Original paper

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

Tairai MINO*, Naoko YOSHIKAWA**, Katsuhiko SUZUKI***
Yataro HORIKAWA**** and Yu ABE*****

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 non-negative 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 Moeschberger2) and by Crowder1), 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 Moeschberger4) who extends the Marshall and Olkin idea3) of multivariate exponential distribution. Using this as-
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 \( Y_i \), is in fact observable with probability \( \pi_i = P(Y_i = \min Y_i) \), 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

\[
\tilde{F}_{Y_i}(y_i) = P(Y_i > y_i) = 1 - \exp \{ - \lambda_1 y_i^{\gamma_1} - \lambda_2 y_i^{\gamma_2} - \lambda_{12} \max (y_{1i}^{\gamma_1}, y_{2i}^{\gamma_2}) \}
\]

(2.1)

where \( \theta = (\theta_1, \theta_2, \theta_3, \theta_4, \theta_5)' = (\lambda_1, \beta_1, \beta_2, \beta_3, \lambda_{12})' \) denotes a parameter vector with \( \beta > 0, \beta > 0 (s = 1, 2 : t = 1, 2) \), \( c_1 \neq c_2 \) 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 \( j = 1, 2 \),

\[
F_{Y_i}(y_i) = 1 - \tilde{F}_{Y_i}(y_i) = 1 - \exp \{ - (\lambda_1 + \lambda_{12}) y_i^{\gamma_2} \}.
\]

From which we have the probability density function

\[
\phi_i(y_i) = \frac{dF_{Y_i}}{dy_i} = c_1 (\lambda_1 + \lambda_{12}) y_i^{\gamma_2 - 1} \exp \{ - (\lambda_1 + \lambda_{12}) y_i^{\gamma_2} \}.
\]

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

\[
\mu(\theta) = E[Y_i] = \int_0^\infty y_i \phi_i(y_i) dy_i
\]

\[
= (\lambda_1 + \lambda_{12})^{-1/\gamma_2} \int_0^\infty u_i^{\gamma_2 + 1} \exp (-u_i) du_i
\]

\[
= (\lambda_1 + \lambda_{12})^{-1/\gamma_2} \Gamma(\gamma_2 + 1) \quad \text{(2.2)}
\]

where a variable transformation for the integration \( u_i = \frac{y_i}{\lambda_1 + \lambda_{12}} \) is performed and \( \Gamma \) stands for the gamma function.

Denoting the observable lifespan of the \( j \)th individual \( (j = 1, 2, \ldots, n) \) dying from \( C_j \) by \( X_{ij} \), we have \( X_{ij} = Y_i \) with \( Y_i = \min Y_i \) for each \( j \) and assume that the probability \( \pi_j = P(Y_i = \min Y_i) \) is positive with \( \pi_1 + \pi_2 = 1 \). Suppose that \( m_1 \) individuals die from \( C_1 \). Also, let \( m_{11} \) and \( m_{12} \) denote the numbers of individuals dying from \( C_1 \) 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 \( X_{ik} \) denote the observed lifespan of the \( j \)th individual dying from \( C_1 \) in the \( k \)th interval. The probability function of \( M_{ik} \)'s is expressed as a multinomial distribution with parameters \( n = m_1 + m_2 \) and \( \pi_{11n}, \pi_{12n}, \pi_{21n}, \pi_{22n} \).
\[ f_{M_1, M_2, M_3}(m_{11}, m_{12}, m_{21}, m_{22} | c_1 > c_3) = \begin{cases} 
!m_{11}!m_{12}!m_{21}!m_{22}! (\pi_{11})^{m_{11}}(\pi_{12})^{m_{12}}(\pi_{21})^{m_{21}}(\pi_{22})^{m_{22}} & 0 \leq m_{it} \leq n, \\
0 & \text{otherwise} \end{cases} \]

