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N.B.: When citing this work, cite the original article.

Original Publication:

Qi Cao, Erik Buskens, Talitha Feenstra, Tiny Jaarsma, Hans Hillege and Douwe Postmus, Continuous-Time Semi-Markov Models in Health Economic Decision Making: An Illustrative Example in Heart Failure Disease Management, 2016, Medical decision making, (36), 1, 59-71.

<http://dx.doi.org/10.1177/0272989X15593080>

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Postprint available at: Linköping University Electronic Press

<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-124110>

Continuous-time semi-Markov models in health economic decision making: an illustrative example in heart failure disease management

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Running head: Continuous-time health economic modeling

Word count: 4,648

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Financial support for this study was provided entirely by a grant 01C-103 and a grant 01C-401 from the Center for Translational Molecular Medicine (www.ctmm.nl). The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report.

ABSTRACT (274/275)

Continuous-time state transition models may end up having large unwieldy structures when trying to represent all relevant stages of clinical disease processes by means of a standard Markov model. In such situations, a more parsimonious, and therefore easier to grasp, model of a patient's disease progression can often be obtained by assuming that the future state transitions do not only depend on the present state (Markov assumption) but also on the past through time since entry in the present state. Despite that these so-called semi-Markov models are still relatively straightforward to specify and implement, they are not yet routinely applied in health economic evaluation to assess the cost-effectiveness of alternative interventions. To facilitate a better understanding of this type of model among applied health economic analysts, the first part of this paper provides a detailed discussion of what the semi-Markov model entails, and how such models can be specified in an intuitive way by adopting an approach called vertical modeling. In the second part of the paper, we use this approach to construct a semi-Markov model for assessing the long-term cost-effectiveness of three disease management programs for heart failure. Compared to a standard Markov model with the same disease states, our proposed semi-Markov model fitted the observed data much better. When subsequently extrapolating beyond the clinical trial period, these relatively large differences in goodness-of-fit translated into almost a doubling in mean total cost and a 60-day decrease in mean survival time when using the Markov model instead of the semi-Markov model. For the disease process considered in our case study, the semi-Markov model thus provided a sensible balance between model parsimoniousness and computational complexity.

Key words: continuous-time semi-Markov model; vertical modeling; heart failure disease management

INTRODUCTION

Continuous-time state-transition models (STMs) are increasingly applied in health economic evaluation to assess the cost-effectiveness of health care interventions.¹⁻⁴ Similar to the routinely applied discrete-time models, this type of model entails defining a set of discrete health states reflecting the different conditions that a patient can be in and a set of transition probabilities governing the transitions between these health states.⁵ However, compared to a discrete-time model in which time progresses in fixed increments (i.e., 1-year cycles), time in a continuous-time STM progresses continuously meaning that transitions are no longer restricted to occur at the beginning or end of pre-defined time intervals.^{1,2} As such, the cost-effectiveness estimates obtained from a continuous-time STM are not affected by the selected cycle length, meaning that there is no need to apply corrective measures such as half-cycle correction.⁶

The best known continuous-time STM is the Markov model, which is based on the premise that the future state transitions only depend on the present and are independent of any knowledge from the past, such as time since entry into the present state or the sequence of prior states leading to the present.^{7,8} As this assumption greatly simplifies the dependence structure, the resulting models can generally still be evaluated analytically.⁷ A downside of this approach is however that without considerably expanding the number of health states a standard Markov model is sometimes too restrictive to be able to accurately reflect subsequent phases of actual clinical disease processes.

The above situation for instance occurs in the modeling of diseases such as chronic obstructive pulmonary disease or heart failure (HF), where periods of stable chronic disease alternate with periods of acute decompensation in which additional medical treatment is required and hence the corresponding treatment costs are increased. As the risk of experiencing an adverse event generally decreases as the time since the last exacerbation

increases, the probability of a patient leaving the stable chronic disease state should depend on the time since the last exacerbation. To realistically represent such a disease process by means of a continuous-time Markov model, one needs to divide the stable chronic disease state into a set of embedded states representing increasingly longer time periods since the occurrence of the last exacerbation, resulting in a relatively complex model with a large number of parameters.²

