The Effects of Anti-Hypertensive Drugs Evaluated Using Markov Modelling for Northern Ireland Chronic Kidney Disease Patients


Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.
The Effects of Anti-Hypertensive Drugs Evaluated Using Markov Modelling for Northern Ireland Chronic Kidney Disease Patients

A.Rainey¹, K.J.Cairns¹, A.H.Marshall¹, M.P.Quinn², G.Savage² and D.Fogarty³
¹Centre for Statistical Science and Operational Research (CenSSOR)
²Department of Public Health and Epidemiology, ³Regional Nephrology Unit
The Queens University, Belfast
a.rainey@qub.ac.uk

Abstract

The aim of this paper is to use Markov modelling to investigate survival for particular types of kidney patients in relation to their exposure to anti-hypertensive treatment drugs. In order to monitor kidney function an intuitive three point assessment is proposed through the collection of blood samples in relation to Chronic Kidney Disease for Northern Ireland patients. A five state Markov Model was devised using specific transition probabilities for males and females over all age groups. These transition probabilities were then adjusted appropriately using relative risk scores for the event death for different subgroups of patients. The model was built using TreeAge software package in order to explore the effects of anti-hypertensive drugs on patients.

1. Introduction

Worldwide, 10% of the adult population have some form of kidney damage and every year millions die prematurely from cardiovascular diseases linked to Chronic Kidney Disease (CKD) [1]. The number of patients receiving renal replacement therapy in the UK is rising rapidly and is unlikely to reach steady state for another 25 years, costing 2% of the total UK National Health Service (UK NHS) budget [2]. There is major concern that demand will soon outstrip resources available in Nephrology care and dialysis centres, of which there are only seven in Northern Ireland (NI). This work focuses on modelling kidney function using estimated Glomerular Filtration Rate (eGFR). GFR represents a person's approximate percentage of kidney function however, considering this is a difficult element to obtain from the blood, one estimates this value using Levey's MDRD equation [3]:

\[
eGFR = 186 \times \left(\frac{\text{Creatinine}}{88.4}\right)^{-1.154} \times \left(\frac{\text{Age}}{100}\right)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})
\]

Previous work has shown that the recently corrected version of the MDRD (known as the IDMS equation) is more accurate and would be advised [4]. Internationally, there are five known stages of CKD defined by eGFR, of which the latter three are more severe [5]. These stages assist in constructing states within the proposed Markov Model (MM) outlined in this paper. An intuitive categorisation method for observing kidney function is used to calculate relative risk of death for different subgroups of patients based on their exposure to treatment drugs. A summary of how the transition probabilities were obtained for the MM is discussed as well as features of the model when built using the software package TreeAge [6]. The relative risk values are used to adjust the current death probabilities for both the No CKD state and CKD state. Analysis is performed which compares survival curves for patients receiving treatment drugs with those who did not receive the drugs.

2. Kidney Movement

A total of 2,892,340 blood samples from Northern Ireland were extracted during 1st Jan 01 - 31st Dec 02 from regional laboratories. These were merged with an enriched General Practice database producing a cohort of 75,434 patients, 20 years or older with a total of 307,663 test results. eGFR for each of these results was obtained using the original MDRD equation as recommended (at the time) by the National Institute for Health and Clinical Excellence (NICE) [7]. In order to observe kidney movement within the dataset a three point assessment was devised (represented by the points ABC on figure 1), where point B represents a patients minimum kidney function over the two year period and points A and C identify the patients maximum kidney function before and after that minimum (if one existed). This three point assessment, for each patient, was categorised depending on whether the points lay above or below a significant value of 60% kidney function [8].
which resulted in 5 different possible groupings as shown in figure 1. For example, group one represents patients who throughout the two years maintained an eGFR above 60mls/min/1.73m² (known as CKD stages 1 and 2) and thus should arguably not pose demand on local kidney services. In complete contrast, at the other end of the scale group 5 represents patients where all blood samples taken over the two year period lay within CKD stages 3-5, that is below 60mls/min/1.73m²; the ‘danger zone’ as such.

