Elderly men with renal dysfunction are most at risk for poor outcome after neck of femur fractures

Sameer K. Khan1, Stephen P. Rushton2, Michael Courtney1, Andrew C. Gray1, David J. Deehan1

1Royal Victoria Infirmary, Newcastle University Hospitals NHS Trust, Newcastle upon Tyne, UK
2School of Biology, Newcastle University, Newcastle upon Tyne, UK

Abstract

Background: both acute and chronic renal dysfunction (ARD and CRD) have been reported to influence outcomes after neck of femur fractures. We have examined the relationship between the length of stay, mortality and renal dysfunction using biomarkers. These included pre-operative (admission) serum concentrations of urea, creatinine and albumin, and estimated glomerular filtration rates (eGFR) derived from four- and six-variable Modification of Diet in Renal Disease (MDRD) study equations.

Methods: complete outcomes data for 566 patients and the patterns of variations in the biomarkers were analysed using generalised linear models. Cox-proportional hazard analyses investigated the association between kidney function (as assessed by the above-mentioned biochemical data) and post-operative length of stay and mortality. All patients were stratified for CRD according to their eGFR.

Results: serum urea and creatinine were significantly, positively correlated with age. After adjusting for age and sex, risk of mortality was positively related to six-variable eGFR and creatinine, and marginally so for urea. One-year mortality risk thus worsened with stages of CRD (1–4), increasing age and male gender. Risk of discharge from trauma ward, the length of stay in trauma ward and the overall length of stay were not related to urea and creatinine, but were negatively related to both four- and six-variable eGFR.

Conclusions: the study has identified elderly renal-impaired males as the subgroup of patients most at risk for poor survival. This subgroup may require a more targeted approach to the management of their fluid and electrolyte homeostasis to help improve their outcomes.

Keywords: neck of femur fractures, renal impairment, post-operative survival, MRDR formulae, older people

Introduction

Mortality after neck of femur (NOF) fracture remains high. Future improvements in outcome could be aided by the reliable identification of patient risk factors that predict prolonged hospital stay and increased mortality rates, at the time of initial presentation. Pre-existent chronic renal disease (CRD) may deleteriously influence outcomes through an enforced delay to surgery and associated limited mobility. NOF fracture and its subsequent reconstruction represent major insults to endovascular homeostasis and may adversely impair renal function through systemic hypovolaemia and renal hypoperfusion, causing an acute-on-chronic effect [1]. On hospital admission there is a short window of opportunity to optimise medical care prior to surgical intervention. NICE recommendations [2] include surgical stabilisation of these injuries within 36 h of diagnosis. The surgeon must balance the recognised risks of surgical delay against the need to medically optimise each patient’s physiological status prior to surgery. The aim of this study was to examine the relationship between the length of stay, mortality and renal dysfunction in a cohort of NOF fracture patients. Our null hypothesis was that altered renal function would not
influence the length of stay and mortality after NOF fracture and surgery.

**Methods**

A retrospective observational cohort study was conducted after institutional ethics approval classified this study as an in-service evaluation of practice. Prospectively collected data on 1,029 consecutive NOF fractures admitted from the emergency department of a tertiary referral hospital over a 24-month period (December 2008–December 2010), and treated surgically at its trauma unit, were considered for inclusion. Patients’ notes were reviewed for information on demographics and physiological status (ASA grade). Blood results were accessed from the online pathology results system (ICE™, Sunquest Information Systems Ltd., Norwich, UK).

eGFR was calculated using both four- and six-variable MDRD study equations [3, 4]. Data on the time of surgery were collected from theatre records. Exclusion criteria included patients with incomplete data, those with pathological fractures, age <65 years, and patients whose samples were not processed due to haemolysis. This produced the final data set of 566 patients. All patients were stratified for CRD using the five-stage classification adopted by the National Kidney Foundation [5].

