Original Article

Multistate Models for Examining the Progression of Intermittently Measured Patient-Reported Symptoms Among Patients With Cancer: The Importance of Accounting for Interval Censoring

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Abstract

Context. Patients with cancer in Ontario, Canada, receive symptom monitoring in a standardized fashion using the Edmonton Symptom Assessment System (ESAS). These measurements can be used to understand symptom progression during the cancer trajectory.

Objectives. This study demonstrates the implementation of multistate models for examining symptom progression, while appropriately accounting for intermittent observation. We also compare the estimates when the panel nature of the data is ignored.

Methods. This was a population-based retrospective cohort study using linked administrative health-care databases. The cohort consisted of patients who were newly diagnosed with a primary cancer and had at least one ESAS assessment completed between 2007 and 2015 in Ontario, Canada. A 5-state model was developed to examine the progression of symptom severity, where estimation was conducted with and without accommodating for the panel nature of the symptom data.

Results. The study cohort consisted of 212,615 patients diagnosed with cancer, collectively having 1,006,360 ESAS assessments within the first year after diagnosis. The median (interquartile range) of the number of ESAS assessments per patient was 3 (1−6), and the average gap time between consecutive assessments was approximately three months. The estimated mean sojourn time in each state was consistently and significantly greater when ignoring interval censoring than when accounting for it. This held true for all states and symptoms.

Conclusion. Our work demonstrates the use of multistate models and the importance of accommodating for intermittent observation when examining symptom progression using ESAS among patients with cancer. This work serves as a methodological guide for applied researchers interested in modeling disease progression under the presence of intermittent observation. J Pain Symptom Manage 2020;■:■−■.

Key Words

Symptom progression, ESAS, panel data, intermittent observation, interval censoring, multistate models, transition probability, sojourn time

Key Messages

- Measurement of symptom burden among patients with cancer occurs on an intermittent basis, giving rise to panel data that are essentially snapshots of a patient's symptom burden experience.
- Multistate models accounting for interval censoring allow researchers to use the *observed*

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progression of symptom burden as a means to estimate the *underlying* progression of symptom burden.
- Ignoring the panel nature of intermittently measured symptom data can lead to significant bias and misleading results.

Introduction

Patients with cancer often experience various symptoms, either stemming from their disease or due to side effects of their cancer treatment.[1–3] Moderate-to-severe symptom burden can have a significant impact on a patient's quality of life and ability to function adequately.[4] Having an understanding about the expected progression of severity for each symptom can be useful to cancer care providers for the planning and management of symptom needs across the disease trajectory. Starting in 2007, Cancer Care Ontario implemented a province-wide program to screen for common cancer symptoms using the Edmonton Symptom Assessment System (ESAS), which is a patient-reported outcome measure. Symptom screening with tools such as ESAS is known to improve symptom identification, symptom monitoring and management, patient-provider communication, and quality of life[5–8]; it has also been used to demonstrate an association between symptom severity with survival, and recent work has shown that information on symptom severity improves the performance of prediction modes for emergency department visit risk.[9] ESAS continues to be widely incorporated into routine clinical care[10,11] and is a common source of measurement for symptom severity among clinicians and health researchers.

Numerous studies examining symptom burden, or similar assessment-based outcomes, use analytic techniques that do not reflect the nature of the data and the manner by which they were measured and do not accommodate their inherent limitations. Symptom assessments using ESAS are conducted intermittently, giving rise to panel data (an intermittent observation scheme) that are essentially snapshots of a patient's symptom burden experience.[4] Also owing to the irregularity of ESAS assessments, there is a wide variation in both the number of ESAS assessments conducted across patients and the gap times between assessments. Moreover, ESAS reflects symptom burden within 24 hours before the assessment.[12] The actual times at which symptoms began and the varying levels of severity experienced between assessments are unknown. Many studies exploring symptom progression have done so by modeling the odds or rates of elevated symptom scores over a prespecified window of time.[13–16] These approaches are limited in several ways: Only patients with an ESAS assessment during the prespecified window of time can be included in the analysis; patients who died without an assessment are handled in the same manner as patients who were alive and did not have an assessment; and patients who, for example, only indicated low symptom severity during their ESAS assessments are assumed not to have experienced elevated symptoms at any other point during this window, which in reality may not be true. Several authors have also examined the rate of transition from various symptom states to hospitalization or death and concluded that severe symptoms lead to shorter time to first hospitalization and shorter survival times; however, their models did not account for the amount of time patients have already spent in that specific symptom state at the time of measurement.[17,18] There are numerous other examples in clinical settings of interval censoring being inappropriately ignored. In a longitudinal study of dementia progression, for example, time to severe dementia was examined using a standard Cox regression model; this approach may not have been suitable as severe dementia could only be determined at assessment times that were often irregularly spaced and several years apart.[19] Another recent study measured quality-of-life scores intermittently among women with breast cancer; however, they implemented standard Cox regression models, not accounting for interval censoring, to examine time to deterioration in quality-of-life score.[20]

