Prognostic Factors Affecting Clinical Outcomes after Coronary Artery Bypass Surgery: Analysis of Patients with Chronic Kidney Disease after 5.9 Years of Follow-Up

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Abstract

Background: Coronary artery bypass grafting (CABG) is a highly successful treatment for prolonging the lives of selected patients; however, preoperative and postoperative renal dysfunction has been an important predictor of adverse cardiovascular events. Concerns have recently grown regarding chronic kidney disease (CKD), which is an independent risk factor for cardiovascular diseases. In the present study we examined the significance of renal function on the basis of the estimated glomerular filtration rate (eGFR) and analyzed other factors as predictors of long-term clinical outcomes after CABG.

Methods: The subjects were 195 patients who underwent CABG from July 1996 through September 2008 at our hospital. Patients who received preoperative dialysis or who died during hospitalization or both were excluded. The patients were divided into 2 groups based on eGFR at the time of discharge (eGFR $\geq 60 \text{ mL/min}/1.73 \text{ m}^2$: non-CKD group; or eGFR <60 mL/min/1.73 m²: CKD group), and long-term outcomes were compared between the groups. The effects of other risk factors on long-term morbidity and mortality were also examined.

Results: The mean age of patients was 64.6 ± 9.3 years, and the mean duration of followup was 69.5 ± 44.5 months. There were no significant differences in either deaths from all causes or cardiovascular deaths between the CKD group and the non-CKD group. Multivariate analysis using the Cox proportional hazards model revealed that age (hazard ratio, 1.044; p=0.001) was a predictor of all-cause death and that age (hazard ratio, 1.154; p<0.001), diabetes mellitus (hazard ratio, 3.122; p=0.046), unstable angina (hazard ratio, 5.012; p=0.003), and proteinuria (hazard ratio, 7.982; p<0.001) were predictors of cardiovascular death.

Conclusions: Our study demonstrates that age, diabetes mellitus, unstable angina, and proteinuria are factors that affect long-term prognosis after CABG, whereas eGFR <60 mL/min/1.73 m² is not a predictive risk factor for either all-cause death or cardiovascular death. Although the predictive value of eGFR <60 mL/min/1.73 m² is generally accepted, analysis of our own data with receiver operating characteristic curves shows that eGFR <50 mL/min/1.73 m² is a more sensitive predictor of long-term outcome.

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Key words: coronary artery bypass grafting, chronic kidney disease, estimated glomerular filtration rate, cardiovascular mortality, proteinuria

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Introduction

Although the hospital mortality rate after coronary artery bypass grafting (CABG) is generally considered to be 1% to 2%, the rate may be at least 3 times as high among patients with preoperative renal dysfunction and nearly 10 times as high among patients with acute postoperative renal failure; thus, postoperative renal dysfunction is considered an important risk factor that affects surgical outcomes and long-term morbidity and mortality¹⁻³.

Recently, concerns have grown regarding chronic kidney disease (CKD), which is an independent risk factor for cardiovascular diseases, and several reports have examined long-term outcomes on the basis of differences in the estimated glomerular filtration rate (eGFR).

CKD is generally defined as a finding of eGFR <60 mL/min/1.73 m², abnormal urinalysis results, or abnormal images or both persisting for 3 months or more, and several studies have examined the risk of long-term cardiovascular events in patients with eGFR <60 mL/min/1.73 m² ⁴⁻⁷.

Liu, et al.⁸ have reported the rate of eGFR <60 mL/min/1.73 m² in patients with coronary artery disease to be as high as 24.8%, and Cooper, et al.⁹ have also reported that 26% of a series of patients undergoing CABG had renal dysfunction, as indicated by eGFR <60 mL/min/1.73 m². According to Imai, et al.⁴, the prevalence of CKD, indicated by eGFR <60 mL/min/1.73 m², in Japanese adults is 18.7%, but there have been few reports concerning the prevalence of CKD in Japanese patients with coronary artery disease.

The purposes of this study were to examine whether CKD, defined as an eGFR <60 mL/min/ 1.73 m², is a predictor of long-term morbidity and mortality after CABG and to assess other risk factors as possible predictors of long-term clinical outcomes.

