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NON-PARAMETRIC INFERENCE FOR CUMULATIVE INCIDENCE FUNCTIONS IN COMPETING RISKS STUDIES

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SUMMARY

In the competing risks problem, a useful quantity is the cumulative incidence function, which is the probability of occurrence by time t for a particular type of failure in the presence of other risks. The estimator of this function as given by Kalbfleisch and Prentice is consistent, and, properly normalized, converges weakly to a zero-mean Gaussian process with a covariance function for which a consistent estimator is provided. A resampling technique is developed to approximate the distribution of this process, which enables one to construct confidence bands for the cumulative incidence curve over the entire time span of interest and to perform Kolmogorov–Smirnov type tests for comparing two such curves. An AIDS example is provided. © 1997 by John Wiley & Sons, Ltd. Stat. Med., Vol. 16, 901–910 (1997).

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1. INTRODUCTION

Analysis of multiple events data is often complicated by the fact that the occurrence of some events may be precluded by the occurrence of others. For example, in a recent controlled trial on the prophylaxis of *Pneumocystis carinii* pneumonia (PCP) in patients with the human immunodeficiency syndrome (AIDS), 154 and 156 patients who had recovered from an initial episode of PCP were randomized to receive trimethoprim sulfamethoxazole (TS) and aerosolized pentamidine (AP), respectively.[1] By the end of the trial, 14 patients in the TS group and 36 patients in the AP group had PCC recurrences. There were 43 and 47 deaths in the TS and AP groups, respectively. Most of these deaths, 36 in each group, occurred prior to recurrences of PCP.

Similar examples also arise frequently in cancer, cardiology and other disease areas. Kalbfleisch and Prentice[2] (Chapter 7) provided an interesting discussion of bone marrow transplant studies, in which the leukaemic relapse is not observable if patients die from non-relapse causes. In addition, they described several biomedical studies to illustrate the classical competing risks problem in which the cause-specific mortality is of interest.

Under the conventional competing risks framework, an individual may fail from only one of several distinct types or causes. In the AIDS study described above, however, a patient might first experience recurrence of PCP and then die. To ease our discussion, we will regard recurrence and non-recurrence death (that is, death occurring without prior recurrence of PCP) as the two types of failure so that the problem fits into the conventional competing risks framework.

Standard survival analysis methods, such as the Kaplan–Meier estimator and the logrank test, have been commonly used to analyse competing risks data. Figure 1 displays (the complement of) the Kaplan–Meier curves for the recurrence of PCP in the AIDS study. For such an analysis,

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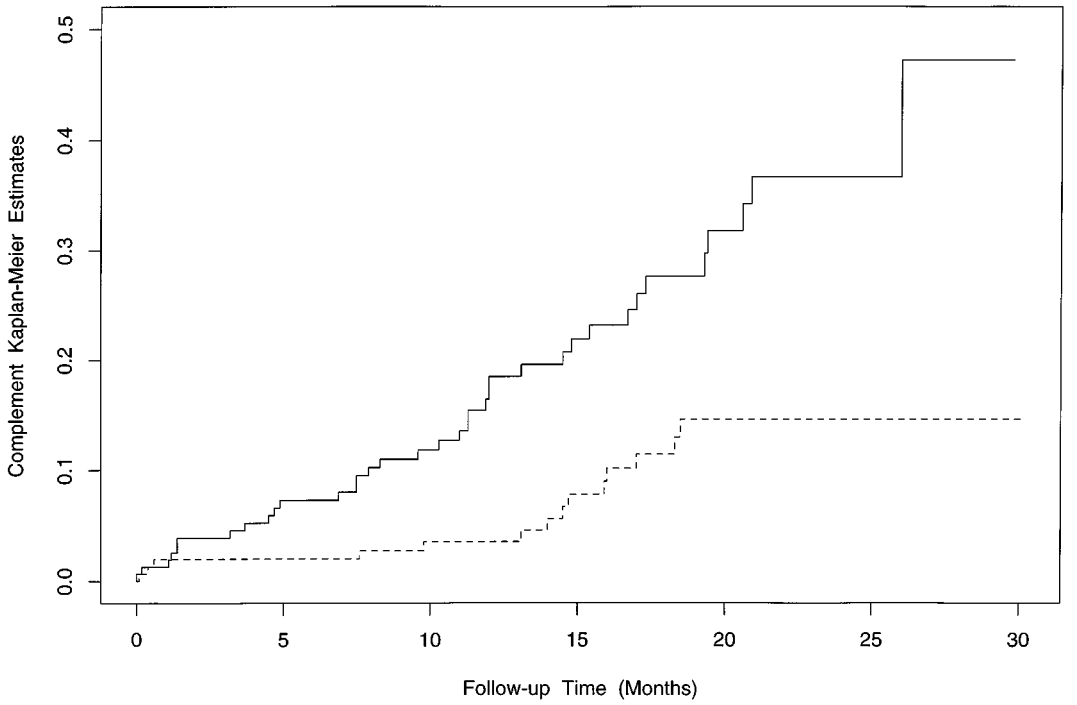

