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A Multistate Transition Model for Analyzing Diseases in Elderly Population

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Abstract: In this study, a competing risk model is proposed to analyze the transitions to diseases among elderly people employing the proportional hazards model. This study provides important findings regarding the disease pattern among the elderly people and the factors associated with such transitions. The Health and Retirement Study data are considered for the period of 1992-2000. The major diseases or complications considered in this study are stroke, lung diseases, diabetes mellitus, blood pressure and arthritis. The transitions to different diseases or complications are explained by selected covariates such as gender, race, marital status, smoking, drinking, physical exercise and BMI. The results indicate that gender, race, smoking and BMI are significantly associated with transitions to different diseases or complications. The results are displayed for transitions to each disease or complication separately for competing risk framework as well as for the combined transition to any of the selected diseases or complications. This paper reveals some important health issues related to the transitions to the selected diseases or complications among the elderly people and the factors associated with such transitions are identified.

Key words: Multistate Model · Hazards Model · Competing Risk · Transition to Diseases · Elderly Population

INTRODUCTION

The elderly people in the society suffer from increasingly complicated health problems with advance in age. There is onset of some most severe chronic diseases that make the elderly people physically handicapped. The Health and Retirement Study (HRS), first conducted in 1992 in the USA, continued to successfully re-interview in the years 1994, 1996, 1998 and 2000. These provide the longitudinal dynamics of the subjects since the beginning of the study in 1992. In other words, the dynamics in respect of the health status of each subject can be studied until death or loss-to- follow-up or end of the study. Analyzing these data, which comprise of both complete and partially censored information on health status of elderly population, poses difficulty to the researchers. The most common chronic diseases and symptoms, affecting the elderly population, such as high blood pressure, heart disease, stroke, arthritis, lung disease and diabetes can pose formidable difficulty to them. The proportional hazard model [1] can be employed for identifying the potential risk factors for the development of these diseases. However, the traditional proportional hazard models take account of the various diseases separately, considering that each disease has separate mechanism. In reality, we observe that the diseases occur under a competing risk framework [2-10].

The functional limitation is a major driver of medical costs. The functional limitation refers to difficulty in performing a task physically. Dunlop *et al*. [11] evaluated the prevalence of functional limitation among adults with arthritis showed that overall 19.7% of this cohort had functional limitation at baseline. Functional decline was most frequent among older women (15.0%) and minorities with arthritis (18% Hispanics, 18.7% African Americans). In the USA, it was found that almost 60% of persons 65 years and older were affected by arthritis. Other significant predictors included cognitive impairment, depressive symptoms, diabetes, physical limitations, no alcohol use, stroke and vision impairment. Stang *et al*. [12] showed the prevalence of self-reported arthritis among the USA household-residing adults was estimated to be 27.3%. The prevalence was higher among females than males, increased with age, was inversely related to education and was lower among Hispanics than other race-ethnic groups. Peters *et al*. [13] used cross-sectional

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analysis and revealed a positive interaction between stress and tibia lead on systolic blood pressure, after adjusting for age, BMI, family history of high blood pressure, education, smoking, alcohol consumption, physical activity and nutritional factors. Valcin *et al*. [14] indicated that prevalence of chronic bronchitis increased with increasing age and increasing BMI. It also shows that chronic bronchitis was not associated with husband's smoking at home. Family history of stroke among a first degree relative was associated with poor functional outcome was observed by Lisabeth *et al*. [15]. It was suggested that family history was related to more severe strokes. DeVon *et al*. [16] showed that women with acute coronary syndromes have more back pain, dyspnea, indigestion, nausea and vomiting and weakness than do men. Men were more likely than women to have chest pain. Ostir *et al*. [17] showed that there were no statistically significant differences between those with and without anti-hypertensive medication in relation to positive emotion score, age and years of schooling. However, individuals on anti-hypertensive medication were significantly more likely to have higher BMI and depressive symptom scores and to report being diabetic. Conversely, individuals not on anti-hypertensive medication were significantly more likely to be men, married, current-smoker and user of alcohol.

