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SURVIVAL MODELING IN PHARMACOECONOMIC STUDIES: MARKOV MODEL VS PARTITIONED SURVIVAL MODEL

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Abstract: *This article compares for the first time in the Russian-speaking literature two approaches of survival modeling in pharmacoeconomic studies. Markov model and partitioned survival model were examined. The following text contains methodological issues, key differences and selection guideline.*

Key words: *pharmacoeconomic study, methodology, modeling, Markov model, partitioned survival model.*

INTRODUCTION

In accordance with pharmacoeconomic methodology, effectiveness analysis of healthcare technology (HT) should be based on criteria that preferably reflect changes in lifetime and/or quality of life [3, 4, 14]. Usually clinical trials (CT) (more rare epidemiological and other types of studies) collect appropriate data, thereafter pharmacoeconomic models use obtained data for cost-effectiveness analysis, budget impact analysis, cost-of-illness analysis etc. [6, 7].

Cohort models are the most widely used type of models in pharmacoeconomic studies. Such models consider effects of HT not for individual patient, but for a group of patients. Main types of the models are «decision tree» model (DTM), Markov model (MM) and partitioned survival model (PSM).

Appropriate choice of the modeling approach determines the probability of reliability and acceptance (by decision makers) of obtained results and, that is important, rational use of resources for development.

Conducted in January 2017 literature review in scientific base «E-library» showed that methodological issues of DTM and MM were widely discussed by Russian-speaking authors [2, 5], but the methodology of PSM has not been ever covered. Despite this, PSM is rather widely used in foreign pharmacoeconomic studies and has advantages in comparison with alternative approaches, therefore we prepare current article (DTM were not examined, as they can't account time factor, therefore it can't analyze the influence of HT on the lifetime).

MARKOV MODEL

In general, MM (or Markov chain) is a sequence of random events with finite or countable number of outcomes (Markov states), which can be described as follows, speaking nonstrict, if the presence is fixed than future does not depend on past [1].

Following MM approach, in the development of a disease it is possible to define particular number of mutually exclusive and exhaustive states that would properly reflect the patient health status. If transition probabilities are available, one can assess effectiveness and costs of HT in a given time period (time horizon) [12].

Time horizon is chosen to fully fit objectives of the study. It is divided into equal periods - Markov cycles. Every cycle modeling group of patients move between states. Transitions within chain of Markov states go through a number of intermediate states and end with an absorption state, in which after a while the group will get in (fig. 1). The direction of transition is defined with respect to the aspects of the disease. MM can incorporate progression, regression, remission of the disease and death.

Transition probabilities are key elements of MM, since they determine distribution of modeling group at a time through the study horizon. The probability should be equal with the probability of an event at a period such as Markovian cycle. It is of importance that MM has "no memory": transition probabilities are chosen only by reference to current state, i.e. the previous history does not bear in view. However, the probabilities can be dynamic and change between cycles, it obviously makes model more complex, but it may be valuable in some diseases, since one can consider changing of probability in time.

Spending time in each Markov state (disease state) is associated with costs. Based on the number of transitions and/or the duration of being in each state, it is possible to calculate costs for the whole group of patients, as well as for one average patient.

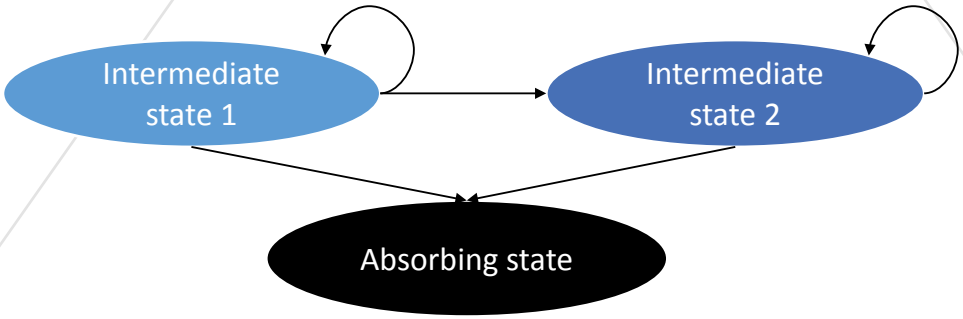

Figure 1. Example of Markov model.