Instead of trying to represent complex clinical disease processes by means of a standard Markov model, Foucher et al.³ proposed to relax the Markov assumption by assuming that the future state transitions do not only depend on the present but also on the past through the time since entry in the present state. Although these so-called semi-Markov models⁹⁻¹¹ allow for a more parsimonious representation of complex medical processes in situations where some form of time dependency needs to be built into the model, they are not yet widely applied in health economic evaluation to assess the cost-effectiveness of alternative health care interventions. One of the reasons for this may be that the parameters of this type of model do not have a clear clinical interpretation when specified according to the cause-specific hazards formulation or the pattern-mixture formulation, which are standard approaches for parameterizing semi-Markov models.¹² An alternative approach that is not hampered by this lack of interpretability is vertical modeling.¹³ However, as this parameterization was only recently introduced in the medical statistical literature, it has not yet been extensively discussed in the context of health economic modeling. To facilitate a better understanding of the continuous-time semi-Markov model among applied health economic analysts, the first part of this paper describes in more detail what such a model entails and how such models can be specified in an intuitive way by applying vertical modeling. The second part of this paper consists of an illustrative case study in which we use

vertical modeling to assess the cost-effectiveness of three disease management programs (DMPs) for HF.

SPECIFICATION, ESTIMATION, AND EVALUATION OF CONTINUOUS-TIME SEMI-MARKOV MODELS

Definition of the continuous-time semi-Markov model

A continuous-time STM is a stochastic process $\{X(t), t \geq 0\}$ with a finite state space $E = \{1, \dots, k\}$ reflecting how a patient's disease progresses over time. For a given time s , let n_s denote the number of transitions within the time interval $[0, s]$, and let v_1, \dots, v_{n_s} denote the consecutive times at which these transitions occurred. The history of the process up to time s can then be expressed as $H(s) = \{(v_i, X(v_i)), 0 \leq i \leq n_s\}$, where v_0 is set equal to 0 so that $X(v_0) = X(0)$ represents the starting state of the process. Relative to $H(s)$, the probability that the process will be in state h at time t given that it is in state g at time s is defined as

$$P_{gh}(s, t | H(s)) = P(X(t) = h | X(s) = g, H(s)); s < t, g, h \in E \quad <1>$$

Finally, the transition intensities are given by

$$\alpha_{gh}(t | H(t)) = \lim_{\Delta t \rightarrow 0} \frac{P_{gh}(t, t + \Delta t | H(t))}{\Delta t}; g \neq h, g, h \in E \quad <2>$$

meaning that the probability that an individual who is in state g at time t will make a transition to state h in the interval $[t, t + dt)$ is approximately equal to $\alpha_{gh}(t, H(t))dt$ for small values of dt .¹⁴

To make this more concrete, consider a patient who, at time 0, has just been discharged alive from hospital after having been admitted because of HF. A possible state

space for describing this patient's disease progression could be $E=\{\text{discharged alive from hospital, HF-related hospital readmission, and dead}\}$. Now, suppose that this patient is readmitted at day 115, is discharged alive from hospital at day 130, and is still alive at day 180. The history of the process up to time 180 would then be equal to $H(180)=\{(0, \text{discharged alive from hospital}), (115, \text{HF-related hospital readmission}), (130, \text{discharged alive from hospital})\}$. In addition, suppose that $P_{dishosp,dead}(180,240|H(180))=0.20$ and that $\alpha_{dishosp,dead}(180|H(180))=0.004$. We then know that the probability of this patient being dead by time 240 is 20% and that the probability of his/her death occurring within the next week (i.e., within the interval $[180,187)$) is approximately equal to $0.004 \cdot 7 \cdot 100\% = 2.8\%$.

For a given starting state distribution, the probability structure of a continuous-time STM is completely determined by its transition intensities, which, in turn, are defined in terms of the limits of the transition probabilities. Different types of STM can therefore be distinguished by changing the extent to which these probabilities depend on the history of the process (i.e., the course of disease). The most straightforward model is the Markov model, which is obtained by assuming that the transition probabilities only depend on the present (i.e., the fact that the system is in state $X(s)$ at time s). In this paper, we focus on the class of semi-Markov models in which, in addition to the present, the transition probabilities depend on the past through the time since entry v_{ns} in the present state $X(s)$. The definition of the transition probabilities in Equation <1> then simplifies to

$$P_{gh}(s, t | H(s)) = P_{gh}(s, t | v_{n_s}) = P(X(t) = h | X(s) = g, v_{n_s}) \quad <3>$$

If, in addition, it holds that $P_{gh}(s, t | v_{n_s})$ is independent of s such that

$$P(X(t) = h | X(s) = g, v_{n_s}) = P(X(t - v_{n_s}) = h | X(s - v_{n_s}) = g, 0) \quad <4>$$

the resulting STM is called a homogeneous semi-Markov model (HSMM).¹⁵

Returning to our HF example, the use of an HSMM corresponds to a situation where patients who are still alive 50 days after being discharged alive from the index admission have the same probability of dying within the next 60 days as patients who are still alive 50 days after being discharged alive from their second HF-related hospital readmission. If we make the additional assumption that this probability does also not depend on the time spent within the present state, the resulting STM becomes a Markov model. In terms of our example, this would imply that patients who are still alive 50 days after being discharged from the hospital have the same probability of dying within the next 60 days as patients who are still alive 10 days after being discharged from the hospital.

