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復發事件區間設限多重狀態模式分析－台灣老人憂鬱狀態變化貫時性資料之應用

Multi-State Models for Recurrent Events with Interval Censored Data－An Application of the Depression Transition Status of the Elderly in Taiwan

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Multi-State Models for Recurrent Events with Interval Censored Data－An Application of the Depression Transition Status of the Elderly in Taiwan

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“All models are wrong, but some are useful.”

George E. P. Box (1919.10.18 – 2013.03.28)

摘要

幾十年來許多國家面臨了有關人口老化的挑戰，其中老人晚年的憂鬱症狀對身體健康及功能的嚴重影響已經引起廣泛的關注。有鑒於此，本研究利用行政院衛生署國民健康局所提供之 1989-2007 年六波「台灣地區老人保健與生活問題長期追蹤調查」資料針對影響老人憂鬱狀態變化趨勢的相關因素，包括人口特徵、家庭與環境條件及健康狀況進行深入的探討研究。研究方法上，基於憂鬱狀態復發具有區間設限的特性，在同一個體於不同區間之事件復發視為相互獨立的假設下，利用區間設限模式探討影響老人憂鬱變化趨勢相關因子，惟區間設限模式的缺點在於無法處理兩種以上事件同時存在的情形，因此，本研究利用具馬可夫鏈特性之 Cox 及 Aalen 多重狀態事件史模式，探討有關老人憂鬱狀態變化趨勢。有關 Cox 比例風險模式假設之驗證，除利用 Aalen 加成模式進行輔助探討時間相依變數的特性外，亦藉由 Schoenfeld 殘差圖進行交叉驗證。另一方面，老人憂鬱狀態變化趨勢之轉移機率亦經由 Cox 及 Aalen 多重狀態模式配適結果進行估算。本研究結果發現年齡、性別、教育程度、有無配偶、與子女同住、經濟狀況、健康自評、日常生活活動能力（ADL）及體能狀況與老人憂鬱狀態變化趨勢有密切的相關；在轉移機率方面，發現初始狀態已有憂鬱之老人，其死亡率相較於無憂鬱之老人有偏高的趨勢。

關鍵詞：*貫時性研究、老年人、憂鬱、Cox 模式、區間設限資料、Aalen 模式、多重狀態模式、轉移機率*

Abstract

Many countries have been facing the challenges of aging population over decades. Depressive symptoms in later life of elderly have serious implications for the health and functioning has caused wide public concern. The purpose of this study is to explore the effect of the covariates related to demographic characteristics, home and environment conditions, and health status, on the changing status of depression of old people in Taiwan. A representative panel sample survey data collected in the six waves of "The Longitudinal Sample Survey of Health and Living Status of the Elderly in Taiwan" conducted from 1989 to 2007 by the predecessor organization of the Bureau of Health Promotion, Department of Health is used for analysis. Since cases of depression status are recurrent events with the characteristics of interval censored data, Cox model with interval-censored approach is applied for investigating the variables related to the changing status of depression among the elderly under the assumption that the observations within a subject are mutually independent. However, a major disadvantage of interval censored model is unable to deal with the situation that two or more different events of interest exist simultaneously, a more general method, multi-state model considered as a Markov chain for event history analysis is used to interpret the changing status of depression. To verify the proportional assumption in the conventional Cox model, Aalen's additive model taking into account instantaneous covariate effects in time is employed as an alternative on a supplement. Also, the scaled Schoenfeld residuals plots are used for investigating the proportional hazard assumption. Furthermore, the transition probabilities for the changing status of depression obtained from Cox and Aalen models are provided. From the results of this study, age, gender, education, spouse, living with children, economic status, self-rated health, ADL function and physical function are significantly related to the depression. Also, the transition probabilities show the death rate has a greater impact on the elderly with initial depression state.

Keywords: panel study, elderly people, depression, Cox model, interval-censored data, Aalen model, multi-state model, transition probability

Contents

List of Tables

List of Figures

Chapter 1

Introductions

Along with the progress in social economy and medical improvement, Taiwan is experiencing a dramatic demographic transition and continuous improvement of the quality of life. The life expectancy at age 60 is about 21 years for males and 25 years for females respectively in 2012. The aging of the population, together with the rapid social and economic change, produces a number of troublesome issues when Taiwan goes through the phase of development. Specifically, physical and mental conditions, and activities of daily living for the elderly will be naturally weakened with aging. Moreover, the prevalence of depression of the elderly is about 12%-27% in Taiwan (Chiu et al., 2005; Tsai et al., 2005). Thus, how to maintain the quality of life for the elderly is a public concerned problem.

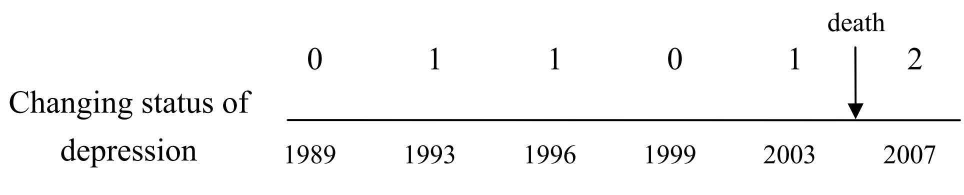
Many studies demonstrate that depressive symptoms increase the risk of mortality in adults (Blazer, 2003), the incidence and prevalence of depression and related problems have a steady increase among the elderly population (Beekman et al., 2002; Birrer and Vemuri, 2004; Crystal et al., 2003; Doraiswamy, 2001; Fischer et al., 2003; Gurland et al., 1980; Kales and Valenstein, 2002; Lundquist et al., 1997; Murrell et al., 1983; Schovers et al., 2000; Williams and Connolly, 1990). Symptoms of depression experienced in late life have serious implications for the health and functioning.

Depression is the most common mental health problem in old age and it may cause the elderly feel unsatisfied with their life (Anderson, 2001; Boey, 1999; Liu and Guo, 2008; Martin and Haynes, 2000). Moreover, Jagger et al. (1998) pointed out that the mental health problems of the elderly will increase with aging, especially by the impact of depression. For deeply understanding the depression changing status in the elderly, Lin et al. (2010) used a representative panel sample survey data collected in the five waves of "The Longitudinal Sample Survey of Health and Living Status of the Elderly in Taiwan" to explore factors affecting the changing status of depression among the elderly in Taiwan from 1989 to 2003 with GEE (Generalized Estimating Equation) (Liang and Zeger, 1986, 1988) and Recurrent Survival Models (Hosmer and Lemeshow, 2008; Kleinbaum and Klein, 2005; Therneau and Grambsch, 2000). In their research, cases of depression status are recurrent event with the characteristics of interval censored data since it changed at some unknown time point between consecutive surveys. In order to obtain more information insight, the interval censored approach wasn't considered by Lin et al. (2010) will be applied to analyze the changing status of depression of old people in Taiwan in this study.

On the other hand, interval censored model, which is used in many practical situations when the event of interest cannot be observed and it is only known to have occurred within a time interval, assumes that no competing event will prohibit any subject from eventually getting the event of interest (Kleinbaum and Klein, 2005). With interval-censoring when a subject was last seen no event and then died, it is not known whether he or she experienced the event of interest before dying or not; then it is not correct to treat death as right-censoring. This will lead to a potential bias (Joly et al., 2002). In addition, the recurrent survival model is unable to deal with the situation when two or more different types of events exist simultaneously, this situation is in a similar matter to interval censored model. In our study about the changing status of depression regards death and depression as a competing risk. Obviously, interval censored model couldn't handle the event caused by death. Multi-state models, a more general approach considers multiple endpoints would be an alternative for this problem.

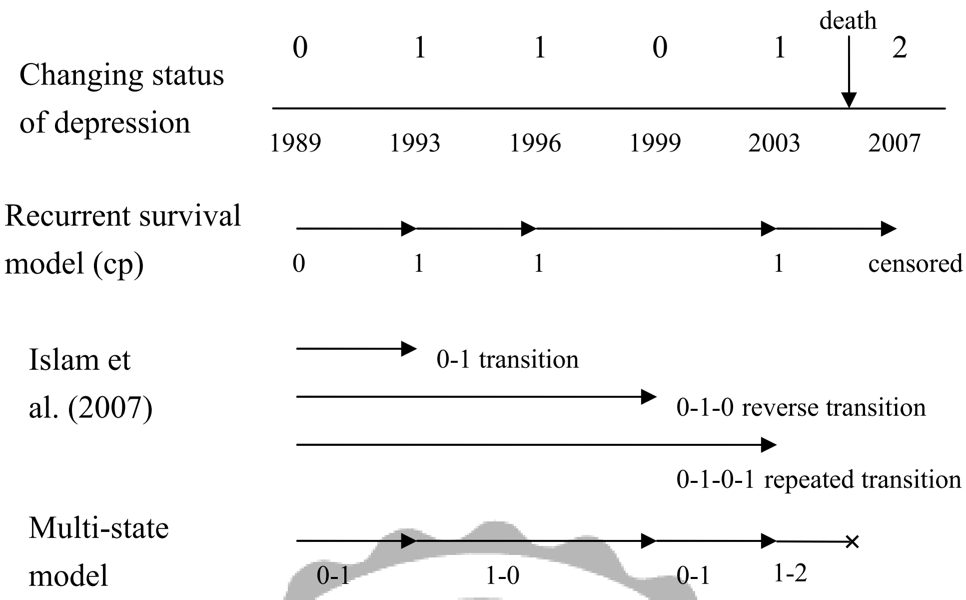
In recent years, multi-state models have been used widely in clinical trials, epidemiology, social sciences, and other fields, in particular to analysis of life histories data from longitudinal surveys with multiple events per subject. For instance, in bone marrow transplantation studies, instead of death, interest is not a single survival outcome. People may be interested in relapse as other indication of treatment failure. This is an example of multiple endpoints (de Wreede et al., 2010; Putter et al., 2007). A multi-state model is a model for that all individuals start in all possible initial states and eventually may end up in one or more absorbing states. Keeping the outcomes of event of interest separately and studying intermediate events may give more detailed and important information. For related studies, a more details about interval-censoring in multi-state models can refer Commenges (2002). Also, Putter et al. (2007) reviewed statistical methods analysis of competing risks and multi-state models. An attractive alternative is the additive models proposed by Aalen et al. (2001) which was extended to multi-state models. Broadly speaking, there are two mainly purposes for multi-state models. One is to obtain how certain covariates influence different phases between the various states. Another is to predict the transition probabilities depended on a given set of covariates (Aalen et al., 2001; Andersen and Keiding, 2002; de Wreede et al., 2010).

To illustrate the multi-state models for the changing status of depression of the elderly in Taiwan, the following is an example of changing status of depression for some individual and suppose that 0, 1 and 2 denote the normal, depression and death, respectively:



This case is normal at 1989 and 1999, and with depression in 1993, 1996, 2003, and dead after 2003. As far as multi-states models is concerned, this subject experienced four transitions, including 0→1 (1989 to 1993), 1→0 (1993 to 1999), 0→1 (1999 to 2003), and 1→2 (2003 to time of death) while recurrent survival model concentrates only on events occurring times, 1993, 1996, and 2003. Consequently, the interval from 2003 to 2007 is treated as censored data since death is not the event of interest for recurrent survival model.

On the other hand, for study related to depression transition data, Islam et al. (2007) concerned the analysis of depression among elderly which includes the identification of risk factors from longitudinal studies. They proposed a covariate dependent Markov model by employing the logistic function to analyze the transition from no depression to depression (0→1), reverse transition from depression to no depression (0→1→0), and repeated transition for those who made a reverse transition at previous stage (0→1→0→1). The reverse and repeated transitions are conditional events based on transition 0→1 and reverse transition 0→1→0 respectively. In addition, multistage model used to demonstrate the transitions, reverse transitions, and repeated transitions for longitudinal data with the proportional hazard model has been developed (Islam, 1994; Islam and Singh, 1992). Similar analysis depended on the logistic link functions are also used (Islam et al., 2004). Consequently, their study focuses on three types of transition of depression and its model assumes the initial state is healthy. The difference among all these models based on the changing status of depression of the individual mentioned before is illustrated as follows:



Different from those models consider healthy initial status only, individuals in multi-state models can start in one or more starting states and eventually may end up in one or more absorbing states. Multi-state models use dynamics data could provide more useful information related to transitions from one state to another than other models.