Figure 1. Complement Kaplan–Meier estimates for PCP recurrence in the AIDS study. The AP and TS groups are shown by the solid and dashed curves, respectively

non-recurrence deaths are treated as censored observations with respect to PCP recurrences. The proportion of patients who have experienced the failure type of interest (such as PCP recurrence) by a given time point has often been estimated from the Kaplan–Meier curve. This is an incorrect use of the Kaplan–Meier method, which has been pointed out by various authors,[2–5] but is still commonplace is medical literature.

The Kaplan–Meier estimator for PCP recurrence actually estimates the quantity $G_1(t) = \exp\{-\int_0^t \lambda_1(u)\mathrm{d}u\}$, where λ_1 is the cause-specific hazard function for recurrence. Specifically, let T be the time to recurrence or death, whichever occurs first, and let J be the failure type indicator, which takes the values 1 and 2 for recurrence and non-recurrence death, respectively. Then

$$\lambda_j(t) = \lim_{\Delta t \to 0} \frac{\Pr(t \leqslant T < t + \Delta t, J = j \mid T \geqslant t)}{\Delta t}, \quad j = 1, 2.$$

In words, $\lambda_1(t)$ is the instantaneous rate of recurrence at time t in the presence of non-recurrence death. The overall hazard function for T is $\lambda(t) = \lambda_1(t) + \lambda_2(t)$. It is important to realize that G_1 cannot be interpreted as the survival function of the (latent) recurrence time even if recurrence and non-recurrence death are independent.

In many applications involving competing risks, the investigators are interested in the (cumulative) probability of occurrence by time t for a particular type of event in the presence of other risks. For example, in the above AIDS study, the proportions of patients who have experienced PCP recurrence by various time points (namely, 12, 18 and 24 months)

were the primary efficacy measures. These probabilities correspond to the cumulative incidence functions[2]

$$F_j(t) = \Pr(T \leqslant t, J = j), j = 1, 2.$$

It is easy to see that

$$F_j(t) = \int_0^t S(u)\lambda_j(u)\,\mathrm{d}u, \quad j = 1, 2, \tag{1}$$

where S is the overall survival function of T, that is, $S(t) = \Pr(T \geqslant t)$.

Note that $S(t) = \exp[-\int_0^t \{\lambda_1(u) + \lambda_2(u)\}\,\mathrm{d}u] = \mathrm{e}^{-\Lambda_1(t)}\mathrm{e}^{-\Lambda_2(t)}$, where $\Lambda_j(t) = \int_0^t \lambda_j(u)\mathrm{d}u$ $(j = 1, 2)$. It follows that $F_1(t) = \int_0^t \mathrm{e}^{-\Lambda_1(u)}\mathrm{e}^{-\Lambda_2(u)}\,\mathrm{d}\Lambda_1(u) \leqslant \int_0^t \mathrm{e}^{-\Lambda_1(u)}\,\mathrm{d}\Lambda_1(u) = 1 - \mathrm{e}^{-\Lambda_1(t)} = 1 - G_1(t)$. The inequality is strict unless $\Lambda_2(t) = 0$. Thus, in the presence of non-recurrence death, the complement of the Kaplan–Meier estimator for PCP recurrence shown in Figure 1 will overestimate the cumulative probability of recurrence.

As mentioned earlier, logrank tests have also frequently been utilized in the competing risks setting. In the presence of non-recurrence death, the two-sample logrank test for PCP recurrence pertains to a comparison of the cause-specific hazard functions of PCP recurrence between the two groups. As can be seen from (1), a reduction in the cause-specific hazard function of PCP recurrence does not necessarily translate into a reduction in the cumulative incidence of PCP recurrence or a delay in the recurrence time. Therefore, it might be misleading to use the result from the logrank test to infer whether TS or AP is the more effective prophylaxis agent.

In the next section, we present estimators for the cumulative incidence functions. We will also describe the large-sample properties of these estimators and demonstrate how to construct simultaneous confidence bands for the cumulative incidence curve over the entire time span of interest. Furthermore, we will develop Kolmogorov–Smirnov type statistics for comparing two cumulative incidence curves. The proposed methods will be illustrated by the above AIDS study.

