

# Renal Disease Is Associated With Poor Outcomes Following Isolated Coronary Artery Bypass Grafting



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## ABSTRACT

**Background:** People with renal disease have a markedly higher risk of cardiovascular disease as well as morbidity and mortality after cardiac surgery. Little is known regarding the post-operative adverse outcomes following isolated coronary artery bypass graft (CABG) in the Australian population with renal disease.

**Objectives:** The aim of this study was to examine the effect of different stages of renal disease on patients' risk of post-operative mortality and complications following isolated CABG in an Australian cohort.

**Methods:** Using the ANZSCTS (Australian and New Zealand Society of Cardiac and Thoracic Surgeons) registry, data from 44,968 patients who underwent isolated CABG between 2001 and 2014 were used. The effect of renal disease stages on short- and long-term outcomes were examined using multivariable logistic and Cox's regression methods respectively.

**Results:** Three of 4 Australian patients (74.6%) who underwent isolated CABG had some degree of renal disease: 50.2% mild; 20.9% moderate; 2.1% severe; and 1.6% dialysis-dependent. Adjusted risk of 30-day mortality increased with deteriorating renal disease from mild (1.6-fold) to dialysis-dependent (4.6-fold). Worsening renal disease was also associated with higher risk of post-operative complications. Hazard ratio for long-term survival shows steady increase of mortality risk with worsening renal disease categories from 1.1-fold for mild to 3.9-fold for patients on dialysis.

**Conclusions:** Pre-existing renal disease is significantly associated with 30-day and long-term mortality, length of intensive care unit and hospital stay as well as several other post-operative complications.

Renal disease (RD) patients have a markedly higher risk of cardiovascular disease [1,2], which is a leading cause of morbidity and mortality among these patients [2–4]. Further renal impairment remains a major risk factor for morbidity and mortality after cardiac surgery [5,6]. A number of studies have shown that RD is a powerful and independent predictor of poor outcomes following isolated coronary artery bypass graft (CABG) [5,7–14]. The majority of these studies, however, were based on a single center [7–13]. Little is known regarding the range of post-operative adverse outcomes that surgeons may expect following CABG in the Australian population. Moreover data are scarce regarding long-term survival, intensive care unit stay, and length of hospital stay. This has significant financial implications on hospital resource utilization for patients undergoing cardiac surgical procedures. The ability to predict the impact of pre-operative renal function on these outcomes may hold the potential to significantly improve the delivery of higher quality and cost-conscious patient care. The study aims to examine the relationship of RD stages

with operative outcome that includes post-operative complications and short- and long-term mortality.

## MATERIAL AND METHODS

### The ANZSCTS database

The ANZSCTS (Australian and New Zealand Society of Cardiac and Thoracic Surgeons) database registry was established in 2001. Since 2001, the program has expanded to include 28 public hospitals and 6 private hospitals across Australia. In each center, a data manager is responsible for the completeness and accuracy of the data collection. The types of cardiac procedures in the database were classified as isolated CABG, valve(s) only, valve(s) + CABG, and others (coded 0, 1, 2, and 3, respectively, in the registry). Pre-operative risk factors, intraoperative details, and post-operative 30-day mortality and complications were also recorded. The long-term mortality was ascertained by record linkage with the National Death Index for the Australian Institute of Health and Welfare. This study has been approved by the Monash University Human

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Research Ethics Committee. The study population was defined as all eligible patients ( $n = 84,135$ ) who underwent isolated CABG ( $n = 44,968$ ) between 2001 and 2014 in Australia and New Zealand.

### GFR and RD staging

The last serum creatinine recorded within 1 week as a pre-operative check-up criteria was used to calculate patients' glomerular filtration rates (GFR). The pre-operative creatinine was missing for 0.01% of patients, and they were excluded from the analysis. The GFR was estimated using the Chronic Kidney Disease—Epidemiology Collaboration (CKD-EPI) creatinine equation for male and female subjects [15]. Patients on dialysis were categorized as a separate group to examine the effect of pre-operative dialysis on isolated CABG outcomes. The remaining were classified into 4 stages (normal:  $\text{GFR} \geq 90 \text{ ml/min/1.73 m}^2$ ; mild:  $\text{GFR} 60 \text{ to } 89 \text{ ml/min/1.73 m}^2$ ; moderate:  $\text{GFR} 30 \text{ to } 59 \text{ ml/min/1.73 m}^2$ ; severe:  $\text{GFR} < 30 \text{ ml/min/1.73 m}^2$ ) [16].

