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Influence of renal dysfunction on mortality after cardiac surgery: Modifying effect of preoperative renal function

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Influence of renal dysfunction on mortality after cardiac surgery: Modifying effect of preoperative renal function.

Background. Acute renal failure (ARF) requiring dialysis is an independent risk factor of mortality after cardiac surgery; the level of preoperative renal function influences the risk of both postoperative ARF and mortality. The relationship between mild renal dysfunction and mortality, and the modifying effect of baseline renal function on this association, is less clear.

Methods. We studied 31,677 patients undergoing cardiac surgery between 1993 and 2002. We used a logistic regression model to assess the relationship between postoperative renal dysfunction and mortality, while adjusting for preoperative renal function, postoperative ARF requiring dialysis, and other risk factors.

Results. The overall postoperative mortality rate was 2.2% (698/31,677). For the entire cohort, a clinically relevant increase in the adjusted risk of mortality occurred beyond 30% decline in postoperative GFR. The mortality rate was 5.9% (*N*, 292/4986) among patients who developed 30% or greater decline in postoperative GFR not requiring dialysis versus 0.4% (*N*, 106/26,136) among those with <30% decline ($P < 0.001$). A significant interaction between preoperative GFR and percent change in postoperative GFR ($P < 0.001$) indicated that at equivalent degrees of renal dysfunction, the mortality risk was greater at a lower preoperative GFR. ARF requiring dialysis was strongly associated with mortality in the model (odds ratio 4.2; 95% CI 3.1–5.7).

Conclusion. Renal dysfunction not requiring dialysis is an independent risk factor of mortality after cardiac surgery. A better preoperative GFR attenuates the effect of postoperative renal dysfunction on mortality; this interaction needs to be considered while defining a clinically relevant threshold of ARF.

Acute renal failure (ARF) is a serious complication after cardiac surgery, with an associated mortality rate in excess of 50% [1–5]. The level of baseline renal function prior to cardiac surgery also influences the risk of both postoperative ARF as well as postoperative mortality [4–6]. ARF was perceived as an unfortunate complication that is proxy to the severity of other medical illnesses; however, it is now apparent that severe ARF requiring dialysis after cardiac surgery is an independent risk factor of death [7]. It is less clear, however, as to whether milder degrees of postoperative renal dysfunction independently influence mortality after cardiac surgery. Furthermore, the modifying effect of preoperative renal function on the association between postoperative renal dysfunction and mortality remains to be examined.

Integral to the association between ARF and mortality is the issue of defining clinically relevant threshold of renal dysfunction. The frequency of ARF varies widely depending upon its definition; when defined in its most severe form as requiring dialysis, the incidence of ARF after cardiac surgery is usually less than 5% [4, 5, 8–10]. This translates into a significant challenge while designing clinical trials because it mandates the enrollment of a large number of patients in order to demonstrate the efficacy of an intervention. Arbitrary definitions of less severe degrees of ARF have been used to circumvent this issue, but they fall short of demonstrating a longitudinal association with "hard" clinical end points such as hospital mortality [11–13].

We aim to study the effect of renal dysfunction not requiring dialysis on mortality, in patients undergoing cardiac surgery; to study the interaction between baseline renal function and postoperative decline in glomerular filtration rate (GFR) for its influence on mortality, after adjusting for other confounding risk factors; and to determine a threshold of clinically relevant renal dysfunction based upon its independent association with mortality. The data indicate that renal dysfunction not requiring dialysis is an independent risk factor of mortality, and that a better preoperative renal function attenuates the

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Table 1. Definitions of risk factors affecting mortality

Risk factor	Definition
Age	In years (per 10-year increase)
Weight	*kg*
Gender	Female vs. male
Race	White (89.1%), black (4%), and other (6.9%)
Albumin	Preoperative serum albumin *g/dL*
Preoperative GFR	Calculated by four-variable MDRD equation $mL/min/1.73m^2$
Diabetes mellitus	Insulin requiring diabetes mellitus
COPD	History of chronic obstructive pulmonary disease requiring medical treatment
Peripheral vascular disease	Evidence of peripheral vascular disease by angiography or noninvasive testing, history of vascular surgery, or symptomatic vascular occlusion
Cerebrovascular disease	History of stroke, carotid artery surgery, or >40% stenosis of either carotid artery proven by ultrasound or angiography
LVF <35%	Left ventricular function as determined by echocardiography, left ventriculography, or MUGA scan during the preoperative period
Left main disease	Left main coronary artery disease with >70% occlusion
Congestive heart failure	History of congestive heart failure including history of dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea prior to open-heart surgery
IABP use	Preoperative use of intra-aortic balloon pump
Year of surgery	Calendar year of surgery, 1993 to 2002
Prior surgery	Previous history of open-heart surgery
Emergency surgery	Emergency surgery as indicated by "E" in the anesthesia record sheet as per the criteria of the American Society of Anesthesiology
CPB time	Cardiopulmonary bypass time (minutes)
Surgery type	Coronary artery bypass grafting (CABG), valve surgery, combined CABG and valve procedures, other cardiac surgeries including pericardectomy, septal defect repair, etc.

mortality risk associated with postoperative decline in GFR.

