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Multistate Analysis of Interval-Censored Longitudinal Data: Application to a Cohort Study on Performance Status Among Patients Diagnosed With Cancer

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In observational studies on cancer patients, progression of performance status over time can be described by using a multistate model in which state-to-state transitions represent changes in a patient's health condition. Although a patient experiences transitions in continuous time, assessments on the patient are often made at irregularly spaced time points. In this paper, the authors formulate a Markov 4-state model for examining longitudinal data on performance status collected under intermittent observation. The cohort consisted of 11,342 patients diagnosed with cancer in Ontario, Canada, from 2007 to 2009. The authors extend the model to estimate the predicted probability of reaching the absorbing state, death, over various time intervals. The authors also illustrate what happens to the estimated transition intensities if the true observational scheme is overlooked. Methods for multistate analysis should be used by epidemiologists, since they prove particularly useful for examining the complexities of disease processes.

intensity function; interval censoring; longitudinal studies; Markov chains; Markov process; transition function; transition matrix

Abbreviations: CI, confidence interval; PPS, Palliative Performance Scale.

Multistate models can be used to describe changes in a patient's health condition over time (1). In the study of chronic illness, these models classify a patient into one of a finite number of distinct states at any given point during his or her follow-up (2, 3). The states represent various health conditions, transitions between states correspond to changes in a patient's health condition, and the transition times correspond to the times at which these changes occur.

In addition to multistate models, several alternate approaches are available for examining longitudinal data on health states of a patient. Deciding which method to use often depends on the questions that need to be answered. A correlated ordinal model may suffice if one is interested in estimating the relation between the probability of being in a particular health state and the time since diagnosis. If the objective is to predict time-to-event probabilities, a survival model can be implemented in which a time-dependent covariate may be used to express events that may affect a person's health condition. Multistate models are particularly useful for describing the complexities of a disease process (4–6). They are more applicable when interest lies in estimating the instantaneous rate of transition between various states, estimating the probability of transition from one state to another within a specific time period, or estimating the average period of a single stay in a state (mean sojourn time). Although methods for multistate analysis have been well studied, epidemiologists and clinicians have not taken advantage of these developments.

When patients are followed continuously and transition times are subject only to right-censoring, a wide range of multistate modeling and estimation strategies are available (7). In reality, however, it is often not possible to observe patients continuously throughout the course of disease, especially when patients are assessed by a physician only at periodic clinic or home visits. In these cases, the exact times of state-to-state transitions other than death are interval-censored. The transition is only known to have occurred within a bounded time interval, usually between

assessments. Under intermittent observation, the data available for an individual consist of the assessment times and the states that are occupied at each of these times. Data emerging from this observation scheme pose a variety of estimation challenges because of the incomplete information on transition times and the fact that the number and timing of assessments may vary dramatically across patients. Thus, standard multistate methods can no longer be applied. See Commenges (8), Cook et al. (9), and Sutradhar and Cook (10) for a review of some recently developed multistate methods under incomplete observation.

The purpose of this paper is 3-fold. First, we provide the fundamental concepts for constructing a multistate model. Approaches for estimating the transition intensities are discussed under both continuous time and intermittent observation schemes. Second, we illustrate the use of the multistate method for analyzing longitudinal data on performance status for patients diagnosed with cancer. We estimate the risks of improvement and deterioration over various time intervals, along with the mean sojourn time in each nonabsorbing state. Our approach accommodates 1) interval-censored transition times, 2) absence of information on the state occupied immediately prior to death, and 3) absence of information on the state occupied at the end of follow-up—that is, at the censoring date (if there is no assessment on this date). Third, we demonstrate what happens to the estimates of the transition intensities if the true observation process is overlooked.

MATERIALS AND METHODS

Basic framework for multistate models

Multistate models are governed by transition intensity functions (1, 3, 7). The transition intensity function represents the *instantaneous* incidence rate of moving from state j to state k at time t:

$$\lambda_{jk}(t) = \lim_{\Delta t \to 0} \frac{P\{Y(t+\Delta t) = k | Y(t) = j\}}{\Delta t}, \quad j \neq k, \qquad (1)$$

where $Y(t)$ is the state occupied at time t. This transition intensity is the (j, k) entry of the transition intensity matrix, denoted by Λ, the rows of which sum to 0; the diagonal entries of Λ are defined by convention as

$$\lambda_{jj}(t) = -\Sigma_{k \neq j} \lambda_{jk}(t). \qquad (2)$$

If a particular instantaneous state-to-state transition is not permitted in the underlying multistate model, then the corresponding transition intensity has a value of 0.

