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A Multistate Transition Model for Osteoarthritis Pain Change

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Abstract

Pain severity of knees is assessed using an ordinal scale in patients with musculoskeletal diseases and often changes over time. Assessment of the effect of a particular risk factor on the change in pain severity will shed light on our understanding of biological mechanisms and provide guidance for rational clinical intervention for recurrent pain. The multistate transition model allows transitions between several different states of pain severity and estimates the transitional intensity using an extension of the Cox proportional hazards model. Using data from a longitudinal study, we applied this model to assess the relation of two psychological factors to the change in knee pain severity over time among patients with osteoarthritis and demonstrated that the multistate transition model can be a valuable tool for rheumatic disease studies.

Keywords

Multistate transition; Pain; Proportional hazards model

1. Introduction

Pain from knee osteoarthritis (OA) is a key symptom in the decision to seek medical care and an important antecedent to disability (Hadler, 1992). Clinically, physicians often notice that patients with OA experience episodic pain exacerbations over the course of the disease. Pain from OA often increases with motion of the involved joints, and decreases or is relieved with rest (Cannon, 2001). Joint pain from knee OA is often intermittent and

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variable, and adaptation and avoidance strategies modify the experience of pain (Gooberman-Hill et al., 2007). In clinical trials and epidemiological studies, one of the commonly used instruments for assessing pain severity is the Western Ontario McMaster pain subscale (WOMAC; Bellamy et al., 1988). Pain severity can be grouped into multi-ordered categories, i.e., none, mild, moderate, and severe pain. During the course of a study, pain severity may fluctuate between these categories. Also censoring may occur at the end of the study or during study visit due to lost to follow-up.

To quantify the impact of a specific risk factor on transitioning from one state of pain severity to another is important because it will help investigators elucidate potential biological mechanisms of disease and provide guidance for rational clinical intervention for recurrent pain. To date, few studies have examined the dynamic relationship between fluctuation of pain severity and its risk factors, and the statistical methods for assessing such dynamic relationships are rudimentary. The multistate stochastic process using proportional hazards regression model (Kay, 1982), an extension of Cox's proportional hazards model, has been applied to study disease transitions in areas such as Crohn's disease (Therneau and Gramsch, 2000), and in cardiovascular disease (Islam, 1994). While other multi-state models have been applied to musculoskeletal disease (Husted et al., 2005), the semi-parametric approach as outlined by Kay has, to our knowledge, not been applied.

The Cox proportional hazards model is a semiparametric relative risk model which has a nonparametric component in the form of an arbitrary baseline hazard function, in addition to the parametric modeling of the relationship between hazard rate and specified covariates. The semiparametric model is flexible in that it allows different baseline hazard rates for different groups that share common covariate effects, and also allows specific covariate effects for different groups. Both of these scenarios can arise in different study populations. The extension of the Cox proportional hazards model to a multistate transition model expanded the time to event from a single endpoint to multiple endpoints. This allows us to simultaneously assess the relative risks and the competing risks of transitions from one state to another. It also allows us to examine multiple reentries to states previously attained for the same study subject more accurately and efficiently. The more relaxed modeling assumptions make possible application of the technique to more general study populations. These characteristics make this method particularly useful for studies involving musculoskeletal diseases, in which symptoms of disease such as pain severity often manifests as an episodic fluctuating course.

In this article, we will introduce the multistate transition model in Sec. 2, illustrate its application using data collected from a longitudinal cohort study in Sec. 3, and conclude with a discussion in Sec. 4.

2. A Multistate Transition Model

In longitudinal OA studies, knee pain severity and risk factors for knee pain are often assessed at multiple time points. At each time point pain severity can be classified into one of K distinctive states. A "transition" occurs when pain severity changes between two adjacent time points.