METHODS

Patient population

We studied 33,217 patients who underwent open-heart surgery at the Cleveland Clinic Foundation between April 1993 and December 2002, as recorded in the database of the department of Cardiothoracic Anesthesiology. This on-going registry is approved by the Institutional Review Board to record perioperative information in cardiac surgery patients. There were 34,562 surgeries performed; for the purpose of this analysis, only the first surgical episode was considered. We excluded 1540 patients from the analysis, including those requiring preoperative dialysis, preoperative extra-corporeal membrane oxygenation, preoperative tracheostomy or mechanical ventilation, heart transplant recipients, patients undergoing procedures for automated implantable cardioverter-defibrillator, left ventricular assist devices, sternal work, and those with missing data. One hundred and sixty-four patients met more than one criterion for exclusion. The demographic distribution for the remaining 31,677 patients included 69.5% males (*N*, 22,012) and 31.5% females (*N*, 9665). Racial categories, as recorded in the database, included white (89.1%; *N*, 28,230), black (4%; *N*, 1264), and others (6.9%; *N*, 2183).

Definitions

The primary outcome was all-cause hospital mortality after cardiac surgery. Renal dysfunction was determined by calculating a percent decline in estimated GFR during the postoperative period relative to baseline, but not requiring dialysis. The preoperative GFR was estimated by using baseline serum creatinine, whereas the postoperative GFR was estimated based upon peak serum creatinine during the immediate postoperative period. Both the four-variable MDRD equation [abstract; Levey AS et al, *J Am Soc Nephrol* 11:A0828, 2000; K/DOQI guidelines for chronic kidney disease] and the Cockroft and Gault equation were used to estimate GFR [14].

The preoperative risk factors considered in the analysis for their association with mortality are shown in Table 1. They include demographic factors such as age, gender, race, weight, and clinical risk factors, including preoperative GFR, serum albumin, diabetes mellitus, chronic obstructive pulmonary disease requiring treatment, peripheral vascular disease, cerebrovascular disease, congestive heart failure, left ventricular dysfunction (ejection fraction <35%), greater than 70% occlusion of left main coronary artery, preoperative use of intra aortic balloon pump (IABP), emergency surgery, and the year of surgery. The intraoperative risk factors included cardiopulmonary bypass time and the type of open-heart surgery, including coronary artery bypass graft (CABG) surgery, valve surgery, combined CABG and valve procedures, and other cardiac surgeries, such as ventricular aneurysm repair, septal defect repair, etc. We also considered significant postoperative complications that can affect mortality, including cardiac morbidity, neurologic morbidity, severe ARF requiring dialysis, and serious infection, including sepsis syndrome and septic shock. A detailed account of the variables in the database, the definitions of all of the risk factors, and the postoperative complications has been reported earlier [5, 15]. The rationale for the selection of the potential risk factors in the present analysis was based upon literature review of the risk factors of mortality in cardiac surgery, our initial validation of the database, and clinical plausibility.

Analysis

We calculated the percent change in the postoperative GFR relative to baseline by using both the Cockroft and Gault equation and the four-variable MDRD equation.

We compared the two estimates of GFR on the ability to predict mortality from percent change in GFR using the DeLong method for comparing two dependent receiver operating characteristics (ROC) curves. The area under the curves, a measure of predictive ability, was 0.9, and was similar for both equations (data not shown); thus, GFR estimated by the four-variable MDRD equation was used for subsequent models.

Patients who died and patients who survived were compared on categorical risk factors using the chi-square test, and on continuous risk factors using Wilcoxon rank sum test. Multivariable logistic regression analysis was used to assess the relationship between postoperative decline in GFR and mortality while adjusting for preoperative GFR, postoperative ARF requiring dialysis, and other risk factors. To assess whether preoperative renal function modified the relationship between renal dysfunction and mortality, we included the interaction of preoperative GFR and percent decline in postoperative GFR in the model. The risk of mortality was expressed as odds ratios and 95% confidence intervals (95% CI), in which the reference group was patients with a preoperative GFR of 90 mL/min/1.73m^2 without any decline in postoperative period.

Statistical analyses were conducted using SAS 8.2 (SAS Institute, Cary, NC, USA). All tests were two tailed and performed at a significance level of 0.05.

