Original paper

The Mean of Lifespan under Dependent Competing Risks with Application to Mice Data

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Abstract

The aim of this article is to consider the property of the mean of the theoretical lifespan of an individual in the case where competing risks are not necessarily independent. We often encounter situations in which the lifespan of an individual dying from one cause may be correlated with that of the same individual dying from a different cause. Assuming that the underlying distribution is a bivariate Weibull, an estimator of the mean of lifespan and its asymptotic distribution can be derived. The test procedure concerning independence of competing risks is given, employing asymptotic distribution of a likelihood ratio statistic. As an alternative to the above test, we present a model selection approach based on an information criterion without use of the asymptotic theory. For a specified risk, we set forth a method to test the difference between the mean lifespan of dependent competing risks and that of independent ones. Then these findings are applied to the analysis of lifespan data of mice irradiated with X-rays. The resultant testing indicates that the theoretical mean lifespans related to some causes of death are significantly shortened due to the presence of dependent competing risks. A computational method for obtaining estimates of two scale parameters, two shape parameters and a correlated parameter is proposed.

Keywords. bivariate Weibull distribution, asymptotic distributions, estimator of mean, test of independence

1. Introduction

The theory of competing risks has recently been developed for analysis of lifespan data. It is often the case that the lifespan of individuals dying from a specified cause are influenced by other causes of death, known as competing risks. Associated with the *i*th cause of death, there is a nonnegative random variable representing the observed time to death if all causes except the *i*th are inoperative, i.e., the theoretical lifespan of an individual whose death is attributed only to the *i*th cause. In most of the contributions, as seen in the reviews by David and Moeschberger[2] and by Crowder[1], it is usually assumed that the causes of death operate independently so that the theoretical lifespan of an individual dying from a specified cause is independent of that of the same individual dying from a different cause. However one often encounters dependent causes of death in many situations. That is, the theoretical lifespan of an individual dying from a specified cause may be correlated with the theoretical lifespan of the same individual dying from a different cause.

In Section 2, we assume a family of bivariate Weibull distributions explored by Moeschberger[4] who extends the Marshall and Olkin idea[3] of multivariate exponential distribution. Using this as-

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sumption, we derive an estimator of the mean of theoretical lifespan of this model based on a maximum likelihood estimator (MLE) of the parameter vector. In Section 3, we describe a test procedure and a model selection approach based on the information criterion for checking the independence in the model. We also derive the asymptotic distribution of the estimator of the mean constructed in the previous section, by using the asymptotic distribution of MLE. In addition, we give test procedures for the difference between the mean lifespan of dependent competing risks and that of independent competing risks, by the use of Wald type test statistics, on the basis of the asymptotic theory developed. In Section 4, we apply these test procedures to sets of experimental data on radiation carcinogenesis realized through the lifelong breeding of female mice[5]. In the analysis, we check the dependence of the theoretical lifespan of a mouse dying from a specified cause and that from another cause. Also we investigate the mean lifespan shortening which results from the causes of death that are supposed to act dependently.

2. Estimation of the mean of theoretical lifespan

We recapitulate the likelihood function in the model mentioned in the Introduction, according to the notations given by Moeschberger[4]. Let Y_i $(i=1, 2)$ denote a nonnegative random variable standing for the theoretical lifespan of an individual dying from a particular cause of death C_i. In the simultaneous presence of both causes only the smallest of the Y_i's, the $\min_i Y_i$, is in fact observable with probability $\pi_l = P(Y_l = \min_i Y_i)$, together with the actual cause of death C_i $(i=1, 2)$. To establish the joint probability distribution of $Y=(Y_1, Y_2)'$, we adopt a Marshall-Olkin type bivariate Weibull distribution. Its survival function is expressed as

$$\begin{aligned}\bar{F}_{Y_1, Y_2}(y_1, y_2) &= P(Y_1 > y_1,\ Y_2 > y_2) \\ &= \exp\left[-\lambda_1 y_1^{c_2} - \lambda_2 y_2^{c_2} - \lambda_{12} \max\left(y_1^{c_1}, y_2^{c_2}\right)\right] \qquad (2.1)\end{aligned}$$

where $\theta=(\theta_1, \theta_2, \theta_3, \theta_4, \theta_5)' = (\lambda_1, c_1, \lambda_2, c_2, \lambda_{12})'$ denotes a parameter vector with $\lambda_s > 0$, $c_t > 0 (s = 1, 2 : t = 1, 2)$, $c_1 \neq c_2$ and $\lambda_{12} \geq 0$. Here the case in which $c_1 = c_2$ in (2.1) is not treated, since the model in this case may be reduced to that concerning an independent Weibull random variable with equal constants[4].