Multistate models offer a flexible approach for studying symptom progression while overcoming these limitations listed previously. These models classify a patient into one of a finite number of symptom states at any given time during their observation period.[21] The states represent distinct and mutually exclusive levels of symptom severity, transitions between states reflect changes in a patient's level of symptom severity, and the transition times correspond to the actual times at which these changes occur. Estimating transition probabilities of a multistate model is straightforward when the exact state-to-state transition times are available (under complete observation).[22] However, as patient-reported symptom data collected via ESAS give rise to panel data (incomplete/intermittent observation), only the assessment times and the corresponding symptom states at that time are available. The actual times at which transitions between symptom states occur are unknown because, in reality, the transitions occurred at some point between consecutive assessments. This implies that the actual state-to-state transition times are interval-censored. If recovery from more-to-less severe states is permitted in the multistate modeling framework, then the number of state-to-state transitions occurring between assessments times is also unknown. Moreover, the

actual symptom state just before the end of a patient's observation period is not known (unless an assessment occurred on this date). In these scenarios, it is necessary that estimation under a multistate model takes the panel nature of the data and interval censoring into account.[23] This important feature of multistate models allows the researcher to use the *observed* progression of symptom burden as a means to estimate the *underlying* progression of symptom burden.

The use of multistate models for examining disease progression under intermittent observation has been well-established in both the statistical and clinical literature.[23–30] A recent book by Cook and Lawless offers numerous approaches for handling panel data under a multistate framework;[25] approaches include estimation of multistate models based on Markov assumptions, estimation based on non-Markov assumptions using frailties, nonparametric estimation of state occupancy risk, and estimation under mixed observation schemes. Prior publications demonstrate various clinical applications of multistate models for panel data. Examples include using multistate models to understand the progression of viral rebound among HIV-positive individuals assessed every few months[26]; the progression of joint damage among patients with psoriatic arthritis seen only intermittently[27]; the development of cardiac allograft vasculopathy among heart transplant recipients[28,29]; bone progression-free survival in patients with lung cancer receiving intermittent bone scans[25]; and progression of bronchiolitis obliterans syndrome among lung transplant recipients.[30]

The msm package in *R* offers convenient ways to implement and estimate Markov multistate models under intermittent observation using piecewise-constant intensities.[31] This statistical software package is particularly useful when interest lies in estimating the instantaneous rate of transition between various states, the probability/risk of transitioning from one state to another within a specific time period, the average period of a single stay in a transient state (mean sojourn time), the forecasted total length of time spent in each transient state between two future time points, expected number of visits to a state, and the relationship between characteristics and transition intensities.[31]

This study has two objectives. The first is to demonstrate the implementation of multistate models, appropriately accounting for intermittent observation and interval-censoring, for examining the progression of symptom severity among patients with cancer. The second is to compare what happens to the estimates from the multistate model when the panel nature of the data is ignored, that is, when it is inappropriately assumed that the exact transition times are the actual assessment times, meaning interval censoring is ignored. This work serves as a methodological guide for applied researchers interested in using multistate models, or similar time-to-event models, for investigating disease progression under the presence of intermittent observation.

Methods

Study Design, Population, and Observation Period

This was a population-based retrospective cohort study using linked administrative health-care databases. The cohort consisted of patients who were newly diagnosed with a primary cancer and had at least one ESAS assessment completed between January 1, 2007, and December 31, 2015, in Ontario, Canada. Ontario is Canada's largest and most ethnically diverse province, with a population of 14 million. Patients had to be eligible for the Ontario Health Insurance Plan (OHIP) and at least 18 years of age at the time of diagnosis; OHIP is Ontario's universal health-care insurance program, which is essentially available to all Ontario residents. Confirmation of OHIP eligibility was obtained from the OHIP administrative database, and the Ontario Cancer Registry that captures all incident cases of cancer in Ontario was used to determine the diagnosis date.[32] To capture an ambulatory cohort, patients were included only if their ESAS assessments occurred in a regional cancer center or partner hospital.

We were interested in the progression of symptom severity among patients during their first year after cancer diagnosis. Starting from diagnosis, every patient was observed until one of the following occurred: one year had elapsed, subsequent cancer diagnosis, loss of OHIP eligibility, entry into homecare facility, death, or study end date on December 31, 2015. Administrative databases were linked using unique encoded identifiers and analyzed at ICES (previously known as the Institute for Clinical Evaluative Sciences). ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.