RESULTS

Postoperative GFR and mortality rates

The overall mortality rate after cardiac surgery was 2.2% (698/31,677). Tables 2 and 3 show the distribution of comorbid risk factors across patients who survived versus those who died after open-heart surgery. Patients who died differed significantly from patients who survived on all of the risk factors. Of note, the median preoperative GFR was 72 mL/min/1.73m^2 among those who survived, whereas it was 57 mL/min/1.73m^2 among those who died. There were 555 patients who developed severe ARF requiring dialysis, with an associated mortality rate of 54%; for the remaining 31,122 patients, the overall mortality rate was 1.3% (*N*, 398). Figure 1 shows the continuous relationship between percent change in postoperative GFR and the risk of mortality by logistic regression model (adjusted for all of the comorbid risk factors and postoperative complications, including dialysis requirement). After considering the median preoperative GFR in the study population, a clinically relevant increase in the risk of mortality occurs beyond 30% decline in postoperative GFR. There were 4986 patients who developed a 30% or greater decline in postoperative GFR but did not require dialysis; the mortality rate among this subgroup of patients was 5.9% (*N*, 292/4986), whereas it was 0.4% (*N*, 106/26,136) among patients with <30% decline in postoperative GFR ($P < 0.001$).

Interaction of preoperative GFR and postoperative renal dysfunction

We hypothesized that the clinically relevant threshold of renal dysfunction for the overall sample, as determined by the risk of death, will be modified by the level of preoperative GFR. In the mortality model, the interaction of preoperative GFR and percent change in postoperative GFR were statistically significant ($P < 0.001$), which supported our hypothesis.

This interaction was examined by calculating odds ratios for mortality at different levels of baseline renal function, as per the categories of chronic kidney disease suggested by the K/DOQI guidelines, versus a reference group with a preoperative GFR of 90 mL/min/1.73m^2 and no decline in their postoperative GFR. Figure 2 shows the odds ratios of mortality associated with postoperative decline in GFR at different levels of baseline renal function. It indicates a curvilinear relationship between an incremental risk of mortality and postoperative decline in GFR, which is altered by the level of baseline renal function. As indicated in Table 4, the odds ratio of mortality was higher with a lower level of preoperative renal function, at equivalent degrees of decline in postoperative GFR. For instance, among patients with preoperative baseline GFR of 90, 60, and 30 mL/min/1.73m^2 and a 30% reduction in postoperative GFR relative to baseline, the odds ratios of mortality were 5.0 (CI, 4.0–6.1), 9.4 (CI, 6.6–13.3), and 17.7 (CI, 10.6–29.5), respectively. We interpret these observations to indicate that a better preoperative renal function offsets the risk of mortality associated with postoperative renal dysfunction.

The distribution of morbidities across patients with different degrees of postoperative renal dysfunction is shown in Table 5. The frequency of all of the morbidities was higher among patients with worsening degrees of renal dysfunction. The multivariate model, after accounting for the interaction of preoperative GFR, also adjusts for the effects of postoperative complications on mortality, including ARF requiring dialysis. Table 6 shows the odds ratios of mortality associated with postoperative

Table 2. Univariate comparison of comorbid risk factors for mortality

Categorical risk factors	Died $N = 698$ (2.2%)	Survived $N = 30{,}979$ (97.8%)	*P* value[c]
Gender			<0.001
Male ($N = 22{,}012$)	389 (55.7%)	21,623 (69.8%)	
Female ($N = 9665$)	309 (44.3%)	9356 (30.2)	
Race			0.035
White ($N = 28{,}230$)	621 (89%)	27,609 (89.1%)	
Black (1264)	39 (5.6%)	1225 (4%)	
Other (2183)	38 (5.4%)	2145 (6.9%)	
Diabetes mellitus			<0.001
Insulin requiring ($N = 2738$)	93 (13.3%)	2645 (8.5%)	
Non-insulin requiring ($N = 5079$)	123 (17.6%)	4956 (16%)	
None ($N = 23{,}860$)	482 (69.1%)	23,378 (75.5%)	
COPD			<0.001
Yes ($N = 2591$)	122 (17.5%)	2469 (8%)	
No ($N = 29{,}086$)	576 (82.5%)	28,510 (92%)	
Peripheral vascular disease			<0.001
Yes ($N = 3805$)	163 (23.4%)	3642 (11.8%)	
No ($N = 27{,}872$)	535 (76.7%)	27,337 (88.2%)	
Cerebrovascular disease			<0.001
Yes ($N = 5435$)	205 (29.4%)	5230 (16.9%)	
No ($N = 26{,}242$)	493 (70.6%)	25,749 (83.1%)	
Left ventricular function <35%			<0.001
Yes ($N = 3541$)	137 (19.6%)	3404 (11%)	
No ($N = 28{,}136$)	561 (80.4%)	25,575 (89%)	
Left main disease			0.001
Yes ($N = 1634$)	55 (7.9%)	1579 (5.1%)	
No ($N = 30{,}043$)	643 (92.1)	29,400 (94.9%)	
Congestive heart failure			<0.001
Yes ($N = 8465$)	365 (52.3%)	8100 (26.2%)	
No ($N = 23{,}212$)	333 (47.7%)	22,879 (73.9%)	
IABP[a] use			<0.001
Yes ($N = 474$)	55 (7.9%)	419 (1.4%)	
No ($N = 31{,}203$)	643 (92.1%)	30,560 (98.7%)	
Prior surgery			<0.001
Yes ($N = 6847$)	257 (36.8%)	6590 (21.3%)	
No ($N = 24{,}830$)	441 (63.2%)	24,389 (78.7%)	
Emergency surgery			<0.001
Yes ($N = 941$)	86 (12.3%)	855 (2.8%)	
No ($N = 30{,}736$)	612 (87.7%)	30,124 (97.2%)	
Surgery type			<0.001
CABG[b] only ($N = 16{,}646$)	265 (38%)	16,381 ($N = 52.9\%$)	
Valve only ($N = 8158$)	154 (22.1%)	8004 ($N = 25.8\%$)	
Combined ($N = 5122$)	196 (28.1%)	4926 ($N = 15.9\%$)	
Other ($N = 1751$)	83 (11.9%)	1668 ($N = 5.4\%$)	

