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## Occult renal dysfunction: a mortality and morbidity risk factor in coronary artery bypass grafting surgery

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**Objective:** Elevated preoperative serum creatinine is considered an independent risk factor for postoperative mortality and morbidity in patients undergoing coronary artery bypass grafting. However, the impact of occult renal dysfunction, defined as an impairment of glomerular filtration rate with normal serum creatinine, is still unknown. The aim of this study was to analyze the effects of occult renal dysfunction on early outcomes after coronary artery bypass grafting.

**Methods:** This was a retrospective, observational, cohort study of prospectively collected data on 9159 consecutive patients with normal serum creatinine levels undergoing coronary artery bypass grafting between April 1996 and February 2009. Patients were divided into two groups based on preoperative creatinine clearance estimated with the Cockcroft-Gault equation: 5484 patients with a creatinine clearance  $\geq 60$  mL/min and 3675 patients with a creatinine clearance  $< 60$  mL/min (occult renal dysfunction group).

**Results:** Overall in-hospital mortality was 1%. Occult renal dysfunction was associated with a doubling in the risk of operative mortality (1.4% vs 0.7%;  $P = .001$ ), postoperative renal dysfunction (5.1% vs 2.5%;  $P < .0001$ ), and need for dialysis (0.8% vs 0.4%;  $P = .014$ ). Moreover, occult renal dysfunction increased the risk of stroke (1% vs 0.3%;  $P < .0001$ ), arrhythmia (28.5% vs 21.2%;  $P < .0001$ ), and hospital stay  $> 7$  days (36.45 vs 24.5%;  $P < .0001$ ). In a multivariable analysis adjusting for preoperative risk factors, occult renal dysfunction was confirmed to be an independent predictor of mortality (odds ratio, 1.72), postoperative renal dysfunction (odds ratio, 1.9), dialysis (odds ratio, 1.82), stroke (odds ratio, 2.6) arrhythmia (odds ratio, 1.42), and hospital stay  $> 7$  days (odds ratio, 1.65).

**Conclusions:** Occult renal dysfunction is an independent risk factor for early mortality and morbidity in patients undergoing coronary artery bypass grafting. (J Thorac Cardiovasc Surg 2011;141:771-6)

Elevated preoperative serum creatinine (SCr) is considered an independent risk factor for postoperative mortality and morbidity in patients undergoing cardiac surgery.<sup>1-4</sup> The overall mortality risk for patients with preoperative SCr  $> 130$   $\mu\text{mol/L}$  (1.5 mg/dL) ranges from 5% to 30% and the probability of death increases with the increasing preoperative SCr level.<sup>2-6</sup>

Serum creatinine is a specific marker of renal dysfunction; however, because its generation is determined by age, race, muscle mass, and dietary intake other than filtration creatinine, it can remain within the normal range when renal function is significantly impaired.<sup>7,8</sup>

Estimated creatinine clearance (eCrCl) has been described as a more sensitive screening test in predicting renal reserve and a better predictor of mortality and morbidity than SCr in cardiac surgery.<sup>5,9-11</sup> On the contrary, Cooper and colleagues<sup>12</sup> analyzed 483,914 patients undergoing coronary artery bypass grafting (CABG) and suggested that various measures of renal function, including SCr, performed similarly well in models predicting operative mortality. However, in all these studies, limited information is given on the risk associated with occult renal dysfunction (ORD).

The National Kidney Foundation defined chronic kidney disease as glomerular filtration rate (GFR)  $< 60$  mL/min/1.73 m<sup>2</sup> for  $\geq 3$  months, with or without kidney damage, and that GFR may be derived by eCrCl.<sup>13</sup> According to this definition, the prevalence of chronic renal disease is among 63 million people in the United States, and it is associated with increased risk of cardiovascular events.<sup>13,14</sup> Given the rising incidence and prevalence of cardiovascular disease with declining renal function, it is important to understand the impact of ORD on adverse events in patients undergoing cardiac surgery.<sup>14,15</sup> Therefore, the aim of our study was to evaluate the effect of ORD, defined as an impairment of glomerular filtration rate with normal SCr, on early clinical outcomes in patients undergoing CABG.

