Challenges in Modelling Time Dependent Transitions in Cost-effectiveness Analysis

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1. Introduction

2. Notation

Table 1: Notation

<table>
<thead>
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<th>Symbol</th>
<th>Definition</th>
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<tbody>
<tr>
<td>$R$</td>
<td>respond</td>
</tr>
<tr>
<td>$LC$</td>
<td>limited complication</td>
</tr>
<tr>
<td>$SC$</td>
<td>severe complication</td>
</tr>
<tr>
<td>$P$</td>
<td>progression</td>
</tr>
<tr>
<td>$D$</td>
<td>die</td>
</tr>
<tr>
<td>$\pi_i(t)$</td>
<td>state $i$ probability at time $t$</td>
</tr>
<tr>
<td>$p_{i,j}(t)$</td>
<td>transition probability from state $i$ to state $j$ at time $t$</td>
</tr>
<tr>
<td>$S(t)$</td>
<td>overall survival probability at time $t$</td>
</tr>
<tr>
<td>$S_{PF}(t)$</td>
<td>progression-free survival probability at time $t$</td>
</tr>
<tr>
<td>$\hat{\pi}_i(t)$</td>
<td>fitted state $i$ probability at time $t$</td>
</tr>
<tr>
<td>$\hat{p}_{i,j}(t)$</td>
<td>fitted transition probability from state $i$ to state $j$ at time $t$</td>
</tr>
<tr>
<td>$\hat{S}(t)$</td>
<td>fitted overall survival probability at time $t$</td>
</tr>
<tr>
<td>$\hat{S}_{PF}(t)$</td>
<td>fitted progression-free survival probability at time $t$</td>
</tr>
<tr>
<td>$I_i$</td>
<td>incidence rate of state $i$</td>
</tr>
</tbody>
</table>
3. Non-stationary probabilities

Our goal is to estimate the transition matrix \([p_{i,j}(t)]\). Where the five states are respond (R), limited complications (LC), severe complications (SC), progression (P) and die (D). In order to do so, we need the following assumptions:

Assumption:

- The only way to go to the complications states is from respond. If the patient develops severe complications she can go to progress in one month.
- Can only reach the die state from the progress state.
- If a patient develops limited complication, then she will go back to respond state in one month.
- \(p_{R,LC}(t), p_{R,SC}(t), p_{SC,P}(t)\) and \(p_{SC,SC}(t)\) are constant in time.

Then the transition matrix can be reduced to:

\[
\begin{bmatrix}
    p_{R,R}(t) & p_{R,LC} & p_{R,SC} & p_{R,P}(t) & 0 \\
    1 & 0 & 0 & 0 & 0 \\
    0 & 0 & p_{SC,SC} & p_{SC,P} & 0 \\
    0 & 0 & 0 & p_{PF}(t) & p_{PF,D}(t) \\
    0 & 0 & 0 & 0 & 1
\end{bmatrix}
\]

From the Kaplan-Meier curves, we are able to obtain \(S(t), S_{PF}(t)\) using the software getdata. Based on the definitions of the five states,

\[
\begin{align*}
\pi_R(t) + \pi_{LC}(t) + \pi_{SC}(t) &= S_{PF}(t) \\
\pi_P(t) &= S(t) - S_{PF}(t) \\
\pi_D(t) &= 1 - S(t)
\end{align*}
\]

(1)

In addition, we can obtain \(I_{LC}\) and \(I_{SC}\) from registration trials, by computing the ratio of total incidences over the total number of patients involved in the study. \(p_{SC,SC}\) could be estimated easily with the knowledge of the duration of severe complications (denote as \(d\)), the relationship is simply:

\[
1 + p_{SC,SC} + p_{SC,SC}^2 + ... = \frac{1}{1 - p_{SC,SC}} = d, \text{ then an estimation of the transition probability is } p_{SC,SC} = \frac{d - 1}{d}. \]

It remains to estimate \(\pi_R(t), \pi_{LC}(t)\) and \(\pi_{SC}(t)\), and the other transition probabilities. The following proposition gives a way to estimate these parameters.