Referring to (2.1), we define the cumulative distribution function of y_i for $i(=1, 2)$,

$$F_{Y_i}(y_i) = 1 - \bar{F}_{Y_i}(y_i) = 1 - \exp\left\{-(\lambda_i + \lambda_{12}) y_i^{c_i}\right\}.$$

From which we have the probability density function

$$f_i(y_i) = \frac{dF_{Y_i}}{dy_i} = c_i(\lambda_i + \lambda_{12}) y_i^{c_i - 1} \exp\left\{-(\lambda_i + \lambda_{12}) y_i^{c_i}\right\}.$$

Therefore, the mean $\mu_i(\theta)$ of each theoretical lifespan Y_i is derived as

$$\begin{aligned}\mu_i(\theta) &= E[Y_i] = \int_0^\infty y_i \cdot f_i(y_i)\, dy_i \\ &= (\lambda_i + \lambda_{12})^{-1/c_i} \int_0^\infty u_i^{(c_i^{-1}+1)-1} \exp(-u_i)\, du_i \\ &= (\lambda_i + \lambda_{12})^{-1/c_i} \Gamma(c_i^{-1} + 1) \qquad (2.2)\end{aligned}$$

where a variable transformation for the integration $u_i = (\lambda_i + \lambda_{12}) y_i^{c_i}$ is performed and Γ stands for the gamma function.

Denoting the observable lifespan of the jth individual $(j=1, 2, \ldots, n)$ dying from C_i by X_{ij}, we have $X_{ij} = Y_i$ with $Y_i = \min_l Y_l$ for each j and assume that the probability $\pi_i = P(Y_i = \min_l Y_l)$ is positive with $\pi_1 + \pi_2 = 1$. Suppose that m_i individuals die from C_i. Also, let m_{i1} and m_{i2} denote the numbers of individuals dying from C_i in the interval [0, 1] and $(1, \infty)$, respectively. These time intervals will be referred to as interval 1 and interval 2, respectively. Let M_{ik} $(i=1, 2;\ k=1, 2)$ be random variables taking values m_{ik}. Also, let $X_{ij,k}$ denote the observed lifespan of the jth individual dying from C_i in the kth interval. The probability function of M_{ik}'s is expressed as a multinomial distribution with parameters $n = m_1 + m_2$ and $\pi_{11t}, \pi_{12t}, \pi_{21t}, \pi_{22t}$, i.e.,

$$f_{M_{11},M_{12},M_{21},M_{22}}(m_{11}, m_{12}, m_{21}, m_{22} \mid c_t > c_s)$$
$$= \begin{cases} \dfrac{n!}{m_{11}!m_{12}!m_{21}!m_{22}!}(\pi_{11t})^{m_{11}}(\pi_{12t})^{m_{12}}(\pi_{21t})^{m_{21}}(\pi_{22t})^{m_{22}} & 0 \le m_{ik} \le n, \\ 0 & \text{otherwise} \end{cases} \tag{2.3}$$

for $t=1, 2$; $s \neq t$, where $n = m_{11}+m_{12}+m_{21}+m_{22}$, $\pi_{11t} = P(Y_1 \le Y_2,\ 0 \le Y_1 \le 1 \mid c_t > c_s)$, $\pi_{12t} = P(Y_1 \le Y_2,\ 1 < Y_1 < \infty \mid c_t > c_s)$, $\pi_{21t} = P(Y_2 \le Y_1,\ 0 \le Y_2 \le 1 \mid c_t > c_s)$, and $\pi_{22t} = P(Y_2 \le Y_1,\ 1 < Y_2 < \infty \mid c_t > c_s)$.