The transition intensities can be used to compute the transition probabilities, that is, the probability of being in state j at time s and then in state k at time t:

$$p_{jk}(s,t) = P\{Y(t) = k | Y(s) = j\}, \quad 0 \leq s < t. \qquad (3)$$

Note that $p_{jk}(s, t)$ does not say anything about the actual time of transition from state j to state k; the process may certainly have entered other states between times s and t. This probability is the (j, k) entry of the transition probability matrix, denoted by $\mathbf{P}(\mathbf{s}, \mathbf{t})$, the rows of which sum to 1 (1, 3).

Multistate models are often based on first-order Markov processes. The first-order Markov assumption has a "memoryless" property, as it claims that future evolution of the disease process depends only on the current state (6, 11). That is, the state occupied at time $t + \Delta t$ is conditional on the state occupied at time t. A Markov multistate model, developed with an adequate number of well-defined states, is often appropriate for examining progression of degenerative diseases such as cancer (3, 4). Compared with a simple survival model without covariates (which is Markov by definition), the inclusion of intermediate states provides the Markov model with additional "memory," that is, additional information on the path of the disease process.

Here we create a multistate model with 4 distinct states (described below). These states provide a considerable amount of detail on the progression of performance status—enough information to reasonably assume that the current state of the patient is the driving factor in determining future performance status. The Markov assumption is adopted throughout this paper.

Assuming a Markov property when it is not appropriate can lead to biased parameter estimates and unreliable standard errors. In the presence of interval-censoring, the statistical literature and available software on methods of estimation for multistate models are primarily founded on Markov assumptions. Recently, there have been approaches developed to handle multistate models under interval-censoring based on conditionally Markov assumptions using a random-effects approach (9, 10).

Parameter estimation under complete and intermittent observation

The typical aim in a multistate model is to estimate the state-to-state transition intensities. The available data and the corresponding observation schemes drive the construction of the likelihood function. Maximization of this function provides estimates of the transition intensity parameters. Consider a multistate process for which we are able to record the exact times at which transitions occur, as well as the corresponding states occupied. To establish notation for such data, suppose the ith individual makes transitions at times $t_{i1} < t_{i2} < \ldots < t_{im_i}$ into states $s_{i1}, s_{i2}, \ldots s_{im_i}$, respectively, according to a Markov process. Conditional on the state occupied at time $t = 0$ being s_{i0}, the likelihood based on complete observation can be written in terms of the transition intensity functions (1, 7) as

$$\prod_{i=1}^{n} \prod_{r=1}^{m_i} \left[\lambda_{s_{i,r-1}, s_{ir}}(t_{ir}) \exp\left\{ -\int_{t_{i,r-1}}^{t_{ir}} \sum_{l \neq s_{i,r-1}} \lambda_{s_{i,r-1}, l}(u) du \right\} \right]$$
$$\exp\left\{ -\int_{t_{im_i}}^{\tau_i} \sum_{l \neq s_{im_i}} \lambda_{s_{im_i}, l}(u) du \right\}, \qquad (4)$$

where $(0, \tau_i)$ is the follow-up period for the ith patient and

$t_{i0} = 0$. The first term in the likelihood (within the square brackets) is the probability of being in state $s_{i,r-1}$ at time $t_{i,r-1}$ and then transitioning to state s_{ir} at time t_{ir} (with no intermediate transitions); the second term is the probability of not transitioning out of state s_{im_i} between time t_{im_i} and τ_i. Several methods, including parametric and nonparametric approaches, may be used to maximize the likelihood in order to obtain estimates of the transition intensity parameters (7).

