# Application of Multi-State Markov Models to Alzheimer's Disease Data

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***Abstract:*** **Objective:** To explore the impact of the probability of metastasis between stages, mean residence time and APOE4 allele count on disease progression during the progression of Alzheimer's disease. **Methods:** 3191 patients initially diagnosed with Alzheimer's disease in the Uniform Data Set UDS maintained by the National Alzheimer's Collaborative Center (NACC) were selected, and a multi-state Markov model with death as the outcome was developed based on the MMSE standard cut-off point delineation criteria with three stages of Alzheimer's disease: mild, moderate and severe. **Results:** The metastatic intensity and probability of metastatic death gradually increased as the disease progressed through mild, moderate and severe stages; the mean length of stay in mild, moderate and severe Alzheimer's disease patients was 2.905, 1.875 and 1.819 years, respectively; with one APOE4 allele [HR 1.176, 95% CI (1.031,1.340)] and [HR 1.426, 95%CI(1.202,1.693)] were risk factors for mild to moderate transfer. **Conclusions:** Alzheimer's disease has a long course with multi-stage progression, risk factors affecting disease progression are more complex, the APOE4 allele is a risk factor for Alzheimer's disease, and having 2 APOE4 alleles is a greater risk than 1 APOE4 allele.

***Keywords:*** Multi-State Markov Model; Alzheimer's Disease; APOE4 Allele; Disease Progression; Probability of Metastasis

## Introduction

In recent years, as the average life expectancy increases, the world's population structure is shifting and the number of elderly people is gradually increasing, diseases of the elderly have become a serious public health problem worldwide. The number of people living with the disease is expected to reach over 100 million between 2040 and 2050[1], placing a heavy burden on healthcare and families. The risk of Alzheimer's disease is 60-80% dependent on genetic factors, with the APOE allele being the most strongly associated with the disease[2]. Among the APOE alleles, the APOE4 allele is the strongest genetic risk factor for sporadic Alzheimer's disease and is an important biomarker of Alzheimer's disease susceptibility[3]. Neuropsychological assessment is an important tool for early detection, monitoring disease progression and assessing the effectiveness of treatment. Clinically, Alzheimer's disease can be staged into "mild", "moderate" and "severe" according to the thresholds of neuropsychological scales such as the Brief Mental State Examination Scale (MMSE)[4] and the Clinical Dementia Rating Summation Scale (CDR-SB) [5]. Alzheimer's disease has an insidious and irreversible onset, with a complex multi-stage progression, and it is important to understand the impact of important risk factors on the various stages of Alzheimer's disease. Multi-state Markov models have many advantages in analysing longitudinal data of complex diseases with multi-stage progression [6,7]. First, multi-state Markov models allow for the simultaneous analysis of multiple outcome states in a single system. Secondly, the model is applicable to process data with arbitrary observation times and censored states. Third, multi-state Markov models can be used to determine the transfer probability between states, the transfer strength and the effect of each covariate on the two-state transfer rate. Fourth, multi-state Markov models can estimate the dwell times of different disease states. In recent years, multi-state Markov models have been widely used in medical research

to analyse the progression of various chronic diseases [8-12], such as hypertension, cervical disease, viruses and cells, breast cancer and childhood lupus nephritis. Therefore, in this study, a multi-state Markov model will be developed to assess the progression of different disease stages of Alzheimer's disease based on the standard cut-off point delineation of MMSE [13], and to investigate the effect of different APOE4 allele counts on disease progression in different stages of Alzheimer's disease.

# 1. Data and Methods

## 1.1 General information

The data for this study were obtained using the Uniform Data Set (UDS) maintained by the National Alzheimer's Coordinating Center (NACC) in the USA. The study cohort began in 2005 with a follow-up interval of approximately one year. The dataset contains information on demographics, neuropsychological measures, lifestyle, co-morbidities, medication use, and clinical diagnoses. A total of 3191 patients with an initial diagnosis of suspected Alzheimer's disease at baseline, with complete baseline data and two or more follow-ups, were included in this study from 2005-2013.

## 1.2 Methods

The number of APOE4 alleles was divided into two groups, i.e. one APOE4 allele and two APOE4 alleles. Patients with Alzheimer's disease were classified into mild, moderate and severe tertiary stages according to the MMSE score, i.e. 20≦MMSE≦30 as mild, 10≦MMSE≦19 as moderate and 0≦MMSE≦9 as severe [13]. With patient death as the outcome absorption state, a multi-state Markov model with 4 states was established, with state 1, state 2, state 3 and state 4 representing mild, moderate, severe and death of the disease respectively. As shown in Figure 1.