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

With the notations described so far, we construct the explicit expression of the loglikelihood function subject to \( c_3 > c_1, \)

\[
\log L_n(\theta | c_2 > c_1) = \log \left( \frac{n!}{m_{11}!m_{12}!m_{21}!m_{22}!} \right) + m_{11} \log (\lambda_1 + \lambda_{12}) + m_{12} \log \lambda_1 \\
+ m_{21} \log \lambda_2 + m_{22} \log (\lambda_2 + \lambda_{12}) \\
+ m_1 \log c_1 + m_2 \log c_2 \sum_{i=1}^2 (c_i - 1) \sum_{j=1}^{m_i} x_{ij,k} \\
- \sum_{j=1}^{m_{11}} [(\lambda_1 + \lambda_{12})x_{1i,j} + \lambda_2 x_{1i,j}] - \sum_{j=1}^{m_{12}} [(\lambda_1 + \lambda_{12})x_{2i,j} + (\lambda_2 + \lambda_{12})x_{2i,j}] \\
- \sum_{j=1}^{m_{21}} [(\lambda_1 + \lambda_{12})x_{3i,j} + \lambda_2 x_{3i,j}] - \sum_{j=1}^{m_{22}} [(\lambda_1 + \lambda_{12})x_{4i,j} + (\lambda_2 + \lambda_{12})x_{4i,j}].
\]

(2.4)

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

\[
\log L_n(\hat{\theta}' | c_i > c_s) = \sup_{\theta} \{ \log L_n(\theta | c_i > c_s) \},
\]

(2.5)
in (2.4). For brevity’s sake, expressions such as “\( c_i > c_s \)” or “\( c_i > c_s \)” will be omitted hereafter.

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

\[
\hat{\mu} = \mu(\hat{\theta}) = (\hat{\lambda}_1 + \hat{\lambda}_{12})^{-1} / (\hat{\lambda}_1 + \hat{\lambda}_{12}) + 1 (i = 1, 2).
\]

(2.6)

3. Asymptotic distributions for hypothetical testing

We first deal with a problem for a composite hypothesis,

\[
H_0 : \lambda_{12} = 0 \quad \text{against} \quad H_1 : \lambda_{12} > 0,
\]

(3.1)

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

\[
\lambda^{(i)} = -2 \log A^{(i)} = -2 \log \left[ \frac{\sup \{ L_n(\hat{\theta} | H_0) \}}{\sup \{ L_n(\theta) \}} \right].
\]

(3.2)

This leads to the following theorem:

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

The null hypothesis \( H_0 \) is rejected at the \( \alpha \) level of significance if \( \hat{\lambda}^{(i)} > \chi^2_{1, \alpha}(0) \).

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 \( \text{SIC} = -2 \log L(\hat{\theta}) + p \log n \), where \( p \) is the number of parameters in the model. In this setting we assume two models corresponding to \( H_0 : \lambda_{12} = 0 \) and \( H_1 : \lambda_{12} > 0 \). The null hypothesis \( H_0 \) is rejected if the following inequality holds:

\[
d_1 = -2 \{ \log L(\hat{\theta}) - \log L(\hat{\theta}^+) \} > \log n,
\]

(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 $n^{-1}I_n(\theta) = n^{-1}E[(\nabla_{\theta} \log L_n(\theta))[\nabla_{\theta} \log L_n(\theta)]']$ converges to a positive definite matrix $I(\theta)$, the MLE $\hat{\theta}(t)$ follows asymptotic penta-variate normal distribution, namely, $\sqrt{\frac{n}{n}}(\hat{\theta}(t) - \theta) \sim N_5(0 : I(\theta)) (n \to \infty)$.

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

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

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

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

We now set a hypothesis,

$$H_0 : \mu_1(\theta_1) - \mu_2(\theta_2) = 0$$
$$H_1 : \mu_1(\theta_1) - \mu_2(\theta_2) \neq 0$$

which concerns the difference between the mean lifespan of dependent competing risks $\mu(\theta) = (\mu_{11}(\theta), \mu_{21}(\theta), \mu_{22}(\theta))'$ and that of independent ones $\mu(\theta) = (\mu_{12}(\theta), \mu_{22}(\theta))'$, where $\mu_{11}(\theta) = (\lambda_{11} + \lambda_{12})^{-1/2} c_{11} \Gamma(c_{11}^{-1} + 1), \mu_{21}(\theta) = (\lambda_{21} + \lambda_{22})^{-1/2} c_{21} \Gamma(c_{21}^{-1} + 1), (i = 1, 2)$.