[a] Intra-aortic balloon pump.
[b] Coronary artery bypass grafting.
[c] Chi-square test.

Table 3. Univariate comparison of continuous variables for mortality

Risk factors	Died ($N = 698$) Median (q1, q3)[a]	Survived ($N = 30{,}979$) Median (q1, q3)	*P* value[b]
Age *years*	71.8 (64.2, 77.0)	65.3 (55.8, 72.6)	<0.001
Weight *kg*	74.0 (64.0, 87.0)	80.0 (70.0, 91.0)	<0.001
Albumin *g/dL*	3.8 (3.3, 4.2)	4.2 (3.8, 4.4)	<0.001
Preoperative GFR $mL/min/1.73m^2$	57.0 (41.6, 74.9)	72 (57.9, 87.9)	<0.001
CPB** time *minutes*	134.5 (95.0, 186.0)	97.0 (71.0, 126.0)	<0.001

CPB, cardiopulmonary bypass; GFR, glomerular filtration rate.
[a] q1, first quartile/25th percentile; q3, third quartile/75th percentile.
[b] Wilcoxon rank-sum test.

morbidities. Expectedly, ARF requiring dialysis increased the risk of mortality with an odds ratio of 4.2 (95% CI, 3.1–5.7). The other postoperative complications that were independent determinants of mortality included cardiovascular morbidity (odds ratio 8.3; 95% CI, 6.2–10.9), neurologic morbidity (odds ratio 6.1; 95% CI, 4.6–8.1), and serious infection (odds ratio 3.3; odds ratio, 2.6–4.2).

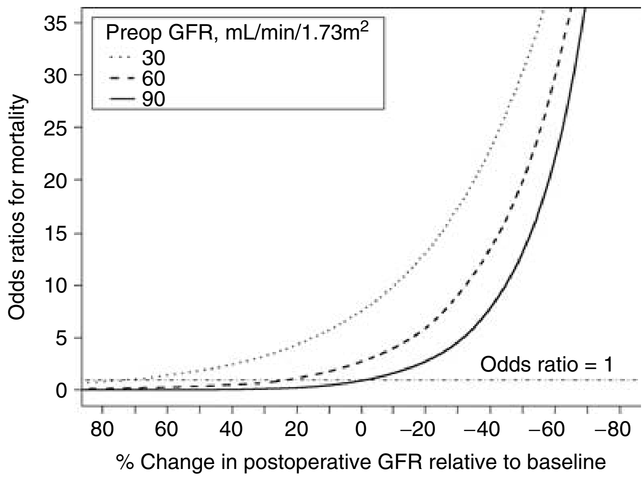

Fig. 1. Continuous relationship between postoperative renal dysfunction and mortality risk. *Logistic regression model adjusted for all of the risk factors in Table 1, as well as postoperative morbidities, including serious infections, cardiovascular morbidity, neurologic morbidity, and acute renal failure requiring dialysis.

DISCUSSION

Although many studies have examined the effect of preoperative comorbid risk factors on mortality after cardiac surgery [6, 16–21], relatively few have studied the independent influence of ARF on mortality [7, 22]. The present study demonstrates that even less severe degrees of renal dysfunction adversely influences patient survival after cardiac surgery. It extends this information by studying the interrelationship between preoperative GFR, postoperative renal dysfunction, and mortality independent of other major risk factors. The study also confirms the association between severe ARF requiring dialysis and mortality after cardiac surgery.

