A multi-state model for the prognosis of non-mild acute pancreatitis

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Outline

Background

Materials

Methods

Application

Future work

References
Acute Pancreatitis (AP)

What is Acute Pancreatitis?

- An inflammatory condition of the pancreas characterized by symptoms of strong abdominal pain, nausea, vomiting, increased heart rate, fever and swollen and tender abdomen.

- A reversible process, most people with AP recover completely.

- It may range from mild discomfort to a severe, life-threatening illness.

- The major causes are biliary lithiasis and alcohol consumption.
Motivation

The most severe forms, and consequently patients with AP admitted to Intensive Care Unit (ICU), showed high mortality.

Prediction of AP mortality is not straightforward due to the low incidence of the most severe forms and because its fluctuating clinical course.
# Objectives

## Clinical goal

Study of the clinical evolution of non-mild AP patients that enter to ICU.

## Methodological goal

Apply multi-state models to obtain risk factors to help for an adequate prognosis of AP.

## Objective of the talk

Describe the clinical problem, introduce the statistical methodology and show preliminary results.
Motivating dataset

- A prospective observational study.

- Carried out in Donostia University Hospital (Gipuzkoa).

- Patients (N = 286) that entered to the Intensive Care Unit with a diagnosis of Acute Pancreatitis.

- Follow-up: until their complete recovery (no longer than 31 Aug, 2017).

- Two treatment protocols conducted: one between 2001 and 2007 (93) and other from 2008 to mid-2017 (193).
Complete process for Acute Pancreatitis
Classical Survival data study → Multi-state modeling

In contrast to the classical statistical methods for analyzing survival data, multi-state models present many advantages:

- Study of multiple events of interest.
- The influence of the time at which intermediate events occur.
- Influence of prognostic factors on each of the intermediate event.
- Account for competing risks, unbiased estimates.
- Potential to obtain dynamic predictions. Predictions of the clinical prognosis of a patient at a certain point in his/her illness course.
The multi-state model

- **State 1**: ICU
The multi-state model

- **X** = \{X(t) : t ≥ 0, X(0) = 1\} multi-state process.
- **S** = \{1, 2, 3, 4\} = \{ICU, Hospital, Death, Home\} state space.
- **F**_\text{t} = σ\{X(s) : s ≤ t\} filtration of the process.
The multi-state model

Notation:
- \( X = \{ X(t) : t \geq 0, X(0) = 1 \} \) multi-state process.
- \( S = \{ 1, 2, 3, 4 \} = \{ ICU, Hospital, Death, Home \} \) state space.
- \( F_t = \sigma \{ X(s) : s \leq t \} \) filtration of the process.
The multi-state model

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- $X = \{X(t) : t \geq 0, X(0) = 1\}$ multi-state process.
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- $\mathcal{F}_t = \sigma\{X(s) : s \leq t\}$ filtration of the process.
**Characterization of the multi-state model**

(i) **Transition probability** between state $i$ and state $j$ for $s \leq t$,

$$P_{ij}(s, t; \mathcal{F}_{s^-}) = P(X_t = j \mid X_s = i; \mathcal{F}_{s^-}). \quad (1)$$

Transition probability $4 \times 4$ matrix for $s \leq t$,

$$P(s, t) = \{P_{ij}(s, t; \mathcal{F}_{s^-}); \quad i, j \in S = \{1, 2, 3, 4\}\} \quad (2)$$

(ii) **Transition intensities**, 

$$\alpha_{ij}(t; \mathcal{F}_{t^-}) = \lim_{\Delta t \to 0^+} \frac{1}{\Delta t} P_{ij}(t, t + \Delta t; \mathcal{F}_{t^-}). \quad (3)$$

(iii) **Cumulative (integrated) transition intensities**, 

$$A_{ij}(t; \mathcal{F}_{t^-}) = \int_0^t \alpha_{ij}(u; \mathcal{F}_{u^-}). \quad (4)$$
Characterization of the multi-state model

Assuming Markov property:

(i) Transition probability between state $i$ and state $j$ for $s \leq t$,

$$P_{ij}(s, t) = P(X_t = j \mid X_s = i).$$  \hspace{1cm} (1)

Transition probability $4 \times 4$ matrix for $s \leq t$,

$$P(s, t) = \{P_{ij}(s, t); \; i, j \in S = \{1, 2, 3, 4\}\}$$  \hspace{1cm} (2)

(ii) Transition intensities,

$$\alpha_{ij}(t) = \lim_{\Delta t \to 0^+} \frac{1}{\Delta t} P_{ij}(t, t + \Delta t).$$  \hspace{1cm} (3)

(iii) Cumulative (integrated) transition intensities,

$$A_{ij}(t) = \int_0^t \alpha_{ij}(u).$$  \hspace{1cm} (4)
Characterization of the multi-state model

Examples:

(i) $P_{14}(0, 21) = P(X_{21} = 4 \mid X_0 = 1)$.

Represents the probability that a patient is completely recovered after 3 weeks given that at time 0 she/he was in ICU.

(ii) $\alpha_{13}(5) = \lim_{\Delta t \to 0^+} \frac{1}{\Delta t} P_{13}(5, 5 + \Delta t)$.

Instantaneous risk of experiencing the $1 \rightarrow 3$ transition at time 5. Rate of dying in ICU at the 5th day.

(iii) $A_{13}(5) = \int_0^5 \alpha_{13}(u)$.

Cumulative risk of dying in ICU by time 5.
Transition probability matrix

Assuming Markov property,

\[
P(s, t) = \begin{pmatrix}
1 - P_{12}(s, t) - P_{13}(s, t) - P_{14}(s, t) & P_{12}(s, t) & P_{13}(s, t) & P_{14}(s, t) \\
0 & 1 - P_{23}(s, t) - P_{24}(s, t) & P_{23}(s, t) & P_{24}(s, t) \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1
\end{pmatrix},
\]

and this can be recovered from the transition intensities, \( A(t) \), through product integration

\[
P(s, t) = \prod_{u \in (s,t]} (1 + dA(u)) .
\]
Transition probability matrix: estimation

To obtain $\hat{P}(s, t)$ it is enough to compute the Aalen-Johansen estimator of the cumulative transition intensity $dA$:

$$d\hat{A}_{ij}(t) = \frac{dN_{ij}(t)}{Y_i(t)},$$

$$\hat{A}_{ij}(t) = \sum_{u \leq t} d\hat{A}_{ij}(u), \; i \neq j \quad \text{and} \quad \hat{A}_{ii}(t) = -\sum_{i \neq j} d\hat{A}_{ij}(t).$$

Being,

$N_{ij}(t) = \text{number of observed direct transitions from state } i \text{ to state } j \text{ up to time } t$

$Y_i(t) = \text{number of individuals under observation in state } i \text{ just before time } t$

$dA(t): \text{matrix of elements } d(A_{ij}(t))_{i,j} = (\alpha_{ij}(t))_{i,j}dt$
## Overall survival time

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Events</th>
<th>Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>period: 2001-2007</td>
<td>93</td>
<td>33</td>
<td>96</td>
<td>71 - ∞</td>
</tr>
<tr>
<td>period: 2008-2017</td>
<td>193</td>
<td>34</td>
<td>-</td>
<td>129 - ∞</td>
</tr>
</tbody>
</table>

### Survival functions according to treatment protocol

- **2001–2007**
  - 0.0
  - 0.2
  - 0.4
  - 0.6
  - 0.8
  - 1.0

- **2008–2017**
  - 0.6
  - 0.4
  - 0.2
  - 0.0

### Treatment

- **2001–2007**: Continuous line
- **2008–2017**: Dashed line
Model features

- Model with 4 states and 4 transitions.
- All the patients follow-up start at ICU, i.e. $X(0) = 1$.
- Overall 5 possible trajectories (see next slide).
- ICU and Hospital states are transient, Death and Home absorbing.
- We assume Markov property.
- We fit a non-parametric model, here.
All the possible paths

