



Long-term prognosis in patients with end-stage renal disease after coronary artery bypass grafting

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Background: Cardiovascular disease is a major cause of morbidity and mortality in patients with end-stage renal disease (ESRD). Coronary artery bypass grafting (CABG) is beneficial in selected patients with ESRD. This study investigates the survival outcomes and prognostic factors in ESRD patients who underwent CABG.

Methods: A retrospective analysis was performed for 149 patients with ESRD who underwent isolated CABG between 2006 and 2015.

Results: Mean age was 59.4±8.7 years and 106 patients (71.1%) were male. Operative mortality occurred in 20 patients (13.4%). Overall survival was 81.1%±3.2% at 1 year, 41.5%±4.3% at 5 years and 19.2%±4.2% at 10 years. Median survival was 4.3 years. Multivariable analysis identified age [P=0.001, odds ratio (OR): 1.15 per 1-year increase, 95% confidence interval (CI): 1.06–1.25], preoperative left ventricular ejection fraction (LVEF) (P=0.020, OR: 0.94, 95% CI: 0.89–0.99) and non-elective status of operation (P=0.049, OR: 3.34, 95% CI: 1.00–11.1) as predictors of operative mortality. Cox regression analysis identified age [P<0.001, hazard ratio (HR): 1.05 per 1-year increase, 95% CI: 1.03–1.08], New York Heart Association (NYHA) class III or IV status (P=0.010, HR: 1.75, 95% CI: 1.15–2.67) and the use of a left internal mammary artery (LIMA) to left anterior descending artery (LIMA-LAD) graft (P=0.029, HR: 0.42, 95% CI: 0.19–0.92) as factors influencing long-term survival.

Conclusions: CABG is associated with high operative mortality and poor long-term survival in ESRD patients. Age and NYHA class influenced late survival. LIMA-LAD grafting conferred a long-term survival advantage.

Keywords: End-stage renal disease (ESRD); dialysis-dependent renal failure; coronary artery bypass grafting (CABG); coronary artery disease

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Introduction

Cardiovascular disease is prevalent and a major cause of mortality in patients with end-stage renal disease (ESRD). This may be attributed to the presence of pre-existing cardiovascular risk factors and pathological mechanisms present in ESRD, collectively predisposing to atherosclerotic disease (1). ESRD is on the rise in Singapore. According to the Singapore Renal Registry, the age standardized incidence rate of definitive dialysis increased significantly from 165 per million population in 2008 to 180 per million population in 2017. The age standardized prevalence rate of definitive dialysis also increased significantly from 884 per million population in 2008 to 1,059 per million population in 2017 (2). With the increasing prevalence and life expectancy of patients with ESRD, the number of patients with concomitant cardiovascular disease who could potentially benefit from coronary revascularization is expected to increase. Coronary artery bypass grafting (CABG) is recommended over percutaneous coronary intervention (PCI) for coronary revascularization in appropriately selected ESRD patients with multi-vessel disease (3). Patients with ESRD face increased perioperative risks, due to the presence of multiple comorbidities and severe atherosclerosis causing diffuse coronary artery and aortic wall disease. Our study aimed to investigate the survival outcomes and prognostic factors of patients with ESRD who underwent isolated CABG at our tertiary referral centre. We present the following article in accordance with the STROBE reporting checklist (4) (available at <http://dx.doi.org/10.21037/jtd-20-2046>).

Methods

This study is a retrospective case-note and database review of all patients with ESRD who underwent isolated CABG between January 2006 and December 2015 at our institution, a tertiary cardiac surgery referral centre in Singapore. The study population included all patients requiring either haemodialysis or peritoneal dialysis for at least 3 months prior to CABG. Patients with acute renal failure, temporary dialysis or chronic renal failure not requiring dialysis were excluded. Prior to surgery, a non-contrasted computed tomography scan of the chest was performed routinely in all patients with ESRD planned for CABG, to assess the burden of calcific plaque in the aorta, in particular the ascending aorta. This information was

useful to stratify the risk of thromboembolic complications and to plan the most appropriate surgical strategy. The study was approved by the local institutional review board with a waiver of patient consent (reference: 2016/3132). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Definitions