The qualitative effects of dialysis requiring ARF on mortality after cardiac surgery have been reported [7]. In a multicenter observational study from the Veterans Affairs health system, Chertow et al analyzed a large cohort that included 42,773 patients, <1% of which were women. After adjusting for the preoperative risk factors as well as other postoperative morbidities that may influence mortality, the odds ratio of mortality associated with ARF requiring dialysis was 7.9. Although this study pointed out an important association between severe ARF and mortality, it did not assess the effects of relatively subtle degrees of renal dysfunction. Moreover, the cohort was not well represented by differences in gender, which is especially important because female gender has been well recognized as an independent risk factor of morbidity and mortality after cardiac surgery [23–25].

The present study demonstrates a link between nondialysis requiring renal dysfunction and an increased risk of mortality after cardiac surgery. This effect was independent of other major risk factors, including severe ARF requiring dialysis. Furthermore, the cohort was well represented by differences in gender (31.5% females) and race, which were accounted for as risk factors in the logistic regression model.

There are few studies that have examined the effects of less severe renal dysfunction on mortality. Levy et al were among the first investigators to address this question in the setting of nephrotoxic renal failure secondary to the administration of radio contrast agents [26]. They performed a retrospective case-control analysis to examine the effect of ARF on mortality independent of other comorbidities. In this single-center study, ARF was arbitrarily defined as a 25% or greater increase in serum creatinine at 2 days after the administration of contrast. There were 174 matched pairs of ARF patients. The overall mortality in patients with ARF was 34% compared to 7% among the matched control patients who did not develop ARF. The adjusted odds ratio of mortality associated with ARF was 5.5. This information regarding the relationship between the magnitude of serum creatinine elevation and mortality has been widely used to define ARF by subsequent clinical trials in the setting of nephrotoxic renal injury [11–13, 27]. It should be noted, however, that 12% of the subjects with ARF, as defined in this study, subsequently went on to require renal replacement therapy; the mortality rate in this subgroup was 62%. Thus, the effects of less severe degrees of renal dysfunction on mortality may have been confounded by the subgroup that subsequently developed severe ARF requiring dialysis. Moreover, using an arbitrary definition of renal dysfunction ad hoc in order to study its association with mortality can introduce an ascertainment bias. In a more recent study, Lassnigg et al [22] examined a cohort of 4118 patients undergoing cardiothoracic surgery. This analysis examined the effects of increments of 0.1 mg/dL in serum creatinine at 48 hours after surgery on mortality. The multivariate analysis adjusted for other preoperative risk factors and postoperative dialysis requirement. However, the relation between change in creatinine and mortality did not account for serious postoperative complications, such as infections, sepsis, cardiac complications, etc., which are known to be major contributors to postoperative mortality independent of ARF [5, 7, 28, 29]. Both of these studies fell short of examining the modifying influence of baseline renal function on a clinically relevant threshold of renal dysfunction.

The present analysis describes the relationship between renal dysfunction and mortality among cardiac surgery patients. We assessed the continuous relationship between renal dysfunction not requiring dialysis and mortality after adjusting for other potential risk factors. We did so by accounting for the major preoperative and intraoperative comorbid risk factors as well serious postoperative morbidities. Thus, effects of less severe degrees of renal dysfunction on mortality were not only independent

