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Risk Factors for Acute Kidney Injury Requiring Continuous Renal Replacement Therapy after Off-Pump Coronary Surgery

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Abstract

Background: Recently, off-pump coronary artery bypass (OPCABG) grafting without cardiopulmonary bypass has become a less stressful surgical procedure for coronary artery bypass grafting (CABG). Many reports have discussed the risk factors involved associated with on-pump coronary artery bypass grafting and acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT). However, only a few papers have evaluated the risk factors for AKI requiring CRRT after OPCABG.

Aim: The purpose of this study was to assess the risk factors for AKI requiring CRRT after OPCAB.

Methods: An observational study of 237 consecutive non dialysis patients who underwent isolated CABG using OPCABG was conducted from September 2010 to June 2012. AKI was defined as proposed by the Acute Kidney Injury Network. Variables with $P<0.05$ in bivariate analysis collected from pre-, intra- and postoperative data were tested in the multivariate and proportional hazards regression analyses for risk factors of AKI requiring CRRT after OPCABG.

Results: Among 237 subjects, 33 patients needed CRRT due to AKI. The risk factors that were independently associated with AKI requiring CRRT were: pre-estimated glomerular filtration rate (GFR) (less than 60 ml/min/1.73m^2), pre-serum albumin level (less than 3.5 g/dl), pre-hemoglobin level (less than 12g/dL), intra-urine volume (less than 600 mL), use of intra-aortic balloon pump (IABP), and post-PaO_2/FiO_2 (P/F) (less than 300).

Conclusion: In conclusion, it is possible that the risk of developing AKI requiring CRRT after OPCABG depended on the levels of GFR, serum albumin and hemoglobin before surgery, on the levels of urine volume and use of IABP during surgery and the levels of P/F after surgery.

Keywords: eGFR; Albumin; Hemoglobin; IABP

Introduction

Acute kidney injury (AKI) has been reported to occur in 30% to 40% of patients undergoing cardiac surgery [1]. Patients with AKI requiring continuous renal replacement therapy (CRRT) have mortality rates in excess of 40% to 50% [2]. To avoid postoperative complications, off-pump coronary-artery bypass grafting (OPCABG) has recently been utilized [3]. Although randomized trials of OPCABG have not demonstrated benefits, reductions in the incidence of AKI were demonstrated [4,5,6]. Previously Thakar et al. [7] proposed a clinical score to predict AKI after cardiac surgery. However, their study was not clear on risk factors in patients undergoing OPCABG. Besides, it has been reported that the risk of AKI requiring CRRT varies substantially among different types of cardiac surgical procedures [8,9]. There are large discrepancies among reports on long-term survival in cardiac surgical patients treated with CRRT, varying from 10% at 1 year to 52% at 5 years [10,11,12]. The identification of risk factors for AKI in patients after OPCABG may result in better care, more appropriate resource utilization, and, finally, better outcome. The purpose of this study was to determine the risk factors that predict AKI requiring CRRT after OPCABG.

Methods

All adult patients who developed AKI-CRRT in the postoperative cardiac surgical intensive care unit at a single academic center from September 2010 through June 2012 were included in this retrospective case-control study. Patients excluded from the study were: 1) those with severe chronic renal failure, which was defined by less than 15 ml/min/1.73m^2 (CKD stage 5) or chronic dialysis therapy; 2) history of chronic obstructive pulmonary disease requiring medical therapy; 3) previous open-heart surgery; and 4) those who died during the first 24 hours after surgery were excluded because these patients died either from acute heart failure or bleeding in direct consequence of cardiac surgery.

Definitions

The AKI was defined according to the Second International Consensus Conference of the Acute Dialysis Quality Initiative Group [13] with reference to RIFLE (risk, injury, failure, loss, and end-stage kidney disease) using the criteria for kidney injury [14]. The primary outcome was AKI that required dialysis during the postoperative period. CRRT was carried out as continuous venovenous hemofiltration (CVVHDF) and was started when at least one of the following institutional protocol requirements was fulfilled: 1) urine output below 0.5 mL/kg/h in 6 hours despite treatment with fluid transfusion, inotropes, and/or vasoconstrictor infusions aimed at optimization of the hemodynamic parameters and the administration of furosemide 100 mg/h over 3 hours or 2) more than a 4-fold increase in plasma creatinine concentration was observed. Hemofiltration treatment