Early or operative mortality was defined as mortality within 30 days and/or death before discharge from the index hospitalization. Elective procedures were defined as routine admissions for surgery. Urgent procedures were defined as patients who were not electively admitted for but required surgery during the current admission for medical reasons. Emergent procedures were those performed before the beginning of the next working day.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as means with standard deviation and analyzed using Student's *t*-test. Categorical data were expressed as percentages and analyzed with the Chi-squared or Fisher's exact test. Survival function was represented using Kaplan-Meier survival curves with 1-, 3-, 5- and 10-year survival estimates. Logistic regression was used to identify predictors of early mortality. Cox regression analysis was used to identify independent predictors of long-term survival. Preoperative and operative variables with a univariable $P < 0.10$ or those judged to be clinically important were entered into the multivariable Cox model. All two-tailed P values < 0.05 were taken as significant.

Results

Between 2006 and 2015, 149 consecutive patients with ESRD underwent isolated CABG at our institution. Preoperative characteristics are shown in *Table 1*. The mean age of patients was 59.4 ± 8.7 years (range, 35–80 years). The mean EuroSCORE II was 3.8 ± 3.5 , ranging from 0.6 to 26.8. Operative variables are summarized in *Table 2*. Thirty-seven patients (24.8%) underwent urgent [29 patients (19.4%)] or emergent surgery [8 patients (5.4%)]. In the urgent surgery group, the indications for surgery were recurrent unstable angina in 24 patients (82.8%), critical left main artery stenosis in 3 patients (10.3%), and hypotension

Table 1 Preoperative variables

Variables	All patients (n=149)
General characteristics	
Age (years)	59.4±8.7
Male/female	106 (71.1)/43 (28.9)
Body surface area (m ²)	1.7±0.2
Co-morbidities	
Diabetes mellitus	109 (73.2)
Hypertension	141 (94.6)
Hyperlipidaemia	113 (75.8)
Peripheral vascular disease	36 (24.2)
Smoking history	48 (32.2)
Cardiac profile	
Number of diseased coronary arteries	2.8±0.4
1	4 (2.7)
2	18 (12.1)
3	127 (85.2)
Left main coronary artery stenosis ≥50%	63 (42.3)
Previous myocardial infarction	107 (71.8)
Left ventricular ejection fraction (%)	43.0±12.6
New York Heart Association Class III or IV	48 (32.2)
EuroSCORE II	3.8±3.5
Renal profile	
Cause of end-stage renal disease	
Diabetes mellitus	106 (71.1)
Hypertension	16 (10.7)
Glomerulonephritis	5 (3.4)
Polycystic kidney disease	3 (2.0)
Systemic lupus erythematosus	3 (2.0)
Renal cell carcinoma	1 (0.7)
Obstructive uropathy	1 (0.7)
Unknown	14 (9.4)
Mode of renal replacement therapy	
Haemodialysis	135 (90.6)
Peritoneal dialysis	14 (9.4)

Values for parametric continuous variables are expressed as mean ± standard deviation. Values for categorical variables are expressed as numbers (%).

during dialysis in 2 patients (6.9%). In the emergent surgery group, surgery was indicated for critical left main artery stenosis with ongoing myocardial ischaemia in 6 patients (75.0%) and ongoing myocardial ischaemia with recurrent ventricular arrhythmias in 2 patients (25.0%). Eleven surgeries (7.4%) were performed off-pump, without the use of cardiopulmonary bypass (CPB). Due to significant ascending aortic calcifications, 21 surgeries (14.1%) were performed on-pump without the use of an aortic cross-clamp and cardioplegia. On-pump beating surgery was the preferred technique in patients where there was sufficient plaque-free area to perform aortic cannulation safely but insufficient safe area for cross-clamping of the aorta. Off-pump surgery was reserved for patients without safe areas for both aortic cannulation and cross-clamping. The in-situ pedicled left internal mammary artery (LIMA) was grafted to the left anterior descending artery (LIMA-LAD) in 140 (94.0%) patients. Nine patients (6.0%) received a saphenous vein graft to the LAD. Within this group, the LIMA was not used in view of haemodynamic stability in 7 patients (77.8%), insufficient LIMA length in 1 patient (11.1%) and poor LIMA quality in 1 patient (11.1%). The mean CPB duration was 95.3±26.8 minutes and the mean aortic cross-clamp time was 50.1±14.4 minutes. The mean number of distal anastomoses was 3.0±0.9.

