ \delta'_{C1}D_CX_1 + \delta'_{C2}D_CX_2 + \cdots + \delta'_{Cp}D_CX_p\big] \end{aligned}$$

The general form of the **LM_{alt}** model is shown at the left. We have used a superscript prime ($'$) to distinguish the hazard model formula for the **LM_{alt}** model from the corresponding formula for the **LM** model given earlier.

- $\mathbf{LM}_{\text{alt}}$ and **LM** models are different
- Estimated regression coefficients will not be identical
- Estimated HRs, test statistics, and interval estimates are identical
- Computational formulas are different

Because the $\mathbf{LM}_{\text{alt}}$ model and the **LM** model are different hazard models, their estimated regression coefficients will not be identical. Nevertheless, when used on the same dataset, the estimated HRs of interest and their corresponding test statistics and interval estimates are identical even though the formulas used to compute these statistics are different for the two models.

$\mathbf{LM}_{\text{alt}}$ *Hazard Model for Event-Type 1*

$$h'_1(t,\mathbf{X}) = h'_{01}(t) \times \exp\left[\delta'_{11}X_1 + \delta'_{12}X_2 + \cdots + \delta'_{1p}X_p\right]$$

$$(D_1 = 1,\ D_2 = D_3 = \cdots = D_C = 0)$$

$$HR_{g=1}(X_1 = 1 \text{ vs. } X_1 = 0) = \exp\left[\delta'_{11}\right]$$

(no products $X_j X_i$ in model)

For g = 1 (i.e., event-type 1), the $\mathbf{LM}_{\text{alt}}$ model simplifies to the expression shown at the left. Note that because g = 1, the values of the dummy variables are $D_1 = 1$, and $D_2 = D_3 = \ldots = D_C = 0$.

Thus, for g = 1, if X_1 is a (0,1) variable, the other Xs are covariates, and there are no product terms of the form X_jX_1 in the model, the formula for the HR for the effect of X_1 adjusted for the covariates is $\exp[\delta'_{11}]$.

LM $HR = \exp[\beta_1]$

Recall that for the **LM** model, the corresponding HR formula also involved the coefficient of the X_1 variable, denoted as β_1.

$\mathbf{LM}_{\text{alt}}$ *Hazard Model for Event-Type g (> 1)*

$$h'_1(t,\mathbf{X}) = h'_{0g}(t) \times \exp\left[\delta'_{g1}X_1 + \delta'_{g2}X_2 + \cdots + \delta'_{gp}X_p\right]$$

$$\left(D_g = 1 \text{ and } D_{g'} = 0 \text{ for g' } \neq g\right)$$

$$HR_g(X_1 = 1 \text{ vs. } X_1 = 0) = \exp\left[\delta'_{g1}\right]$$

(no products X_jX_1 in model)

For any g greater than 1, the general hazard model simplifies to a hazard function formula that contains only those product terms involving the subscript g, because $D_g = 1$ and $D_{g'} = 0$ for $g' \neq g$.

Thus, for g > 1, if X_1 is a (0,1) variable, the other Xs are covariates, and there are no products $X_j X_1$ in model, the formula for the HR for the effect of X_1 adjusted for the covariates is $\exp[\delta'_{g1}]$.

LM $HR = \exp[\beta_1 + \delta_{g1}]$

Recall that for the **LM** model, the exponential in the HR formula involved the sum $(\beta_1 + \delta_{g1})$.

Statistical inferences (i.e., Wald test, 95% CI)

Thus for $g > 1$, statistical inferences about HRs using the **LM_{alt}** model only require use of the standard error for $\hat{\delta}'_{g1}$ that is directly provided in the output.

LM_{alt} model: need standard error for $\hat{\delta}'_{g1}$ (directly provided by output)

LM model: standard error of $(\hat{\beta}_1 + \hat{\delta}_{g1})$. (more complicated computation)

In contrast, the **LM** model requires computing the more complicated standard error of the sum $(\hat{\beta}_1 + \hat{\delta}_{g1})$.

Next: Byar data example of **LM_{alt}** model

We now illustrate the above general **LM_{alt}** model formation using the Byar data.

LM_{alt} *SC Model for Byar Data*

$g = 1, 2, 3$

$$h'_g(t,\mathbf{X}) = h'_{0g}(t) \times \exp\left[\delta'_{11}D_1Rx + \cdots + \delta'_{18}D_1SG + \delta'_{21}D_2Rx + \cdots + \delta'_{28}D_2SG + \delta'_{31}D_3Rx + \cdots + \delta'_{38}D_3SG\right]$$

The stratified Cox (SC) **LM_{alt}** model that incorporates the $C = 3$ event-types is shown at the left. The strata, denoted by $g = 1, 2, 3$, identify the three event-types, **Cancer, CVD**, and **Other**.

$D_1 =$ **CA**, $D_2 =$ **CVD**, and $D_3 =$ **OTH** are (0,1) dummy variables for the 3 event-types

Notice that in the exponential part of the model, the first row contains product terms of the dummy variable D_1 (the **CA** indicator) with each of the 8 predictors Rx, Age, Wt, PF, HX, HG, SZ, SG. Recall that in the **LM** version of this model, the first row contained main effects of the predictors instead of product terms.

1st row: products
$D_1Rx, D_1Age, \ldots, D_1SG$
(**LM** predictors, Rx, Age,..., SG)
2nd row: products
$D_2Rx, D_2Age, \ldots, D_2SG$
3rd row: products
$D_3Rx, D_3Age, \ldots, D_3SG$

The second and third rows, as in the **LM** model, contain product terms of the dummy variable D_2 (the **CVD** indicator) and D_3 (the **OTH** indicator), respectively, with each of the 8 - predictors.

$$HR_{\mathbf{Ca}}(Rx = 1 \text{ vs. } Rx = 0) = \exp\left[\delta'_{11}\right]$$
$$HR_{\mathbf{CVD}}(Rx = 1 \text{ vs. } Rx = 0) = \exp\left[\delta'_{21}\right]$$
$$HR_{\mathbf{OTH}}(Rx = 1 \text{ vs. } Rx = 0) = \exp\left[\delta'_{31}\right]$$

From the above model, it follows that the HR formulas for the effects of Rx corresponding to each event-type are of the form $\exp(\delta'_{g1})$, where δ'_{g1} is the coefficient of the product term D_gRx in the **LM_{alt}** model.

$$\text{Wald}_g = \left[\frac{\hat{\delta}'_{g1}}{SE_{\hat{\delta}'_{g1}}}\right]^2$$

g = 1 (**CA**), 2 (**CVD**), 3 (**OTH**)

Consequently, Wald test statistics (shown at the left) and confidence intervals for these HRs use standard errors that are directly obtained from the standard error column from the output obtained for the $\mathbf{LM_{alt}}$ model.

Statistical inference information

$\mathbf{LM_{alt}}$ model: directly provided by output

LM model: not directly provided by output (requires additional computer code)

Thus, the $\mathbf{LM_{alt}}$ model allows the user to perform statistical inference procedures using the information directly provided in the computer output, whereas the **LM** model requires additional computer code to carry out more complicated computations.

Table 9.15. Edited Output for SC $\mathbf{LM_{alt}}$ Model—Byar Data

Var	DF	Coef	Std. Err.	p > |z|	Haz. Ratio
RxCa	1	−0.550	0.170	0.001	0.577
AgeCa	1	0.005	0.142	0.970	1.005
WtCa	1	0.187	0.138	0.173	1.206
PFCa	1	0.253	0.262	0.334	1.288
HxCa	1	−0.094	0.179	0.599	0.910
HGCa	1	0.467	0.177	0.008	1.596
SZCa	1	1.154	0.203	0.000	3.170
SGCa	1	1.343	0.202	0.000	3.830
RxCVD	1	0.354	0.174	0.042	1.429
AgeCVD	1	0.337	0.134	0.012	1.401
WtCVD	1	0.041	0.150	0.783	1.042
PFCVD	1	0.475	0.270	0.079	1.608
HxCVD	1	1.141	0.187	0.000	3.131
HGCVD	1	0.018	0.202	0.929	1.018
SZCVD	1	−0.222	0.364	0.542	0.801
SGCVD	1	−0.023	0.186	0.900	0.977
RxOth	1	−0.578	0.279	0.038	0.561
AgeOth	1	0.770	0.204	0.000	2.159
WtOth	1	0.532	0.227	0.019	1.702
PFOth	1	0.541	0.422	0.200	1.718
HxOth	1	0.023	0.285	0.935	1.023
HGOth	1	0.357	0.296	0.228	1.428
SZOth	1	0.715	0.423	0.091	2.045
SGOth	1	−0.454	0.298	0.127	0.635

log likelihood = − 1831.916

Table 9.15 shows edited output obtained from fitting the above $\mathbf{LM_{alt}}$ model.