2. INFERENCE PROCEDURES

It is natural to estimate the cumulative incidence functions $F_j(t)$ given in (1) by

$$\hat{F}_j(t) = \int_0^t \hat{S}(u)\,\mathrm{d}\hat{\Lambda}_j(u), \quad j = 1, 2,$$

where $\hat{S}$ is the Kaplan–Meier estimator for S and $\hat{\Lambda}_j$ $(j = 1, 2)$ are the Nelson–Aalen estimators for Λ_j. For technical reasons, the left-continuous version of the Kaplan–Meier estimator is used.

Let $X_i = \min(T_i, C_i)$, where T_i and C_i are the failure time and censoring time for the ith patient. Also, let

$$\delta_i = \begin{cases} 1 & \text{if the } i\text{th patient has recurrence,} \\ 2 & \text{if the } i\text{th patient dies prior to recurrence,} \\ 0 & \text{if the } i\text{th patient is censored.} \end{cases}$$

The data may be represented by (X_i, δ_i) $(i = 1, \ldots, n)$. The Nelson–Aalen estimators are

$$\hat{\Lambda}_j(t) = \sum_{i=1}^{n} \frac{I(X_i \leqslant t, \delta_i = j)}{\sum_{l=1}^{n} I(X_l \geqslant X_i)}, \quad j = 1, 2,$$

where $I(\cdot)$ is the indicator function.

For theoretical developments, it is convenient to introduce the counting process-martingale formulation. Let $Y_i(t) = I(X_i \geqslant t)$, $N_{ji}(t) = I(X_i \leqslant t, \delta_i = j)$, and $M_{ji}(t) = N_{ji}(t) - \int_0^t Y_i(u)\lambda_j(u)\mathrm{d}u$. Also, let $\bar{Y}(t) = \sum_{i=1}^n Y_i(t)$, $\bar{N}_j(t) = \sum_{i=1}^n N_{ji}(t)$ and $\bar{M}_j(t) = \sum_{i=1}^n M_{ji}(t)$. In the counting process notation, the data (X_i, δ_i) $(i = 1, \ldots, n)$ are represented by $\{Y_i(\cdot), N_{ji}(\cdot)\}$ $(j = 1, 2; i = 1, \ldots, n)$. It can be shown that M_{ji} $(j = 1, 2; i = 1, \ldots, n)$ are orthogonal marginale.[6]

Define $W(t) = n^{1/2}\{\hat{F}_1(t) - F_1(t)\}$. We demonstrate in the Appendix that

$$W(t) = n^{1/2}\left[\int_0^t \frac{\{1 - F_2(u)\}^2\,\mathrm{d}\bar{M}_1(u)}{\bar{Y}(u)} + \int_0^t \frac{F_1(u)\,\mathrm{d}\bar{M}_2(u)}{\bar{Y}^2(u)} - \hat{F}_1(t)\int_0^t \frac{\mathrm{d}\bar{M}_1(u) + \mathrm{d}\bar{M}_2(u)}{\bar{Y}(u)}\right] + o_p(1). \tag{2}$$

By the martingale theory,[7] the process $W(t)$ converges weakly to a zero-mean Gaussian process; the limiting covariance function $\xi(t, s)$ $(t \leqslant s)$ can be consistently estimated by

$$\hat{\xi}(t_1, t_2) = n\left[\int_0^t \frac{\{1 - \hat{F}_2(u)\}^2\,\mathrm{d}\bar{N}_1(u)}{\bar{Y}^2(u)} + \int_0^t \frac{\hat{F}_1^2(u)\,\mathrm{d}\bar{N}_2(u)}{\bar{Y}^2(u)} + \hat{F}_1(t)\hat{F}_1(s)\int_0^t \frac{\mathrm{d}\bar{N}_1(u) + \mathrm{d}\bar{N}_2(u)}{\bar{Y}^2(u)} - \{\hat{F}_1(t) + \hat{F}_1(s)\}\int_0^t \frac{\{1 - \hat{F}_2(u)\}\,\mathrm{d}\bar{N}_1(u)}{\bar{Y}^2(u)} - \{\hat{F}_1(t) + \hat{F}_1(s)\}\int_0^t \frac{\hat{F}_1(u)\,\mathrm{d}\bar{N}_2(u)}{\bar{Y}^2(u)}\right]. \tag{3}$$

Given the above asymptotic results, one can easily make inference about F_1 at fixed time points. In order to make more general simultaneous inference about F_1, it is necessary to evaluate the distribution of $W(\cdot)$ as a process. For instance, to construct a $(1 - \alpha)$ simultaneous confidence band for F_1 over the time interval $[t_1, t_2]$, one needs to obtain the boundary value d which solves the equation

$$\Pr\left\{\sup_{t_1 \leqslant t \leqslant t_2} |W(t)| > d\right\} = \alpha.$$

Due to the complicated nature of the limiting covariance function ξ, the above probability function is intractable. We will instead employ a resampling technique to evaluate such functions.