Early postoperative outcomes

Operative mortality occurred in 20 patients (13.4%) and was higher in patients undergoing non-elective (emergent and urgent) surgery [27% (10 of 37 patients) *vs.* 8.9% (10 of 112 patients), $P=0.005$]. Amongst the 37 patients who underwent non-elective surgery, patients suffering early mortality had a higher EuroSCORE II compared to those who survived (10.4 *vs.* 5.2, $P=0.008$). Operative mortality was 40% (2 of 5 patients) in patients receiving only vein grafts (non-LIMA-LAD group) compared to 25% (8 of 32 patients) in LIMA-LAD graft recipients ($P=0.482$). The median duration of postoperative hospitalization was 11 days (25th percentile: 7 days, 75th percentile: 18 days). Causes of death included multi-organ failure in 11 patients (55.0%), sepsis in 5 (25.0%) and mesenteric ischaemia in 4 patients (20.0%). No patients suffered stroke or limb ischaemia.

Low cardiac output syndrome occurred in 36 patients (24.2%). Postoperative low cardiac output syndrome was associated with lower preoperative LVEF (38.2% *vs.* 44.5%,

Table 2 Operative variables

Variables	All patients (n=149)
Urgency of operation	
Elective	112 (75.2)
Urgent	29 (19.5)
Emergent	8 (5.3)
Number of grafts	3.0±0.9
Left internal mammary artery to left anterior descending artery graft	140 (94.0)
Number of venous grafts	2.1±0.9
Aortic cross clamp time (min) (n=117)	50.1±14.4
Cardiopulmonary bypass time (min) (n=138)	95.3±26.8

Values for parametric continuous variables are expressed as mean ± standard deviation. Values for categorical variables are expressed as numbers (%).

P=0.009), higher EuroSCORE II (6.3 *vs.* 3.0, P<0.001) and higher inpatient mortality [52.8% (19 of 36 patients) *vs.* 0.9% (1 of 113 patients), P<0.001], when compared to patients without this complication. Seventeen patients (11.4%) required insertion of an intra-aortic balloon pump for haemodynamic support.

Sepsis occurred in 32 patients (21.5%). The most common sources of sepsis were pneumonia in 21 patients (14.1%), intra-abdominal in 4 patients (2.7%), central venous catheter in 4 patients (2.7%), superficial sternal wound infection in 3 patients (2.0%), saphenous vein graft harvest site infection in 2 patients (1.3%) and urinary tract infection in 2 patients (1.3%). One patient (0.7%) developed deep sternal wound infection and mediastinitis.

Univariable analysis (*Table 3*) identified age (P<0.001), hyperlipidaemia (P=0.026), LVEF (P=0.005), NYHA class III or IV (P=0.019), left main coronary artery stenosis ≥50% (P=0.007), non-elective status of operation (P=0.01), and EuroSCORE II (P=0.002) as predictors of operative mortality. Multivariable analysis (*Table 4*) showed that age [P=0.001, odds ratio (OR): 1.15, 95% confidence interval (CI): 1.06–1.25], preoperative LVEF (P=0.020, OR: 0.94, 95% CI: 0.89–0.99) and non-elective status of operation (P=0.049, OR: 3.34, 95% CI: 1.01–11.1) were significant risk factors for operative mortality. Being a derived variable, EuroSCORE II (P=0.002) was excluded from multivariable analysis.