### Exposure and outcome definition

Definitions of post-operative outcomes are available in the [Online Appendix](#).

### Statistical analysis

Summary statistics were reported using mean  $\pm$  SD for continuous data and percentages for categorical data. Multivariable mixed-effect logistic regression was used to assess the association between RD status with post-operative outcomes adjusting for hospital variation and AusSCORE (Australian System for Cardiac Operative Risk Evaluation) II predictors, which include age, sex, ejection fraction estimate, previous cardiac surgery, urgency of procedure, New York Heart Association functional class,

inotrope administration, myocardial infarction, peripheral vascular disease, anticoagulant medication, cardiogenic shock, and intravenous nitrate administration [17]. Multivariable mixed-effect linear regression was used to assess the association of RD with operative events adjusting for hospital variation [17]. Kaplan-Meier survival curve and Cox proportional hazard regression model were used for survival analysis. Proportional hazards assumptions were checked using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals.

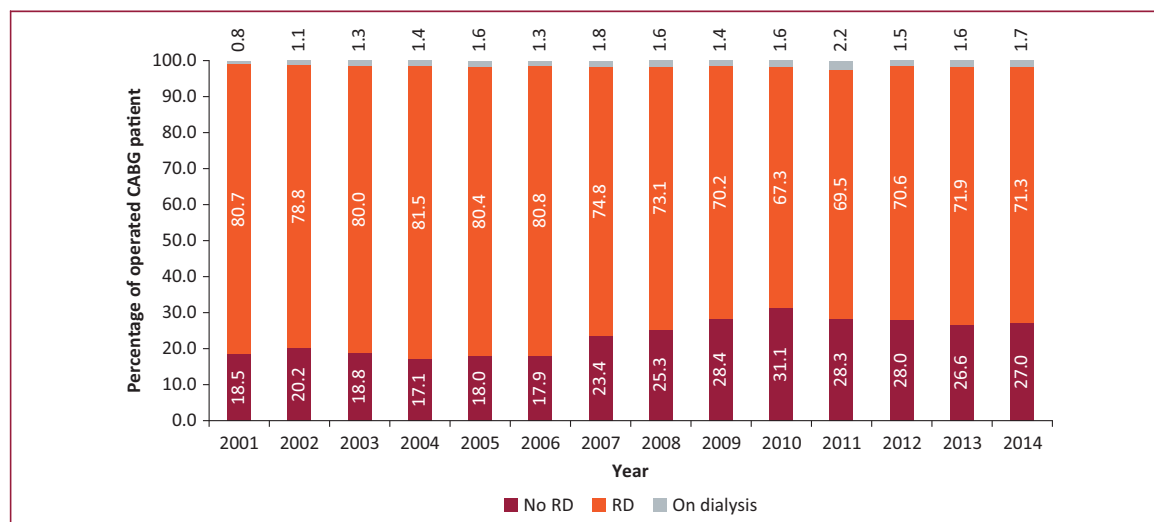
Our data had some missing values that ranged between 3.8% for New York Heart Association functional class and 0.02% for age. Ejection fraction estimate, readmission within  $\leq 30$  days, and perioperative myocardial infarction had 2.2%, 1.4%, and 0.2% of the data missing, respectively. The percentage of missing observations in the remaining variables was  $< 0.2\%$ . Overall, 6.9% patients had at least 1 missing value. Missing data were imputed using the multiple imputation by chained equations method. All analyses were performed using Stata software version 14 (Stata Corp., College Station, Texas).