By replacing $\bar{M}_j(\cdot)$ with $\sum_{i=1}^n G_{ji}N_{ji}(\cdot)$ $(j = 1, 2)$, where $G_{ji}(j = 1, 2; i = 1, \ldots, n)$ are independent standard normal variables, and also replacing other unknown quantities in (2) with their sample estimators, we obtain

$$\hat{W}(t) = n^{1/2}\sum_{i=1}^n \left[\int_0^t \frac{\{1 - \hat{F}_2(u)\}G_{1i}\,\mathrm{d}N_{1i}(u)}{\bar{Y}(u)} + \int_0^t \frac{\hat{F}_1(u)G_{2i}\,\mathrm{d}N_{2i}(u)}{\bar{Y}(u)} - \hat{F}_1(t)\int_0^t \frac{G_{1i}\,\mathrm{d}N_{1i}(u) + G_{2i}\,\mathrm{d}N_{2i}(u)}{\bar{Y}(u)}\right].$$

By a slight extension of the arguments of Lin *et al.*,[8] the conditional distribution of $\hat{W}(\cdot)$ given the data $\{Y_i(\cdot), N_{ji}(\cdot)\}$ $(j = 1, 2; i = 1, \ldots, n)$ is asymptotically equivalent to the (unconditinal) distribution of $W(\cdot)$. Hence, to approximate the distribution of $W(\cdot)$, we obtain a large number of realizations from $\hat{W}(\cdot)$ by repeatedly generating the normal random sample $\{G_{ji}\}$ $(j = 1, 2; i = 1, \ldots, n)$ while fixing the data $\{Y_i(\cdot), N_{ji}(\cdot)\}$ $(j = 1, 2; i = 1, \ldots, n)$ at their observed values.

Various types of confidence bands for F_1 can be developed by considering the following class of transformed processes:

$$B(t) = n^{1/2} g(t)\{\phi(\hat{F}_1(t)) - \phi(F_1(t))\},$$

where ϕ is a known function with non-zero continuous derivative ϕ' and g is a weight function which converges to a nonnegative bounded function. By the functional delta-method,[7] the process $B(t)$ is asymptotically equivalent to $g(t)\phi'(\hat{F}_1(t))W(t)$, the distribution of which can be approximated by $\hat{B}(t) = g(t)\phi'(\hat{F}_1(t))\hat{W}(t)$. Let q_α be the boundary value satisfying

$$\Pr\left\{\sup_{t_1 \leqslant t \leqslant t_2} |\hat{B}(t)| > q_\alpha\right\} = \alpha,$$

the probability being evaluated through simulation. Then an approximate $(1-\alpha)$ confidence band for $\phi(F_1(\cdot))$ is $\phi(\hat{F}_1(t)) \mp n^{-1/2} q_\alpha / g(t) (t_1 \leqslant t \leqslant t_2)$, which can be converted to a band for F_1.

We choose $\phi(x) = \log\{-\log(1-x)\}$, which is analogous to the log-log transformation for the Kaplan–Meier estimator.[2] This transformation not only ensures that the boundaries of the confidence bands for F_1 are contained in [0, 1], but also improves the coverage accuracy in small samples. We consider two weight functions: $g_1(t) = \log\{1-\hat{F}_1(t)\}/\hat{\sigma}(t)$ and $g_2(t) = \log\{1-\hat{F}_1(t)\}/\{1+\hat{\sigma}^2(t)\}$, where $\hat{\sigma}^2(t) = \hat{\xi}(t,t)/\{1-\hat{F}_1(t)\}^2$. The resulting bands for F_1 reduce, respectively, to the familiar equal-precision bands[9] and Hall–Wellner bands[10] (with the log-log transformation) for the distribution function of T if $\lambda_2(\cdot) = 0$. Due to these relationships, the confidence bands for F_1 corresponding to g_1 and g_2 will be referred to as the equal-precision and Hall–Wellner bands, respectively.

Because the asymptotic approximations tend to be poor at the left and right tails, we will restrict all our bands between the first and last observed recurrence times. The equal-precision bands will be further restricted to the time interval $[t_1^*, t_2^*]$ such that $\hat{c}_1 = 1 - \hat{c}_2 = 0{\cdot}01$, where $\hat{c}_k = \hat{\sigma}^2(t_k^*)/\{1+\hat{\sigma}^2(t_k^*)\}$ $(k = 1, 2)$. Similar restrictions have been found necessary for the usual distribution function.[8,9,11]