Outcome and Additional Measures

All ESAS assessments occurring over the course of observation were retrieved for each patient. The ESAS assessment dates and the corresponding ESAS scores for each of the nine symptoms were retrieved from the Symptom Management Reporting Database held by Cancer Care Ontario. Symptoms included anxiety, appetite, depression, drowsiness, nausea, pain, shortness of breath, fatigue, and well-being. At each assessment, ESAS scores for each symptom were

captured as continuous measures, ranging from 0 to 10 (with 10 being most severe).

Sex and date of birth were captured from the Registered Persons Database, which is a population-based registry maintained by the provincial Ministry of Health to manage publicly funded health-care services. It contains sociodemographic information on all residents of Ontario eligible for the universal government-funded health-care plan.[33] Year of cancer diagnosis and type of cancer diagnosis were obtained from the Ontario Cancer Registry.

Statistical Analyses

Model Building. A multistate model was developed to understand the progression of symptom severity among patients during their first year after cancer diagnosis. At any given time during a patient's observation period, for each symptom, the level of severity could belong to one of these five distinct states: State 1 (none state) if the ESAS score was 0; State 2 (mild state) if the ESAS score was 1−3; State 3 (moderate state) if the ESAS score was 4−6; State 4 (severe state) if the ESAS score was 7−10; and State 5 (dead state) if the patient was dead. These state classifications were based on familiar ESAS cutoffs used in prior work.[4]

An illustration of the 5-state model is provided in Figure 1. Patients may move back and forth between consecutive symptom states and may reach the absorbing state of death from any of the nonabsorbing states. Death times are considered exact transition times, as the date of transitioning to death is available through our administrative databases. It should be emphasized that the directions of arrows in a multistate model must be determined based on the *underlying* progression of symptom burden, not on the *observed* progression of symptom burden. A patient may be observed to be in the none state during an ESAS assessment and then in the severe state at the next assessment, but this does not imply that a direct arrow should be placed between the none and severe states in Figure 1. In reality (if measurements could be taken in instantaneous time), the patient would have passed through the mild and moderate states, even if for a short moment of time, before reaching the severe state. Therefore, the directions of the arrows must represent only the instantaneous state-to-state transitions that occur in reality. Figure 2 provides an illustration of the underlying versus observed symptom progression for a hypothetical patient. Although this patient was recorded to be in the moderate state at 5.2 months and then dead at 11.3 months, in reality, they started experiencing moderate symptoms at some point between 3.5 and 5.2 months and also experienced severe symptoms between 5.2 months and death. By accounting for intermittent observation when estimating our multistate model, we will be able use the observed progression data to gain a better understanding of the underlying progression.

To be consistent with prior work using multistate models for patient-reported outcomes, the Markov assumption under time homogeneity was adopted throughout the article.[4] This common assumption is based on a first-order Markov process; it is founded on a memoryless property that assumes that future evolution of symptom burden is dependent on an individual's current symptom state. Markov and time-homogeneity assumptions can be assessed via diagnostic plots of fitted vs. empirical survival probabilities and by comparing observed vs. expected prevalence estimates at a series of time points.[34]

Model Estimation. Estimation under this Markov multistate model framework was conducted under two approaches: 1) accounting for interval censoring and 2) ignoring interval censoring. To provide a description of the state space in our data, a frequency table of pairs of consecutive observed states was first calculated for each symptom. The transition intensity matrix and the 6-month transition probabilities to death were estimated for each symptom, with and without accounting for interval censoring. The estimates of the mean sojourn times in each of the nonabsorbing states for every symptom accounting for interval censoring were compared with those estimates ignoring interval censoring. The mean sojourn time is

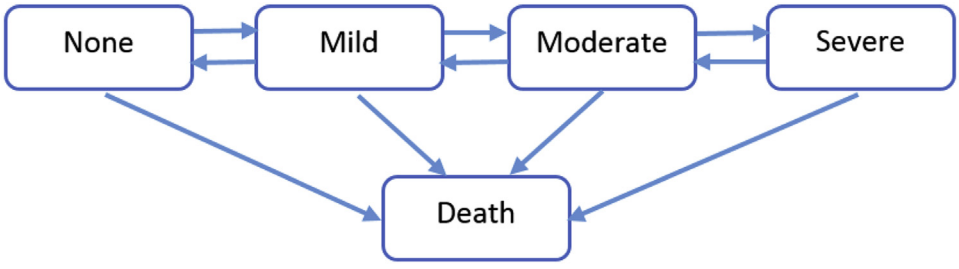

Fig. 1. Underlying 5-state model for examining the progression of symptom severity using Edmonton Symptom Assessment System among patients with cancer.