GRBIO: March 6th, 2018
Multi-state modeling: observed transitions

All the possible trajectories,

1 \rightarrow 
1 \rightarrow 2
1 \rightarrow 2 \rightarrow 3
1 \rightarrow 2 \rightarrow 4
1 \rightarrow 3

Table: Number of patients experiencing each transition during the follow-up. Frequencies and Proportions

<table>
<thead>
<tr>
<th>From</th>
<th>ICU</th>
<th>Hospital</th>
<th>Death</th>
<th>Home</th>
<th>no event</th>
<th>total entering</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU</td>
<td>0</td>
<td>230 (80.4)</td>
<td>56 (19.5)</td>
<td>0</td>
<td>0</td>
<td>286</td>
</tr>
<tr>
<td>Hospital</td>
<td>0</td>
<td>0</td>
<td>11 (4.8)</td>
<td>219 (95.2)</td>
<td>0</td>
<td>230</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>67 (100)</td>
<td>67</td>
</tr>
<tr>
<td>Home</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>219 (100)</td>
<td>219</td>
</tr>
</tbody>
</table>

\(^1\)Via \texttt{paths()} function from \texttt{mstate} \texttt{R} package
Multi-state modeling: duration of stay

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Min.</td>
</tr>
<tr>
<td>ICU</td>
<td>93</td>
<td>1</td>
</tr>
<tr>
<td>Hospital</td>
<td>69</td>
<td>5</td>
</tr>
</tbody>
</table>

Table: Duration of stay (in days) in the two transient states
MS modeling: cumulative transition intensities

2001–2007 period protocol

2008–2017 period protocol

Figure: Estimated cumulative transition intensities, $\hat{A}_{ij}$, per each $i \rightarrow j$ transition. Left first period protocol group, right second period protocol group.
Multi-state modeling: transition probabilities

Fixing a starting time of $s=0.5$

**Figure:** Transition probabilities, starting in state 1 (ICU) at time 0.5, i.e. $P_{1j}(0.5, t)$, for all $j = 1, 2, 3, 4$ and $t \geq 0$. Left first period protocol group, right second period protocol group.
Fixing a starting time of $s=0.5$ and $t=21$ days, 3 weeks.

Figure: Transition probabilities, starting in state 1 (ICU) at time 0.5, i.e. $P_{1j}(0.5, t)$ for all $j = 1, 2, 3, 4$ and $t \geq 0$. Left first period protocol group, right second period protocol group.
# Multi-state modeling: transition probabilities

## 2001-2007 period protocol

\[
\hat{P}(0.5, 21) = \begin{pmatrix}
I & 0.280 & 0.344 & 0.172 & 0.204 \\
H & 0 & 0.583 & 0 & 0.417 \\
D & 0 & 0 & 1 & 0 \\
Rec. & 0 & 0 & 0 & 1 \\
\end{pmatrix}
\]

s.e. :

\[
\begin{pmatrix}
I & 0.045 & 0.048 & 0.037 & 0.041 \\
H & 0 & 0.069 & 0 & 0.069 \\
D & 0 & 0 & 0 & 0 \\
Rec. & 0 & 0 & 0 & 0 \\
\end{pmatrix}
\]

## 2008-2017 period protocol

\[
\hat{P}(0.5, 21) = \begin{pmatrix}
I & 0.289 & 0.326 & 0.111 & 0.274 \\
H & 0 & 0.380 & 0 & 0.016 \\
D & 0 & 0 & 1 & 0 \\
Rec. & 0 & 0 & 0 & 1 \\
\end{pmatrix}
\]

s.e. :

\[
\begin{pmatrix}
I & 0.032 & 0.034 & 0.022 & 0.033 \\
H & 0 & 0.050 & 0.015 & 0.050 \\
D & 0 & 0 & 0 & 0 \\
Rec. & 0 & 0 & 0 & 0 \\
\end{pmatrix}
\]

Via `msfit()` and `probtrans()` functions from `mstate` R package.
Multi-state modeling: transition probabilities

Another representation,

**Figure:** Transition probabilities, starting in state 1 (ICU) at time 0.5, i.e. $P_{1j}(0.5, t)$ for all $j = 1, 2, 3, 4$ and $t \geq 0$. Left first period protocol group, right second period protocol group.
Future work

- **Fit a model** to determine those risk factors that have a stronger influence in the course of patients with AP.