## RESULTS

### Baseline characteristics

Figure 1 depicts the distribution of RD among patients who had undergone isolated CABG from 2001 to 2014. Over this period, the prevalence of RD among patients have declined overall, yet it hovers around 70%.

The average age of the patients was  $65.4 \pm 10.4$  years, of them 79.4% were male. Overall, 61.4% patients were categorized as “elective,” 34.6% were “urgent,” 3.7% were “emergency,” and 0.2% were “salvage.” Based on estimated GFR categories, only one-quarter (25.3%) of the patients had undergone isolated CABG but had no RD. Around, 50.2% had mild RD, 20.9% had moderate RD, 2.1% had



**FIGURE 1.** Secular trend in renal impairment and dialysis dependence among patients undergoing isolated coronary artery bypass graft (CABG). RD, renal disease.

severe RD, and 1.6% were on dialysis. Results presented in Table 1 show that across worsening RD categories, patients were older, more often diabetic and hypertensive, and more likely to have comorbidities such as respiratory disease, peripheral vascular disease, and cerebrovascular disease. There was a marked increase in the frequency of cardiac comorbidities with worsening RD categories. Table 2 shows that, in general, there appears an increasing trend of 30-day mortality and complications with worsening RD.

### Association of RD with post-operative events after adjusting for AusSCORE II predictors

Results presented in Table 3 show that worsening RD was significantly associated with 30-day mortality as well as post-operative complications namely prolonged ventilation (>24 h), post-operative cerebrovascular disease, cardiac arrest, deep sternal infection, septicemia, gastrointestinal tract complication, multisystem failure, return to theater, and readmission. Risk of 30-day mortality increases

**TABLE 1.** Descriptive statistics for patients' demographic and clinical characteristics by RD stages

	No RD n = 11,376 (25.3%)	Mild RD n = 22,550 (50.15%)	Moderate RD n = 9,403 (20.91%)	Severe RD n = 933 (2.07%)	Dialysis n = 706 (1.57%)
<b>Demographics</b>					
Age, yrs	58.0 ± 9.1	67.0 ± 9.4	72.4 ± 8.3	70.5 ± 10.3	63.0 ± 10.6
Female	14.8	18.7	30.7	34.9	23.7
BMI, kg/m <sup>2</sup>	29.0 ± 7.8	28.8 ± 10.1	28.8 ± 8.2	29.2 ± 8.8	28.4 ± 5.9
BSA >1.73 m <sup>2</sup>	76.9	77.1	75.8	73.6	72.6
Ever smoking	72.1	65.1	61.0	61.9	61.1
<b>Pre-operative noncardiac</b>					
Diabetes	33.5	30.9	41.6	55.7	64.0
Hypercholesterolemia	80.4	80.7	82.4	83.7	81.5
Hypertension	73.2	78.9	87.7	90.4	86.4
CBVD	6.3	9.3	15.9	18.1	15.9
PVD	7.1	10.3	17.4	22.5	26.5
Respiratory disease	9.9	11.9	15.5	14.5	15.3
<b>Pre-operative cardiac</b>					
Previous MI	53.1	51.1	57.8	67.1	61.6
Current CHF	3.7	4.8	9.8	16.9	13.5
NYHA functional class IV	2.5	3.9	6.4	11.6	9.5
Cardiogenic shock	1.3	1.2	2.5	4.5	3.0
Resuscitation	0.9	0.7	1.2	2.3	0.9
Previous heart surgery	3.1	3.8	5.1	4.2	4.0
Ejection fraction <30%	3.1	3.4	6.1	7.7	5.8
Arrhythmia	5.7	8.6	13.2	14.6	13.1
Pacemaker in situ	0.5	1.0	1.9	2.5	1.6
Left main disease >50%	24.7	26.8	28.7	27.9	23.4
3-vessel disease	68.2	70.7	74.8	77.6	72.3
<b>Operative</b>					
<b>Operative status</b>					
Elective	61.6	62.9	58.8	54.3	55.2
Urgent	34.0	33.8	36.7	39.9	40.4
Emergency	4.1	3.2	4.2	5.5	4.1
Salvage	0.2	0.1	0.3	0.3	0.3
Intra-aortic balloon pump	5.2	4.7	6.5	8.5	6.1
IV nitrate at day of surgery	6.4	6.1	7.7	9.0	7.0
Inotropes at day of surgery	1.6	1.6	2.5	3.2	3.6
Anticoagulants at day of surgery	23.5	21.8	23.8	25.2	22.6
Steroid use at surgery	1.2	1.3	2.2	2.3	3.3
Immunosuppressive treatment	1.4	1.7	2.4	2.9	4.4

Values are mean ± SD or %.

