What to do with missing data in clinical registry analysis?

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Missing data

|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
At analysis…

- Too late?
  - Ideally data collection is designed in a way to minimise missing data, e.g. ANZDATA
  - Not always possible to anticipate how data will be used, e.g. Predict survival forward from 3 months on dialysis
- Too difficult?
  - Complex methods, major assumptions...
- Ignore the problem?
  - “Complete case” analysis
What is a reasonable assumption?

• Assume values are missing completely at random,
  • i.e. patients with missing values are a random sample
• Assume missing values are dependent only on observed characteristics, e.g. age, sex, disease severity.
• Assume values are missing precisely because of their unobserved value

• MCAR, “MAR”, “MNAR”
The mechanism that gives rise to missing values is usually unknown

- Possible to investigate in detail a random sample of missing data to obtain true values?

Extra assumptions are required for analysis

- Different assumptions give different results

The validity of the assumptions cannot be determined from the data at hand

Assessing the sensitivity of conclusions to the assumptions made about the missingness mechanism should play a central role.

Adapted from Carpenter
Methods for dealing with missing data

• Complete case analysis (CC)
  – deletion of cases with missing observations

• Single imputation (SI)
  – Insert “reasonable” value
    • Mean imputation
    • Median imputation
    • “Last observation carried forward”
    • Missing “as normal”

? Possibly biased.
X Reduced precision due to ignoring observed data in the people excluded.
X Almost certainly biased.
X Over-estimates precision due to “making up” data.
Multiple imputation (MI)

- Uses observed values to generate a range of plausible values, based on existing associations between variables

- “m” complete datasets created, each dataset analysed

- “m” sets of results; combined using “Rubin’s rules”

- Improved precision due to use of all observed data √
- Possibly biased – assumes MAR given the model used for imputation (CC assumes MAR given the covariates in model used for analysis) ?
Multiple imputation

- Early days of multiple imputation suggested that imputation could be a separate process from analysis
- Now more widely accepted that imputation should be specific to a project / defined set of analyses
- Choice of imputation model is critical
  - Include any variables in analysis model
  - Including the outcome of study
  - Sampling weights etc
  - Care with survival outcome – time and censoring status – using estimate of hazard recommended
  - Interactions if necessary
Inverse probability weighting

- Weights determined from a regression model for “missingness”
- Current work looks at combined MI and inverse prob weighting approach

- Full maximum likelihood
- Fully Bayesian approach
One common use of registry data is the development and/or validation of risk prediction models / prognostic tools. What approach to take to missing data? Multiple imputation shown to have advantages under MAR assumption in model development.

- Evidence base incomplete
- Little work done for model validation
- We are undertaking statistical simulations to assess MI v CC
Hierarchical / longitudinal data

- Guidelines now exist for imputation strategies with longitudinal data – may be relevant to registries
- Imputation in hierarchical data
  - Eg ASCTS cardiac surgery cases by hospital
- UK Renal Registry – exploration of widely differing rates of missing data by reporting centre
Conclusions

- Ignoring missing data is not an option

- Any method of analysis makes assumptions – the only issue is whether those assumptions are explicitly stated or not

- Sensitivity analysis is vital – but time-consuming and never-ending (MNAR unlimited)?

- Prevention always better than cure – do what is possible to collect data in first place
Appropriately handling missing data is not a panacea for all potential problems that confront the measurement of quality. Attention must also be focused on issues such as case ascertainment, small per-hospital patient numbers, unmeasured confounders, and risk adjustment modeling strategies that fully account for differences in case mix between hospitals.

However, with appropriate attention to missing data during the development and implementation of quality initiatives, we might ameliorate one potential threat. Missing data present an example where poor choices in data collection and oversimplified approaches to data analyses can threaten a well-intentioned health policy initiative. With informed merging of statistical methodology and health policy, we might better understand the devilish details and actually use them to improve the care of our patients and our health care system.
Missing in Action:
A Case Study of the Application of
Methods for Dealing with Missing Data
to Trauma System Benchmarking

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Background

• Trauma registry data are usually incomplete

• Various methods for dealing with missing data have been used, some of which lead to biased results

• There is no standardisation of the approach to missing data across trauma registries
Objective

• This study examined the effect of using selected methods for handling missing data on a recognised trauma outcome measure.
Methods (1)

• Data from the Victorian State Trauma Registry (VSTR) were used for the period July 2003 to June 2008.

• Three methods for handling missing data were investigated:
  1. Complete case analysis (CC)
  2. Single imputation (SI): 2 approaches
  3. Multiple imputation (MI): 5 different models (combination of variables)
Methods (2)

• Following each method (for dealing with missing data)
  – TRISS analysis was performed
  – The W-score was derived
## Glasgow Coma Scale

<table>
<thead>
<tr>
<th>GCS motor response</th>
<th>GCS verbal response</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 – moves limb to command</td>
<td>5 – oriented</td>
</tr>
<tr>
<td>5 – localizes to painful stimulus</td>
<td>4 – confused</td>
</tr>
<tr>
<td>4 – withdraws from painful stimulus</td>
<td>3 – inappropriate words</td>
</tr>
<tr>
<td>3 – abnormal flexion response</td>
<td>2 – incomprehensible</td>
</tr>
<tr>
<td>2 – abnormal extension response</td>
<td>1 – no verbal</td>
</tr>
<tr>
<td>1 – no motor response</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GCS eye response</th>
<th>GCS total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 – spontaneous</td>
<td>motor + verbal + eye</td>
</tr>
<tr>
<td>3 – open to speech</td>
<td>Range: 3 (worst) to 15 (best)</td>
</tr>
<tr>
<td>2 – open to pain</td>
<td></td>
</tr>
<tr>
<td>1 – none</td>
<td></td>
</tr>
</tbody>
</table>
Revised Trauma Score (RTS)