Statistical model specification

By substituting Equations <3> and <4> in Equation <2>, it follows that the transition intensities of an HSMM can be expressed as

$$\alpha_{gh}(t|H(t)) = \lim_{\Delta t \rightarrow 0} \frac{P(X(t + \Delta t - v_{nt}) = h | X(t - v_{nt}) = g, 0)}{\Delta t} = \lim_{\Delta u \rightarrow 0} \frac{P(X(u + \Delta u) = h | X(u) = g)}{\Delta u} = \alpha_{gh}(u) \quad <5>$$

Where $u = t - v_{nt}$ denotes the duration in state g . One way of specifying the HSMM would therefore be to directly express the transition intensities as functions of the duration u .¹⁶

Although this so-called cause-specific hazards formulation is a standard approach for specifying continuous-time STMs, it has the disadvantage that these model entities cannot be directly interpreted in terms of survival curves or event frequencies. This may make it difficult to discuss the face validity of the model with clinical experts or to communicate the results of the cost-effectiveness analysis to decision makers. Alternatively, one could specify the HSMM at the level of a set of directly observable quantities that can be uniquely derived from the transition intensities. This is the approach taken in both the pattern-mixture

formulation¹⁷, which is based on modeling the time to the next state transition conditional on the new state visited, and vertical modeling¹³, which is based on modeling the new state visited conditional on the time spent in the current state.

Although mathematically feasible, Andersen and Keiding¹² criticized the use of the pattern-mixture formulation in real-life decision making contexts as it determines how long a patient stays in a certain health state conditional on what will happen to him/her in the future, which, in reality, is not known beforehand. Vertical modeling, as an alternative formulation, does not suffer from this lack of interpretability as it “sticks to this world” and “does not condition on the future”.¹² In addition, estimation under the pattern mixture formulation is time-consuming and difficult because of the need to infer the next state visited for censored observations¹³, while estimation under vertical modeling is still relatively straightforward as we will discuss in more detail in the next section. Because of these clear practical advantages, vertical modeling is the approach that we consider in more detail in the remainder of this paper.

Let the random variable U , referred to as the sojourn time hereafter, denote the amount of time spent in a state before making a transition to a next state, and let the random variable D indicate the new state visited. The vertical modeling approach is based on specifying the marginal distribution of U and the conditional distribution of D given U , which can both be expressed in terms of the transition intensities $\alpha_{gh}(t/H(t))$.¹² In particular, it follows from Equation <5> that for an HSMM the cumulative distribution function of the sojourn time for each state $g \in E$ can be expressed in terms of the transition intensities $\alpha_{gh}(u)$ as

$$F_g(u) = P(U \leq u \mid X(0) = g) = 1 - \exp\left(-\int_0^u \sum_{h \neq g} \alpha_{gh}(w) dw\right) \quad <6>$$

Similarly, it holds that the probability mass function of the conditional distribution of the new state indicator can be expressed as

$$\pi_{gh}(u) = P(D = h | X(0) = g, U = u) = \frac{\alpha_{gh}(u)}{\sum_{h \neq g} \alpha_{gh}(u)} \quad <7>$$

By combining Equations <6> and <7>, it follows that the transition intensities can be

$$\text{expressed in terms of } \pi_{gh}(u) \text{ and } F_g(u) \text{ as } \alpha_{gh}(u) = \pi_{gh}(u) \times \frac{f_g(u)}{1 - F_g(u)}, \text{ where } f_g(u) = \frac{dF_g(u)}{du}$$

is the probability density function of the sojourn time in state g . This shows that the specification of $F_g(u)$ and $\pi_{gh}(u)$ is indeed sufficient to fully capture an HSMM's probability structure.