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ceased when patients recovered urine output exceeding 1 mL/kg/h, provided that no indications for RRT were observed subsequently. Patients were accessed through double-lumen catheters (Vas-cath, Medicon Co., Chicago, IL), which were inserted into the right or left femoral vein and connected to a continous hemodialyzer (KM8600, Kurary Co. Ltd., Tokyo, Japan). An anticoagulant, nafamostat mesilate (Futhan, Torii Pharmaceutical Co. Ltd. Tokyo, Japan), was used at 30 IU/hr. CRRT was started as under conditions of water elimination rate of 60 mL/hr, dialysate (HF Solita, Shimizu Pharmaceutical Co., Ltd., Shimizu, Japan) flow rate (Q_D) of 16 mL/min, blood flow rate (Q_B) of 100 mL/min and predilution replacement solution flow rate (Q_{REF}) of 30 mL/min. The dialyzers used in this study were Panflow APF-S (Asahi Medical Co., Ltd., Tokyo, Japan) and Hemofeel SH (Toray Medical Co., Ltd., Tokyo, Japan). Both preoperative and intraoperative variables were examined for possible predictors of AKI to develop the scoring model. Preoperative: age, gender, body mass index (BMI), ejection fraction, diabetes mellitus evaluated by hemoglobin A1C, preoperative estimated glomerular filtration rate (eGFR) (eGFR was calculated using a modified three-variable equation for eGFR in Japanese patients: eGFR=194xage$^{-0.287}$ x SCr$^{-1.094}$(x0.739, if female), where SCr=serum creatinine [15] and preoperative levels of serum albumin, hemoglobin, and C-reactive protein (CRP) as indication of inflammation. Intraoperative: emergency surgery, use of intra-aortic balloon pump during surgery, number of grafted coronary vessels, cardiopulmonary bypass (CPB) time, urine volume, and doses of furosemide. The following intraoperative data were also recorded: mean arterial pressure (mm Hg), doses of catecholamines (μg/kg/min), cardiac index (L/min/m^2), central venous pressure (cmH_2O), and PaO_2/FiO_2). The rationale for using these variables in the scoring model was based on the findings reported by Thaker et al. [7].

Statistical Analyses

Data were analyzed by using SAS 1999 program (release 8.00 by SAS Institute Inc, Cary, NC). Continuous measures are expressed as mean ± standard deviation or as median (50th percentile) and compared with a "*t*-test" for unpaired data, as appropriate. Comparison of continuous variables between the two groups was performed with the Mann-Whitney's U test, and categorical data were analyzed by using Fisher's exact test. Variables with univariate significance P<0.001 were identified and then the following variables were used as dichotomous variables: Preoperative: age, 65 years; eGFR, 60 mL/min/1.73 m^2; albumin, 3.5g/dL; hemoglobin, 12 g/dL; and CRP, 0.5 mg/dL. These values were arbitrarily determined with the following reasons; in Japan, elderly people are defined as 65 years and over. Also, less than 60 ml/min/1.73m^2 is defined as CKD. The anemia was defined less than 12.0g/dL. The lower limit of serum albumin was 3.5g/dL.

Intraoperative: presence of IABP; catecholamine index, 5 μg/kg/min; urine volume, 600 ml; and use of furosemide. Postoperative: mean arterial pressure, 70 mm Hg; and P/F ratio, 300 using sequential organ failure assessment (SOFA) score. These variables for AKI requiring CRRT identified by univariate logistic regression analysis were further tested by multivariate regression. Score points were assigned to each risk factor using regression coefficients and rounded to the nearest integer. Receiver operating characteristic plots of the score models predicting AKI requiring CRRT were produced.