Figure 1. Three point assessment and categorisation of patient kidney function

In addition the gradient slopes were calculated for each patient and those of particular interest, as directed by clinical expert opinion, were patients who had a rapid progressive slope \( >5 \text{mls/min/yr} \) per year (represented by line AB for each group in figure 1). Using this categorisation the following descriptives were obtained from the data for 20+ year olds, using the original MDRD equation.

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>Neph</th>
<th>Deaths</th>
<th>Rapids</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56356 (74.7)</td>
<td>341 (29.2)</td>
<td>992 (28.5)</td>
<td>13600 (55.9)</td>
</tr>
<tr>
<td>2</td>
<td>2477 (3.3)</td>
<td>50 (4.3)</td>
<td>328 (9.4)</td>
<td>2363 (9.7)</td>
</tr>
<tr>
<td>3</td>
<td>2540 (3.4)</td>
<td>56 (4.8)</td>
<td>298 (8.6)</td>
<td>735 (3.0)</td>
</tr>
<tr>
<td>4</td>
<td>2812 (3.7)</td>
<td>73 (6.3)</td>
<td>495 (14.2)</td>
<td>2699 (11.1)</td>
</tr>
<tr>
<td>5</td>
<td>11249 (14.9)</td>
<td>647 (55.4)</td>
<td>1367 (39.3)</td>
<td>4919 (20.2)</td>
</tr>
<tr>
<td>Total</td>
<td>75434</td>
<td>1167</td>
<td>3480</td>
<td>24316</td>
</tr>
</tbody>
</table>

Notes: The values presented in brackets are the % within the column
*Neph* represents patient referrals to Nephrology
*Rapids* indicates patients with \( >5 \text{mls/min/yr} \) progression

Table 1. Categorisation Descriptives

Early detection is a key factor in CKD, however its silent symptoms make this a difficult, almost impossible task for the majority affected. Ideally Nephrologists would like to capture the rapid progressors, particularly those in groups 4 and 5, since these patients are in most danger of reaching CKD stage 5, more commonly known as End Stage Renal Failure (ESRF). The shaded cells in table 1 show that Nephrologists in Northern Ireland had a potential 7,618 rapidly progressing patients (10.1% of the total dataset) in 2001/02 from groups 4 and 5 alone, of which only 720 were known to their care, possibly due to non-referrals and/or lack of resources.

2.1. Relative Risk

Anti-hypertensive therapy (AHT) is used to reduce the mortality and morbidity for patients with cardiovascular complications. Considering hypertension is one of the main risk factors for CKD, the use of Ace Inhibitors (ACEI) and Antiotensin II Receptor Blocker (ARBs), two forms of AHT, have been proven to slow the progression and development of CKD [9]. This study examines the relative risk (RR) for the event death when patients are exposed to the treatment of ACEI/ARBs (AA) in comparison to those who did not receive treatment (no AA). The RR was calculated as shown

\[
RR = \frac{P(\text{dying AA})}{P(\text{dying No AA})} = \frac{\text{Number died AA}}{\text{Total AA}} \times \frac{\text{Total No AA}}{\text{Number died No AA}}
\]

Adult kidney function starts to decay naturally beyond the age of 40 (an approximate rule of thumb is 1ml/min/year). Hence RR was calculated for different lower age boundaries starting from 40+ year olds and also for those belonging to groups 1-3 compared to those in groups 4-5 (figure 1), in order to find the optimal subgroup of patients affected by ACEI/ARBs in relation to death.