All patients received intravenous fluids in the peri-operative period and had their fractures treated surgically. All patients were given NSAID-sparing analgesia, unless they were already on such medication for rheumatoid disease or other related conditions. A uniform blood transfusion policy was in place during this study period. Urinary tract infections were treated with antibiotics as per hospital antimicrobial guidelines. The daily medical management of all patients was supervised by an orthogeriatrician. Data on in-patient mortality and the length of stay were obtained from the hospital records, whereas community mortality data were gathered from the NHS Care Records Service [6].

We investigated the relationship between biomarkers (urea, creatinine and eGFR) at admission and length of stay and post-discharge survival (outcomes) using event analysis. We used Cox proportional hazards analysis [7] to investigate the association between these biomarkers, and length of stay in trauma ward, length of stay in rehabilitation ward, total length of stay in hospital and post-operative survival of patients, while adjusting for patient demographics of age and sex. We first fitted full models with all explanatory variables and identified the best model by a stepwise removal of non-significant variables. For significant models’ modelling post-operative survival, we assessed the assumptions of proportionality of hazard using the Schoenfeld residuals following the methodology of Therneau and Grambsch [8]. We then used the best models for each biomarker to predict the survival of males and females with levels of individual biomarkers for individuals of different ages in the highest and lowest quartiles of those observed in the data set.

**Results**

**Demographics**

The cohort of 566 patients included 427 females and 139 males. The mean age was 80.6 years (median 82; range 65–100 years). The mean ASA grade was 2.9 (SD: 0.7). There were a total of 567 fractures (one patient had simultaneous bilateral injuries) including 255 (45%) extracapsular and 311 (55%) intracapsular fractures.

**Biochemical data**

Our institution’s laboratory reference values range for urea and creatinine were 3.3–6.8 mmol/L and 77–133 μmol/L, respectively. The mean (range) urea and creatinine at admission were 8.1 mmol/L (1.7–31.8 mmol/L) and 96.6 μmol/L (37–779 μmol/L), respectively (Supplementary data are available in Age and Ageing online, Appendix 1). 79.7% patients had some degree of renal impairment (Stage 2 or worse), as depicted in Table 1. Serum urea and creatinine were significantly correlated ($t = 17.3239$, $P < 0.001$). These were also significantly, positively correlated with patient age, although the relationship was stronger for urea than creatinine ($t = 5.4924$, $P < 0.001$; creatinine $t = 2.2434$, $P = 0.025$).

**Hospital stay**

The mean post-operative length of hospital stay was 19 days. Risk of discharge from trauma ward, length of stay on the rehabilitation ward and total length of hospital stay were not related to levels of urea and creatinine. Risk of discharge was negatively associated with both four- and six-variable eGFR ($z = 2.81$, $P = 0.0226$ and $z = 2.715$, $P = 0.00662$, respectively), indicating that patients with high eGFR were more likely to be discharged earlier from hospital than those with renal dysfunction.

**Table 1. Five stages of CRD (adapted from the National Kidney Foundation [5]) and the percentages of patients in each stage**

<table>
<thead>
<tr>
<th>Stage of CRD</th>
<th>%age of patients</th>
<th>One-year survival</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19.9</td>
<td>0.819</td>
<td>0.775</td>
<td>0.858</td>
</tr>
<tr>
<td>2</td>
<td>41.8</td>
<td>0.779</td>
<td>0.741</td>
<td>0.816</td>
</tr>
<tr>
<td>3</td>
<td>33.3</td>
<td>0.734</td>
<td>0.666</td>
<td>0.802</td>
</tr>
<tr>
<td>4</td>
<td>3.7</td>
<td>0.709</td>
<td>0.617</td>
<td>0.802</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The 1-year survival probabilities (95% limits) are tabulated for patients in each stage.
Mortality