With the notations described so far, we construct the explicit expression of the loglikelihood function subject to $c_2 > c_1$,

$$\begin{aligned} &\log L_n(\theta \mid c_2 > c_1) \\ &= \log \left\{ \frac{n!}{m_{11}!m_{12}!m_{21}!m_{22}!} \right\} + m_{11} \log (\lambda_1 + \lambda_{12}) + m_{12} \log \lambda_1 \\ &\quad + m_{21} \log \lambda_2 + m_{22} \log (\lambda_2 + \lambda_{12}) \\ &\quad + m_1 \log c_1 + m_2 \log c_2 + \sum_{i=1}^{2} (c_i - 1) \sum_{k=1}^{2} \sum_{j=1}^{m_{ik}} \log x_{ij,k} \\ &\quad - \sum_{j=1}^{m_{11}} [(\lambda_1 + \lambda_{12}) x_{1j,1}^{c_1} + \lambda_2 x_{1j,1}^{c_2}] - \sum_{j=1}^{m_{12}} [\lambda_1 x_{1j,2}^{c_1} + (\lambda_2 + \lambda_{12}) x_{1j,2}^{c_2}] \\ &\quad - \sum_{j=1}^{m_{21}} [(\lambda_1 + \lambda_{12}) x_{2j,1}^{c_1} + \lambda_2 x_{2j,1}^{c_2}] - \sum_{j=1}^{m_{22}} [\lambda_1 x_{2j,2}^{c_1} + (\lambda_2 + \lambda_{12}) x_{2j,2}^{c_2}]. \end{aligned} \tag{2.4}$$

The loglikelihood function subject to $c_1 > c_2$ is similarly expressed. We can consider an MLE, $\hat{\theta} = (\hat{\theta}_1, \hat{\theta}_2, \hat{\theta}_3, \hat{\theta}_4, \hat{\theta}_5)' = (\hat{\lambda}_1, \hat{c}_1, \hat{\lambda}_2, \hat{c}_2, \hat{\lambda}_{12})'$ of the parameter θ whose value is selected from $\hat{\theta}^{(t)}$ as the one realizing the max $[\log L_n(\hat{\theta}^{(t)} \mid c_t > c_s;\ s, t = 1, 2,\ s \neq t]$. Here each $\theta^{(t)} (t = 1, 2)$ denotes an MLE of θ subject to a constraint $c_t > c_s$, i.e., an estimator satisfying

$$\log L_n(\hat{\theta}^{(t)} \mid c_t > c_s) = \sup_{\theta} \{\log L_n(\theta \mid c_t > c_s)\}, \tag{2.5}$$

in (2.4). For brevity's sake, expressions such as "$\mid c_t > c_s$" or "$\mid c_{t'} > c_{s'}$" will be omitted hereafter.

By use of an MLE $\hat{\theta}$, we obtain an estimator of the mean $\mu_i(\theta)$ in (2.2),

$$\hat{\mu}_i = \mu_i(\hat{\theta}) = (\hat{\lambda}_i + \hat{\lambda}_{12})^{-1/\hat{c}_i} \Gamma(\hat{c}_i^{-1} + 1) \quad (i = 1, 2). \tag{2.6}$$

3. Asymptotic distributions for hypothetical testing

We first deal with a problem for a composite hypothesis,

$$\mathrm{H}_0 : \lambda_{12} = 0 \text{ against } \mathrm{H}_1 : \lambda_{12} > 0, \tag{3.1}$$

which checks the independence of competing risks. For the hypothesis, we construct a likelihood ratio statistic $\lambda^{(t)}$ as

$$\lambda^{(t)} = -2 \log \Lambda^{(t)} = -2 \log \left[\frac{\sup \{L_n(\theta) : \mathrm{H}_0)\}}{\sup \{L_n(\theta)\}} \right]. \tag{3.2}$$

This leads to the following theorem:

Theorem 3.1 *Under the null hypothesis H_0, the statistic $\lambda^{(t)}$ has an asymptotic central chi-square distribution with one degree of freedom $\chi_1^2(0)$ as $n \to \infty$.*

The null hypothesis H_0 is rejected at the α level of significance if $\hat{\lambda}^{(t)} > \chi_{1,\alpha}^2(0)$.