Materials and Methods

From July 1996 through September 2008, 211

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consecutive patients underwent isolated CABG at our hospital. Patients with preoperative renal failure requiring dialysis (n=13) and patients who during hospitalization (n=3) were excluded from the analysis. The study population consisted of the remaining 195 patients. The patients were divided into 2 groups based on the eGFR at the time of discharge (eGFR $\geq 60 \text{ mL/min/1.73 m}^2$: non-CKD group; or eGFR <60 mL/min/1.73 m²: CKD group), and total mortality and cardiovascular mortality were retrospectively compared to examine whether eGFR of 60 mL/min/1.73 m² is an appropriate cut-off value affecting long-term outcomes. Furthermore, we performed multivariate analysis using the Cox proportional hazards model to assess other categorical variables as possible predictors of longterm clinical outcomes: age; preoperative complications, including diabetes and hypertension; preoperative circulatory dynamics (requiring inotropic supports or nitrates); use of cardiopulmonary bypass (CPB); and proteinuria.

The eGFR was calculated with the Modification of Diet in Renal Disease (MDRD) equation based on serum creatinine levels at the time of discharge. (eGFR=194 × $age^{-0.287}$ × creatinine^{-1.094} mL/min/1.73 m² × 0.739 (if female)¹⁰. Moreover, to determine whether proteinuria was present, urine dipstick tests were performed at the time of discharge.

Patient Follow-up and Outcomes

All patients who were discharged from the hospital (n=195) were included in this series. All patients were followed up with telephone questionnaires, and if patients could not be contacted, the study was ended on the date of the last examination. The endpoint of the cumulative survival rate was death from any cause. Cardiovascular death was defined as deaths from myocardial infarction, congestive heart failure, fatal arrhythmias, acute aortic dissection, rupture of aneurysm, or stroke.

Statistical analyses: Statistical analysis was performed with SPSS version 16.0 for Windows (SPSS Inc, Chicago, IL, USA). Continuous data are expressed as means \pm standard deviations, and categorical data are expressed as absolute values (percentages). Univariate analysis was initially performed to assess the association between explanatory variables and outcome, Student's t-tests or Mann-Whitney U-tests were used for continuous variables, and χ^2 tests or Fisher's exact tests were used for categorical variables. The cumulative survival and cardiovascular event-free survival were described with the Kaplan-Meier method. The logrank test was used to calculate the statistical significance of differences in survival curves between groups. All variables with significance level of p < 0.10 in this univariate test were included in a multivariate model proposed by the Cox proportional hazards model. Differences were considered significant at p < 0.05 on multivariate testing.

Results

Baseline Characteristics

The mean patient age was 64.6 ± 9.3 years, and the mean duration of follow-up was 69.5 ± 44.5 months. There were 27 (13.8%) late deaths from all causes. The 5-year and 10-year survival rates were 88% and 78%, respectively. The patient and disease characteristics are shown in Table 1, and the clinical outcomes are shown in Table 2. The CKD and non-CKD groups showed significant differences in renal function, such as preoperative and postoperative serum creatinine and the presence of proteinuria, as well as the use of intra-aortic balloon pump among preoperative factors, but there were no differences in age or the rate of diabetes mellitus. The number of bypass grafts and the use of bilateral internal mammary arteries were higher in the non-CKD group (Table 1). There were no differences in clinical outcomes between these groups except for the requirement for hemodialysis (Table 2).

All-cause Death

There were no significant differences in all-cause death between the groups (p=0.441; Fig. 1). The variables with a significance level of p<0.10 on univariate analysis were age, diabetes mellitus, hypertension, stroke, unstable angina, and

proteinuria (**Table 3**). These variables were included in a multivariate analysis model. Multivariate analysis using the Cox proportional hazards model revealed that only age (p=0.001) was a predictor of all-cause death (**Table 4**).