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If effectiveness criteria reflects lifetime (for example, progression free survival, overall survival), than the duration of being in each state can be used to calculate LYG and QALY.

PARTITIONED SURVIVAL MODEL

Partitioned survival model is based on the survival curves.

Similarly to MM, PSM needs to define exhaustive states which could accurately reflect the health status of the group of patients at a time through the study horizon [11].

If the CT uses survival criteria (overall survival, progression free survival) as an effectiveness criteria, than survival curves for the defined states can be built (fig. 2). Kaplan-Mayer curve is the most common way of presenting survival analysis in CT.

In a simple case (time limits, financial limits etc.), modeling is conducted with Kaplan-Mayer curves.

But in most cases, survival curves from CT are modified. The point is that alternative HT usually have no direct comparison, therefore it is necessary to conduct an indirect comparison with correction of effectiveness data. Besides, survival curves usually do not run to zero, i.e. the prolongation of curves across the horizon of CT is needed. For this purpose curves are digitized and extrapolated with the best fitted parametric distribution (the most common: exponential, Weibull and Gauss). There are a number of possible approaches of carrying out mentioned changes, but two are the most widely used: Hoyle & Henley (2011) and Guyot et al. (2012) [9, 10].

The duration of being in a health state is equal to the area under the curve. There are two ways to calculate it:

1. Graphically: rectangular or trapezoidal method;
2. Numerically: survival function equations (only for parametric functions).

To calculate effectiveness and costs associated with the HT, the time spent in each state is used.

MARKOV MODEL VS PARTITIONED SURVIVAL MODEL

Radical departure between described modeling approaches is that PSM critically depends on availability of individual patient data enabling to build a survival curve. In the absence of the data, such a model cannot be built.

MM are much more flexible and can unite results of separate studies. To conduct calculations, both survival curves and results of observational studies, statistical sources of medical information, experts' opinion etc. It may be worth in case of lack of data.

Consequently, MM may use not only the same health states that are in CT of analyzed HT. MM are able to consider infinite number of states, therefore modeling of health history is more accurate. However, excessive detailing may be unnecessary and may complicate constructing and interpreting results of pharmacoeconomic study.

Alongside this, PSM are more transparent, since they base only on the results of CT of comparing HT, allowing to quick check the data used in calculations with published result of CT.

At that, in cases of usage of Kaplan-Mayer survival curves both modeling approaches usually require fitting of parametric curve and prolongation of survival curve tail. By contrast, PSM compared with MM do not need additional computations of transition probabilities.

A principal aspect determines the necessity of transformation probabilities on Kaplan-Mayer curve into probabilities compliant with MM: the former is a cumulative event probability in a period between the survey beginning and a time of interest; the latter is an event probability in a period between previous and of next Markov cycles. For example, if the length of cycles is t_1-t_0, than the mapped on the figure probability P_3 is a proportion of patients in the study, who outlast time intervals t_{0-1}, t_{1-2} and t_{2-3} (fig. 3). From there, to construct MM it is necessary derive required probabilities within cycle length and note that MM, in contrast with Kaplan-Meyer curves, consider probabilities of being alive, but not probabilities of death. Formula to calculate probabilities:

Formula 1. Formula to calculate transition probability based on a survival curve

$$P_{State\ 1-Death}(t_{2-3}) = 1 - \frac{P_3}{P_2},$$

where – probability of transition from «State 1*» into «Death» within period ;*

P_2 – probability of being alive in «State 1*» within period ;*

P_3 – probability of being alive in «State 1*» within period .*

As previously stated, MM does not consider the history of previous transitions, which is valuable in pharmacoeconomic studies in oncology, HIV-infection and other diseases, where the probability of disease progression