To test this hypothesis, defining for each $c_{1i} > c_{1s}, c_{2i} > c_{2s}$

$$Q^{(i, t)}(\theta) = [D(\theta)]' [n I(\theta)]^{-1} D(\theta) + [D(\theta)]' [n I(\theta)]^{-1} D(\theta),$$

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

$$W^{(t, t')} = (\hat{\mu}_{1(t')}(t) - \hat{\mu}_{2(t')}(t)) [Q(\theta)]^{-1} (\mu_{1(t')} - \mu_{2(t')}),$$

where $\hat{\mu}_{1(t)}$ and $\hat{\mu}_{2(t)}$ are MLE’s subject to $c_{1i} > c_{1s}, c_{2i} > c_{2s}$, 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 $W^{(t, t') \sim} \chi^2_2(0) \quad (n \to \infty)$.

Using this theorem, we can determine an asymptotic critical region of $H_0$ against $H_1$. Accordingly, $H_0$ is rejected if $W^{(t, t')} > \chi^2_2(0)$.

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 mouse and hence without censoring. As a specified risk $C$ 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 experimenters5) 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 $m_{i1}$ of mice whose observed lifespans are in the interval 1 (in which each observed lifespan $\leq 470$ days) and the number $m_{i2}$ of mice whose observed lifespans are in the interval 2 (in which each observed lifespan $> 470$ days) and the total $m_t = m_{i1} + m_{i2}$.

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 $\leq 470$ (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 $\leq 470$ (interval 1) and $> 470$ (interval 2), respectively.

<table>
<thead>
<tr>
<th>Lifespan</th>
<th>No. of mice</th>
<th>(1) $i=1$</th>
<th>ANH</th>
<th>$i=2$</th>
<th>ANH</th>
<th>(2) $i=1$</th>
<th>ANH</th>
<th>$i=2$</th>
<th>ANH</th>
<th>(3) $i=1$</th>
<th>ANH</th>
<th>$i=2$</th>
<th>ANH</th>
<th>(4) $i=1$</th>
<th>ANH</th>
<th>$i=2$</th>
<th>ANH</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 470$</td>
<td>$m_{11}$</td>
<td>37</td>
<td>50</td>
<td>21</td>
<td>66</td>
<td>25</td>
<td>62</td>
<td>4</td>
<td>83</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&gt; 470$</td>
<td>$m_{12}$</td>
<td>5</td>
<td>23</td>
<td>15</td>
<td>13</td>
<td>7</td>
<td>21</td>
<td>1</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(total)</td>
<td>$m_i$</td>
<td>42</td>
<td>73</td>
<td>36</td>
<td>79</td>
<td>32</td>
<td>83</td>
<td>5</td>
<td>110</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Estimate</th>
<th>Specified risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MLL</td>
</tr>
<tr>
<td>Independent</td>
<td>$\hat{\lambda}_1$</td>
<td>0.05540</td>
</tr>
<tr>
<td></td>
<td>$\hat{c}_1$</td>
<td>4.21677</td>
</tr>
<tr>
<td></td>
<td>$\hat{\lambda}_2$</td>
<td>0.28865</td>
</tr>
<tr>
<td></td>
<td>$\hat{c}_2$</td>
<td>3.49490</td>
</tr>
<tr>
<td>Dependent</td>
<td>$\hat{\lambda}_1$</td>
<td>0.45461</td>
</tr>
<tr>
<td></td>
<td>$\hat{c}_1$</td>
<td>2.14629</td>
</tr>
<tr>
<td></td>
<td>$\hat{\lambda}_2$</td>
<td>0.72490</td>
</tr>
<tr>
<td></td>
<td>$\hat{c}_2$</td>
<td>2.84478</td>
</tr>
<tr>
<td></td>
<td>$\hat{\lambda}_{12}$</td>
<td>0.19745</td>
</tr>
</tbody>
</table>

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 $Y = (Y_1, Y_2)'$ is assumed to be a random vector corresponding to the Weibull model described in Section 2. Through the above transformation, $Z = (Z_1, Z_2)'$ follows the model consisting of a bivariate Weibull distribution.