Cardiovascular Death

There was no significant difference in cardiovascular death between the groups (p=0.261; **Fig. 1**). The variables with a significance level of p < p0.10 in the univariate tests were age, diabetes mellitus, left ventricular (LV) ejection fraction <40%, unstable angina, Canadian Cardiovascular Society angina class, and proteinuria (Table 3). These values were included in a multivariate analysis model. Multivariate analysis identified 4 independent risk factors that were related to cardiovascular death: age (p < 0.001), diabetes mellitus (p = 0.046), unstable angina (p=0.003), and proteinuria (p<0.001), whereas the use of CPB and eGFR <60 mL/min/1.73 m² were not factors affecting morbidity and mortality (Table 5).

Discussion

Patients with renal failure have a high risk for an adverse outcome after CABG1-3. Several studies have shown that patients with renal failure are at an increased risk of death within 30 days after CABG^{11,12}. Many studies have used the serum creatinine level as an index of renal function^{3,11-13}. Nakayama, et al.¹¹ have demonstrated that patients with a preoperative serum creatinine level of 1.5 mg/dL or greater had a lower 10-year survival rate than did patients with a normal creatinine level (<1.0 mg/dL), and Brown, et al.³ have reported that patients with large creatinine increases after CABG have a higher 90-day mortality rate than do patients with small increases. Most previous studies of patients undergoing CABG have relied on serum creatinine levels to determine renal function. Because the serum creatinine level does not increase until GFR has decreased by more than 50%, when the creatinine level increases to 1.5 mg/dL or greater, significant renal dysfunction has already developed.

Several recent reports have concerned long-term

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	$eGFR \ge 60$ (n=121)	eGFR<60 (n=74)	p Value
Demographics			
Age	63.4 ± 10.0	66.5 ± 7.6	0.058
Sex, female	25 (21%)	21 (28%)	0.218
BMI	23.6 ± 3.1	23.4 ± 3.9	0.736
Medical history			
Diabetes mellitus	48 (40%)	33 (44%)	0.498
Hypertension	85 (70%)	58 (78%)	0.213
Dyslipidemia	77 (64%)	42 (57%)	0.339
COPD	6 (5%)	2 (3%)	0.356
PVD	7 (6%)	7 (9%)	0.335
Stroke	13 (11%)	13 (18%)	0.174
Preoperative cardiac status			
Prior CABG	1 (1%)	0 (0%)	0.621
Prior PCI	20 (17%)	11 (15%)	0.769
LVEF	60.0 ± 13.8	60.4 ± 13.2	0.986
Left main stenosis ≥75	16 (13%)	9 (12%)	0.830
Unstable angina	12 (10%)	4 (5%)	0.265
Previous MI	60 (50%)	36 (49%)	0.899
MI in prior 3 months	30 (25%)	13 (18%)	0.238
Preoperative IABP	19 (16%)	4 (5%)	0.031
Preoprative PCPS	4 (3%)	3 (4%)	0.536
CCS angina status		· · · ·	
I/II	58 (48%)	41 (55%)	0.311
III/IV	63 (52%)	33 (45%)	0.311
EuroScore	3.9 ± 3.7	3.9 ± 2.9	0.405
Blood and urine results			
Preoperative creatinine	0.83 ± 0.20	1.22 ± 0.49	< 0.001
Preoperative eGFR	71.9 ± 16.0	48.0 ± 13.4	< 0.001
Preoperative hemoglobin	13.1 ± 1.6	12.4 ± 1.8	0.003
Postoperative creatinine	0.75 ± 0.15	1.24 ± 0.57	< 0.001
Postoperative eGFR	78.6 ± 13.1	47.4 ± 11.5	< 0.001
Proteinuria	10 (9%)	19 (39%)	0.001
Operative details			
Elective	108 (89%)	70 (95%)	0.200
Urgent	6 (5%)	3 (4%)	0.534
Emergent	7 (6%)	1 (1%)	0.124
Off-pump	60 (50%)	32 (43%)	0.389
Number of grafts	2.8 ± 1.0	2.5 ± 0.9	0.022
Bilateral ITA use	41 (34%)	15 (20%)	0.041
Postoperative IABP	15 (12%)	4 (5%)	0.110

Table 1 Patients Characteristics

BMI, body mass index; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; MI, myocardial infarction; IABP, intraaortic balloon pump; PCPS, percutaneous cardiopulmonary support; CCS, Canadian Cardiovascular Society; eGFR, estimated glomerular filtration rate; ITA, internal thoracic artery.

outcomes of patients with CKD based on eGFR after CABG^{29,14-16}. Brown, et al.¹⁴ have reported that the postoperative eGFR is superior to the percentage

change in creatinine for assessing long-term mortality and that postoperative eGFR is associated with a lower 5-year survival rate.