The first eight rows of output in this table are identical to the eight rows of output in the previously shown **Table 9.1** obtained from Method 1, which fits a separate model for **Cancer** deaths only, treating **CVD** and Other deaths as censored.

The next eight rows in the table are identical to the eight rows of output in the previous **Table 9.2**, which fits a separate model for **CVD** deaths only, treating **Cancer** and **Other** deaths as censored.

The last eight rows in the table are identical to the eight rows of output in the previous **Table 9.3**, which fits a separate model for **Other** deaths only, treating **Cancer** and **CVD** deaths as censored.

Table 9.15 ($\mathbf{LM_{alt}}$) output identical to **Tables 9.1, 9.2, 9.3 (Method 1)** output combined

Thus, the output in Table 9.15 using the single $\mathbf{LM_{alt}}$ model gives identical results to what is obtained from fitting 3 separate models in **Tables 9.1, 9.2**, and **9.3**.

X. Method 1 (Separate Models) versus Method 2 (LM Approach)

Why bother with **LM** or $\mathbf{LM_{alt}}$ models when you can simply fit 3 separate models?

Answer: Can perform statistical inferences that cannot be done when fitting 3 separate models

The reader may have the following question at this point: Why bother with the **LM** or $\mathbf{LM_{alt}}$ models as long as you can get the same results from fitting three separate models using Method 1? The answer is that the **LM** or $\mathbf{LM_{alt}}$ model formulation allows for performing statistical inferences about various features of the competing risk models that cannot be conveniently assessed when fitting three separate models using Method 1.

LM *Model for Byar Data*

$$
\begin{aligned}
&g = 1, 2, 3\\
&h^*_g(t, \mathbf{X}) = h^*_{0g}(t)\\
&\quad \times \exp[\beta_1 RX + \beta_2 Age + \cdots + \beta_8 SG\\
&\quad + \delta_{21} D_2 Rx + \delta_{22} D_2 Age + \cdots + \delta_{28} D_2 SG\\
&\quad + \delta_{31} D_3 Rx + \delta_{32} D_3 Age + \cdots + \delta_{38} D_3 SG]
\end{aligned}
$$

We illustrate such "extra" inference-making using the **LM** model previously described for the Byar data example. This model is shown again at the left. Equivalent inferences can be made using the $\mathbf{LM_{alt}}$ model (see Exercises at end of this chapter).

Inference question: Byar data

No-interaction SC **LM** model
versus
interaction SC **LM** model

One inference question to consider for the Byar data is whether a no-interaction SC **LM** model is more appropriate than the interaction SC **LM** model defined above.

No-interaction SC model

$$
\begin{aligned}
&g = 1, 2, 3\\
&h^*_g(t, \mathbf{X}) = h^*_{0g}(t)\\
&\quad \times \exp[\beta_1 RX + \beta_2 Age + \cdots + \beta_8 SG]
\end{aligned}
$$

The no-interaction SC model is shown here at the left.

Assumes

$$
\begin{aligned}
HR_{\mathbf{CA}}(X_i) &= HR_{\mathbf{CVD}}(X_i)\\
&= HR_{\mathbf{OTH}}(X_i)\\
&\equiv HR(X_i) \text{ for any } X_i \text{ variable}
\end{aligned}
$$

This model assumes that the hazard ratio for the effect of a single predictor (say, binary) X_i adjusted for the other variables in the model is the same for each event-type of interest.

for example, Rx = 0 vs Rx = 1:

$$
\begin{aligned}
HR_{\mathbf{CA}}(Rx) &= HR_{\mathbf{CVD}}(Rx)\\
&= HR_{\mathbf{OTH}}(Rx)\\
&= \exp[\beta_1]
\end{aligned}
$$

For example, in the above no-interaction SC **LM** model the hazard ratio for the effect of Rx is $\exp[\beta_1]$ for each g, where β_1 is the coefficient of Rx.

H_0: all $\delta_{gj} = 0$,
$g = 2, 3; j = 1, 2, \ldots, 8$
where δ_{gj} is coefficient of $D_g X_j$ in the interaction SC **LM** model

To carry out the comparison of the interaction with the no-interaction SC **LM** models, the null hypothesis being tested is that the coefficients of the 16 product terms (δ_{gj}) in the interaction SC model are equal to zero.

Likelihood Ratio Test

$$LR = -2 \log L_R - (-2 \log L_F)$$
$$\text{approx } \chi^2_{16} \text{ under } H_0$$
$$R = \text{no interaction SC (reduced) model}$$
$$F = \text{interaction SC (full) model}$$

This null hypothesis is conveniently tested using the **LM** model with a likelihood ratio test statistic obtained by subtracting −2 log L statistics from the two models being compared. The degrees of freedom being tested is 16, the number of δ_{gj} coefficients being set equal to zero under H_0.

Table 9.16. Edited Output – No-Interaction SC **LM** Model–Byar Data

Var	DF	Coef	Std. Err.	p > |z|	Haz. Ratio
Rx	1	−0.185	0.110	0.092	0.831
Age	1	0.287	0.087	0.001	1.332
Wt	1	0.198	0.093	0.032	1.219
PF	1	0.402	0.170	0.018	1.495
Hx	1	0.437	0.112	0.000	1.548
HG	1	0.292	0.120	0.015	1.339
SZ	1	0.672	0.159	0.000	1.958
SG	1	0.399	0.115	0.001	1.491

log likelihood = −1892.091

Table 9.16 gives the output resulting from the no-interaction SC **LM** model for the Byar dataset. In this table, there is one coefficient corresponding to each of the eight predictors in the model, as should be the case for a no-interaction SC model. Nevertheless, baseline hazard functions $h^*_{0g}(t)$ are allowed to be different for different g even if the coefficients are the same for different g.

Table 9.16: Log likelihood$_R$ = −1892.091
Table 9.14: Log likelihood$_F$ = −1831.916

From **Table 9.16**, we find that the log-likelihood statistic for the reduced (no-interaction SC) model is −1892.091. From **Table 9.14** (or **9.15**), the log-likelihood statistic for the full (interaction SC) model is −1831.916.

$$LR = -2 \log L_R - (-2 \log L_F)$$
$$= -2(-1892.091) - (-2(-1831.916))$$
$$= 120.35 \text{ approx } \chi^2_{16} \text{ under } H_0$$
$$(P < 0.001)$$

The likelihood ratio test statistic (LR) is then calculated to be 120.35, as shown at the left. This statistic has an approximate chi-square distribution with 16 degrees of freedom under H_0.

Reject H_0: interaction SC model more appropriate than no-interaction SC model

The P-value is less than .001, which indicates a highly significant test result, thus supporting use of the full-interaction SC model.

Cancer and **CVD** very different clinically

$$\Downarrow$$

$HR_{\mathbf{Ca}}(Rx = 1 \text{ vs. } 0) \neq HR_{\mathbf{CVD}}(Rx = 1 \text{ vs. } 0)$

For the Byar dataset, the decision to reject the no-interaction SC model makes sense when considering that two of the competing risks are **Cancer** deaths and **CVD** deaths. Because **Cancer** and **CVD** are clinically very different diseases, one would expect the effect of any of the predictors, particularly Rx, on time to failure to be different for these different disease entities.

DIFFERENT STUDY EXAMPLE

Competing risks: Stage 1 vs. Stage 2 Breast Cancer

$$\Downarrow$$

HR_{stg1} (Rx = 0 vs. 1) = HR_{stg2} (Rx = 0 vs. 1)

$$\Downarrow$$

No-interaction SC Cox reasonable depending on similarity of competing risks

Suppose, however, the competing risks for a different study had been, say, two stages of breast cancer. Then it is plausible that the effect from comparing two treatment regimens might be the same for each stage. That is, a no-interaction SC **LM** model may be (clinically) reasonable depending on the (clinical) similarity between competing risks.

Unstratified **LM** model ($\mathbf{LM}_U$):

$$h^*(t, \mathbf{X}) = h_0^*(t) \times \exp[\gamma_1 CVD + \gamma_2 OTH + \beta_1^\bullet Rx + \beta_2^\bullet Age + \cdots + \beta_8^\bullet SG + \delta_{21}^\bullet D_2 Rx + \delta_{22}^\bullet D_2 Age + \cdots + \delta_{28}^\bullet D_2 SG + \delta_{31}^\bullet D_3 Rx + \delta_{32}^\bullet D_3 Age + \cdots + \delta_{38}^\bullet D_3 SG]$$

Returning again to the Byar data example, another variation of the **LM** model is shown at the left and denoted $\mathbf{LM}_U$. This is a Cox PH model applied to the augmented data of **Table 9.12** that is not stratified on the competing risks (i.e., there is no subscript g in the model definition). We have used a superscript bullet ($\bullet$) to distinguish the $\mathbf{LM}_U$ model from the **LM** and $\mathbf{LM_{alt}}$ models.