Parameter estimation under vertical modeling

In this paper, we assume that the model is fitted to patient-level data in which the sojourn time is either observed exactly or subject to right-censoring within each state. In addition, the starting state and all subsequently visited states are assumed to be observed without misclassification (i.e., the event indicator should be available to accurately identify the current state and the next state visited). The contribution to the likelihood function of the HSMM for an individual subject with history $H(s)$ can then be expressed as

$$(1 - F_{X(v_{n_s})}(s - v_{n_s})) \prod_{i=0}^{n_s-1} f_{X(v_i)}(v_{i+1} - v_i) \pi_{X(v_i)X(v_{i+1})}(v_{i+1} - v_i) \quad <8>$$

if $X(v_{n_s})$ is a transient state (i.e., all states for which the probability of leaving exceeds 0) and the observations are censored at time s and

$$\prod_{i=0}^{n_s-1} f_{X(v_i)}(v_{i+1} - v_i) \pi_{X(v_i)X(v_{i+1})}(v_{i+1} - v_i) \quad <9>$$

if $X(v_{ns})$ is an absorbing state (i.e., all states for which the probability of leaving is equal to 0) and the process terminates at time $s=v_{ns}$. In addition, as the likelihood contributions from the different subjects in the dataset are independent, the full likelihood becomes the product of the individual likelihoods.

Because the log-likelihood factors into separate components for $F_g(u)$ and $\pi_{g1}(u), \dots, \pi_{gh}(u)$ for each state $g \in E$, parameter estimation under vertical modeling proceeds by fitting separate statistical models for the sojourn-time distributions and the future state probabilities. Depending on the amount of covariates and on whether extrapolation beyond the follow-up period of the clinical trial is required, non-parametric, semi-parametric Cox models, or fully parametric survival models can be used to capture the sojourn-time distribution in each transient state.¹⁸⁻²⁰ When using parametric survival models, there may be clear biological grounds to prefer one specification over another specification. If such knowledge is lacking, the best fitting model can alternatively be selected based on a statistical criterion, such as the widely applied Akaike information criterion (AIC) or the Bayesian information criterion. The future state probabilities can be estimated by applying multinomial logistic regression models with the observed sojourn time included as a covariate. Fractional polynomials²¹ or piecewise type splines²² can be used to check for possible non-linearity in the relationship between the sojourn time and the future state probabilities. Finally, it should be noted that the continuous-time Markov model corresponds to the special case when the sojourn-time distributions $F_g(u)$ are exponential and the future state probabilities $\pi_{gh}(u)$ are constant (i.e., independent of the sojourn time u).

Model evaluation under vertical modeling

In general, evaluating a fitted HSMM to predict costs and health effects is too complex to be conducted analytically.^{16,23} The simulation process depicted in Figure 1 can then be applied

to approximate these outcomes numerically.²⁴ In short, given that the system has just entered (or starts in) state g , the sojourn time u is randomly sampled from $F_g(u)$, after which the next state is determined in terms of $\pi_{gh}(u)$. This process is repeated until the system reaches an absorbing state or the total simulation time exceeds the time horizon selected for the analysis. As usual, the simulation needs to be replicated a large number of times (say 10,000) in order to diminish the influence of Monte Carlo error on the results of the cost-effectiveness analysis.

ILLUSTRATIVE CASE STUDY

The Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH) is a multicenter, randomized controlled trial in which 1,023 patients who were discharged alive from the hospital after having been admitted for reasons related to HF were randomly assigned to either the control group (follow-up by a cardiologist) or one of the two intervention groups with basic or intensive additional support by a nurse specialized in the management of HF patients.^{25,26} The average age of the study population was 71 years and 38% was female. During the 18 months follow-up period, 411 patients (40%) reached the primary endpoint of death or HF-related hospital readmission, of whom 260 (63%) were readmitted because of HF. The all-cause mortality rate was 29% in the control group, 27% in the basic support group, and 24% in the intensive support group. The study complied with the Declaration of Helsinki, and a central appointed ethics committee approved the research protocol. Informed consent was obtained from all subjects.

In this case study, we will illustrate how vertical modeling can be applied to construct an HSMM for assessing the long-term cost-effectiveness of the three disease management programs (DMPs) considered in COACH. We will also compare the goodness-of-fit of our

proposed model against that of a Markov model to explore to what extent the use of the HSMM results in more reliable cost-effectiveness estimates.

Statistical model specification and parameter estimation

The state space for the two models was as follows (Figure 2): discharged alive (state 1), HF-related hospital readmission (state 2), and dead (state 3). To specify the sojourn-time distributions of the two transient health states, the available patient-level data was first transformed into long format where each row represents one patient at risk of making a transition. Patients who were readmitted at least once have been at risk for subsequent transitions during different periods of their follow-up, meaning that these patients are represented multiple times in this dataset. For example, a patient entering state 1 at some point during his or her follow-up was from this point onwards at risk of making a transition to either state 2 or state 3. For this patient, a row was therefore included in the dataset with the event time set equal to the amount of time spent in state 1 (or the time to censoring if this observation was subjected to right-censoring), a censoring indicator set equal to 1 if the transition was observed and 0 if the transition was censored, and a new state indicator set equal to the next state visited (if the transition was observed). All time variables were recorded in days.