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	$\begin{array}{c} \text{eGFR} \geq 60\\ \text{(n=121)} \end{array}$	eGFR <60 (n=74)	p Value
Postoperative complications			
Hemodialysis required	0 (0%)	4 (5%)	0.020
Atrial fibrillation	25 (21%)	19 (26%)	0.416
Low output syndrome	5 (4%)	4 (5%)	0.466
Return to OR for bleeding	2 (2%)	4 (5%)	0.148
Q-wave myocardial infarction	6 (5%)	4 (5%)	0.573
Mediastinitis	3 (2%)	2 (3%)	0.629
Pneumonia	1 (1%)	1 (1%)	0.616
Stroke	2 (2%)	1 (1%)	0.678

Table 2 Clinical Outcomes

OR, operating room.



Fig. 1 Effect of eGFR \geq 60 mL/min/1.73 m² or eGFR <60 mL/min/1.73 m² on freedom from all-cause death (a) and freedom from cardiovascular death (b) after CABG.

There is some debate as to whether either preoperative or postoperative eGFR should be used for a predictor of long-term outcome after CABG. Thadhani, et al.¹⁷ have reported that acute renal failure after surgery can result from decreased renal perfusion without cellular injury; an ischemic, toxic, or obstructive insult to the renal tubule; or a tubulointerstitial process with inflammation and edema. Furthermore, patients with mild-to-moderate renal dysfunction before surgery may require hemodialysis after CABG¹³. Therefore, we used postoperative eGFR at the time of discharge.

The eGFR is commony calculated with either the Cockcroft-Gault formula or the MDRD equation¹⁸⁻²⁰. According to Lin, et al.¹⁶, the Cockcroft-Gault formula and the MDRD equation are better indices for assessing in-hospital mortality and long-term mortality than is a simple serum creatinine level. The Cockcroft-Gault formula is adjusted for body weight and body surface area and, therefore, is a more powerful tool for predicting in-hospital mortality than is the MDRD equation. On the basis of a report²¹ that the MDRD equation has significantly better accuracy than do other formulas for estimating GFR, including the Cockcroft-Gault formula, we used the MDRD equation in the present study.

Several studies have examined the relationship between eGFR and long-term morbidity and mortality in patients after cardiac surgery. Brown, et al. divided postoperative eGFR into 5 groups (\geq 90, 60–89, 30–59, 15–29, and <15 mL/min/1.73 m²) in