Results

(Table 1) shows the characteristics of all patients. The variables including age, preoperative CRP, requiring emergency operation, use of IABP, use of furosemide during surgery, doses of catecholamine (CAI) during surgery, and postoperative PaO2/FiO2 (P/F) were significantly higher in patients requiring CRRT. In contrast, variables including preoperative eGFR, preoperative serum albumin and hemoglobin, urine volume during surgery, and postoperative mean arterial pressure were significantly lower in patients requiring CRRT. In (Table 2), univariate analysis was performed to identify risk factors for AKI requiring CRRT and analysis of simple regression of these variables are shown. Significant associations with AKI were shown for eGFR, ALB, HGB, IABP, urine volume, and P/F ratio. The analysis was

		ALL(n=237)	Non RRT(n=204)	RRT (n=33)	p-value
	Age(yr)	70 [64～75]	69 [63～75]	73 [67～80]	.021
Pre	Sex(M:F)	173～64	152～52	21～12	.207
	BMI(kg/m^2)	23.1[20.6～25.3)	23.2 [20.5～25.3]	23.1 [21.3～25.4]	.487
	HbA1c(%NGSP)	5.8 [5.3～6.7]	5.7 [5.3～6.8]	6 [5.4～6.7]	.581
	Ejection fraction (%)	53 [42～64]	54 [43～66]	48 [33～59]	.061
	eGFR(mL/min/1.73m^2)	58.3 [47.2～74.2]	62.8 [50.8～76.2]	26.9 [19.4～47.5]	<.001
	ALB(g/dL)	3.8 [3.4～4.15]	3.9 [3.5～4.2]	3.4 [3.1～3.7]	<.001
	HGB(g/dL)	12.2 [10.9～13.8]	12.5 [11.2～13.9]	10.5 [9.5～11.9]	<.001
	CRP(mg/dL)	0.24 [0.07～0.97]	0.22 [0.07～0.83]	0.60 [0.10～2.23]	. 043
Intra	Emergency	60(25%)	43(21%)	17(51.5%)	<.001
	IABP	66(28%)	48(23.5%)	18(54.5%)	<.001
	Number of vessels(number)	3(3～4)	3(3～4)	3(3～4)	.477
	Duration of anesthesia(Hr)	6.93 [5.88～7.63]	7.0 [5.95～7.55]	6.35 [5.55～7.81]	.646
	Urine volume(mL)	700 [450～1050]	730 [485～1075]	450 [300～590]	<.001
	furosemide	42(18%)	28(14%)	14(42.5%)	<.01
Post	Mean arterial pressure (mmHg)	68 [63～75]	68.5 [63～75]	64 [58～69]	.002
	CAI(μg/kg/min)	4.1 [2.0～7.42]	3.94 [1.98～7.38]	5.8 [2.76～9.45]	.043
	Cardiac index(L/min/m2)	2.4 [2.1～2.8]	2.4 [2.2～2.8]	2.3 [2.05～2.75]	.245
	Central venous pressure	7.0 [5～10]	7.0 [5～9.8]	8.0 [5.5～10]	.540
	(CmH_2O) P/F ratio	309 [256～371]	316 [260～374]	262 [199～313]	<.001

Values are expressed as mean + standard deviation. BMI: body mass index; ALB: serum albumin; eGFR,: estimated glomerular filtration; HGB, hemoglobin; CRP: c-reactive protein; IABP: intra-aortic balloon pumping; CAI: catecholamine index; P/F, PaO_2/FiO_2.

Table 1: Characteristics of the patients.

	Risk factors	Regression coefficient	Odds ratio(95% CI)	p-value
Pre	Age(yr)	0.531	1.060(1.012～1.112)	.013
	eGFR(mL/min/1.73m²)	-2.262	0.903(0.875～0.932)	<.001
	ALB(g/dL)	-0.914	0.183(0.086～0.387)	<.001
	HGB(g/dL)	-1.048	0.583(0.461～0.739)	<.001
	CRP(mg/dL)	0.422	1.192(1.058～1.343)	.003
Intra	emergency	0.600	3.978(1.858～8.515)	<.001
	IABP	0.610	3.900(1.828～8.320)	<.001
	Urine volume(mL)	-1.281	0.997(0.996～0.999)	<.001
	furosemide	0.585	4.631(2.086～10.27)	<.001
Post	Mean arterial pressure (mmHg)	-0.577	0.936(0.890～0.985)	.011
	CAI(μg/kg/min)	0.449	1.093(1.026～1.163)	.005
	P/F ratio	-0.724	0.991(0.986～0.996)	<.001

Values are expressed as mean + standard deviation. AKI:cute kidney injury; CRRT, continuous renal replacement therapy. BMI, body mass index; ALB, serum albumin; eGFR: estimated glomerular filtration; HGB, hemoglobin; CRP: c-reactive protein; IABP: intra-aortic balloon pumping; CAI:catecholamine index; P/F, PaO_2/FiO_2.