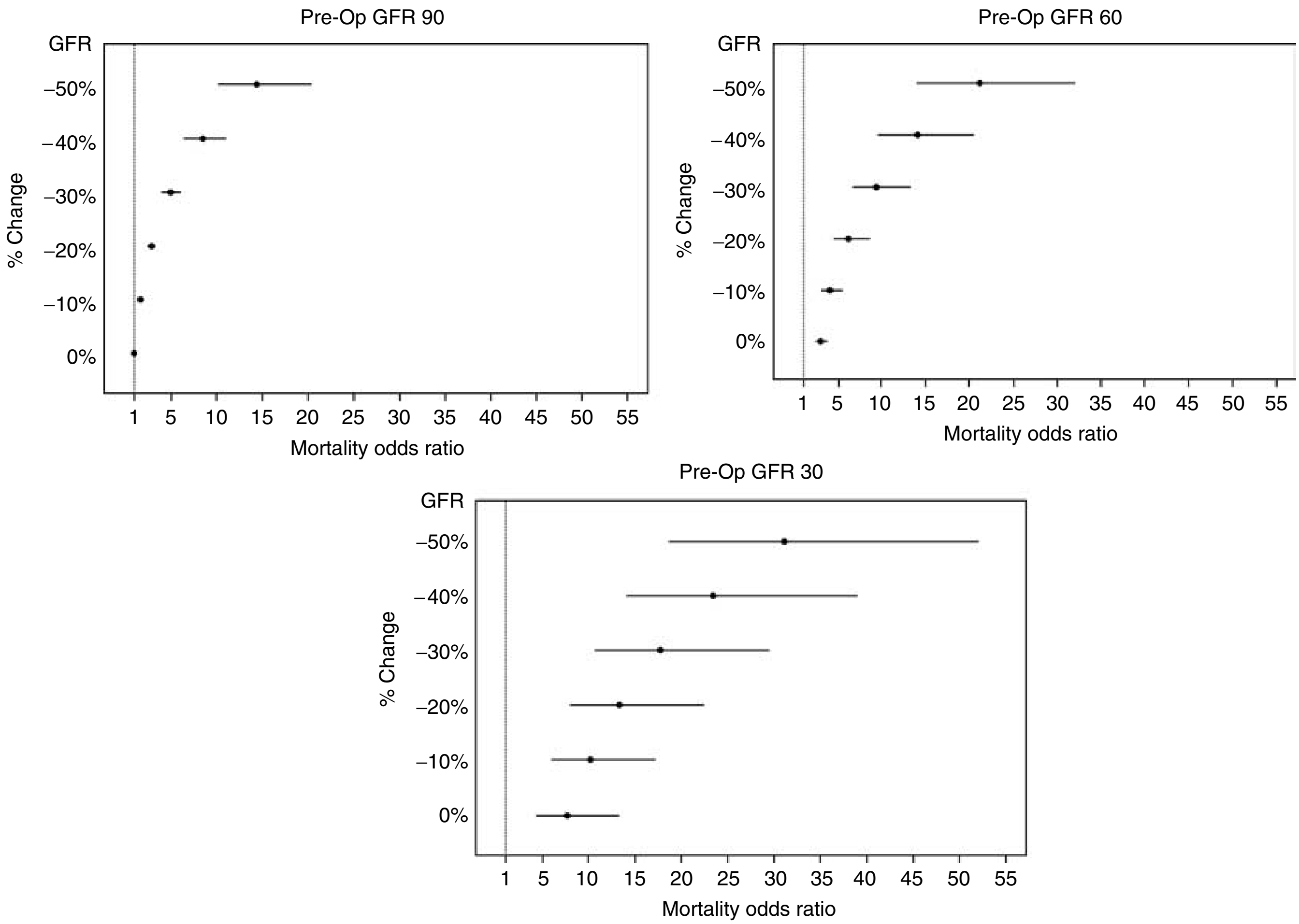

Fig. 2. Modifying effect of various levels of baseline renal function on the threshold of postoperative renal dysfunction. *Logistic regression model adjusted for all other variables in Table 1 and all of the postoperative morbidities listed in Table 5. GFR, glomerular filtration rate.

Table 4. Modifying effect of preoperative GFR on the risk of mortality associated with postoperative renal dysfunction[a]

	Odds ratio (95% CI) for mortality[c]		
Baseline GFR[b]	10% drop in GFR	30% drop in GFR	50% drop in GFR
90 mL/min/1.73 m^2	1.7 (1.6–1.8)	5.0 (4.0–6.1)	14.4 (10.2–20.4)
60 mL/min/1.73 m^2	4.1 (3.1–5.6)	9.4 (6.6–13.3)	21.2 (14.0–32.1)
30 mL/min/1.73 m^2	10.1 (5.9–17.2)	17.7 (10.6–29.5)	31.1 (18.6–52.0)

[a]Logistic regression model adjusted for all of the other risk factors in Table 1 and postoperative morbidities listed in Table 3.
[b]Glomerular filtration rate estimated by the four-variable MDRD equation.
[c]Odds ratios of mortality calculated with reference to a baseline GFR of 90 mL/min/1.73m^2 without any decline in postoperative GFR.

of the influence of dialysis requiring ARF, but also adjusted for other major determinants of mortality.

Baseline renal function before cardiac surgery is an independent risk factor of both postoperative ARF as well as postoperative mortality. We hypothesized that a threshold of clinically relevant renal dysfunction in a given cohort will be modified by the level of preoperative baseline renal function. To test the hypothesis statistically, we examined a model of interaction between preoperative GFR and postoperative renal dysfunction for its independent effect on mortality. Expectedly, at equivalent degrees of postoperative renal dysfunction, the risk of mortality was higher at a lower level of preoperative GFR. Said in another way, the risk of mortality after cardiac surgery associated with renal dysfunction is offset by a better preoperative renal function. It should be noted, however, that the median preoperative GFR in our cohort was 72 mL/min/1.73m^2, and that the number of patients with severe impairment of baseline renal function was relatively small.

