ORIGINAL ARTICLE

Acute kidney injury following coronary artery bypass graft surgery in a tertiary public hospital in Malaysia: an analysis of 1228 consecutive cases

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ABSTRACT

Background: Acute kidney injury (AKI) following cardiac surgery is well established but the reported incidence is variable due to varying definitions and criteria. Furthermore there is a paucity of such data from Southeast Asia.

Objectives: To determine the incidence of AKI, the associated risk factors, and its impact on early mortality and intensive care unit/hospital stay.

Method: This is a single centre retrospective observational study to evaluate outcomes on 1260 consecutive patients from a multi-ethnic Southeast Asian population who underwent a primary isolated coronary artery bypass graft (CABG) operation. Data was collected from the hospital's electronic database and analysed using basic descriptive statistics and logistic regression.

Results: Overall incidence was 36.2% including 5.5% of patients who required renal replacement therapy (RRT). Multivariate analysis identified age, insulin-dependent diabetes mellitus (IDDM), baseline serum creatinine level (SCr), recent myocardial infarction (MI), cardiopulmonary bypass (CPB) time and intra-aortic balloon pump (IABP) use as independent risk factors for AKI. For patients who required RRT, the SCr and IDDM remained independent predictors. Early 30-day mortality (11.5% vs 0.9%) was significantly higher in patients who developed AKI following CABG. Similarly, AKI was associated with a slight but statistically significant increase in intensive care unit (ICU) and hospital stay.

Conclusion: Better prognostication and preventative strategies are required to better risk stratify patients undergoing CABG and optimise utilisation of limited healthcare resources.

KEY WORDS:
Acute kidney injury; AKI; CABG; Coronary artery bypass graft; Southeast Asian

INTRODUCTION

Acute kidney injury (AKI) is one of the known potential major complications of cardiac surgery with a reported incidence of 8.9% to 42.5%,[1-6] depending on the definition. The incidence of AKI in patients with isolated coronary artery bypass graft (CABG) surgery is comparable at 12% to 48.5%,[7-11] with an associated mortality of 12.6%.[10] Of this, 3.8-7.0% of patients would require renal replacement therapy (RRT).[7, 9] Aside from death and the development of end-stage renal failure (ESRF), AKI following CABG is associated with an increased long-term risk of heart failure[11] and stroke.[12]

Currently there is a paucity of data regarding CABG related AKI in South-East Asia. Data from studies in Western populations may vary due to racial, cultural, and geographical differences.

The aim of this study was to determine the incidence of AKI after CABG in our multi-ethnic population and identify contributing risk factors. Additionally, we sought to evaluate the impact of AKI on early mortality and on duration of intensive care unit (ICU) and hospital stay.

MATERIALS AND METHODS

Cohort

This was a single-centre retrospective observational study that evaluated outcomes in 1260 consecutive patients who underwent an isolated primary CABG procedure at our institution (Hospital Serdang) between January 2011 and September 2014. All operations were conducted with use of moderate hypothermic cardiopulmonary bypass and hyperkalaemic induced cardioplegic myocardial arrest. Thirty-two patients with pre-existing renal replacement therapy or eGFR < 15 ml/min were excluded from this study. By definition any patient having a concomitant cardiac procedure or re-do surgery was also excluded. In total 1228 consecutive CABG patients met our inclusion criteria. Our centre serves patients mainly from the central region of Peninsular Malaysia, with a proportionate representation of all major ethnic groups.

Data collection

Data was retrieved from our hospital's electronic database by online review of each patient's individual records. Various pre-operative and intra-operative risk factors with a known or expected association to AKI was collected. We defined AKI as ≥ 50% increase in the serum creatinine (SCr) from baseline

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Table I: Demographic and clinical parameters in the acute kidney injury (AKI) and dialysis dependent AKI (AKI-D) group