Using this dataset, the estimation of the HSMM proceeded as follows. First, the goodness-of-fit of six different parametric survival models (log-normal, exponential, log-logistic, Weibull, Gaussian, and logistic) with the event time and censoring indicator as defined previously and the treatment indicator included as a covariate was compared in terms of the AIC to obtain the best fitting models for $F_1(u)$ and $F_2(u)$. This resulted in a log-normal distribution for both the sojourn time in state 1 and the sojourn time in state 2. The future state probabilities $\pi_{13}(u)$ and $\pi_{23}(u)$ were estimated by fitting a logistic regression model to the

observed binary outcomes of out-of-hospital death and in-hospital death, respectively, with the treatment indicator and the sojourn time included as the two covariates. Possible non-linearity in the associations between sojourn time and these two future state probabilities were assessed using a closed test procedure based on fractional polynomials, with the significance levels for the variable inclusion and for comparing the fit of different fractional polynomial functions both set equal to 0.05.²⁷ For out-of-hospital death, a quadratic relationship was found between the sojourn time and the log-odds of this future state probability. Possible interaction between the treatment indicator and the included sojourn time effects was also tested for, but none of these interaction terms were statistically significant. No association was found between the sojourn time and the log-odds of in-hospital mortality. This latter probability was therefore assumed to be a constant, with values equal to 0.20, 0.14, and 0.13 for patients in the care-as-usual, basic support, and intensive support group, respectively. For the Markov model, $F_1(u)$ and $F_2(u)$ were estimated by fitting two exponential distributions, while the future state probabilities were estimated by fitting two logistic regression models that did not include any sojourn time effects. The results of the statistical model specification and parameter estimation for both the HSMM and the Markov model are summarized in Table 1. All the above analyses were performed using R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Goodness-of-fit of the estimated sojourn-time distributions

Figure 3 and Figure 4 display, per treatment group, the goodness-of-fit of $F_1(u)$ and $F_2(u)$ for both our proposed HSMM and the Markov model. The observed sojourn-time distributions were obtained by taking the complement (i.e., one minus) of the Kaplan-Meier curves of the time spent in each of the health states. From these figures, we can conclude that the sojourn-

time distributions of our proposed HSMM fit the empirical data much better than the sojourn-time distributions of the Markov model.

Model validation

The performance on overall survival of both our proposed HSMM and the Markov model was internally validated by comparing the predicted (average across 100,000 simulation runs) versus the observed (Kaplan-Meier estimate) survival curves.²⁸ As is shown in Figure 5, the predicted survival curves obtained from the HSMM closely matched the observed survival curves, whereas a clear deviation from the observed survival curves was observed while using the Markov model.

Cost-effectiveness analysis

To evaluate the long-term cost-effectiveness of the three DMPs considered in COACH, the simulation process depicted in Figure 1 was repeated 100,000 times with the discharged alive state as the starting state and survival time as the measure of health effect. The maximum follow-up time for each simulation run was set to be 5 years. As our case study is illustrative in nature, we did neither consider patient heterogeneity nor stochastic uncertainty. Our results therefore represent the expected 5-year cost-effectiveness of the three DMPs in a population with the same distribution of covariates as in the COACH study population.

To obtain the cost attached to the discharged alive state, we divided the mean aggregated intervention costs taken from our previously conducted trial-based economic evaluation²⁹ by the average observed out-of-hospital days within the COACH follow-up period. This resulted in a state cost of €0.86 per day for care-as-usual, €1.56 per day for basic support, and €2.34 per day for intensive support. The cost attached to the HF-related hospital

readmission state was set to be €769 per day and was assumed to be the same for all three DMPs.

Table 2 depicts the results of the cost-effectiveness analysis using both our proposed HSMM and the Markov model with costs and survival time discounted at respective annual rates of 4% and 1.5% as described in the Dutch manual for costing.³⁰ These results show that the differences in model fit between the HSMM and the Markov model translate into relatively large differences with respect to the estimates of the mean total cost, the mean survival time, and the mean incremental cost-effectiveness ratio (ICER) between intensive support and basic support.

In the above analysis, we assumed that the level of care provided within each treatment group was the same for the clinical trial period as for the period between 18 months and 5 years. To investigate the impact of this assumption on the results of the cost-effectiveness analysis, we reduced, for each DMP, the level of care provided after the first 18 months to a half-yearly visit and a yearly visit to the cardiologist. For the period between 18 months and five years, this resulted in state costs for the discharged alive state of €0.60 per day and €0.30 per day, respectively. For the HSMM, these reductions in state costs reduced the ICER between intensive support and basic support from 15,825 (base case) to 11,167 (half-yearly follow-up) and 11,083 (yearly follow-up). For the Markov model, this ICER reduced from 20,406 (base case) to 17,318 (half-yearly follow-up) and 17,259 (yearly follow-up). In addition, we repeated the analysis with annual discount rates of 3% for both costs and survival time, but this hardly had any impact on the results of the cost-effectiveness analysis.