As we noted above, it is rare to witness the exact times at which transitions occur during the follow-up period. Although transitions are experienced in continuous time, it is often the case that observations are made at irregularly spaced time points, which may differ substantially across patients. As a result, the exact transition times are interval-censored. To develop notation under this incomplete observation scheme, suppose the ith individual is examined intermittently at times $b_{i1} < b_{i2} < \ldots < b_{im_i}$ and the states occupied at these times are $s_{i1}, s_{i2}, \ldots s_{im_i}$, respectively; the actual transitions are still assumed to occur according to a Markov process. Conditional on the state occupied at time $t = 0$ being s_{i0}, the likelihood based on intermittent observation can be written in terms of the transition probability functions (8, 9) as

$$\prod_{i=1}^{n}\prod_{r=1}^{m_i} p_{s_{ir-1},s_{ir}}\left(b_{ir-1}, b_{ir}\right), \qquad (5)$$

where $b_{i0} = 0$. A quasi-Newton algorithm can be used to maximize this likelihood to obtain estimates of the transition intensity parameters. This method requires only the computation of first-order derivatives; the second-order derivatives are replaced by estimates of their expectations using a scoring procedure (8–10). Recently, there has been progress in the development of software for implementing these methods for multistate models. The msm package in R allows a general multistate model to be fitted to longitudinal data (12, 13).

Study population

Under the initiative known as the Ontario Cancer Symptom Management Collaborative, since January 1, 2007, cancer centers across the province of Ontario, Canada, have been implementing the systematic collection of symptom screening data using the Edmonton Symptom Assessment System and performance status assessment data obtained using the Palliative Performance Scale (PPS) in cancer outpatients (14–16). Patients eligible for assessment include those living in all regions of the province, with any cancer diagnosis, of any age, from ambulatory and/or home settings, and with any treatment intent. Assessments happen on an opportunistic basis depending on how each cancer center or home-care program implements the Ontario Cancer Symptom Management Collaborative initiative.

The longitudinal outcome of interest in this study was the PPS. The PPS is a validated tool for assessing both the performance status of a patient (16) and prognosis in a palliative population, and it is known to be predictive of survival (17, 18). It is an ordinal 10-point scale with scores ranging to 100 (the higher the score, the better the performance status) that describes a patient's level of ambulation, activity level, evidence of disease, ability to carry out self-care, intake (alertness), and level of consciousness. The PPS is administered by a physician or nurse at the time of a visit to a cancer center or at the time of a visit from a home-care nurse.

The cohort included patients who were diagnosed with cancer after January 1, 2007, and had at least 1 PPS assessment after diagnosis. Information on diagnosis date and type of cancer diagnosis was retrieved from the Ontario Cancer Registry, a comprehensive population-based cancer registry created to capture all incident cases of cancer in the province (19, 20). Patients were followed until their date of death (which was retrieved from administrative databases) or March 31, 2009, at which time they were considered censored.

Multistate analysis

When a patient has been diagnosed with cancer in Ontario, his or her performance status at each clinic visit or home-care assessment is characterized on the basis of the PPS score. The origin of the time scale is the date of diagnosis, where time is measured in months. To formulate a multistate model, we identify well-defined states which represent the performance status of a patient over time. In particular, a patient is classified as being in one of the following 4 states: state 1 (the stable state) if the PPS score is 70–100; state 2 (the transitional state) if the PPS score is 40–60; state 3 (the end-of-life state) if the PPS score is 10–30; and state 4 if deceased. The PPS cutoffs of 70 and 40, as well as the descriptions of each state, are selected on the basis of clinical reasoning (21, 22).

In our data, although a patient can be in state 3 at an assessment and then in state 1 at the next assessment, this does not imply that an instantaneous transition from state 3 to state 1 is clinically possible. The form of the multistate model should describe the *underlying* progression of PPS scores, rather than the *observed* progression of PPS scores. Figure 1 illustrates the underlying 4-state model; the arrows indicate the directions in which instantaneous transitions are permitted. Based on clinical expertise on the progression of performance status, transitions between states 1 and 2 and between states 2 and 3 are considered to be bidirectional. A patient may instantaneously experience a transition into state 3 from state 1; however, he or she may not reach state 1 from state 3 without experiencing state 2. Once state 4 has been reached, no further transitions can be made, since death is an absorbing state.