We now turn to the two-sample problem. Let $F_1^{(1)}$ and $F_1^{(2)}$ be the cumulative incidence functions of PCP recurrence for the TS and AP groups, respectively. We are interested in testing the null hypothesis $H_0: F_1^{(1)}(\cdot) = F_1^{(2)}(\cdot)$ and perhaps also in constructing a confidence band for $F_1^{(1)}(\cdot) - F_1^{(2)}(\cdot)$. For these purposes, we consider the following class of processes:

$$D(t) = K(t)[\{\hat{F}_1^{(1)}(t) - \hat{F}_1^{(2)}(t)\} - \{F_1^{(1)}(t) - F_1^{(2)}(t)\}],$$

where $\hat{F}_1^{(1)}$ and $\hat{F}_1^{(2)}$ are the estimators of $F_1^{(1)}$ and $F_1^{(2)}$, and K is a weight function. Assuming that the observations from the two groups are independent, one may use the resampling technique developed earlier to generate the approximate distributions of $\{\hat{F}_1^{(1)}(\cdot) - F_1^{(1)}(\cdot)\}$ and $\{\hat{F}_1^{(2)}(\cdot) - F_1^{(2)}(\cdot)\}$ and then evaluate the distribution of $D(\cdot)$. Note that $\{\hat{F}_1^{(1)}(t) - \hat{F}_1^{(2)}(t)\}$ converges to $\{F_1^{(1)}(t) - F_1^{(2)}(t)\}$, which will be non-zero for some t if H_0 does not hold. Hence, the use of the Kolmogorov–Smirnov type statistic

$$Q = \sup_t K(t) |\hat{F}_1^{(1)}(t) - \hat{F}_1^{(2)}(t)|$$

will yield an omnibus test, consistent against any alternatives under which $F_1^{(1)}(t) \neq F_1^{(2)}(t)$ for some t within the range of the data.

Table I. Empirical coverage probabilities of the 0·95 confidence bands for F_1

n	Equal-precision		Hall-Wellner	
	$c = 1$	$c = 2$	$c = 1$	$c = 2$
100	0·94	0·94	0·96	0·95
200	0·96	0·95	0·96	0·95

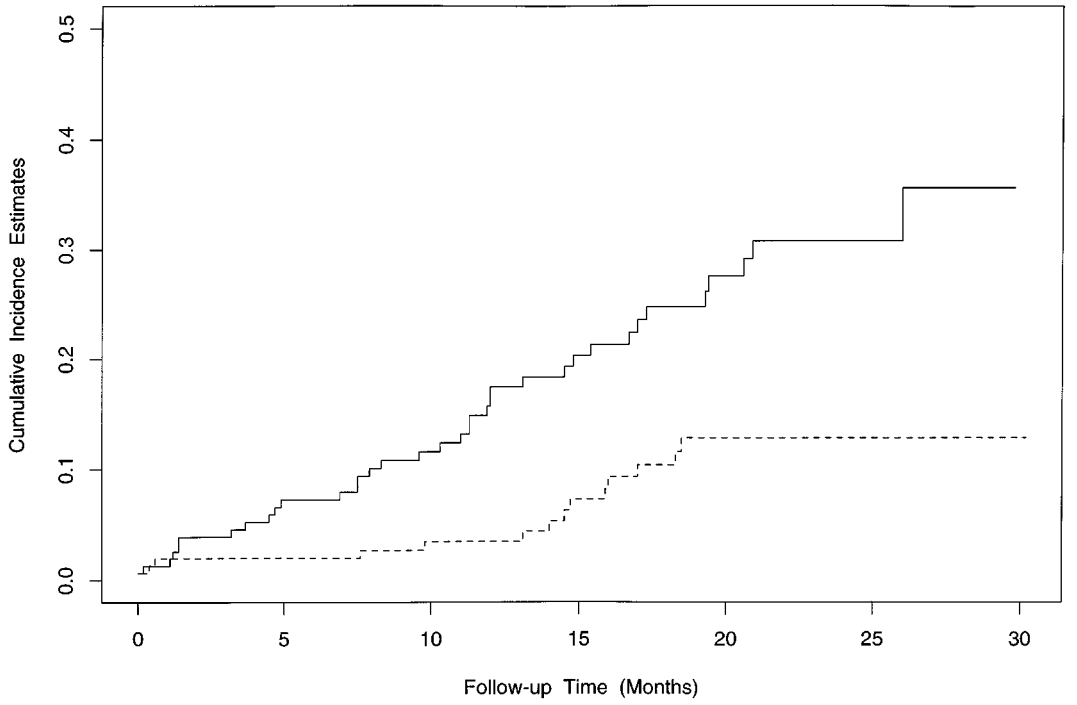

Figure 2. Cumulative incidence estimates for PCP recurrence in the AIDS study. The AP and TS groups are shown by the solid and dashed curves, respectively

Gray[6] and Pepe and Mori[4] have, respectively, proposed the following statistics for testing H_0:

$$\int K(t)[\{1-\hat{F}_1^{(1)}(t-)\}^{-1}\,\mathrm{d}\hat{F}_1^{(1)}(t)-\{1-\hat{F}_1^{(2)}(t-)\}^{-1}\,\mathrm{d}\hat{F}_1^{(2)}(t)],$$

$$\int K(t)\{\hat{F}_1^{(1)}(t)-\hat{F}_1^{(2)}(t)\}\,\mathrm{d}t.$$

Unlike the Kolmogorov–Smirnov type test Q, these two tests are not omnibus, but they may be more sensitive to some specific alternatives. It would be worthwhile to compare the three tests.