Overall speaking, our study is to investigate the factors affect the changing status of depression of the elderly in Taiwan. In a similar matter to recurrent event (counting process, CP) model assumption, we assume that the observations within a subject are mutually independent. That is the numbers of events in nonoverlapping time intervals are independent, given the covariates (Therneau and Grambsch, 2000). Cox model with interval-censored approach will be applied for exploring the variables related to the changing status of depression among the elderly in Taiwan. Also, the multi-state model considered as a Markov model means that given the present state and the event history of an individual, the next state to be visited and the time at which this will occur will only depend on the present state (Putter et al., 2007). Multi-state models of event history analysis will be used for interpreting the covariates affecting the changing status of depression. In addition, since Cox model might lead to potentially biased if hypothesis of constant effects of covariates do not hold (Aalen, 1993), Aalen's additive model which keeps account of instantaneous covariate effects on time, is used as a supplement to Cox model for detecting the nature of time-varying effects of covariates. Also, the scaled Schoenfeld residuals plots are applied for verifying the proportional hazard assumption (Grambsch and Therneau, 1994). Finally, the transition probabilities of the changing status of depression are provided.

Chapter 2

Material and methods

2.1. Data

The data used in this study is from the survey data collected in the six waves of "The Longitudinal Sample Survey of Health and Living Status of the Elderly in Taiwan" conducted from 1989 to 2007 by the predecessor organization of the Bureau of Health Promotion, Department of Health. A random sample of individuals (≥ 60 years old) taken from the entire elderly population of Taiwan were conducted by face-to-face interviews. Among 4,412 persons for the survey, 4,049 responded were taken from the six waves of survey held in 1989, 1993, 1996, 1999, 2003, and 2007. For each respondent, the basic demographic characteristics (e.g. age, gender, level of education), occupational history, social relationships, health status, health care, and survival status of the respondents were tracked over the 18-year period in six studied periods.

In this study, depressive symptoms were measured using the 10-item version of the Center for Epidemiological Studies Depression Scale (CES-D) developed and validated for use in the Established Populations for Epidemiological Studies of the Elderly (Kohout, 1993). The 10 items of depressive symptoms, including eight negative symptoms and two positive symptoms, were scored from 0 to 3 (0: hardly ever, 1: seldom, 2: sometimes, 3: most of the time). The total score, the sum of the eight negative items minus the two positive items, ranged from 0 to 30 and a higher score indicated serious symptoms of depression. An individual with depression indicates that the CESD score is less than 10. Table 1 is the characteristics of the respondents at the time of the initial interview without considering a few missing cases in 1989.

All the variables related to demographics, health status, and home and environment conditions were used to investigate the effect of changing status of depression in the elderly.

Table 1 Characteristics and status of respondents at initial interview in 1989

Variables		size	%	Variables		size	%
Demographics				Living with children			
Age					No	1,010	26.01
	60-64	1,482	36.60		Yes	2,873	73.99
	65-69	1,152	28.45				
	70-74	725	17.91	Economic status			
	75-79	438	10.82		Good	1,683	43.20
	80~	252	6.22		Fair	1,524	39.12
					Poor	689	17.68
Gender							
	Female	1,738	42.92	**Health Status**			
	Male	2,311	57.08	Self-rated health			
Level of education					Good	1,528	37.74
	Illiterate	1,685	41.62		Fair	1,494	36.90
	Elementary	1,596	39.42		Poor	1,027	25.36
	Junior high	329	8.12	ADL function			
	Senior high+	439	10.84		Good	3,282	81.06
Ethnicity					Fair	624	15.41
	Fukien	2,477	61.18		Poor	143	3.53
	Hakka	603	14.89	Physical function			
	Mainlander	900	22.23		Good	3,361	83.01
	Aborigine	69	1.70		fair	478	11.81
Home and Environment					poor	210	5.18
Spouse				Depression			
	Yes	2,603	64.29		No	3,195	81.99
	No	285	7.04		Yes	702	18.01
	Widowed	1,161	28.67				

2.2. Interval censored

Assume that the observations of depression within a subject are mutually independent. In interval censored problem, let $T_1, T_2, \cdots, T_n$ are all the event times unobserved and these times are only observed in the observable data set

$$D = \{(l_i, r_i] \mid i = 1, \cdots, n\}$$

For interval censored data, the exactly time of event of interest is not observed. Observations available are only $(l_i, r_i], i = 1, \cdots, n$. Assume that the event time T_i and $(l_i, r_i]$ are independent. We are interested in estimating the survival function of event of interest from D. Then the contribution to the likelihood of the *i*th individual with observed interval $(l_i, r_i]$ is given by the probability $P(l_i < T_i \le r_i)$, hence the overall log-likelihood is as follows

$$\begin{aligned} L(F) &= \sum_{i=1}^{n} \ln P(l_i < T_i \le r_i) \\ &= \sum_{i=1}^{n} \ln\left(F(r_i) - F(l_i)\right) = \sum_{i=1}^{n} \ln\left(S(l_i) - S(r_i)\right) \end{aligned} \tag{1}$$

where $S = 1 - F$ denoted the survival function of event of interest. This likelihood function can be used for obtaining the NPMLE of the survival function under interval censoring.

A modified method for estimating the NPMLE of the survival function under interval censoring was provided by Turnbull (1976). Define that

$$(q_j, p_j], j = 1, \cdots, m$$

are intervals obtained from the set of all left and right interval endpoints that q_j and p_j are the left and right endpoints respectively and there is no other endpoint between q_j and p_j. Turnbull (1976) also suggests how to reduce the number of intervals from D. These intervals are called Turnbull intervals also. Hence a maximum likelihood estimator of the survival function under interval censoring concentrated on these Turnbull intervals can be obtained by the following likelihood function

$$L_T(w_1, w_2, \cdots, w_m) = \prod_{i=1}^{n}\left(S(l_i) - S(r_i)\right) = \prod_{i=1}^{n}\left(\sum_{j=1}^{m}\alpha_j^i w_j\right) \tag{2}$$

where $w_j = P(q_j < T \le p_j) = S(q_j) - S(p_j)$ and $\alpha_j^i = I\{(q_j, p_j] \subseteq (l_i, r_i]\}$. Then the NPMLE for the survival function within each Turnbull interval is given by

$$\hat{S}_n(t) = \begin{cases} 1, & t \le q_1 \\ 1 - \left(\hat{w}_1 + \hat{w}_2 + \cdots + \hat{w}_j\right), & p_j \le t \le q_{j+1}, 1 \le j \le m-1 \\ 0, & t \ge p_m \end{cases} \tag{3}$$

where $\hat{w}_1, \hat{w}_2, \cdots, \hat{w}_m$ are the self-consistent estimators obtained by the solution of following simultaneous equations

$$\hat{w}_j = \frac{1}{n}\sum_{i=1}^{n}\frac{\alpha_j^i}{\sum_{l=1}^{m}\alpha_l^i \hat{w}_l}\hat{w}_j, 1 \le j \le m \tag{4}$$

This is called the self-consistency algorithm for interval censored data.

For a more efficient algorithm, such as the ICM algorithm (the iterative convex minorant algorithm), have been proposed (Groeneboom and Wellner, 1992; Wellner and Zahn, 1997). Pan (1999) extends the ICM algorithm for obtaining the NPMLE of the survival function under these Turnbull intervals. Suppose that $\hat{F}$ can only have jumps between the order statistics $\tau_1, \tau_2, \cdots, \tau_k$ of $(q_j, p_j], j = 1, \ldots, m$. Let the first derivative and second derivative of L, with respect to $F = \left(F(\tau_1), \ldots, F(\tau_k)\right)^T$, be ∇L and $\nabla^2 L$ respectively. G is a $k \times k$ diagonal matrix with the same diagonal elements as $-\nabla^2 L$. To obtain the NPMLE of the distribution function, Pan's extended ICM-algorithm for interval censored data without covariates is as follows

$$F^{(m+1)} = \text{Proj}\left[F^{(m)} + \alpha G\left(F^{(m)}\right)^{-1} \nabla L\left(F^{(m)}\right), G\left(F^{(m)}\right), \Re\right] \quad (5)$$

where

$$\text{Proj}\left[y, G, \Re\right] = \arg\min_{x}\left\{\sum_{i=1}^{k}\left(y_i - x_i\right)^2 G_{ii} : 0 \le x_1 \le x_2 \le \cdots \le x_k \le 1\right\}$$

and α is a suitably chosen stepsize, which can be simply chosen by

$$\alpha = \max\left\{\frac{1}{2^i} : L\left(F^{(m+1)}\right) > L\left(F^{(m)}\right), i = 0, 1, 2, \ldots\right\}$$

When the intensity of event of interested combines the covariates is considered as follows

$$\lambda\left(t \mid x(t)\right) = \lambda_0(t)\exp\left(\beta^{\mathrm{T}} x(t)\right) \quad (6)$$

where $\lambda_0(t)$ for the unknown baseline hazard function and $x(t)$ for the covariate vector at time t and β for the regression coefficient vector. The simplified log-likelihood function based on the observed interval censored data $D = \{(l_i, r_i] \mid i = 1, \cdots, n\}$ is expressed as

$$\begin{aligned} L(F_0, \beta) &= \sum_{i=1}^{n} \ln\left\{S_0\left(l_i\right)^{\exp\left(\beta^{\mathrm{T}} x_i\right)} - S_0\left(r_i\right)^{\exp\left(\beta^{\mathrm{T}} x_i\right)}\right\} \\ &= \sum_{i=1}^{n} \ln\left\{\left(1 - F_0\left(l_i\right)\right)^{\exp\left(\beta^{\mathrm{T}} x_i\right)} - \left(1 - F_0\left(r_i\right)\right)^{\exp\left(\beta^{\mathrm{T}} x_i\right)}\right\} \end{aligned} \quad (7)$$

where $S_0(t)$ denotes the baseline survival function. Pan (1999) obtained the non-parametric maximum likelihood estimate of β by ICM-algorithm. Let $\nabla_1 L(F_0, \beta)$ and $\nabla_2 L(F_0, \beta)$ be the first derivatives of F_0 and β, respectively; $G_1(F_0, \beta)$ and $G_2(F_0, \beta)$ the corresponding diagonal matrices of the negative second derivatives. Pan's extended ICM iterates is as follows

$$F_0^{(m+1)} = \text{Proj}\left[F_0^{(m)} + \alpha G_1\left(F_0^{(m)}, \beta^{(m)}\right)^{-1} \nabla_1 L\left(F_0^{(m)}, \beta^{(m)}\right), G_1\left(F_0^{(m)}, \beta^{(m)}\right), \Re\right] \quad (8)$$

$$\beta^{(m+1)} = \beta^{(m)} + \alpha G_2\left(F_0^{(m)}, \beta^{(m)}\right)^{-1} \nabla_2 L\left(F_0^{(m)}, \beta^{(m)}\right) \quad (9)$$

where α and Proj are defined as before. As for interval censored data, tutorial on methods for interval censored data, including frequentist non-parametric, parametric and semiparametric estimating approaches, non-parametric tests for comparing survival curves are also provided by Gómez et al. (2009).

To investigate the factors related to the depressive status in the framework for interval-censored data, the method proposed by Pan (1999) was used for analyzing. In addition, the R package 'intcox' developed by Henschel et al. (2007) was employed for implementing the extended Cox model. Unfortunately, it didn't provide standard errors of regression parameters. As suggested by Henschel et al. (2007), we used bootstrap intervals to check whether the association between the depressive symptoms and all the covariates related to depressive status. The 95% bootstrap intervals for each parameter contained zero implies there is no significant association between the related variables and depressive status.