<table>
<thead>
<tr>
<th>Age Criteria</th>
<th>Relative Risk with 95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Groups</td>
<td>Groups 1-3</td>
</tr>
<tr>
<td>40+</td>
<td>0.862</td>
</tr>
<tr>
<td></td>
<td>[0.791,0.939]</td>
</tr>
<tr>
<td>50+</td>
<td>0.777</td>
</tr>
<tr>
<td></td>
<td>[0.713,0.847]</td>
</tr>
<tr>
<td>60+</td>
<td>0.734</td>
</tr>
<tr>
<td></td>
<td>[0.672,0.801]</td>
</tr>
<tr>
<td>70+</td>
<td>0.742</td>
</tr>
<tr>
<td></td>
<td>[0.676,0.814]</td>
</tr>
</tbody>
</table>

Notes: *Groups* are outlined in figure 1

Table 2. Relative Risk Calculated for Different Age Boundaries and Kidney Flow Groups

A RR<1 indicates that the event is less likely to occur in the treatment group whereas a RR>1 suggests event is more likely to occur in the treatment group. In this case, it can be seen from the shaded cells in table 2 that the least risk of death occurred for subjects who were 60 years of age and above receiving the treatment drugs ACEI/ARBs. Using this subgroup of patients the RR was calculated again for those who were rapidly declining (\( >5 \text{mls/min/year} \)), since these patients are in most danger and of extreme interest to Nephrologists. This resulted in a RR of 0.515 ([0.427,0.622] lower and upper 95% confidence intervals) for patients in groups 1-3 and 0.728 ([0.654,0.812]) for groups 4-5. In order to investigate this further, the following 5 state Markov model was utilised.
3. The 5 State Markov Model for CKD

Internationally recognised CKD stages, as previously discussed, help define states within the MM whereby stages 1 and 2 represent No CKD (>60% kidney function) and stages 3-5 represent the CKD state (<60% kidney function) in addition to the absorbing state Death. The typical length of stay for patients highlighted that in fact a 5 state MM was necessary in order to capture the two-term mixed exponential flow of patients. This lead to the design of the 5 state MM as shown in figure 2. It is important to note at this point that the new corrected version of the MDRD equation known as the IDMS was implemented for 18 year olds and beyond as recommended by recent guidelines [7] leading to a new larger dataset consisting of 77,615 patients with a total of 312,120 blood sample results [4].

![Figure 2. The Five State Markov Model for CKD](image)

This model can be represented by a system of equations, however for the purposes of this paper only a selection of the system is shown. For example the probability that a patient stays in No CKD state for at least $x$ days is of the general form

$$ A_1e^{-\beta_1(x-1)} + A_2e^{-\beta_2(x-1)} $$

(3)

where

$$ e^{-\beta_1} = 1 - r_{12} - r_{13} - r_{15} $$

(4)

$$ e^{-\beta_2} = 1 - r_{25} $$

(5)

$$ A_1 = \frac{r_{25} - r_{13} - r_{15}}{r_{25} - r_{12} - r_{13} - r_{15}} = 1 - k_1 $$

(6)

$$ A_2 = \frac{-r_{12}}{r_{25} - r_{12} - r_{13} - r_{15}} = k_1 $$

(7)

That is, $\beta_1$ and $\beta_2$ are the rates being estimated, $r_{ij}$ represents the transition probability from state $i$ to $j$ and $k_1$ is a constant. By symmetry one can also calculate the probability for the CKD state. Furthermore, it is possible to obtain the number of patients in any state at time $t$, as an example the Death state can be represented as follows:

$$ \frac{dD(t)}{dt} = NS(t)r_{15} + NL(t)r_{25} + CS(t)r_{35} + CL(t)r_{45} $$

(8)

where $NS$ and $CS$ represent the No CKD and CKD short stay states and $NL$ and $CL$ represent the No CKD and CKD long stay states.