The 30-, 90-, 120-day and 1-year mortality rates for all patients were 5.8, 10.7, 12.9 and 19.1%, respectively. After adjusting for age and sex, risk of mortality was positively related to serum creatinine and marginally so for urea (Supplementary data are available in Age and Ageing online, Appendix 2). Increased age and male gender were associated with a higher mortality risk. The high correlation between serum urea and creatinine meant that inclusion of both markers in a single model would lead to confounding and so the model is not presented here. Analysis of the Schoenfeld residuals for the creatinine model (Figure 1) suggested that the proportionality of hazard assumptions were not true for age and gender ($\chi^2 = 3.6272, P = 0.057$ and $\chi^2 = 3.8054, P = 0.051$, respectively). Being male and having high serum creatinine leads to a substantially lower survival probability 2 years after injury (Supplementary data are available in Age and Ageing online, Appendix 3).

Risk of mortality was significantly and negatively related to the six-variable eGFR ($z = -2.099, P = 0.0358$), but not for four-variable eGFR ($z = -1.474, P = 0.14$). Models based on log-transformed eGFR were significant for both four- and six-variable models ($z = -3.534, P = 0.00041$ and $z = -3.105, P = 0.0019$). The assumption of proportionality was met in all models (Supplementary data are available in Age and Ageing online, Appendix 4). Figure 2 illustrates predicted survival curves for patients admitted with CRD classes 1–4, whereas Table 1 summarises their probabilities of 1-year survival (with associated confidence limits). There were too few cases in class 5. It is evident that the probability of survival declined with the extent of disease, although the confidence limits were very wide and overlapped for all classes of disease.

Discussion

This study has examined the association between commonly used indices of renal function and outcome for patients with NOF fracture. There were four key findings. Firstly, serum urea and creatinine at admission did not reliably

Figure 1. Diagnostic plots showing constancy of Cox regression coefficients through time for the model relating survival to blood creatinine levels, age and sex at admission. The plot shows Schoenfeld residuals against time measured in days since admission.
predict in-patient length of stay; secondly, the risk of mortality was significantly related to creatinine; thirdly, the six-variable eGFR was significant risk factor for mortality and fourthly, male gender and advancing age significantly and reliably predicted the poorest outcome. This work has thus identified the very elderly, renal-impaired male as the ‘most at risk’ patient subgroup.

The relationship between renal dysfunction and NOF fracture remains complex. The use of admission values, which can be expected to be higher than baseline for patients after fracture haemorrhage (and the associated hypotension), may have produced acute and temporary renal dysfunction [1]. However, most elderly patients with moderate to severe CRD are known to be at an increased risk of sustaining a NOF fracture [9–13]. Our data show that 80% of patients were CRD class 2 or worse (with 4.7% in class 4 or worse levels of dysfunction). In the wider population, the prevalence of dysfunction is an order of magnitude lower at 7.7 and 0.4%, respectively [14].

The exclusion of a number of patients due to incomplete medical records is a potential limitation of this study. However, its methodology has allowed for the analysis of a data set across a large and wide-ranging cohort of patients. Owing to the potential pitfalls with using creatinine alone, we have tried to standardise by using eGFR. The MDRD formulae (four- and six-variable) were used in preference to the Cockcroft–Gault equation [15], as the latter has been reported by some researchers to overestimate GFR [16]. Renal dysfunction undoubtedly leads to raised serum creatinine and decreased eGFR, and the strong correlation found in our opinion is relevant and makes serum creatinine and eGFR useful markers that could help predict outcomes.

Delayed surgical intervention has been shown to lead to increased hospital stay [17]. Pre-operative medical optimisation [18] and early mobilisation [19] are generally associated with a decreased length of stay in this fracture cohort. However, in this study, we found a correlation between the eGFR and the length of stay, but this effect was not observed for urea and creatinine. We believe this is due to the unreliability of such an outcome given the confounding influences of surgical delay, medical comorbidities, post-operative complications and logistics (e.g. lack of community beds, unavailable assisted-care facilities and need for special transport).

