A survival analysis approach for assessing risk factors associated with adverse drug reactions in a inpatient paediatric population.

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Presented by:
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University of Liverpool
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INTRODUCTION
The ADRIC Research Programme

Adverse drug reactions (ADRs) are the unwanted effects of medication and cause iatrogenic harm to patients of all ages.

In the UK one third of drug prescriptions on paediatric wards were either off label (OL) or unlicensed (UL).
Adverse Drug Reaction (ADR)

DEFINITION:

“an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dose regimen, or withdrawal of the product”

Edwards and Aronson (2000)
OTHER DEFINITIONS:

Off-label medicine (OL)

A drug prescribed to an individual with unapproved indication or in an unapproved age group, dose or form of administration.

Unlicensed medicine (UL)

A medicine which is not licensed in the country in which it is being prescribed.
Introduction

Extensive literature investigating ADRs in children

- Incidence rates in children exposed to a drug differ significantly (0.6%-16.8%)
- Majority of studies focus on general paediatric populations which may not include surgical patients.
- Very few studies have included a wide range of specialist paediatric patients
  - Surgical specialities
  - Oncology
  - Haematoma-oncology

*Thus the true incidence, character and burden of ADRs in children remains unclear.*
Objectives

1. Determine the incidence of ADRs in a paediatric inpatient population
2. To explore risk factors that may increase a patient’s likelihood of an ADR.
3. To characterise those ADRs identified by
   - Type
   - Causality
   - Severity
Study Description

**Design**
A prospective cohort study carried out over 1 year

**Study Setting**
Single centre: Alder Hey Children’s NHS Foundation Trust
Study population

Included:

Any child (ages 0-16 years) admitted to hospital after the start of the study who then remains an inpatient for more than 48 hours.

Excluded:

- All patients in transition care unit
- All patients receiving follow up treatment at home
- All patients treated on the paediatric intensive care unit
1446 ADRs
6609 admissions/5126 patients

Incidence calculation

- 152 admissions without drug exposure
- 129 ADRs with identical start date
  (>1 ADR/day during same admission = 1 ADR event)
  Censored from time of PICU admission
  356 admissions: PICU from day 1
  43 ADRs occurred in patients in PICU from day 1
  Further 118 ADRs occurred in patients admitted to PICU throughout admission.

1156 ADRs
6101 admissions/4732 patients

Multi-admission and multi-event analysis

- 769 patients with > 1 admission
  303 ADRs “multi-admissions”
- 118 patients had a total >1 ADRs during first admission
  148 ADRs = “multi-event” during first admission

705 ADRs 4732 patients
705 patients with at least one ADR
4027 patients without ADR

Univariate and multivariate analysis
...to assess the burden of adverse drug reactions in an inpatient paediatric setting.

Statistical Analysis

INCIDENCE
Incidence

The dataset that follows patients up to first ADR for the first admission only is used to construct this Kaplan Meier plot.
Incidence

Patient ADR burden

\[
\frac{\text{Number of children with at least one ADR}}{\text{Number of children regardless of drug exposure}} = \frac{907}{5126} = 17.69\% 
\]

Hospital ADR burden

\[
\frac{\text{Number of admissions with at least one ADR}}{\text{Number of admissions regardless of drug exposure}} = \frac{1051}{6609} = 15.90\% 
\]
...to explore patients that may be more susceptible to ADRs.
Analysis of first admission data

**RESPONSE:** Time to first ADR (in days)

- **Event:** Time between the date of first admission and the date of the first ADR

- **No Event:** If no ADR occurred during the first admission then the outcome was censored, with follow-up time recorded as the time between date of admission and the discharge date
Risk factors

- Gender (Male vs. Female)
- Age (continuous)
- Daily number of ward medicines (discrete time-varying)
- Admission to theatre (binary time-varying)
- Oncology status (binary)
Statistical Analysis

UNIVARIATE ANALYSIS
Aims

To determine whether the patterns of ADRs/no ADRs differ within each risk factor.