The computational method for obtaining values of the MLE $\hat{\theta}$ 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 $\tilde{\lambda}_1^{(0)}$ and $\tilde{c}_1^{(0)}$ of parameters $\lambda_1$ and $c_1$ concerning the specified risk MLL.

2) estimates $\tilde{\lambda}_2^{(0)}$ and $\tilde{c}_2^{(0)}$ of parameters $\lambda_2$ and $c_2$ for the specified risks TMR, INF and OTH together.

II. Calculate estimates of parameters including $\lambda_{12}$ by means of Monte Carlo simulation, using the following steps:

1) create random numbers $u_i$ (i = 1, 2, ..., 5) generated from a standard normal distribution.

2) let

$$\hat{\lambda}_1 = \tilde{\lambda}_1^{(0)}(1 + 0.1u_1), \quad \hat{c}_1 = \tilde{c}_1^{(0)}(1 + 0.1u_2),$$

$$\hat{\lambda}_2 = \tilde{\lambda}_2^{(0)}(1 + 0.1u_3), \quad \hat{c}_2 = \tilde{c}_2^{(0)}(1 + 0.1u_4), \quad \hat{\lambda}_{12} = 0.2 | u_5 |$$
Table 3 Approximate values of the likelihood ratio statistic $\hat{\lambda}^{(0)}$, 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.

<table>
<thead>
<tr>
<th>Approximate values</th>
<th>Specified risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MLL</td>
</tr>
<tr>
<td>$\hat{\lambda}^{(0)}$</td>
<td>10.9701</td>
</tr>
<tr>
<td>$p$</td>
<td>0.00093</td>
</tr>
<tr>
<td>$\hat{\rho}$</td>
<td>0.14339</td>
</tr>
</tbody>
</table>

Table 4 Estimates of the means of theoretical lifespans $\hat{\mu}_{11}$, $\hat{\mu}_{12}$, $\hat{\mu}_{21}$, $\hat{\mu}_{22}$ when competing risks are assumed to be independent and dependent, respectively. In the bottom two rows, approximate values of the Wald type test statistics $\hat{W}^{(v,f)}$ and their significance probability $p$ regarding MLL and INF are shown.

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Specified risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MLL</td>
</tr>
<tr>
<td>Independent $\hat{\mu}_{11}$</td>
<td>563.976</td>
</tr>
<tr>
<td>$\hat{\mu}_{12}$</td>
<td>437.604</td>
</tr>
<tr>
<td>Dependent $\hat{\mu}_{21}$</td>
<td>502.345</td>
</tr>
<tr>
<td>$\hat{\mu}_{22}$</td>
<td>436.671</td>
</tr>
<tr>
<td>For Test $\hat{W}^{(v,f)}$</td>
<td>21.0889</td>
</tr>
<tr>
<td>$p$</td>
<td>0.00003</td>
</tr>
</tbody>
</table>

3) compute the value of
$$
\log L_n = \begin{cases} 
\log L_n(\hat{\theta} | c_2 > c_1) & \text{if } \hat{c}_2 > \hat{c}_1 \\
\log L_n(\hat{\theta} | c_1 > c_2) & \text{if } \hat{c}_1 > \hat{c}_2 
\end{cases}
$$

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

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 $\lambda^{(v)}$ 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 $\lambda^{(v)}$ stated above, so that the value is not listed again in Table 3.

Although the correlation of $Z_1$ and $Z_2$ cannot be explicitly expressed, the probability $\rho$ of the dependence between $Z_1$ and $Z_2$ is proposed as $\rho = P(Z_1^{(v)} = Z_2^{(c)}) = \lambda_{12}(\lambda_1 + \lambda_2 + \lambda_{12})^{-1}$. 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 specified risk $C_i$ is MLL or INF.

We yield an estimate $\hat{\mu}^*$ of the mean vector $\mu^*$ of $Z$ for each specified risk $C_i$ under independent competing risks by substituting the values in Table 2 into (2.6) with $\lambda_{12} = 0$. In similar fashion, we can obtain estimates $\hat{\mu}^*$ 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,

\[ H_0 : \mu_1^* - \mu_2^* = 0 \text{ against } H_1 : \mu_1^* - \mu_2^* \neq 0, \]

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