- **Prediction.** Develop a predictive process to obtain predictions of the clinical prognosis.

- **Build up a shiny app.**
Future work: fitting

Semi-parametric approach, Cox models:

<table>
<thead>
<tr>
<th>Transition</th>
<th>(Semi-)Markov stratified hazards</th>
<th>(Semi-)Markov proportional hazards</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU → Hospital</td>
<td>( \alpha_{12}(t \mid \mathbf{Z}<em>{12}) = \alpha</em>{12,0}(t) \exp(\mathbf{\beta}^T \mathbf{Z}_{12}) )</td>
<td>( \alpha_{12}(t \mid \mathbf{Z}<em>{12}) = \alpha</em>{12,0}(t) \exp(\mathbf{\beta}^T \mathbf{Z}_{12}) )</td>
</tr>
<tr>
<td>ICU → Death</td>
<td>( \alpha_{13}(t \mid \mathbf{Z}<em>{13}) = \alpha</em>{13,0}(t) \exp(\mathbf{\beta}^T \mathbf{Z}_{13}) )</td>
<td>( \alpha_{13}(t \mid \mathbf{Z}<em>{13}) = \alpha</em>{3,0}(t) \exp(\mathbf{\beta}^T \mathbf{Z}_{13}) )</td>
</tr>
<tr>
<td>Hospital → Death</td>
<td>( \alpha_{23}(t \mid \mathbf{Z}<em>{23}) = \alpha</em>{23,0}(t) \exp(\mathbf{\beta}^T \mathbf{Z}_{23}) )</td>
<td>( \alpha_{23}(t \mid \mathbf{Z}<em>{23}) = \alpha</em>{3,0}(t) \exp(\mathbf{\beta}^T \mathbf{Z}_{23}) )</td>
</tr>
<tr>
<td>Hospital → Home</td>
<td>( \alpha_{24}(t \mid \mathbf{Z}<em>{24}) = \alpha</em>{24,0}(t) \exp(\mathbf{\beta}^T \mathbf{Z}_{24}) )</td>
<td>( \alpha_{24}(t \mid \mathbf{Z}<em>{24}) = \alpha</em>{24,0}(t) \exp(\mathbf{\beta}^T \mathbf{Z}_{24}) )</td>
</tr>
</tbody>
</table>

**Covariates:** period, age, bmi, gender, etiology, surgery, mechanical ventilation.

**Global covariates.** Single effect estimate assumed to be common for all transitions.

**Transition-specific.** Different covariate effect estimates accross all transition.
Future work: prediction

Based on the best fit: estimate the conditional probability of some clinical feature event, given an history, and a set of values for prognostic factors $Z$ of a patient.

Given an alcoholic 67 years-old male patient who is in ICU since 10 days, what is the probability of being discharged 10 days later, i.e. after 20 days from admission? How does this probability compare to a baseline patient?
References


Moltes gràcies!
Independent censoring? Watch out!

Those censored individuals at time $t$ are **NOT** representative for those still at risk at that time.
We should consider another state (*Home*): competing event of total recovery.

A subject that is censored because of failure from a competing event risk, will with certainty **NOT** experience the event of interest.
Kaplan-Meier BIASED!
It takes competing events as censored.

Example

- The event of interest: the onset of a disease.
- Interested in: estimate $F(t)$.
- Obviously, individuals may die without getting the disease.
- KM could consider death without the disease as “independent censoring”.
- An hypothetical population where individuals could not never die without the disease.
Make inference for disease risks and rates acknowledging “the presence of the competing risks”.

**Figure:** Cumulative incidence estimates of death and discharge, shown as survival and incidence curves, respectively; naïve Kaplan-Meier estimates are shown in grey.