It is important to consider the reasons why the assessments were made at the given times. Assessments can be fixed in advance, random and independent of the patient's current state, based on a physician's recommendation, or based on patient self-selection. If based on a physician's recommendation, only information about the patient's status at the current visit determines the time of the next visit, whereas under patient self-selection, a patient can decide to see the doctor immediately based on how he or she is

feeling at that moment. Grüger et al. (23) have shown that when assessments are based on a physician's recommendation, the joint likelihood of the assessment times and the transition times is proportional to the likelihood obtained if the assessment times were fixed in advance. This implies that assessment times arising from a physician's recommendation are noninformative.

Grüger et al. (23) have shown that only assessment schemes based on patient self-selection are informative. In our data, times for assessing performance status were scheduled depending on how each cancer center or home-care program was implemented within the patient's region. As far as it is known, assessment times were either fixed, random, or based on a physician's recommendation—that is, noninformative.

Because the PPS is administered at arbitrary clinic or home visits, it is extremely unlikely that the assessment times are the actual times at which the instantaneous transitions occur. It is important to account for the fact that the exact transition times are not known; rather, they are interval-censored. Figure 2 demonstrates how a patient's underlying PPS progression is viewed under intermittent observation. The dotted vertical lines represent the assessment times (in months from cancer diagnosis), and the solid horizontal arrows represent the true lengths of stay in each state. For example, at 5 months from diagnosis, this hypothetical patient was observed to be in state 2; the patient then died 11 months from diagnosis. In reality, however, between 5 and 11 months from diagnosis, this patient made a transition from state 2 to state 1 and then from state 1 to state 3 before finally reaching state 4.

In addition to accommodating interval-censoring, our approach accounts for other limitations in observation. The time of death is available. However, under intermittent observation, the state occupied at the instant prior to death is not known. Moreover, if a patient is alive at the end of follow-up and does not have an assessment on this date, then the state occupied at this time is also not known; we can only infer that the patient is in state 1, 2, or 3 at this time. As was shown above, all limitations in the available data must be reflected in the construction of the likelihood.

Based on the underlying 4-state model (Figure 1) and assuming a time-homogeneous Markov process (9, 10), we express the corresponding transition intensity matrix as

$$\Lambda = \begin{bmatrix} -(\lambda_{12}+\lambda_{13}+\lambda_{14}) & \lambda_{12} & \lambda_{13} & \lambda_{14} \\ \lambda_{21} & -(\lambda_{21}+\lambda_{23}+\lambda_{24}) & \lambda_{23} & \lambda_{24} \\ 0 & \lambda_{32} & -(\lambda_{32}+\lambda_{34}) & \lambda_{34} \\ 0 & 0 & 0 & 0 \end{bmatrix}. \quad (6)$$

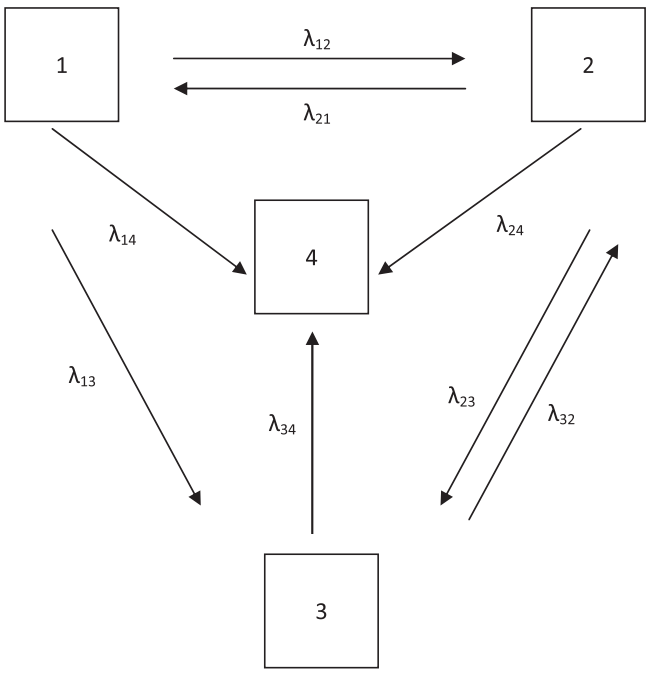

Figure 1. Underlying 4-state model for examining disease progression among cancer patients using the Palliative Performance Scale (PPS), PPS Cohort Study, Ontario, Canada, 2007–2009. (1—stable state; 2—transitional state; 3—end-of-life state; 4—deceased).