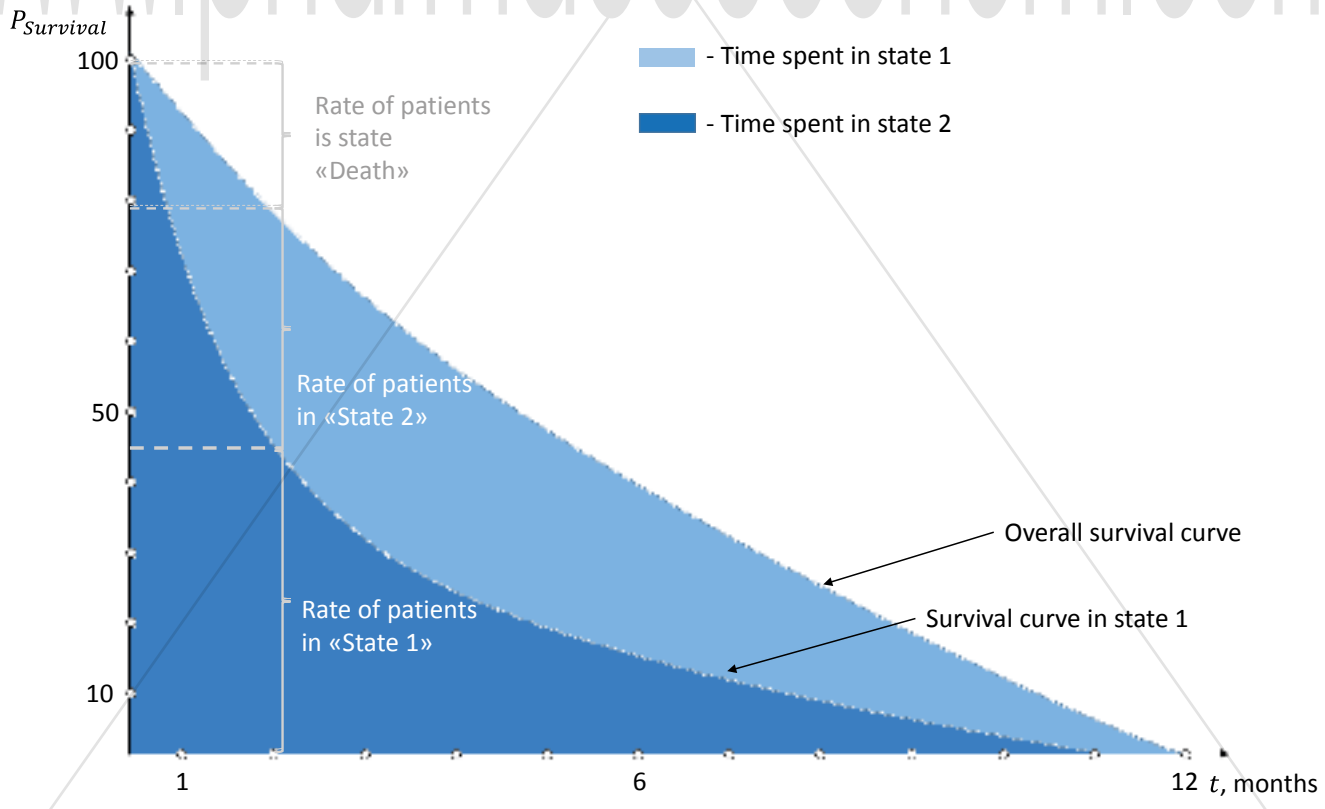


Figure 2. Example of parametric survival curve in partitioned survival model

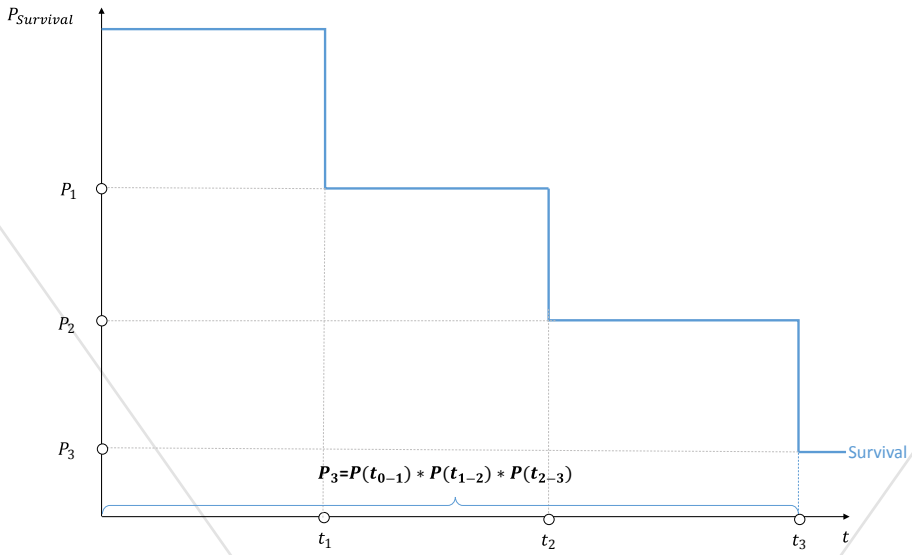


Figure 3. Example of derivation of event probability from the Kaplan-Mayer curve

increases over time regardless of the effectiveness of treatment. Therefore, it is necessary to use not static, but dynamic probabilities, i.e. it is necessary to calculate each of transition probabilities for each of Markov cycles (fig. 4). As a result, the computation process may be rather complicated.

Unlike with MM, PSM does not formally require cycles, since the duration of being in each state is equal to the square of area under curve. Despite this, the study horizon usually is divided into periods, since it is needed for discounting.