3.1. Model Assumptions and Methods

Transitions in this model between states (represented by the arrows in figure 2) occur on a one day cycle length. Often Markov modelling is used to follow patient movement in a health care setting, for example Taylor et al. [10] focused on geriatric patient movement within a hospital and its community. However, the states outlined in this MM are not actual physical places, instead they are a measure of patient kidney function, given eGFR via blood sampling. Considering the average patient does not require daily or even weekly blood samples (unless perhaps hospitalised in departments such as ICU or a dialysis unit etc), it is therefore necessary to assume that a particular patients kidney function remains in the same state (i.e. condition) between blood samples. Furthermore, it is assumed that whichever state a patient initially enters the study, throughout the two year period, then that is where the patients kidney function would have been on the start date 1st Jan 2001, and vice versa for when a patient is leaving the study. A unique code was written in MATLAB [11] to calculate the length of stay before transition to another state for each patient as well as the total number of patients in each state at any given time $t$, where $t$ ranges from 1 to 730 days.

The flow of patients leaving the No CKD or CKD states was obtained by using Kaplan Meier in the software package SAS [12] to construct survivor distribution function estimates which were then fitted to the two-term mixed exponential equations, an example of which are shown in equations 3-7. In addition, the number of patients in the death state were fitted to equation 8 using ordinary differential equations numerically in MATLAB via least squares minimisation. The optimal fits were found using a Nelder-Mead method compiled in the fminsearch function in MATLAB. Simulations were carried out in order to validate the resulting model for age and gender subcategories. The model was further refined using Northern Ireland Statistics Research Agency (NISRA) 2001 death rates [13] as a selection criteria.
Figure 3. The 5 State Markov Model Built in TreeAge
4. TreeAge

TreeAge is a software package designed to facilitate users in building various types of decision trees. In this case, figure 3 displays the resulting MM built in TreeAge using the structure previously illustrated in figure 2 as its basis. The MM is reflected to make a mirror-image of the model to allow for comparison of strategies. The aim of this paper is to use Markov modelling to investigate survival for particular types of kidney patients in relation to their exposure to treatment, namely ACEI/ARBs. This stratification can be seen in the branches labelled ‘No AA’ and ‘AA’. Beyond these branches a Markov node is in place consisting of the 5 established states. A ‘chance’ node is attached to each state followed by the path (branches) a patient may travel. Below these branches the transition probabilities are stored (in this case in the form of tables since the model is age and gender dependent as discussed below). These branches also have a ‘terminal’ node placed at the end represented by a triangle; this indicates the last event in each path during a cycle. At this point a patient is redirected to a state for the next cycle length provided the model has not terminated (in this case the model is set to run for 40 years, that is 14,600 cycle lengths).

It is important to note that the patients who die from the No CKD state are patients who belong to groups 1-3 (see figure 1) and must move to the death state using transition probabilities \(r_{15}\) or \(r_{25}\). Alternatively, patients in groups 4-5 die from the CKD state and journey via transition probabilities \(r_{35}\) or \(r_{45}\). An adjustment must be made to these death probabilities \(r_{15}, r_{25}, r_{35}\) and \(r_{45}\) (see figure 2), using the previously calculated relative risk values (0.515 for RR groups 1-3 and 0.728 for RR groups 4-5). Consider as an example \(r_{15}\), firstly for patients who did not receive the drug

\[
\text{New } r_{15} = \frac{\text{Original } r_{15}}{(\text{RR group } 1-3 \times (\frac{\text{Total AA}}{\text{Total Pats}} + \frac{\text{Total No AA}}{\text{Total Pats}}))}
\]

and then for patients who did receive the drug

\[
\text{New } r_{15+} = \text{RR group } 1-3 \times (\text{New } r_{15-})
\]

Similar calculations were performed for the three remaining death probabilities \(r_{25}, r_{35}\) and \(r_{45}\) at each age level and for both genders.