Methods

- Kaplan Meier curves
- Log rank test
- Log rank test for trend (where appropriate)
Gender

Log rank statistic: \( p = 0.83 \)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Total patients</th>
<th>No. patients with ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>2608</td>
<td>389</td>
</tr>
<tr>
<td>Females</td>
<td>2122</td>
<td>316</td>
</tr>
</tbody>
</table>

*Missing gender data for one patient.*
Age (by category)

Log-rank test for trend: p < 0.001

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Total patients</th>
<th>No. patients with ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant (&lt;1 years)</td>
<td>1350</td>
<td>78</td>
</tr>
<tr>
<td>Pre-school (1-4 years)</td>
<td>1277</td>
<td>161</td>
</tr>
<tr>
<td>School-aged (5-11 years)</td>
<td>942</td>
<td>227</td>
</tr>
<tr>
<td>Adolescent (12-16 years)</td>
<td>1162</td>
<td>239</td>
</tr>
</tbody>
</table>

Cumulative probability of ADR (%)

No. days since admission

Total patients | No. patients with ADR
1350 | 78
1277 | 161
942  | 227
1162 | 239
Oncology patients

Log rank statistic: p < 0.001

<table>
<thead>
<tr>
<th></th>
<th>Total patients</th>
<th>No. patients with ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology patients</td>
<td>106</td>
<td>45</td>
</tr>
<tr>
<td>Non-oncology patients</td>
<td>4625</td>
<td>660</td>
</tr>
</tbody>
</table>
## Summary of univariate analysis

<table>
<thead>
<tr>
<th>Gender*</th>
<th>Male</th>
<th>Total patients</th>
<th>No. Patients with ADR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2608</td>
<td>389</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2122</td>
<td>316</td>
<td></td>
<td></td>
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</tbody>
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<th>Total patients</th>
<th>No. Patients with ADR</th>
<th>P-value</th>
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<tr>
<td>Infant (&lt;1 years)</td>
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<td>78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-school (1-5 years)</td>
<td>1277</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td>School-aged (5-11 years)</td>
<td>942</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>Teenage (&gt;11 years)</td>
<td>1162</td>
<td>239</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oncology</th>
<th>Total patients</th>
<th>No. Patients with ADR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>106</td>
<td>45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>4625</td>
<td>660</td>
<td></td>
</tr>
</tbody>
</table>

*Missing gender data for one patient.
Statistical Analysis

MULTIVARIATE ANALYSIS
**Aims**
To assess the influence of multiple independent variables (risk factors) on the hazard of an ADR occurring.

**Methods**
Multivariate Cox proportional hazards regression model

**Model selection**
Due to clinical importance, all risk factors will be forced into the model.

**Diagnostics**
- Index plot to assess outlying individuals. Using *overall martingale residuals* for each subject.
- Formal test for proportional hazards by introducing an additional time-varying covariate to time invariant risk factors and comparing $-2 \log \hat{L}$.
- Assess influential values on individual parameter estimates using the *delta-betas*.
The multivariate time-varying Cox PH Model

\[
\hat{h}_i(t) = \exp\{\beta_1 \text{Gender}_i + \beta_2 \text{Age}_i + \beta_3 \text{Oncology}_i + \beta_4 \text{Theatre}_i(t) + \beta_5 \text{NumMeds}_i(t)\} h_0(t)
\]

For the \(i\)th patient at time \(t\).

Age (in years) and the number of medicines take the values observed for each at time \(t\).

Indicator variables for gender, oncology and admission to theatre take the following values at time \(t\) (as appropriate).

\[
\text{Gender}_i = \begin{cases} 
\text{Female} & = (0) \\
\text{Male} & = (1)
\end{cases}
\]

\[
\text{Oncology}_i = \begin{cases} 
\text{No} & = (0) \\
\text{Yes} & = (1)
\end{cases}
\]

\[
\text{Theatre}_i = \begin{cases} 
\text{No} & = (0) \\
\text{Yes} & = (1)
\end{cases}
\]
### Results (time to first ADR)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Coefficient ($\beta_j$)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-0.063</td>
<td>0.939 (0.809, 1.089)</td>
<td>0.405</td>
</tr>
<tr>
<td>Age</td>
<td>0.055</td>
<td>1.057 (1.043, 1.071)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oncology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.802</td>
<td>2.230 (1.639, 3.034)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission to theatre (time-varying)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.649</td>
<td>5.200 (4.387, 6.165)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of ward meds (time-varying)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.218</td>
<td>1.244 (1.214, 1.275)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
CONCLUSIONS
Conclusions

- Patient ADR burden 17.69%
- Hospital ADR burden 15.90%
- Age, oncology status, admission to theatre and number of ward medicines are significant risk factors.
- Gender is not a significant risk factor.
What’s next...

Off-label and unlicensed medicine use and adverse drug reactions in children

Mason et al.

For further information regarding other works of the ADRiC team:

www.adric.org.uk