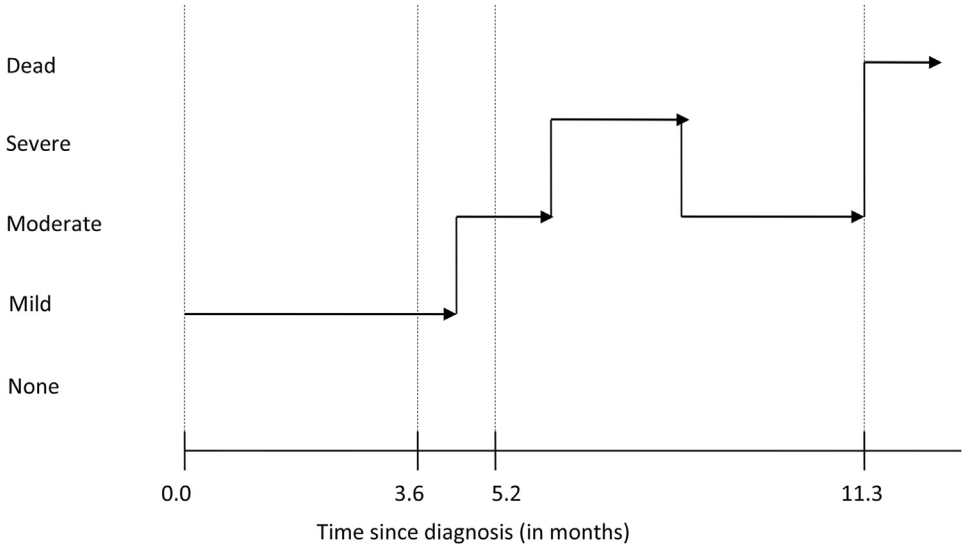

Fig. 2. Plot of observed vs. underlying progression of well-being for a hypothetical patient.

the average amount of time spent during a *single stay* in a state.[31] All analyses were carried out using the msm function in R version 3.1.2.[31]

Results

The study cohort consisted of 212,615 unique patients diagnosed with cancer between January 1, 2007, and December 31, 2015. Table 1 provides the distribution of cohort characteristics at the time of diagnosis. The median age at diagnosis was 63 years (interquartile range, 54–72 years), and 53.9% of the cohort were women. The three most common types of cancer diagnoses were breast (22%), genitourinary (17.2%), and gastrointestinal (17.1%). Within the first year after diagnosis, patients collectively had 1,006,360 ESAS assessments. The median (interquartile range) of the number of ESAS assessments per patient was 3 (1–6), and the average gap time between consecutive assessments was approximately three months. Fatigue, well-being, and anxiety were the most prominent symptoms at the time of diagnosis; nausea was the least severe symptom (with 80.4% of patients reporting they had no nausea at the time of diagnosis).

A descriptive state table over the first year after diagnosis was computed for each symptom (Table 2 provides the state table for symptom well-being, as an example). There were 3693 instances where individuals went from the worst feeling of well-being to the best feeling of well-being between consecutive assessments. There were 2213 instances where individuals reported the best feeling of well-being before dying within a year, without any assessments in between.

Under the 5-state model, the estimated 6-month state-to-state transition probabilities, with and without accounting for interval censoring, were calculated for each symptom (Table 3 provides the transition probability results for symptom well-being, as an example). Among patients currently experiencing the worst feeling of well-being (State 4), the estimated risk of

Table 1
Distribution of Cohort Characteristics at the Time of Cancer Diagnosis (n = 212,615)

Characteristic	Value	Frequency	Percentage	Median	Q1	Q3
Age at diagnosis	Continuous	—	—	63	54	72
Sex	Female	114,665	53.9	—	—	—
Cancer type	Breast	46,881	22.0	—	—	—
	Central nervous system	3073	1.4	—	—	—
	Gastrointestinal	36,394	17.1	—	—	—
	Genitourinary	36,626	17.2	—	—	—
	Gynecologic	17,663	8.3	—	—	—
	Hematology	25,341	11.9	—	—	—
	Head and neck	11,109	5.2	—	—	—
	Other	3417	1.6	—	—	—
	Primary unknown	1303	0.6	—	—	—
	Skin	6117	2.9	—	—	—
	Lung	24,691	11.6	—	—	—

Table 2
Frequency Table of Pairs of Consecutive Observed States for Well-being

	State at Next Assessment				
State at Current Assessment	State 1 (None)	State 2 (Mild)	State 3 (Moderate)	State 4 (Severe)	State 5 (Dead)
State 1 (none)	155,120	38,576	9732	3895	2213
State 2 (mild)	39,061	215,367	42,625	10,239	5140
State 3 (moderate)	9602	44,611	115,434	18,467	7825
State 4 (severe)	3693	10,651	18,280	36,827	6339

dying (State 5) within 6 months is 0.168; however, estimation ignoring interval censoring provides a corresponding risk of 0.195. Patients currently experiencing the best feeling of well-being (State 1) are estimated to have a 31% chance of being in this state 6 months from now; however, ignoring interval censoring provides a corresponding estimate of 47%.