This study concentrate primarily on chronic diseases outcomes and the impact of the covariates is assessed on the chronic disease outcomes for elderly population. Chronic diseases that are included in the analysis are: hypertension, diabetes, stroke, arthritis, heart and lung disease.

The purpose of this study is to: (i) focus on respondents aged 50 years and above and also those without the chronic disease in wave 1 (1992), (ii) identify the competing risk model for six types of selected chronic diseases in the application to health status from the Health and Retirement Study, (iii) assess the proportional hazards (PH) assumption in competing risk model, (iv) conduct stratified analysis for the predictor that does not satisfy the PH assumption. The use of time dependent covariates and the theory of competing risks have been applied in the analysis of survival data involving several different failure types.

MATERIALS AND METHODS

Data and Variables: The original HRS sample consists of individuals born between 1931 and 1941, inclusive. This sample came from a screening of 69336 households that was conducted in 1992. That sample of households was generated using a multi-stage, clustered area probability frame. The second sample was generated for what began as a separate study. The response rate and at each follow-up wave, for each of the five samples, are shown as Table 1.

The HRS has collected data in five follow-up periods, 1992, 1994, 1996, 1998 and 2000. The study obtained detailed information on health status, employment of respondent, disability and types of diseases. There are five distinct samples included in the overall design. Each of these samples is restricted to those living in households in the conterminous 48 states of the USA at the time of the baseline wave of interviews for each sample. Individuals are eligible for follow-up interviews

Table 1: Response rate

	Wave 1	Wave 2	Wave 3	Wave 4	Wave 5
Total interviews	12654	11596	11200	10856	10371
Overall response rate	81.7%	89.1%	86.3%	84.4%	81.8%

Table 2: Variables of risk factors

Description and Code	Variable name
Gender of respondent Female =0, Male=1	SEX
Race of respondent 1. White (reference category) 2. Black (if Black then 1, else 0) 3. Others (if Others then 1, else 0)	RACE
Marital status Single=1, else 0	MARITAL
No. of cigarettes/ packs smoke in a day 0. 0 (reference category) 1. If 1-10, then Smoke1=1, else 0, 2. If 11-20 then Smoke2=1, else 0, 3.If >20, then Smoke3=1, else 0	SMOKE
Drink alchohol No = 0, Yes = 1	DRINK
Exercise No = 0, Yes = 1	EXERCISE
Body mass index Obesity = 1, else 0	BMI

whether or not they continue to live in a household in that geographic area. The incidence/prevalence of chronic diseases which have occurred during 1992-2000 have been considered as the dependent variables. Meanwhile the baseline risk factors that might be associated with the development of the selected chronic diseases are listed in Table 2.

The variable DIS takes a value of 0 indicating a chronic disease-free state (censoring indicator) throughout the five follow-up periods, otherwise the value 1, denoting the presence of the chronic diseases under consideration. The selected chronic diseases for the elderly population are hypertension, heart diseases, arthritis, stroke, lung diseases and diabetes. The variable YR, is the survival time, that is the age of the respondent at the time of occurrence in which there is one or more events, otherwise the age of the respondent at the time of his last observation in the study, if the disease did not occur during the period from 1992-2000.

Competing Risk for Analyzing Incidence of Chronic Diseases: The word "competing risk problem" is a study of any failure process in which there is more than one distinct cause or type of failure (eg. death from any of several causes or existence from any of the several diseases). The competing risk or failure causes from the survival data arise in medical, financial, engineering and many other contexts when death or failure of an individual or unit is classified into one of a variety of types of causes. Usually, the occurrence of first event is considered.

Statistical Model: Let $T_i = (T_{i1}, T_{i2}, \ldots, T_{ip})$ be a p-dimensional vector of failure times. Each coordinate is the time to failure from a specific cause such as, for example heart failure, diabetes etc. The subject is observable only up to the time of the first failure. The failure times for all the other causes are censored by the failure of the system at the first failure time. The observation quantities are

$T_i = \min(T_{i1}, T_{i2}, \ldots, T_{ip})$ and $\delta = (\delta_{1p}, \delta_{2p}, \ldots. \delta_{ip}) = (I(T_{i1} \leq T_i), \ldots. (T_{ip} \leq T_i))$

The indicator vector δ denotes the specific causes of the failure.