Factors	AKI				AKI-D[a]	
	No (783)		Yes (445)		Yes (67)	
	N	%	N	%	N	%
Age (years)[b]	56.3	8.4	60.0	8.3	59.7	7.9
Body mass index (kg/m2)[b]	26.9	4.0	26.6	4.5	26.8	5.3
Baseline serum creatinine (mmol/l)[c]	86	73, 100	95	80, 126	170	119, 253
Bypass Time (min)[c]	127	108, 150	134	116, 162	134	114, 154
Cross-clamp time (min)[c]	71	58, 84	71	59, 90	71	58, 86
Race						
Malay	317	62.0	194	38.0	32	6.3
Indian	227	62.5	136	37.5	19	5.2
Chinese	233	67.7	111	32.3	16	4.7
Others	6	60.0	4	40.0	0	0.0
Gender						
Male	641	63.5	369	36.5	50	5.0
Female	142	65.1	76	34.9	17	7.8
Pre-op left ventricular function (ejection fraction)						
Good (> 50%)	467	67.7	223	32.3	32	4.6
Moderate (31% – 50%)	289	60.0	193	40.0	29	6.0
Poor (≤ 30%)	27	48.2	29	51.8	6	10.7
Status of surgery						
Elective	490	66.1	251	33.9	39	5.3
Urgent	293	60.3	193	39.7	27	5.6
Salvage	0	0.0	1	100.0	1	100.0
Insulin-dependent diabetes mellitus						
No	585	68.2	273	31.8	16	1.9
Yes	198	53.5	172	46.5	51	13.8
Myocardial infarction within 90 days pre-op						
No	650	66.3	331	33.7	56	5.7
Yes	133	53.8	114	46.2	11	4.5
Coronary angiogram within 7 days pre-op						
No	748	64.3	415	35.7	64	5.5
Yes	35	53.8	30	46.2	3	4.6
Intra-aortic balloon pump use during surgery						
No	659	66.6	330	33.4	52	5.3
Yes	124	51.9	115	48.1	15	6.3

[a]AKI-D is treated as a subset of AKI in this study and they are not mutually exclusive.
[b]Reported in mean (SD), [c] Reported in median (first quartile, third quartile)

or a ≤ 25% decrease in eGFR within 72 hours of surgery. This was consistent with the R stage in RIFLE criteria[13] but we excluded the oliguric component due to difficulty in data collection. The baseline SCr was determined using the most recent SCr before surgery, and the eGFR derived from the Cockcroft-Gault equation. Any patient who required RRT at any stage post-operatively during the same admission was categorised as dialysis dependent (AKI-D).

Statistical Analysis
Descriptive analysis were performed, reporting the mean (SD) or median (Q_1, Q_3) for continuous variables, and frequency with percentage for categorical variables. The distribution of variables was confirmed by skewness and kurtosis values (range between ±1) and histogram.

The variables of interest in this study were Age (years), Race (Malay, Chinese, Indian), Gender, BMI (kg/m^2), SCr (mmol/l), pre-operative left ventricular (LV) function (ejection fraction by echocardiography), status of surgery (elective, urgent or emergency), presence of insulin dependent diabetes mellitus (IDDM), myocardial infarction (MI) within 90 days prior to surgery, coronary angiography (COROS) within 7 days of surgery, intra-operative use of an intra-aortic balloon pump (IABP), cardio-pulmonary bypass (CPB) time (min), and aortic cross-clamp time (min). Both primary outcomes of this study, AKI and its subset AKI-D group are not mutually exclusive.

All the variables were analysed in univariate analysis using logistic regression. The crude odds ratio (OR) with 95% confidence interval (CI) and p-value was reported. The significant factors with p-value <0.05 were selected to be included into multiple stepwise logistic regression models. Multicollinearity between the variables were tested in order to confirm that all factors were independent of each other. The variance inflation factor (VIF) value of all the variables from collinearity coefficient statistics showed no serious multicollinearity of < 5. The Hosmer-Lemeshow test showed the dataset fits well to the logistic model (p-value > 0.05).

All data were analysed using SPSS (IBM SPSS version 20.0, IBM. Corp., Armonk, NY, USA).

RESULTS
By definition, the incidence of AKI following CABG in the 1228 consecutive patients evaluated was 36.2% (n=445 patients). This included 67 (5.5%) patients with AKI-D who required RRT. The demographic and clinical characteristics of the patients are summarised in Table I.

Table II: Association of factors with acute kidney injury (AKI) and dialysis dependent AKI (AKI-D) using simple logistic regression

Factors	AKI			AKI-D		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (years)	1.053	1.038, 1.068	<0.001	1.029	1.000, 1.060	0.053
Baseline SCr (mmol/l)	1.016	1.013, 1.020	<0.001	1.031	1.025, 1.036	<0.001
Bypass Time (min)	1.008	1.005, 1.011	<0.001	1.002	0.996, 1.007	0.565
Cross-clamp time (min)	1.007	1.003, 1.012	0.002	1.002	0.992, 1.011	0.738
Pre-op left ventricular function (ejection fraction)						
Good (> 50%)	(ref.)		0.001	(ref.)		0.134
Moderate (31% – 50%)	1.399	1.098, 1.782		1.316	0.785, 2.207	
Poor (≤ 30%)	2.249	1.300, 3.890		2.467	0.985, 6.180	
Status of surgery						
Elective	(ref.)		0.038	(ref.)		0.824
Urgent	1.286	1.015, 1.630		1.059	0.639, 1.754	
Insulin-dependent diabetes mellitus						
No	(ref.)		<0.001	(ref.)		<0.001
Yes	1.861	1.450, 2.390		8.413	4.729, 14.970	
Myocardial infarction within 90 days pre-op						
No	(ref.)		<0.001	(ref.)		0.439
Yes	1.683	1.268, 2.234		0.770	0.397, 1.493	
Intra-aortic balloon pump use during surgery						
No	(ref.)		<0.001	(ref.)		0.534
Yes	1.852	1.391, 2.465		1.207	0.667, 2.183	
Body mass index (kg/m^2)	0.978	0.951, 1.006	0.120	1.010	0.952, 1.074	0.722
Race						
Chinese	(ref.)		0.198	(ref.)		0.579
Malay	1.285	0.963, 1.714		1.370	0.739, 2.537	
Indian	1.258	0.922, 1.715		1.132	0.572, 2.239	
Gender						
Male	(ref.)		0.641	(ref.)		0.096
Female	0.930	0.684, 1.263		1.624	0.918, 2.874	
Coronary angiogram within 7 days pre-op						
No	(ref.)		0.090	(ref.)		0.759
Yes	1.545	0.935, 2.553		0.831	0.254, 2.720	