For every symptom, estimates of the mean sojourn time spent in each nonabsorbing state, and corresponding 95% confidence intervals, derived with and without accounting for interval censoring can be seen in Figure 3. The estimated average amount of time spent during a single stay in each state is consistently much greater when ignoring interval censoring than when accounting for it. This holds true for all states and all symptoms. As an example, the average amount of time spent feeling a stretch of severe anxiety is estimated to be 1 month if we account for intermittent observation, whereas it is 3.5 months if we inappropriately ignore it. Similarly, the average amount of time spent feeling a stretch of moderate fatigue is estimated to be 0.57 months if we account for intermittent observation, whereas it is 3.4 months if we inappropriately ignore it. The discrepancies in mean sojourn time estimates, with and without accounting for interval censoring, are most drastic for State 1 (none state) across all symptoms.

Figure 4 illustrates the survival probabilities over time from each nonabsorbing state, with and without accounting for interval censoring (only symptom well-being shown). It should be noted that a patient can contribute information and jump between lines in the plot, depending on their changing well-being status. The risk of death is highest among patients feeling the worst sense of well-being and is lowest among those who have the best feeling of well-being. The survival probabilities from each nonabsorbing state are consistently overestimated when ignoring interval censoring, compared with when interval censoring is accounted for.

Discussion

This study demonstrates the use of multistate models for examining progression in symptom severity among patients diagnosed with cancer. As information on symptom status is collected intermittently over time for each patient, the multistate models were estimated based on the true (intermittent) observation scheme accounting for interval-censoring. We then further illustrated the bias in estimation that can arise when ignoring the panel nature of symptom data and showed that mistakenly assuming the symptom assessment times as the exact times of symptom status transition can provide misleading results.

From a clinical perspective, multistate models offer a broader view of symptom progression and opportunity for more in-depth interpretation. This is a considerable improvement compared with prior cross-sectional approaches and methodologically limited regression techniques for examining ESAS as an outcome. The

Table 3
Estimated 6-Month State-To-State Transition Probabilities for Well-being, With and Without Accounting for Interval-censoring (Rows Sum to 1.0)

	State 1 (None)	State 2 (Mild)	State 3 (Moderate)	State 4 (Severe)	State 5 (Dead)
Accounting for Interval-censoring					
State 1 (none)	0.310	0.341	0.201	0.083	0.064
State 2 (mild)	0.264	0.339	0.213	0.090	0.095
State 3 (moderate)	0.241	0.330	0.212	0.091	0.127
State 4 (severe)	0.225	0.315	0.204	0.088	0.168
State 5 (dead)	0.000	0.000	0.000	0.000	1.000
Ignoring interval-censoring					
State 1 (none)	0.470	0.292	0.130	0.047	0.061
State 2 (mild)	0.225	0.429	0.194	0.065	0.086
State 3 (moderate)	0.157	0.312	0.306	0.092	0.133
State 4 (severe)	0.139	0.258	0.228	0.180	0.195
State 5 (dead)	0.000	0.000	0.000	0.000	1.000