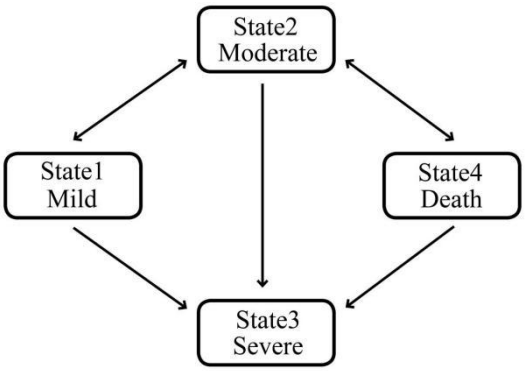


Figure 1. Structure of Alzheimer's disease staging transfer in a 4-state Markov model

## 1.3 Statistical analysis

R4.1.3 software was used to describe the data statistically, with measures expressed as mean ± standard deviation and counts expressed as frequency (composition ratio). Multi-state Markov models were performed in the MSM package in R software version 4.1.3.

# 2. Results

## 2.1 Basic information

Of the 3191 patients, 1520 (47.6%) were male and 1671 (52.4%) were female with a mean age of 74.87 ± 9.334 years, 1455 (45.6%) had one APOE4 allele and 420 (13.2%) had two APOE4 alleles.

In total, patients had 1143 metastases from mild to moderate and 431 from moderate to severe, with 201, 348 and 255 patients dying in mild, moderate and severe respectively. As shown in Table 1.

Table 1 Frequency of metastasis in Alzheimer's disease patients

| | Mild | Moderate | Severe | Death |
|---|---|---|---|---|
| Mild | 3646 | 1143 | 59 | 201 |
| Moderate | 214 | 1330 | 431 | 348 |
| Severe | 0 | 14 | 339 | 255 |

## 2.2 Transition intensity matrix

The model-estimated transition intensity matrix for patients with Alzheimer's disease by subperiod is shown in Table 2. Mild to moderate transfer is more likely than transfer to death (0.323>0.022), moderate to severe transfer is 1.858 (0.262/0.141) and 2.015 (0.262/0.130) times more likely than moderate reversion to mild and progression to death, and patients in severe highest likelihood of death (0.515). As shown in Table 2.

Table 2 Multi-state Markov model transition strength matrix (95% CI)

| | Mild | Moderate | Severe | Death |
|---|---|---|---|---|
| Mild | -0.344(-0.364,-0.326) | 0.323 (0.304, 0.342) | - | 0.022(0.016,0.030) |
| Moderate | 0.141 ( 0.123, 0.162) | -0.533(-0.568,-0.501) | 0.262(0.238,0.288) | 0.130(0.109,0.155) |
| Severe | - | 0.035 ( 0.021, 0.059) | -0.550(-0.621,-0.487) | 0.515(0.454,0.583) |

## 2.3 Probability of metastasis and mean length of stay

The probability of death increased progressively with disease severity over 8 years, with the probability of death at severe being 0.970, and the probability of patients metastasising to moderate at mild being the highest (0.138) among those with adjacent stages of disease progression. As shown in Table 3. The mean length of stay for patients was 2.905 [95% CI (2.751,3.067)] years for mild, 1.875 [95% CI (1.760,1.998)] years for moderate and 1.819 [95% CI (1.610,2.022)] years for severe.

Table 3 Estimated transfer probabilities from multi-state Markov models

| | Mild | Moderate | Severe | Death |
|---|---|---|---|---|
| Mild | 0.140 | 0.138 | 0.087 | 0.636 |
| Moderate | 0.060 | 0.068 | 0.057 | 0.815 |
| Severe | 0.005 | 0.008 | 0.018 | 0.970 |
| Death | 0.000 | 0.000 | 0.000 | 1.000 |

## 2.4 Effect of different APOE4 allele numbers on disease metastasis

Model fitting results showed that having 1 APOE4 allele [HR 1.176, 95% CI (1.031,1.340)] and 2 APOE4 alleles [HR 1.426, 95% CI (1.202,1.693)] were both risk factors for transfer from mild to moderate in patients with Alzheimer's disease, with the risk of having 2 APOE4 alleles was higher, being 1.213 (1.426/1.176) times higher than 1 APOE4 allele. As shown in Table 4.

