

Association of ethnicity and acute kidney injury after cardiac surgery in a South East Asian population

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Editors' key points

- This study tested the hypothesis that ethnicity is an independent predictor of postoperative acute kidney injury (AKI) in patients undergoing cardiac surgery in a South East Asian population.
- Ethnicity was shown to be an independent predictor of AKI after cardiac surgery.
- Other clinical risk factors that predicted AKI in this study include hypertension, diabetes mellitus, and poor EuroSCORE.

Background. Postoperative acute kidney injury (AKI) is a frequent and serious complication after cardiac surgery. Clinical factors alone have failed to accurately predict the incidence of AKI after cardiac surgery. Ethnicity has been shown to be a predictor of AKI in the Western population. We tested the hypothesis that ethnicity is an independent predictor of AKI in patients undergoing cardiac surgery in a South East Asian population.

Methods. A total of 1756 consecutive patients undergoing cardiac surgery were prospectively recruited. Among them, data of 1639 patients met the criteria for analysis. There were 1182 Chinese, 195 Indian, and 262 Malay patients. The main outcome was postoperative AKI, defined as a 25% or greater increase in preoperative to a maximum postoperative serum creatinine level within 3 days after surgery.

Results. Five hundred and seventy-nine patients (35.3%) developed AKI after cardiac surgery. Ethnicity was shown to be an independent predictor of AKI after cardiac surgery with Indians and Malays having a higher risk of developing AKI when compared with Chinese patients (odds ratio: Indian vs Chinese 1.44, Malay vs Chinese 1.51).

Conclusions. Indians and Malays have a higher risk of developing AKI after cardiac surgery than Chinese in a South East Asian population. Ethnicity was shown to be an independent predictor of AKI after cardiac surgery.

Keywords: acute kidney injury; cardiac surgery; ethnicity

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Introduction

A significant number of patients undergoing cardiac surgery worldwide experiences complications including acute kidney injury (AKI).¹ Post cardiac surgery AKI occurs in 5–30% of patients, and up to 1% of patients that develop AKI will require dialysis.^{1,2} The effect on patients and healthcare services is amplified as even relatively modest degrees of postoperative AKI were associated with increases in hospital morbidity, mortality, and cost of care.³ Mortality exceeds 60% for patients requiring dialysis.^{2,4} Discharge to an extended-care facility for survivors of a postoperative AKI is increased two- to three-fold compared with those without AKI.

Patient ethnicity in Western populations (Caucasians vs African Americans) independently predicts post-cardiac surgery AKI.⁵ The impact of ethnicity (Chinese vs Indians vs Malays) on AKI in the South East Asian population is however unknown. We tested the hypothesis that ethnicity in this population has an independent association with AKI in patients undergoing cardiac surgery, over and above

known risks of AKI such as increased age, diabetes, poor cardiac reserves, hypertension, and prior cardiac failure.

Methods

With institutional review board approval, we prospectively recruited 1756 patients who underwent cardiac surgery at the two main heart centres in Singapore in 2009 and 2010. Perioperative genetic, safety, and outcomes data were prospectively collected and entered into a cardiac anaesthesia database. Patients who were on either haemodialysis or peritoneal dialysis were excluded. Other exclusion criteria included history of emergency surgery and severe hepatic, cerebrovascular (past history of stroke, transient ischaemic attack, or carotid artery stenosis of >70%), or renal (pre-operative serum creatinine >177 µmol litre⁻¹) disease. Data extracted from the patients include patient characteristics, risk factors, surgical data, and postoperative outcomes up to 30 days post surgery.

