MODELING SURVIVAL IN ALZHEIMER’S DISEASE: AN ALTERNATIVE TO PROPORTIONAL HAZARDS

Elizabeth Johnson¹
Ron Brookmeyer¹
Kathryn Ziegler-Graham²

¹ Johns Hopkins Bloomberg School of Public Health, Baltimore MD
² St Olaf College, Northfield MN;
Background

• Alzheimer’s disease is a critical global public health problem.

• Projections have suggested that the prevalence of Alzheimer’s disease will quadruple in the next 50 years. (Brookmeyer, Johnson, Ziegler-Graham, Arrighi, 2007).

• Projections depend on models that rely on two critical input factors:
  – the incidence of disease
  – mortality from the disease

• The focus of this work is on models that describe the impact of Alzheimer’s disease on mortality.
Background

• Lethality of disease is typically measured by the mortality rate ratio
  – Mortality rate among cases divided by mortality rate among general population of the same age and gender

• Proportional hazards model is the natural model for the mortality rate ratio

• Studies suggest that mortality rate ratios for Alzheimer’s patients are
  – less than 1.5
  – over 10 times

(Guehne, Riedel-Heller, Angermeyer, 2005).

• Evidence that mortality rate ratios decrease with age and may vary by gender
Goal

• Find a measure to describe lethality of Alzheimer’s disease that
  – Is simple and parsimonious
  – Describes the complex nature of the mortality rate ratios reported in the literature
Our Model

- Multi-state discrete time Markov model
- \( t \) indexes the age of the person
- \( g \) indexes the gender of the subject
Our Model

• Mortality Rates by Stage of disease
  
  – Healthy Stage:
    • Background mortality rates, $d_{0,t,g}$
    • Age-gender specific U.S. vital statistics
      (Human Mortality Database, 2005)
  
  – Early Stage:
    • Patients require modest assistance
    • No inflation in mortality rates, $d_{1,t,g} = d_{0,t,g}$
  
  – Late Stage:
    • Patients require intensive care equivalent to services provided by a nursing home
    • Mortality rates are increased by an additive constant,
      $d_{2,t,g} = d_{0,t,g} + k_2$
Our Model

• Transition probabilities
  – Incidence rates \( r_t \) are the conditional probabilities of being diagnosed with early stage disease at age \( t \)
  – Progression rate \( \gamma \) is the conditional probability of transitioning from early to late stage disease at any age
    • The mean duration of early stage disease is approximately \( \gamma^{-1} \)
    • The Consortium to Establish a Registry for Alzheimer’s disease suggested that 6 years is the mean time from mild to severe disease using the Clinical Dementia Rating scale, \( \gamma^{-1} = 6 \) (Neumann, Araki, and Arcelus, 2002)
    • Therefore, \( \gamma = 1/6 = 0.167 \)
Survival Function

- Survival function is the probability of being at risk of death at age $t$ (includes the possibility that death occurs at age $t$) for an Alzheimer’s case diagnosed at age $a$ with gender $g$
- Sum of the probability of being at risk of death at age $t$ in early stage or late stage disease

\[
S(t; a, g) = p_{1,t,a,g} + p_{2,t,a,g}
\]

\[
p_{1,t,a,g} = \left(\prod_{k=a}^{t-1} (1 - \gamma)(1 - d_{1,k,g})\right)(1 - \gamma)
\]

\[
p_{2,t,a,g} = \sum_{l=a}^{t} \left\{ \left[\prod_{k=a}^{l-1} (1 - \gamma)(1 - d_{1,k,g})\right] [\gamma] \left[\prod_{k=l}^{t-1} (1 - d_{2,k,g})\right] \right\}
\]
Median Survival

- The figure below displays how the predicted median survival varies as a function of the additive lethality parameter $k_2$ and the mean duration of early stage disease $\gamma^{-1}$.
Application

- We applied the model to a study of survival of Alzheimer’s cases enrolled in the Baltimore Longitudinal Study of Aging (BLSA) (Brookmeyer, Corrada, Curriero, Kawas, 2002)
- 108 incident cases of Alzheimer’s disease
- 71 deaths
- Data was the
  - age of disease onset (a)
  - age at last follow-up (t)
  - censoring indicator ($\delta = 1$ if death occurred, $\delta = 0$ if censored)
- Stage of disease data was not available.
- Likelihood function

$$L = \prod_{i=1}^{n} \left[ S(t; a, g) \right]^{1-\delta_i} \left[ p_{1,t,a,g} d_{1,t,g} + p_{2,t,a,g} d_{2,t,g} \right]^{\delta_i}$$
Application

• The maximum likelihood estimate was $= 0.078$.