Let T_{zz^*} denote the elapsed time it takes for transition z to z^* to occur ($z, z^* = 1, \dots, K, z \neq z^*$), the transition specific intensity function $\lambda_{zz^*}(t)$, the instantaneous probability of transition $z \rightarrow z^*$ occurs in $[t, t + \Delta t)$ given that no transition occurs at time t , is defined as

$$\lambda_{zz^*}(t) = \lim_{\Delta t \rightarrow 0} P(t \leq T_{zz^*} < t + \Delta t \mid T_{zz^*} \geq t) / \Delta t.$$

For the simplest case where there is only one endpoint such as death, the endpoint and censoring are two “absorbing” state that once they are reached, there is no going back, and one “transient” state, in which the study subjects are still “alive” and in the study, the intensity function $\lambda(t)$ of such event occurring can be modeled using the Cox proportional hazards regression model (Cox, 1972), a useful model to assess relative risks.

Let $X_{ij}(t)$ be the j th covariate of the i th subject, where $i = 1, \dots, n$ and $j = 1, \dots, p$, and $X_i(t) = (X_{i1}(t), \dots, X_{ip}(t))$, a $1 \times p$ vector, denote the covariate of the i th subject. The values of these covariates can be fixed or can vary over time. The Cox proportional hazards regression model specifies the hazard function for subject i as

$$\lambda_i(t) = \lambda_0(t) e^{X_i(t)\beta}, \quad (1)$$

where $\lambda_0(t)$ is an unspecified nonnegative baseline hazard function, β is a $p \times 1$ column vector of coefficient, and e^β is the measure of relative risks.

When there are multiple endpoints, Prentice et al. (1978) extended the Cox model (1) to incorporate competing risks revolving around the specification of cause specific hazards of the “event” from cause j^* , $j^* = 1, \dots, J$, by

$$\lambda_{j^*}(t | X_i(t)) = \lambda_{0j^*}(t) e^{X_i(t)\beta_{j^*}}. \quad (2)$$

The underlying stochastic process in this consideration involves $J + 2$ ‘disease’ states: the J event causes (endpoints), the right censoring, and the absorbing state.

If there are more than one transient state, between which study subjects can transition from one state to another, Kay (1982) extended model (2) to a more general multistate stochastic process allowing several transient disease states between entry and death or event. This model is highly suitable for the study of multistate pain transitions as may occur in OA. We will use a longitudinal study of knee pain to illustrate its application to musculoskeletal diseases.

Consider a multistate transition model depicted in Fig. 1. Assume that t is the transition time from state z to state z^* . There are K states, and transitions from any state to another is possible. For $z, z^* \in K$, an extension of (1) and (2) assumes that for subject i , the transition intensity function for transition from state z to state z^* at time t is

$$\lambda(t, z^* | z; X_i(t)) = \lambda_{0zz^*}(t) e^{X_i(t)\beta_{zz^*}}, \quad (3)$$

where β_{zz^*} is the vector of coefficient specific to transition z to z^* . This model allows for a transition-specific baseline intensity $\lambda_{0zz^*}(t)$ as well as a transition-specific covariate effect β_{zz^*} .

To estimate and make inference about the transition-specific covariate effect β_{zz^*} , let $t_1 < t_2 < \dots < t_N$ be all the ordered transition times from state z to z^* , $X_k(\cdot)$ be the covariate for the subject transitioning from state z to z^* at time t_k , and $R(t_k, z)$, $k = 1, \dots, N$, be the individuals at risk in state z at time t_k , counting multiple transitions from z to z^* of the same subject as if they were independent transitions. The partial likelihood (Cox, 1972) for β_{zz^*} is then

$$\begin{aligned}
 L(\beta_{zz^*}) &= \prod_{k=1}^N \left\{ \frac{\lambda_{0zz^*}(t_k) e^{X_k(t_k)\beta_{zz^*}}}{\sum_{j \in R(t_k, z)} \lambda_{0zz^*}(t_k) e^{X_j(t_k)\beta_{zz^*}}} \right\} \\
 &= \prod_{k=1}^N \left\{ \frac{e^{X_k(t_k)\beta_{zz^*}}}{\sum_{j \in R(t_k, z)} e^{X_j(t_k)\beta_{zz^*}}} \right\}.
 \end{aligned} \tag{4}$$

The partial likelihood function (4) here is similar to the usual partial likelihood function except that the risk set is defined differently. In model (4), only observed transitions from state z to z^* are considered to be a “failure” event, and all potential transitions from z to states other than z^* are treated as censored event, since they did not occur in that time interval.