Lemma 1 Let \(z\) denote \(\sum_{t=0}^{\infty} \pi_R(t)\), then

\[
z = \sum_{t=0}^{\infty} S_{PF}(t) - \left( I_{LC} + I_{SC} \frac{1}{1 - p_{SC,SC}} \right)
\]
Proof of Proposition 1 From the first equation in (1), if we sum the equation over $t$

$$\sum_{t=0}^{\infty} \pi_R(t) + \sum_{t=0}^{\infty} \pi_{LC}(t) + \sum_{t=0}^{\infty} \pi_{SC}(t) = \sum_{t=0}^{\infty} S_{PF}(t)$$

(2)

On the LHS, the first term is $z$ by definition. From the transition matrix, we know the only way to go to limited complication is from respond.

$$\pi_{LC}(t+1) = \pi_R(t) * p_{R,LC}$$

If again we sum over $t$ the above equation

$$\sum_{t=0}^{\infty} \pi_{LC}(t+1) = \sum_{t=0}^{\infty} \pi_R(t) * p_{R,LC}$$

Since at time 0, we assume all patients start from respond state, then, $\pi_{LC}(0) = 0$. Also from the definition of $z$, the above equation is equivalent to

$$\sum_{t=0}^{\infty} \pi_{LC}(t) = z p_{R,LC}$$

(3)

Since at time $t+1$, the new added incidence rate is $\pi_R(t)p_{R,i}$, where $i = LC, SC$. Therefore, the total incidence rate equals the sum of new incidence rate over time

$$\sum_{t=0}^{\infty} \pi_R(t)p_{R,i} = I_i, i = LC, SC$$

(4)

Using the definition of $z$, we could prove Proposition 1(2): $p_{R,i} = \frac{I_i}{z}$. Further, we can write equation (3) as

$$\sum_{t=0}^{\infty} \pi_{LC}(t) = z p_{R,LC} = I_{LC}$$

(5)

From the transition matrix, there are two ways to go to severe complication: from respond and from severe complication. We can get the following relationship

$$\pi_{SC}(t+1) = \pi_R(t) * p_{R,SC} + \pi_{SC}(t) * p_{SC,SC}$$
Sum the above equation over $t$

$$
\sum_{t=0}^{\infty} \pi_{SC}(t+1) = \sum_{t=0}^{\infty} \pi_R(t) \ast p_{R,SC} + \sum_{t=0}^{\infty} \pi_{SC}(t) \ast p_{SC,SC}
$$

$$\sum_{t=0}^{\infty} \pi_{SC}(t+1) = \sum_{t=0}^{\infty} \pi_{SC}(t)$$

because of the fact that $\pi_{SC}(0) = 0$. We can rewrite the above equation as

$$
\sum_{t=0}^{\infty} \pi_{SC}(t) = \sum_{t=0}^{\infty} \pi_R(t) \ast p_{R,SC} = \frac{I_{SC}}{1-p_{SC,SC}} \tag{6}
$$

Where the last equality is from equation (4). Substitute (5) and (6) into (2)

$$
z + I_{LC} + \frac{I_{SC}}{1-p_{SC,SC}} = \sum_{t=0}^{\infty} S_{PF}(t) \tag{7}
$$

Solve for $z$

$$
z = \sum_{t=0}^{\infty} S_{PF}(t) - \left( I_{LC} + I_{SC} \frac{1}{1-p_{SC,SC}} \right) \tag{8}
$$

From Proposition 1(1)-(2), we are able to obtain an estimation of $p_{R,LC}$ and $p_{R,SC}$. At time 0, we know $\pi_R(0) = 1$ and $\pi_{LC}(0) = \pi_{SC}(0) = 0$, thus, we can use Proposition 1(3) to obtain $\pi_R(t)$, $\pi_{LC}(t)$ and $\pi_{SC}(t)$ iteratively. In this way, we can obtain $\pi_i(t)$ for each state $i$ and each time $t$.

The next algorithm provides a way to calculate transition probabilities from state probabilities.

**Initial step:** $p_{R,R}(0) = \pi_R(1)/1 = \pi_R(1)$, $p_{R,P}(0) = 1 - p_{R,R}(0) - p_{R,LC} - p_{R,SC}$

**Step 1:** at loop $t$, we know $p_{i,j}(t-1)$

**Step 2:** $p_{R,R}(t) = \frac{\pi_R(t+1) - \pi_{LC}(t)}{\pi_R(t)}$, $p_{R,P}(t) = 1 - p_{R,R}(t) - p_{R,LC} - p_{R,SC}$, $p_{P,D}(t) = \frac{\pi_D(t+1) - \pi_D(t)}{\pi_D(t)}$, $p_{P,P}(t) = 1 - p_{P,D}(t)$

**Step 3:** $t = t + 1$, go back to step 1.

In the next section, we consider several ways to fit our existing data, and compare the fitted results.

### 3.1 Fitting Kaplan-Meier curves

We fit $S(t)$ and $S_{PF}(t)$ using the data collected from the Kaplan-Meier curves, and then use the fitted values $\hat{S}(t)$ and $\hat{s}_{PF}(t)$ to estimate the state probabilities and transition probabilities.