EXAMPLE

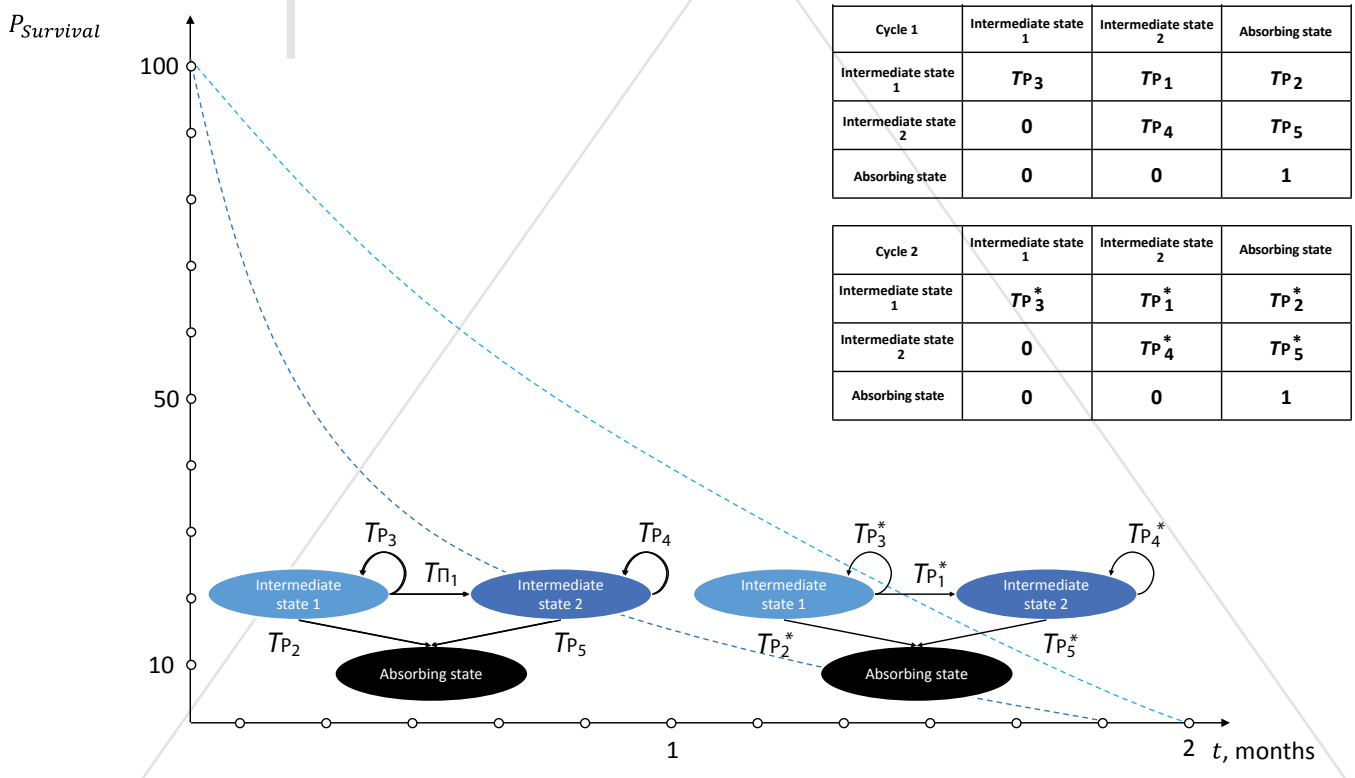
Put the case that the pharmacoeconomic analysis of two HT (medicine A and B) for treatment of the disease that decreases duration and quality of life is needed. In accordance with clinical guidelines, the history of the disease can be presented as two health states: state 1 (S1) and state 2 (S2). To access the effectiveness in clinical practice, surrogate points are used. It is assumed that alongside with achievement of surrogate effectiveness targets, there can be no increase of lifetime and quality of life. Thus to assess effectiveness of medicines in CT, endpoints reflecting survivability or mortality are applied for.