DISCUSSION

In reality, a patient's future disease status may depend on disease history, co-morbidity, and many other factors through complex interactions. Without considerably expanding the number

of health states, such interactions may however be difficult to capture by means of a standard Markov model. Although in such situations a more parsimonious representation of a patient's disease progression can often be obtained by replacing the Markov model by an HSMM, this latter type of model is not yet routinely applied in health economic evaluation to assess the cost-effectiveness of alternative health care interventions. To facilitate a better understanding of this model among applied health economic analysts, this paper provided a detailed discussion on how the different parameters of such a model can be specified using vertical modeling. We subsequently illustrated the use of this approach in a case study related to the disease management of HF.

To illustrate the potential biases resulting from not including any form of time dependency in the definition of the transition intensities, we fitted in our case study both an HSMM and a Markov model. The subsequent assessment of the goodness-of-fit showed that especially for the sojourn-time distribution of the discharged alive from hospital state, the Markov model yielded a poor fit with the observed data. As a consequence of this, the use of the Markov model resulted in an overestimation of the mean survival time for the COACH study period (Figure 5) and an underestimation of the mean survival time when extrapolating these curves to a 5-year period (Table 2). The HSMM, in contrast, closely resembled the observed data for all of the performed goodness-of-fit tests. In terms of cost-effectiveness, these relatively large differences in goodness-of-fit translated into almost a doubling in mean total cost and a 60-day decrease in mean survival time when using the Markov model instead of the HSMM.

The cost-effectiveness analysis that we conducted as part of our case study has two limitations. First, since the aim of this case study was to illustrate model specification and parameter estimation under vertical modeling, and not to conduct a full economic evaluation in support of a real-life decision problem, we felt that it would be sufficient to conduct a

relatively straightforward deterministic analysis. We obviously recognize that in applied health economic evaluation it is a standard practice to complement the results of such a deterministic assessment with probabilistic sensitivity analyses to evaluate how uncertainty in the model inputs accumulates in overall uncertainty in the modeled outcomes.³¹ One way to obtain a joint probability distribution for the parameters of the sojourn-time distributions and the future state probabilities under vertical modeling would be to apply bootstrapping, which is relatively straightforward to implement when patient-level data is available.³² Second, the regression models that we used to specify the different entities of our HSMM (i.e., the parametric survival models for the sojourn-time distributions and the logistic regression models for the future state probabilities) did not contain any covariates apart from the treatment indicator (for all models) and the sojourn time (to estimate the probability of out-of-hospital death). Our model therefore does not allow for the assessment of patient heterogeneity as described by Groot Koerkamp et al..³³ This potential limitation, however, can easily be overcome by adding patient characteristics, such as sex, age, and comorbidity as additional covariates in the regression models. For a more concrete and extensive discussion on how to deal with patient heterogeneity within the context of a health economic evaluation, we refer the reader to Grutters et al..³⁴

The fundamental assumption underlying the HSMM is that the future state transitions only depend on the history of the process through the time since entry in the present state. A limitation of this type of model is therefore that the possible influence that other time scales such as general ageing of an individual may have on a patient's disease progression are ignored. For the modeling of chronic diseases, this could for instance result in an overestimation of the mean survival time when age is not included as a fixed-time covariate in the regression models, which would allow us to update this variable each time that a transition into a new state occurs. Alternatively, one could overcome this limitation by switching from a

homogeneous to a non-homogeneous semi-Markov model, in which age would then be included as a time-dependent covariate.³⁵ The specification and estimation of this latter type of model is however far less straightforward as the transition intensities as well as all functionals directly derived from these intensities then become functions of both the time since entry in the model and the time since entry in the present state. Another way to relax the assumptions behind the HSMM would be to let the transition intensities not only depend on the time since entry in the present state but also on how often this state has previously been visited. For example, Bakal et al.³⁶ have recently established that the time between consecutive HF-related hospitalizations decreases as the number of previous admissions increases. When using vertical modeling, such dependencies can be easily included in the model specification of the sojourn-time distributions by including the number of previous HF hospitalizations as an additional covariate in the regression equations. However, as the resulting STM is then strictly speaking no longer a semi-Markov model, we refrained from doing so in our case study.