Table 2: Univariate analysis for AKI patient requiring CRRT.

then taken to another level of multivariate analysis shown in (Table 3) of the significant variables that emerged from univariate analysis. (Table 3) shows the variables after multiple regression analysis. Preoperative albumin, and intraoperative urine volume were the only variables showing significance at P<0.01 as predictable factors for AKI requiring CRRT. In (Table 4), scores for selected variables are shown. Figure 1 illustrates the frequencies of AKI. There were few patients at higher score levels; no patients had a score of >8. Abrupt increases in frequency of AKI requiring CRRT were found at score 5. (Figure 2) demonstrates that the area under the curve for the score in the test data was 0.914, indicating a good capability of the score model to predict AKI requiring CRRT. Cut off values at 5 was 72% in sensitivity and 92.2% at specificity. The area under the curve for the score in the test data was 0.914, indicating a good capability of the score model to predict AKI requiring CRRT.

Discussion

The present study demonstrated that risk factors for AKI requiring CRRT after OPCABG were preoperative eGFR, ALB, HGB, urine volume and use of IABP during surgery and postoperative P/F ratio. Recently, Kiers et al. [16] compared the predictive value of eight models reported up to 2011. They found a significant relationship with predicting AKI requiring CRRT for patients with cerebral vascular disease, pulmonary disease and pulmonary hypertension, preoperative renal disease and reduced GFR, prior cardiac surgery, type of surgery, reduced left ventricular function and congestive heart failure, emergency surgery, cardiogenic shock and need for IABP, prolonged CBP and cross-cramp time, postoperative elevated central venous pressure and low cardiac output. Thakar et al. [7] proposed a clinical score model that included consideration of the following variables: female, presence of congestive heart failure and low ejection fraction, use of IABP, chronic lung disease, diabetes mellitus requiring insulin therapy, previous history of cardiac surgery, emergency operation, and preoperative renal function. Similarly, Wijeysundera et al. [17] proposed another model that included preoperative renal function, presence of diabetes mellitus and left ventricular dysfunction, previous history of cardiac surgery, emergency operation, and use of IABP. Thus, from these previous reports [7,13,14] as well as our present study preoperative renal function merits consideration as a powerful predictor for risk for AKI requiring CRRT after cardiac surgery. Compared to the previous data, our analysis revealed that preoperative levels of ALB and HGB were independent risk factors for AKI requiring CRRT after OPCABG. These factors were not extracted from the previous studies. In our models, the cut off levels of ALB and HGB were 3.5 g/dL and 12 g/dL, respectively. It is generally uncommon for patients with CKD stage 3a to have levels of ALB less than 3.5 g/dL and for HGB of less than 12 g/dL._Our analysis clearly demonstrated that slightly lower levels of albumin and hemoglobin should be recognized as predictors for development of AKI requiring CRRT in conjunction with reduced eGFR. In the present study, we excluded patients with eGFR of less than 15 ml/min/1.73 m² (CKD stage 5 without dialysis). The factors extracted from our study e.g., use of IABP and reduction of urine volume are closely associated with combination of low cardiac output and reduction of renal function. This combination

Pre ALB <3.5g/dL	Regression-coefficient 1.145	Standard Deviation .534	95% confidential interval Lower 1.103	Upper 8.950	p-value .032
Pre eGFR< 60mL/min/1.73m²	2.545	.711	3.164	51.30	.000
Pre HGB < 12g/dL	1.313	.574	1.207	11.44	.022
Intra urine volume< 600mL	1.662	.522	1.894	14.66	.001
Intra use of IABP	1.490	.533	1.561	12.61	.005
Post P/F ratio <300	1.146	.517	1.142	8.667	.027

Values are expressed as mean + standard deviation. BMI: body mass index; ALB: serum albumin; eGFR: estimated glomerular filtration; HGB: hemoglobin; CRP: c-reactive protein; IABP: intra-aortic ballon pumping; CAI: catecholamine index; P/F, PaO_2/FiO_2.

Table 3: Multiple logistic regression analysis.

	Points
Pre ALB <3.5g/dL	1
Pre eGFR< 60mL/min/1.73m²	2
Pre HGB < 12g/dL	1
Intra urine volume< 600mL	1
Intra use of IABP	1
Post P/F Ratio <300	1

Table 4: Score for risk factors.

