Background

- Survival of red blood cells (RBCs) is decreased in anaemia of chronic kidney disease (CKD) due to either:¹
  - increase in random destruction.
  - accelerated senescence.
- Commonly, only a mean RBC lifespan value is determined based on RBC labelling experiments.²
  - Better insight into the processes of RBC destruction is desirable.
- A statistical model for the survival time of RBCs has been developed based on the plausible physiological processes of RBC destruction:³
  - Early destruction of unviable RBCs, reduced lifespan of misshapen RBCs, random destruction and senescence.
- The model accounts for short-comings associated with known RBC labelling techniques, such as random labelling with radioactive chromium (⁵¹Cr).⁴

Objectives

- To apply the previously developed model for RBC survival to clinical data.
- To investigate differences in the RBC lifespan in anaemic CKD patients compared to healthy controls.

Materials & Methods

- Available RBC survival data using ⁵¹Cr labelling method:⁵

<table>
<thead>
<tr>
<th>Table I: Demographics</th>
<th>CKD group (n = 14)</th>
<th>Controls (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) ±SD</td>
<td>57.2 ± 8.6</td>
<td>57.3 ± 7.9</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>8:6</td>
<td>8:6</td>
</tr>
<tr>
<td>Haemoglobin (g/L) ±SD</td>
<td>122 ± 12</td>
<td>143 ± 10</td>
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</tbody>
</table>

- Two estimation scenarios were considered based on the model:
  - Estimating the main parameter controlling senescence.
  - Estimating the parameter controlling random destruction.

- Two analysis methods were used:
  1. A classical two-stage approach using generalized least square.
     - Preference towards one of the scenarios across the individuals?
  2. A full population approach using MONOLIX 1.1.⁶
     - Goodness of fit was assessed based on objective function value and visual predictive checks.
     - Wald test and likelihood ratio test were used to assess significance of the tested covariates.

Results

1. Two-stage approach:
  - Estimation of random destruction preferred in majority of individuals (11 out of 14 in both groups).
  - Significant reduction in RBC survival in CKD patients: -28% compared to healthy controls (p = 0.0002).

   Figure 1: Two-stage approach – Data & individual predictions

2. Population analysis:
  - A combined error model best described the data.
  - Preference for estimating random destruction confirmed.
  - Only CKD was found to be a significant covariate in the full model.
  - Mean RBC lifespan in CKD = 56.2 days, controls = 69.4 days.

<table>
<thead>
<tr>
<th>Table II: Population Approach Results</th>
<th>̂θ</th>
<th>̂Ω</th>
<th>Mean LS</th>
<th>CV% prop</th>
<th>σ₀²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base model</td>
<td>0.0133 days¹</td>
<td>0.1296</td>
<td>56.0 days</td>
<td>2.27</td>
<td>0.0234</td>
</tr>
<tr>
<td>Full model</td>
<td>0.0106 days¹</td>
<td>0.0721</td>
<td>69.4 days</td>
<td>2.05</td>
<td>0.0256</td>
</tr>
<tr>
<td>with covariate effect</td>
<td>0.0170 days¹</td>
<td>(-44%)</td>
<td>56.2 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

   Figure 2: Population approach – Full model

Conclusions

- RBC survival in CKD patients decreased by 20-30%.
  - Increase in random destruction the preferred underlying mechanism.
- Initial over-prediction due to non-specific loss of label.
  - Care should be taken when interpreting RBC lifespan values.

References


Otago Pharmacometrics Group ~ www.pharmacometrics.co.nz