Although there is an unequivocal association between severe ARF and mortality, the event rate of ARF

Table 5. Distribution of morbidities across patients with different degrees of renal dysfunction

Morbidities	ARF[a] requiring dialysis $N = 555$ (%)	30% or greater decline in GFR[b] (no dialysis) $N = 4986$ (%)	<30% decline in GFR[b] (no dialysis) $N = 26,136$ (%)	P value[c]
Cardiac morbidity				<0.001
Yes	169 (30.5)	253 (5.1)	174 (0.67)	
No	386 (69.5)	4733 (94.9)	25,962 (99.3)	
Neurologic morbidity				<0.001
Yes	85 (15.3)	272 (5.5)	313 (1.2)	
No	470 (84.7)	4714 (94.5)	25,823 (98.8)	
Serious infection				<0.001
Yes	322 (58)	518 (10.4)	222 (0.85)	
No	233 (42)	4468 (89.6)	25,914 (99.2)	

[a]Acute renal failure.
[b]Glomerular filtration rate.
[c]Chi-square test for all pairwise comparisons.

requiring dialysis is very low, with a frequency of less than 5%. This limits the ability of clinical trials pertaining to the prevention or treatment of ARF to demonstrate clear benefits by necessitating the enrollment of a large number of patients. To circumvent this difficulty, several studies have used arbitrary definitions of less severe degrees of renal failure. Using the relatively "liberal" definition of outcome optimizes the event rate, allowing us to enhance the assessment of efficacy of therapy. It then becomes pivotal, however, to demonstrate that whether relatively subtle degree of renal dysfunction does indeed affect mortality, independent of other comorbidities. In the present study, instead of arbitrarily defining renal dysfunction, we describe the interrelationship between decline in GFR and mortality; the data indicate that a clinically relevant threshold of renal dysfunction can be significantly altered by the interaction of baseline renal function, even after accounting for other major risk factors.

There are limitations to this analysis. The use of any of the available equations to estimate GFR in the setting of ARF has its own drawbacks. However, the purpose of this analysis was not to accurately quantify the GFR, but rather to attempt to objectively define postoperative renal dysfunction based upon its ability to identify a group of patients with an increased risk of mortality. Another limitation of the study is that the database does not record either the cause of death or the temporal association between the postoperative complications on all patients. Thus, the reasons why patients with mild renal dysfunction are at an increased risk of death can only be speculated. The data do indicate, however, that the presence of complications, such as serious infection or cardiac morbidity, which can be attributed as causes of death, were more frequent among patients with worsening degree of renal dysfunction. Thus, even if a particular morbidity was related partly to preceding renal dysfunction (e.g., serious infections), it would have been identified as an independent contributor to patient mortality by the multivariate model. Consequently, we believe that the influence of renal dysfunction on mortality may actually be a conservative estimate. There could be other factors that may influence mortality, and were not recorded in the database. But we have accounted for the majority of clinically relevant variables that can affect mortality after cardiac surgery, including the major postoperative complications and the interaction of preoperative GFR.

Table 6. Adjusted odds ratios[a] for mortality associated with postoperative complications

Postoperative morbidity	Odds ratio (95% confidence interval)	P value
Cardiac morbidity	8.3 (6.2–10.9)	<0.001
Neurologic morbidity	6.1 (4.6–8.1)	<0.001
Serious infection	3.3 (2.6–4.2)	<0.001
ARF requiring dialysis	4.2 (3.1–5.7)	<0.001

[a]Odds ratios adjusted for all of the preoperative comorbid variables in Table 1, including the interaction of preoperative renal function.

CONCLUSION

Renal dysfunction not requiring dialysis is an independent risk factor of mortality after cardiac surgery. A better preoperative renal function attenuates the effect of postoperative renal dysfunction on mortality, and that this interaction needs to be considered while defining a clinically relevant threshold of ARF. We interpret these observations to indicate that prevention or treatment of even subtle degrees of renal dysfunction may portend a significant survival benefit.