When there are ties among the uncensored failure time, the partial likelihood can be adjusted in various ways. The approximations to the partial likelihood function suggested by Peto (1972), Breslow (1974), and Efron (1977) can all be applied in a similar fashion and the estimation and inference of β_{zz^*} based on the approximations are straightforward. The recursion (Gail et al., 1981) which permit rapid computation of the partial likelihood estimate in studies with tied survival time is another way for parameter estimations.

The maximum likelihood estimate, $\hat{\beta}_{zz^*}$, can be obtained as a solution to the score equation

$$U(\hat{\beta}_{zz^*}) = \partial \log L / \partial \beta_{zz^*} = \sum_{k=1}^N [X_k(t_k) - \mathcal{E}(\hat{\beta}_{zz^*}, t_k)] = 0, \tag{5}$$

where

$$\mathcal{E}(\beta_{zz^*}, t_k) = \sum_{j \in R(t_k, z)} X_j(t_k) p_j(\beta_{zz^*}, t_k),$$

and

$$p_j(\beta_{zz^*}, t_k) = \frac{e^{X_j(t_k)\beta_{zz^*}}}{\sum_{l \in R(t_k, z)} e^{X_l(t_k)\beta_{zz^*}}},$$

The solution $\hat{\beta}_{zz^*}$ to the score Eq. (5) can be obtained using the Newton–Raphson algorithm, and the asymptotic properties of $\hat{\beta}_{zz^*}$ are analogous to those for partial likelihood under general conditions.

The transition-specific underlying intensity function λ_{0zz^*} , although left unspecified, can be estimated nonparametrically. Let $\lambda_{zz^*}^{(l)} = \lambda_{0zz^*}(t)$, $t \in (b_{(l-1)zz^*}, b_{lzz^*}] = I_{lzz^*}$ denote the transition intensity from state z to z^* , where $b_{0zz^*} = 0 < b_{1zz^*} < \dots < b_{(r-1)zz^*} < b_{rzz^*} = \infty$ is a subdivision of time scale. Let $D_{izz^*}^{(l)}$ be the time spent in state z by subject i during I_{lzz^*} , and let

$$d_{zz^*}^{(i)} = \begin{cases} 1 & \text{if subject } i \text{ move from state } z \text{ to } z^* \text{ in } I_{zz^*} \\ 0 & \text{otherwise} \end{cases}$$

and let $m_{zz^*}^{(l)} = \sum_{i=1}^n d_{zz^*}^{(i)}$ be the number of transitions from z to z^* in I_{zz^*} . If the covariates X_i are constant, the likelihood function for the transition z to z^* is

$$\prod_{i=1}^n \prod_{l=1}^r \left\{ \hat{\lambda}_{zz^*}^{(l)} e^{X_i \hat{\beta}_{zz^*}} \right\}^{d_{zz^*}^{(i)}} e^{-\left\{ \hat{\lambda}_{zz^*}^{(1)} e^{X_i \hat{\beta}_{zz^*}} D_{zz^*}^{(1)} \right\}},$$

where the maximum likelihood estimate of $\hat{\lambda}_{zz^*}^{(l)}$ is

$$\hat{\lambda}_{zz^*}^{(l)} = m_{zz^*}^{(l)} \left\{ \sum_{i=1}^n e^{X_i \hat{\beta}_{zz^*}} D_{zz^*}^{(l)} \right\}^{-1}. \quad (6)$$

If X_i is a time-varying covariate, the component $e^{X_i \hat{\beta}_{zz^*}} D_{zz^*}^{(l)}$ in (6) can be replaced by

$$\int_{\max(b_{(i-1)zz^*}, u_{izz^*})}^{\min(b_{izz^*}, v_{izz^*})} e^{X_i(t) \hat{\beta}_{zz^*}} dt, \quad (7)$$

where u_{izz^*} and v_{izz^*} are times of transition to state z and out of state z .