To conclude, the continuous-time semi-Markov model provides a sensible balance between model parsimoniousness and computational complexity for many clinical disease processes. In this paper, we described and illustrated how such models can be estimated from right-censored time-to-event data. Future research effort may be directed at how one could conduct the estimation when the data is subjected to other types of censoring, such as interval censoring.

ACKNOWLEDGMENTS

The authors declare that there are no conflicts of interest. This research was performed within the framework of CTMM, the Center for Translational Molecular Medicine (www.ctmm.nl),

project TRIUMPH (grant 01C-103) and ENGINE (grant 01C-401), and supported by the Dutch Heart Foundation.

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Table 1: The specification of the regression models and the results of the parameter estimation for both the HSMM and the Markov model

	Log(ρ)	α	$\beta_T T$	$\beta_{u1}(u/100)$	$\beta_{u2}(u/100)^2$
	coef. (s.e.)	coef. (s.e.)	coef. (s.e.)	coef.(s.e.)	coef. (s.e.)
HSMM					
$F_1(u)$					
Care-as-usual	0.76 (0.06)	6.45 (0.14)			
Basic	0.85 (0.06)	6.45 (0.14)	0.12 (0.20)		
Intensive	0.90 (0.06)	6.45 (0.14)	0.13 (0.21)		
$F_2(u)$					
Care-as-usual	-0.11 (0.07)	2.33 (0.08)			
Basic	-0.02 (0.07)	2.33 (0.08)	-0.30 (0.12)		
Intensive	-0.11 (0.06)	2.33 (0.08)	-0.11 (0.12)		
$\pi_{13}(u)$					
Care-as-usual		-0.09 (0.21)		-0.60 (0.20)	0.13 (0.04)
Basic		-0.09 (0.21)	-0.09 (0.21)	-0.60 (0.20)	0.13 (0.04)
Intensive		-0.09 (0.21)	-0.35 (0.22)	-0.60 (0.20)	0.13 (0.04)
π_{23}					
Care-as-usual		-1.38 (0.23)			
Basic		-1.38 (0.23)	-0.46 (0.36)		
Intensive		-1.38 (0.23)	-0.48 (0.35)		
Markov					
$F_1(u)$					
Care-as-usual		6.66 (0.07)			
Basic		6.66 (0.07)	0.03 (0.10)		
Intensive		6.66 (0.07)	0.03 (0.10)		
$F_2(u)$					
Care-as-usual		2.70 (0.09)			
Basic		2.70 (0.09)	-0.21 (0.13)		
Intensive		2.70 (0.09)	-0.10 (0.13)		
π_{13}					
Care-as-usual		-0.43 (0.15)			
Basic		-0.43 (0.15)	-0.05 (0.21)		
Intensive		-0.43 (0.15)	-0.34 (0.21)		
π_{23}					
Care-as-usual		-1.38 (0.23)			
Basic		-1.38 (0.23)	-0.46 (0.36)		
Intensive		-1.38 (0.23)	-0.48 (0.35)		
HSMM: $\begin{cases} F_1(u; \lambda, \rho) = F_2(u; \lambda, \rho) = \Phi(\frac{\log u - \lambda}{\rho}) \\ \lambda = \alpha + \beta_T T \end{cases}$ $\begin{cases} \theta(\pi_{13}(u)) = \alpha + \beta_T T + \beta_{u1}(u/100) + \beta_{u2}(u/100)^2 \\ \theta(\pi_{23}) = \alpha + \beta_T T \end{cases}$					
Markov: $\begin{cases} F_1(u; \lambda) = F_2(u; \lambda) = 1 - \exp(-\lambda u) \\ \lambda = \exp(-\alpha - \beta_T T) \end{cases}$ $\begin{cases} \theta(\pi_{13}) = \alpha + \beta_T T \\ \theta(\pi_{23}) = \alpha + \beta_T T \end{cases}$					
Note: Care-as-usual is the reference category for $\beta_T T$ $\theta(\pi) = \log(\pi/(1-\pi))$ is the logit function					

Table 2: Results of the cost-effectiveness analysis. In the ICER column, basic support is compared against care-as-usual and intensive support is compared against basic support.