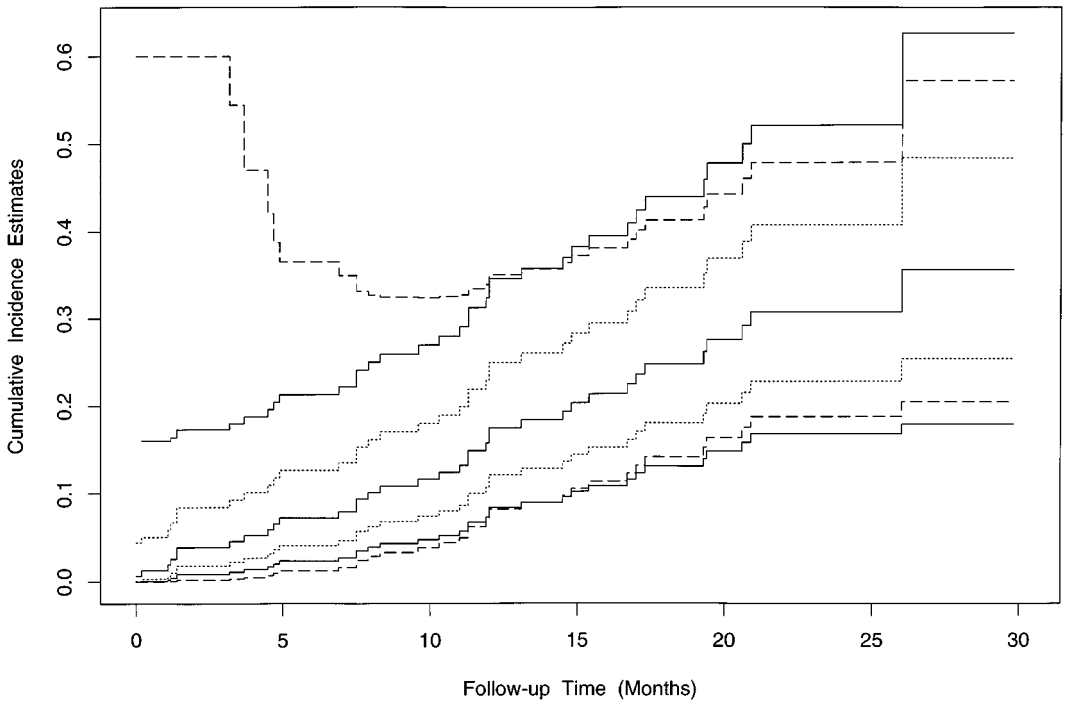

Figure 3. Confidence bands for the cumulative incidence of PCP recurrence in the AP group of the AIDS study. The pointwise estimate is shown by the middle solid curve, the pointwise 95 per cent confidence intervals by the dotted curves, the 95 per cent equal-precision band by the outside solid curves, and the 95 per cent Hall–Wellner band by the dashed curves

3. NUMERICAL RESULTS

3.1. Simulation studies

Simulation studies were conducted to assess how reliable the proposed resampling technique is in approximating the distribution of the ciumulative incidence function estimator for limited sample sizes. The focus was placed on the coverage accuracy of the one-sample confidence bands, but the two-sample procedures are expected to perform similarly. The failure times were generated using constant hazard rate of 1 for each of the two failure types, and censoring times from the uniform $(0, c)$ distribution, where $c = 1$ and 2 correspond to 43 per cent and 24 per cent censoring proportions, respectively. The sample sizes of 100 and 200 were considered. The empirical coverage probabilities of the confidence bands were estimated from 1000 simulation samples; for each simulated data set, the boundary value q_α was estimated from 1000 realizations of $\hat{B}(\cdot)$. The main results of these studies are summarized in Table I. Evidently, the proposed bands have accurate coverage probabilities.