Let us suppose that during literature review results of CT of mentioned medicines were obtained. The CT contained graphical results – survival curves, that were derived from Kaplan-Mayer curves into parametric curves (fig. 5). Besides, the results of the study dedicated to analyzing of average monthly costs were retrieved too.

Taking into account the results of literature review the researcher decided to conduct a pharmacoeconomic study based on modeling approach for a hypothetical group of patients in number X.

Provided below text, described possible steps needed to build MM and PSM with similar results (fig.6).

At the first stage of developing MM the Markov states (S1, S2 and death), time horizon (three months) and cycle (one month) should be defined. Next,



Cycle 1	Intermediate state 1	Intermediate state 2	Absorbing state
Intermediate state 1	TP_3	TP_1	TP_2
Intermediate state 2	0	TP_4	TP_5
Absorbing state	0	0	1

Cycle 2	Intermediate state 1	Intermediate state 2	Absorbing state
Intermediate state 1	TP_3^*	TP_1^*	TP_2^*
Intermediate state 2	0	TP_4^*	TP_5^*
Absorbing state	0	0	1

Figure 4. Example of building MM based on parametric survival curve.

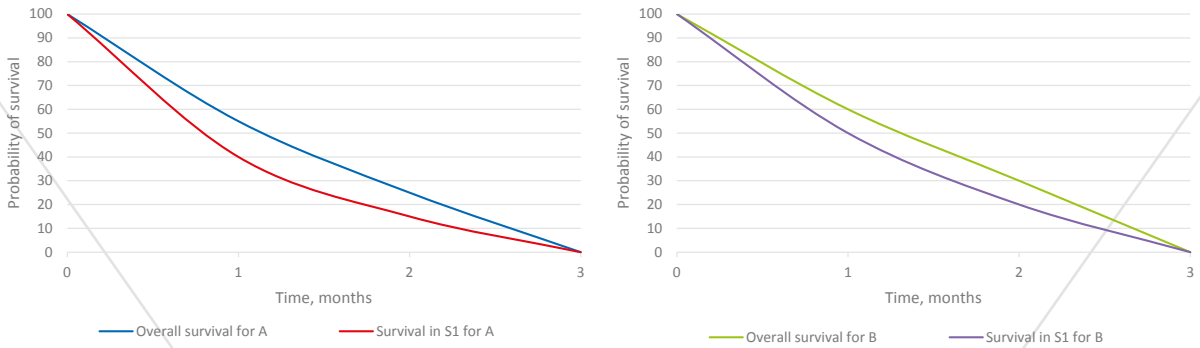


Figure 5. Example of survival curves used in pharmacoeconomic studies

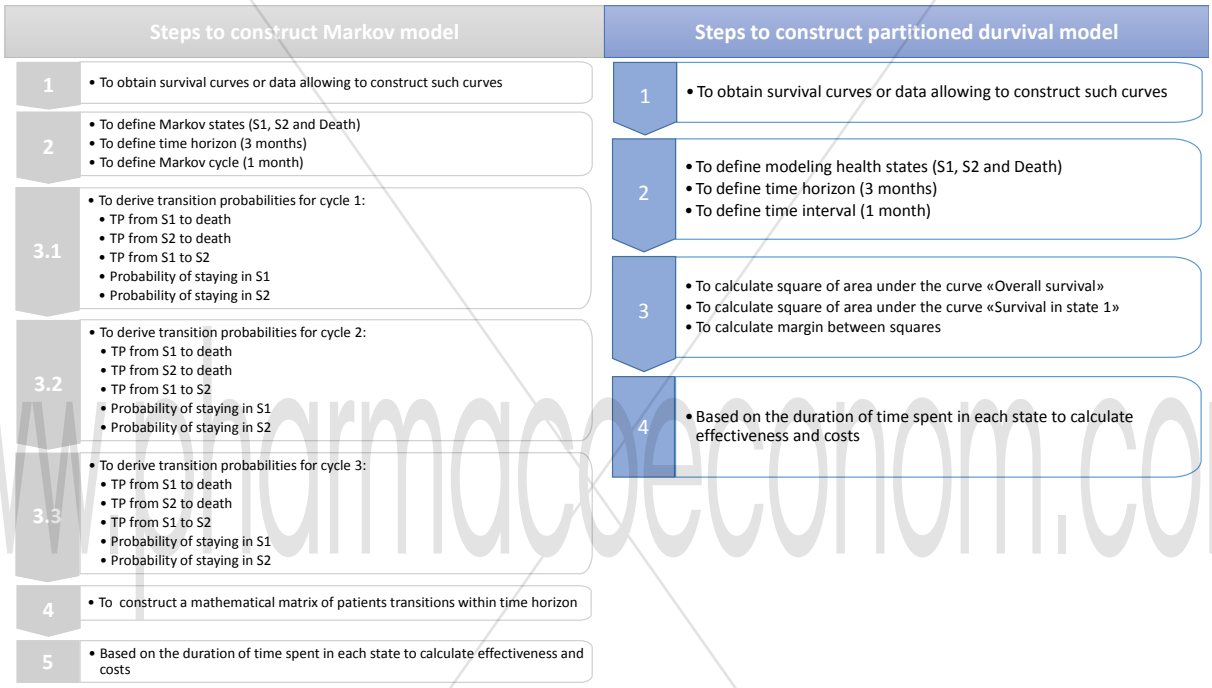


Figure 6. Example of steps needed to develop MM and PSM with similar results

following mentioned approach (fig. 3, formula 1), the transitions' probabilities should be computed: transition probability from S1 to death, transition probability from S2 to death, transition probability from S1 to S2, transition probability of staying in S1 and transition probability of staying in S2. Then, the same step should be repeated for the second and the third cycles. Take notice of the requirement of, alongside with published survival curves in results of CT, curves for transition of patients from S1 to S2 or some data to build such curves. After that, the transition matrix should be constructed, making possible to find time that patient spends in each state. Knowing average monthly costs of being in S1 and S2, it is possible to calculate costs associated with A and B.