CI: Confidence interval; OR: Odds ratio; SCr: serum creatinine

Table III: Association of factors with acute kidney injury (AKI) and dialysis dependent AKI (AKI-D) using multiple logistic regression

Factors[a]	AKI			AKI-D		
	OR	95% CI	p-value	OR	95% CI	p-value
Baseline SCr	1.013	1.010, 1.017	< 0.001	1.027	1.022, 1.033	<0.001
Recent MI	1.446	1.057, 1.978	0.021			
Bypass Time	1.007	1.004, 1.010	< 0.001			
IABP during surgery	1.484	1.071, 2.057	0.018			
Insulin dependent DM	1.592	1.207, 2.100	0.001	4.370	2.275, 8.392	<0.001
Age	1.046	1.030, 1.062	< 0.001			

CI: Confidence interval; OR: Odds ratio; SCr: Serum creatinine; MI: Myocardial infarction; IABP: Intra-aortic balloon pump; DM: Diabetes mellitus
[a]All variables significant in univariate analysis were entered into the model. For the AKI group, apart from the factors shown in the table, pre-op left ventricular function, status of surgery, and cross clamp time were also included into the model but not significant in multivariate analysis. For the AKI-D group, only age (not significant), baseline SCr, and insulin dependent DM were included into the model for analysis.

Table IV: Association of acute kidney injury (AKI) and dialysis dependent AKI (AKI-D) towards clinical outcomes[a]

Outcome	AKI				AKI-D			
	No (783)		Yes (445)		No (1161)		Yes (67)	
	Median	Q_1, Q_3	Median	Q_1, Q_3	Median	Q_1, Q_3	Median	Q_1, Q_3
Post-op ICU Stay (days)	3	2, 4	4	2, 6	3	2, 4	7	4, 11
Post-op Hospital Stay (days)	7	6, 9	8	7, 13	7	6, 9	15	10, 21
30-days Mortality[b]	7	0.9	51	11.5	46	4.0	12	17.9

ICU: intensive care unit; Q_1: first quartile; Q_3: third quartile
[a]significant at univariate level, [b]reported in frequency (%)

For AKI cases, the mean patient age was higher compared to non-AKI group. The median baseline SCr and median CPB times were also higher in the AKI group. There was a higher prevalence of patients with poor LV function in those who developed AKI and slightly more urgent (39.7%) versus elective (33.9%) cases in patients with AKI. The incidence of IDDM, MI and IABP use was all higher in the AKI group. All the mentioned variables were significantly associated ($p < 0.05$) at univariate level with crude OR > 1.00 (Table II).

In the AKI-D group, there was a statistically significant higher proportion of patients with IDDM and an elevated pre-operative baseline SCr.

The results of stepwise multivariate analysis for both outcomes; AKI and AKI-D are detailed in Table III. Six variables were associated with AKI, namely age, SCr, IDDM, recent MI, CPB time, and IABP use ($P < 0.05$).

The OR for age was 1.05 with 95% CI (1.03 -1.06). Hence, for every unit increase in age, the odds of having AKI is increased by 1.05. The OR for SCr was 1.01 with 95% CI (1.01, 1.02), indicates that for every unit increase in SCr, the odds of having AKI is increased by 1.01. The DM patient has 1.59 odds (95% CI = 1.21, 2.10) to be associated with AKI compared with the non-diabetic group. The odds of having AKI among those who had an intra-operative IABP was 1.48 (95% CI = 1.07, 2.06). For every minute increase in bypass time, the odds of having AKI will be increased by 1.01. Patients who had a recent MI has 1.45 odds of having AKI (95% CI = 1.06, 1.98). Overall, IDDM had the most impact on AKI status compared to the other variables.