2.3. Multi-state model

A multi-state model is a model for time to event data in which individuals start in one or possibly more starting states and may end up in one (or more) absorbing or final states. In a multi-state process, denote the states in the multi-state model with $\mathbb{S}=\{0,1,\ldots,S\}$, and let $X(t)$ be a multi-state process with a finite state space $\mathbb{S}$. In the structure of multi-state model, define $P_{hj}(s,t)$ be the transition probability from state h to state j in the time interval $(s,t]$, and is expressed as

$$P_{hj}(s,t)=P\left(X(t)=j \mid X(s)=h\right) \tag{10}$$

for $h, j\in\mathbb{S}$, $s\le t$ and transition intensities from state h into state j at time t can be expressed as

$$\lambda_{hj}(t)=\lim_{\Delta t\to 0}\frac{P(X(t+\Delta t)=j \mid X(t)=h)}{\Delta t} \tag{11}$$

The Markov assumption is implicitly present in equation (11). It means the future depends on history only through the present. That is

$$P\left(X(t+\Delta t)=j \mid X(t)=h,\left\{X(s), s<t\right\}\right)=P\left(X(t+\Delta t)=j \mid X(t)=h\right)$$

In addition, assume that the transition intensities are the same for all subjects and allowed to vary with time. The cumulative transition hazard is defined as

$$\Lambda_{hj}(t)=\int_0^t \lambda_{hj}(u)du \tag{12}$$

Note that if a direct transition between state h and state j is impossible, then $\Lambda_{hj}(t)=0$.

An important feature of multi-state models is to estimating transition probabilities. Define $\mathrm{A}(t)$ be the transition intensities matrix with diagonal elements

$$\Lambda_{hh}(t)=-\sum_{h\neq j}\Lambda_{hj}(t) \tag{13}$$

which expresses that no transition remain in state *h* at time *t*. Therefore, given $\mathrm{A}(t)$, our quantity of interest in multi-state model is the transition probability matrix $\mathrm{P}(s,t)$, which can be calculated by means of a product integral (Andersen et al., 1993) as follows

$$\mathrm{P}(s,t)=\prod_{(s,t]}\left(I+d\mathrm{A}(u)\right) \tag{14}$$

To understand the multi-state approach, there are some examples to illustrate. The most simple multi-state model is the two-state model for survival data illustrated in Figure 1. This simple model is with one transient state '0: alive' and one absorbing state '1: dead'. Let *T* be the time of the occurrence of the event 'death'. The transition probability from state 0 to state 1 for the time interval from 0 to *t* may also be characterized by the intensity function

$$\lambda(t)=-d\log S(t)/dt=\lim_{\Delta t\to 0}\frac{P(T\leq t+\Delta t \mid T\geq t)}{\Delta t} \tag{15}$$

and

$$S(t) = \exp\left(-\int_0^t \lambda(u)du\right) \tag{16}$$

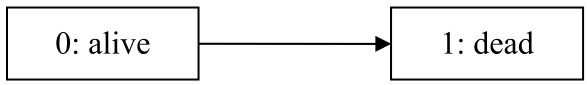


Figure 1 The two-state model for survival data.

Another one of multi-state model is competing risks model illustrated in Figure 2. It has one starting state, at least two absorbing states and no intermediate states. Let T and C denote the event time and the type of event, respectively. The cause-specific hazard functions $\lambda_k(t), k = 1,\ldots, K$ as the transition intensities are given by

$$\lambda_k(t) = \lim_{\Delta t \to 0} \frac{P(t \le T < t + \Delta t, C = k \mid T \ge t)}{\Delta t} \tag{17}$$

For this consideration, the transition probabilities can be written as the survival function and the cumulative incidence functions, which are given by

$$P_{00}(0,t) = S(t) = \exp\left(-\int_0^t \sum_{k=1}^{K} \lambda_k(u)du\right) \tag{18}$$

and

$$P_{0k}(0,t) = \int_0^t S(u^-)\lambda_k(u)du, \quad k = 1,\ldots, K \tag{19}$$

Like the competing risks model included the effect of covariates is of interest, the cause-specific hazards in proportional hazards regression are commonly considered.

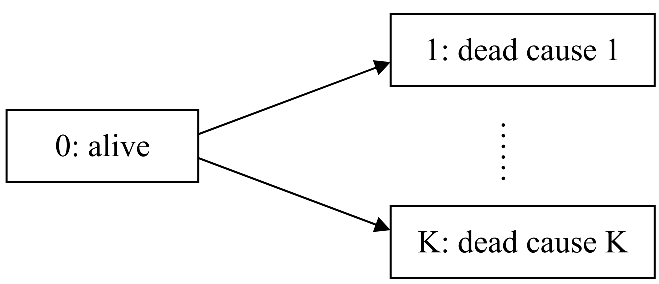


Figure 2 Competing risks model for K causes.

Furthermore, a slightly more complex example is the illness-death model. This model is one of the most important multi-state models illustrated in Figure 3. Thus the transition probabilities in this model can be expressed simply

$$P_{00}(s,t)=\exp\left(-\int_s^t\left(\lambda_{01}(u)+\lambda_{02}(u)\right)du\right)\quad P_{01}(s,t)=\int_s^t P_{00}(s,u^-)\lambda_{01}(u)P_{11}(u,t)du \quad (20)$$

where

$$P_{11}(s,t)=\exp\left(-\int_s^t\lambda_{12}(u)du\right) \quad (21)$$

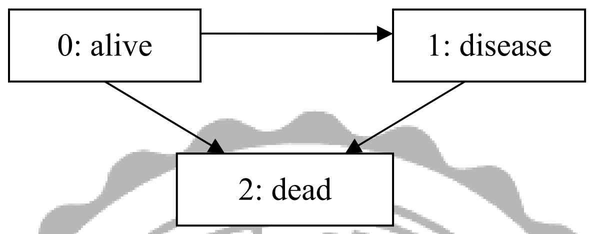


Figure 3 The Illness-death model.

In this study, a more general model of illness-death process is considered in Figure 4. This model includes two transient states: normal and depression. Both of states can be the initial state. There is one absorbing state: dead. Individuals can travel between the two transient states and visit each of them more than once. On the other hand, the transition back from state 1 to 0 is possible. A model with this feature is called reversible.

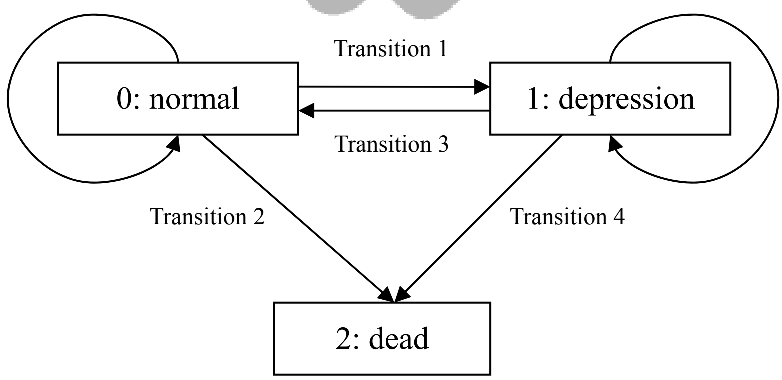


Figure 4 The multi-state model with the possibility of reversibility.

2.3.1. Transition intensities in nonparametric models

For the consideration illustrated in Figure 4, let $\mathrm{N}_q^i(t)$ be the counting process for the type q transition ($q = 1, 2, 3, 4$) for subject $i = 1, \ldots, n_q$. Similarly, $Y_q^i(t)$ denotes the at risk process, that is $Y_q^i(t) = 1$ if subject *i* is at risk for type *q* transition at time t^-. Also let $\mathrm{N}_q(t) = \sum_{i=1}^{n_q} \mathrm{N}_q^i(t)$ and $Y_q(t) = \sum_{i=1}^{n_q} Y_q^i(t)$ denote the number of events and the size of the risk set for type *q* transition at time *t*. Thus, in nonparametric models, estimators of the intensity of type *q* transition are given by

$$d\hat{\Lambda}_q(t) = \frac{d\mathrm{N}_q(t)}{Y_q(t)} \tag{22}$$

with variance estimator calculated as

$$\widehat{\mathrm{var}}\left(d\hat{\Lambda}_q(t)\right) = \frac{d\mathrm{N}_q(t)}{Y_q^2(t)} \tag{23}$$

where $d\mathrm{N}_q(t)$ is the number of transitions of type *q* at time *t*. Then by summing over all event times up to time t, the Nelson-Aalen estimator $\hat{\Lambda}_q(t)$ of the cumulative hazard for type *q* transition can be obtained

$$\hat{\Lambda}_q(t) = \int_0^t \frac{J_q(u)}{Y_q(u)} d\mathrm{N}_q(u) \tag{24}$$

where $J_q(u) = I\left\{Y_q(u) > 0\right\}$ with $I\{\cdot\}$ being the indicator function. The Aalen-Johansen estimator of $\mathrm{P}(s,t)$ is obtained by plugging $\hat{\Lambda}_q(t)$ into the formula

$$\hat{\mathrm{P}}(s,t) = \prod_{(s,t]}\left(I + d\hat{\mathrm{A}}(u)\right) \tag{25}$$

2.3.2. Transition intensities in Cox regression models

When there are covariate effects to be considered, the Cox model (Cox, 1972) is the most commonly used. In this study, we assume that the transition intensities of type *q* at time *t* is

$$\lambda_q\left(t \mid x_q(t)\right) = \lambda_{q0}(t)\exp\left(\beta_q^{\mathrm{T}} x_q(t)\right) \quad q = 1, 2, 3, 4 \tag{26}$$

where $\lambda_{q0}(t)$ indicates the baseline hazard for type *q*, $\beta_q = \left(\beta_{q1}, \ldots, \beta_{qp}\right)^T$ is the vector of coefficients for these covariates corresponding to the type *q* transition, and $x_q(t) = \left(x_{q1}(t), \ldots, x_{qp}(t)\right)^T$ is specified covariates vector at time *t*.

Consider now again equation (26), parameter estimation in the multi-state model can be obtained by maximization of the partial likelihood function

$$\prod_{q=1}^{4}\prod_{i=1}^{n_q} \frac{\exp\left(\beta_q^T x_q^i(t)\right)}{\sum_{l=1}^{n_q} \exp\left(\beta_q^T x_q^l(t)\right) Y_q^l(t)} \tag{27}$$

where $Y_q^l(t)$ denotes the at-risk process for type *q* transition at time *t*. Based on the estimation of parameters, the baseline hazard of type *q* transition given a vector of specified covariates $x(t)$ is estimated by

$$d\hat{\Lambda}_{q0}\left(t, \hat{\beta}_q\right) = \frac{d\mathrm{N}_q(t)}{\sum_{l=1}^{n_q} \exp\left(\hat{\beta}_q^T x(t)\right) Y_q^l(t)} \tag{28}$$

where $d\mathrm{N}_q(t)$ is the number of events of transition *h*→*j* at time *t*. Equation (28) is also called the Breslow estimator. The estimator of the cumulative baseline hazard $\hat{\Lambda}_{q0}\left(t, \hat{\beta}_q\right)$ is the sum over the event time $u \le t$ of $d\hat{\Lambda}_{q0}\left(t, \hat{\beta}_q\right)$ and this estimator is the weighted version of Nelson-Aalen estimator contained the information of covariates. Therefore, the transition probability matrix in the time interval $(s, t]$ is expressed as

$$\hat{\mathrm{P}}(s, t) = \prod_{(s, t]}\left(I + d\hat{\mathrm{A}}(u, \hat{\beta})\right) \tag{29}$$

where $d\hat{\mathrm{A}}(u, \hat{\beta})$ is the baseline hazards of all possible transitions.

More detailed multi-state models for event history analysis can refer Andersen and Keiding (2002). Moreover, studies covered competing risks models and interval censored data for multi-state models are also mentioned by Andersen et al. (2002), Commenges (2002), and de Wreede et al. (2010). Furthermore, applications with multi-state models, likes on bone marrow transplantation, have been provided (Therneau and Grambsch, 2000; Klein and Shu, 2002; Putter et al., 2007).