$\mathbf{LM}_U$ model: **CVD** and **OTH** included in model

LM model: **CVD** and **OTH** not included in model

(Both $\mathbf{LM}_U$ and **LM** models use augmented dataset)

The $\mathbf{LM}_U$ model includes the two event-type dummy variables **CVD** and **OTH** in the model, rather than stratifying on these variables. As for the **LM** model, the fit of the $\mathbf{LM}_U$ model is based on the augmented dataset given in **Table 9.12**.

$\mathbf{LM}_U$ model: need to check PH assumption (Chapter 4)

PH assumption not satisfied

$$\Downarrow$$

Use **LM** instead of $\mathbf{LM}_U$ model

Because the $\mathbf{LM}_U$ model is an unstratified Cox PH model, we would want to use the methods of Chapter 4 to assess whether the PH assumption is satisfied for the **CVD** and **OTH** variables (as well as the other variables). If the PH assumption is found wanting, then the (stratified Cox) **LM** model should be used instead.

PH assumption satisfied
⇓
Determine HRs using exponential formula (Chapter 3)

If the PH assumption is satisfied, hazard ratios for the effects of various predictors in the $\mathbf{LM}_U$ model can be determined using the standard exponential formula described in Chapter 3 for the Cox PH model.

Cancer survival (**CVD** = **OTH** = 0):

$$\mathrm{HR}_{\mathbf{Ca}}(\mathrm{Rx}=1 \text{ vs. } \mathrm{Rx}=0) = \exp\left[\beta_1^{\bullet}\right]$$

CVD survival (**CVD** = 1, **OTH** = 0):

$$\mathrm{HR}_{\mathbf{CVD}}(\mathrm{Rx}=1 \text{ vs. } \mathrm{Rx}=0) = \exp\left[\gamma_1+\beta_1^{\bullet}+\delta_{21}^{\bullet}\right]$$

Other survival (**CVD** = 0, **OTH** = 1):

$$\mathrm{HR}_{\mathbf{OTH}}(\mathrm{Rx}=1 \text{ vs. } \mathrm{Rx}=0) = \exp\left[\gamma_2+\beta_1^{\bullet}+\delta_{31}^{\bullet}\right]$$

In particular, to obtain the hazard ratio for the effect of Rx on **Cancer** survival, we would specify **CVD** = **OTH** = 0 in the model and then exponentiate the coefficient of the Rx variable in the model, as shown at the left.

Similar HR expressions (but involving γ_1 and γ_2 also) are obtained for the effect of Rx when **CVD** deaths and **Other** deaths are the event-types of interest.

Essential point

Use of single **LM**-type model offers greater flexibility for the analysis than allowed using Method 1

At this point, we omit further description of results from fitting the $\mathbf{LM}_U$ model to the Byar dataset. The essential point here is that the use of a single **LM**-type model with augmented data allows greater flexibility for the analysis than can be achieved when using Method 1 to fit separate hazard models for each event-type of interest.

XI. Summary

Competing Risks

Each subject can experience only one of several different types of events over follow-up

This chapter has considered survival data in which each subject can experience only one of several different types of events over follow-up. The different events are called **competing risks**.

Typical approach

- Cox PH model
- Separate model for each event-type
- Other (competing) event-types treated as censored

We have described how to model competing risks survival data using a Cox PH model. The typical approach for analyzing competing risks data is to perform a survival analysis for each event-type separately, where the other (competing) event-types are treated as censored categories.

Drawbacks

1. Require independent competing risks that is, censored subjects have same risk as non-censored subjects in risk set

There are two primary drawbacks to the above method. One problem is the requirement that competing risks be independent. This assumption will not be satisfied if those subjects censored from competing risks do not have the same risk for failing as subjects who are not censored from the cause-specific event of interest at that same time.

2. Product-limit (e.g., KM) curve has questionable interpretation

A second drawback is that the estimated product-limit survival curve obtained from fitting separate Cox models for each event-type has questionable interpretation when there are competing risks.

Several alternative strategies regarding independence assumption: No single strategy is always best

Regarding the independence assumption, several alternative strategies for addressing this issue are described, although no single strategy is always best.

Sensitivity analysis: worst-case violations of independence assumption

For example, subjects censored from competing risks treated in analysis as if

- All event-free
- All experience event of interest

A popular strategy is a sensitivity analysis, which allows the estimation of parameters by considering worst-case violations of the independence assumption. For example, subjects censored from competing risks might be treated in the analysis as either all being event-free or all experiencing the event of interest.

- Independence assumption not easily verifiable
- Typical analysis assumes independence assumption is satisfied

Unfortunately, the independence assumption is not easily verifiable. Consequently, the typical competing risks analysis assumes that the independence assumption is satisfied even if this is not the case.

CIC *Alternative to KM*

- Derived from cause-specific hazard function
- Estimates **marginal probability** when competing risks are present
- Does not require independence assumption
- Useful to assess treatment utility in cost-effectiveness analyses

To avoid a questionable interpretation of the KM survival curve, the primary alternative to using KM is the **Cumulative Incidence Curve** (**CIC**), which estimates the **marginal probability** of an event. Marginal probabilities are relevant for assessing treatment utility whether competing risks are independent.

$$\mathrm{CIC}(t_{(f)}) = \sum_{f'=1}^{f} \hat{I}_{\mathbf{c}}(t_{f'}) = \sum_{f'=1}^{f} \hat{S}(t_{f'-1})\hat{h}_{\mathbf{c}}(t_{f'})$$

The formula for the calculating the **CIC** is shown at the left. The $h_{\mathbf{c}}(t_f)$ in the formula is the estimated hazard at survival time t_f for the event-type (**c**) of interest. The term $S(t_{f-1})$ denotes the **overall** survival probability of previous time (t_{f-1}), where "overall survival" indicates a subject that survives all competing events.

$\hat{h}_{\mathbf{c}}(t_f)$ = estimated hazard at ordered failure time t_f for the event-type (**c**)

$S(t_{f-1})$ = **overall** survival probability of previous time (t_{f-1})

CIC

- Does not use product limit formulation
- Not included in mainstream commercially available statistical packages (e.g., SAS, STATA, SPSS, R)

As the formula indicates, the **CIC** is not estimated using a product-limit formulation. Also, its computation is not included in mainstream commercially available standard statistical packages.

PH model used to obtain **CIC**

⇓

Independence of competing risks required

If a proportional hazard model is used to obtain hazard ratio estimates for individual competing risks as an intermediate step in the computation of a **CIC**, the assumption of independent competing risks is still required.

Modeling **CIC** with covariates using PH model: Fine and Gray (1999)

Software available (Gebski, 1997) Fine and Gray model analogous to Cox PH model

Recent work of Fine and Gray (1999) provides methodology for modeling the **CIC** with covariates using a proportional hazards assumption. Software is available for this method (Gebski, 1997, Tai et al., 2001), although not in standard commercial packages.

Alternative to **CIC**

$\mathbf{CPC_c} = \Pr(T_{\mathbf{c}} \leq t \mid T \geq t)$

where $T_{\mathbf{c}}$ = time until event c occurs

T = time until any competing risk event occurs

An alternative to the **CIC** is the Conditional Probability Curve (**CPC**). For risk type **c,** $\mathbf{CPC_c}$ is the probability of experiencing an event **c** by time t, *given that an individual has not experienced any of the other competing risks by time t*.

$\mathbf{CPC_c} = \mathrm{CIC_c}/(1 - \mathrm{CIC_{c'}})$

where $\mathrm{CIC_{c'}}$ = CIC from risks other than **c**

The **CPC** can be computed from the **CIC** through the formula $\mathbf{CPC_c} = \mathrm{CIC_c}/(1 - \mathrm{CIC_{c'}})$, where $\mathrm{CIC_{c'}}$ is the cumulative incidence of failure from risks other than risk **c** (i.e., all other risks considered together).

Tests to compare CPCs:

Pepe and Mori (1993) – 2 curves
Lunn (1998) – g curves

Pepe–Mori provide a test to compare two **CPC** curves. Lunn (1998) extended this test to g-groups and allows for strata.

Method 2: **LM** Approach

- Uses a single Cox (PH) model
- Gives identical results as obtained from Method 1
- Allows flexibility to perform statistical inferences not available from Method 1

We have also described an alternative approach, called the **Lunn–McNeil** (**LM**) approach, for analyzing competing risks data. The **LM** approach allows only one model to be fit rather than separate models for each event-type (Method 1). This method is equivalent to using Method 1. The **LM** model also allows the flexibility to perform statistical inferences to determine whether a simpler version of an initial **LM** model is more appropriate.

Augmented Data for ith Subject at Time t Using **LM** Approach

Subj	Stime	Status	D_1	D_2	$D_3 \ldots D_C$	$X_1 \ldots X_p$
i	t_i	e_1	1	0	0 … 0	$X_{i1} \ldots X_{ip}$
i	t_i	e_2	0	1	0 … 0	$X_{i1} \ldots X_{ip}$
i	t_i	e_3	0	0	1 … 0	$X_{i1} \ldots X_{ip}$
i	t_i	e_C	0	0	0 … 1	$X_{i1} \ldots X_{ip}$

To carry out the **LM** approach, the data layout must be augmented. If there are C competing risks, the original data must be duplicated C times, one row for each failure type.