Long-term prognosis

Data regarding follow-up was obtained by direct assessment

during scheduled clinic reviews at our institution. Clinical follow-up was 100% complete for the 129 patients who survived to hospital discharge. The mean period of follow-up was 4.0±3.1 years. Ninety-nine patients (66.4%) died during the follow-up period. Kaplan-Meier analysis of long-term overall survival is shown in *Figure 1*. Overall survival was 81.1%, 63.5%, 41.5% and 19.2% at 1, 3, 5 and 10 years, respectively. The median survival was 4.3 years. Multivariable Cox-regression analysis (*Table 5*) showed that age (P<0.001, HR: 1.05, 95% CI: 1.03–1.08), NYHA Class III or IV status (P=0.010, HR: 1.75, 95% CI: 1.15–2.67) and the use of a LIMA-LAD graft (P=0.029, HR: 0.42, 95% CI: 0.19–0.92) were factors influencing long-term survival.

Discussion

There is a rising trend of ESRD worldwide, including in Singapore. Coronary artery disease is prevalent in these patients, with 35.9% of deaths in ESRD patients attributable to cardiac causes (2). This may be attributed to the presence of co-existing cardiovascular risk factors such as hypertension, hyperlipidaemia and diabetes. Pathological mechanisms in ESRD such as chronically elevated inflammatory markers and electrolyte derangements, in particular hypercalcaemia and hyperphosphataemia, predispose to vascular calcification and coronary atherosclerosis. Medical treatment of ESRD patients is challenging due to the presence of multiple concomitant comorbidities and drug interactions.

According to the Singapore Renal Registry, the overall

Table 3 Univariable analysis of factors contributing to operative mortality

Variables	Survivors (n=129)	Non-survivors (n=20)	P value
General characteristics			
Age	58.2±8.2	67.3±8.1	<0.001
Gender			
Male	92 (71.3)	14 (70.0)	0.904
Female	37 (28.7)	6 (30.0)	
Body surface area (m ²)	1.70±0.19	1.70±0.20	0.876
Comorbidities			
Diabetes mellitus	94 (72.9)	15 (75.0)	0.841
Hypertension	122 (94.6)	19 (95.0)	0.937
Hyperlipidaemia	102 (79.1)	11 (55.0)	0.026
History of smoking	42 (32.6)	6 (30.0)	0.820
Peripheral vascular disease	29 (22.5)	7 (35.0)	0.262
Cardiac profile			
Prior myocardial infarction	91 (70.5)	16 (80.0)	0.382
Left ventricular ejection fraction (%)	44.1±12.5	35.8±10.9	0.005
New York Heart Association Class III or IV	37 (28.7)	11 (55.0)	0.019
Left main coronary artery stenosis ≥50%	49 (38.0)	14 (70.0)	0.007
Number of diseased coronary arteries	2.8±0.5	2.8±0.4	0.785
EuroSCORE II	3.2±2.6	7.8±5.6	0.002
Renal profile			
Mode of dialysis (haemodialysis/peritoneal dialysis)	116 (89.9)/13 (10.1)	19 (95.0)/1(5.0)	0.694
Operative variables			
Non-elective surgery	27 (20.9)	10 (50.0)	0.010
Off-pump surgery	10 (7.8)	1 (5.0)	1.000
Cardiopulmonary bypass time (min)	95.7±27.5	93.0±23.1	0.696
Aortic cross clamp time (min)	50.5±14.8	47.8±12.3	0.460
Number of distal anastomoses	3.0±0.9	3.0±0.9	0.943
LIMA to LAD graft	122 (94.6)	18 (90.0)	0.346
Number of venous grafts	2.1±0.9	2.1±0.9	0.888

Values for parametric continuous variables are expressed as mean ± standard deviation. Values for categorical variables are expressed as numbers (%). LAD, left anterior descending artery; LIMA, left internal mammary artery; CI, confidence interval.