As an alternative to the asymptotic test, we may perform a model selection approach based on the Schwarz information criterion (SIC). The criterion is defined as $\mathrm{SIC} = -2 \log L(\hat{\theta}) + p \log n$, where p is the number of parameters in the model. In this setting we assume two models corresponding to $\mathrm{H}_0 : \lambda_{12} = 0$ and $\mathrm{H}_1 : \lambda_{12} > 0$. The null hypothesis H_0 is rejected if the following inequality holds:

$$d_1 \equiv -2\{\log L(\hat{\theta}^0) - \log L(\hat{\theta}^+)\} > \log n, \tag{3.3}$$

where $\hat{\theta}^+$ and $\hat{\theta}^0$ are parameter vectors of dependent ($p = 5$) and of independent ($p = 4$) competing

risks, respectively.

Since each sequence $n^{-1}I_n(\boldsymbol{\theta})=n^{-1}E\{[\nabla_\theta \log L_n(\boldsymbol{\theta})][\nabla_\theta \log L_n(\boldsymbol{\theta})]'\}$ converges to a positive definite matrix $I(\boldsymbol{\theta})$, the MLE $\hat{\boldsymbol{\theta}}^{(t)}$ follows asymptotic penta-variate normal distribution, namely,

$\sqrt{n}\,(\hat{\boldsymbol{\theta}}^{(t)}-\boldsymbol{\theta})\sim N_5(\mathbf{0}\,\vdots\, I(\boldsymbol{\theta}))\quad (n\to\infty)$.

To find the asymptotic distribution of the estimator $\hat{\boldsymbol{\mu}}^{(t)}$ of the mean vector $\boldsymbol{\mu}(\boldsymbol{\theta})=(\mu_1(\boldsymbol{\theta}), \mu_2(\boldsymbol{\theta}))'$, we write

$$[D(\boldsymbol{\theta})]'=\begin{pmatrix}[\nabla_\theta(\mu_1(\boldsymbol{\theta}))]'\\ [\nabla_\theta(\mu_2(\boldsymbol{\theta}))]'\end{pmatrix}=\begin{pmatrix}\dfrac{\partial\mu_1(\boldsymbol{\theta})}{\partial\theta_1} & \dfrac{\partial\mu_1(\boldsymbol{\theta})}{\partial\theta_2} & \cdots & \dfrac{\partial\mu_1(\boldsymbol{\theta})}{\partial\theta_5}\\ \dfrac{\partial\mu_2(\boldsymbol{\theta})}{\partial\theta_1} & \dfrac{\partial\mu_2(\boldsymbol{\theta})}{\partial\theta_2} & \cdots & \dfrac{\partial\mu_2(\boldsymbol{\theta})}{\partial\theta_5}\end{pmatrix}.$$

Thus the estimator $\hat{\boldsymbol{\mu}}^{(t)}$ of the mean vector $\boldsymbol{\mu}(\boldsymbol{\theta})$ for each $t(=1, 2)$ has an asymptotic bivariate normal distribution,

$$\sqrt{n}\,(\boldsymbol{\mu}^{(t)}-\boldsymbol{\mu})\sim N_2((0, [D(\boldsymbol{\theta})]'[I(\boldsymbol{\theta})]^{-1}D(\boldsymbol{\theta}))\quad (n\to\infty). \tag{3.4}$$

We now set a hypothesis,

$$H_0:\boldsymbol{\mu}_1(\boldsymbol{\theta}_1)-\boldsymbol{\mu}_2(\boldsymbol{\theta}_2)=\mathbf{0} \text{ against } H_1:\boldsymbol{\mu}_1(\boldsymbol{\theta}_1)-\boldsymbol{\mu}_2(\boldsymbol{\theta}_2)\neq\mathbf{0} \tag{3.5}$$

which concerns the difference between the mean lifespan of dependent competing risks $\boldsymbol{\mu}_1(\boldsymbol{\theta}_1)=(\mu_{11}(\boldsymbol{\theta}_1), \mu_{12}(\boldsymbol{\theta}_1))'$ and that of independent ones $\boldsymbol{\mu}_2(\boldsymbol{\theta}_2)=(\mu_{21}(\boldsymbol{\theta}_2), \mu_{22}(\boldsymbol{\theta}_2))'$, where

$\mu_{1i}(\boldsymbol{\theta}_1)=(\lambda_{1i}+\lambda_{112})^{-1/c_{1i}}\Gamma(c_{1i}^{-1}+1)$,

$\mu_{2i}(\boldsymbol{\theta}_2)=(\lambda_{2i}+\lambda_{212})^{-1/c_{2i}}\Gamma(c_{2i}^{-1}+1)$, $(i=1, 2)$.