BMI, body mass index; BSA, body surface area; CBVD, cerebrovascular disease; CHF, congestive heart failure; IV, intravenous; MI, myocardial infarction; NYHA, New York Heart Association; PVD, peripheral vascular disease; RD, renal disease.

**TABLE 2.** Descriptive statistics for intraoperative events and post-operative outcomes by RD stages

	No RD n = 11,376 (25.3%)	Mild RD n = 22,550 (50.15%)	Moderate RD n = 9,403 (20.91%)	Severe RD n = 933 (2.07%)	Dialysis n = 706 (1.57%)
<b>Intraoperative events</b>					
Perfusion time, min	89.7 ± 40.4	90.0 ± 37.4	93.0 ± 39.7	92.1 ± 41.6	91.5 ± 43.4
Cross-clamp time, min	64.5 ± 31.4	64.5 ± 30.4	65.8 ± 30.8	63.4 ± 30.3	61.3 ± 32.6
<b>Post-operative outcomes</b>					
Septicemia	0.5	0.7	1.3	2.5	2.6
Pneumonia	3.5	3.6	5.2	5.4	7.0
Deep sternal infection	0.5	0.5	1.0	1.2	2.3
Post-operative CBVD	0.5	1.0	2.1	1.5	1.7
Peri-operative MI	0.8	0.8	0.9	1.0	1.1
Prolonged ventilation >24 h	6.0	7.1	12.0	17.2	17.5
New cardiac arrhythmia	20.4	28.9	33.8	31.3	31.7
Cardiac arrest	0.7	1.0	1.9	2.6	3.3
Red blood cells transfusion	33.6	39.5	55.5	66.0	71.7
Continuous coma	0.1	0.2	0.5	0.4	0.3
Anticoagulation complications	0.2	0.3	0.6	1.5	0.6
GIT complications	0.6	1.0	1.6	3.1	2.8
Multisystem failure	0.3	0.6	1.3	2.6	2.6
Return to theater	3.4	4.4	6.8	7.6	9.7
Readmission within ≤30 days	8.1	8.8	10.8	13.3	22.8
Any post-operative complication	50.0	56.7	63.5	62.9	66.2
30-day mortality	0.5	1.2	2.6	5.0	4.5
<b>Post-operative events</b>					
Hours in ICU	46.6 ± 55.5	51.0 ± 89.0	67.6 ± 108.0	93.3 ± 138.1	99.2 ± 175.4
Days in hospital	10.6 ± 11.2	11.4 ± 10.7	14.3 ± 12.7	17.9 ± 14.2	19.8 ± 17.7

Values are mean ± SD or %.  
GIT, gastrointestinal tract; ICU, intensive care unit; other abbreviations as in Table 1.

between 1.6- to 4.6-fold for mild to dialysis-dependent patients, respectively. Table 4 shows that with worsening RD, there is an increasing trend in length of intensive care unit (ICU) stays and total hospital stays.

### Association with long-term survival

The Kaplan-Meier survival estimates for each category of RD were presented in Figure 2. A statistically significant decreasing survival is evident with worsening RD status (log-rank p value < 0.001). The multivariable hazard ratio (HR) for long-term survival shows steady increase with worsening RD categories: for mild RD, the HR = 1.1 (95% confidence interval [CI]: 1.0 to 1.2); for moderate RD, the HR = 1.5 (95% CI: 1.3 to 1.7); for severe RD, the HR = 2.5 (95% CI: 2.1 to 2.9); and for the patients on dialysis, the adjusted HR = 3.9 (95% CI: 3.4 to 4.7) compared with no RD.

