The long-term effects of developing renal failure post-coronary artery bypass surgery, in patients with normal preoperative renal function

John Chalmers, Neeraj Mediratta, James McShane, Mathew Shaw, Mark Pullan and Michael Poullis*

Department of Cardiac Surgery, Liverpool Heart and Chest Hospital, Liverpool, UK

* Corresponding author. Liverpool Heart and Chest Hospital, Thomas Drive, Liverpool L14 3PE, UK. Tel: +44-0151-2281616; fax: +44-0151-2932254; e-mail: mike.poullis@lhch.nhs.uk (M. Poullis).

Received 24 January 2012; received in revised form 20 April 2012; accepted 27 April 2012.

Abstract

OBJECTIVES: Renal failure post-cardiac surgery is associated with an increased in hospital morbidity and mortality. We investigated the effect of new onset renal risk, injury or failure [risk, injury, failure, loss and end-stage kidney disease (RIFLE)] post-coronary artery bypass graft (CABG) on long-term survival, in patients with normal preoperative renal function.

METHODS: The effect of developing postoperative renal risk, injury or failure as defined by the RIFLE criteria on the long-term survival of patients undergoing isolated CABG with a normal renal function was studied. Two separate multivariate analyses were performed based on preoperative serum creatinine or glomerular filtration rate (GFR). Univariate, multivariate, interaction and confounding factor analyses were performed.

RESULTS: A total of 4029 isolated CABG patients were included in the study. 46.5% of patients had chronic kidney disease (CKD) stage 1 (GFR >90 ml/min/1.73 m²), 50.4% had CKD stage 2 (GFR 60–89 ml/min/1.73 m²) and 3.1% had CKD stage 3 (GFR 30–59 ml/min/1.73 m²) on admission, despite having a normal serum creatinine. The study group had a median follow-up of 3.6 years (95% CI 0–13.7). Renal risk, injury and failure were associated with a significantly reduced long-term survival (P < 0.001). In patients with normal preoperative serum creatinine, Cox regression analysis revealed that age (P = 0.026), preoperative creatinine (P = 0.006) and logistic EuroSCORE (P < 0.0001) were significant factors in addition to the development of postoperative renal risk, injury or failure (P < 0.0001), with regard to determining long-term survival. A confounding factor analysis revealed that discharge creatinine (P = 0.0001) and discharge GFR (P = 0.0006) were significant determinants of long-term survival. In patients with a preoperative GFR >90 ml/min, Cox regression analysis revealed that diabetes (P = 0.004) sex (P = 0.019) and logistic EuroSCORE (P < 0.0001), were also significant factors in addition to the development of postoperative renal risk, injury or failure (P < 0.0001) with regard to determining long-term survival. A significant interaction between diabetes and the development of renal risk, injury or failure exists (P = 0.04). A confounding factor analysis revealed that discharge creatinine was a significant determinant (P = 0.0001) of long-term survival, and discharge GFR was not.

CONCLUSIONS: Despite being a biochemically reversible process, the development of renal risk, injury and failure as defined by the RIFLE criteria post-cardiac surgery in patients with a normal preoperative renal function is associated with a significantly worse long-term outcome.

Keywords: Coronary • Survival • Renal • EuroSCORE

INTRODUCTION

Renal failure post-cardiac surgery is associated with an increase in hospital morbidity and mortality [1, 2]. Numerous factors have been identified as causative, and have prompted the development of predictive models [3]. The success of modern renal replacement therapy has dramatically improved the prognosis in the acute setting of renal failure [4]; however, the long-term outcome of those who develop acute renal failure post-cardiac surgery is significantly worse than those who do not [5, 6].

Creatinine is known to be a poor marker of renal function compared with glomerular filtration rate (GFR) [7]; however, its use remains widespread [6, 8]. The normal range of adult serum creatinine varies slightly from laboratory to laboratory, and between different populations, however, an upper limit of 120 μmol/l for males and 110 μmol/l for females is frequently used [9]. A GFR above 90 ml/min is usually classified as normal.

We investigated the effect of new onset renal risk, injury or failure post-coronary artery bypass graft (CABG) on long-term survival, in patients with normal preoperative renal function.

METHODS

Institutional review

Local institutional review was granted for this retrospective analysis of a prospective cardiac surgery database that is validated by an independent data analysis department.
Patients

All patients with a normal preoperative creatinine, from a single institution who had undergone isolated coronary artery bypass surgery were included, n = 4029, between 1 April 1997 and 31 March 2010.

Benchmarking

We benchmarked our in-hospital mortality figures against the UK national results.

Renal risk, injury, failure, loss and end-stage kidney disease criteria

The risk, injury, failure, loss and end-stage kidney disease (RIFLE) criteria [10] were utilized in this manuscript: risk—increased creatinine × 1.5 or GFR decrease >25, injury—increased creatinine × 2 or GFR decrease >50%, failure—increase creatinine × 3 or GFR decrease >75. Loss and end-stage renal disease data were not available. Patients with risk, injury or failure were combined as our marker of renal failure for analysis. The highest creatinine postoperatively was utilized for the determination of the RIFLE stage.