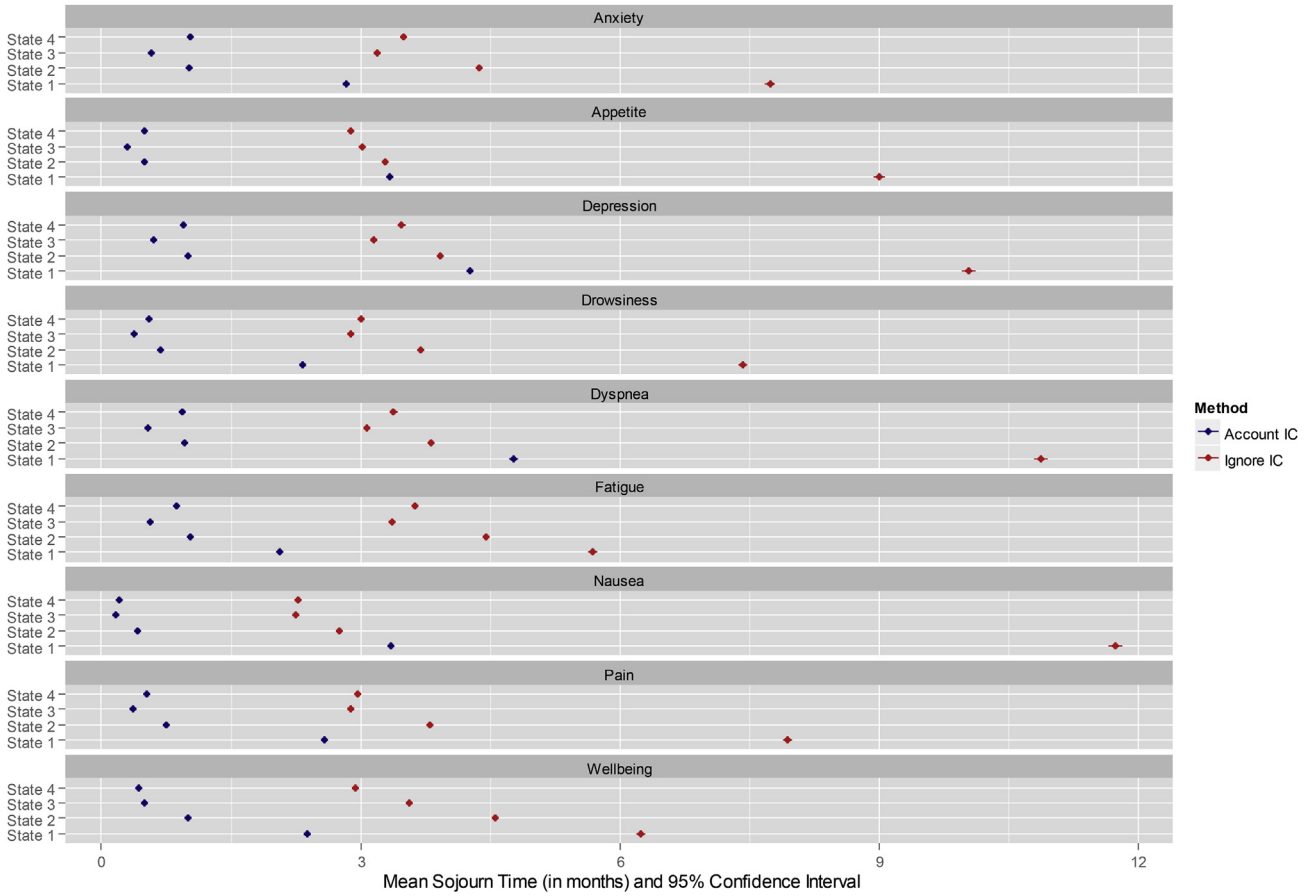

Fig. 3. Estimated mean sojourn time (in months) and corresponding 95% confidence intervals in each nonabsorbing state for every symptom, estimated by accounting for interval censoring (blue) and by ignoring interval censoring (red). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

multistate model allows one to make full use of patient-level longitudinal symptom data and provides a deeper understanding of the risk of deterioration and improvement over time for each symptom. Not only do these models add to the prognostic information available by the ESAS tool but also contribute to the physician's ability to anticipate a patient's future needs. The state-to-state transition probabilities can be used to recognize which symptoms worsen more rapidly over time, helping physicians to identify areas for improving symptom management. Estimates of the mean sojourn time may assist physicians in determining which symptom or group of symptoms requires more attention for relief. Longer periods of time in the symptom-free

