Analyzing Supportive Care in ALS: An Intro to Causal Inference Methods

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Objective: Estimate effects of feeding tube placement and non-invasive ventilation (NIV) on survival in ALS patients.

- **Background**
  - ALS
  - Confounding by indication
  - Counterfactual outcomes

- **Causal Inference Methods and Example Analyses**
  - Marginal Structural Models
  - Structural Nested Models

- **Discussion**
Background: Amyotrophic Lateral Sclerosis

- **Incidence**
  - 1.89 per 100,000 per year

- **Prognosis**
  - Usually results in death by respiratory failure within 2-5 years

- **Available Treatment**
  - Riluzole
  - Supportive care (Feeding tube, NIV)

Do supportive care measures improve survival?
Those who receive treatment and those who don’t differ by another predictor of outcome.
Background: Confounding by Indication

FVC is a confounder, so we need to adjust for it.

But FVC is also a mediator. Some of the effect of NIV on survival flows through FVC.
• $A = \text{Binary treatment (0=no, 1=yes)}$

• $Y^A = \text{Counterfactual (hypothetical) outcome under treatment } A$

• We act as if $Y^0$ and $Y^1$ both exist for each patient

• Causal effect of $A$ on $Y = Y^1 - Y^0$

• We only observe either $Y^0$ or $Y^1$ for a patient depending on whether patient received treatment.
Background: Counterfactual Outcomes

Time 1

A=1

Time 2

A=1

Y^{(1, 1)} = 12 months

A=0

Y^{(1, 0)} = 9 months

A=0

Y^{(0, 1)} = 8 months

A=1

Y^{(0, 0)} = 4 months
Assumptions of Causal Inference Models

- **Consistency**
  - If you receive treatment $A$, your observed outcome is $Y^A$

- **No Unmeasured Confounders**
  - There is a vector of covariates $L$ such that given past treatment $\tilde{A}$ and $L$, $A$ is random

- **Positivity**
  - At every level of $L$, there are non-zero probabilities of both $A=0$ and $A=1$
Marginal Structural Model
Marginal Structural Model: Definition

1. Estimate the probabilities of receiving treatment $p(A)$ over time given past treatment $\tilde{A}$ and confounders $L$.

2. Model the outcome $Y$ as a function of $A$, weighting each observation by $1/p(A=a)$ (i.e. the inverse probability of observed treatment).

The weights generate copies of each observation to create a “pseudopopulation” in which the effect of $A$ on $Y$ is unconfounded.
Marginal Structural Model: Analysis

Atassi, Cudkowicz, Schoenfeld (2011)

- **Treatments:** Feeding tube placement and NIV
- **Outcome:** Survival free of tracheostomy and permanent assisted ventilation (PAV)
- **Population:**
  - 331 ALS patients from 2 clinical trials of celecoxib and coenzyme Q10
  - Vital capacity \( \geq 50 \) and \( \geq 60 \)
  - Symptom onset no earlier than 5 years
  - No/steady riluzole, no other unstable medical condition
## Marginal Structural Model: Analysis

Confounders L to estimate $p(A)$

<table>
<thead>
<tr>
<th>Feeding Tube analysis</th>
<th>NIV analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced Vital Capacity</td>
<td>Forced Vital capacity</td>
</tr>
<tr>
<td>Relevant ALSFRS-R questions (swallow, speech, saliva)</td>
<td>Relevant ALSFRS-R questions (total score, dyspnea, orthopnea)</td>
</tr>
</tbody>
</table>
Marginal Structural Model: Analysis

Results

- Complete data on 300 patients
- Follow-up time for the two trials: 8 and 12 months

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<th>Feeding Tube analysis</th>
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<tr>
<td>13% eventually received feeding tube</td>
<td>21% eventually received NIV</td>
</tr>
<tr>
<td>Feeding tube placement causes 0.28 increase in</td>
<td>NIV has no effect on survival (p=0.5)</td>
</tr>
<tr>
<td>hazard of death (p=0.02)</td>
<td></td>
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Structural Nested Model
Assume that treatment A expands survival time $Y$ by $\Psi$:

$$\Psi = \text{Survival Time Ratio} = \frac{Y^1}{Y^0}.$$  

Let $t =$ time at which patient goes on treatment.

By the Consistency assumption:

$$Y^o = t + \frac{(Y-t)}{\Psi}$$
Structural Nested Model: Definition

Instead of modeling observed $Y$ as we did with Marginal Structural Models, we model $A$:

$$P(A=1|t) = \beta_1 \bar{A}(t) + \beta_2 L(t) + \beta_3 Y^o$$

By the No Unmeasured Confounders assumption, $p(A)$ should be independent of $Y^o$ given $\bar{A}$ and $L$.

If $\Psi$ were correctly specified, then $Y^o$ would be correctly calculated, and thus $\beta_3 = 0$. 
1. Conduct a grid search for $\Psi$.

2. With each $\Psi$, calculate $Y^o$ for all patients.

3. Fit the model for $A$ over time adjusting for past treatment $\tilde{A}$, confounders $L$, and $Y^o$.

4. Choose the $\Psi$ that makes $\beta_3 = 0$.

5. Use a bootstrap method to obtain standard error.
Structural Nested Model: Analysis

- **Treatments:** Feeding tube placement and NIV.
- **Outcome:** Survival free of tracheostomy and PAV.
- **Population:**
  - 513 ALS patients from clinical trial of Ceftriaxone
  - Vital capacity $\geq 60$
  - Symptom onset no earlier than 3 years
  - No/steady riluzole
### Structural Nested Model: Analysis

#### Confounders L to model p(A)

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<tr>
<td>ALSFRS-R bulbar and gross motor sub scores</td>
<td>ALSFRS-R breathing sub score</td>
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</table>
## Structural Nested Model: Analysis

### Results

- 392 patients with complete baseline data had not received either treatment before baseline
- Mean follow-up time: $20 \pm 12$ months

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<th>Feeding Tube analysis</th>
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<tr>
<td>45% eventually received feeding tube</td>
<td>44% eventually received NIV</td>
</tr>
<tr>
<td>Survival Time Ratio $\Psi = 0.61$</td>
<td>Survival Time Ratio $\Psi = 1.49$</td>
</tr>
<tr>
<td>Feeding tube placement decreases survival time by 39% ($p=0.027$)</td>
<td>NIV increases survival time by 49% ($p=0.034$)</td>
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Discussion: Feeding Tube Analysis

- Why might the use of feeding tubes be harmful?
  - “[Feeding tube] placement is a relatively invasive procedure that requires hospitalization, fasting, and anesthesia, and has potential complications such as bleeding and infection.”
Discussion: NIV Analysis

- Why did the 2 analyses disagree on the effect of NIV on survival?
  - Length of follow up:
    - SNM analysis follow up duration was about twice as long as MSM analysis
  - Assumptions about treatment:
    - SNM analysis accommodated dynamic treatment patterns
    - MSM analysis assumed monotonic treatment
Discussion: MSM vs. SNM

Marginal Structural Models
• Arguably more intuitive
• Can accommodate binary outcomes

Structural Nested Models
• Can include interactions with time-varying covariates
• Can accommodate violations in positivity assumption
Conclusion

- Standard methods can produce biased estimates in the presence of time-varying confounding.

- Choice of causal inference method may vary with research question.

- Properly adjusting for confounding by indication we found that:
  - Feeding tube placement is harmful in terms of survival.
  - NIV may have beneficial impact on survival.
Useful References


