Attributable mortality due to nosocomial infections: a simple and useful application of multistate models

Martin Schumacher, Matthias Wangler, Martin Wolkewitz and Jan Beyersmann

Department of Medical Biometry and Statistics
Institute of Medical Biometry and Medical Informatics
University Medical Center Freiburg

Outline

- Introduction and basic definitions
- Multistate modelling approach
- SIR 3-study on nosocomial infections
- Conclusions
Basic quantities in a cohort study

- $P(D|E^+)$: conditional probability of developing the disease ($D$) (of death), given exposure to risk factor ($E^+$)

- $P(D|E^-)$: conditional probability of developing the disease ($D$) (of death), given no exposure to risk factor ($E^-$)
Basic quantities in a cohort study

- $P(D|E^+)$: conditional probability of developing the disease ($D$) (of death), given exposure to risk factor ($E^+$)

- $P(D|E^-)$: conditional probability of developing the disease ($D$) (of death), given no exposure to risk factor ($E^-$)

- $RR = \frac{P(D|E^+)}{P(D|E^-)}$: relative risk
Measures of attributable risk (mortality)

- $P(D|E^+) - P(D|E^-)$

risk difference, attributable risk, absolute excess risk

- $P(E^+) \left[ P(D|E^+) - P(D|E^-) \right]$ population attributable risk

- $P(E^+) \left[ P(D|E^+) - P(D|E^-) \right] \frac{P(D)}{P(D)} = PAF$

population attributable fraction
Alternative representations of $PAF$

- $PAF = \frac{P(D) - P(D|E^-)}{P(D)}$
- $PAF = \frac{P(E)[RR - 1]}{P(E)[RR - 1] + 1}$
- $PAF = P(E^+|D)\frac{[RR - 1]}{RR}$
Alternative representations of $PAF$

- $PAF = \frac{P(D) - P(D|E^-)}{P(D)}$

- $PAF = \frac{P(E)[RR - 1]}{P(E)[RR - 1] + 1}$

- $PAF = P(E^+|D)\frac{[RR - 1]}{RR}$

- In case-control studies, the latter formula is used thereby replacing $RR$ through the corresponding odds ratio
Questions to be addressed:

- How should one define $PAF$ and related quantities when exposure to risk factor is time-dependent (as for nosocomial infections)?
Questions to be addressed:

- How should one define $PAF$ and related quantities when exposure to risk factor is time-dependent (as for nosocomial infections)?

- How should one estimate $PAF$ and related quantities if mortality is of interest, competing events (e.g. discharge) and potential censoring have to be taken into account?
The model: Progressive Disability Model

No Exposure (No Infection) 0 1 Exposure (Infection)

2 3 4 5
Discharge Death Discharge Death
Multistate modelling approach (1)

- $X_t \in \{0, 1, \ldots, 5\}$ stochastic process describing state occupied at time $t$

Transition probabilities:

$P_{ij}(s; t) = P(X_t = j | X_s = i)$

Time-dependent vital status

$D(t) = 1$ if $X_t \in \{3, 4, 5\}$

Time-dependent exposure status

$E(t) = 1$ if $X_t \in \{1, 2, 3\}$
Multistate modelling approach (1)

- $X_t \in \{0, 1, \ldots, 5\}$ stochastic process describing state occupied at time $t$

- Transition probabilities: $P_{ij}(s, t) = P(X_t = j | X_s = i)$
Multistate modelling approach (1)

- $X_t \in \{0, 1, \ldots, 5\}$ stochastic process describing state occupied at time $t$

- Transition probabilities: $P_{ij}(s, t) = P(X_t = j | X_s = i)$

- Time-dependent vital status

$$\begin{cases} D(t) = 1 \\ X_t = 3, 5 \end{cases} \quad \left( ”D(t) = 1” : D \right)$$
Multistate modelling approach (1)

- $X_t \in \{0, 1, \ldots, 5\}$ stochastic process describing state occupied at time $t$