4.1. Features and Limitations

Transition probabilities were recorded for every age group 18-40, 40-50, 50-60, 70-80 and 80+ year olds. However since the optimal effects were found for 60+ year olds, this means that the initial age for each subject in the tree is defined as 21,900 (since the cycle length is recorded in days) which can be observed at the start node in figure 3. This feature allowed the model to track patients over time and adjust their transitions accordingly by selecting the appropriate row in the tables used (namely NoAA or AA). A special feature is built into the model regarding gender, whereby it is defined and randomly assigned at the start node according to the ratio of females:males above 60 years of age in the dataset. This is generated using the statement gender=if(rand<=0.581;1;2) where 1 represents females and 2 the males. Therefore branches of the tree are able to select the appropriate column in a table dependent on gender. It is essential in TreeAge to indicate what state(s) subjects should enter the model by indicating a proportion ranging from 0 to 1. This MM assumes that all patients initially enter via No CKD short or CKD short states. To calculate the proportions accurately, the first blood sample for all 60-70 year old patients in the dataset was recorded and grouped depending if the eGFR was greater than 60mls/min (No CKD state) or below that value (CKD state) thus resulting in proportions 0.794 and 0.206 respectively. All other states were rewarded a 0 to indicate that subjects should not enter the model via this route, as can be seen beneath the states in figure 3.

One limitation of the five state MM is that the short stay states lose their patients throughout the 2 year study period. Considering the model in TreeAge spans 40 years (that is the model has been set to terminate after 14,600 cycle lengths), this meant that after a period of time patients would move to No CKD long, leaving them no route to enter the CKD state. In order to allow the model to function realistically in TreeAge over long time periods a logic branch was added to the tree using a function known as ‘modulo’. This loops the patients in the No CKD state back into the No CKD short state, on two yearly intervals, hence reassesses their kidney function and allows for transition to CKD state, if necessary, which clinically resembles real life in that patients are often reassessed via a visit to their local GP.

4.2. Survival

At each state an incremental reward was added to tally the average life years gained for the no treatment MM versus the treatment MM. A state reward is a specified value that is assigned to individuals when they spend one cycle in a particular state. For this model, a variable was defined at the start node as ‘ALE’ which equalled \(1/365\) considering cycle length is one day. Running the analysis on both strategies and plotting the outcome shows the difference in survival (see figure 4). Graphically, patients 60 years of age and above receiving ACEI/ARBs who are rapidly declining have significantly higher survival (solid line) than those
who do not receive the treatment (dashed line). The significance of this result was strengthened by adjusting transition probabilities according to patients RR for groups 1-3 and 4-5 separately, over all age groups and gender; thus indicating that it is worthwhile to categorise patients in this way in order to maximise knowledge on the effects of these drugs. In addition the incremental reward showed a difference of 3.9 life years gained for patients on ACEI/ARBs.

Methods outlined above were repeated for other forms of AHT drugs (not including ACEI/ARBs) however it is important to note that these drugs did not have a significant effect on death when calculating the RR.

5. Conclusions and Further Work

A five state Markov model (MM) has been successfully created for Northern Ireland Chronic Kidney Disease (CKD) patients using a unique, robust technique for calculating transition probabilities. This paper has shown that the devised three point assessment and categorisation is a worthwhile method of observing patient kidney function. This assessment emphasises the amount of patients who potentially required Nephrology care in 2001/2002 but were not being captured by the system possibly due to non-referral or lack of resources. Relative risk was used for a practical example of how the MM could be exploited in the software package TreeAge. It explored the effect of treatment drug ACEI/ARBs and found that 60+ year old patients who were rapidly declining (>5mls/min/year) were less likely to die when prescribed with ACEI/ARBs compared to those without the treatment. Further work will involve attaching costs and utilities to the model in order to evaluate the cost-effectiveness of administering these drugs to more CKD patients, which also explores the suggestion that primary care could have a high impact in caring for CKD patients hence relieving the pressure of secondary care facilities. The model will be expanded to seven states, involving the separation of the current CKD state to include an End Stage Renal Failure state for dialysis patients.

References