Glomerular filtration rate estimation


Chronic kidney disease stage

Chronic kidney disease (CKD) stage is defined as: stage 1 GFR ≥90 ml/min/1.73 m², stage 2 GFR 60–89 ml/min/1.73 m², stage 3 GFR 30–59 ml/min/1.73 m², stage 4 GFR 15–29 ml/min/1.73 m² and stage 5 GFR <15 ml/min/1.73 m² [12].

Normal range

We defined normal preoperative renal function in two ways. A GFR >90 ml/min, or a serum creatinine <120 µmol/l for males and 110 µmol/l for females. The analysis for each definition of ‘normal’ was performed separately.

Patient characteristics

Patient characteristics are shown in Table 1.

National strategic tracing

As previously described, the national strategic tracing service in the UK [13] was utilized to study the effect of renal failure and impairment on long-term survival. This service tracks all deaths of patients who undergo treatment at a UK hospital, regardless of location(s) of treatment(s), place of death or interval period.

Table 1: Pre-, peri- and postoperative characteristic of patients in study group

<table>
<thead>
<tr>
<th>Data (n = 4029)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Female (%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Heart failure (%)</td>
</tr>
<tr>
<td>Critical preop state (%)</td>
</tr>
<tr>
<td>Previous CVA (%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
</tr>
<tr>
<td>Previous MI (%)</td>
</tr>
<tr>
<td>PVD (%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>Preop IABP (%)</td>
</tr>
<tr>
<td>Ejection fraction</td>
</tr>
<tr>
<td>Good (%)</td>
</tr>
<tr>
<td>Moderate (%)</td>
</tr>
<tr>
<td>Poor (%)</td>
</tr>
<tr>
<td>Previous PCI (%)</td>
</tr>
<tr>
<td>Status</td>
</tr>
<tr>
<td>Elective (%)</td>
</tr>
<tr>
<td>Urgent (%)</td>
</tr>
<tr>
<td>Emergency (%)</td>
</tr>
<tr>
<td>Log EuroSCORE</td>
</tr>
<tr>
<td>Operative</td>
</tr>
<tr>
<td>LIMA (%)</td>
</tr>
<tr>
<td>No. of grafts</td>
</tr>
<tr>
<td>Cross clamp time (min)</td>
</tr>
<tr>
<td>CPB time (min)</td>
</tr>
<tr>
<td>Postoperative</td>
</tr>
<tr>
<td>CKMB</td>
</tr>
<tr>
<td>Peak creatinine</td>
</tr>
<tr>
<td>AKI</td>
</tr>
<tr>
<td>No AKI</td>
</tr>
<tr>
<td>Renal—risk, injury or failure</td>
</tr>
<tr>
<td>Dialysed (%)</td>
</tr>
<tr>
<td>ITU LOS (days)</td>
</tr>
<tr>
<td>AKI</td>
</tr>
<tr>
<td>No AKI</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
</tr>
<tr>
<td>AKI</td>
</tr>
<tr>
<td>No AKI</td>
</tr>
<tr>
<td>Mortality (%)</td>
</tr>
<tr>
<td>Median follow-up (years)</td>
</tr>
<tr>
<td>Mean follow-up (years)</td>
</tr>
<tr>
<td>Long-term mortality (%)</td>
</tr>
</tbody>
</table>

Continuous variables are shown as mean with 95% confidence intervals shown in brackets. Categorical variables are shown as a percentage. BMI: body mass index; CVA: cerebral vascular accident; MI: myocardial infarction; PVD: peripheral vascular disease; IABP: intra-aortic balloon pump; PCI: percutaneous coronary intervention; LIMA: left internal mammary artery; CPB: cardiopulmonary bypass; CKMB: creatinine kinase myocardial isoenzyme; ITU LOS: intensive care length of stay; AKI: acute kidney injury.

Univariate analysis

Kaplan–Meier survival curves were constructed to investigate the effect of acute renal risk, injury or failure on long-term survival. To partially take account of operative risk and complexity,
survival curves for all patients (Fig. 1A) and those with a logistic EuroSCORE <10 (Fig. 1B) were constructed.

**Cox multivariate analysis**

An univariate analysis of all variables was performed first, with the objective of identifying the significant factors for inclusion in a multivariate Cox regression model. Stepwise Cox proportional hazards regression analysis was utilized for the study. Entry criteria was $P < 0.05$ and removal criteria was $P > 0.1$. Cox risk adjusted survival curves (Figs 2 and 3) were created to demonstrate the effect of postoperative renal risk, injury and failure on long-term survival. The covariates were plotted at their mean.

Two separate analyses were performed for all CABG patients: patients with a normal preoperative creatinine and patients with a preoperative GFR >90 ml/min.

**Interaction analysis**

An interaction analysis [14] was performed between logistic EuroSCORE, preoperative GFR and diabetes and the development of renal risk, injury and failure, with regard to long-term survival.

**Confounding factor**

The possible confounding effect of residual abnormalities of discharge creatinine and GFR on long-term survival in patients was analysed.

**Statistical software**

All statistical analysis was performed with MedCalc for Windows (version 12.1.4, MedCalc Software, Mariakerke, Belgium).