In medical applications there is more than one type of failure possible. If k specifies the type of failure then the cause-specific hazard function [2,4] is defined by

$$\lambda_k(t) = \lim_{\Delta t \to 0} P(t < T < t + \Delta t, K = k \mid T > t)/\Delta t \quad (1)$$
$$For\ k = 1, 2, \ldots m$$

The function $\lambda_k(t)$ gives the instantaneous failure rate from cause k at time t in the presence of the other types of failure. Here, cause k refers to any specific complication such as high blood pressure, arthritis, stroke, etc. The overall failure rate is

$$\lambda(t) = \sum_k \lambda_k(t) \quad (2)$$

The stratified Cox model is a modification of the Cox proportional hazard model that allows to control by stratification of a predictor that does not satisfy the PH assumption. (Kleinbaum, 1996). The proportional hazard model requires that, for any two covariate sets x_1 and x_2, the hazard function are related by

$$\lambda(t; x_1) \alpha\ \lambda(t; x_2), 0 < t < \infty$$

Although this relation is descriptive of many situations, sometimes there are important factors, the different levels of which produce hazard functions which differ markedly from proportionality.

The proportional hazards model [1] for the stratified analysis is

$$\lambda_j(t, x) = \lambda_{oj}(t) \exp\left\{\beta' x(t)\right\} \quad (3)$$

where $x(t)$ is a vector of covariate values, possibly depending on time,

β = is a vector of coefficients

$\lambda_{oj}(t)$ are unspecified arbitrary functions corresponding to different strata of patients where j indexes the strata.
The competing risk or a cause –specific hazard function model [6]

$$\lambda_{jk}(t; x) = \lambda_{ojk}(t) \exp\left\{\beta'_k x(t)\right\} \quad (4)$$

Which has been used by Holt [4] in the competing risk problem. With the usual competing risk data, a single time of failure t and cause of failure k for each subject, the functions t are estimable functions which determine the likelihood.

The combined proportional hazards model specifies that the hazard function for the failure time T associated with a $px1$ column covariates vector Z takes the form

$$\lambda(t;Z) = \lambda_o(t)e^{\beta'' Z} \quad (5)$$

where $\lambda_o(.)$ is an unspecified baseline hazard function and β is a *px1* column vector of regression parameters.

The combined proportional hazards model (5) is simple but as all the competing risk hazards are combined, the risk factors associated with each cause of failure cannot be identified properly. In other words, the results will reflect only the common factors attributing to failure for all the underlying causes and the factors associated with each cause of failure are beyond the scope of such model. However, the competing risk hazards model provides the detailed analysis pertaining to the relationship between risk factors and the occurrence of a specific complication with more direct and meaningful interpretations.

Checking the Proportional Hazards Assumption: The proportional hazards model for the combined and competing risk frameworks are shown in (5) and (4) respectively. In both the cases, we can apply the check for proportional hazards assumptions. Lin *et al*. [18] present graphical and numerical methods for model assessment based on the cumulative sums of martingale residuals and their transforms over certain coordinates (e.g. covariate values or follow-up times). Each observed residual pattern can then be compared, both graphically and numerically, with a number of realizations from the null distribution. Such comparisons enable to assess objectively whether the observed residual pattern reflects anything beyond random fluctuation. The graphical inspections of the proportional hazard assumption is by comparing the observed score processes with the simulated ones.