At the first step of developing PSM the health states (S1, S2 and death) and time horizon (three month) should be defined. Next, following one of the mentioned approaches the square of areas under the curve «Overall surveillance» and «Surveillance in S1», and the margin between them should be calculated. The area under the curve «Surveillance in S1» and the margin between squares reflect the duration of time spent by patients in each state. Knowing average monthly costs of being in S1 and S2, it is possible to calculate costs associated with A and B.

DISCUSSION

Overall, MM are more multifunctional and complex models in comparison with PSM, that usually need more data and more complex calculations. Whereas, PSM are simpler in developing, more transparent and rather accurate in survival analysis.

In case of usage the same basic data, methods of transforming (for example, prolongation of survival curve) and, above all, similar assumptions, than both of modeling approaches can provide similar results [8]. However, as it was done in the article Williams C. (2016), the assumptions in MM and PSM usually are different. For example, MM usually have a standard Markovian assumption, concerning absence of changing the probability of event happening over time, that leads to results different to PSM results [13].

In general, the selected modeling approach should sufficiently reflect the real-world situation, should be the simplest in developing and using, and should have the most transparent mathematical structure.

If the disease can be reasonably modeled by a few states and survival curves or data for building such curves are available, than PSM are the gold standard. Even if only one point is not satisfied, than MM should be preferred.

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