Perioperative renal data

Serum creatinine values were obtained daily from the pre-operative day till discharge from the intensive care unit. Pre-operative serum creatinine (CrPre) was the value obtained closest to surgery. Peak serum creatinine (CrMax) was the highest creatinine value obtained within the first 3 post-operative days. The peak fractional change in postoperative serum creatinine level (% Δ Cr) was the primary outcome variable used in the study, defined as the percentage of difference between preoperative serum creatinine and highest postoperative value. This is a continuous variable generally unaffected by baseline renal function. The serum creatinine level is determined by using a dry-slide enzymatic reflectance technique. Creatinine levels typically peak on the second postoperative day and return to baseline by Day 5.

Perioperative anaesthesia, surgical, and perfusion management

Perioperative surgical management and clinical practices at the two heart centres were similar and followed international standards. Typically, anaesthesia was induced with i.v. induction agents (etomidate or propofol) and maintained with balanced anaesthesia regime of low-dose fentanyl ($10\text{--}20\text{ }\mu\text{g kg}^{-1}$) and volatile agents (primarily sevoflurane). Conventional cardiopulmonary bypass circuits with roller pumps, membrane oxygenators, heat exchangers, venous reservoirs, cardiotomy suction, and arterial blood filters were used. Perfusion targets were mild-to-moderate hypothermia ($32\text{--}35^{\circ}\text{C}$), haematocrit levels of $>22\%$, activated clotting times of $>400\text{ s}$, glucose levels of $<10\text{ mmol litre}^{-1}$, non-pulsatile flow rate of $2.2\text{ to }2.4\text{ litre m}^{-2}$, and mean arterial pressure of $50\text{--}70\text{ mm Hg}$. Myocardial protection was achieved with cold blood cardioplegia. Aprotinin was not used in any of the patients.

Patient characteristic variables included several previously reported risk factors for perioperative kidney injury after cardiac surgery, including age, gender, cardiopulmonary bypass time, weight, hypertension, history of diabetes, and preoperative ejection fraction. Other variables included pre-operative use of reno-active drugs such as angiotensin-converting enzyme inhibitors and loop diuretics, and also total cholesterol levels.

Statistical analysis

An initial, unadjusted analysis compared CrPre, CrMax, and % Δ Cr among the three major ethnic groups. Known patient characteristic and surgical risk factors were also compared with Student's *t*-test for parametric data and χ^2 test for non-parametric data. The association of the three major ethnic groups with % Δ Cr was then evaluated with the use of logistic regression analysis. Significant patient characteristic and surgical risk factors were added to the model, and non-significant covariates were removed from the multi-variate analysis in a stepwise manner. *Post hoc* pair-wise comparison between the ethnic groups was performed manually.

Analyses were performed with the use of SPSS 18.0 (SPSS, Inc., Chicago, IL, USA); significance was judged at $\alpha=0.05$.

Results

Out of 1756 patients, 1639 patients met the criteria for analysis. One hundred and seventeen patients were not included in the analysis because of incomplete data (11 patients) or belonging to other ethnic groups (106 patients). Of 1639 patients, 1182 were Chinese, 262 were Malays, and 195 were Indians. Baseline clinical details are shown in Table 1. Overall, 32.7% of Chinese, 42.7% of Malay, and 41% of Indians developed AKI after cardiac surgery (Fig. 1). Those who developed AKI were more likely to be older, female, hypertensive, diabetic, and with poor ventricular function. These patients also had longer cardiopulmonary bypass times and aortic cross-clamping times (Table 2). A total of 21 patients (1.3%) developed a new need for dialysis. The creatinine level at discharge in patients with AKI was $111.9 \pm 86.4\text{ }\mu\text{mol litre}^{-1}$ (range: $30\text{--}903\text{ }\mu\text{mol litre}^{-1}$).