To test this hypothesis, defining for each $c_{1t}>c_{1s}$, $c_{2t'}>c_{2s'}$

$$Q^{(t,t')}(\boldsymbol{\theta})=[D(\boldsymbol{\theta}_1)]'[nI(\boldsymbol{\theta}_1)]^{-1}D(\boldsymbol{\theta}_1)+[D(\boldsymbol{\theta}_2)]'[nI(\boldsymbol{\theta}_2)]^{-1}D(\boldsymbol{\theta}_2), \tag{3.6}$$

we construct a Wald type test statistic for each t and t'

$$W^{(t,t')}=(\hat{\boldsymbol{\mu}}_1^{(t)}-\hat{\boldsymbol{\mu}}_2^{(t')})'[Q(\hat{\boldsymbol{\theta}})]^{-1}(\hat{\boldsymbol{\mu}}_1^{(t)}-\hat{\boldsymbol{\mu}}_2^{(t')}), \tag{3.7}$$

where $\hat{\boldsymbol{\mu}}_1^{(t)}$ and $\hat{\boldsymbol{\mu}}_2^{(t')}$ are MLE's subject to $c_{1t}>c_{1s}$, $c_{2t'}>c_{2s'}$, respectively. Then we derive the following theorem:

Theorem 3.2 *Under the null hypothesis H_0, the statistic $W^{(t,t')}$ has an asymptotic central chi-square distribution with two degrees of freedom $\chi_2^2(0)$, namely $W^{(t,t')}\xrightarrow{d}x_2^2(0)$ $(n\to\infty)$.*

Using this theorem, we can determine an asymptotic critical region of H_0 against H_1. Accordingly, H_0 is rejected if $\hat{W}^{(t,t')}>x_{2,\alpha}^2(0)$.

4. Application to analysis of experimental data on radiation carcinogenesis

The sets of data used here are provided from an experiment described in detail in Sato et al.[5]. We take a set of lifespans of $115(=n)$ ddY female mice whose whole bodies were irradiated with X-rays, 600R. These data sets were obtained through the lifelong breeding of the female mice and hence without censoring. As a specified risk C_i assumed to be the only risk present, each of the following diseases was observed: (1)Malignant lymphoma (MLL), (2)Tumor (TMR), (3)Inflammatory diseases (INF) and (4)Others (OTH). The experimenters[5] indicated that Weibull distributions fitted these data sets well for every specified risk, showing that linearities were observed in the sets of cumulative mortality ratio plots on Weibull probability paper.

In Table 1 we observe that for each specified risk C_i the number m_{11} of mice whose observed lifespans are in the interval 1 (in which each observed lifespan $\leq$470 days) and the number m_{12} of mice whose observed lifespans are in the interval 2 (in which each observed lifespan $>$470 days) and the total $m_1=m_{11}+m_{12}$.

Also we see the numbers m_{21} and m_{22}, representing those dying from other risks (ANH) than the specified risk, whose observed lifespans are in the interval 1 and in the interval 2, respectively. The total $m_2=m_{21}+m_{22}$. The constant $\alpha=470$ is taken as a value approximately representing the medi-

Table 1 The numbers m_{11} and m_{12} represent the numbers of mice dying from each specified risk. The observed lifespans are ≤ 470 (interval 1) and >470 (interval 2), respectively. The numbers m_{21} and m_{22} represent the numbers of mice dying from other risks. The observed lifespans are ≤ 470 (interval 1) and >470 (interval 2), respectively.

Lifespan	No. of mice	(1)		(2)		(3)		(4)	
		$i=1$ MLL	$i=2$ ANH	$i=1$ TMR	$i=2$ ANH	$i=1$ INF	$i=2$ ANH	$i=1$ OTH	$i=2$ ANH
≤ 470	m_{i1}	37	50	21	66	25	62	4	83
>470	m_{i2}	5	23	15	13	7	21	1	27
(total)	m_i	42	73	36	79	32	83	5	110

Table 2 MLE's of the parameters when the theoretical lifespans are assumed to be independent and dependent.