When the time interval are divided by possible failure times, then

$$\hat{\lambda}_{zz^*}^{(l)} = m_{zz^*}^{(1)} \left\{ \sum_{i \in R(b_{izz^*})} e^{X_i \hat{\beta}_{zz^*}} \right\}^{-1}.$$

3. Analysis of Leap Study

Included in this analysis were subjects from the Longitudinal Examination of Arthritis Pain (LEAP) study (Hutchings et al., 2007). 287 subjects were recruited from 16 primary care and rheumatology practices in the U.S. who were followed with weekly telephone interviews for up to 12 weeks. All subjects had a clinical diagnosis of either hip or knee OA or both. Standardized instruments were used during the weekly telephone interview, including the WOMAC pain subscale (0–10 scale), 5-item Mental Health Inventory (MHI-5, 5–30 scale), and 8-item Short-Form health survey mental component score (SF-8, 0–100 scale). We will use the multistate transition model to investigate how each of the the psychological factors, i.e., MHI-5 and SF-8, affect the transitional intensity (i.e., relative risk, hazard) from one pain category to another, adjusting for age, sex, and BMI.

We divided WOMAC pain into three states: “none/mild” pain (WOMAC pain score: 0–2.2), “moderate” pain (WOMAC : 2.3–5), and “severe” pain (WOMAC > 5) state. A transition is considered to have occurred whenever WOMAC pain score resulted in an individual changing changed from one state to another within an eight day period of time. Transitions were possible between any of the three pain states (Fig. 2). We examined the relation of

each psychological factor, i.e., MHI-5 and SF-8, to the transitional intensity from one pain category to another using the multistate transition model, adjusting for age, sex and BMI. The coxph procedure in R package “survival” (R Development Core Team, 2008) was used for analysis.

A total of 598 transitions occurred during the study. The majority of the transitions occurred between adjacent pain categories (Table 1). For illustration purpose, let (1, 2, 3) represent (“none/mild”, “moderate pain”, “severe pain”), so that the transitions from one state to another can be simply denoted by stratum zz^* , where $z, z^* = 1, 2, 3$ and $z \neq z^*$. A new data set needed to be created for coxph to work properly for the multistate transition model. First, we created a stratum variable to represent each transition from one state to another, and a status variable with a value 1 or 0 to indicate whether a failure time or a censoring time is observed. For example, if a subject made a transition $1 \rightarrow 3$, then the two new entries for the new data set are stratum = “13” and status = 1 (transition $1 \rightarrow 3$ observed failure), and stratum = “12” with status = 0 (censored, since transition $1 \rightarrow 2$ not observed during the same time period). The time variable is the time from the last state moving into the new state. The three-state transition model was fit to investigate pain fluctuation with psychological scores MHI-5 and SF-8 separately, adjusting for age, gender, and BMI, and assumed no error in the pain classifications.

Table 2 shows the estimates of relative risk $e^{\beta_{zz^*}}$, $z, z^* = 1, 2, 3, z \neq z^*$ with 95% confidence interval and p-values for every 5 units of improvement in the two psychological factor scores using the multistate transition model. After adjusting for age, gender, and BMI, psychological improvement is associated with lower risk of pain severity worsening (all upper triangle of Table 2 $e^{\beta_{12}}, e^{\beta_{13}},$ and $e^{\beta_{23}}$ are less than 1), whereas psychological improvement was associated with higher risks of pain severity reduction (all lower triangle of Table 2 $e^{\beta_{21}}, e^{\beta_{31}},$ and $e^{\beta_{32}}$ are greater than 1). For every 5-unit improvement in MHI-5, the risk of transitioning from none/mild to moderate pain decreased by 17% ($e^{\beta_{12}} = 0.83$), the risk of transition from moderate to severe pain decreased by 14% ($e^{\beta_{13}} = 0.86$), and the risk of transition from none/mild to severe pain decreased by more than 50% ($e^{\beta_{13}} = 0.49$). For every 5-unit improvement of psychological state as measured by MHI-5, the risk of transition from moderate to none/mild pain increased by 53% ($e^{\beta_{21}} = 1.53$), the risk of transition from severe to moderate pain increased by 51% ($e^{\beta_{31}} = 1.51$), and the risk of transition from severe to none/mild pain more than doubled ($e^{\beta_{31}} = 2.11$). Similar results were also observed if the psychological well-being was measured with SF-8.