### DISCUSSION

This study provides valuable data on the risk of adverse outcomes among patients with RD undergoing CABG surgery. The findings are synonymous with the published evidence, this illustrates the important relationship of RD

with cardiac surgical outcomes [6,18,19]. As three-fourths (74.6%) of patients with isolated CABG in Australia had a degree of RD, the issue warrants adequate attention of a surgeon prior to the surgery.

Increasing severity of renal dysfunction in our study was found to be associated with worsening post-operative outcomes following CABG in the Australian patient cohort. RD stages were found to be predictors for 30-day mortality as well as for the risk of prolonged ventilation (>24 h), cardiac arrest, deep sternal infection, septicemia, gastrointestinal tract complications, multisystem failure, return to theater, and readmission. These findings support the evidence presented by previous studies [5,7–14] that there exists a strong independent effect of RD stages on poor outcomes following isolated CABG. The study by Cooper et al. [5] reported almost similar finding to ours. Cooper et al. [5], however, had also found that with worsening RD, there is an increase in the risk of stroke and deep sternal infection after isolated CABG. In the current study, no progressive increase was observed in the risk of stroke across RD stages, whereas the risk of deep sternal infection was higher for moderate RD and dialysis groups. However, an increase in the risk of red blood cell transfusion and septicemia were found in this study.

**TABLE 3.** Adjusted relationship between RD and post-operative complications following isolated CABG

	Mild RD	Moderate RD	Severe RD	Dialysis
	n = 22,550 (50.15%)	n = 9,403 (20.91%)	n = 933 (2.07%)	n = 706 (1.57%)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Prolonged ventilation, >24 h	1.1 (1.0–1.2)	1.6 (1.4–1.8)*	2.1 (1.7–2.5)*	2.7 (2.1–3.3)*
Post-operative CBVD	1.5 (1.1–2.0) <sup>†</sup>	2.2 (1.6–3.1)*	1.5 (0.8–2.7)	2.3 (1.2–4.2) <sup>†</sup>
Perioperative MI	1.1 (0.8–1.5)	1.2 (0.8–1.6)	1.0 (0.5–2.2)	1.3 (0.6–2.7)
New cardiac arrhythmia	1.1 (1.1–1.2)*	1.2 (1.1–1.2)*	1.1 (0.9–1.3)	1.5 (1.3–1.8)*
Cardiac arrest	1.2 (0.9–1.6)	1.9 (1.4–2.6)*	2.1 (1.2–3.5) <sup>†</sup>	3.4 (2.1–5.6)*
Pneumonia	1.1 (0.9–1.2)	1.3 (1.1–1.6)*	1.2 (0.9–1.8)	1.7 (1.2–2.4) <sup>†</sup>
Deep sternal infection	0.8 (0.6–1.2)	1.5 (1.0–2.2) <sup>‡</sup>	1.7 (0.9–3.4)	3.8 (2.1–6.8)*
Septicemia	1.3 (0.9–1.8)	2.0 (1.4–2.9)*	3.5 (2.1–5.1)*	4.2 (2.3–7.5)*
Anticoagulation complication	1.1 (0.7–1.8)	1.5 (0.9–2.6)	3.1 (1.5–6.4) <sup>†</sup>	1.7 (0.5–5.3)
GI complication	1.4 (1.0–1.9) <sup>‡</sup>	1.8 (1.3–2.5) <sup>†</sup>	3.1 (1.9–4.9)*	3.3 (1.9–5.6)*
Multisystem failure	1.8 (1.1–2.8) <sup>‡</sup>	2.5 (1.5–4.2) <sup>†</sup>	3.7 (2.0–6.7)*	5.6 (2.6–12.3)*
Return to theater	1.1 (1.0–1.3)	1.5 (1.3–1.8)*	1.7 (1.3–2.3)*	2.5 (1.8–3.4)*
Readmission	1.1 (1.0–1.2)	1.2 (1.1–1.4)*	1.4 (1.2–1.9)*	2.9 (2.4–3.5)*
Any complication	1.0 (1.0–1.1) <sup>‡</sup>	1.2 (1.1–1.3)*	1.2 (1.0–1.4) <sup>‡</sup>	1.8 (1.5–2.1) <sup>‡</sup>
30-day mortality	1.6 (1.2–2.1) <sup>†</sup>	2.1 (1.5–2.9)*	3.0 (1.9–4.6)*	4.6 (2.9–7.6)*