Assumption	Estimate	Specified risk			
		MLL	TMR	INF	OTH
Independent	$\hat{\lambda}_1$	0.05540	0.10075	0.12566	0.05812
	$\hat{c}_1$	4.21677	4.01752	3.49185	2.33381
	$\hat{\lambda}_2$	0.28865	0.24325	0.21874	0.28218
	$\hat{c}_2$	3.49490	3.44574	3.70410	3.84411
Dependent	$\hat{\lambda}_1$	0.45461	0.35236	0.36699	0.06001
	$\hat{c}_1$	2.14629	3.36685	2.39783	2.07128
	$\hat{\lambda}_2$	0.72490	0.85076	0.84422	1.30696
	$\hat{c}_2$	2.84478	2.20271	2.68280	2.32723
	$\hat{\lambda}_{12}$	0.19745	0.17466	0.24197	0.07081

an of the ranges of the observed lifespans of mice.

Considering the circumstance appearing in Table 1, we take a linear transformation $Y_i = Z_i/\alpha (i = 1, 2)$, where Z_i denotes a theoretical lifespan of a mouse dying from a specified risk C_i, assumed to be the only risk present. Also Y_i denotes a theoretical lifespan and $\boldsymbol{Y} = (Y_1, Y_2)'$ is assumed to be a random vector corresponding to the Weibull model described in Section 2. Through the above transformation, $\boldsymbol{Z} = (Z_1, Z_2)'$ follows the model consisting of a bivariate Weibull distribution.

The computational method for obtaining values of the MLE $\hat{\boldsymbol{\theta}}$ with respect to a specified risk, say MLL, falls into two stages:

I. Assuming that Z_1 and Z_2 are independent, calculate the following values by the Newton–Raphson method,
   1) estimates $\hat{\lambda}_1^{(0)}$ and $\hat{c}_1^{(0)}$ of parameters λ_1 and c_1 concerning the specified risk MLL.
   2) estimates $\hat{\lambda}_2^{(0)}$ and $\hat{c}_2^{(0)}$ of parameters λ_2 and c_2 for the specified risks TMR, INF and OTH together.

II. Calculate estimates of parameters including λ_{12} by means of Monte Carlo simulation, using the following steps:
   1) create random numbers u_i $(i = 1, 2, \ldots, 5)$ generated from a standard normal distribution.
   2) let
   $\hat{\lambda}_1 = \hat{\lambda}_1^{(0)}(1 + 0.1u_1)$, $\hat{c}_1 = \hat{c}_1^{(0)}(1 + 0.1u_2)$,
   $\hat{\lambda}_2 = \hat{\lambda}_2^{(0)}(1 + 0.1u_3)$, $\hat{c}_2 = \hat{c}_2^{(0)}(1 + 0.1u_4)$, $\hat{\lambda}_{12} = 0.2|u_5|$

Table 3　Approximate values of the likelihood ratio statistic $\hat{\lambda}^{(t)}$, the asymptotic significance probability p for the test of independence, and an estimate of the probability $\hat{\rho}$ of dependence between the specified risk and other risks.

Approximate values	Specified risk			
	MLL	TMR	INF	OTH
$\hat{\lambda}^{(t)}$	10.9701	1.89228	17.1730	4.07367
p	0.00093	0.16895	0.00003	0.04356
$\hat{\rho}$	0.14339	0.12677	0.16651	0.04925

Table 4　Estimates of the means of theoretical lifespans $\hat{\mu}_{11}$, $\hat{\mu}_{12}$ and $\hat{\mu}_{21}$, $\hat{\mu}_{22}$ when competing risks are assumed to be independent and dependent, respectively. In the bottom two rows, approximate values of the Wald type test statistics $\hat{W}^{(t,t')}$ and their significance probability p regarding MLL and INF are shown.