Another observation from Table 2 is that it seems transition intensities between adjacent categories are almost identical, evidenced by the fact that for MHI-5, $e^{\beta_{12}} = 0.83$ vs $e^{\beta_{23}} = 0.86$, and $e^{\beta_{21}} = 1.53$ vs $e^{\beta_{32}} = 1.51$; for SF-8, $e^{\beta_{12}} = 0.93$ vs $e^{\beta_{23}} = 0.89$, and $e^{\beta_{21}} = 1.21$ vs $e^{\beta_{32}} = 1.21$. This suggests that a model reduction by combining the one-step transitions of $1 \rightarrow 2$ and $2 \rightarrow 3$, and $2 \rightarrow 1$ and $3 \rightarrow 2$. We refit the models using a one-step transition (transition to adjacent categories) and two-step transition (transition between none/mild and severe) models, and the likelihood ratio test statistics are 15 on 8 degrees of freedom (df) for MHI-4 and 17.4 on 8 df for SF-8. Since $\chi^2_{8,0.975} = 17.5$, the multistate transition models can be simplified to the one-step and two-step transition models. Table 3 shows the parameter estimates for the simplified one and two-step transition model, and the parameter estimates are similar to that in Table 2. The cumulative effect of every 5 unit worsening of MHI-5 of transition from none/mild pain to moderate pain and then from moderate pain to severe pain is $e^{\beta_{12}} \times e^{\beta_{23}} = 0.89^2 = 0.79$. That is, if we consider the two one-step transition separately, every 10 units of worsening in MHI-5 (5 units worsening for each transition), the cumulative relative risk of transition from none/mild pain to severe pain is increased by 79%. Now every 5 units worsening in MHI-5 was associated with 50% of increased risk of transition from no-mild to severe pain ($e^{\beta_{13}}$ is 0.49). To make the cumulative relative risk of $1 \rightarrow 2$

and then $2 \rightarrow 3$ comparable to that of $1 \rightarrow 3$ directly, we calculated that for every 10 unit worsening of MHI-5, the relative risk of transition from none/mild pain to severe pain is increased by 24% with 95% confidence interval of (.07, 0.76), which does not include 0.79. Apparently the worsening of MHI-5 on the relative risk of transition from none/mild to severe is far smaller than the magnitude of effect of the product of the two separate adjacent relative risk of transition, which suggests that neither the proportional odds model nor the proportional adjacent odds model would be appropriate. Without using transition specific multistate transition model, it is difficult to discover this kind of effect pattern.

4. Discussions

There has been very little work describing factors associated with pain variability, partly due to methodological difficulties on addressing this issue. Some research has shown that psychological factors and coping are associated with change in OA related pain (Affleck et al., 1999; Keefe et al., 2004); further exploration of these relationships as well as other factors is warranted, particularly as this represents a potential new avenue for interventions aimed at pain reduction. Additional research is needed to understand associations of demographic characteristics, medication, physical activity, and biological factors with pain variability. In addition to clinical advances in the research of pain variability, statistical methods that are well suited for the analysis of data collected in this type of study should be utilized and developed to improve the validity of study results. We have demonstrated in this article that the multistate transition model can be a useful addition to more commonly used statistical methodologies in this area. The proposed models allow different baseline transition intensities and transition-specific relative risks for transitions between different states of pain severity. They also carry less restrictive assumptions than proportional odds models which assume that proportional odds ratios moving from one state to another are simply multiplicative in nature, which could be an unreasonable assumptions in pain variability studies. As we showed in Sec. 3, some transition specific effect are difficult for other models to detect but can be captured by the multistate transition model. Thus, this method carries important advantages for studies examining fluctuations of pain severity over time.

There are other applications of statistical models for multistate processes (Cook et al., 2004; Jackson, 2003; Kay, 1986) that potentially can be useful for the long term study of musculoskeletal disease fluctuation or progression and its risk factors, especially if diseases are evaluated at fixed time points, and we will explore appropriate applications and extensions of these methods in future research.