$g = 1, 2, \ldots, C$

$$h_g^*(t, \mathbf{X}) = h_{0g}^*(t) \times \exp\Big[\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p + \delta_{21} D_2 X_1 + \delta_{22} D_2 X_2 + \cdots + \delta_{2p} D_2 X_p + \delta_{31} D_3 X_1 + \delta_{32} D_3 X_2 + \cdots + \delta_{3p} D_3 X_p + \cdots + \delta_{C1} D_C X_1 + \delta_{C2} D_C X_2 + \cdots + \delta_{Cp} D_C X_p\Big]$$

To use the **LM** approach with augmented data to obtain identical results from fitting separate models (Method 1), an interaction version of a stratified Cox (SC) PH model is required. A general form for this model is shown at the left.

LM model: need standard error of $\left(\hat{\beta}_1 + \hat{\delta}_{g1}\right)$

(special syntax required for computation)

The **LM** model can be used to obtain Wald test statistics and 95% confidence intervals for HRs separately for each competing risk. These statistics require obtaining standard errors of the sums of estimated regression coefficients (e.g., $\hat{\beta}_1 + \hat{\delta}_{g1}$). Such computations require special syntax available in standard computer packages such as SAS, STATA, SPSS, and R.

Alternative **LM** *formulation*: $\mathbf{LM_{alt}}$ model

Nevertheless, there is an alternative formation of the **LM** model that avoids the need for special syntax. This alternative formulation, called the $\mathbf{LM_{alt}}$ model, yields output that is identical to the output from the separate models (Method 1) approach for analyzing competing risk data.

$\mathbf{LM_{alt}}$ yields output identical to Method 1

1st row of $\mathbf{LM_{alt}}$ model
$\Downarrow$
Product terms D_1X_1, D_1X_2, ..., D_1X_p Coefficients $\delta'_{11}, \ldots, \delta'_{1p}$

1st row of **LM** model
$\Downarrow$
Predictors $X_1, X_2, \ldots, X_p$
Coefficients $\beta_1, \ldots, \beta_p$

The primary difference in the two formulas is that the first row of the exponential term in the $\mathbf{LM_{alt}}$ model contains product terms D_1X_1, D_1X_2, ..., D_1X_{p1} with coefficients denoted $\delta'_{11}, \ldots, \delta'_{1p}$ whereas the first row in the **LM** model contains the predictors X_1, X_2, ..., X_p without product terms and coefficients denoted $\beta_1, \ldots, \beta_p$.

$\mathbf{LM_{alt}}$ model: $\text{Wald}_g = \left[\dfrac{\delta'_{g1}}{\text{SE}_{\hat{\delta}'_{g1}}}\right]^2$ directly obtained from output

Using the $\mathbf{LM_{alt}}$ model, Wald test statistics (shown at the left) and confidence intervals use standard errors that are directly obtained from the standard error column from the output obtained for the $\mathbf{LM_{alt}}$ model.

Statistical inference information

$\mathbf{LM_{alt}}$ model: directly provided by output
LM model: not directly provided by output (requires additional computer code)

Thus, the $\mathbf{LM_{alt}}$ model allows the user to perform statistical inference procedures using the information directly provided in the computer output, whereas the **LM** model requires additional computer code to carry out more complicated computations.

Advantage of **LM** (Method 2) over method 1:
LM offers flexibility for statistical inferences to consider simpler models

An advantage of using either the **LM** or $\mathbf{LM_{alt}}$ approach instead of fitting separate models (Method 1) is the flexibility to perform statistical inferences that consider simpler versions of an interaction SC **LM** model.

For example,
No-interaction SC **LM** model
versus
interaction SC **LM** model

Unstratified **LM** model
versus
SC **LM** model

Overall,

- Can use standard computer packages
- Independence assumption required

For example, one inference question to consider is whether a no-interaction SC **LM** model is more appropriate than an interaction SC model. A different question is whether an unstratified **LM** model is more appropriate than a stratified **LM** model. These questions can be conveniently addressed using a single (i.e., **LM**) model instead of fitting separate models (Method 1).

Overall, in this chapter, we have shown that competing risks data can be analyzed using standard computer packages provided it can be assumed that competing risks are independent.

Detailed Outline

I. **Overview** (page 430)
   A. Focus: **competing risks** – analysis of survival data in which each subject can experience only one of different types of events over follow-up.
   B. Analysis using Cox PH model.
   C. Drawbacks to typical approach that uses Cox model.
   D. Alternative approaches for analysis.

II. **Examples of Competing Risks Data** (pages 430–432)
   A. Dying from either lung cancer or stroke.
      1. Assess whether lung cancer death rate in exposed" persons is different from lung cancer death rate in "unexposed," allowing for competing risks.
      2. Also, compare lung cancer with stroke death rates controlling for predictors.
   B. Advanced cancer patients either dying from surgery or getting hospital infection.
      1. If focus on hospital infection failure, then death from surgery reduces burden of hospital infection control required.
   C. Soldiers dying in accident or in combat.
      1. Focus on combat deaths.
      2. If entire company dies from accident on way to combat, then KM survival probability for combat death is undefined.
      3. Example illustrates that interpretation of KM curve may be questionable when there are competing risks.
   D. Limb sarcoma patients developing local recurrence, lung metastasis, or other metastasis.
      1. None of failure types involves death, so recurrent events are possible.
      2. Can avoid problem of recurrent events if focus only on time to first failure.
      3. Analysis of recurrent events and competing risks in same data not addressed.

III. **Byar Data** (pages 433–434)
   A. Randomized clinical trial comparing treatments for prostate cancer.
   B. Three competing risks: deaths from prostate cancer; CVD, or other causes.

C. Covariates other than treatment are Age, Weight (Wt), Performance Status (PF), History of CVD (Hx), Hemoglobin (Hg), Lesion size (SZ), and Gleeson score (SG).

D. Competing risks considered independent, for example, death from CVD independent of death from death from cancer.

IV. Method 1: Separate Models for Different Event Types (pages 434–437)

A. Use Cox (PH) model to estimate separate hazards and HRs for each failure type, where other competing risks are treated as censored in addition to usual reasons for censoring: loss to follow-up, withdrawal from study, or end of study.

B. Cause-specific hazard function:
$h_{\mathbf{c}}(t) = \lim_{\Delta t \to 0} P(t \le T_{\mathbf{c}} < t + \Delta t | T_{\mathbf{c}} \ge t)/\Delta t$
where $T_{\mathbf{c}}$ = time-to-failure from event **c,** $\mathbf{c} = 1, 2, \ldots, C$ (# of event types).

C. Cox PH cause-specific model (event-type **c**):

$$h_{\mathbf{c}}(t, \mathbf{X}) = h_{0\mathbf{c}}(t) \exp\left[\sum_{i=1}^{p} \beta_{i\mathbf{c}} X_i\right]$$

where $\mathbf{c} = 1, \ldots, C$, and $\beta_{i\mathbf{c}}$ allows effect of X_i to differ by event-type.

D. Byar data example: Cancer, CVD, Other Deaths are C = 3 competing risks.

1. Cause-specific (no-interaction) model for **Cancer:**

$$\begin{aligned} h_{\mathbf{Ca}}(t, \mathbf{X}) = h_{0\mathbf{Ca}}(t) \exp[&\beta_{1\mathbf{Ca}} Rx + \beta_{2\mathbf{Ca}} Age \\ &+ \beta_{3\mathbf{Ca}} Wt + \beta_{4\mathbf{Ca}} PF + \beta_{5\mathbf{Ca}} Hx \\ &+ \beta_{6\mathbf{Ca}} HG + \beta_{7\mathbf{Ca}} SZ + \beta_{8\mathbf{Ca}} SG] \end{aligned}$$

where **CVD** and **Other** deaths treated as censored observations

$$HR_{\mathbf{Ca}}(RX = 1 \text{ vs. } RX = 0) = \exp[\beta_{1\mathbf{Ca}}]$$

2. Separate cause-specific (no-interaction) models for **CVD** and **Other**.

3. Edited output presented for each cause-specific model:

a. Cause-specific **Cancer** results for RX (with **CVD** and **Other** censored):

$$\widehat{HR}_{\mathbf{Ca}}(RX = 1 \text{ vs. } Rx = 0) = 0.575 \; (P = 0.001)$$

b. Cause-specific **CVD** results for RX (with **Cancer** and **Other** censored):

$$\widehat{HR}_{\mathbf{CVD}}(\mathrm{RX}=1 \text{ vs. } \mathrm{Rx}=0)=1.429\ (\mathrm{P}=0.040)$$

c. Cause-specific **Other** results for RX (with **Cancer** and **CVD** censored):

$$\widehat{HR}_{\mathbf{OTH}}(\mathrm{RX}=1 \text{ vs. } \mathrm{Rx}=0)=0.560\ (\mathrm{P}=0.038)$$

V. The Independence Assumption (pages 437–443)

A. **Independent** censoring: h(t) for censored subjects at time t is the same as for non-censored subjects in the same subgroup at time t

1. Typical (chapter 1) context: no competing risks;
2. Informative censoring can lead to bias results.

B. **(Independent)** censoring with **competing risks.** Censored subjects in the risk set at time t with a given set of covariates have the same failure rate as non-censored subjects in the risk set at time t with the same set of covariates regardless of whether the reason for censoring is a competing risk, withdrawal from study, or loss to follow-up.