**RESULTS**

**Patients**

The preoperative and operative characteristics of the patients, $n = 4029$, included in this study are shown in Table 1. The study group had a median follow up of 3.6 years (95% CI 0–13.7).

![Figure 1](https://example.com/fig1.png)

**Figure 1:** Survival curves for (A) all patients, and (B) those with a logistic EuroSCORE <10, $n = 2840$. Yes and no indicate the development of any of the RIFE criteria postoperatively.

![Figure 2](https://example.com/fig2.png)

**Figure 2:** Risk adjusted survival depending on the development of renal risk, injury or failure post-CABG, (A) normal preoperative creatinine, (B) preoperative GFR >90 ml/min. Yes and no indicate the development of any of the RIFE criteria postoperatively.
artery usage and CKD stage were excluded from the model.

Benchmarking

Benchmarking failed to reveal any significant difference in our in hospital mortality rates compared with the rest of the UK.

Chronic kidney disease breakdown

46.5% (n = 1873) of patients had CKD stage 1, 50.4% (n = 2030) had CKD stage 2 and 3.1% (n = 125) had CKD stage 3 on admission, despite having a normal serum creatinine. The correlation coefficient between preoperative serum creatinine levels and preoperative GFR was $r = -0.85$ ($P < 0.001$).

Univariate analysis

3.9% (n = 157) of patients with a normal preoperative serum creatinine (n = 4029), and 3.0% (n = 56) of patients with a preoperative GFR > 90 ml/min (n = 1873) developed renal risk, injury or failure.

Renal risk, injury and failure (n = 140) were associated with a significantly reduced long-term survival ($P < 0.0001$; Fig. 1A). This association of renal risk injury and failure (n = 98) also existed for those with a logistic EuroSCORE < 10 (n = 2840, $P < 0.0001$) (Fig. 1B).

Multivariate analysis

Normal preoperative serum creatinine. A Cox regression analysis revealed (Table 2) that age, preoperative creatinine and logistic EuroSCORE were also significant factors in addition to the development of postoperative renal risk, injury or failure with regard to determining long-term survival. Age, body mass index, diabetes, sex, preoperative GFR, internal mammary artery usage and CKD stage were excluded from the model.

Preoperative glomerular filtration rate > 90 ml/min. A Cox regression analysis revealed (Table 2), that diabetes, sex and logistic EuroSCORE were also significant factors in addition to

<table>
<thead>
<tr>
<th>Table 2: Cox proportional hazards model for normal preoperative creatinine, and preoperative GFR &gt; 90 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent variable</td>
</tr>
<tr>
<td>Normal preoperative creatinine</td>
</tr>
<tr>
<td>RIF</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>EuroSCORE</td>
</tr>
<tr>
<td>Preoperative creatinine</td>
</tr>
<tr>
<td>Preoperative GFR &gt; 90 ml/min</td>
</tr>
<tr>
<td>RIF</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>EuroSCORE</td>
</tr>
</tbody>
</table>

RIF: postoperative renal risk, injury or failure.

Interaction analysis

Normal preoperative serum creatinine. No evidence of any interaction between preoperative GFR, logistic EuroSCORE and diabetes or preoperative GFR and renal risk, injury or failure was found.

Preoperative glomerular filtration rate > 90 ml/min. No evidence of any interaction between preoperative GFR and logistic EuroSCORE, or preoperative GFR and renal risk, injury or failure was found. There was a, however, a significant interaction between diabetes and the development of renal risk, injury or failure ($P = 0.04$).

Confounding factor analysis

Normal preoperative serum creatinine. Discharge creatinine ($P = 0.0001$) and GFR ($P = 0.0006$) was a significant determinant, of long-term survival. The preoperative and discharge creatinines were significantly different ($P < 0.0001$) (preop mean 85, SD15.4, discharge mean 96, SD36.9), and the preoperative and discharge GFR were significantly different ($P < 0.0001$) (preop mean 102, SD22.1, postop mean 96, SD29.5), for the whole group.

Preoperative glomerular filtration rate > 90 ml/min. Discharge creatinine was a significant determinant ($P = 0.0001$) of long-term survival, and discharge GFR was not. The preoperative and discharge creatinines were significantly different ($P < 0.0001$).
In conclusion, despite frequently being a biochemically reversible process, the development of renal injury and failure as defined by the RIFLE criteria post-cardiac surgery in patients with a normal preoperative GFR is associated with a significantly worse long-term outcome. The exact mechanism of this association needs further investigation.

LIMITATIONS

Renal function was assessed solely on a derived GFR. This technique may miss subtle renal dysfunction that pre-exists in some patients, predisposing them to develop renal impairment failure post-CABG.

We do not have any post-hospital discharge creatinine data to assess if the creatinine fell to preoperative levels.

Our database does not allow the accurate delineation of CKD stage 0 and 1, as we did not document renal abnormalities in urine or imaging studies. We grouped them together which is incorrect by the strict definition of the CKD classification system, but we feel this does not interfere with the conclusions of the paper.

Conflict of interest: none declared.

References