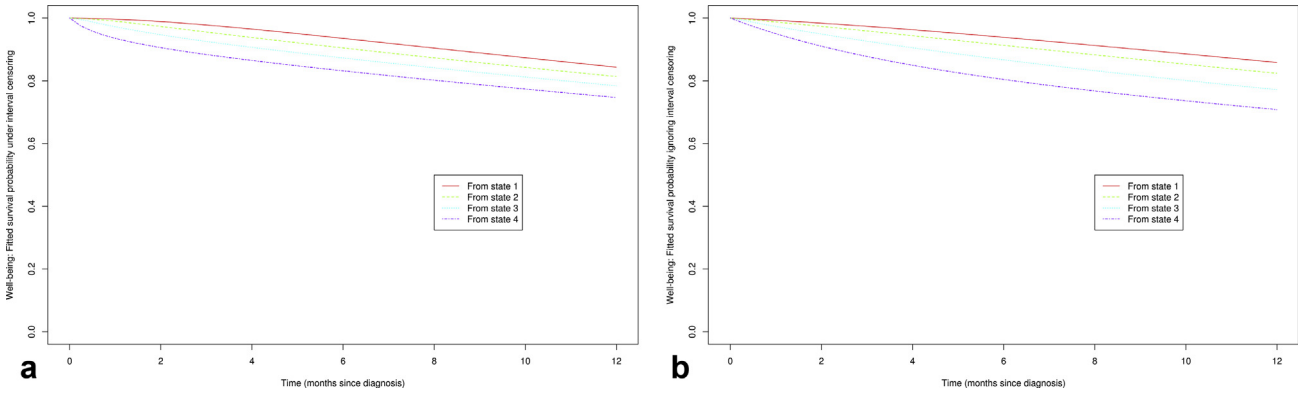

Fig. 4. Estimated survival probability over time (in months since diagnosis) from each nonabsorbing state to death for well-being, a) while accounting for interval-censoring and b) while ignoring interval-censoring.

state, along with limited time in the remaining severe states, are indications that the symptom is being well managed.[4]

From a statistical perspective, the multistate model parameters can be estimated while accommodating for intermittent observation. This implies that the estimation process is able to account for limitations such as not knowing the actual times of state-to-state transitions and not knowing the actual state occupied before the end of observation. This important feature allows the researcher to use the *observed* progression of symptom burden as a means to estimate the *underlying* progression of symptom burden. Modeling techniques such as logistic and Poisson regression, which are most often used to analyze symptom burden, are not able to handle these major limitations. These approaches are also subject to misclassification, as the underlying state of symptom burden is not considered during the modeling process.

It is important to consider the reasons why ESAS assessments were made at the given times. Gruger et al.[35] have shown that assessment schemes based on patient self-selection are informative, which can lead to biased estimates under the standard multistate modeling framework. ESAS is meant to be used as a symptom screening tool that patients are asked to complete during their scheduled visits to the cancer clinic before seeing their oncologist. Times for assessing symptom severity are scheduled depending on how each cancer center implemented the ESAS tool 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.

To our knowledge, this is first study demonstrating the impact of ignoring intermittent observation when examining the progression of symptom burden using ESAS. Despite the numerous strengths discussed previously, this study has several limitations. Only ESAS assessments conducted at regional cancer centers and participating hospitals were included in the analysis; symptom data from patients at home or in hospital are not available. Although having additional symptom information would assist in better understanding the trajectory of symptom severity, accounting for intermittent observation of symptoms during the analytic phase remains extremely important (even if ESAS assessments from other care settings were included). Our current work did not incorporate patient-level characteristics or covariates into the multistate model; that is, we did not examine the associations between covariates and state-to-state transition intensities. Although multistate models certainly allow for the inclusion of covariates, the focus of this study was on estimating overall state-to-state transition intensities, transition risks, and sojourn times and illustrating what occurs to these estimates when intermittent observation is inappropriately ignored. Ultimately, this work serves as a methodological guide for applied researchers interested in using multistate models, or similar time-to-event models, for investigating disease progression under the presence of intermittent observation.

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Conflict of interest: The authors declare that they have no conflicts of interest.

Ethical Standards: This study involved secondary data analyses only and was thus exempt from requiring Research Ethics Board approval because the Institute for Clinical Evaluative Sciences is a designated "45.1 entity" under the Personal Health Information Protection Act (PHIPA) enabling the use of personal health information.

References

1. Sutradhar R, Atzema C, Seow H, et al. Repeated assessments of symptom severity improve predictions for risk of death among patients with cancer. J Pain Symptom Manage 2014;48:1041−1049.

2. Howell D, Husain A, Seow H, et al. Symptom clusters in a population-based ambulatory cancer cohort validated using bootstrap methods. Eur J Cancer 2012;48:3073−3081.

3. Barbera L, Seow H, Howell D, et al. Symptom burden and performance status in a population-based cohort of ambulatory cancer patients. Cancer 2010;116:5767−5776.

4. Jia J, Barbera L, Sutradhar R. Using Markov multistate models to example the progression of symptom severity among an ambulatory population of cancer patients: are certain symptoms better managed than others? J Pain Symptom Manage 2016;51:232−239.

5. Kotronoulas G, Kearney N, Maguire R, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A

systematic review of controlled trials. J Clin Oncol 2014;32:1480–1501.

6. Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. BMC Health Serv Res 2013;13:211.

7. Yang LY, Manhas DS, Howard AF, et al. Patient-reported outcome use in oncology: a systematic review of the impact on patient-clinician communication. Support Care Cancer 2018;26:41–60.

8. Howell D, Liu G. Can routine collection of patient reported outcome data actually improve person-centered health? Healthc Pap 2011;11:42–47; discussion 55-58.