1. Non-independent censoring: Subjects in the risk set at time t who are censored from a competing risk do not have the same failure rate as non-censored subjects in the risk set at time t.
2. Synonym: **Competing risks are independent**.

C. **Assessing the independence assumption**.

1. No method available to directly assess the independence assumption nor guarantee unbiased estimates if independence assumption is violated.
2. Consequently, the typical analysis of competing risks assumes that the independence assumption is satisfied, even if not.
3. Strategies for considering independence assumption
   a. Decide that assumption holds on clinical/biological/other grounds:
   b. Include in your model variables that are common risk factors for competing risks.

c. Use a frailty model containing a random effect that accounts for competing risks.
d. Perform a sensitivity analysis by considering worst-case violations of independence assumption.
e. All of above strategies rely on assumptions that cannot be verified from observed data.

4. Example of sensitivity analysis using Byar data.
a. Treat all subjects that die of competing risks CVD and Other as Cancer deaths.
b. Treat all subjects that die of competing risks CVD and Other as surviving as long as the largest survival time in the study.
c. Results suggest that if competing risks are not independent, then conclusions about the effect of Rx could be very different.
d. Alternative sensitivity approach: randomly select a subset (e.g., 50%) of subjects who have CVD or Other deaths and assume everyone in subset dies of Cancer.

VI. Cumulative Incidence Curves (CIC)
(pages 444–453)

A. Hypothetical study: n = 100 subjects, all subjects with prostate cancer

Survt (months)	# Died	Cause
3	99	CVD
5	1	Cancer

Study goal: cause-specific Cancer survival
Censored: CVD deaths
$KM_{\mathbf{Ca}}$: $S_{\mathbf{Ca}}(t = 5) = 0$ and $Risk_{\mathbf{Ca}}(T \leq 5) = 1$

B. How many of 99 deaths from CVD would have died from Cancer if not dying from CVD?
1. No answer is possible because those with CVD deaths cannot be observed further.
2. Sensitivity analysis A: 99 CVD deaths die of Cancer at t = 5.
a. $KM_{\mathbf{Ca}}$: $S_{\mathbf{Ca}}(t = 5) = 0$ and $Risk_{\mathbf{Ca}}(T \leq 5) = 1$ because KM assumes independent censoring; that is, those censored at t = 3 were as likely to die from cancer at t = 5 as those who were in the risk set at t = 5.
b. Same KM result as obtained for actual data.

3. Sensitivity analysis B: 99 CVD deaths survive past $t = 5$.
   a. $KM_{\mathbf{Ca}}$: $S_{\mathbf{Ca}}(t = 5) = 0.99$ and $Risk_{\mathbf{Ca}}(T \leq 5) = 0.01$.
   b. Different KM result than actual data.
   c. Can be derived directly from actual data as a **marginal probability**.
4. Main point: KM survival curve may not be very informative.

C. **Cumulative Incidence Curve (CIC)**: alternative to KM for competing risks.
1. Derived from cause-specific hazard function.
2. Estimates marginal probability.
3. Does not require independence assumption.
4. Has a meaningful interpretation in terms of treatment utility.
5. CIC formula:

$$\mathbf{CIC}(t_f) = \sum_{f'=1}^{f} \hat{I}_c(t_{f'}) = \sum_{f'=1}^{f} \hat{S}(t_{f'-1})\hat{h}_{\mathbf{c}}(t_{f'})$$

6. Calculation of CIC for another hypothetical dataset.
7. Tests have been developed (Pepe and Mori, 1992) for comparing the equality of **CIC**s for two or more groups: analogous to log rank test.
8. When a PH model is used to obtain hazard ratio estimates in the computation of a **CIC**, the independence of competing risks is required.
9. Fine and Gray (1999) provide methodology for modeling the **CIC** (also called **subdistribution function**) with covariates using a proportional hazards assumption: analogous to fitting Cox PH model.
10. Example of Fine and Gray output compared with Cox PH output for Byar data.

VII. Conditional Probability Curves (CPC) (pages 453–455)

A. $\mathbf{CPC_c} = Pr(T_{\mathbf{c}} \leq t | T \geq t)$ where $\mathbf{T_c}$ = time until event **c** occurs, T = time until any competing risk event occurs.
B. Formula in terms of CIC: $\mathbf{CPC_c} = CIC_{\mathbf{c}}/(1 - CIC_{\mathbf{c}'})$ where $CIC_{\mathbf{c}'}$ = CIC from risks other than **c**.
C. Graphs of CPCs can be derived from graphs of CICs.
D. Tests to compare CPCs: Pepe and Mori (1993) – 2 curves; Lunn (1998) – g curves.

VIII. Method 2—The Lunn-McNeil (LM) Approach (pages 455–461)

A. Allows only one Cox PH model to be fit rather than fitting separate modes for each event type (Method 1).

B. **LM** uses an augmented data layout.

1. for ith subject at time t_i, layout has C rows of data, where C = # event-types.
2. Dummy variables D_1, D_2,..., D_C are created to distinguish the C event-types.
3. The Status variable, $e_{\mathbf{c}}$, $\mathbf{c} = 1,\ldots, C$, equals 1 for event-type **c** and 0 otherwise.
4. Predictors are denoted by $X_1,\ldots, X_p$.
5. Example of data layout for Byar dataset.

C. General form of **LM** model (interaction SC model).

$$\underset{g=1,2,\ldots,C}{h^*_{\mathbf{g}}(t,\mathbf{X})} = h^*_{0g}(t)\exp\Big[\beta_1X_1+\beta_2X_2+\cdots+\beta_pX_p + \delta_{21}D_2X_1+\delta_{22}D_2X_2+\cdots+\delta_{2p}D_2X_p + \delta_{31}D_3X_1+\delta_{32}D_3X_2+\cdots+\delta_{3p}D_3X_p + \cdots + \delta_{C1}D_CX_1+\delta_{C2}D_CX_2+\cdots+\delta_{Cp}D_CX_p\Big]$$

1. **LM** model for event-type g = 1:
   a. $h^*_1(t,\mathbf{X}) = h^*_{01}(t) \times \exp\Big[\beta_1X_1+\beta_2X_2+\cdots+\beta_pX_p\Big]$
   b. $D_2 = D_3 = \ldots = D_C = 0$
   c. $HR_{\mathbf{g=1}}(X_1 = 1 \text{ vs. } X_1 = 0) = \exp[\beta_1]$
2. **LM** model for event-type g (> 1):
   a. $h^*_g(t,\mathbf{X}) = h^*_{0g}(t) \times \exp\big[(\beta_1+\delta_{g1})X_1 + (\beta_2+\delta_{g2})X_2 + \cdots + \big(\beta_p+\delta_{gp}\big)X_p\Big]$
   b. $HR_{\mathbf{g}}(X_1 = 1 \text{ vs. } X_1 = 0 = \exp[(\beta_1+\delta_{g1})]$

D. **LM** model for Byar data.

1. $h^*_g(t,X) = h^*_{0g}(t) \times \exp[\beta_1\,\mathrm{Rx} + \beta_2\mathrm{Age}+\cdots+\beta_8\mathrm{SG} + \delta_{21}D_2\mathrm{Rx}+\delta_{22}D_2\mathrm{Age}+\cdots+\delta_{28}D_2\mathrm{SG} + \delta_{31}D_3\mathrm{Rx}+\delta_{32}D_3\mathrm{Age}+\cdots+\delta_{38}D_3\mathrm{SG}]$
   $g = 1,2,3$
2. D_2 = CVD and D_3 = OTH are (0,1) dummy variables for 3 event-types.

3. $HR_{\mathbf{Ca}}(Rx = 1 \text{ vs. } Rx = 0) = \exp[\beta_1]$
   $HR_{\mathbf{CVD}}(Rx = 1 \text{ vs. } Rx = 0) = \exp[\beta_1 + \delta_{21}]$
   $HR_{\mathbf{OTH}}(Rx = 1 \text{ vs. } Rx = 0) = \exp[\beta_1 + \delta_{31}]$
4. Mathematical formulas for Wald tests and confidence intervals require standard errors for sums $\left(\hat{\beta}_1 + \hat{\delta}_{g1}\right)$ for g = 2 and 3; requires special syntax for computer.
5. Output provided and compared to output from Method 1.