Table 1 Clinical characteristics and acute kidney injury after cardiac surgery. Figures are *n* (%) or mean \pm sd. AKI, acute kidney injury; LVEF, left ventricular ejection fraction

	AKI	No AKI	P-value
<i>n</i>	579	1060	
Age (yr)	61.6 ± 9.9	57.2 ± 10.8	<0.001
Female gender	147 (25.4%)	207 (19.5%)	0.006
History of hypertension	473 (81.7%)	744 (70.2%)	<0.001
Ethnicity			
Chinese	387 (32.7%)	785 (67.3%)	0.002
Malay	112 (42.7%)	150 (57.3%)	
Indian	80 (41%)	115 (59%)	
History of diabetes mellitus	310 (53.5%)	445 (42%)	<0.001
LVEF 30–50%	198 (34.2%)	356 (33.6%)	0.812
LVEF $<30\%$	71 (12.3%)	69 (6.5%)	<0.001
EuroSCORE (logistic)	5.3 ± 7.0	3.5 ± 4.7	<0.001

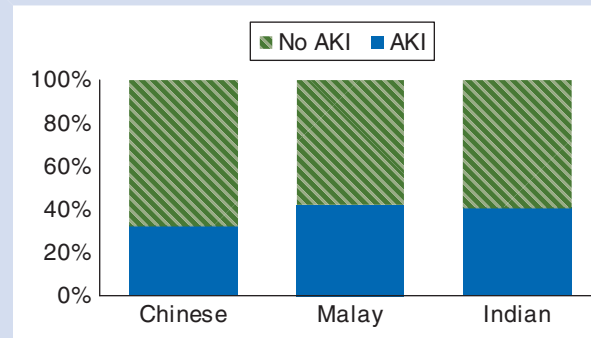


Fig 1 The percentage of patients in each ethnic group that developed acute kidney injury after cardiac surgery.

Table 2 Operative data and acute kidney injury after cardiac surgery. Figures are *n* (%) or mean \pm sd. AKI, acute kidney injury; IABP, intra-aortic balloon pump; CPB, cardiopulmonary bypass

	AKI	No AKI	P-value
<i>n</i>	579	1060	
Bypass time (min)	123 \pm 72	106 \pm 43	<0.001
Aortic cross-clamping time (min)	70 \pm 41	62 \pm 32	<0.001
Number of vein grafts	3.0 \pm 0.9	2.9 \pm 0.9	0.124
Lowest haematocrit during CPB (%)	23.1 \pm 3.7	25.0 \pm 7.2	<0.001
Use of IABP	102 (17.6%)	78 (7.5%)	<0.001

In about one-third (31.3%) of the patients with AKI, creatinine levels remained elevated above the normal range at the time of discharge. More significantly, 19.7% of the patients with AKI had creatinine levels that remained at least 25% higher than baseline at hospital discharge.

After multi-variate analysis, factors that affect AKI are shown in Table 3. Ethnicity was shown to be an independent predictor of AKI after cardiac surgery with Indians and Malays having a higher risk of developing AKI when compared with Chinese patients [odds ratio: Indian vs Chinese 1.44, Malay vs Chinese 1.51 (Fig. 1)].

Discussion

AKI is a significant cause of morbidity and mortality after cardiac surgery. Clinical **risk factors** that predicted AKI in this study include hypertension, diabetes mellitus, and poor **EuroSCORE**; these are similar to previous reports.^{6–9} Additionally, Indians and Malays have higher risks of developing postoperative AKI than Chinese. This is the first reported study linking ethnicity to AKI in a multiethnic South East Asian society. A similar effect was demonstrated previously in African Americans compared with Caucasians.⁵ This corroborates with increasing evidence that **ethnicity plays a role in atherosclerosis**, coronary **heart disease**, and its associated complications, including **AKI**.^{10–11} Currently, there is a **lack of effective therapy for AKI** and even with aggressive medical care and **dialysis**, the morbidity, mortality, and costs of care are **significantly increased**. The finding that ethnicity influences the incidence of post cardiac surgery AKI poses an **irreducible risk** which is separate from the usual risk factors quoted above. It is important to understand the role of ethnicity in the pathogenesis of AKI after cardiac surgery.