- Transition probabilities: $P_{ij}(s, t) = P(X_t = j | X_s = i)$

- Time-dependent vital status

\[
\begin{align*}
\{ D(t) = 1 \} &= \{ X_t = 3, 5 \} \\
("D(t) = 1": D)
\end{align*}
\]

- Time-dependent exposure status

\[
\begin{align*}
\{ E(t) = 1 \} &= \{ X_t = 1, 4, 5 \} \\
("E(t) = 1": E^+) \\
\{ E(t) = 0 \} &= \{ X_t = 0, 2, 3 \} \\
("E(t) = 0": E^-)
\end{align*}
\]
The model: Progressive Disability Model

Free of nosocomial infection

0 -> 1

1

Nosocomial infection

2

Discharge

3

Death

4

Discharge

5

Death
The model: Progressive Disability Model

- time-dependent exposure: 
  \[ P(X_0 = 0) = 1 \]
  
  (nosocomial infections)
**The model: Progressive Disability Model**

- time-dependent exposure: \( P(X_0 = 0) = 1 \)
  
  (nosocomial infections)

- exposure known at \( t = 0 \):
  \[
  P(X_0 = 0) = P(E^-) \\
  P(X_0 = 1) = P(E^+) \\
  \text{and } P_{01}(t) = 0
  \]
  
  (infections on admission)
Multistate modelling approach (2)

- \( P(D, t) = P(D(t) = 1) = P(X_t = 3, 5) \)

\[
= P(X_0 = 0) \cdot P(X_t = 3, 5 | X_0 = 0) + P(X_0 = 1)P(X_t = 3, 5 | X_0 = 1) \\
= P(X_0 = 0) \left[ P_{03}(t) + P_{05}(t) \right] + P(X_0 = 1)P_{15}(t)
\]

- \( P(D|E^-, t) = P(D(t) = 1|E(t) = 0) \)

\[
= \frac{P(X_t = 3 \cap X_0 = 0)}{P(X_t = 0, 2, 3, \cap X_0 = 0)} = \frac{P_{03}(t)}{P_{00}(t) + P_{02}(t) + P_{03}(t)}
\]

- \( P(D|E^+, t) = P(D(t) = 1|(E(t) = 1) = \ldots \)
Multistate approach (3):

- All quantities of interest are functions of time and can be expressed in terms of transition probabilities.
Multistate approach (3):

- All quantities of interest are functions of time and can be expressed in terms of transition probabilities.

- \( P(D, t) \), \( P(D|E^-, t) \), \( P(D|E^+, t) \)

- \( P(D|E^+, t) - P(D|E^-, t) \) ”Attributable Mortality”

- \( PAF(t) = \frac{P(D, t) - P(D|E^-, t)}{P(D, t)} \) ”Population Attributable Fraction”
Multistate approach (3):

- All quantities of interest are functions of time and can be expressed in terms of transition probabilities.

- \( P(D, t), \ P(D|E^-, t), \ P(D|E^+, t) \)

- \( P(D|E^+, t) - P(D|E^-, t) \)  "Attributable Mortality"

- \( PAF(t) = \frac{P(D, t) - P(D|E^-, t)}{P(D, t)} \)  "Population Attributable Fraction"

- Estimation with Aalen-Johansen estimator of transition probabilities will properly account for censoring; standard errors via bootstrap
SIR 3-study

- Prospective cohort study on the incidence of nosocomial infections in intensive care unit (ICU) patients.

- All patients who stayed 48 hours or longer in the ICUs were included and followed until discharge or death on ICU (1.6% censored).

- 5 ICUs (72 ICU beds); study period 2/2000 - 7/2001.