IX. Method 2a: Alternative Lunn–McNeil ($\mathbf{LM_{alt}}$) Approach (pages 461–464)

A. An alternative LM formulation that gives identical output to that obtained from Method 1 (separate models approach).
B. Same data layout as for LM model, but only product terms in $\mathbf{LM_{alt}}$ model.
C. General form of $\mathbf{LM_{alt}}$ (interaction SC) model:

$$g = 1, \ldots, C$$
$$h'_g(t,\mathbf{X}) = h'_{0g}(t) \times \exp\left[\delta'_{11}D_1X_1 + \delta'_{12}D_1X_2 + \cdots + \delta'_{1p}D_1X_p + \delta'_{21}D_2X_1 + \delta'_{22}D_2X_2 + \cdots + \delta'_{2p}D_2X_p + \cdots + \delta'_{C1}D_CX_1 + \delta'_{C2}D_CX_2 + \cdots + \delta'_{Cp}D_2X_p\right]$$

D. Hazard ratio formula involves only coefficients of product terms for all g:

$$HR_g(X_1 = 1 \text{ vs. } X_1 = 0) = \exp\left[\delta'_{g1}\right], \quad g = 1, 2, 3$$

   a. Statistical inference information directly provided by $\mathbf{LM_{alt}}$ output.

E. Example of output for $\mathbf{LM_{alt}}$ model using Byar data.

X. Method 1 (Separate Models) versus Method 2 (LM Approach) (pages 465–468)

A. **LM** and $\mathbf{LM_{alt}}$ models allow flexibility to perform statistical inferences about features of competing risks model not conveniently available using separate models (Method 1) approach.
B. **LM** and $\mathbf{LM_{alt}}$ models can assess whether a no-interaction SC model is more appropriate than the initial interaction SC **LM** model.

C. Example of comparison of no-interaction with interaction SC model using Byar data.
D. **LM** and $\mathbf{LM_{alt}}$ models can assess whether an unstratified LM model (called $\mathbf{LM_U}$) is more appropriate than a stratified **LM** model.
E. Example of $\mathbf{LM_U}$ model involving Byar data.

XI. Summary (pages 468–473)

A. Competing risks survival data can be analyzed using Cox PH models and standard computer packages.
B. There are two alternative methods that use a Cox PH model formulation.
   1. Fit separate models for each cause-specific event type, treating the remaining event types as censored.
   2. Use the **Lunn–McNeil (LM)** approach to fit a single model that incorporates the analysis for each cause-specific event.
C. Each of the above approaches requires that competing risks be independent (i.e., independent censoring).
D. Without the independence assumption, methods for competing risks analysis are unavailable.
E. The **Cumulative Incidence Curve (CIC)** or the **Conditional Probability Curve (CPC)** are alternatives to the KM curve, when use of a KM curve has questionable interpretation.

Practice Exercises

Answer questions 1 to 15 as true or false (circle T or F).

T F 1. A competing risk is an event-type (i.e., failure status) that can occur simultaneously with another event of interest on the same subject.
T F 2. An example of competing risks survival data is a study in which patients receiving radiotherapy for head and neck cancer may either die from their cancer or from some other cause of death.
T F 3. if all competing risks in a given study are different causes of death, then it is possible to have both competing risks and recurrent events in the same study.

T F 4. Suppose patients with advanced-stage cancer may die after surgery before their hospital stay is long enough to get a hospital infection. then such deaths from surgery reduce the hospital's burden of infection control.

T F 5. The typical approach for analyzing competing risks using a Cox PH model involves fitting separate models for each competing risk ignoring the other competing risks.

T F 6. Suppose that a cause-specific risk of interest is development of lung metastasis, and a competing risk is local recurrence of a lung tumor. Then a patient who develops a local recurrence is treated as a failure in a competing risk analysis.

T F 7. When there are no competing risks, then any study subject in the risk set at a given time has the same risk for failing as any other subject in the risk set with the same values for covariate predictors at time t.

T F 8. If, when analyzing competing risks survival data, it is assumed that censoring is independent, then a subject in the risk set at time t is as likely to fail from any competing risk as to be lost to follow-up.

T F 9. When a sensitivity analysis indicates that a worst-case scenario gives meaningfully different results from an analysis that assumes independence of competing risks, then there is evidence that the independence assumption is violated.

T F 10. The typical competing risk analysis assumes that competing risks are independent even if this assumption is not true.

T F 11. The Cumulative Incidence Curve (CIC) provides risk estimates for the occurrence of a cause-specific event in the presence of competing risks.

T F 12. CIC = 1 − KM, where KM denotes the Kaplan–Meier curve.

T F 13. A CIC for a cause-specific event that ignores the control of covariates does not require the assumption of independent competing risks.

T F 14. A Cumulative Probability Curve (CPC) gives the probability of experiencing an event c by time t, given that an individual has experienced any of the other competing risks by time t.

T F 15. If $CIC_c = .4$, then $CPC = .4/.6 = .667$.

T F 16. The Lunn–McNeil (LM) approach fits a single stratified Cox model using an augmented dataset to obtain the same results as obtained by fitting separate Cox models for each cause-specific competing risk.

T F 17. An advantage of the Lunn–McNeil (LM) approach over the approach that fits separate Cox models is that the LM approach allows for testing whether a no-interaction SC model might be preferable to an interaction SC model.

T F 18. **Given the LM model** stratified on two cause-specific events, Cancer and CVD:

$$h^*_g(t, \mathbf{X}) = h^*_{0g}(t) \exp[\beta_1 Rx + \beta_2 Age + \delta_1(D \times Rx) + \delta_2(D \times Age)],$$

$$g = 1,\ 2 \text{ where}$$

$$D = 0 \text{ if Ca and} = 1 \text{ if CVD}$$

then

$$HR_{\mathbf{CVD}}(Rx = 1 \text{ vs. } Rx = 0) = \exp[\beta_1 + \delta_1]$$

T F 19. **Given the $\mathbf{LM_{alt}}$** model for two cause-specific events, Cancer and CVD:

$$h'_g(t, \mathbf{X}) = h'_{0g}(t) \times \exp[\delta'_{11} D_1 Rx + \delta'_{12} D_1 Age + \delta'_{21} D_2 Rx + \delta'_{22} D_2 Age],$$

$$g = 1, 2 \text{ where}$$

$D_1 = 1$ if Ca or 0 if CVD, and
$D_2 = 0$ if Ca or 1 if CVD,

then

$$HR_{\mathbf{CVD}}(Rx = 1 \text{ vs. } Rx = 0) = \exp[\delta'_{21}]$$

T F 20. The $\mathbf{LM_U}$ model that would result if the **LM** model of Question 18 were changed to an unstratified Cox PH model can be written as follows.

$$h^\bullet(t, \mathbf{X}) = h^\bullet_0(t) \exp\left[\beta^\bullet_1 Rx + \beta^\bullet_2 Age + \delta^\bullet_{21}(D \times Rx) + \delta^\bullet_{22}(D \times Age)\right]$$

Consider a hypothetical study of the effect of a bone marrow transplant for leukemia on leukemia-free survival, where transplant failures can be of one of two types: relapse of leukemia and nonrelapse death (without prior relapse of leukemia). Suppose that in hospital A, 100 patients undergo such a transplant and that within the first 4 years post-transplant, 60 die without relapse by year 2 and 20 relapse during year 4. Suppose that in hospital B, 100 patients undergo such a transplant but post-transplant, there are 20 non-relapse deaths by year 1, 15 relapses during year 2, 40 non-relapse deaths between years 3 and 4, and 5 relapses during year 4.

21. What are the competing risks in this study?
22. What is the proportion of initial patients in hospitals A and B, respectively, that have leukemia relapse by 4 years?

The following tables provide the Kaplan–Meier curves for relapse of leukemia for each study.

Hospital A

t_j	n_j	m_j	q_j	$S(t_j)$
0	100	0	60	1
2	40	0	0	1
4	40	20	20	.5

Hospital B

t_j	n_j	m_j	q_j	$S(t_j)$
0	100	0	20	1
1	80	0	0	1
2	80	15	0	0.8125
3	65	0	40	0.8125
4	25	5	20	0.65

23. How have both tables treated the competing risk for nonrelapse death in the calculation of the KM probabilities?
24. Why are the KM probabilities different at 4 years for each hospital?