A possible causative mechanism involves the **atherosclerotic pathway**, in which patients who are **genetically predisposed** will develop atherosclerotic disease of not only the cardiac vasculature but also the **renal vasculature**, leading eventually to renal ischaemia and the development of AKI during cardiac surgery. In the Study of Heart Assessment and Risk in Ethnic Groups (**SHARE**), **South Asians** (including Indians) were found to have a **greater prevalence** of

Table 3 Results of multivariate logistic regression analysis of significant ethnicity, clinical characteristics and operative data. LVEF, left ventricular ejection fraction; IABP, intra-aortic balloon pump

Factor	Odds ratio (95% confidence interval)	P-value
History of diabetes mellitus	1.248 (0.986–1.580)	0.026
History of hypertension	1.391 (1.045–1.852)	0.024
Weight	1.023 (0.993–1.012)	0.395
LVEF <30%	1.483 (0.983–2.236)	0.041
Use of IABP	1.928 (1.347–2.758)	<0.001
Malay vs Chinese	1.507 (1.113–2.040)	0.008
Indian vs Chinese	1.449 (1.026–1.058)	0.035

atherosclerosis. This increased risk has been found not only in South Asians living in their countries of origin,¹² but in **immigrants** as well.^{13–14} The greater prevalence of atherosclerosis is an **independent predictor** of cardiovascular risk, even after adjustment for conventional risk factors such as lipid profile and diabetes mellitus. As our local population of **Indians** are largely descendents of **immigrants**, it would not be unreasonable to expect that this accelerated rate of atherosclerosis that affects the coronary vasculature in Indians can also affect the renal vasculature, hence predisposing the patient to AKI after cardiac surgery. On the other hand, the **Malays** are **native** to the country and the rate of atherosclerosis in this group has not been well documented.

Ethnic differences impact the incidence of diabetes mellitus and its associated complications. Our study shows that the incidence of **diabetes mellitus** is **higher** in our population when compared with the **West** (46% vs 12–38%).¹⁵ Moreover, there are also inter-ethnic differences in the incidence of diabetes mellitus within the local population with the Indians and Malays having the higher incidence (64 and 58%, respectively) and Chinese patients having an incidence of 41%, similar to a study conducted in Hong Kong which has a predominantly Chinese population.¹⁶ Although the **higher incidence** of **diabetes mellitus** can account for the **higher incidence** of post cardiac surgery **AKI** in **Indians** and Malays, **ethnicity remains an independent predictor** for development of AKI even in the absence of diabetes. Numerous studies have shown that **South Asians** have **decreased sensitivity** to **insulin** when compared with **other ethnic** groups which may be related to **increased** levels of **visceral fat** resulting in a **blunted response** to **insulin**. Moreover, South Asians may have a susceptibility to insulin resistance because of **genetic polymorphisms** with higher prevalence of (PC-1) K121Q and PPARGC1A in the South Asian population.^{17–22} The higher lipid and glucose abnormalities in the Indians and Malays are associated with a **higher** degree of **atherosclerosis** and **decreased stability** of atherosclerotic plaques in coronary vasculature.²³ **Diabetic native coronary arteries**

are also inferior in quality to those of non-diabetic patients undergoing coronary artery revascularization.^{24 25} It is not inconceivable that these same mechanisms could exist in the renal vasculature and in the prothrombotic environment caused by the stress of surgery and cardiopulmonary bypass, predisposing these patients to AKI.