2.4. Aalen model

An attractive alternative method used for survival data is the additive model. Aalen (1989) proposes an approach to deal with the hazard function followed a linear additive regression model

$$h(t \mid x) = \alpha_0(t) + \alpha_1(t)x_1 + \alpha_2(t)x_2 + \cdots + \alpha_p(t)x_p \tag{30}$$

where $\alpha_j(t)\left(j = 0, 1, \ldots, p\right)$ are unknown regression function allowed to vary over time. By integrating the hazard function in (30), the cumulative hazard function is

$$H(t \mid x) = \int_0^t h(u \mid x)\,du = \sum_{j=0}^{p} x_j \int_0^t \alpha_j(u)\,du = \sum_{j=0}^{p} x_j B_j(t) \tag{31}$$

where $x_0 = 1$, $B_j(t)$ is the cumulative regression function for the *k*th covariate, and $B_0(t)$ is the baseline cumulative hazard function. Assume that there are *n* independent observations of time, a design matrix X_j for the subjects at risk at time t_j, in which there is one row for each individual, if the *i*th individual is still at risk, the row contains the data for the *i*th subject; otherwise the row consists zeros. Aalen's estimator of the vector of the regression function at time t_j is a least-squares-like estimator as follows

$$\hat{b}(t_j) = \left(\mathrm{X}_j^T \mathrm{X}_j\right)^{-1} \mathrm{X}_j^T y_j \tag{32}$$

where y_j is a *n* by 1 vector, in which the *j*th element is 1 if the *j*th subject's observed time t_j; otherwise, all the values in the vector are 0. Aalen (1989) showed that the vector of cumulative regression functions may be estimated by

$$\hat{B}(t) = \sum_{t_j \le t} \hat{b}(t_j) \tag{33}$$

and the estimator of the cumulative hazard function for the *i*th subject at time *t* is

$$\hat{H}\left(t \mid x_i\right) = \sum_{j=0}^{p} x_{ij} \hat{B}_j(t) \tag{34}$$

and the estimator of survival function adjusted for covariates is

$$\hat{S}\left(t \mid x_i\right) = \exp\left[-\hat{H}\left(t \mid x_i\right)\right] \tag{35}$$

To examine for time-varying effects of covariates, the plot of $\hat{B}_j(t)$ versus *t*, along with the upper and lower bands of a 95 percent confidence interval, is also provided by

$$\hat{B}_j(t) \pm z_{1-\alpha/2} \times \widehat{SE}\left[\hat{B}_j(t)\right] \tag{36}$$

where $z_{1-\alpha/2}$ is the upper $100(1-\alpha/2)$ percentile of the standard normal distribution, and $\widehat{SE}\left[\hat{B}_j(t)\right]$ is the estimator of the standard error of $\hat{B}_j(t)$ obtained as the square root of the variance estimator $\sum_{t \le t_k} \hat{b}_j^2(t_k)$.

For testing the hypotheses that the coefficients in the additive model are equal to zero, Aalen (1989) provides a testing statistics formed from the components of the vector

$$\hat{U} = \sum \mathrm{K}_j \hat{b}(t_j) \tag{37}$$

This summation in above equation is over all event times when $\left(\mathrm{X}_j^T \mathrm{X}_j\right)$ is nonsingular, and K_j is a $\left(p+1\right) \times \left(p+1\right)$ diagonal matrix of weights. There are two choices for weights suggested by Aalen (1989). One is based on the number in the risk set at t_j; other choice is based on the inverse of the square root of the diagonal elements of $\left(\mathrm{X}_j^T \mathrm{X}_j\right)^{-1}$.

The variance estimator of $\hat{U}$ is

$$\begin{aligned}\widehat{\operatorname{var}}\left(\hat{U}\right) &= \sum_{t_j} \mathrm{K}_j \left(\mathrm{X}_j^T \mathrm{X}_j\right)^{-1} \left(\mathrm{X}_j^T \mathrm{I}_j \mathrm{X}_j\right) \left(\mathrm{X}_j^T \mathrm{X}_j\right)^{-1} \mathrm{K}_j \\ &= \sum_{t_j} \mathrm{K}_j \widehat{\operatorname{var}}\left[\hat{b}(t_j)\right] \mathrm{K}_j\end{aligned} \tag{38}$$

When testing for significance of individual coefficients, Aalen showed this ratio, the individual elements of the vector U scaled by the estimator of their standard error obtained as the square root of the appropriate element from the diagonal of the matrix, has approximately the standard normal distribution when the hypothesis of no effect is true and the sample is sufficiently large.

2.4.1. Multi-state models with the additive approach

Another regression model that extends to multi-state models is Aalen's nonparametric additive model (Aalen et al., 2001). For the consideration in this study, we also assume that each transition intensity $h_q\left(t \mid x_q(t)\right)$ ($q = 1, 2, 3, 4$) depended on covariates, $x_q(t) = \left(x_{q1}(t), \ldots, x_{qp}(t)\right)^T$, follows an additive regression model

$$h_q\left(t \mid x_q(t)\right) = \alpha_{q0}(t) + \alpha_{q1}(t) x_{q1}(t) + \alpha_{q2}(t) x_{q2}(t) + \cdots + \alpha_{qp}(t) x_{qp}(t) \tag{39}$$

where the baseline transition intensities $\alpha_{q0}(t)$ and the regression functions $\alpha_{qk}, k = 1, \ldots, p$ may be obtained using a generalized least squares procedure. Now, define a design matrix $\mathrm{X}_q(t)$, in which there is one row for each individual, if an individual is still at risk, the row is $\left(1, x_{q1}(t), \ldots, x_{qp}(t)\right)$ otherwise the row consists zeros. In addition, let $\mathrm{N}_q(t)$ be the multivariate counting process, counting for each subject the type q transition. Aalen (1989) showed that the vector of cumulative regression functions may be estimated by

$$\tilde{B}_q(t) = \int_0^t Z_q(s) dN_q(s) \tag{40}$$

where Z_q is a generalized inverse of design matrix X_q.

To calculate the transition probabilities in the multi-state model dependent on covariate information, for individuals with a vector of possibly time-dependent covariate $x^0(t)$, the cumulative intensities for type *q* transition are estimated by

$$\tilde{\Lambda}_q\left(t, x^0(t)\right) = \int_0^t x^0(s)^T d\tilde{B}_q(s) \tag{41}$$

For a given fixed covariate vector x^0, the above equation can be expressed as

$$\tilde{\Lambda}_q(t) = x^{0T}\tilde{B}_q(t) \tag{42}$$

Similarly, define

$$\tilde{\Lambda}_{ii}(t) = -\sum_{j \neq i} \tilde{\Lambda}_{ij}(t) \tag{43}$$

then the transition probability matrix in the time interval $(s, t]$ is estimated by the product integral

$$\tilde{P}(s,t) = \prod_{(s,t]} \left(I + d\tilde{A}(u)\right) \tag{44}$$

where $\tilde{A}(t)$ is the estimated intensity matrix obtained from Aalen multi-state model. Comparing equation (28) with equation (41), the estimates for the cumulative transition intensities from Cox model is based on risk set of event time and averaging effect of covariates. The cumulative intensities obtained by Aalen model is concentrated on the cumulative regression function, this function not only depends on risk set but also changes over time. In other words, Aalen model picks up changes in the effects of covariates which gives some additional information about the time varying effect.

2.5. Schoenfeld residuals

When the Cox model is considered, a key assumption is proportional hazards. That is the relative hazard for any two subjects is independent of time. Nevertheless, if the effects of covariates do not support the hypothesis of constant relative risk, the Cox model can lead to potentially biased conclusions (Aalen, 1993). To deal with this problem, an easily expressed alternative to proportional hazards is provided by models with a time-dependent coefficient

$$\lambda\left(t \mid x(t)\right) = \lambda_0(t)\exp\left(\beta(t)^T x(t)\right) \tag{45}$$

The restriction $\beta(t) = \beta$ implies proportional hazards, and then a plot of $\beta_j(t)$ versus time will be a horizontal line.

Let $0 < t_1 < \cdots < t_k < \infty$ be the event times. Consider each subject to be an independent counting process $\{N_i(t), t \geq 0, i = 1, \ldots, n\}$. From the Cox model, the Schoenfeld residual for the *j*th event is defined as

$$s_j = \int_{t_{j-1}}^{t_j} \sum_i \left(x_i - \bar{x}(\hat{\beta}, s)\right) dN_i(s) \tag{46}$$

where $\hat{\beta}$ is the coefficient from an ordinary fit of the Cox model, and

$$\bar{x}(\hat{\beta}, s) = \frac{\sum_{i=1}^{n} Y_i(s)\exp\left(\hat{\beta}^T x_i(s)\right) x_i(s)}{\sum_{i=1}^{n} Y_i(s)\exp\left(\hat{\beta}^T x_i(s)\right)} \tag{47}$$

with $Y_i(s)\exp\left(\hat{\beta}^T x_i(s)\right)$ as weights and $Y_i(s)$ is an indicated function whether the *i*th subject is at risk at time *s*. When there are no tied event times, the Schoenfeld residual for the *j*th event can be written as

$$s_j = x_{(j)} - \bar{x}(\hat{\beta}, t_j) \tag{48}$$

where $x_{(j)}$ is the covariate vector of the individual experiencing the *j*th event, at the time of that event. Grambsch and Therneau (1994) show that

$$E\left(s_{jk}^{*}\right)+\hat{\beta}_{k} \approx \beta_{k}(t_{j}) \tag{49}$$

where s_j^* is the scaled Schoenfeld residual

$$s_{j}^{*}=V^{-1}\left(\hat{\beta}, t_{j}\right) s_{j} \tag{50}$$

and $V\left(\beta, t\right)$ is the weighted variance of x

$$V\left(\beta, t\right)=\frac{\sum_{i=1}^{n} Y_{i}(s) \exp\left(\beta^{T} x_{i}(s)\right)\left(x_{i}(s)-\bar{x}(\beta, s)\right)\left(x_{i}(s)-\bar{x}(\beta, s)\right)^{T}}{\sum_{i=1}^{n} Y_{i}(s) \exp\left(\beta^{T} x_{i}(s)\right)} \tag{51}$$

A method for visualizing the nature and extent of nonproportional hazards is by plotting $s_{jk}^{*}+\hat{\beta}_{k}$ versus time and a nonzero slope is evidence against proportional hazards.

In this study, cases of depression status are recurrent event with the characteristics of interval censored data since it happened at some unknown time point between consecutive surveys. Interval-censored model is applied for investigating the variables related to the changing status of depression among the elderly in Taiwan. Because of the limitation of focusing on a single event for interval censored model, a more general method, Cox with multi-state model of event history analysis considered as a Markov chain will be used for interpreting the relation between the changing status of depression and covariates, also Aalen model is employed to supplement Cox model for detecting the nature of time-varying effects of covariates. In addition, the scaled Schoenfeld residuals plots are used for verifying proportional hazard assumption. Finally, the transition probabilities obtained from Cox and Aalen with multi-state model in all possible paths of the changing status of depression of the elderly in Taiwan, are provided.

Chapter 3

Results

3.1. Interval-censored model for the depressive status

Table 2 shows the results of the extended Cox model and 95% bootstrap intervals in 1000 replications. Among the 10 variables used in this study, there are 8 variables e.g. age, gender, level of education, spouse, living with children, economic status, self-rated health and physical function, are related to the depressive status significantly. As for the demographics characteristics, the elderly with 70-74, 75-79 and 80+ years old have higher hazard ratio than younger people. The hazard ratio of the elderly is between 1.547 to 3.507 times that of those ages 60-64. Females are more likely to have depressive symptoms than males. The hazard ratio for males is 0.662 times that of females. For the levels of education, those with higher education have a relatively better mental health than that with lower education. The hazard ratios of the levels of education from the elementary school to the senior high school+ are 0.818, 0.688 and 0.685 times that of illiterate, respectively.