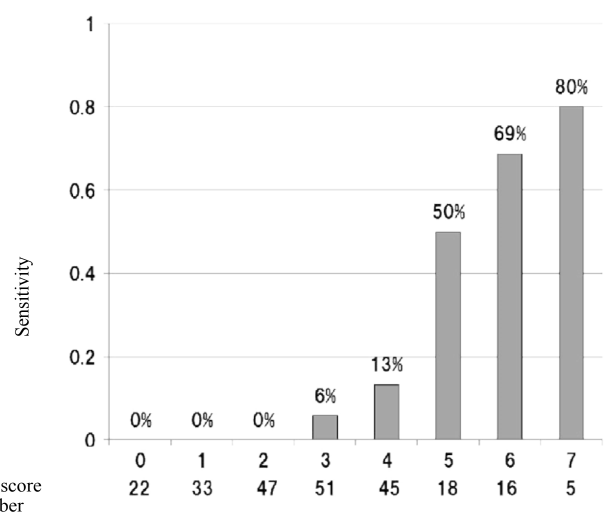

Figure 1: Frequency of AKI requiring CRRT corresponding to risk score.

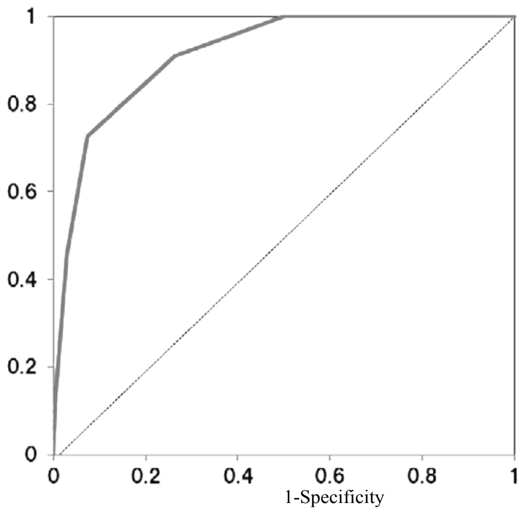

Figure 2: Receiver operating characteristic curve analysis for the test of predictor scores.

reduces renal blood flow and leads to AKI. Several factors influence AKI development after cardiac surgery and perioperative patient management significantly affects AKI occurrence. Predictive models can be improved by the addition of these variables [18]. In the present study, we did not compare the data of outcomes between off-pump and on-pump coronary surgery. Previously, Di Mauro et al. [19] reported the incidence of postoperative AKI comparison between off-pump and on-pump coronary artery bypass surgery. In their report, off-pump surgery had a beneficial effect for early and late outcome in patients with normal preoperative renal function. However, there were no significant differences in early and late outcomes when the preoperative renal function was impaired. Originally, it is suggested that off-pump coronary artery surgery preserves circulation and perfusion in the kidney during operation, providing some advantages over on-pump surgery. However, in patients with reduced renal function, this favorable effect might disappear. Accordingly, our present findings might coincide with this data; impaired renal function is one of the predictable factors for incidence of AKI. A limitation of the present study lies in the derivation of data from a single center. Although our observational study was valuable in identifying associations it does not address causality. Nevertheless, it can improve individual patient care by allowing us to identify patients who have a greater likelihood of developing AKI. It should be noted that our proposed scoring model predicts a severe form of AKI defined by requirement of dialysis. In our multiple logistic regression analysis, continuous variables, such as age, hemoglobin, and eGFR were used as dichotomous variables. This might lead to misinterpretation of data. In spite of the limitations, we provide one of a clinical score validated in our population of patients that predicts AKI after open-heart surgery. The score might enhance the accuracy of prediction by accounting for the effect of all major risk factors of AKI. In addition, the score identifies patients who have a lower- as well as a higher-than-average risk for AKI. This will increase the clinical utility of the score in improving both individual patient care and by providing a vital tool in planning future clinical trials of early diagnosis and intervention in AKI.

Conclusion

In conclusion, it is possible that the risk of developing acute kidney injury requiring continuous renal replacement therapy after off-pump coronary artery bypass depended on the levels of GFR, serum albumin and hemoglobin before surgery, on the levels of urine volume and use of IABP during surgery and the levels of P/F after surgery.

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The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Conflict of Interest

The authors declare no conflict of interest in this study.

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