3.2. The AIDS study

Figure 2 displays the estimated cumulative incidence curves for the AIDS study described in Section 1. As expected, these curves are lower than those of Figure 1. In particular, the proportions of patients who have experienced PCP recurrence by 24 months are estimated at 14·7

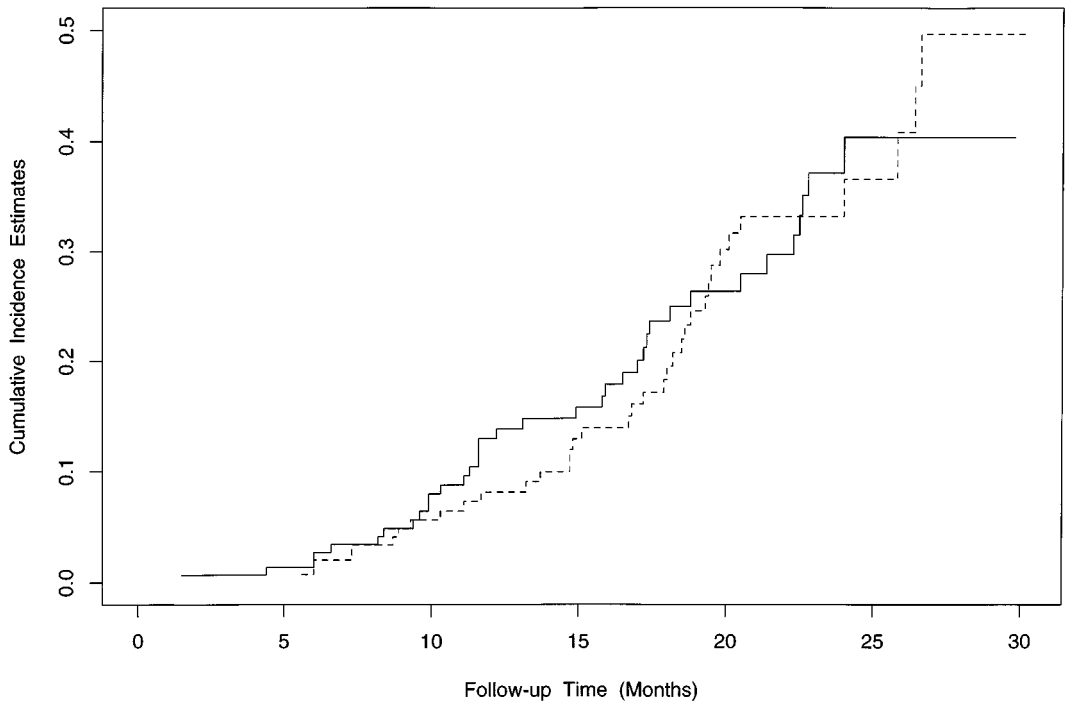

Figure 4. Cumulative incidence estimates for non-recurrence in the AIDS study. The AP and TS groups are shown by the solid and dashed curves, respectively

per cent and 36·1 per cent for the TS and AP groups, respectively, in Figure 1 and at 12·8 per cent and 30·7 per cent in Figure 2.

The confidence bands for PCP recurrence in the AP group are shown in Figure 3. Due to the small number of events, the bands are quite wide. The pointwise confidence intervals are much narrower than the equal-precision band. The Hall–Wellner band is outside the equal-precision band for the first 13 months but is narrower than the latter after 13 months.

The Kolmogorov–Smirnov test Q with $K(\cdot) = 1$ yields a p-value of approximately 0·0011 for comparing the cumulative incidence curves of PCP recurrence between the TS and AP groups. The p-value for the corresponding logrank test is about 0·0002, which is smaller. Because the ultimate goal of an intervention is to prolong life and because a low cumulative incidence of PCP recurrence might be caused by a high incidence of non-recurrence death, it is also important to compare the TS and AP groups with respect to non-recurrence death. The two cumulative incidence curves for non-recurrence death are shown in Figure 4. The p-value for the Q test with $K = 1$ is 0·675. Since the cumulative incidence of PCP recurrence was significantly lower in the TS group than in the AP group while no group difference was observed with respect to non-recurrence death, TS is preferable to AP for the prophylaxis of PCP.

4. DISCUSSION

In the competing risks setting, it has been customary to base the primary therapeutic comparison on the time to the first event that occurs to a patient. For the AIDS example, this corresponds to

recurrence-free survival. Since the main purpose of this study was to compare the efficacies of TS and AP agents for the prophylaxis of PCP, it would not be entirely satisfactory to examine recurrence-free survival only. In general, because different types of failure may not be of equal importance and because the differential effects of treatment may depend markedly on the type of failure, an analysis of time to first event may well be inadequate. Comparisons of the cumulative incidence for specific types of failure may provide additional information about the treatment differences.