As for home and environment conditions, the hazard ratio of depression for the elderly without spouse is 1.784 times that with spouse. Besides, the widowed elderly have a lower hazard ratio than that with spouse. On the other hand, the elderly living without children have a better mental health than that with children. For the economic status, people with better economics status have lower hazard ratio to depression than worse economics condition. The hazard ratios of fair economics status and poor economics status are 1.703 times and 2.299 times that of good economics status, respectively. As for health status, the elderly with worse condition of self-rated health are more likely to experience depression. The hazard ratios of fair and poor self-rated health are 1.582 and 2.791 times that of good status. In addition, the hazard ratio of depression for fair physical function is 0.823 times that of good physical function.

Table 2 The results of the interval-censored Cox model and the 95% bootstrap intervals

Variables		coef	exp(coef)	lower bound	upper bound
Demographics Characteristics					
Age	60-64	0.000	1.000		
	65-69	0.101	1.107	-0.028	0.224
	70-74	0.436	1.547	0.263	0.623
	75-79	0.713	2.040	0.491	0.938
	80~	1.255	3.507	0.871	1.621
Gender	Female	0.000	1.000		
	Male	-0.412	0.662	-0.557	-0.271
Level of education	Illiterate	0.000	1.000		
	Elementary	-0.202	0.818	-0.335	-0.077
	Junior high	-0.374	0.688	-0.642	-0.114
	Senior high+	-0.379	0.685	-0.636	-0.151
Ethnicity	Fukien	0.000	1.000		
	Hakka	-0.036	0.964	-0.209	0.107
	Mainlander	-0.015	0.985	-0.191	0.140
	Aborigine	0.096	1.101	-0.320	0.453
Home and Environment					
Spouse	Yes	0.000	1.000		
	No	0.579	1.784	0.388	0.769
	Widow	-0.425	0.654	-0.578	-0.304
Living with children	No	0.000	1.000		
	Yes	0.175	1.191	0.065	0.302
Economic	Good	0.000	1.000		
status	Fair	0.533	1.703	0.408	0.681
	Poor	0.832	2.299	0.681	1.008
Health Status					
Self-rated	Good	0.000	1.000		
health	fair	0.459	1.582	0.255	0.649
	poor	1.026	2.791	0.859	1.219
ADL	Good	0.000	1.000		
function	fair	0.194	1.214	-0.095	0.488
	poor	-0.007	0.993	-0.366	0.401
Physical	Good	0.000	1.000		
function	fair	-0.195	0.823	-0.340	-0.057
	poor	-0.037	0.964	-0.219	0.139

3.2. The multi-state model

In this section, we employ the multi-state model for different transition paths between depression status (Figure 4) in this study. Cox model is applied for interpreting the relation between the changing status of depression and covariates. Besides, in order to receive more information insight, plots of the cumulative regression coefficients from Aalen model is employed for assisting to investigate whether time-varying effect exists in some covariates. The scaled Schoenfeld residuals plots are also used for verifying the proportional hazard assumption. A nonzero slope is an evidence against proportional hazards.

3.2.1. Transition 0→1

Table 3 shows there are 7 variables e.g. age, gender, level of education, spouse, living with children, economic status and self-rated health, significantly related to the transition 0→1 (from normal to depression). Based on Cox model, these results are similar to the interval-censored Cox model for depressive status except physical function. The average effects of the multi-state Cox model for the transition 0→1 are slightly lower than the effects obtained by interval-censored model. However, the trends are consistent between the two models.

To confirm the time-varying effects, the results of Aalen model are shown in Table 3 also. Generally, the significant variables from the Cox model and Aalen model are similar except variable physical functions. Figure 5 presents the cumulative coefficients and the scaled Schoenfeld residuals for the fair physical function. When the time varying effect of covariates are taken into account, the variable fair physical function is significant slightly in Aalen model and the cumulative coefficients plot shows that the fair physical function may have an early effect, up to 170 months, and no effect after that. Also, the scaled Schoenfeld residuals plot had a nonzero slope.

Both of the plots show slightly time-varying effect for this covariate.

Table 3 The results of Cox model and Aalen model for transition 0→1

Variables		Cox model coef	Cox model exp(coef)	Aalen model |z|	Aalen model *P*>|z|
Demographics Characteristics					
Age	60-64	0.000	1.000		
	65-69	0.043	1.044	0.443	0.658
	70-74	0.269^{**}	1.308	2.786	0.005
	75-79	0.380^{**}	1.462	2.540	0.011
	80~	0.674^{***}	1.961	2.229	0.026
Gender	Female	0.000	1.000		
	Male	-0.453^{***}	0.636	6.529	<0.001
Level of education	Illiterate	0.000	1.000		
	Elementary	-0.185^{**}	0.831	3.193	0.001
	Junior high	-0.380^{**}	0.684	3.501	<0.001
	Senior high+	-0.376^{**}	0.687	3.412	0.001
Ethnicity	Fukien	0.000	1.000		
	Hakka	-0.048	0.954	1.432	0.152
	Mainlander	0.101	1.106	0.444	0.657
	Aborigine	0.318	1.374	0.959	0.338
Home and Environment					
Spouse	Yes	0.000	1.000		
	No	0.362^{***}	1.436	4.117	<0.001
	Widow	-0.348^{***}	0.706	5.508	<0.001
Living with children	No	0.000	1.000		
	Yes	0.159^{**}	1.172	3.121	0.002
Economic status	Good	0.000	1.000		
	Fair	0.451^{***}	1.569	5.822	<0.001
	Poor	0.788^{***}	2.198	8.547	<0.001
Health Status					
Self-rated health	Good	0.000	1.000		
	fair	0.326^{**}	1.385	3.057	0.002
	poor	0.852^{***}	2.344	9.075	<0.001
ADL function	Good	0.000	1.000		
	fair	0.055	1.056	0.345	0.730
	poor	0.014	1.014	1.060	0.289
Physical function	Good	0.000	1.000		
	fair	-0.103	0.902	2.034	0.042
	poor	0.086	1.089	0.066	0.948

$^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$

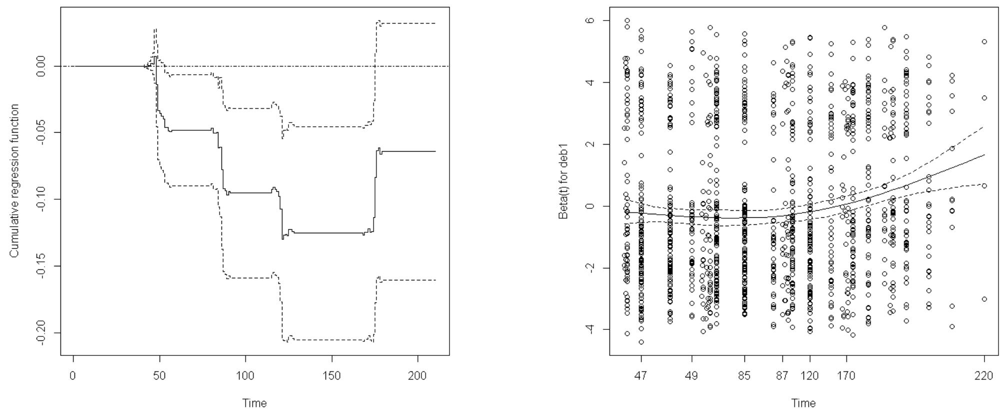


Figure 5 Plots of the cumulative regression coefficient and the scaled Schoenfeld residuals for fair physical function in transition 0→1.

3.2.2. Transition 1→0

Transition from depression to normal status (1→0) obtained by Cox model are presented in Table 4. Seven variables e.g. education, spouse, living with children, economic status, self-rated health, ADL function and physical function, are related to the recovered transition 1→0 significantly. It is interested that the elderly with the senior high+ education are less likely to go back to normal status than that of low level of education. As for the home and environment conditions, people with spouse and living with children are more likely to be in good mental health status. In particular, the hazard ratio of recover to the normal status for the widowed elderly is 0.668 times that with spouse. For the economics status, the elderly with a poor economics status have a relatively worse mental health than that in good economics status. The hazard ratio of recovering to normal for the poor economics status is 0.670 times that in good economics status. As for health status, the elderly with worse conditions of self-rated health, ADL functions and physical functions are less likely to recover from depression to normal. These situations are consistent with what people acknowledged.

Table 4 The results of Cox model and Aalen model for transition 1→0

Variables		Cox model		Aalen model	
		coef	exp(coef)	$\lvert z\rvert$	$P>\lvert z\rvert$
Demographics Characteristics					
Age	60-64	0.000	1.000		
	65-69	0.117	1.124	1.229	0.219
	70-74	0.139	1.149	0.769	0.442
	75-79	0.216	1.241	0.682	0.495
	80~	0.155	1.168	0.703	0.482
Gender	Female	0.000	1.000		
	Male	-0.1141	0.892	1.282	0.200
Level of education	Illiterate	0.000	1.000		
	Elementary	-0.142	0.868	1.050	0.294
	Junior high	-0.194	0.824	0.359	0.720
	Senior high+	-0.297*	0.743	1.063	0.288
Ethnicity	Fukien	0.000	1.000		
	Hakka	0.0368	1.038	0.213	0.831
	Mainlander	0.0845	1.088	0.360	0.719
	Aborigine	-0.034	0.967	0.016	0.987
Home and Environment					
Spouse	Yes	0.000	1.000		
	No	-0.028	0.972	0.059	0.953
	Widow	-0.403***	0.668	4.588	<0.001
Living with children	No	0.000	1.000		
	Yes	0.216**	1.241	2.480	0.013
Economic status	Good	0.000	1.000		
	Fair	-0.087	0.917	0.373	0.709
	Poor	-0.400***	0.670	3.713	<0.001
Health Status					
Self-rated health	Good	0.000	1.000		
	fair	-0.239**	0.788	2.062	0.039
	poor	-0.531***	0.588	4.526	<0.001
ADL function	Good	0.000	1.000		
	fair	-0.647**	0.524	2.530	0.011
	poor	-0.658*	0.518	0.246	0.806
Physical function	Good	0.000	1.000		
	fair	-0.437***	0.646	5.944	<0.001
	poor	-0.823***	0.439	7.267	<0.001

P*<0.05；*P*<0.01；****P*<0.001

Similarly, both of the results of Cox model and Aalen model shown in Table 4 are similar except some slight differences. Although the average effects for variables the senior high+ education and the poor ADL function in Cox model are significant, results for these two covariates in Aalen model show they are nothing to do with transition 1→0 by taking into account covariate effects in time. Besides, Figure 6 and Figure 7 present the plots of the cumulative regression coefficients and the scaled Schoenfeld residuals for the senior high+ education and the poor ADL function, respectively. The cumulative regression coefficients of the senior high+ education and the poor ADL function showed that the zero line is contained within the 95% confidence bands. Also, the scaled Schoenfeld residuals show in the two plots with a near zero slope means the proportional hazard assumption is hold. These plots indicate that there is no time-varying effect for the two covariates.

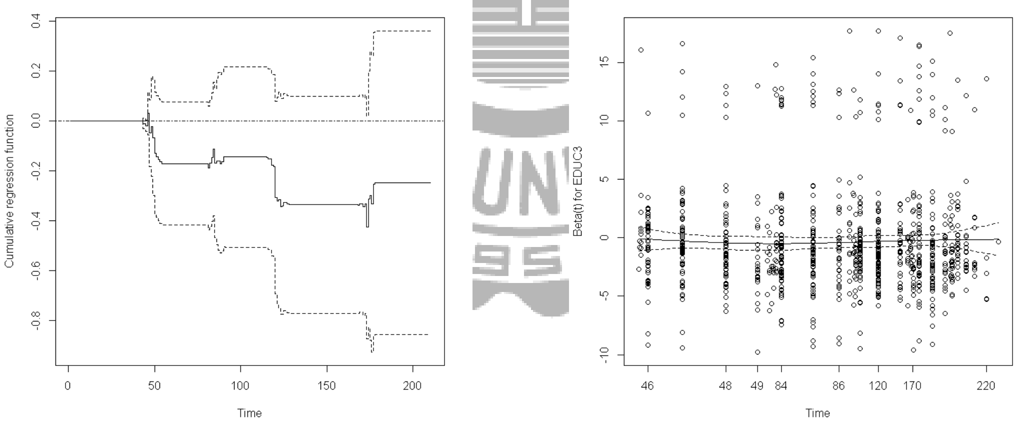


Figure 6 Plots of the cumulative regression coefficient and the scaled Schoenfeld residuals for the senior high+ education in transition 1→0.