• We inverted a likelihood ratio test to obtain a 95% confidence interval for $k_2$ of $(0.016, 0.162)$.

• The interpretation is that Alzheimer’s disease acts to increase background death rates by about 8% per year once patients progress to late stage disease.

• We also performed likelihood ratio tests to determine if $k_2$ varied either by gender (male versus female) or by age of disease onset (<75 versus $\geq$75).

• We found no significant differences either by age ($p=0.15$) or by gender ($p=.79$).
Application

We compared the predicted median survival times from our model to those obtained

• by a very flexible parametric model with up to 5 parameters
  – this model was in close agreement to non-parametric model predictions of survival
  – Brookmeyer, Corrada, Curriero, Kawas, 2002

• by a simple multiplicative model
  – assumed one stage of disease
  – equivalent to a proportional hazards model
  – MLE for the mortality rate ratio was 2.05
  – the data supported that the mortality rate ratio varied by age of disease onset and gender ($p < 0.001$, 11.0 and 1.5 for females and 8.2 and 2.5 for males with age of onset < 75 or $\geq 75$, respectively).
## Application

<table>
<thead>
<tr>
<th>Age of Onset</th>
<th>Semi-parametric(^1)</th>
<th>Two stage additive model(^2)</th>
<th>One stage multiplicative model(^3)</th>
<th>Semi-parametric</th>
<th>Two stage additive model</th>
<th>One stage multiplicative model</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>9.3</td>
<td>11.5</td>
<td>14.8</td>
<td>10.6</td>
<td>12.5</td>
<td>18.9</td>
</tr>
<tr>
<td>65</td>
<td>7.8</td>
<td>10.3</td>
<td>11.2</td>
<td>8.9</td>
<td>11.6</td>
<td>14.9</td>
</tr>
<tr>
<td>70</td>
<td>6.5</td>
<td>9.0</td>
<td>8.4</td>
<td>7.5</td>
<td>10.4</td>
<td>11.4</td>
</tr>
<tr>
<td>75</td>
<td>5.5</td>
<td>7.5</td>
<td>6.1</td>
<td>6.3</td>
<td>9.0</td>
<td>8.4</td>
</tr>
<tr>
<td>80</td>
<td>4.6</td>
<td>6.1</td>
<td>4.4</td>
<td>5.2</td>
<td>7.4</td>
<td>6.0</td>
</tr>
<tr>
<td>85</td>
<td>3.8</td>
<td>4.7</td>
<td>3.1</td>
<td>4.4</td>
<td>5.8</td>
<td>4.1</td>
</tr>
<tr>
<td>90</td>
<td>3.2</td>
<td>3.6</td>
<td>2.3</td>
<td>3.7</td>
<td>4.3</td>
<td>2.8</td>
</tr>
<tr>
<td>95</td>
<td>2.7</td>
<td>2.7</td>
<td>1.8</td>
<td>3.1</td>
<td>3.1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

\(^1\) Based on 5 parameter Weibull regression model to Alzheimer’s disease cases that included linear and quadratic terms for age of onset, gender, intercept and shape parameter  
\(^2\) Based on two stage additive model for Alzheimer’s disease mortality. Parameter \(k2\) was estimated as .078.  
\(^3\) Based on one stage multiplicative model that assumes Alzheimer’s disease acts to multiply background mortality rates by a constant estimated to be 2.05
Application

• We investigated a key assumption of our model that Alzheimer’s disease only increases background mortality once a person progress to late stage disease.

\[ d_{1,t,g} = d_{0,t,g} + k_1 \]
\[ d_{2,t,g} = d_{0,t,g} + k_2 \]

• We fit this model to the data with the constraint that \( 0 \leq k_1 < k_2 \) and tested \( k_1 = 0 \) (Self and Liang, 1987).