	Estimate	Specified risk			
		MLL	TMR	INF	OTH
Independent	$\hat{\mu}_{11}$	563.976	526.758	566.465	1375.24
	$\hat{\mu}_{12}$	437.604	421.642	415.305	379.624
Dependent	$\hat{\mu}_{21}$	502.345	—	506.073	—
	$\hat{\mu}_{22}$	436.671	—	414.844	—
For Test	$\hat{W}^{(t,t')}$	21.0889	—	20.1102	—
	p	0.00003	—	0.00004	—

3)　compute the value of

$$\log L_n = \begin{cases} \log L_n(\hat{\theta} \mid c_2 > c_1) \text{ if } \hat{c}_2 > \hat{c}_1 \\ \log L_n(\hat{\theta} \mid c_1 > c_2) \text{ if } \hat{c}_1 > \hat{c}_2 \end{cases}$$

4)　go back to step 1) of stage II until $\log L_n$ attains local maximum giving $\hat{\theta} = (\hat{\lambda}_1, \hat{c}_1, \hat{\lambda}_2, \hat{c}_2, \hat{\lambda}_{12})'$.

The performance of stage I results in Table 2, in which estimates of the MLE $\hat{\theta}$ are listed when $\lambda_{12} = 0$, namely, the independence between Z_1 and Z_2 is assumed for each specified risk C_i.

After carrying out stage II, we obtain estimates of the MLE $\hat{\theta}$ for each specified risk C_i under $\lambda_{12} > 0$, also shown in Table 2.

In order to test (3.1), Table 3 displays a value of likelihood ratio statistic $\lambda^{(t)}$ in Theorem 3.1 and its asymptotic significance probability p for each specified risk C_i.

To decide whether H_0 should be rejected or not from SIC viewpoint, we calculate a value of d_1 for each C_i to which the value of $\log n = \log 115 = 4.74493$ in the right-hand side of (3.3) is compared. We here remark that d_1 is identical to $\lambda^{(t)}$ stated above, so that the value is not listed again in Table 3.

Although the correlation of Z_1 and Z_2 cannot be explicitely expressed, the probability ρ of the dependence between Z_1 and Z_2 is proposed[4] as $\rho = P(Z_1^{c_1} = Z_2^{c_2}) = \lambda_{12}(\lambda_1 + \lambda_2 + \lambda_{12})^{-1}$. The values $\hat{\rho}$ are given in Table 3.

From Table 3, we may conclude that the null hypothesis $H_0 : \lambda_{12} = 0$ is rejected in the case where

the specifed risk C_i is MLL or INF.

We yield an estimate $\hat{\boldsymbol{\mu}}^*$ of the mean vector $\boldsymbol{\mu}^*$ of $\boldsymbol{Z}$ for each specified risk C_i under independent competing risks by substituting the values in Table 2 into (2.6) with $\hat{\lambda}_{12}=0$. In similar fashion, we can obtain estimates $\hat{\boldsymbol{\mu}}^*$ for MLL or INF, in both of which cases the dependences are admitted by the previous tests. Values with respect to the mean lifespans are listed in Table 4.

In order to test the hypothesis,

$H_0 : \boldsymbol{\mu}_1{}^* - \boldsymbol{\mu}_2{}^* = \mathbf{0}$ against $H_1 : \boldsymbol{\mu}_1{}^* - \boldsymbol{\mu}_2{}^* \neq \mathbf{0}$,

we use a Wald type test statistic $W^{(t,\,t')}$ given by (3.7). Table 4 also shows the value of $W^{(t,\,t')}$ and its asymptotic significance probability. Thus the null hypothesis H_0 is rejected for MLL and INF. This suggests that the theoretical mean lifespan of a mouse dying from malignant lymphoma or inflammatory diseases is significantly different and shortened due to the presence of dependent competing risks.

Acknowledgements

This research was partially supported by Juntendo University, under joint research grant number 3(2001). Thanks are due to the anonymous referees for their helpful suggestions.

References

1) Crowder, M. J. (2001) *Classical Competing Risks*. London: Chapman and Hall.
2) David, H. A. and Moeschberger, M. L. (1978) *The Theory of Competing Classical Risks*. London: Charles Griffin.
3) Marshall, A. W. and Olkin, I. (1967) A multivariate exponential distribution, *J. Amer. Statist. Assoc*. 62, 30–44.
4) Moeschberger, M. L. (1974) Life tests under dependent competing causes of failure. *Technometrics* 16, 39–47.
5) Sato, F., Noda, K., Kato, H., Murakami, M., Endo, D. and Hashimoto, N. (1990) An analysis of experimental radiation carcinogenesis with model setting for competing risks, *J. Radiat. Res*., 31, 147–155.

（平成14年11月30日 受付
平成15年 1 月22日 受理）