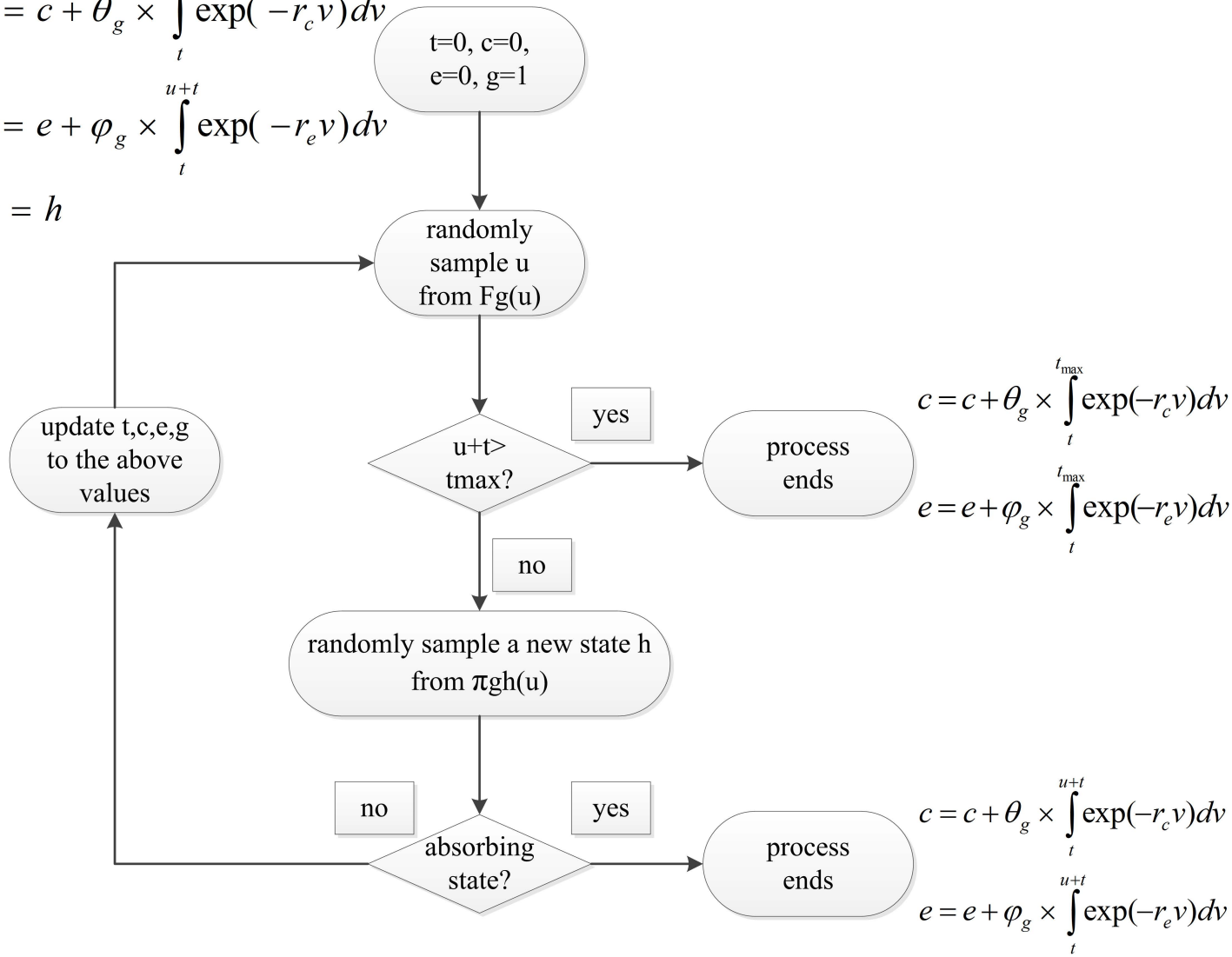
Patient subgroup (Sample size)	Mean total cost (€)	Mean survival time (years)	ICER
HSMM			
Care-as-usual (N=339)	5736	2.99	
Basic support (N=340)	5656	3.18	Dominates c-a-u
Intensive support (N=344)	7555	3.30	15825
Markov			
Care-as-usual (N=339)	10430	2.83	
Basic support (N=340)	9811	3.00	Dominates c-a-u
Intensive support (N=344)	13280	3.17	20406

$$t = u + t$$

$$c = c + \theta_g \times \int_t^{u+t} \exp(-r_c v) dv$$

$$e = e + \varphi_g \times \int_t^{u+t} \exp(-r_e v) dv$$

$$g = h$$



t : simulation time in years

c : cost estimate

e : effectiveness estimate

u : state sojourn time

$F_g(u)$: sojourn time distribution within state g

t_{\max} : study time horizon

r_c : continuous-time discount rate for costs

θ_g : cost attached to state g

r_e : continuous-time discount rate for health effects

φ_g : utility attached to state g

Note: To get annual discount rates of DR_c for costs and DR_e for health effects, r_c and r_e should be set as follows:

$$r_c = \ln(1 + DR_c)$$

$$r_e = \ln(1 + DR_e)$$