Our primary aim is to estimate the transition intensity parameters, meaning the elements of matrix $\mathbf{\Lambda}$. This will be done by maximizing the likelihood function, which will be constructed on the basis of our specific intermittent observation scheme. In addition, we will estimate the mean sojourn time in each nonabsorbing state. We will also estimate the elements of the transition probability matrix over a specific period of time $\mathbf{P(t)}$; this provides the estimated probability of eventually going from one state to another over time t. Finally, we will demonstrate what happens to the estimates of

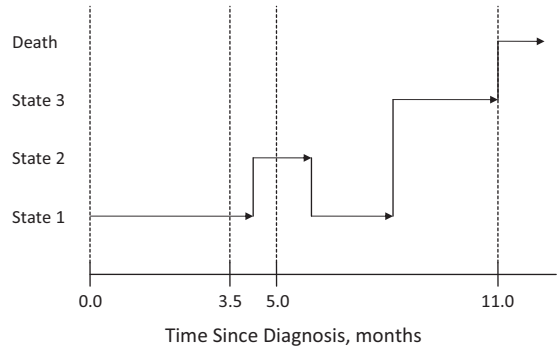

Figure 2. Observed progression versus underlying progression of performance status for a hypothetical cancer patient, PPS Cohort Study, Ontario, Canada, 2007–2009. (PPS, Palliative Performance Scale).

Table 1. Distribution of Pairs of Consecutive Observed States Among Cancer Patients in the PPS Cohort Study, Ontario, Canada, 2007–2009

State[a] at Current Assessment	State at Next Assessment			
	State 1	State 2	State 3	State 4
State 1	35,436	4,360	184	2,192
State 2	1,489	11,932	180	2,341
State 3	20	57	549	273
State 4	0	0	0	0

Abbreviation: PPS, Palliative Performance Scale.
[a] A patient was classified as being in state 1 (the stable state) if the PPS score was 70–100; state 2 (the transitional state) if the PPS score was 40–60; state 3 (the end-of-life state) if the PPS score was 10–30; and state 4 if deceased.

the transition intensity parameters if the true observation process is ignored. We will do this by assuming that the assessment times are the exact times of state transitions.

In all analyses, we used the msm package available in R (12, 13).

RESULTS

Of all patients diagnosed with cancer in Ontario during the study period, 9% had at least 1 PPS assessment after diagnosis. The cohort in our multistate analyses thus consisted of 11,342 cancer patients. The median time between assessments was 0.7 months.

Table 1 provides the frequencies of pairs of consecutive observed states. For each state j and k, we counted the number of times there was an assessment of state j followed by an assessment of state k (over all patients). There were 2,192 deaths recorded from the stable state; only on 20 occasions was there an assessment of end-of-life performance status followed by an assessment of stable performance status.

The results from Table 1 should be interpreted with caution. They are simply observed frequencies and do not reflect the underlying progression of performance status. As an example, if an additional assessment could have been made just prior to death for those patients observed to die from the stable state, it may have shown that the patient was actually in the transitional or end-of-life state before dying.

The primary results from our multistate analyses are presented in Table 2. The table shows the maximum likelihood estimate and corresponding 95% confidence interval for each possible instantaneous transition. For patients in the transitional state (state 2), the rates of transition to the stable state (state 1) and the end-of-life state (state 3) are equal; this is interpreted from comparing the estimates 0.144 and 0.145 in the second row. However, the rate of transition from the transitional state to death (state 4) is 1.6 times higher (0.239/0.144) than these estimates, implying that the more likely transition from state 2 is to death. Once a patient is in the end-of-life state, the rate of progression to death is 10 times higher (1.446/0.142) than the rate of recovery to the transitional state. Moreover, the rate of transition to death is 6 times higher (1.446/0.239) from the end-of-life state than from the transitional state. Note that we reran the likelihood maximization routine several times, using different sets of initial values and different optimization algorithms. All reruns provided very similar results (within 1 decimal place) for the transition intensity parameter estimates, ensuring that we had reached convergence to the global maximum (13).

The multistate analyses also provided the estimated mean sojourn time in each nonabsorbing state, along with the corresponding 95% confidence interval. The average amount of time a patient spent in state 1 before transitioning into another state was 16.74 months (95% confidence interval (CI): 16.35, 17.14). More drastically, the average amount of time spent in state 2 before making a transition was 1.88 months (95% CI: 1.83, 1.94), and the average amount of time spent in state 3 before making a transition (into either a healthier state or death) was 0.63 months (95% CI: 0.56, 0.69).