25. Compute the CIC curves for each hospital using the following tables.

Hospital A

t_f	n_f	m_f	$\hat{h}_{ca}(t_f)$	$\hat{S}(t_{f-1})$	$\hat{I}_{ca}(t_f)$	$CIC(t_f)$
0	100	0	0	–	–	–
2	40	0	0	1	0	0
4	40	20	–	–	–	–

Hospital B

t_f	n_f	m_f	$\hat{h}_{ca}(t_f)$	$\hat{S}(t_{f-1})$	$\hat{I}_{ca}(t_f)$	$CIC(t_f)$
0	100	0	0	–	–	–
1	80	0	0	1	0	0
2	80	15	–	–	–	–
3	65	0	–	–	–	–
4	25	5	–	–	–	–

26. Why are the CIC probabilities the same at 4 years?

Consider a hypothetical study to assess the effect of a new hospital infection control strategy for patients who undergo heart transplant surgery in a given hospital. The exposure variable of interest is a binary variable Group (**G**): $\mathbf{G} = 0$ for those patients receiving heart transplants from 1992 through 1995 when the previous hospital control strategy was used; $\mathbf{G} = 1$ for those patients receiving heart transplants from 1996 through 1999 when the new hospital infection control strategy was adopted. The primary event of interest is getting a hospital infection after surgery. A competing risk is death during recovery from surgery without getting a hospital infection. Control variables being considered are tissue mismatch score (TMS) at transplant and AGE at transplant. The outcome variable of interest is time (DAYS after surgery) until a patient developed a hospital infection.

27. State a cause-specific no-interaction Cox PH model for assessing the effect of group status (**G**) on time until a hospital infection event.
28. When fitting the model given in Question 27, which patients should be considered censored?
29. Describe or provide a table that would show how the data on the ith patient should be augmented for input into a Lunn–McNeil (LM) model for this analysis.

30. State a LM model that can be used with an augmented dataset that will provide identical results to those obtained from using the model of Question 27.
31. For the LM model of Question 30, what is the formula for the hazard ratio for the group effect **G**, controlling for **TMS** and **AGE**.
32. Describe how you would test whether a no-interaction SC LM model would be more appropriate than an interaction SC LM model.
33. State a LM_{alt} model that can be used with an augmented dataset that will provide identical results to those obtained from using the model of Question 27.
34. For the LM_{alt} model of Question 33, what is the formula for the hazard ratio for the group effect **G**, controlling for **TMS** and **AGE?**

Test

The dataset shown below describes a hypothetical study of recurrent bladder cancer. The entire dataset contained 53 patients, each with local bladder cancer tumors who are followed for up to 30 months after transurethral surgical excision. Three competing risks being considered are local recurrence of bladder cancer tumor (**event** = 1), bladder metastasis (**event** = 2), or other metastasis (**event** = 3). The variable **time** denotes survival time up to the occurrence of one of the three events or censorship from loss to follow-up, withdrawal, or end of study. The exposure variable of interest is drug treatment status (**tx**, 0 = placebo, 1 = treatment A), The covariates listed here are initial number of tumors (**num**) and initial size of tumors (**size**) in centimeters.

id	event	time	tx	num	size
1	1	8	1	1	1
2	0	1	0	1	3
3	0	4	1	2	1
4	0	7	0	1	1
5	0	10	1	5	1
6	2	6	0	4	1
7	0	10	1	4	1
8	0	14	0	1	1
9	0	18	1	1	1
10	3	5	0	1	3
11	0	18	1	1	3
12	1	12	0	1	1
13	2	16	1	1	1
14	0	18	0	1	1
15	0	23	1	3	3

(Continued on next page)

(*Continued*)

id	event	time	tx	num	size
16	3	10	0	1	3
17	1	15	1	1	3
18	0	23	0	1	3
19	2	3	1	1	1
20	3	16	0	1	1
21	1	23	1	1	1
22	1	3	0	3	1
23	2	9	1	3	1
24	2	21	0	3	1
25	0	23	1	3	1
26	3	7	0	2	3
27	3	10	1	2	3
28	1	16	0	2	3
29	1	24	1	2	3
30	1	3	0	1	1
31	2	15	1	1	1
32	2	25	0	1	1
33	0	26	1	1	2
34	1	1	0	8	1
35	0	26	1	8	1
36	1	2	0	1	4
37	1	26	1	1	4
38	1	25	0	1	2
39	0	28	1	1	2
40	0	29	0	1	4
41	0	29	1	1	2
42	0	29	0	4	1
43	3	28	1	1	6
44	1	30	0	1	6
45	2	2	1	1	5
46	1	17	0	1	5
47	1	22	1	1	5
48	0	30	0	1	5
49	3	3	1	2	1
50	2	6	0	2	1
51	3	8	1	2	1
52	3	12	0	2	1
53	0	30	1	2	1

1. Suppose you wish to use these data to determine the effect of **tx** on survival time for the cause-specific event of a local recurrence of bladder cancer. State a no-interaction Cox PH model for assessing this relationship that adjusts for the covariates **num** and **size**.

2. When fitting the model given in Question 1, which subjects are considered censored?
3. How would you modify your answers to Questions 1 and 2 if you were interested in the effect of **tx** on survival time for the cause-specific event of finding metastatic bladder cancer?
4. For the model considered in Question 1, briefly describe how to carry out a sensitivity analysis to determine how badly the results from fitting this model might be biased if the assumption of independent competing risks is violated.
5. The following two tables provide information necessary for calculating CIC curves for local recurrence of bladder cancer (**event** = 1) separately for each treatment group. The CIC formula used for both tables is given by the expression

$$\mathbf{CIC_1}(t_f) = \sum_{f'=1}^{f} \hat{I}_1(t'_f) = \sum_{f'=1}^{f} \hat{S}(t_{f'} - 1)\hat{h}_1(t_{f'})$$

where $\hat{h}_1(t_f) = m_{1f}/n_f$, m_{1f} is the number of local recurrent failures at time t_f and $S(t_{f-1})$ is the overall (event-free) survival probability for failure from either of the two competing risks at time t_{f-1}.

tx = 1 (Treatment A)

t_f	n_f	d_{1f}	$\hat{h}_1(t_f)$	$\hat{S}(t_{f-1})$	$\hat{I}_1(t_f)$	$CIC_1(t_f)$
0	27	0	0	—	—	—
2	27	0	0	1	0	0
3	26	0	0	.9630	0	0
4	24	0	0	.8889	0	0
8	**23**	**1**	**.0435**	**.8889**	**.0387**	**.0387**
9	21	0	0	.8116	0	.0387
10	20	0	0	.7729	0	.0387
15	17	1	.0588	.7343	.0432	.0819
16	15	0	0	.6479	0	.0819
18	14	0	0	.6047	0	.0819
22	12	1	.0833	.6047	.0504	.1323
23	11	1	.0910	.5543	.0504	.1827
24	8	1	.1250	.5039	.0630	.2457
26	7	1	.1429	.4409	.0630	.3087
28	4	0	0	.3779	0	.3087
29	2	0	0	.2835	0	.3087
30	1	0	0	.2835	0	.3087

tx = 1 (Placebo)

t_f	n_f	d_{1f}	$\hat{h}_1(t_f)$	$\hat{S}(t_{f-1})$	$\hat{I}_1(t_f)$	$CIC_1(t_f)$
0	26	0	0	—	—	—
1	26	1	.0400	1	.0400	.0400
2	24	1	.0417	.9615	.0400	.0800
3	23	2	.0870	.9215	.0801	.1601
5	21	0	0	.8413	0	.1601
6	20	0	0	.8013	0	.1601
7	18	0	0	.7212	0	.1601
10	16	0	0	.6811	0	.1601
12	15	1	.0667	.6385	.0426	.2027
14	13	0	0	.6835	0	.2027
16	12	1	.0833	.5534	.0461	.2488
17	10	1	.1000	.4612	.0461	.2949
18	9	0	0	.4150	0	.2949
21	8	0	0	.4150	0	.2949
23	7	0	0	.3632	0	.2949
25	**6**	**1**	**.1667**	**.3632**	**.0605**	**.3554**
29	4	0	0	.2421	0	.3554
30	2	1	0	.2421	0	.3554

a. Verify the CIC_1 calculation provided at failure time $t_f = 8$ for persons in the treatment group ($\mathbf{tx} = 1$); that is, use the original data to compute $\hat{\mathbf{h}}_1(\mathbf{t}_f)$, $\hat{S}(\mathbf{t}_{f-1})$, $\hat{\mathbf{I}}_1(\mathbf{t}_f)$, and $\mathbf{CIC}_1(\mathbf{t}_f)$, assuming that the calculations made up to this failure time are correct.

b. Verify the CIC_1 calculation provided at failure time $t_f = 25$ for persons in the placebo group ($\mathbf{tx} = 0$).

c. Interpret the CIC_1 values obtained for both the treatment and placebo groups at $t_f = 30$.

d. How can you calculate the CPC_1 values for both treatment and placebo groups at $t_f = 30$?