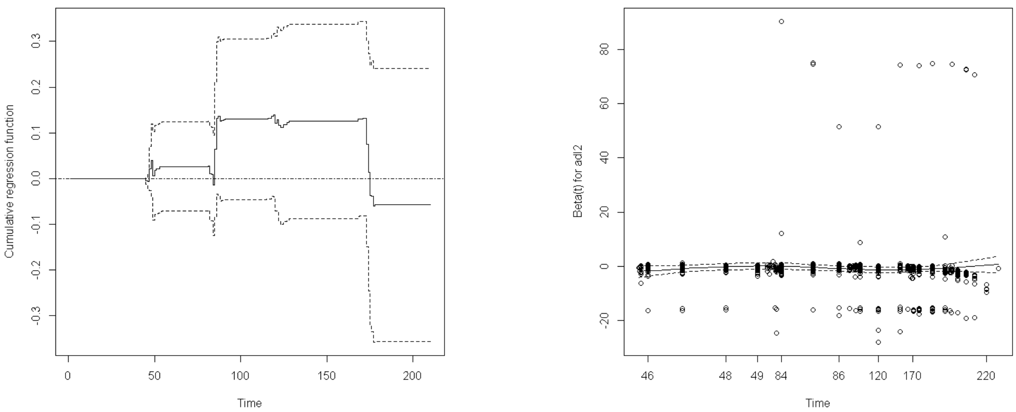


Figure 7 Plots of the cumulative regression coefficient and the scaled Schoenfeld residuals for the poor ADL function in transition 1→0.

3.2.3. Transitions 0→2 and 1→2

For the association between the depressive status and the survival status of the elderly, Table 5 and 6 are the results obtained by Cox model of transitions 0→2 (from normal to death) and 1→2 (from depression to death), respectively. From these results, there are 10 variables e.g. age, gender, level of education, ethnicity, spouse, living with children, economic status, self-rated health, ADL function and physical function, are strongly related to the survival status of the elderly for the transition 0→2. In demographics characteristics, the elderly men with older age and lower level of education have higher death rate. Also, the hazard ratio of the elderly from mainland China is 0.671 times that of Fukien Taiwanese. In particular, the aboriginal Taiwanese have a higher hazard rate than that of Fukien Taiwanese. For the home and environment conditions, people without spouse and living with children are with higher hazard rate. In particular, the widowed elderly with a poor economics condition have higher survival rate. As for health status, the hazard ratio of the elderly with poor ADL function is 1.463 times that with good ADL function. Conversely, results of transition 0→2 show the elderly with worse self-rated health and physical functions are less likely to death. This will be explained in conclusion more detailed.

Table 5 The results of Cox model and Aalen model for transition 0→2

Variables		Cox model coef	Cox model exp(coef)	Aalen model |z|	Aalen model *P*>|z|
Demographics Characteristics					
Age	60-64	0.000	1.000		
	65-69	0.580***	1.786	7.574	<0.001
	70-74	1.220***	3.386	12.372	<0.001
	75-79	1.728***	5.628	12.152	<0.001
	80~	2.123***	8.357	9.682	<0.001
Gender	Female	0.000	1.000		
	Male	0.331***	1.392	3.498	<0.001
Level of education	Illiterate	0.000	1.000		
	Elementary	-0.099	0.906	1.123	0.261
	Junior high	-0.359***	0.698	2.723	0.006
	Senior high+	-0.384***	0.681	3.302	0.001
Ethnicity	Fukien	0.000	1.000		
	Hakka	-0.041	0.960	0.518	0.604
	Mainlander	-0.399***	0.671	5.794	<0.001
	Aborigine	0.589**	1.801	2.035	0.042
Home and Environment					
Spouse	Yes	0.000	1.000		
	No	0.561***	1.752	7.192	<0.001
	Widow	-0.793***	0.453	12.377	<0.001
Living with children	No	0.000	1.000		
	Yes	0.335***	0.335	6.825	<0.001
Economic status	Good	0.000	1.000		
	Fair	0.044	1.045	0.958	0.338
	Poor	-0.255**	0.775	2.517	0.012
Health Status					
Self-rated health	Good	0.000	1.000		
	fair	-0.134*	0.875	2.844	0.004
	poor	-0.221**	0.802	3.769	<0.001
ADL function	Good	0.000	1.000		
	fair	-0.082	0.921	1.421	0.155
	poor	0.381**	1.463	1.578	0.114
Physical function	Good	0.000	1.000		
	fair	-0.258***	0.773	3.679	<0.001
	poor	-0.429***	0.651	3.737	<0.001

*$P<0.05$; **$P<0.01$; ***$P<0.001$

Table 6 The results of Cox model and Aalen model for transition 1→2

Variables		Cox model coef	Cox model exp(coef)	Aalen model |z|	Aalen model *P*>|z|
Demographics Characteristics					
Age	60-64	0.000	1.000		
	65-69	0.405***	1.500	2.923	0.003
	70-74	1.010***	2.747	6.029	<0.001
	75-79	1.354***	3.872	6.531	<0.001
	80~	1.592***	4.916	5.038	<0.001
Gender	Female	0.000	1.000		
	Male	0.441***	1.554	2.719	0.007
Level of	Illiterate	0.000	1.000		
	Elementary	-0.122	0.886	0.764	0.445
	Junior high	0.226	1.254	0.456	0.649
	Senior high+	-0.433*	0.649	1.541	0.123
Ethnicity	Fukien	0.000	1.000		
	Hakka	0.185	1.204	1.442	0.149
	Mainlander	-0.270*	0.763	2.667	0.008
	Aborigine	0.130	1.139	1.125	0.261
Home and Environment					
Spouse	Yes	0.000	1.000		
	No	0.484***	1.622	4.192	<0.001
	Widow	-0.712***	0.491	7.033	<0.001
Living with	No	0.000	1.000		
	Yes	0.184*	1.201	3.051	0.002
Economic	Good	0.000	1.000		
status	Fair	0.094	1.099	0.783	0.434
	Poor	0.216	1.242	1.545	0.122
Health Status					
Self-rated	Good	0.000	1.000		
health	fair	0.594***	1.811	2.304	0.021
	poor	0.905***	2.472	4.828	<0.001
ADL	Good	0.000	1.000		
function	fair	0.372**	1.451	2.852	0.004
	poor	0.245	1.277	2.251	0.024
Physical	Good	0.000	1.000		
function	fair	0.234*	1.263	2.006	0.045
	poor	0.227*	1.255	0.940	0.347

*P<0.05；**P<0.01；***P<0.001

Results of Cox and Aalen models in Table 5 are similar except the variable poor ADL function. Considering the time varying effects of covariates in time, the variable poor ADL function is nonsignificant in Aalen model. Its cumulative regression coefficients and the scaled Schoenfeld residuals are shown in Figure 8. The plot of the cumulative regression coefficients for the poor ADL function may have an early effect till 160 months, and no effect after then. Besides, the scaled Schoenfeld residuals plot with negative slope means that the proportional hazards assumption does not hold.

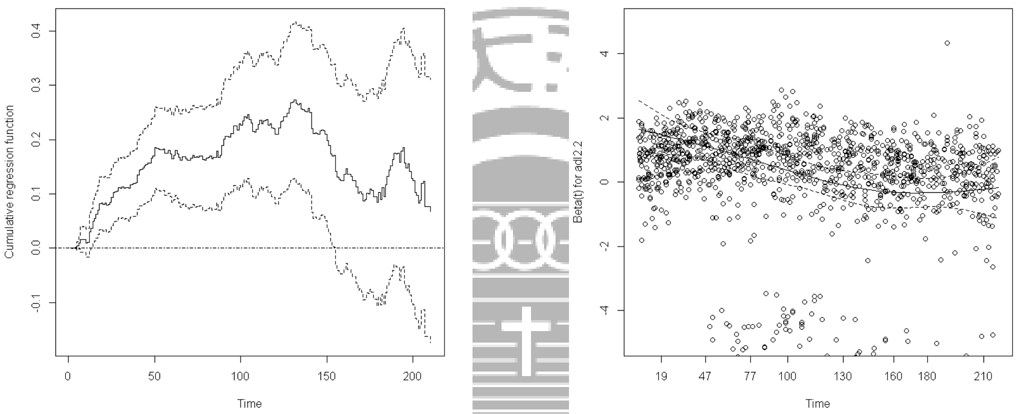


Figure 8 Plots of the cumulative regression coefficient and the scaled Schoenfeld residuals for the poor ADL function in transition 0→2.

As for the transition 1→2, there are 9 variables e.g. age, gender, level of education, ethnicity, spouse, living with children, economic status, self-rated health, ADL function and physical function, strongly related to the survival status for the elderly from depression status to death. From the results of Cox model in Table 6, similar to the situations happened in transition 0→2, the older elderly men with lower level of education have higher hazard rate than younger people with higher education, and the elderly from mainland China are with higher survival rate. Hazard ratio of Mainlander is 0.763 times that of Fukien Taiwanese. For home and environment conditions, people without spouse and living with children have higher hazard rate.

Health status, on the contrary to transition 0→2, the hazard ratios of the elderly with worse self-rated health, ADL function and physical function are higher than those who in good health status. The hazard ratio of fair self-rated health and poor self-rated health is 1.811 times and 2.472 times that of good self-rated health, respectively. Moreover, the hazard ratio of fair ADL function, fair physical function and poor physical function is 1.451 times, 1.263 times and 2.472 times that in good condition, respectively.

In Table 6, covariates related to transition 1→2 between Cox and Aalen models are almost the same except variables senior high+ education, poor ADL function and poor physical function. When the time varying effect of covariates are taken into account, poor ADL function is significant in Aalen model, but not for senior high+ education and poor physical function. In Figure 9, the cumulative regression coefficients plot of senior high+ education appeared its upper confidence band contained the zero line except the interval from 50 to 110 months. Also, the scaled Schoenfeld residuals plot of senior high+ education showed a near zero slope. Both plots indicated there is no time-varying effect for this covariate. Figure 10 showed the plot of cumulative regression coefficients for poor ADL function increase linearly in the first 60 months, and its lower band did not include the zero line for most of months. Besides, the scaled Schoenfeld residuals appeared to have a slight negative slope. Both plots showed that the time-varying effect exists in the poor ADL function. The plot of cumulative regression coefficients for the poor physical function in Figure 11 showed there is no consistent trend in any time interval, and the zero line is contained within the 95% confidence bands. This implies no time-varying effect in Aalen model. The scaled Schoenfeld residuals show a near zero slope, means proportional hazard assumption is hold in Cox model also.

