Model comparison for analysis of population surveillance data

Rosie Meng
Richard Woodman
Steven Coles
Erin Symonds

Email: rosie.meng@flinders.edu.au
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Overview

- Research questions & background
- Data
- Models
- Stata routines
Research question

- What characteristics of colorectal adenoma diagnosed at index colonoscopy are associated with degree of neoplasia advancement at 1st surveillance colonoscopy?

Application: which patients diagnosed with adenoma at index would not be at significant risk of developing an advanced neoplasia at 1st surveillance colonoscopy - allow colonoscopy interval to be extended.
Research question background

- Uncertainty and deviation from surveillance guideline regarding surveillance interval.
- Few studies that provide evidence for duration of surveillance based on lesion features.
- Conservative approach is common: evidence based professional guidelines versus specialist’s preference to minimize chance of a future finding of advanced neoplasia
- Consequences: surveillance colonoscopy interval shortened, colonoscopy service overloaded, and increased risk of complication (e.g. bowel perforation).
Data

- Database: South Australian Southern Cooperative Program for the Prevention of Colorectal Cancer (SCOOP)
- Study period: 25 Jan 2000 – 21 Dec 2010 (n=379)

Index colonoscopy
  - Low risk adenoma
  - High risk adenoma

1st surveillance colonoscopy
6 Dec 2001 – 27 Dec 2010
  - Normal/hyperplastic polyp - censored
  - Low risk adenoma – event 1
  - High risk adenoma/CRC – event 2
Data cont.

- Study cohort at index colonoscopy (379 subjects)
  - Low risk adenoma (n=187)
  - High risk adenoma (n=192)

- Outcomes at 1\textsuperscript{st} surveillance colonoscopy:
  - Normal/hyperplastic polyp
  - Low risk adenoma
  - High risk adenoma/CRC

- Predictors
  - Time between two colonoscopies
  - Risk category at the index
  - Gender
  - Age at the index
  - Reason for the index colonoscopy
  - Reason for the 1\textsuperscript{st} surveillance colonoscopy
Risk grouping:

- High risk adenoma has one or more following features
  - ≥10mm size
  - High grade dysplasia
  - Villous or serrated morphology
  - ≥3 polyps

- Low risk adenoma - all patients with a diagnosis of adenoma other than high risk adenoma.
Data cont. - Censoring

- Right censoring – most common type
- Interval censoring
- Left censoring

No difference mathematically

Index colonoscopy
Onset of risk (t0)

1st surveillance colonoscopy
Censored (t1)

Left censoring: failure occurs before entering study

Interval censoring: We do not know exactly when failure occurred. Only know it occurred between t0 & t1.

Right censoring: not experience the event during observation.
Results – risk of low risk adenoma diagnosis

Kaplan-Meier failure estimates (low risk adenoma diagnosis)

<table>
<thead>
<tr>
<th>Analysis time (months since entry)</th>
<th>Low risk adenoma</th>
<th>High risk adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>187</td>
<td>192</td>
</tr>
<tr>
<td>20</td>
<td>162</td>
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<tr>
<td>40</td>
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<td>80</td>
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<tr>
<td>100</td>
<td>0</td>
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</tbody>
</table>

Risk at baseline colonoscopy

- Blue line: low risk adenoma
- Red line: high risk adenoma

p = .02
Results – risk of high risk adenoma/CRC diagnosis

Kaplan-Meier failure estimates (high risk adenoma/CRC diagnosis)

Risk at baseline colonoscopy

Risk at baseline colonoscopy

Number at risk

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</table>

Risk at baseline colonoscopy

- Low risk adenoma
- High risk adenoma

p < .001
## Results – model comparison

<table>
<thead>
<tr>
<th></th>
<th>Semi-parametric Cox model (stcox)</th>
<th>Parametric model (streg – Weibull)</th>
<th>Competing-risks survival model (stcrreg)</th>
<th>Stratified Cox model (stcox,...strata())</th>
<th>Multinominal logistic model mlogit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR [95% CI]</td>
<td>HR [95% CI]</td>
<td>SHR [95% CI]</td>
<td>HR [95% CI]</td>
<td>IRR [95% CI]</td>
</tr>
<tr>
<td><strong>Low risk adenoma</strong></td>
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<tr>
<td>Risk category at index</td>
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</tr>
<tr>
<td>Low risk adenoma</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>High risk adenoma</td>
<td>1.58 [1.03,2.42] *</td>
<td>1.58 [1.04,2.42] *</td>
<td>1.05 [0.69,1.58]</td>
<td>2.78 [1.98,3.89] ***</td>
<td>0.49 [0.28,0.84] **</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Female</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td><strong>Age at index (years)</strong></td>
<td>1.02 [1.00,1.04] *</td>
<td>1.02 [1.00,1.04] *</td>
<td>1.01 [1.00,1.03]</td>
<td>1.01 [0.99,1.02]</td>
<td>1.03 [1.01,1.05] *</td>
</tr>
<tr>
<td><strong>Reason for 1st surveillance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scheduled surveillance</td>
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<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>FOBT positive</td>
<td>2.08 [1.23,3.52] **</td>
<td>2.01 [1.20,3.37] **</td>
<td>1.48 [0.84,2.62]</td>
<td>1.10 [0.77,1.57]</td>
<td>1.33 [0.69,2.58]</td>
</tr>
<tr>
<td>Time between two colonoscopy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.99 [0.98,1.01]</td>
</tr>
<tr>
<td><strong>High risk adenoma/CRC</strong></td>
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<td>Risk category at index</td>
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<td>1.00</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.91 [0.52,1.59]</td>
<td>0.95 [0.54,1.65]</td>
<td>0.81 [0.46,1.43]</td>
<td>1.31 [0.70,2.47]</td>
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<td>NA</td>
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* p<0.5; ** p<.01; *** p<.001
Results - adjusted cumulative hazard function of diagnoses at surveillance colonoscopy by index risk groups (*stcurve, cumhaz.....after stcox model*)