If Z is expressed as $I^{-1/2}(\hat{\beta})U(\hat{\beta},t)$ then this test statistic is demonstrated as asymptotically normal for

$$\underset{t}{Sup}\{I^{-1}(\hat{\beta})_{jj}\}^{1/2}\left|U(\hat{\beta},t)\right\}, \quad j = 1,\ldots,p.$$

For assessing the overall proportionality, consider the test statistic

$$\underset{t}{\sup} \| U(\hat{\beta},t) \| \; or \; \underset{t}{\sup} \sum_{\substack{j=1 \\ t}}^{p} \{I^{-1}(\hat{\beta})_{jj}\}^{1/2}\left|U(\hat{\beta},t)\right\} (6)$$

RESULTS AND DISCUSSION

The HRS data were applied for examining the risk factors of the selected diseases among the elderly people. Two models are fitted, one for the combined selected diseases and the other one for the competing risks. The results for the combined diseases are displayed in Table 3 and the competing risk estimates are shown in Table 4. The first model reveals a general pattern of potential risk factors among the elderly people and the second model reveals the risk factors for each disease. The first model may give misleading results sometimes due to difference in risk factors for cause-specific models. In other words, each complication is attributable to risk factors due to underlying mechanism of the incidence of such complication which may vary for another complication for obvious reasons. If we combine the hazards for all these complications then the risk factors identified from such model will refer to only the common or influential risk factors.

Model for Combined Diseases: The model for combined diseases is fitted to the HRS data for elderly people and the results are shown in Table 3.

Table 3: Estimates of Parameters of Proportional Hazards Model for Combined Selected Diseases among Elderly People

Variables	Parameter estimate	Standard Error	p-value	Significant Risk Factor
Gender	-0.32556	0.05543	<.0001***	/ (-)
Black	0.30472	0.08491	0.0003***	/ (+)
Others	0.15998	0.08411	0.0572*	
Single	-0.06742	0.07289	0.3550	
Smoke1	0.01942	0.09811	0.8431	
Smoke2	0.05700	0.08598	0.5074	
Smoke3	0.24257	0.10377	0.0194**	/ (+)
Drink	0.09984	0.05747	0.0823*	
Exercise	0.06635	0.10760	0.5375	
Obesity	0.37639	0.07137	<.0001***	/ (+)

*** Significant at 1% level **Significant at 5% level *Significant at 10% level

Table 4: Estimates of Parameters of Proportional Hazards Model for Competing Risks for Selected Chronic Diseases among Elderly People

Variable	HBP	Arthritis	Stroke	Lung	Diabetes	Heart
Gender						
Parameter Estimate	-0.36517	-0.65164	0.32494	-0.06103	0.2834	0.19862
(Standard Error)	-0.09956	-0.08866	-0.36139	-0.24191	-0.19444	-0.16777
p-value	0.0002***	<.0001***	0.3686	0.8008	0.145	0.2365
Black						
Parameter Estimate	0.64857	-0.02593	1.21015	-0.33677	1.01596	-0.44194
(Standard Error)	-0.13756	-0.14963	-0.40633	-0.47829	-0.24377	-0.32069
p-value	<.0001***	0.8624	0.0029***	0.4814	<.0001***	0.1682
Others						
Parameter Estimate	0.38829	-0.07754	0.2913	-0.39372	1.1669	-0.68048
(Standard Error)	-0.14648	-0.14374	-0.46699	-0.4108	-0.218	-0.31849
p-value	0.0080***	0.5896	0.5328	0.3378	<.0001***	0.0326**
Single						
Parameter Estimate	0.08843	-0.15247	-0.42885	0.19791	-0.36465	-0.07438
(Standard Error)	-0.12383	-0.11658	-0.50526	-0.29234	-0.2644	-0.22933
p-value	0.4751	0.1909	0.396	0.4984	0.1678	0.7457
Smoke1						
Parameter Estimate	-0.31522	0.16246	0.11089	0.33759	0.14518	0.15311
(Standard Error)	-0.18981	-0.14751	-0.56	-0.49881	-0.30281	-0.29163
p-value	0.0968*	0.2707	0.843	0.4985	0.6316	0.5996
Smoke2						
Parameter Estimate	-0.21842	-0.14172	0.82513	1.73882	-0.16013	0.16816
(Standard Error)	-0.16805	-0.14515	-0.39495	-0.27822	-0.31093	-0.25005
p-value	0.1937	0.3289	0.0367**	<.0001***	0.6065	0.5013
Smoke 3						
Parameter Estimate	0.01585	-0.12897	0.12417	1.96892	0.1281	0.68514
(Standard Error)	-0.2022	-0.19066	-0.74413	-0.30757	-0.37313	-0.24649
p-value	0.9375	0.4988	0.8675	<.0001***	0.7314	0.0054***
Drink						
Parameter Estimate	0.26803	0.03523	0.27593	-0.2295	-0.17216	0.1508
(Standard Error)	-0.10555	-0.08966	-0.3563	-0.24035	-0.18906	-0.17165
p-value	0.0111**	0.6944	0.4387	0.3397	0.3625	0.3797
Exercise						
Parameter Estimate	0.1943	-0.05543	-0.07215	-0.12551	0.02997	0.41125
(Standard Error)	-0.20556	-0.16749	-0.61449	-0.3797	-0.32176	-0.36765
p-value	0.3445	0.7407	0.9065	0.741	0.9258	0.2633
Obesity						
Parameter Estimate	0.41916	0.08484	-0.14734	0.38346	1.15353	0.46528
(Standard Error)	-0.12479	-0.1259	-0.48628	-0.31851	-0.19223	-0.20648
p-value	0.0008***	0.5004	0.7619	0.2286	< .0001***	0.0242**