Cardiac surgery incites a strong systemic inflammatory response¹ and it is possible that cardiopulmonary bypass in Indians and Malays are especially deleterious to the renal vasculature. This can involve numerous signal transduction pathways, including endothelial dysfunction of the renal vasculature which is characterized by an impaired nitric oxide-dependent and prostaglandin-dependent vasorelaxation.^{26 27} Adenosine-induced vasoconstriction of the afferent arterioles, which occurs as a result of mitochondrial ATP hydrolysis during renal ischaemia, is also markedly exacerbated in the diabetic renal vasculature and causes a much more profound ischaemia-induced reduction of renal blood flow when compared with non-diabetic conditions. This apparent increase in risk for developing AKI in the diabetic milieu is linked to a higher sensitivity of the renal vasculature to adenosine-induced renal vasoconstriction via adenosine A1 receptors, as a result of a diminished renal prostaglandin- and nitric oxide-dependent vasodilatory capacity.^{28 29} To further strengthen the proinflammatory link, inflammatory markers such as cytokines (such as TNF α , TGF β , and NF κ B), apoptotic markers, and nitric oxide will be studied subsequently to establish the link between the genetic predisposition and the mediator through which the gene expresses the outcome.

The major implications in our study are twofold. We have reported that ethnicity is associated with the development of AKI in patients subjected to the stresses of cardiac surgery. This corroborates with previous studies and validates that genetics play a role in the development of AKI post cardiac surgery. Secondly, this study emphasizes the need for ethnic-based data unique to each population group. Using these data will enable clinicians to better manage gene–environment interaction.

Our study has several strengths; it is a prospective study of patients with similar cardiovascular risk factors subjected to the same, predictable, and quantifiable stressor, namely that of cardiac surgery and cardiopulmonary bypass in a controlled environment of anaesthesia with intense monitoring and follow up. Although socioeconomic factors can contribute to the severity of disease, the major advantage in this study is that the study population is relatively homogenous with patients having ready and equal access to healthcare. This is the first data comparing outcomes after cardiac surgery in Chinese vs other ethnic groups in a South East Asian setting. Interestingly, the published data by the predominantly Chinese population from Hong Kong with a similar incidence of diabetes mellitus did not show any significant increase in mid- and long-term mortality after coronary artery bypass grafting although AKI was not primarily studied.¹⁶

One of the challenges in studying AKI remains that of a uniform definition. We chose to use the postoperative

change in serum creatinine levels as the index varies little among patients with different baseline creatinine levels; moreover, it correlates with relative reductions in renal filtration, is independently associated with adverse outcomes after cardiac surgery, including mortality and morbidity, is highly sensitive to perioperative renal insult, and is always done as part of the routine postoperative laboratory workup. Although the clinical significance of a 25% increase in creatinine in the perioperative period is unknown, it is of note that in about 20% of these patients, the creatinine level remained elevated more than 25% above preoperative creatinine at discharge. Brown and colleagues has shown that not only is acute AKI associated with poor outcomes after cardiac surgery, persistent AKI at discharge is also associated with worse survival.³⁰ Apart from mortality, the progression of the AKI to chronic kidney disease needs attention and further studies. We postulate that by using the cardiopulmonary bypass as a 'real-time' clinical stress model and following up these patients long-term will demonstrate whether these groups of patients will develop chronic renal disease and end-stage renal disease over time. In a population with a high incidence of diabetes mellitus, this combination with renal ischaemia that develops during cardiopulmonary bypass can play a major role in the subsequent development of diabetic nephropathy. Long-term cohort studies of this 'at risk' group will reveal the significance of the increase in serum creatinine during the perioperative period and renal outcome in this group of patients. As South Asians and Chinese represent over half the world's population, it is important to validate that the same high-risk genetic polymorphisms that contribute to AKI in the West are also validated in this population. This will contribute to understanding of the pathogenesis of the disease and thus risk modification.

In conclusion, we present the first evidence that ethnicity is an independent risk factor for the development of AKI after cardiac surgery in a South East Asian population. Clinical and perioperative factors can only predict 5–10% of the variability in AKI after cardiac surgery; hence our study provides additional evidence for the increasing important role of ethnicity and genetic predisposition in affecting the incidence of AKI after cardiac surgery. Further analysis of the genetics in each ethnic group can identify new clues to the pathogenesis of AKI and refine the risk profile specific to each ethnic group and bring personalized risk stratification closer to reality.

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Declaration of interest

None declared.

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