Challenges in Modelling Time Dependent Transitions in Cost-effectiveness Analysis

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1. Introduction

2. Notation

Table 1: Notation

Symbol	Definition
R	respond
LC	limited complication
SC	severe complication
P	progression
D	die
$\pi_i(t)$	state i probability at time t
$p_{i,j}(t)$	transition probability from state i to state j at time t
$S(t)$	overall survival probability at time t
$S_{PF}(t)$	progression-free survival probability at time t
$\hat{\pi}_i(t)$	fitted state i probability at time t
$\hat{p}_{i,j}(t)$	fitted transition probability from state i to state j at time t
$\hat{S}(t)$	fitted overall survival probability at time t
$\hat{S}_{PF}(t)$	fitted progression-free survival probability at time t
I_i	incidence rate of state i

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:

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

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,

$$\begin{aligned} &\pi_R(t) + \pi_{LC}(t) + \pi_{SC}(t) = S_{PF}(t) \\ &\pi_P(t) = S(t) - S_{PF}(t) \\ &\pi_D(t) = 1 - S(t) \end{aligned} \tag{1}$$

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: $1+p_{SC,SC}+p_{SC,SC}^2+... = \frac{1}{1-p_{SC,SC}} = d$, 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 $z = \sum_{t=0}^{\infty} S_{PF}(t) - \left(I_{LC} + I_{SC}\frac{1}{1-p_{SC,SC}}\right)$*

Proposition 1 *(a)* $\pi_R(t+1) = S_{PF}(t+1) - \pi_{LC}(t+1) - \pi_{SC}(t+1)$
(b)$\pi_{LC}(t+1) = \pi_R(t) * p_{R,LC}$
(c)$\pi_{SC}(t+1) = \pi_R(t) * p_{R,SC} + \pi_{SC}(t) * p_{SC,SC}$
(d)$p_{R,LC} = \frac{I_{LC}}{z}$
(e) $p_{R,SC} = \frac{I_{SC}}{z}$

Proof of Proposition 1 From the first equation in (1), if we sum the equation over t

$$\sum_{t=0}^{\infty} \pi_R(t) + \sum_{t=0}^{\infty} \pi_{LC}(t) + \sum_{t=0}^{\infty} \pi_{SC}(t) = \sum_{t=0}^{\infty} S_{PF}(t) \tag{2}$$

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

$$\sum_{t=0}^{\infty} \pi_{LC}(t) = z p_{R,LC} \tag{3}$$

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

$$\sum_{t=0}^{\infty} \pi_R(t) p_{R,i} = I_i, i = LC, SC \tag{4}$$

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

$$\sum_{t=0}^{\infty} \pi_{LC}(t) = z p_{R,LC} = I_{LC} \tag{5}$$

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

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

$\sum_{t=0}^{\infty} \pi_{SC}(t+1) = \sum_{t=0}^{\infty} \pi_{SC}(t)$ because of the fact that $\pi_{SC}(0) = 0$. We can rewrite the above equation as

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

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

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

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

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.