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	During median follow-up of 69.5 months			
	All-cause death		Cardiovascular death	
Variable	HR (95% CI)	p value	HR (95% CI)	p value
Age >64.6 years	1.211 (1.414-1.468)	< 0.001	1.130 (1.055-1.210)	< 0.001
Sex, female	1.659 (0.754-3.693)	0.215	2.216 (0.788-6.227)	0.131
BMI >25	1.141 (0.508-2.561)	0.749	0.852 (0.267-2.720)	0.787
Diabetes mellitus	2.117 (0.982-4.563)	0.056	3.242 (1.022-9.423)	0.042
Hypertension	2.517 (0.869-7.293)	0.089	2.785 (0.628-12.349)	0.178
Dyslipidemia	0.886 (0.414-1.896)	0.755	1.048 (0.373-2.947)	0.930
Stroke	2.394 (0.903-6.342)	0.079	2.623 (0.738-9.327)	0.136
CCS angina status (III/IV)	1.252 (0.585-2.679)	0.562	2.789 (0.886-8.777)	0.079
Prior PCI	0.693 (0.208-2.310)	0.551	0.038 (0.000-18.524)	0.300
Unstable angina	2.287 (0.864-6.052)	0.096	5.786 (1.784-16.424)	0.002
LVEF <40%	1.627 (0.488-5.422)	0.428	3.162 (0.891-11.219)	0.075
Previous MI	0.826 (0.386-1.764)	0.621	0.911 (0.330-2.512)	0.857
Hemoglobin <12.0 mg/dL	1.170 (0.404-3.384)	0.772	1.424 (0.487-4.167)	0.519
Urgent/Emergent	1.656 (0.571-4.799)	0.353	2.259 (0.637-8.011)	0.207
On-pump	0.701 (0.305-1.614)	0.404	0.715 (0.237-2.157)	0.552
3-vessel disease	0.867 (0.407-1.845)	0.711	0.901 (0.327-2.487)	0.841
LMT disease	1.260 (0.435-3.648)	0.670	1.098 (0.247-4.868)	0.903
Total arterial revascularization	1.092 (0.473-2.523)	0.836	1.202 (0.380-3.798)	0.754
Bilateral ITA use	0.865 (0.325-2.300)	0.772	0.584 (0.131-2.606)	0.481
Creatinine \geq 1.5 mg/dL	1.998 (0.473-8.449)	0.347	4.038 (0.908-17.961)	0.067
eGFR <60 mL/min/1.73 m ²	1.347 (0.629-2.884)	0.444	1.776 (0.643-4.905)	0.268
Proteinuria	3.302 (1.379-7.906)	0.007	7.702 (2.779-21.343)	< 0.001

Table 3 Univariate hazard ratios (95% confidence intervals) for all-cause death and cardiovascular death of statistically significant predictors and other predictors for either all-cause death or cardiovascular death

BMI, body mass index; CCS, Canadian Cardiovascular Society; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; MI, myocardial infarction; LMT, left main trunk; ITA, internal thoracic artery; HR, hazard ratio; CI, confidence intervals.

Table 4	Multivariate proportional intervals) for significant p all-cause dea	hazard hazards n or all-cause oredictors a ath	ratios nodel (death nd othe	by 195% c of st er prec	the onfide atistic	Cox ence cally s for
Predictiv	e variable	Hazard Ra	atio (95%	6CI)	рV	alue
Age >64.	6 years	1.044 (1.0)22-1.42	8)	0.0	001
Diabetes	mellitus	1.317 (0.5	578-2.98	1)	0.5	523
Hyperter	ision	1.978 (0.7	768-2.54	8)	0.7	723
Stroke		2.078 (0.7	737-5.85	2)	0.1	172
Unstable	angina	1.515 (0.5	537-4.25	8)	0.4	140
Proteinu	ria	1.698 (0.6	547-4.42	8)	0.2	287

their study of long-term survival among patients after CABG and reported that patients with an eGFR <60 mL/min/1.73 m² had a lower 5-year survival rate than did patients with an eGFR ≥ 60 mL/min/1.73 m² ¹⁴. Cooper, et al.⁹ have demonstrated that preoperative eGFR is a powerful predictor of

CABG operative mortality, and that patients with renal dysfunction (eGFR \geq 30 and \leq 59 mL/min/1.73 m²) has a higher odds ratio for operative mortality than do patients with normal renal function. Hillis, et al.22 have reported that among patients with reduced LV systolic function, as indicated by an LV ejection

Table 5 Multivariate hazard ratios by the Cox proportional hazards model (95% confidence intervals) for cardiovascular death of statistically significant predictors and other predictors for cardiovascular death

	Hazard Ratio (95%CI)	p Value
Age >64.6 years	1.156 (1.049–1.273)	< 0.001
Diabetes mellitus	3.122 (1.146-8.680)	0.046
LVEF <40%	1.967 (0.630-4.568)	0.768
Unstable angina	5.012 (1.723-15.286)	0.003
CCS angina status (III/IV)	1.884 (0.798-4.545)	0.232
Proteinuria	7.982 (2.782-22.082)	< 0.001

LVEF, left ventricular ejection fraction; CCS, Canadian Cardiovascular Society

fraction of 35% or less, after CABG, those with preoperative eGFR <45 mL/min/1.73 m² are at particularly high risk of death in the medium term. On the basis of these reports, the appropriate cut-off value of eGFR affecting long-term prognosis remains unclear. In our study, there were no significant differences in long-term morbidity and mortality between patients with eGFR \geq 60 mL/min/1.73 m² and patients with eGFR <60 mL/min/1.73 m².