Both acute renal dysfunction (ARD) [1, 20] and CRD [21] are associated with higher early mortality. White et al. [22] found 30-day mortality to be significantly higher in all patients with a reduced GFR. Singh Mangat et al. [23] demonstrated that raised urea and creatinine, and a reduced eGFR, were all significantly related to 30-day mortality. Lewis has previously reported that urea is a prognostic indicator for longer-term survival out to 2 years. We did not
find this effect, and feel that creatinine is a more reliable indicator, as pre-renal factors (that would normally increase urea) have little influence on creatinine, and hence on the eGFR.

Both male gender and increasing age are associated with a poorer outcome after NOF fractures. Frost et al. [24] demonstrated similar findings in a large (n > 1,500) mixed patient cohort, where male sex and increasing age were clear and independent risk factors for increased early hospital mortality. A large population-based study in New South Wales found males aged more than 85 years to have the poorest 1-year cumulative relative survival [25]. A recently published meta-analysis of 94 publications involving 64,316 patients found advancing age and male gender to be the strongest two pre-operative predictors of mortality [26]. In the present work, the risk of post-operative mortality with increased age at admission decreased with time. Similarly, the risk of mortality for males initially increased and then stabilised a year after surgery. This might reflect a degree of post-operative recovery, or a ‘survival of the fittest’ effect where the frailest and most vulnerable patients initially belonged to these cohorts (male and/or elderly), but with time their relative proportion decreased to become more balanced in terms of medical co-morbidity compared with the younger and female groups.

In summary, this work has confirmed the importance of admission indices of renal function upon survival for NOF patients. In particular, we have refined the key variables and shown the interplay between, such, gender and age. The elderly male with raised serum creatinine and diminished eGFR is most at risk for poor survival. This highlights the need for a focused multidisciplinary approach (orthogeriatricians, nephrologists, anaesthetists etc.) in this subgroup, with the expectation of an improved outcome for the cohort as a whole. This would include pre-operative stratification using creatinine and six-variable eGFR, optimisation of fluid and electrolyte balance and biochemical surveillance to monitor and ensure post-operative homoeostasis.

**Key points**

- Serum urea and creatinine levels at admission do not reliably predict the in-patient length of stay.
- The risk of mortality is significantly related to the creatinine level at admission.
- The six-variable eGFR was a significant risk factor for mortality. Male gender and advancing age significantly and reliably predicted the poorest outcome.

**Acknowledgements**

The authors would like to thank Prof. Tim Goodship, professor of renal medicine at Newcastle University, for his valuable suggestions in this work.

**Conflicts of interest**

None declared.

**Supplementary data**

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

**References**

16. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the Modification of Diet in Renal Disease
Adult macronutrient intake and physical capability in the MRC National Survey of Health and Development

U. ZEINAB MULLA1, RACHEL COOPER1, GITI D. MISHRA1, DIANA KUH1, ALISON M. STEPHEN2*

1MRC Unit for Lifelong Health and Ageing, 33 Bedford Place, London, WC1B 5JU UK
2MRC Human Nutrition Research - Population Nutrition and Health, Elsie Widdowson Laboratory, 120 Fulbourn Road, Cambridge CB1 9NL, UK

*Address of the correspondence to: A. M. Stephen. Tel: (+44) 1223 426356; Fax (+44) 1223 437515.
Email: alison.lennox@mrc-hnr.cam.ac.uk

Abstract

Background: poor physical capability is associated with higher subsequent risk of disability and mortality in older people. Energy and macronutrient intakes may play a role in the maintenance of physical capability. This analysis aimed to examine the role of intakes of energy and the macronutrients, protein, carbohydrate and fat in early and mid-adulthood on objective measures of physical capability in later adulthood in the MRC National Survey of Health and Development (1946 British birth cohort).

Methods: adult diet assessed by a 5-day diary at 36 years (1982) and 43 years (1989). Physical capability was assessed at 53 years. Objective measures were height, weight and three measures of physical capability: grip strength, standing balance time and chair rises.