6. The following output was obtained using separate models for each of the 3 event-types.

Event = 1

Var	DF	Coef	Std.Err.	p > |z|	Haz.ratio
tx	1	−0.6258	0.5445	0.2504	0.535
num	1	0.0243	0.1900	0.8983	1.025
size	1	0.0184	0.1668	0.9120	1.125

Event = 2

Var	DF	Coef	Std.Err.	p > |z|	Haz.ratio
tx	1	−0.0127	0.6761	0.9851	0.987
num	1	−0.1095	0.2281	0.6312	0.896
size	1	−0.6475	0.3898	0.0966	0.523

Event = 3

Var	DF	Coef	Std.Err.	p > |z|	Haz.ratio
tx	1	−0.3796	0.6770	0.5750	0.684
num	1	−0.1052	0.3135	0.7372	0.900
size	1	−0.0238	0.2177	0.9128	0.976

   a. What is the effect of treatment on survival from having a local recurrence of bladder cancer, and is it significant?
   b. What is the effect of treatment on survival from developing metastatic bladder cancer, and is it significant?
   c. What is the effect of treatment on survival from other metastatic cancer, and is it significant?

7. Below is the output from fitting a LM model to the bladder cancer data.

Var	DF	Coef	Std.Err.	p > |z|	Haz.ratio
txd2	1	0.6132	0.8681	0.4800	1.846
txd3	1	0.2463	0.8688	0.7768	1.279
numd2	1	−0.1337	0.2968	0.6523	0.875
numd2	1	−0.1295	0.3666	0.7240	0.879
sized2	1	−0.6660	0.4239	0.1162	0.514
sized3	1	−0.0423	0.2742	0.8775	0.959
tx	1	−0.6258	0.5445	0.2504	0.535
num	1	0.0243	0.1900	0.8983	1.025
size	1	0.0184	0.1668	0.9120	1.125

   a. State the hazard model formula for the LM model used for the above output.
   b. Determine the estimated hazard ratios for the effect of each of the 3 cause-specific events based on the above output.
   c. Verify that the estimated hazard ratios computed in Part b are identical to the hazard ratios computed in Question 6.

8. Below is the output from fitting a $\mathbf{LM_{alt}}$ model to the bladder cancer data.

Var	DF	Coef	Std.Err.	p > |z|	Haz.ratio
txd1	1	−0.6258	0.5445	0.2504	0.535
txd2	1	−0.0127	0.6761	0.9851	0.987
txd3	1	−0.3796	0.6770	0.5750	0.684
numd1	1	0.0243	0.1900	0.8983	1.025
numd2	1	−0.1095	0.2281	0.6312	0.896
numd3	1	−0.1052	0.3135	0.7372	0.900
sized1	1	0.0184	0.1668	0.9120	1.125
sized2	1	−0.6475	0.3898	0.0966	0.523
sized3	1	−0.0238	0.2177	0.9128	0.976

   a. State the hazard model formula for the $\mathbf{LM_{alt}}$ model used for the above output.
   b. Determine the estimated hazard ratios for the effect of each of the 3 cause-specific events based on the above output.
   c. Verify that the estimated hazard ratios computed in Part b are identical to the hazard ratios computed in Questions 6 and 7.

9. State the formula for a no-interaction SC LM model for these data.
10. Describe how you would test whether a no-interaction SC LM model would be more appropriate than an interaction SC LM model.

Answers to Practice Exercises

1. F: Only one competing risk event can occur at a given time.
2. T
3. F: You can die only once.
4. T
5. F: Competing risks must be treated as censored observations, rather than ignored.
6. F: A patient who develops a local recurrence will be treated as censored.
7. F: The statement would be true providing censoring is independent.
8. T
9. F: A sensitivity analysis can never provide explicit evidence about whether the independence assumption is satisfied; it can only suggest how biased the results might be if the assumption is not satisfied.
10. T
11. T
12. F: The formula is correct only if there is one risk. See Section V in the text for the general formula.
13. T
14. F: The correct statement should be: CPC gives the probability of experiencing an event c by time t, given that an individual has **not** experienced any of the other competing risks by time t.

15. F: the correct formula for CPC is:
$\mathbf{CPC}_c = \mathrm{CIC}_{\mathbf{c}}/(1 - \mathrm{CIC}_{\mathbf{c}'})$ where $\mathrm{CIC}_{\mathbf{c}} = .4$ and $\mathrm{CIC}_{\mathbf{c}'} =$ CIC from risks other than **c**, where the latter is not necessarily equal to .4.
16. T
17. T
18. T
19. T.
20. F: The correct $\mathbf{LM}_U$ model is

$$h^{\bullet}(t,\mathbf{X}) = h_0^{\bullet}(t)\exp\left[\gamma_1 D + \beta_1^{\bullet}\mathrm{Rx} + \beta_2^{\bullet}\mathrm{Age} + \delta_{21}^{\bullet}(\mathrm{D}\times\mathrm{Rx}) + \delta_{22}^{\bullet}(\mathrm{D}\times\mathrm{Age})\right]$$

21. The competing risks are (1) relapse of leukemia and (2) nonrelapse death.
22. 20/100 = 0.2.
23. Both tables have treated the competing risks as if they were censored observations.
24. The KM probabilities are different for the two hospitals because the competing risks contribute a different pattern of censorship in the two hospitals.
25. The CIC curves for each hospital are calculated as follows.

Hospital A

t_f	n_f	m_f	$\hat{h}_{ca}(t_f)$	$\hat{S}(t_{f-1})$	$\hat{I}_{ca}(t_f)$	$\mathrm{CIC}(t_f)$
0	100	0	0	—	—	—
2	40	0	0	1	0	0
4	40	20	0.5	0.4	0.20	0.20

Hospital B

t_f	n_f	m_f	$\hat{h}_{ca}(t_f)$	$\hat{S}(t_{f-1})$	$\hat{I}_{ca}(t_f)$	$\mathrm{CIC}(t_f)$
0	100	0	0	—	—	—
1	80	0	0	1	0	0
2	80	15	0.1875	0.8	0.15	0.15
3	65	0	0	0.65	0	0.15
4	25	5	0.20	0.25	0.05	0.20

26. The CIC probabilities are the same at 4 years because they give marginal probabilities that are not influenced by the pattern of censorship of the competing risks that are treated as censored. In hospital B, for example, the marginal probability of 0.15 at year 2 is given by the proportion of the initial risk set of 100 subjects that had a relapse of leukemia by year 2, regardless of the number of nonrelapse deaths prior to year 2. Similarly for hospital B, the marginal probability of .20 at year 4 adds to the marginal probability at year 2 the proportion of the initial risk set of 100 subjects that had a relapse between year 2 and year 4, regardless of the number of nonrelapse deaths that occurred between year 2 and 4.
27. $h_{HI}(t,\mathbf{X}) = h_0(t)\exp[\beta_{1HI}G + \beta_{2HI}TMS + \beta_{3HI}AGE]$ where HI denotes a hospital infection event
28. Patients who die after surgery without developing a hospital infection are censored. Also censored are any patients who are either lost to follow-up or withdraw from the study, although such patients are unlikely.
29. Augmented Data for LM Approach

Subj	Stime	Status	D_1	D_2	G	TMS	AGE
i	t_i	e_{1i}	1	0	G_i	TMS_i	AGE_i
i	t_i	e_{2i}	0	0	G_i	TMS_i	AGE_i

where e_{1i} = 1 if the ith subject develops a hospital infection, 0 otherwise
e_{2i} = 1 if ith subject dies after surgery, 0 otherwise
D_1 = indicator for hospital infection event
D_2 = indicator for death after surgery event

30. $$h^*_{\substack{g\\g=1,2}}(t,\mathbf{X}) = h^*_{0g}(t)\exp[\beta_1 G + \beta_2 TMS + \beta_3 AGE + \delta_{21}D_2G + \delta_{22}D_2TMS + \delta_{23}D''_2AGE]$$
31. $HR_{HI}(RX = 1 \text{ vs. } RX = 0) = \exp[\beta_1]$

32. Carry out a likelihood ratio test to compare the following two models. Full (SC Interaction LM) model:

$$\underset{g=1,\,2}{h^*_g}(t, \mathbf{X}) = h^*_{0g}(t) \exp[\beta_1 G + \beta_2 TMS + \beta_3 AGE + \delta_{21} D_2 G + \delta_{22} D_2 TMS + \delta_{23} D_2 AGE]$$

Reduced (no-interaction SC LM) model:

$$\underset{g=1,\,2}{h^*_g}(t, \mathbf{X}) = h^*_{0g}(t) \exp[\beta_1 G + \beta_2 TMS + \beta_3 AGE]$$

LR test statistic $= -2 \ln L_R - (-2 \ln L_F)$ is distributed χ^2_3 under H_0: no-interaction model

33. $$\underset{g=1,\,2}{h'_g}(t, \mathbf{X}) = h'_{0g}(t) \exp[\delta'_{11} D_1 G + \delta'_{12} D_1 TMS + \delta'_{13} D_1 AGE + \delta'_{21} D_2 G + \delta'_{22} D_2 TMS + \delta'_{23} D_2 AGE]$$

34. $HR_{HI}(RX = 1 \text{ vs. } Rx = 0) = \exp[\delta'_{11}]$