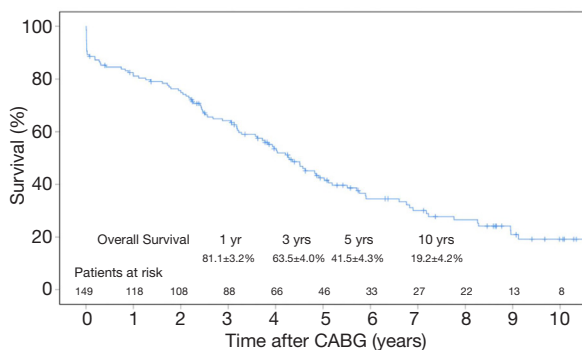
survival of ESRD patients without ischaemic heart disease (IHD) was 92.7% at 1 year, 67.6% at 5 years and 44.9% at 10 years. The median survival was 8.6 years (2). IHD was associated with poorer survival in patients with ESRD (HR 1.50, 95% CI: 1.42–1.57, P<0.001) (2). For

appropriately selected patients with ESRD and multi-vessel coronary artery disease, the 2014 ESC/EACTS guidelines recommends CABG over PCI for revascularization (3). Chang *et al.* analyzed data from the United States Renal Data system and found CABG to be associated with lower

Table 4 Multivariable analysis of factors contributing to operative mortality

Parameter	95% CI	Odds ratio	P value
Age	1.06–1.25	1.15	0.001
Hyperlipidaemia	0.12–1.45	0.42	0.170
Peripheral vascular disease	0.45–5.47	1.57	0.477
Left ventricular ejection fraction	0.89–0.99	0.94	0.020
New York Heart Association Class III or IV	0.63–6.92	2.10	0.225
Left main coronary artery stenosis $\geq 50\%$	0.55–6.80	1.94	0.301
Non-elective operation	1.01–11.1	3.34	0.049

CI, confidence interval.

**Figure 1** Overall survival of ESRD patients after CABG. CABG, coronary artery bypass grafting; ESRD, end-stage renal disease.

risks of death and cardiac events, when compared to PCI (5).

Compared with CABG in patients without ESRD, the perioperative risk and mortality is increased in ESRD patients, due to co-existing extracardiac comorbidities such as diabetes mellitus, cerebrovascular disease, peripheral vascular disease, uraemia, anaemia, mineral bone disease and electrolyte disturbances. Extensive coronary artery calcifications are often encountered in patients with ESRD, making CABG technically difficult. The risks of systemic embolism from aortic manipulation, bleeding and postoperative infections are also higher in patients with ESRD (6). Perioperative fluid management in ESRD patients is particularly challenging, and requires close collaboration between the surgical, intensive care and renal medicine teams.

There are limited studies reporting the long-term outcomes of isolated CABG in patients with ESRD. Sample sizes range from 24 to 152 patients in single-centre reports and larger cohorts of 326 to 14,316 patients from multicenter studies or data from national databases (5,7-14).

Some of these studies include heterogenous populations of patients undergoing both CABG and concomitant valvular or aortic surgery (5,10,14). In a cohort of 6,874 non-ESRD patient and 174 ESRD patients who underwent CABG, Bianco *et al.* identified dialysis dependence as an independent predictor of mortality at 30 days [hazard ratio (HR), 3.86; 95% confidence interval (CI), 2.96, 5.03; $P < 0.001$] (7). In patients with ESRD undergoing CABG, age, diabetes mellitus, peripheral vascular disease, a history of stroke, mode of dialysis, emergent surgery, LVEF, NYHA class, use of CPB and postoperative continuous haemofiltration have been identified as predictors of inpatient mortality and long-term survival (8,11,15-18).