Reference category—no RD. Odds ratio (OR) and 95% confidence interval (CI) were generated employing multivariable mixed-effect logistic regression for adjusting hospital variation and AusSCORE (Australian System for Cardiac Operative Risk Evaluation) variables as potential confounders. Statistical significance: \*p < 0.001; <sup>†</sup>p < 0.01; <sup>‡</sup>p < 0.05. Abbreviations as in Tables 1 and 2.

The rate of 30-day mortality was lower (1.63%) in our study compared with in the study by Cooper et al. (2.52%) [5]. Our study, however, showed that the effect of RD stages on the risk of 30-day mortality after accounting for other risk factors is slightly higher across all stages of RD when compared with the study by Cooper et al. [5]. One possible explanation for this finding is that the use of the CKD-EPI creatinine equation is more accurate in estimating GFR than the MDRD equation is [20], which was used by Cooper et al. [5]. Another possible explanation is that in the current study, the effect of RD stages was adjusted for a different set of risk factors that were found to be significantly related to 30-day mortality in the Australian risk prediction (AusSCORE II) model [17]. The AusSCORE II is a parsimonious 30-day mortality risk prediction model following isolated CABG where the model was developed using bootstrapping methods [21,22]. Cooper et al. [5]

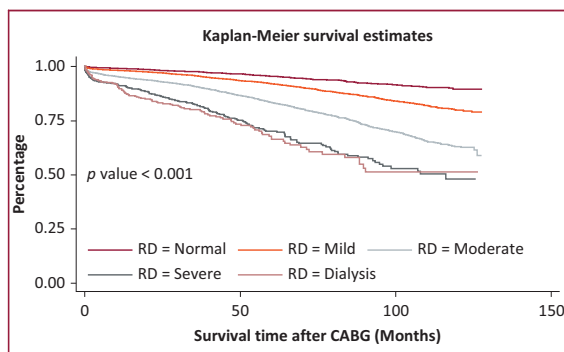
adjusted the effect of RD stages for all variables in the AusSCORE II model except for inotropes, anticoagulation, and intravenous nitrates. They also used another 18 additional variables for adjustment. Three of these 18 variables—aortic stenosis, mitral valve insufficiency and per-cutaneous coronary intervention within 6 h before the procedure—were not available in the ANZSCTS registry and the remaining variables did not appear as significant in the AusSCORE II model [17].

Possible explanation of the association between RD and worse outcomes after CABG surgery lies in the link between renal dysfunction and adverse cardiovascular events. Cardiovascular disease by itself is a frequent consequence of renal dysfunction [3]. Impairment of endothelial function in renal dysfunction patients is probably the key process that leads to atherosclerosis, which subsequently leads to increased prevalence of

**TABLE 4.** Adjusted relationship of RD and intraoperative and post-operative events

	Mild RD	Moderate RD	Severe RD	Dialysis
	n = 22,550 (50.15%)	n = 9,403 (20.91%)	n = 933 (2.07%)	n = 706 (1.57%)
	$\beta$ (95% CI)	$\beta$ (95% CI)	$\beta$ (95% CI)	$\beta$ (95% CI)
Perfusion time	−0.5 (−1.4 to 0.4)	0.4 (−0.8 to 1.5)	−1.9 (−4.6 to 0.6)	−1.9 (−4.8 to 0.9)
Cross-clamp time	−0.5 (−1.2 to 0.2)	−0.2 (−1.1 to 0.7)	−2.8 (−4.8 to −0.8)*	−3.5 (−5.7 to −1.3)*
Hours in ICU	3.0 (0.9 to 5.2) <sup>†</sup>	12.4 (9.6 to 15.1) <sup>‡</sup>	27.3 (21.3 to 33.4)	34.9 (28.0 to 41.7)
Days in hospital	0.1 (−0.2 to 0.3)	1.5 (1.1 to 1.8) <sup>‡</sup>	4.1 (3.3 to 4.9) <sup>‡</sup>	6.5 (5.7 to 7.5) <sup>‡</sup>