Diagnosis at 1st surveillance colonoscopy

- **Low risk adenoma**
  - Cumulative Hazard
  - Months between two colonoscopies
  - Risk at baseline colonoscopy:
    - Low risk adenoma
    - High risk adenoma
  - $p = 0.037$

- **High risk adenoma/CRC**
  - Cumulative Hazard
  - Months between two colonoscopies
  - Risk at baseline colonoscopy:
    - Low risk adenoma
    - High risk adenoma
  - $p < 0.001$
Results – CIF from competing risks model (*stcrreg*)

Cumulative incidence function at 1st surveillance colonoscopy

- CIF of low risk adenoma
  - Cumulative Incidence
  - Months between 2 colonoscopies
  - Risk at baseline colonoscopy
  - CIF of low risk adenoma
  - p=.83

- CIF of low risk adenoma
  - Cumulative Incidence
  - Months between 2 colonoscopies
  - Risk at baseline colonoscopy
  - CIF of low risk adenoma
  - p<.001
Summary of the differences between models

- Logistic regression vs. survival analysis
  High risk adenoma at index had reduced risk of advancing to low risk adenoma, and no difference in risk of advancing to high risk adenoma compared to low risk adenoma cohort.
  - Contradicted to Kaplan-Meier results (reason?)

- Stratified Cox model
  No estimates for the stratified variable – but the variable is our interest

- Cox model (semi-parametric) vs. parametric survival model
  Estimates are similar

- Cause-specific parametric survival model vs. competing risks model
  HR attenuated in competing risks model
Discussion

Why not nonparametric survival analysis?
Kaplan-Meier (*sts graph*); with log-rank test (*sts test*)

Demerit:
• can not take into account of the effect of covariates.

Merits:
• good preliminary assessment for individual risk factors.
• Visualization for proportional hazard assumption.
Discussion cont.

Why not multinomial logistic regression (*mlogit*)?

Demerits:
- Cannot assess the relationship between predictors and survival time – time is a predictor in logistic regression.
- Cannot take into account of censoring
- Can misinterpret the effect of time – a bit complicated

Merits:
- Easy to perform the analysis
- Easy to interpret – although results could be misleading
Discussion cont.

Why not stratified Cox model (`stcox…, strata(type of events)`)?

Demerits & merits:

- Single estimate and easy to interpret – but only if we are not interested to know the difference between different type of events.

```
stset time, failure(event)
stcox i.index_risk i.sex age_index…, strata(surveillance)
```

Competing risks model example:

*primary interest - low risk adenoma*
```
stset time, failure(surveillance==1) stcrreg i.index_risk i.sex age_index, compete(surveillance==2)
```

*primary interest - high risk adenoma/CRC*
```
stset time, failure(surveillance==2) stcrreg i.index_risk i.sex age_index, compete(surveillance==1)
```
Discussion cont.

Why not parametric survival mode (*streg*)?

Demerits:
- Have the assumptions on the shape of hazard
- Whatever the hazard shape is, it is the same for everybody

Merits:
- When the assumption on shape of hazard for intervening is correct, parametric estimates are more efficient
Why not competing risks survival analysis (*stcrreg*)?

**Merits:**

- Incidence-rate curve represent the observed data in the presence of competing failure events – more close to real life scenario.
- Describe covariates effect is more straightforward.

**Demerits:**

- Competing events assumptions
  For this particular data, the events are not actually mutually excluded. Classification was based on the highest pathology rating.
- More difficult to interpret subdistribution hazard ratio (SHR).
Discussion cont.

Why Cox cause-specific proportional hazard model (\textit{stcox})?

- No assumption need to be made for the shape of the hazard over time – can be any shape
- Whatever the hazard shape is, it is the same for everybody
- Effect of covariates and HR are easy to interpret
Discussion cont.

So…

• Test the PH assumption and see if it is met.
• If PH assumption is met, then stick with survival analysis models, such as Cox, competing risks, stratification or multiple events analysis, depending on research questions and primary interest.
• Multinomial logistic is clearly inappropriate for such data.

More:
If have time varying predictor(s), try “stpm2” (flexible parametric survival model).
References


Thank you!