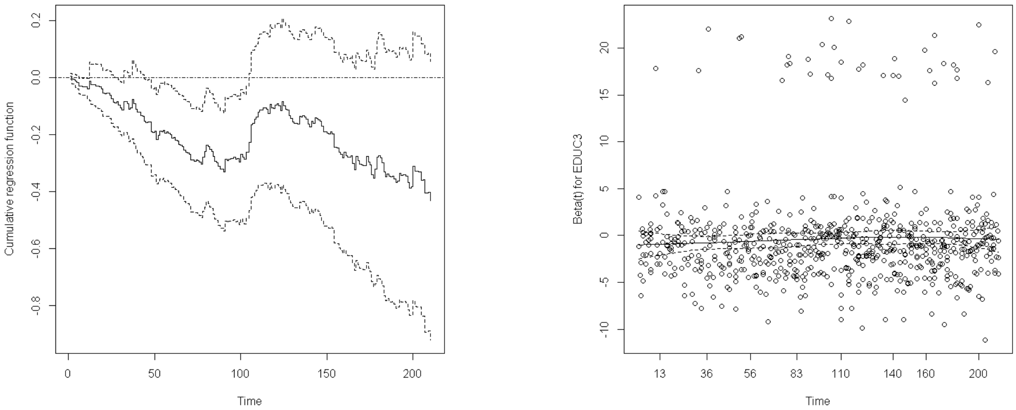


Figure 9 Plots of the cumulative regression coefficient and the scaled Schoenfeld residuals for the senior high+ education in transition 1→2.

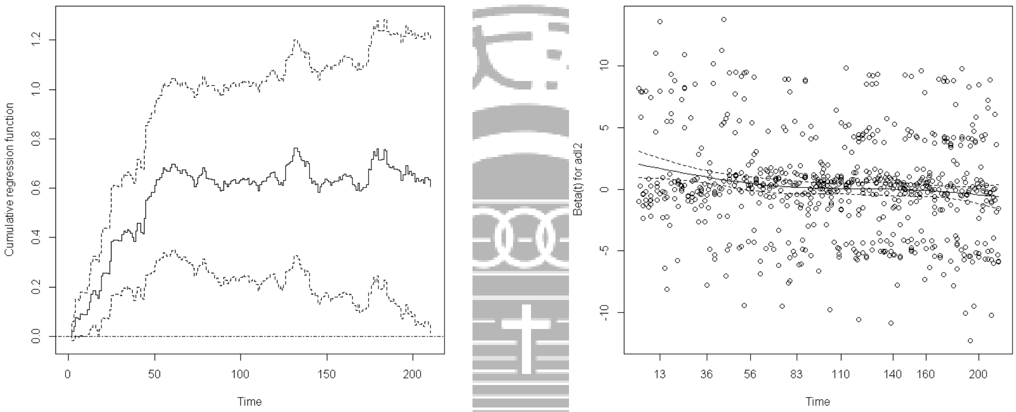


Figure 10 Plots of the cumulative regression coefficient and the scaled Schoenfeld residuals for the poor ADL function in transition 1→2.

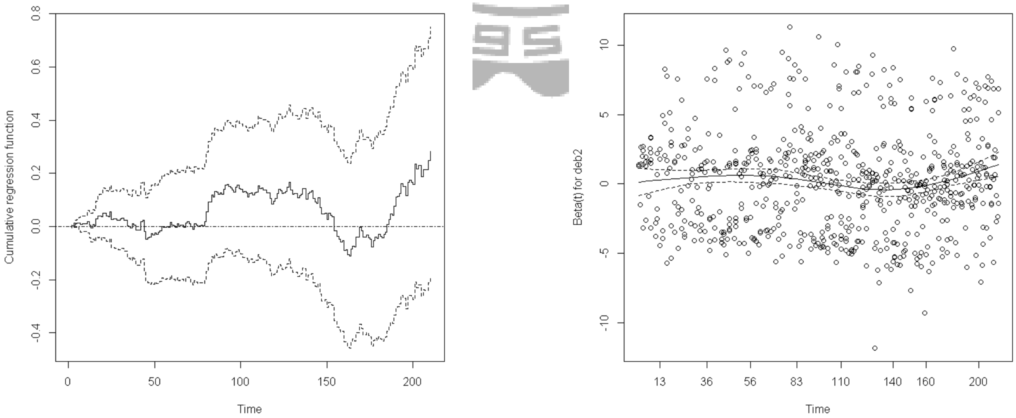


Figure 11 Plots of the cumulative regression coefficient and the scaled Schoenfeld residuals for the poor physical function in transition 1→2.

3.2.4. The transition probability

The transition probabilities from different starting states to all possible states adjusted by Cox model are summarized in Figure 12. It is not surprised that the transition probability to death from the elderly (transition 0→2) increases as time increases. The transition probability to depression (0→1) increases in the first 120 months and declines slowly after then. On the other hand, the transition probability of transition 1→2 increases as time increases. As for depression recover to normal (transition 1→0), the transition probability implies the effect of recovery increases in the first 120 months and decreases after then.

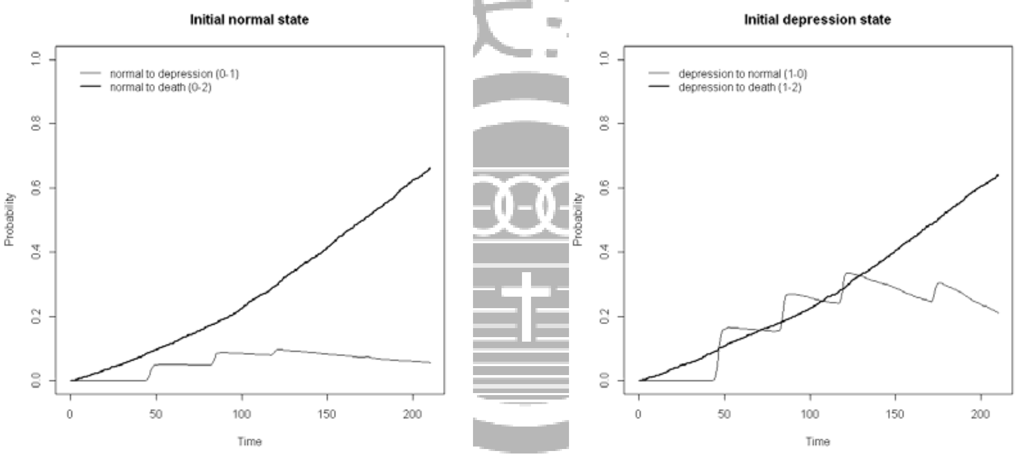


Figure 12 Estimated transition probabilities from different initial states of the multi-state Cox model.

Different from Cox model average possibly time-dependent covariate effects over the whole survey time period, Aalen model is used for picking up changes in the effects of covariates. Figure 13 and Figure 14 compare the transition probabilities of all possible paths for Cox model and Aalen model respectively. The left part in Figure 13, transition probabilities of 0→1 obtained by Aalen model are similar to that of Cox model. On the other hand, transition probabilities of 0→2 (the right side of Figure 13) have a rapid rise before 140 months and slow down slightly after then. As regard to the initial state depression in Figure 14, transition probabilities of 1→0 of Aalen model have a prompt increase during the first 90 months and decrease after then. Moreover, the transition probabilities of 1→2 increase overwhelmingly in the first 50 months and the speed rising is comparatively relaxed after then. In addition, the transition probabilities of 0→2 and 1→2 obtained by Aalen model are higher than that in Cox model. This is obvious for the elderly with initiate depression state specially.

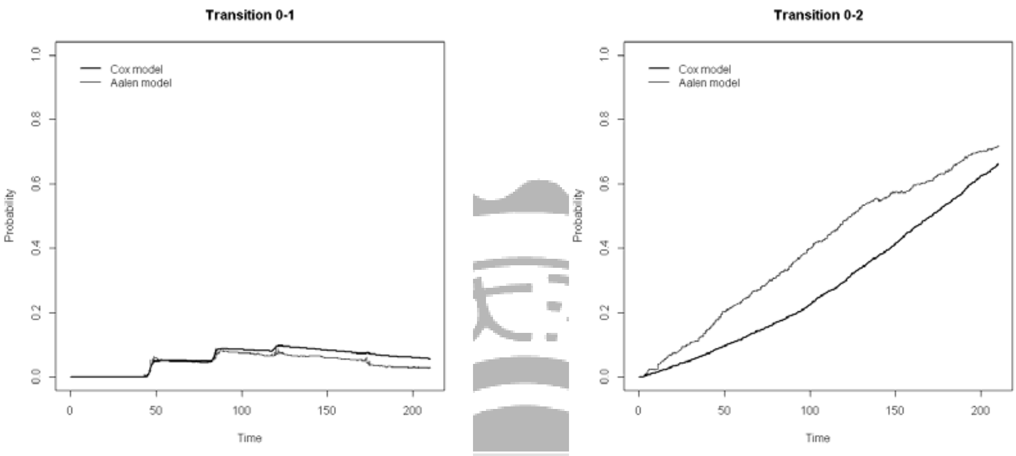


Figure 13 Estimated transition probabilities from the normal state of Cox model and Aalen model.

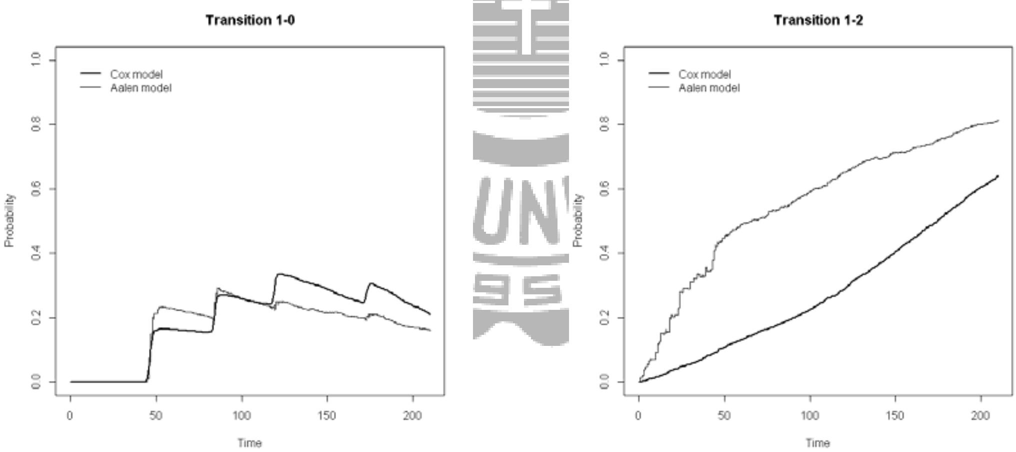


Figure 14 Estimated transition probabilities from the depression state of Cox model and Aalen model.

Estimated transition probabilities of death for Cox and Aalen models are presented in Figure 15. The average effect from Cox model shows that whether or not the subject is suffer from depression in the initial state the transition probabilities to death are almost the same. On the contrary, once time varying covariates are introduced, the transition probabilities to death between 0→2 and 1→2 obtained by Aalen model are much different with each other, both states does increase as time increases, the former keeps a constant slope increasing while the slope of latter increases up 50 months promptly, decreases with keeping constant thereafter.

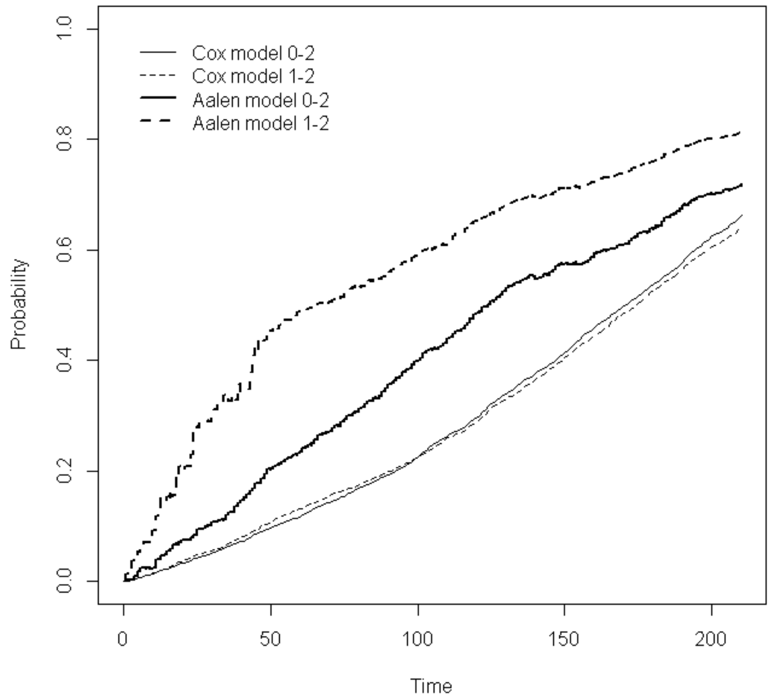


Figure 15 Estimated transition probabilities of death of Cox model and Aalen model.