- Study has been conducted within the network ”Spread of nosocomial infections and resistant pathogens (SIR)”.
## SIR 3-study

<table>
<thead>
<tr>
<th>Category</th>
<th># deaths</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1876 admissions</td>
<td>214</td>
<td>(11.4)</td>
</tr>
<tr>
<td>220 pneumonia on admission (POA)</td>
<td>48</td>
<td>(21.8)</td>
</tr>
<tr>
<td>1656 no POA</td>
<td>166</td>
<td>(10.0)</td>
</tr>
<tr>
<td>158 nosocomial pneumonia (NP)</td>
<td>33</td>
<td>(20.9)</td>
</tr>
<tr>
<td>1718 no NP</td>
<td>181</td>
<td>(10.5)</td>
</tr>
</tbody>
</table>
SIR 3-study (NP): Mortality

![SIR 3-Study (Nosocomial Pneumonia): Mortality](image_url)

Attributable mortality due to nosocomial infections: ..., GMDS Leipzig 2006 – p. 15/27
SIR 3-study (NP): Attributable Mortality

Attributable mortality due to nosocomial infections: ..., GMDS Leipzig 2006 – p. 16/27
SIR 3-study (NP): Population Attributable Fraction

SIR 3-Study (Nosocomial Pneumonia): Attributable Fraction

Attributable mortality due to nosocomial infections: ..., GMDS Leipzig 2006 – p. 17/27
## SIR 3-study: Summary of results

<table>
<thead>
<tr>
<th></th>
<th>NP Multistate model</th>
<th>Crude rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P(D, t = 120)$</td>
<td>0.117</td>
<td>0.114</td>
</tr>
<tr>
<td>$P(D</td>
<td>E^-, t = 120)$</td>
<td>0.108</td>
</tr>
<tr>
<td>$P(D</td>
<td>E^+, t = 120)$</td>
<td>0.213</td>
</tr>
<tr>
<td>$P(D</td>
<td>E^+, t = 120) - P(D</td>
<td>E^-, t = 120)$</td>
</tr>
<tr>
<td>$PAF(t = 120)$</td>
<td>0.077</td>
<td>0.077</td>
</tr>
<tr>
<td>$SE(PAF(1 = 120))$</td>
<td>0.026</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Attributable mortality due to nosocomial infections: ..., GMDS Leipzig 2006 – p. 18/27
Conclusions

- Application of a multistate model turns out to be a useful and easily understandable approach for the estimation of attributable mortality and related quantities taking temporal dynamics, competing events and potential censoring into account.
Conclusions

- Application of a multistate model turns out to be a useful and easily understandable approach for the estimation of attributable mortality and related quantities taking temporal dynamics, competing events and potential censoring into account.

- The multistate model provides a general framework for both time dependent exposure and exposure known at $t = 0$. 
Conclusions

- Application of a multistate model turns out to be a useful and easily understandable approach for the estimation of attributable mortality and related quantities taking temporal dynamics, competing events and potential censoring into account.

- The multistate model provides a general framework for both time dependent exposure and exposure known at $t = 0$.

- If there is no (or little) censoring, crude rates lead to identical (similar) results for large $t$. 
Conclusions

- Application of a multistate model turns out to be a useful and easily understandable approach for the estimation of attributable mortality and related quantities taking temporal dynamics, competing events and potential censoring into account.

- The multistate model provides a general framework for both time dependent exposure and exposure known at $t = 0$.

- If there is no (or little) censoring, crude rates lead to identical (similar) results for large $t$.

- So far, exposure to single risk factors has only been considered in isolation; in order to properly adjust for confounding, a simultaneous analysis, e.g. based on a suitable regression model, is necessary. (SIR 3-study: nosocomial pneumonia, pneumonia on admission, SAPS II-categories at admission)

- ”Case-control study” in surgical ICU (Matched cohort study) (4002 admitted patients, 107 with nosocomial sepsis)
- ”Cases”: patients with nosocomial sepsis
  ”Controls”: patients without nosocomial sepsis, matched for age, sex, length of stay to infection, comorbidities etc.