We attempted to identify another cut-off value of eGFR affecting long-term prognosis after CABG using a receiver operating characteristic (ROC) curve (Fig. 2). The cut-off value of eGFR determined with ROC curve analysis was $50.9 \text{ mL/min}/1.73 \text{ m}^2$ (sensitivity=0.810, specificity=0.643, and area under the curve=0.706). With these results, we compared 2 groups divided with an eGFR of 50 mL/min/1.73 m². Although there was no significant difference in allcause death (p=0.195), patients with eGFR $\geq 50 \text{ mL}/$ $min/1.73 m^2$ had significantly lower rates of cardiovascular death than did patients with eGFR <50 mL/min/1.73 m² (p=0.013) (Fig. 3). Furthermore, multivariate analysis with eGFR <50 mL/min/ 1.73 m² as a predictor of cardiovascular death identified 4 independent risk factors, i.e., age (p <0.001), unstable angina (p=0.004), eGFR <50 mL/min/ 1.73 m^2 (p=0.020), and proteinuria (p<0.001) (Table 6). Because the area under the ROC curve was 0.706, further examination and investigation are warranted.

The presence of proteinuria is a risk factor for the end-stage renal failure²³²⁴, but few studies have



1-Specificity



examined the effects of proteinuria after cardiac surgery. In our study, patients with eGFR \geq 50 mL/ min/1.73 m² were further divided into those with proteinuria and those without proteinuria, and longterm outcomes were compared between these groups. We found that patients with proteinuria had significantly worse outcomes than did patients without proteinuria (5-year freedom from cardiovascular death: 0.771 versus 0.954; 8-year freedom from cardiovascular death: 0.579 versus 0.941; *p*<0.001), but among patients with eGFR <50

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Table 6 Multivariate hazard ratios by the Cox proportional hazards model (95% confidence intervals) for cardiovascular death of statistically significant predictors and other predictors for cardiovascular death (including eGFR <50 mL/min/1.73 m² as predictors for cardiovascular death)

Predictive variable	Hazard Ratio (95%CI)	p Value
Age >64.6 years	1.130 (1.064-1.212)	< 0.001
Diabetes mellitus	2.917 (0.998-8.514)	0.051
LVEF <40%	1.813 (0.570-3.884)	0.795
Unstable angina	4.864 (1.662-14.250)	0.004
CCS angina status (III/IV)	1.297 (0.684-2.456)	0.437
eGFR <50 mL/min/1.73 m ²	3.424 (1.218-9.627)	0.020
Proteinuria	7.704 (2.782-21.336)	< 0.001

LVEF, left ventricular ejection fraction; CCS, Canadian Cardiovascular Society



Fig. 3 Effect of eGFR \geq 50 mL/min/1.73 m² or eGFR <50 mL/min/1.73 m² on freedom from all-cause death (a) and freedom from cardiovascular death (b) after CABG.





mL/min/ 1.73 m^2 , there was no difference in longterm outcome on the basis of the presence or absence of proteinuria (p=0.061; Fig. 4).

According to our results, even among patients with eGFR \geq 50 mL/min/1.73 m², patients with proteinuria cases had a worse long-term prognosis than did patients without proteinuria. Thus, in addition to eGFR, proteinuria also affects long-term outcomes after CABG. On the basis of these results, we conclude that proteinuria is a strong predictor of long-term morbidity and mortality, even in patients with eGFR >50 mL/min/1.73 m².

In summary, our findings demonstrate that age, unstable angina, eGFR <50 mL/min/1.73 m², and proteinuria are factors that affect cardiovascular death after CABG and that adverse cardiovascular events are not associated with eGFR <60 mL/min/ 1.73 m^2 but are associated with GFR <50 mL/min/ 1.73 m^2 . Both eGFR <50 mL/min/ 1.73 m^2 and proteinuria are independent risk factors for longterm cardiovascular mortality, and efforts should be made to identify patients at risk for renal dysfunction after surgery.

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