Chapter 4

Conclusions

For investigating the changing status of depression of the elderly in Taiwan, this study used representative panel sample survey data during 1989 to 2007 collected in the six waves of "The Longitudinal Sample Survey of Health and Living Status of the Elderly in Taiwan" to explore the effect of various covariates on depression. Since cases of depression status are recurrent event with the characteristics of interval censored data, Cox model with interval-censored approach is applied for exploring the variables related to the changing status of depression among the elderly under the assumption that the observations within a subject are mutually independent. However, a major disadvantage of interval censored model is that it couldn't deal with the situation when two or more different types of events exist simultaneously (Kleinbaum and Klein, 2005), a more general method, Cox with multi-state model of event history analysis considered as a Markov chain is used to interpret the changing status of depression due to the multiple endpoints. Furthermore, to verify the proportional assumption in the conventional Cox model, Aalen's additive model taking into account instantaneous covariate effects in time is employed as an alternative on a supplement. Also, plots of the cumulative regression coefficients from Aalen model and the scaled Schoenfeld residuals plots are used for investigating the proportional hazard assumption. Finally, the transition probabilities for the changing status of depression obtained from Cox and Aalen models are provided. Some important findings emerged from the multi-state analysis are also obtained.

In our study, interval censored model shows age, gender, education, spouse, living with children, economic status, self-rated health, and physical function are significantly related to the depression. The elderly female in older age and lower level of education have higher hazard to depression. From some related depression studies, Chong et al. (2001) and Beekman et al. (2002) indicated that females are more likely to have depressive symptoms than males. Besides, Chen et al. (2000) pointed out that gender is one of the factors related to depression of elderly. As for home and environment conditions, the hazard of suffering from depression increases as people without a spouse and with worse economic status. In addition, the elderly with better self-rated health have better mental health. Besides, Lin et al. (2010) pointed out age, education, economic status and self-rated health are affected factors related to depression with recurrent survival model. Their results are in the similar matter to our study except variable gender.

Models with multi-state approach show that results of transition 0→1 are similar to the interval-censored Cox model for depressive status except variable physical function. For the recovered transition 1→0, education, spouse, living with children, economic status, self-rated health, ADL function and physical function are significant variables for Cox model with multi-state approach. It is not surprised that the elderly with worse economic status and health status (self-rated health, ADL and physical functions) are less likely to go back to normal than those in good conditions. The effect of widowhood on depressive symptoms (Leon et al., 1994) was observed. The widowed elderly have a relatively lower opportunity to recover from depression than those with a spouse. Some related studies indicated the association between the widowed elderly and depression (Bruce et al., 1990; Oxman et al., 1992; Turvey et al., 1999) also.

For the association between depression and death (transitions 0→2 and 1→2), all covariates considered in this study are strongly related to the survival status of the elderly no matter its initial state is depression or not. It is surprised that self-rated health, physical function, and economic status are negatively associated with transition $0 \rightarrow 2$. The hazard rate to death for the elderly with good health and economic status is higher than those with worse conditions. We may see something from Figure 16 and Figure 17. Figure 16 shows that the proportion of health status in good condition is decreasing when time is increased. Also, the averaged death rate of the health status in good condition from 1989 to 2007 is much higher than that of fair and poor condition in Figure 17. This is not only be attributed to aging in health status of the elderly is naturally weakened, but the elderly with worse health get more attention than those in good health condition from family members and medical institutions might have a better chance for their life prolonged. It possibly lead the death rate to the risk set for good health status is higher than those in worse health conditions. On the contrary, variables self-rated health and physical function are positively associated with transition $1 \rightarrow 2$. It is not surprised that the elderly with worse health conditions have higher hazard rate to death than that in good conditions. Obviously, symptoms of depression experienced in late life have serious implications for the health and functioning.

(a) (b)

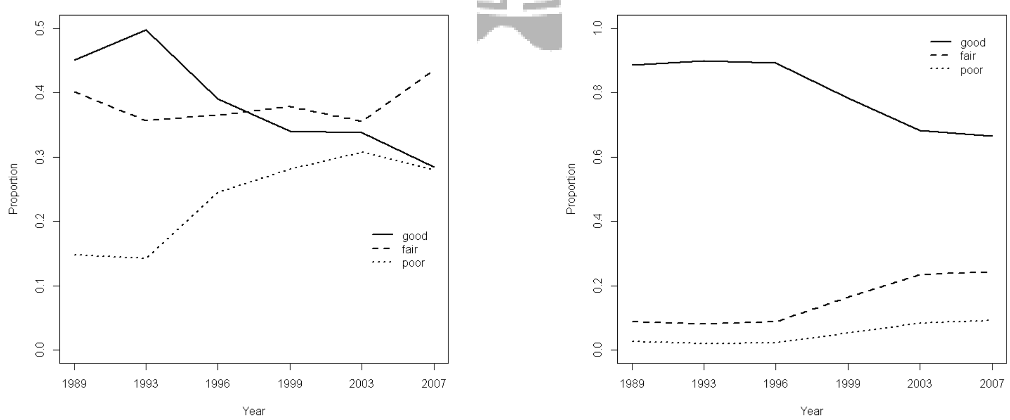


Figure 16 Changing proportions of health status of the elderly without depression in each period for (a) self-rated health, and (b) physical functions.

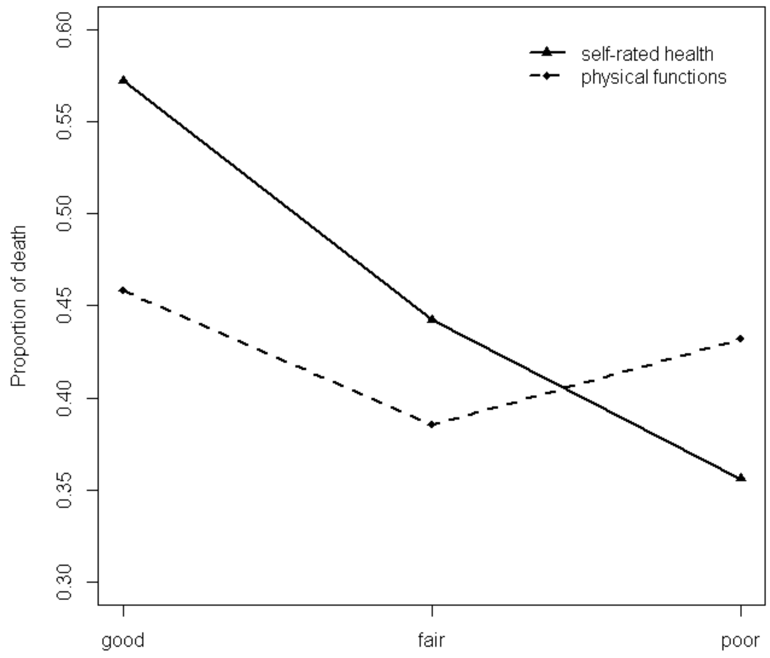


Figure 17 Proportions of death of transition 0→2 during the period from 1989 to 2007 for self-rated health, and physical functions.

Comparing with some related literatures, Prince et al. (1999) discussed the effects of age, gender, and mental status on depressive symptoms. Previous studies have shown that age, gender, level of education, and physical activities and physical health can be protective factors for depression (Cassidy et al., 2004; Geerlings et al., 2000; Penninx et al., 1999; Vink et al., 2009). Anstey et al. (2007) also evaluated demographic, medical, health behavior, functional and cognitive measures as factors for depression. Chiao et al. (2009) pointed out social position is associated with effects on depression symptoms of the elderly. Previous studies established that depressive symptoms were negatively related to life satisfaction (Chi, 1995; Mitchell et al., 1993), self-rated health (Blazer et al., 1995; McCallum et al., 1994) and social support (Cervilla and Prince, 1997; Forsell and Winblad, 1998; Okwumabua et al., 1997). Depressive symptoms were also found to be associated with impairments of daily functioning (Bruce et al., 1994; Rogers et al., 1994). In addition, Islam et al.

(2007) identified the association between risk factors (age, gender, education and ethnicity) and depression among elderly based on three types of depressive transition. In our study, results related to the changing status of depression from interval censored model and Cox model for all transitions are summarized in Table 7. It obvious that among all covariates considered in this study, education, spouse, living with children, and self-rated health are the main affecting covariates related to the changing status of depression of the elderly in Taiwan. Although these findings are in similar matter to the previous studies, the multi-state model considers the affected factors in different transition pathways simultaneously.

Table 7 Covariates related to the changing status of depression of the elderly in Taiwan

Variables	Interval censored	Transition types			
		0→1	1→0	0→2	1→2
Age	●	●		●	●
Gender	●	●		●	●
Level of education	●	●	●	●	●
Ethnicity				●	●
Spouse	●	●	●	●	●
Living with children	●	●	●	●	●
Economic status	●	●	●	●	
Self-rated health	●	●	●	●	●
ADL function			●	●	●
Physical function	●		●	●	●

In this study, multi-state models are an useful extension of classical survival analysis and they provide more insight into the changing status of depression of the elderly. Moreover, they obtain underlying information usefully. On the other hand, in order to confirm the hypothesis of constant effects of covariates in the conventional Cox model, Aalen model resolves this issue in a more natural way by taking into account covariate effects in time. Both of Cox and Aalen models have been used for some studies. For examples, Rosato et al. (2007) combined both models for evaluating cardiovascular mortality in type 2 diabetes patients. Liu and Lin (2012) also identified the risk factors for the survival status of the elderly in Taiwan by Cox and Aalen models.

Multi-state coefficients obtained by Cox model act in a multiplicative way on unknown baseline hazard, while coefficient function of Aalen model provides estimates of additive effect at each observed time. Moreover, Cox model averages possibly time-dependent covariate effects over a long time period, while Aalen model keeps account of instantaneous covariate effects on time. In this study, Cox and Aalen models with multi-state approach were used for dealing with the changing status of depression concentrated on a more general model for illness-death process. Here, results between Cox and Aalen models are almost the same for all paths of the changing status of depression except few variables. For example, the poor ADL function for transition 1→2 is significant in Aalen model, but not in Cox model. This difference might be caused by the time varying effect of covariates that are taken into account by Aalen model. In addition, to verify the assumption of proportional hazard, the cumulative regression coefficients and the scaled Schoenfeld residuals plots showed that the time-varying effect do exist in the poor ADL function and provided an interpretation of the nonproportionality.

On the other hand, the transition probabilities of all paths of the changing status of depression are remarkably different in the Cox and Aalen estimates, especially the transition probabilities of death. Although the average effect from Cox model shows the transition probabilities to death are almost the same no matter the subject is suffer from depression in the initial state, some findings indicate that the transition probabilities to death between 0→2 and 1→2 obtained by Aalen model are much different with each other. It is obvious that death rate has a greater impact on the elderly with initial depression state and this couldn’t be found by Lin and Lin (2006) and Liu and Lin (2012) when the survival analysis with healthy initial state and single endpoint was concerned. This is found in recurrent survival model and Islam et al. (2007) also. Multi-state models are interested in multiple endpoints and studying intermediate events may obtain more underlying information usefully.

In conclusion, this study uses interval censored and multi-state models for analyzing the changing status of depression of the elderly in Taiwan. The application of multi-state models to depression data provides some useful findings relating to transitions from one state to another. This study shows multi-state models with Cox and Aalen models capture the risk process for the elderly with more profiles very well. Moreover, Aalen model is shown to be better at identifying risk of death by taking into account instantaneous covariate effects in time. Finally, the transition probabilities of the changing status of depression are provided. In summary, the analysis of depression dynamics data in this study would provide very useful information for researchers, policy markers, and the public health system in dealing with mental health issues of the elderly.

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