Table 4 Effect of different APOE4 allele counts on disease metastasis

| Variable | Multivariable model [Hazard ratio (95% CI)] |
|---|---|
| One APOE4 allele | Multivariable model |

| | |
|---|---|
| Mild→Moderate | 1.176* (1.031,1.340) |
| Mild→Death | 0.649 (0.339,1.240) |
| Moderate→Mild | 0.783 (0.586,1.046) |
| Moderate→Severe | 0.929 (0.753,1.145) |
| Moderate→Death | 0.936 (0.646,1.356) |
| Severe→Moderate | 1.250 (0.407,3.844) |
| Severe→Death | 0.945 (0.720,1.241) |
| One APOE4 alleles | |
| Mild→Moderate | 1.426* (1.202,1.693) |
| Mild→Death | 0.046 (0.000,8.431) |
| Moderate→Mild | 0.628 (0.392,1.007) |
| Moderate→Severe | 1.158 (0.876,1.531) |
| Moderate→Death | 0.759 (0.424,1.357) |
| Severe→Moderate | 0.554 (0.064,4.775) |
| Severe→Death | 1.054(0.717,1.548) |

# Conclusion

In many longitudinal studies of clinical disease, the data are characterised by multi-state or multi-stage progression, with chronic disease being more distinctive and the data complex. Different disease types can be staged according to the diagnostic and stage classification criteria of the respective specialties. The multi-state Markov model is suitable for longitudinal data on complex disease stages. The model can estimate the probability of transition between states, calculate the effect of disease covariates on the probability of state shift, estimate the duration of disease stay in each disease stage and predict disease prognosis. The APOE4 allele is an important risk factor for the progression of Alzheimer's disease from mild to moderate, and the higher the number of APOE4 alleles, the greater the risk and the greater the clinical concern for having multiple APOE4 alleles. Patients with multiple APOE4 alleles need to be of high clinical concern. The multi-state Markov model has good application in the study of clinical disease staging, which can understand the dwell time and transition pattern of different disease stages, and dynamically estimate the disease progression, which is important for clinical decision making and guidance of therapeutic interventions, and has a clear use value in dynamically assessing disease stage progression.

# References

[1] Cummings J, Lee G, Zhong K, et al. Alzheimer's disease drug development pipeline: 2021[J]. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 2021, 7(1): e12179.

[2] Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease[J]. The Lancet, 2021, 397(10284): 1577–1590.

[3] Zhao J, Fu Y, Yamazaki Y, et al. APOE4 exacerbates synapse loss and neurodegeneration in Alzheimer’s disease patient iPSC-derived cerebral organoids[J]. Nature communications, 2020, 11(1): 1-14.

[4] Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician[J]. Journal of psychiatric research, 1975, 12(3): 189-198.

[5] Hughes CP, Berg L, Danziger W, et al. A new clinical scale for the staging of dementia[J]. The British journal of psychiatry, 1982, 140(6): 566-572.

[6] Jackson C. Multi-state modeling with R：the msm package (version 1.0). 2011.

[7] Andersen, PK, Wandall, E.N.S. & Pohar Perme, M. Inference for transition probabilities in non-Markov multi-state

models. Lifetime Data Analysis (2022) 28:585–604.

[8] Zheng X, Xiong J, Zhang Y, et al. Multistate Markov model application for blood pressure transition among the Chinese elderly population: a quantitative longitudinal study[J]. BMJ open, 2022, 12(7): e059805.

[9] Taguchi A, Hara K, Tomio J, et al. Multistate markov model to predict the prognosis of high-risk human papillomavirus-related cervical lesions[J]. Cancers, 2020, 12(2): 270.

[10] Dessie ZG, Zewotir T, Mwambi H, et al. Modelling of viral load dynamics and CD4 cell count progression in an antiretroviral naive cohort: using a joint linear mixed and multistate Markov model[J]. BMC infectious diseases, 2020, 20(1): 1-14.

[11] Farahani MV, Dizaji PA, Rashidi H, et al. Application of Multi-State Model in Analyzing of Breast Cancer Data[J]. Journal of Research in Health Sciences, 2019, 19(4): e00465.

[12] Smith EMD, Eleuteri A, Goilav B, et al. A Markov Multi-State model of lupus nephritis urine biomarker panel dynamics in children: Predicting changes in disease activity[J]. Clinical Immunology, 2019, 198: 71-78.

[13] Wattmo C, Wallin AK, Minthon L. Progression of mild Alzheimer's disease: knowledge and prediction models required for future treatment strategies[J]. Alzheimer's research & therapy, 2013, 5(5): 1-15.