The estimated 1-month and 6-month transition probability matrices are given in Table 3. A patient in the transitional state had an 11% chance of being in the stable state at the end of 1 month, a 5% chance of being in the end-of-life state at the end of 1 month, and a 24% chance of being dead at the end of this time. The probability of being dead at the end of 1 month was 0.8% for a patient in the stable state and 74% for a patient in the end-of-life state. As Table 3 shows, a patient in the stable state had a 15% probability of being dead at the end of 6 months and a 75% probability of still being in the stable state at the end of 6 months. A patient in the transitional state had a 22% chance of being in the stable

Table 2. Estimated Transition Intensity Matrix of the Multistate Model Among Cancer Patients in the PPS Cohort Study, Ontario, Canada, 2007–2009

State[a]	State 1		State 2		State 3		State 4	
	MLE	95% CI	MLE	95% CI	MLE	95% CI	MLE	95% CI
State 1	−0.059	−0.061, −0.058	0.058	0.056, 0.059	$1.2e^{-03}$	$8.2e^{-04}$, $1.7e^{-03}$	$4.4e^{-04}$	$2.0e^{-04}$, $9.9e^{-04}$
State 2	0.144	0.137, 0.151	−0.529	−0.545, −0.514	0.145	0.126, 0.166	0.239	0.221, 0.259
State 3	0.0		0.142	0.113, 0.178	−1.588	−1.757, −1.436	1.446	1.298, 1.611
State 4	0.0		0.0		0.0		0.0	

Abbreviations: CI, confidence interval; MLE, maximum likelihood estimate; PPS, Palliative Performance Scale.
[a] A patient was classified as being in state 1 (the stable state) if the PPS score was 70–100; state 2 (the transitional state) if the PPS score was 40–60; state 3 (the end-of-life state) if the PPS score was 10–30; and state 4 if deceased.

Table 3. Estimated 1-Month and 6-Month Transition Probabilities Among Cancer Patients in the PPS Cohort Study, Ontario, Canada, 2007–2009

Month and State[a]	Maximum Likelihood Estimate			
	State 1	State 2	State 3	State 4
1 month				
State 1	0.945	0.044	0.003	0.008
State 2	0.109	0.596	0.053	0.242
State 3	0.005	0.052	0.207	0.735
State 4	0.0	0.0	0.0	1.0
6 months				
State 1	0.750	0.087	0.009	0.154
State 2	0.216	0.068	0.008	0.708
State 3	0.019	0.008	0.001	0.972
State 4	0.0	0.0	0.0	1.0

Abbreviation: PPS, Palliative Performance Scale.

[a] A patient was classified as being in state 1 (the stable state) if the PPS score was 70–100; state 2 (the transitional state) if the PPS score was 40–60; state 3 (the end-of-life state) if the PPS score was 10–30; and state 4 if deceased.

state at the end of 6 months and a 0.83% chance of being in the end-of-life state at the end of 6 months; the latter probability was low because most patients in the transitional state are already deceased at the 6-month mark (probability = 71%). Patients in the end-of-life state had only a 2.7% chance of experiencing an improvement in performance status (i.e., of being in state 1 or state 2) at the end of 6 months.

The estimates of the transition probability matrices can be used to plot the estimated survival probability against time (in months from cancer diagnosis) from each of the nonabsorbing states, as illustrated in Figure 3. The survival probability for patients in the end-of-life state diminished very rapidly within the first few months after diagnosis. The 12-month survival probability for a patient with end-of-life performance status was approximately 0.02, as opposed to 0.20 and 0.66 for patients with transitional and stable performance status, respectively.