- Points scoring system, 0 (worst) to 12 (best), combining GCS, systolic blood pressure, respiratory rate

- Field RTS: to predict death/survival for blunt & penetrating injury
Abbreviated Injury Scale (AIS)

- Points score for each injury
  0=no injury
  1=minor
  2=moderate
  3=severe (non life-threatening)
  4=severe (life threatening, survival probable)
  5=critical (survival uncertain)
  6=fatal injury for anatomic area

- Eg, abdominal; muscle ache=1, organ contusion=3, spine fracture with neurologic signs=4
Injury Severity Scale (ISS)

- Most severe injury to each body region: head & neck, chest, abdominal, extremity, general

- Points score for injury using AIS

- ISS = sum of squared AIS scores from three most severely injured regions
  - Range 0 (best) to 75 (worst)
  - 75 is automatic score if AIS=6, fatal, for any region

- To retrospectively assess treatment in terms of patient mortality
TRISS

- To retrospectively assess treatment in terms of patient mortality

- Survival related to age, ISS (anatomical injuries and their severity) and RTS (hence respiratory rate, SBP, GCS)

- Logistic regression-based model

\[
\text{probability of survival} = \frac{1}{1 + e^{a + b(\text{RTS}) - c(\text{ISS}) - d(\text{Age}>55\text{yr})}}
\]
TRISS – the W-score

• **W-score**
  - the absolute difference between observed and expected number of deaths per 100 patients.
  - \( \frac{(O-E)}{(N/100)} \)
    - \( N \)=number of patients included
    - \( O \)=observed number of deaths,
    - \( E \)=expected number of deaths obtained by summing over all patients their probability of death, i.e one minus TRISS predicted probability of survival
Results

- There were 10,180 cases

- 2,398 (23.6%) were missing at least one TRISS variable observation (at primary hospital)

- The variable with the greatest proportion of missing observations was GCS
## Missing data in 10,180 patients

<table>
<thead>
<tr>
<th>TRISS variable</th>
<th>Missing</th>
<th>Missing %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>ISS</td>
<td>31</td>
<td>0.3</td>
</tr>
<tr>
<td>sBP (primary hospital)</td>
<td>612</td>
<td>6</td>
</tr>
<tr>
<td>sBP (primary hospital + prehospital)</td>
<td>498</td>
<td>5</td>
</tr>
<tr>
<td>sBP (primary hospital + prehospital + definitive hospital)</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>RR (primary hospital)</td>
<td>1,449</td>
<td>14</td>
</tr>
<tr>
<td>RR (primary hospital + prehospital)</td>
<td>630</td>
<td>6</td>
</tr>
<tr>
<td>RR (primary hospital + prehospital + definitive hospital)</td>
<td>221</td>
<td>2</td>
</tr>
<tr>
<td>GCS (primary hospital)</td>
<td>2,030</td>
<td>20</td>
</tr>
<tr>
<td>GCS (primary hospital + prehospital)</td>
<td>765</td>
<td>8</td>
</tr>
<tr>
<td>GCS (primary hospital + prehospital + definitive hospital)</td>
<td>448</td>
<td>4</td>
</tr>
</tbody>
</table>
Single imputation methods

1. Missing ISS, RR, or GCS imputed using corresponding prehospital value if available.
   • If unavailable then patient omitted from analysis

2. Missing ISS, RR, or GCS imputed using corresponding prehospital value. If prehospital value also missing, the corresponding definitive hospital observation (in the case of hospital transfer) was used.
   • If unavailable then patient omitted from analysis

3. Median and mean imputation also explored
<table>
<thead>
<tr>
<th>MI Method</th>
<th>Variables used for imputation model in MI (in addition to mortality outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Primary hospital TRISS variables</td>
</tr>
<tr>
<td>2</td>
<td>Primary hospital TRISS variables Pre-hospital SBP, RR, GCS</td>
</tr>
<tr>
<td>3</td>
<td>Primary hospital TRISS variables Pre-hospital SBP, RR, GCS Transfer to Primary hospital by ambulance</td>
</tr>
<tr>
<td>4</td>
<td>Primary hospital TRISS variables Pre-hospital SBP, RR, GCS Transfer to Primary hospital by ambulance Transfer from Primary hospital to Definitive hospital</td>
</tr>
<tr>
<td>5</td>
<td>Primary hospital TRISS variables Pre-hospital SBP, RR, GCS Transfer to Primary hospital by ambulance Transfer from Primary hospital to Definitive hospital “Legitimate” Primary hospital GCS*</td>
</tr>
</tbody>
</table>
Display of W-score and 95% confidence interval for each method for dealing with missing data.

Median and mean imputation gave more extreme results than SI 1, 2 but in opposite direction!
Discussion

• **Complete case analysis (CC)**
  – survival *benefit*

• **Single imputation (SI)**
  – survival *benefit* of greater magnitude than CC

• **Multiple imputation (MI)**
  – survival *benefit* when care taken with variables used in imputation model

• Demonstrates disparity in results and need for sensitivity analyses – did they go far enough?

• TRISS W-score not necessarily the perfect benchmarking tool
Conclusion

- Using the TRISS-derived W-score as the outcome measure, different methods for managing missing data can result in a positive or negative assessment of trauma care performance.
- Where analyses are used for benchmarking hospitals and/or systems, the impact can be considerable.
- It is important that validated standardised approaches to handling missing data are universally adopted and reported.
- If MI is to be the chosen method, it must be adapted to the specific analysis, with variables appropriately included and reported.
- Studies comparing trauma outcomes must state:
  - The number of cases with missing data
  - The approach used to address missing data