For the interest of having an idea of major causes we consider the following diseases: heart disease, stroke, lung diseases, diabetes, arthritis and high blood pressure. The model for all diseases is fitted with a proportional hazards model without considering competing risks as shown in Table 3. This table indicates the pattern of occurrence of any disease to the elderly people. The incidence of the diseases is negatively associated male respondent i.e. the risk is lower among the male compared to the female respondent ($p<0.01$). The risk is higher for the respondent belonging to black races than that of white races ($p<0.01$). It is also observed that the respondent belonging to other races have significant higher risk than that of white races ($p<0.10$). The subjects who smoke more than 20 cigarettes per day have a higher risk to the incidence of the diseases than that of non-smokers ($p<0.05$). Drinking habit is positively associated with the incidence of diseases ($p<0.10$). Meanwhile the obesity person have higher risk to the incidence of the diseases than that of the normal persons ($p<0.01$).

Table 5: Significant Risk Factors for Competing Risks

	Diseases					
Risk Factors	HBP	Arthritis	Stroke	Lung	Diabetes	Heart
Gender	x(-)	x(-)				
Black	x(+)		x(+)		x (+)	
Others	x(+)				x(+)	x(-)
Single						
Smoke1	x(-)					
Smoke2			x(+)	x(+)		
Smoke3				x(+)		x(+)
Drink	x(+)					
Exercise						
Obesity	x(+)				x(+)	x(+)

(+): positive association; (-): negative association

Table 6: Test for Proportional Hazards Assumption for Combined Selected Disease

Variable	Max. Absolute Value	Pr > MaxAbsVal
Gender	1.2301	0.9370
Black	1.2117	0.9360
Others	1.3070	0.9260
Single	0.7523	0.9840
Smoke1	1.4659	0.9100
Smoke2	1.0290	0.9500
Smoke3	0.8537	0.9720
Drink	0.7270	0.9730
Exercise	0.5241	0.9990
Obesity	1.2060	0.9360

Model for Competing Risks: The model for competing risks for the selected diseases is fitted and the results are displayed in Table 4. The selected diseases are: heart disease,stroke, lung diseases, diabetes, arthritis and high blood pressure We have considered the covariates gender, race of respondent, marital status, smoking habit, drinking habit, exercising and body mass index.

- The results are described below.

High Blood Pressure (HBP): The statistically significant risk factors of high blood pressure are: gender, black races, other races, smoking more than 20 cigarettes per day (SMOKE 3), drinking habit and obesity. The incidence of HBP is lower among males as compared to that of females ($p<0.01$). The risk is higher for the respondent belonging to the black and other races compared to the white races ($p<0.01$). For smoking habit, those who smoke less than 10 cigarettes per day, have lower risk of this disease than that of non-smokers ($p<0.10$). Drinking habit is positively associated with the incidence of HBP ($p<0.05$). Similarly, the subjects whose BMI is in the category of obesity appear to have higher risk ($p<0.01$).