9. Sutradhar R, Rostami M, Barbera L. Patient-reported symptoms improve performance of risk prediction models for emergency department visits among patients with cancer: a population-wide study in Ontario using administrative data. J Pain Symptom Management 2019;58:745–755.

10. Snyder CF, Aaronson NK. Use of patient-reported outcomes in clinical practice. Lancet 2009;374:369–370.

11. Greenhalgh J, Meadows K. The effectiveness of the use of patient-based measures of health in routine practice in improving the process and outcomes of patient care: a literature review. J Eval Clin Pract 1999;5:401–416.

12. Hui D, Bruera E. The Edmonton Symptom Assessment System 25years later: past, present and future developments. J Pain Symptom Manage 2017;53:630–643.

13. Davis LE, Bubis LD, Mahar AL, et al. Patient-reported symptoms after breast cancer diagnosis and treatment: a retrospective cohort study. Eur J Cancer 2018;101:1–11.

14. Gupta V, Allen-Ayodabo C, Davis L, et al. Patient-reported symptoms for esophageal cancer patients undergoing curative intent treatment. Ann Thorac Surg 2020;109:367–374.

15. Hallet J, Davis LE, Mahar AL, et al. Patterns of symptoms burden in neuroendocrine tumors: a population-based analysis of prospective patient-reported outcomes. Oncologist 2019;24:1384–1394.

16. Bubis LD, Davis L, Mahar A, et al. Symptom burden in the first year after cancer diagnosis: an analysis of patient-reported outcomes. J Clin Oncol 2018;36:1103–1111.

17. Liu Y, Xi QS, Xia S, Zhuang L, Zheng W, Yu S. Association between symptoms and their severity with survival time in hospitalized patients with far advanced cancer. Palliat Med 2011;25:682–690.

18. Yang N, Ornstein KA, Reckrey JM. Association between symptom burden and time to hospitalization, nursing home placement, and death among the chronically ill urban homebound. J Pain Symptom Manage 2016;52:73–80.

19. Peters ME, Schwartz S, Han D, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County Dementia Progression Study. Am J Psychiatry 2015;172:460–465.

20. Hamidou Z, Dabakuyo-Yonli TS, Guillemin F, et al. Impact of response shift on time to deterioration in quality of life scores in breast cancer patients. PLoS One 2014;9:e96848.

21. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26:2389–2430.

22. Andersen PK, Keiding N. Multi-state models for event history analysis. Stat Methods Med Res 2002;11:91–115.

23. Sutradhar R, Barbera L, Seow H, et al. Multistate analysis of interval-censored longitudinal data: application to a cohort study on performance status among patients diagnosed with cancer. Am J Epidemiol 2011;173:468–475.

24. Kalbfleisch JD, Lawless JF. The analysis of panel data under a Markov assumption. J Am Stat Assoc 1985;80:863–871.

25. Cook R, Lawless J. Multistate Models for the Analysis of Life History Data. New York: Chapman and Hall/CRC, 2018.

26. Lawless JF, Nazeri Rad N. Estimation and assessment of Markov multistate models with intermittent observations on individuals. Lifetime Data Anal 2015;21:160–179.

27. Sutradhar R, Cook RJ. Analysis of interval-censored data from clustered multi-state processes: application to joint damage in psoriatic arthritis. J R Stat Soc - Ser C 2008;57:553–566.

28. Sharples LD, Jackson CH, Parameshwar J, Wallwork J, Large SR. Diagnostic accuracy of coronary angiography and risk factors for post-heart-transplant cardiac allograft vasculopathy. Transplantation 2003;76:679–682.

29. Titman AC. Flexible nonhomogeneous Markov models for panel observed data. Biometrics 2011;67:780–787.

30. Jackson CH, Sharples LD, Thompson SG, Duffy SW, Couto E. Multistate Markov models for disease progression with classification error. The Statistician 2003;52:1–17.

31. Jackson CH. Multi-state models for panel data: the msm package for R. J Stat Softw 2011;38:1–29.

32. Clarke EA, Marrett LD, Kreiger N. Cancer registration in Ontario: a computer approach. In: Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG, eds. Cancer Registration Principles and Methods. Lyon, France: IARC Publications, 1991:246–257.

33. Iron K, Zagorski BM, Sykora K, Manuel DG. Living and dying in Ontario: an opportunity for improved health information. ICES Investigative Report. Toronto, ON, Canada: Institute for Clinical Evaluative Sciences, 2008.

34. Titman AC, Sharples LD. Model diagnostics for multi-state models. Stat Methods Med Res 2010;19:621–651.

35. Gruger J, Kay R, Schumacher M. The validity of inferences based on incomplete observations in disease state models. Biometrics 1991;47:595–605.