• Our estimates were \( k_1 = 0.0 \) and \( k_2 = 0.078 \) and we failed to reject \( k_1 = 0 \) \( (p=0.50) \).

• Thus, the simplifying assumption that excess mortality from Alzheimer’s disease occurs when person progress to late stage disease appears supported by the data.
Mortality Rate Ratio Function

- The mortality rate for a person with Alzheimer’s disease at age $t$ with gender $g$ is called $d_{t,g}$.
- We define the mortality rate ratio at age $t$, called $m(t)$, as the ratio of the death rates at age $t$ among persons with Alzheimer’s disease to that versus persons without disease.

\[
m(t) = \frac{d_{t,g}}{d_{0,t,g}}
\]

- The mortality rate $d_{t,g}$ is a weighted average of the death rate for early and late stage disease.

\[
d_{t,g} = \left(\frac{p_{1,t,g}}{p_{1,t,g} + p_{2,t,g}}\right) d_{1,t,g} + \left(\frac{p_{2,t,g}}{p_{1,t,g} + p_{2,t,g}}\right) d_{2,t,g}
\]

where $p_{1,t,g}$ and $p_{2,t,g}$ are the probabilities that an individual with gender $g$ who was born $t$ years ago is alive at age $t$ with early and late stage disease, respectively.
Mortality Rate Ratio Function

- $p_{1,t,g}$ and $p_{2,t,g}$ are marginalized (or averaged) over the age of onset $a$

\[
p_{1,t,g} = \sum_{a=1}^{t} \left[ \prod_{1 \leq j \leq a-1} (1 - r_j)(1 - d_{0,j,g}) \right] \left[ r_a \left[ \prod_{k \geq a} (1 - \gamma)(1 - d_{1,k,g}) \right] \right]
\]

\[
p_{2,t,g} = \sum_{a=1}^{t} \sum_{l=a}^{t} \left[ \prod_{1 \leq j \leq a-1} (1 - r_j)(1 - d_{0,j,g}) \right] \left[ r_a \left[ \prod_{k=a}^{l} (1 - \gamma)(1 - d_{1,k,g}) \right] \gamma \left[ \prod_{k=l}^{t} (1 - d_{2,k,g}) \right] \right]
\]

NOTE: We used the following for the incidence rates, $r_t$
- Obtained via meta-analysis
- Incidence rate (% per year) $= 0.132 e^{0.121(t-60)}$
- Implies that incidence grows exponentially with a doubling time of about 5.7 years.
Mortality Rate Ratio Function

The figure below is a graph of $m(t)$ for males and females observed in calendar year 2005 with the disease progression rate $\gamma = 0.167$ and $k_2 = 0.078$. 
Mortality Rate Ratio Function

The figure below shows the sensitivity of $m(t)$ to different assumptions about the mean duration of early stage disease ($\gamma^{-1}$). The figure shows the mortality rate ratio curves for various values of $\gamma^{-1}$ with $k_2=0.078$ in calendar year 2005.
Conclusions

• Our model suggests that Alzheimer’s disease acts to increase background mortality rates by about 8% per year once a patient progresses to the late stage of disease from our model that assumes no increased risk of mortality during early stage disease.

• These conclusions were the same regardless of the age of onset or the gender of the case.

• Our model had only one parameter ($k_2$), yet we were able to obtain predicted median survival times that were in excellent agreement with semi and nonparametric analyses.
Conclusions

• Our model also predicts that mortality rate ratios decline with age, as has been empirically reported.

• That decline may suggest the naïve and incorrect interpretation that the lethality of Alzheimer’s disease decreases with age, and perhaps that Alzheimer’s disease is more aggressive in younger victims than older victims.

• In fact, our model makes clear that the lethality of Alzheimer’s disease does not diminish with age. Regardless, of age, late stage Alzheimer’s disease adds about 8% to annual death rates.

• Why then does the mortality rate ratio decline with age?
  – The explanation lies in the fact that as persons age they are at increasing risk from many competing causes of death including cancer and cardiovascular disease.
  – Alzheimer’s disease represents an increasingly smaller fraction of the all-cause mortality rate