Arthritis: It is surprising that Arthritis is associated with only one out of all the selected diseases. It appears from the results that the incidence of arthritis is lower among men as compared to that of women ($p<0.01$).

Stroke: Table 4 reveals two risk factors are identified as potential risk factors, black race and smoking (SMOKE 2). The respondents belonging to black race have significantly higher risk of stroke than that of white ($p<0.01$). It is evident that those who have apparently been smoking more than 10 but less than 20 cigarettes per day, have higher risk of stroke than that of non-smokers ($p<0.05$).

Lung Diseases: Both moderate (SMOKE 2) and heavy smokers (SMOKE 3) are exposed to lung diseases. It is evident that elderly smokers, who have apparently been smoking more than 10 cigarettes per day, have higher risk of lung disease than that of non-smoker ($p<0.01$).

Diabetes: There are two significant risk factors for diabetes mellitus, race and obesity. It is observed that both the black and respondents belonging to other races have significantly higher risk of diabetes mellitus as compared to that of white elderly population ($p<0.01$). The incidence of diabetes is substantially higher among obese persons as compared to that of normal persons ($p<0.01$).

Heart: The heart disease among the elderly people is found to be associated with other races, heavy smoking (SMOK 3) and obesity. The respondent belonging to other races is negatively associated with the incidence of heart disease i.e. lower risk of suffering from heart disease than that of white races ($P<0.05$). The heavy smokers appear to have higher risk than those of non-smokers. On the other hand, obesity appears to have positive association with the incidence of heart disease.

- The results are summarized in Table 5.

As there is no violation of proportionality assumption due to any of the selected variables, we have not conducted the stratified analysis.

Applications: The models for competing risks were applied to the combined selected chronic diseases and also for the selected chronic diseases separately. Checking the PH assumptions are done by using both the graphical approach and also the method described above.

Combined Diseases: By referring to Table 6, it was found that the test is not significant (p>0.05). This indicates that the PH assumption is satisfied for all the variables. The results are summarized in Table 6.

Selected Disease: The results obtained from the test for checking the proportionality assumption indicate that there is evidence of no violation of proportionality (p>0.05) for all selected chronic diseases. This shows that the PH assumption is satisfied for every disease separately. The results are not displayed here.

CONCLUSION

In this study, an attempt is made to identify the competing risk behavior of the incidence of the diseases. A comparison of the estimates indicate that both the models for combined chronic diseases as well as the chronic diseases separately reveal some important findings concerning the incidence of chronic diseases among the elderly people. Checking of the proportional hazard assumption in competing risk model is conducted and the findings confirm that the assumptions are satisfied for both the combined and the chronic diseases separately. Since the proportional hazards assumption is satisfied, stratification is not employed.

As expected, it was observed that the risk factors of high blood pressure are gender, black races, other races, smoking more than 20 cigarettes per day (SMOKE 3), drinking habit and obesity. The prevalence of arthritis appears to be higher among the females, compared to the males, in this study. Stang *et al*. [12] also reported that gender is associated with the prevalence of arthritis indicating higher prevalence in females than males. These studies identified two potential risk factors for stroke, namely, black race and smoking (SMOKE 2). The black race have significantly higher risk of stroke than that of white and those who smoke more than 10 but less than 20 cigarettes per day have higher risk of stroke than that of non-smokers. Lisbeth [17] observed that family history of stroke may lead to more severe strokes. This study reveals that both moderate and heavy smoking may increase the prevalence of lung diseases. Valcin *et al*. [14] reported that the chronic bronchitis may increase with age and BMI but not associated with the smoking of husband's smoking at home. Ostir *et al*. [17] revealed that individuals with anti-hypertensive medication had significantly higher BMI.

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