The mean age of our study cohort (59.4 years) is similar to other similar studies, ranging from 63.0 to 65.4 years (5,7,8,11). Early postoperative mortality rates range between 7.8% to 18.7% (7,8,10,11,14,15). The operative mortality rate of 13.4% at our centre is comparable with previous reports. In the present study, age, LVEF and non-elective status of surgery were associated with a higher risk of early mortality. This is consistent with other studies (8,11). Five-year survival of ESRD patients undergoing CABG range widely from 25% to 60% (5,10,11). Takami *et al.* reported a 10-year survival of 36% (11). Results from our study show that the long-term prognosis of patients with ESRD remains guarded despite CABG. Long-term survival following CABG were 81.1%, 41.5%, 19.2% at 1, 5 and 10 years respectively, with a median survival of 4.3 years.

From our study, advanced age and NYHA class III or IV were negative predictors of long-term survival. Other predictors of death during long-term follow-up reported previously include age, peripheral vascular disease, diabetes mellitus, and emergency surgery (10,11). The proportion of patients with diabetes mellitus in studies comprising

Table 5 Multivariable analysis of long-term survival

Parameter	95% CI	Hazard ratio	P value
Age	1.03–1.08	1.05	<0.001
Gender (male)	0.50–1.20	0.80	0.277
Peripheral vascular disease	0.90–2.10	1.30	0.203
Prior myocardial infarction	0.60–1.70	1.00	0.865
New York Heart Association Class III or IV	1.15–2.67	1.75	0.010
Mode of renal replacement therapy (peritoneal dialysis)	0.98–3.50	1.80	0.071
Non-elective surgery	0.97–2.40	1.50	0.064
LIMA to LAD graft	0.19–0.92	0.42	0.029

CI, confidence interval; LAD, left anterior descending artery; LIMA, left internal mammary artery.

patients with ESRD undergoing isolated CABG ranges from 54% to 70% (7,8,11). Although a large proportion (73.2%) of the patients in our study had diabetes mellitus, we did not demonstrate an association with poorer long-term survival.

The presence of an IMA graft significantly improves survival of patients undergoing CABG (19). In the present study, multivariable analysis identified LIMA-LAD grafting as a factor conferring a long-term survival benefit in patients with ESRD. Bechtel *et al.* reported results from a retrospective multi-centre study of 522 patients with ESRD undergoing CABG, of which 326 patients underwent isolated CABG. In this study, the authors found that the use of an IMA graft was associated with a survival benefit in ESRD patients (10). Subsequent renal transplantation was also associated with improved long-term survival (10,12).

The proportion of patients undergoing off-pump surgery in previous reports ranges from 2.7% to 64.4% (7-9,11-13). In the present study, only 7.4% of our cohort underwent off-pump CABG. Several studies have compared off-pump and on-pump CABG in ESRD patients, with varying results. Ariyoshi *et al.* reported significant differences in morbidity rates amongst patients who underwent off-pump CABG compared to those who underwent conventional CABG (16). Ueki *et al.* reported significantly lower surgical mortality (OR: 0.68 95% CI: 0.51–0.90) favouring off-pump CABG (17). Chen *et al.* did not find a significant difference in survival between on and off-pump groups (9).

Limitations

This is a retrospective observational study with inherent biases in data collection. There is a likelihood of selection

bias, as LIMA-LAD grafting may not have been performed in patients who were in a more critical preoperative state. Due to the small sample size, statistical analyses may have been underpowered, especially in the subgroups of patients undergoing off-pump CABG and those not receiving a LIMA-LAD graft. Being conducted at a single centre, the surgical technique and postoperative care adopted were standardized. The same group of surgeons performed the surgeries throughout the study period. However, our results may not be generalizable to all centres. We did not compare outcomes of our surgical cohort with ESRD patients with coronary artery disease who had undergone PCI or received medical therapy alone.

Conclusions

This study investigates the survival outcomes and prognostic factors of 149 patients with ESRD who underwent isolated CABG. Operative mortality was 13.4%. Five and ten-year survival rates were 41.5% and 19.2% respectively. Age, NYHA class, urgency of surgery and preoperative LVEF could be useful prognostic factors for risk stratification. LIMA-LAD grafting conferred a long-term survival advantage and should be the standard of care in ESRD patients undergoing CABG.

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-2046>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the local institutional review board with a waiver of patient consent (reference: 2016/3132). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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