For AKI-D cases, both SCr and IDDM remain associated at multivariate level. An increase in SCr by one unit increased the odds of having AKI-D by 1.03 (95% CI = 1.02, 1.03). The odds of diabetic patients developing AKI-D was 4.37 compared to the non-diabetic group (95% CI = 2.28, 8.39). IDDM has a more significant impact towards AKI-D as compared to the SCr.

There is a significant difference in duration of ICU stay and hospital stay between the AKI and non-AKI groups. However, the difference is only 1 day. The 30-day mortality was significantly higher in the AKI group (11.5%). The findings were similar in the AKI-D group, albeit with greater differences (Table IV).

DISCUSSION

The incidence of AKI following CABG in our population is fairly consistent with published data worldwide despite the various definitions used. The actual incidence in this study might be higher if the oliguria component of the RIFLE criteria was incorporated, as shown in a previous study comparing the incidence of AKI after cardiac surgery with and without the oliguria component as per the Acute Kidney Injury Network (AKIN) criteria. However, the same study also found no significant difference in the measured adverse outcomes when oliguria was omitted.[14]

Independent risk factors identified in our study include a higher pre-op SCr, recent MI within 90 days before surgery, IDDM, age, prolonged CPB duration, and IABP use during surgery, similar to previous studies.[2-6, 15] All the risk factors are known to directly or indirectly cause cellular ischaemia, which is the well-established pathophysiology of AKI following CABG.[16]

A similar study done in Singapore showed that patients of Malay and Indian ethnicity have significantly higher risk of developing AKI post-CABG compared to the Chinese.[2] While our study demonstrated a similar relationship, the association was not significant at univariate analysis. This might be attributed to the different ethnic proportions; majority of our patients are Malay whilst the Singaporeans are predominantly Chinese.

Unfortunately, most of the independent risk factors identified in this study are not modifiable, except prolonged CPB duration and IABP usage. The extent to which we can decrease the CPB time is limited. Perhaps patients with higher risk of AKI should be assigned to a more senior surgeon than a trainee. Off-pump CABG would nullify CPB time, however outcomes to attenuate the incidence of AKI after cardiac surgery[17-20] remain equivocal. Furthermore, there are concerns about durable graft patency and incomplete revascularization with this technique. A more judicious use of the IABP may be required although admittedly most surgeons only use the device prophylactically in patients with poor LV function or for unstable symptoms due to critical anatomy.

Our excellent in-hospital 30-day mortality rate of < 1% in non-AKI patients however increased substantially 13-fold in patients who developed post-operative AKI and there was an alarming 20-fold increase in early mortality for those who required RRT. This illustrates the importance of pre-operative prognostic risk stratification for AKI in patients undergoing CABG and will facilitate a better informed consent process between surgeon and the patient.

Although the median post-operative ICU stay for patients with AKI (but who did not require RRT) was significantly increased by only 1 day, it is actually a 33% increase, and its impact on healthcare costs and utilisation of limited ICU beds and staff will undoubtedly be considerable. The 1-day delay in hospital discharge is most likely a surrogate of a prolonged ICU stay. Unsurprisingly the impact of AKI on patients who required RRT (AKI-D) was greater, with a doubling of duration of ICU and hospital stay. Many patients who developed AKI requiring RRT would have a poorer general condition and other associated comorbidities like pneumonia and sepsis. Severe AKI will naturally require multiple RRT sessions and take a longer time to resolve, hence the prolonged hospital stay. These patients will be predisposed to complications related to a prolonged ICU and hospital stay.

The limitations of this study are inherent to its observational nature (retrospective and non-randomized) and thus may be subject to inherited bias. Our study establishes association but not causality. As a single centre study the sample size is relatively small and the generalizability of this study limited. Nevertheless, our study group was a homogenous isolated CABG population with well-defined criteria and objective outcome measures. We intend to collate data from a much larger sample across several institutions with the aim of developing an accurate, validated and prognostic scoring system to reliably predict AKI post CABG in the region. Further studies should be done to identify more risk factors that are modifiable. Some potentially modifiable risk factors that have shown significant association include preoperative anaemia,[3,21] perioperative red blood cell transfusions, renal vasculopathy[22], and surgical re-exploration,[3] however the evidence is lacking.

In conclusion, AKI following isolated CABG surgery is not an uncommon event that occurred in over a third of our patients. Risk factors include increasing age, diabetes mellitus, a higher pre-operative SCr, recent myocardial infarction, prolonged cardiopulmonary bypass time, and use of an IABP. In view of its significant impact on early mortality and morbidity, and increased healthcare costs as a consequence of prolonged ICU and hospital stays, further studies with a focus on developing a better prognostication tool and preventative strategies in addition to conventional treatment would be beneficial.

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