Thus far, all results from our multistate analyses have been based on the true intermittent observation scheme with interval-censoring. Unfortunately, in many studies, interval-censoring is often ignored and unaccounted for in the analyses, primarily because likelihood construction and parameter estimation become increasingly complicated. Mistakenly assuming that the assessment times are the exact times of transition can provide misleading results. Table 4 shows estimates of the 6-month transition probabilities for reaching death from the stable, transitional, and end-of-life states under both intermittent and complete observation schemes. If we assume that the change in a patient's performance status occurs at the time of assessment, then the probability of transitioning from the stable state to death within 6 months is slightly overestimated. On the other hand, the probabilities of transitioning from the transitional state to death and from the end-of-life state to death within 6 months are underestimated. In fact, by assuming complete observation, a patient in the end-of-life state would believe that he or she has an 85% chance of dying within the next 6 months, whereas in reality, by correctly assuming intermittent observation, this patient has a 97% chance of dying within the next 6 months.

DISCUSSION

The multistate analysis presented in this paper provides insight into the nature of the progression of performance status over time. A patient in the transitional state has a reasonable chance of experiencing an improvement in performance status at the end of 6 months. However, once

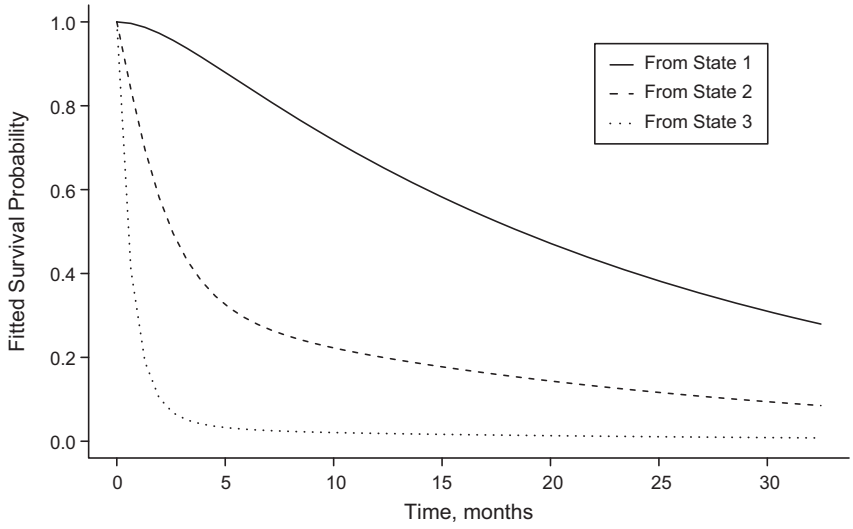

Figure 3. Estimated survival probability over time (months) from each nonabsorbing state to death among cancer patients in the PPS Cohort Study, Ontario, Canada, 2007–2009. (PPS, Palliative Performance Scale).

Table 4. Estimated 6-Month Transition Probabilities for Reaching Death From Each Nonabsorbing State Under Intermittent and Complete Observation Among Cancer Patients in the PPS Cohort Study, Ontario, Canada, 2007–2009

Transition[a]	Maximum Likelihood Estimate	
	Intermittent Observation Scheme	Complete Observation Scheme
State 1 to state 4	0.154	0.161
State 2 to state 4	0.708	0.566
State 3 to state 4	0.972	0.851

Abbreviation: PPS, Palliative Performance Scale.

[a] A patient was classified as being in state 1 (the stable state) if the PPS score was 70–100; state 2 (the transitional state) if the PPS score was 40–60; state 3 (the end-of-life state) if the PPS score was 10–30; and state 4 if deceased.

a patient reaches the end-of-life state, it is very unlikely that his or her performance status will improve; for these patients, the probability of being dead at the end of 6 months is 97%. In this paper, we estimated the multistate model parameters based on the natural intermittent observation scheme. In addition, we highlighted the misleading results and dangers in interpretation that arise if the true observation scheme is ignored.

From a clinical perspective, the multistate model offers a different view and interpretation of the PPS than the existing literature (17, 21). It adds to the prognostic information provided by the instrument and contributes to a clinician's ability to anticipate a patient's future needs. The mean sojourn times provided by this multistate model have policy implications if, for example, home-care services are rationed by PPS score. These results show that waiting until a patient reaches the end-of-life state may be too late for discussing hospice/palliative-care options, since patients usually spend less than 1 month in this state. Instead, the transitional state may be the right time for providers to begin palliative-care discussions, since the time spent in this state is often sufficient (1.88 months). Such estimates are not available from a more traditional survival model. Unfortunately, under intermittent observation, the exact time at which a patient reaches the transitional state is unknown, making it difficult for clinicians to advise patients in a timely manner. This should motivate clinicians to decrease the gap between assessments; in this way, the window of time during which a patient enters the transitional state is narrowed down. The cohort included in this study was primarily ambulatory, making the results generalizable to an outpatient clinic setting rather than a palliative-care setting.