- Attributable mortality
  \[
  \text{Attributable mortality} = \text{mortality rate of cases} - \text{mortality rate of controls}
  \]
  \[
  = \frac{43}{86} - \frac{13}{86} = 50\% - 15\% = 35\%
  \]

- \( PAF \) (reconstructed)
  \[
  PAF = 0.0267 \times \frac{0.35}{0.16} = 0.058 \ (= 5.8\%)
  \]

- Case-control study in a 800-bed, tertiary care, hospital
- "Cases": patients dying in hospital (524 deaths)
  "Controls": patients discharged alive after 48 hours, matched for primary diagnosis and date of admission
- $PAF$ (via Odds-Ratio formula, adjusted for various factors)

  All NI’s : 21.3%
  Lower respiratory tract : 5.3%
  Bacteremia or sepsis : 7.7%

- Case study in 16 northern French hospitals (14222 beds)
- ”Cases”: All patients who died at least 48 hours after admission ($n = 1945$ deaths, review of patient’s charts and interview of patient’s treating physician by infection-control practitioner)
- ”NI-associated mortality” (AM)

\[
AM = \frac{\# \text{ deaths associated with NI}}{\# \text{ deaths included into the study}}
\]

All NI’s : 26.6%
Lower respiratory tract : 10.3%
Bacteremia or sepsis : 4.5%
"Associated Mortality"

\[ P(E^+ | D) = \frac{P(E^+ \cap D)}{P(D)} = AM \]

"Percent deaths associated (attributable) to risk factor"

Relationship to \( PAF \):

\[ PAF = AM - \frac{P(E^+)}{1 - P(E^+)}(1 - AM) \]

\[ = AM \frac{RR - 1}{RR} \]

- Cohort study in surgical ICU
  (676 admitted patients, 383 patients with NI, 176 deaths)
- \( PAF \) (for all NI’s; reconstructed)

\[
\begin{align*}
\text{PAF} & = 0.57 \frac{0.285 - 0.228}{0.26} = 0.125 \quad (= 12.5\%) 
\end{align*}
\]
SIR 3-study (POA): Mortality

Mortality
0.25
0.2
0.15
0.1
0.05
0.0

P(death)
P(death | risk factor absent)
P(death | risk factor present)

Time t
0 20 40 60 80 100 120

Attributable mortality due to nosocomial infections: ..., GMDS Leipzig 2006 – p. 25/27
SIR 3-study (POA): Population Attributable Fraction

Attributable mortality due to nosocomial infections: ..., GMDS Leipzig 2006 – p. 26/27
** SIR 3-study: Summary of results

<table>
<thead>
<tr>
<th></th>
<th>POA</th>
<th></th>
<th>NP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multistate model</td>
<td>Crude rate</td>
<td>Multistate model</td>
<td>Crude rate</td>
</tr>
<tr>
<td>$P(D, t = 120)$</td>
<td>0.117</td>
<td>0.114</td>
<td>0.117</td>
<td>0.114</td>
</tr>
<tr>
<td>$P(D</td>
<td>E^-, t = 120)$</td>
<td>0.102</td>
<td>0.100</td>
<td>0.108</td>
</tr>
<tr>
<td>$P(D</td>
<td>E^+, t = 120)$</td>
<td>0.234</td>
<td>0.218</td>
<td>0.213</td>
</tr>
<tr>
<td>$P(D</td>
<td>E^+, t = 120) - P(D</td>
<td>E^-, t = 120)$</td>
<td>0.132</td>
<td>0.118</td>
</tr>
<tr>
<td>$PAF(t = 120)$</td>
<td>0.132</td>
<td>0.121</td>
<td>0.077</td>
<td>0.077</td>
</tr>
<tr>
<td>$SE(PAF(1 = 120))$</td>
<td>0.030</td>
<td>0.033</td>
<td>0.026</td>
<td>0.027</td>
</tr>
</tbody>
</table>