The cumulative incidence functions can also be used to construct other useful probability functions for competing risks. For example, Pepe[12] and Pepe and Mori[4] advocated the use of the conditional probability function $P_1(t) = F_1(t)/\{1 - F_2(t)\}$, which is estimated by $\hat{P}_1(t) = \hat{F}_1(t)/\{1 - \hat{F}_2(t)\}$. It is straightforward to show that

$$\hat{P}_1(t) - P_1(t) = \frac{\hat{F}_1(t) - F_1(t)}{1 - F_2(t)} + \frac{F_1(t)\{\hat{F}_2(t) - F_2(t)\}}{\{1 - F_2(t)\}^2} + o_p(n^{-1/2}).$$

Thus, the resampling technique developed in Section 2 can be used to approximate the distribution of $\{\hat{P}_1(\cdot) - P_1(\cdot)\}$.

As mentioned in Section 1, the AIDS example used in this paper is somewhat different from the classical competing risks problem in that PCP recurrence does not preclude subsequent death. In fact, the patients were monitored closely for their other opportunistic infections and deaths after they had experienced the recurrences of PCP. By taking advantage of this special data structure, Lin *et al.*[13] recently developed a method for estimating the location difference between the two marginal distributions of time to PCP recurrence. On the natural logarithmic scale, the point estimate for the location difference between the TS and AP groups is 0·72 with an approximate 95 per cent confidence interval of (0.21, 2.05). The p-value for testing no group difference is 0·0042. The Lin *et al.* model postulates that there exists a latent time to PCP recurrence event for a subject who dies before PCP recurrence. By contrast, the cumulative incidence function is defined on observable quantities only and does not rely on latent variables for its interpretation.

APPENDIX:

Martingale Representation for $n^{1/2}\{\hat{F}_1(t) - F_1(t)\}$

Several authors[4,12,14,15] have studied the estimator $\hat{F}_1$ and related quantities. Here, we provide a martingale representation for $n^{1/2}\{\hat{F}_1(t) - F_1(t)\}$, which is crucial to the proposed resampling method. To this end, we make the following decomposition:

$$n^{1/2}\{\hat{F}_1(t) - F_1(t)\} = n^{1/2}\left\{\int_0^t \hat{S}(u)\,\mathrm{d}\hat{\Lambda}_1(u) - \int_0^t S(u)\,\mathrm{d}\Lambda_1(u)\right\}$$

$$= n^{1/2}\int_0^t \hat{S}(u)\,\mathrm{d}\{\hat{\Lambda}_1(u) - \Lambda_1(u)\} + n^{1/2}\int_0^t \{\hat{S}(u) - S(u)\}\,\mathrm{d}\Lambda_1(u) + o_p(1).$$

Due to the consistency of $\hat{S}(\cdot)$, the asymptotic equivalence of $\hat{S}(\cdot)$ and $\mathrm{e}^{-\hat{\Lambda}(\cdot)}$, where $\hat{\Lambda}(\cdot) = \hat{\Lambda}_1(\cdot) + \hat{\Lambda}_2(\cdot)$, and definition (1), we have

$$n^{1/2}\{\hat{F}_1(t) - F_1(t)\} = n^{1/2}\int_0^t S(u)\,\mathrm{d}\{\hat{\Lambda}_1(u) - \Lambda_1(u)\} - n^{1/2}\int_0^t \{\hat{\Lambda}(u) - \Lambda(u)\}\,\mathrm{d}F_1(u) + o_p(1).$$

Integrating by parts shows that the second term on the right side of the above equation is

$$n^{1/2}\{\hat{\Lambda}(t)-\Lambda(t)\}F_1(t)-n^{1/2}\int_0^t F_1(u)\,\mathrm{d}\{\hat{\Lambda}(u)-\Lambda(u)\}.$$

It is well-known that

$$n^{1/2}\{\hat{\Lambda}_j(t)-\Lambda_j(t)\}=n^{1/2}\int_0^t\frac{\mathrm{d}\bar{M}_j(u)}{\bar{Y}(u)}+o_p(1),\quad j=1,2.$$

Therefore,

$$\begin{aligned}n^{1/2}\{\hat{F}_1(t)-F_1(t)\}=n^{1/2}\int_0^t\frac{S(u)\,\mathrm{d}\bar{M}_1(u)}{\bar{Y}(u)}-n^{1/2}F_1(t)\int_0^t\frac{\mathrm{d}\bar{M}_1(u)+\mathrm{d}\bar{M}_2(u)}{\bar{Y}(u)}\\+n^{1/2}\int_0^t\frac{F_1(u)\{\mathrm{d}\bar{M}_1(u)+\mathrm{d}\bar{M}_2(u)\}}{\bar{Y}(u)}+o_p(1)\end{aligned}$$

which is equal to (2) since $S(t)=1-F_1(t)-F_2(t)$.

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