Reference category—no RD. Beta coefficient ( $\beta$ ) and 95% CI were generated employing multivariable mixed-effect linear regression for adjusting hospital variation and AusSCORE variables as potential confounders. Statistical significance: \*p < 0.05; <sup>†</sup>p < 0.01; <sup>‡</sup>p < 0.001. Abbreviations as in Tables 1 to 3.



**FIGURE 2. Kaplan-Meier probability of survival after isolated CABG by RD stage.** Abbreviations as in Figure 1

cardiovascular disease and many other morbidities [23]. Furthermore, RD may lead to abnormal calcium and/or phosphate metabolism, anemia, extracellular fluid volume overload, hypertension, electrolyte imbalance, oxidative stress, peripheral vascular disease, and abnormal lipid and glucose levels [24–26]. Hence the assault caused by cardiac surgery is likely to affect the already labile and ailing coronary microvasculature and body homeostasis and make the patient susceptible to development of worse outcomes following surgery.

Additionally, RD contributes to impaired platelet function, increasing patients' risk for perioperative bleeding complications that may affect convalescence time. Further impaired renal function may also delay the convalescence following any surgery, which is correctly reflected in our finding of increasing trend in ICU stay and length of hospital stay with worsening RD category. Cloyd et al. [27] showed, with the example of abdominal surgery, that any degree of pre-operative kidney impairment, even mild asymptomatic disease, was associated with clinically significant increases in 30-day post-operative morbidity and mortality following major surgery.

Our study showed RD as a significant predictor of longer ICU and hospital stay as well as poor long-term survival. Chonchol et al. [9] reported similar findings regarding long-term survival among patients with CABG with renal dysfunction. They showed that pre-operative moderate-to-severe RD is an independent long-term predictor of cardiovascular events and total mortality after CABG [9]. Dacey et al. [28] reported a similar impact among dialysis-dependent patients with CABG.

The strong association between RD and the longer ICU and hospital stays should encourage clinicians to consider the fiscal and logistic dimensions, as well as the clinical benefit-risk balance. As worsening kidney function leads to increasing ICU and hospital stays, it may affect benchmarking of institution and surgeons. LaPar et al. [29] reported similar finding as ours. They went further and showed that worsening RD also results in incurring higher costs, while optimizing renal function before heart surgery can substantially improve the outcomes and lower the

costs. They proposed the use of pre-operative renal function assessment for predicting cost and resource utilization. This has important implications especially for resource-limited developing countries where the prevalence of CKD is rising due to the rising prevalence of diabetes and hypertension.

The prospective collection of the data and the large study population that comes from 34 centers throughout Australia are 2 very strong aspects of this study. Another factor that adds strength to this study was the use of CKD-EPI creatinine equation to calculate estimated GFR, which has improved accuracy compared with other GFR estimation equations [20]. The examination of various demographic, clinical, and intraoperative risk factors also give strength to this study. However, renal function measurements were based on a single serum creatinine value, and it was not possible to examine the effect of a rising or falling creatinine trajectory, which is a limitation of this study. Using a single creatinine value to define stages of RD might also lead to misclassification of the exposure. Another limitation of this observational cohort study is the descriptive nature that makes it prone to residual confounding and that causal associations cannot be confirmed from the findings.

This study concludes that pre-existing renal dysfunction is a significant predictor for 30-day and long-term mortality, length of ICU and hospital stays, and on many other post-operative complications. Hence, assessment of pre-operative renal status should be incorporated into clinical risk prediction for mortality and complications following isolated CABG surgery.

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