In this paper, we have not discussed the use of covariates to understand how risk factors may change the transition rates. The available data consisted of information on age, sex, income quintile, and cancer type for each patient. It is of future interest to examine the association of such variables with the transition intensities of our multistate model under interval-censoring. These methods are currently under investigation.

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REFERENCES

1. Andersen PK, Keiding N. Multi-state models for event history analysis. *Stat Methods Med Res.* 2002;11(2):91–115.
2. Andersen PK, Green A. Robustness to differential mortality of incidence estimation in an illness-death-emigration model. *Scand J Stat*. 1985;12:63–68.
3. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. 2nd ed. New York, NY: John Wiley & Sons, Inc; 2002.
4. Lawless JF. *Statistical Models and Methods for Lifetime Data*. 2nd ed. New York, NY: John Wiley & Sons, Inc; 2003.
5. Kay R. The analysis of transition times in a multistate stochastic process using proportional hazard regression models. *Commun Stat Theory Methods*. 1983;11:1743–1756.
6. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York, NY: Springer Publishing Company; 2000.
7. Andersen PK, Borgan O, Gill RD, et al. *Statistical Models Based on Counting Processes*. New York, NY: Springer-Verlag New York; 1993.
8. Commenges D. Inference for multi-state models from interval-censored data. *Stat Methods Med Res.* 2002;11(2):167–182.
9. Cook RJ, Yi GY, Lee KA, et al. A conditional Markov model for clustered progressive multistate processes under incomplete observation. *Biometrics*. 2004;60(2):436–443.
10. Sutradhar R, Cook RJ. Clustered progressive multi-state processes under incomplete observation: application to joint damage in psoriatic arthritis. *J R Stat Soc Ser C*. 2008;57(5):553–566.

11. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med*. 2007; 26(11):2389–2430.
12. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2009. (http://www.R-project.org). (Accessed January 15, 2010).
13. Jackson C. *msm: Multi-State Markov and Hidden Markov Models in Continuous Time.* (R, version 0.9.5). Vienna, Austria: R Foundation for Statistical Computing; 2009. (http://cran.r-project.org/web/packages/msm/). (Accessed January 15, 2010).
14. Ripamonti CI, Farina G, Garassino MC. Predictive models in palliative care. *Cancer.* 2009;115(suppl 13):3128–3134.
15. Bruera E, Kuehn N, Miller MJ, et al. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care*. 1991;7(2):6–9.
16. Anderson F, Downing GM, Hill J, et al. Palliative Performance Scale (PPS): a new tool. *J Palliat Care*. 1996;12(1):5–11.
17. Downing M, Lau F, Lesperance M, et al. Meta-analysis of survival prediction with Palliative Performance Scale. *J Palliat Care*. 2007;23(4):245–252.
18. Ho F, Lau F, Downing MG, et al. A reliability and validity study of the Palliative Performance Scale. *BMC Palliat Care*. 2008;7:10. (doi: 10.1186/1472-684X-7-10).
19. Clarke EA, Marrett LD, Kreiger N. Cancer registration in Ontario: a computer approach. In: Jenson OM, Parkin DM, MacLennan R, et al, eds. *Cancer Registration: Principles and Methods*. Lyon, France: International Agency for Research on Cancer; 1991:246–257.
20. Robles SC, Marrett LD, Clarke EA, et al. An application of capture-recapture methods to the estimation of completeness of cancer registration. *J Clin Epidemiol*. 1988;41(5): 495–501.
21. Lau F, Downing M, Lesperance M, et al. Using the Palliative Performance Scale to provide meaningful survival estimates. *J Pain Symptom Manage*. 2009;38(1):134–144.
22. Barbera L, Seow H, Howell D, et al. Symptom burden and performance status in a population-based cohort of ambulatory cancer patients. *Cancer.* 2010;116(24): 5767–5776.
23. Grüger J, Kay R, Schumacher M. The validity of inferences based on incomplete observations in disease state models. *Biometrics*. 1991;47(2):595–605.