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REFERENCES

1. Abel RM, Buckley MJ, Austen WG, *et al*: Etiology, incidence, and prognosis of renal failure following cardiac operations. Results of a prospective analysis of 500 consecutive patients. *J Thorac Cardiovasc Surg* 71:323–333, 1976
2. Hilberman M, Myers BD, Carrie BJ, *et al*: Acute renal failure following cardiac surgery. *J Thorac Cardiovasc Surg* 77:880–888, 1979
3. Mangano CM, Diamondstone LS, Ramsay JG, *et al*: Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. *Ann Intern Med* 128:194–203, 1998
4. Chertow GM, Lazarus JM, Christiansen CL, *et al*: Preoperative renal risk stratification. *Circulation* 95:878–884, 1997
5. Thakar CV, Liangos O, Yared JP, *et al*: ARF after open-heart surgery: Influence of gender and race. *Am J Kidney Dis* 41:742–751, 2003
6. Higgins TL, Estafanous FG, Loop FD, *et al*: Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. A clinical severity score. *JAMA* 267:2344–2348, 1992
7. Chertow GM, Levy EM, Hammermeister KE, *et al*: Independent association between acute renal failure and mortality following cardiac surgery. *Am J Med* 104:343–348, 1998
8. Frost L, Pedersen RS, Lund O, *et al*: Prognosis and risk factors in acute, dialysis-requiring renal failure after open-heart surgery. *Scand J Thorac Cardiovasc Surg* 25:161–166, 1991
9. Andersson LG, Ekroth R, Bratteby LE, *et al*: Acute renal failure after coronary surgery—A study of incidence and risk factors in 2009 consecutive patients. *Thorac Cardiovasc Surg* 41:237–241, 1993
10. Conlon PJ, Stafford-Smith M, White WD, *et al*: Acute renal failure following cardiac surgery. *Nephrol Dial Transplant* 14:1158–1162, 1999
11. Tepel M, van der Giet M, Schwarzfeld C, *et al*: Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* 343:180–184, 2000
12. Kay J, Chow WH, Chan TM, *et al*: Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: A randomized controlled trial. *JAMA* 289:553–558, 2003
13. Merten GJ, Burgess WP, Gray LV, *et al*: Prevention of contrast-induced nephropathy with sodium bicarbonate: A randomized controlled trial. *JAMA* 291:2328–2334, 2004
14. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976
15. Thakar CV, Yared JP, Worley S, *et al*: Renal dysfunction and serious infections after open-heart surgery. *Kidney Int* 64:239–246, 2003
16. Kennedy JW, Kaiser GC, Fisher LD, *et al*: Multivariate discriminant analysis of the clinical and angiographic predictors of operative mortality from the Collaborative Study in Coronary Artery Surgery (CASS). *J Thorac Cardiovasc Surg* 80:876–887, 1980
17. Kennedy JW, Kaiser GC, Fisher LD, *et al*: Clinical and angiographic predictors of operative mortality from the collaborative study in coronary artery surgery (CASS). *Circulation* 63:793–802, 1981
18. Grover FL, Johnson RR, Marshall G, Hammermeister KE: Factors predictive of operative mortality among coronary artery bypass subsets. *Ann Thorac Surg* 56:1296–1306, 1993
19. Grover FL, Johnson RR, Shroyer AL, *et al*: The Veterans Affairs Continuous Improvement in Cardiac Surgery Study. *Ann Thorac Surg* 58:1845–1851, 1994
20. Magovern JA, Sakert T, Magovern GJ, *et al*: A model that predicts morbidity and mortality after coronary artery bypass graft surgery. *J Am Coll Cardiol* 28:1147–1153, 1996
21. Tu JV, Jaglal SB, Naylor CD: Multicenter validation of a risk index for mortality, intensive care unit stay, and overall hospital length of stay after cardiac surgery. Steering Committee of the Provincial Adult Cardiac Care Network of Ontario. *Circulation* 91:677–684, 1995
22. Lassnigg A, Schmidlin D, Mouhieddine M, *et al*: Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: A prospective cohort study. *J Am Soc Nephrol* 15:1597–1605, 2004
23. O'Connor GT, Morton JR, Diehl MJ, *et al*: Differences between men and women in hospital mortality associated with coronary artery bypass graft surgery. The Northern New England Cardiovascular Disease Study Group. *Circulation* 88:2104–2110, 1993
24. Roques F, Nashef SA, Michel P, *et al*: Risk factors and outcome in European cardiac surgery: Analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* 15:816–822, 1999
25. Edwards FH, Carey JS, Grover FL, *et al*: Impact of gender on coronary bypass operative mortality. *Ann Thorac Surg* 66:125–131, 1998
26. Levy EM, Viscoli CM, Horwitz RI: The effect of acute renal failure on mortality. A cohort analysis. *JAMA* 275:1489–1494, 1996
27. Kurnik BR, Allgren RL, Genter FC, *et al*: Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis* 31:674–680, 1998
28. Rady MY, Ryan T, Starr NJ: Perioperative determinants of morbidity and mortality in elderly patients undergoing cardiac surgery. *Crit Care Med* 26:225–235, 1998
29. Welsby IJ, Bennett-Guerrero E, Atwell D, *et al*: The association of complication type with mortality and prolonged stay after cardiac surgery with cardiopulmonary bypass. *Anesth Analg* 94:1072–1078, 2002