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Figure 1.
 K State transition model.

Figure 2.
Three-state pain transition model.

Table 1

Numbers of transitions between different pain state

From	To		
	None/Mild	Moderate pain	Severe pain
None/Mild	209	155	9
Moderate pain	172	375	115
Severe pain	12	135	186

Table 2

Relative risks ($e^{\hat{\beta}_{zz^*}}$, $z, z^* \in (1, 2, 3), z \neq z^*$) of transition between states for every 5 unit psychological factor score improvement

From	To		
	None/Mild	Moderate pain	Severe pain
<i>MHI-5</i>			
None/Mild		$e^{\hat{\beta}_{12}} = 0.83$ 95% CI (0.68, 1.01) $p = 0.061$	$e^{\hat{\beta}_{13}} = 0.49$ 95% CI (0.25, 0.94) $p = 0.032$
Moderate pain	$e^{\hat{\beta}_{21}} = 1.53$ 95% CI (1.12, 2.10) $p = 0.008$		$e^{\hat{\beta}_{23}} = 0.86$ 95% CI (0.62, 1.19) $p = 0.35$
Severe pain	$e^{\hat{\beta}_{31}} = 2.11$ 95% CI (0.87, 5.09) $p = 0.098$	$e^{\hat{\beta}_{32}} = 1.51$ 95% CI (1.15, 1.98) $p = 0.03$	
<i>SF-8</i>			
None/Mild		$e^{\hat{\beta}_{12}} = 0.93$ 95% CI (0.82, 1.06) $p = 0.29$	$e^{\hat{\beta}_{13}} = 0.75$ 95% CI (0.44, 1.26) $p = 0.27$
Moderate pain	$e^{\hat{\beta}_{21}} = 1.21$ 95% CI (1.07, 1.39) $p = 0.004$		$e^{\hat{\beta}_{23}} = 0.89$ 95% CI (0.77, 1.03) $p = 0.11$
Severe pain	$e^{\hat{\beta}_{31}} = 1.60$ 95% CI (1.00, 2.55) $p = 0.098$	$e^{\hat{\beta}_{32}} = 1.21$ 95% CI (1.08, 1.36) $p = 0.03$	

Table 3

Relative risks ($e^{\hat{\beta}_{zz^*}}$, $z, z^* \in (1, 2, 3)$, $z \neq z^*$) of one and two-step transition between states for every 5 unit psychological factor score improvement

From	To		
	None/Mild	Moderate pain	Severe pain
<i>MHI-5</i>			
None/Mild		$e^{\hat{\beta}_{12}} = 0.89$ 95% CI (0.75, 1.07) $p = 0.02$	$e^{\hat{\beta}_{13}} = 0.49$ 95% CI (0.25, 0.94) $p = 0.032$
Moderate pain	$e^{\hat{\beta}_{21}} = 1.45$ 95% CI (1.23, 1.81) $p < 0.0001$		$e^{\hat{\beta}_{23}} = e^{\hat{\beta}_{12}}$
Severe pain	$e^{\hat{\beta}_{31}} = 2.11$ 95% CI (0.87, 5.09) $p = 0.098$	$e^{\hat{\beta}_{32}} = e^{\hat{\beta}_{21}}$	
<i>SF-8</i>			
None/Mild		$e^{\hat{\beta}_{12}} = 0.95$ 95% CI (0.86, 1.04) $p = 0.29$	$e^{\hat{\beta}_{13}} = 0.75$ 95% CI (0.44, 1.26) $p = 0.27$
Moderate pain	$e^{\hat{\beta}_{21}} = 1.20$ 95% CI (1.11, 1.30) $p < 0.0001$		$e^{\hat{\beta}_{23}} = e^{\hat{\beta}_{12}}$
Severe pain	$e^{\hat{\beta}_{31}} = 1.60$ 95% CI (1.00, 2.55) $p = 0.098$	$e^{\hat{\beta}_{32}} = e^{\hat{\beta}_{21}}$	