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### Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CI	= confidence interval
CrCl	= creatinine clearance
eCrCl	= estimated creatinine clearance
GFR	= glomerular filtration rate
ORD	= occult renal dysfunction
MI	= myocardial infarction
OR	= odds ratio
PRD	= postoperative renal dysfunction
SCr	= serum creatinine

## MATERIALS AND METHODS

### Patient Selection and Data Definitions

This was a retrospective, observational, cohort study of prospectively collected data from consecutive patients undergoing CABG at the Bristol Heart Institute between April 1996 and February 2009. The study was approved by the clinical audit committee of the University Hospital Bristol National Health Service Foundation Trust to meet ethical and legal requirements and individual consent was waived. The data collection form is entered in a database (Patient Analysis & Tracking System; Dendrite Clinical Systems, London, UK) and includes 5 sections that are filled in consecutively by anesthetists, surgeons, and intensive care unit, high dependency unit, and ward nurses.

The normal range for SCr was defined as 30 to 130  $\mu\text{mol/L}$  (0.34–1.47 mg/dL) and these limits represent the 97.5 percentile of the distribution of SCr levels in healthy male and female volunteers.<sup>8</sup> We analyzed data on all of the patients undergoing isolated CABG with a preoperative SCr  $\leq$  130  $\mu\text{mol/L}$  ( $\leq$  1.47 mg/dL). Exclusion criteria were patients who had unknown SCr concentration before surgery (210 patients) and SCr  $>$  130  $\mu\text{mol/L}$  ( $>$  1.47 mg/dL; 1480 patients). According to the National Kidney Foundation,<sup>13</sup> preoperative renal dysfunction was defined as GFR  $<$  60 mL/1.73 m<sup>2</sup>, and measurement of GFR was estimated on the basis of the Cockcroft and Gault<sup>16</sup> equation as follows:

$$\text{eCrCl} = \frac{(140 - \text{Age}) \times \text{Weight}[\text{kg}] (\times 0.85 \text{ if woman})}{72 \times (\text{Scr}[\mu\text{mol/L}]/88.4)}$$

in which 88.4 is a conversion factor to express SCr in mg/dL.

The final sample size was made of 9159 patients who were divided into two groups based on eCrCl level: 5484 patients with an eCrCl  $\geq$  60 mL/min (control patients group) and 3675 (40.1%) patients with eCrCl  $<$  60 mL/min (ORD group). Baseline characteristics were defined according to EuroSCORE model.<sup>1</sup> The decision to perform off-pump or on-pump CABG technique was based on individual surgeon preference.

### Study End Points

The primary end point was in-hospital mortality, defined as any death occurring within 30 days of operation. Secondary end points were postoperative renal dysfunction (PRD), need for postoperative dialysis/hemofiltration, arrhythmia, myocardial infarction (MI), stroke, and hospital stay  $>$  7 days. A diagnosis of postoperative MI was based on the presence of Q waves  $>$  0.04 ms, and/or a reduction in R waves  $>$  25% in at least two contiguous leads on echocardiogram. The PRD was defined as SCr level  $>$  200  $\mu\text{mol/L}$ , plus an increase of at least 1.5 times preoperative baseline concentrations. Postoperative arrhythmia was defined as any presence of supraventricular arrhythmia. A diagnosis of stroke was made if there was evidence of new neurologic deficit with morphologic substrate confirmed by computer tomography or nuclear magnetic resonance imaging.

### Anesthetic, Surgical Technique, and Postoperative Management

Anesthetic and surgical techniques were standardized for all patients and have been reported previously.<sup>17,18</sup> In brief, for patients undergoing on-pump CABG, cardiopulmonary bypass was instituted with the use of ascending aortic cannulation and two-stage venous cannulation of the right atrium. The membrane oxygenator was primed with 1000 mL of Hartmann's crystalloid, 500 mL Gelofusine (B Braun Medical Ltd, Emmenbrücke, Switzerland), 0.5 g/kg mannitol, 7 mL of 10% calcium gluconate, and 6000 IU heparin. Alpha-stat pH management was used, and the systemic temperature was kept between 34°C and 36°C. Myocardial protection was achieved with intermittent hyperkalaemic warm blood cardioplegia. For off-pump CABG, the Bristol technique was used to expose the coronaries and provide stabilization to undertake the anastomosis.<sup>18</sup> At the end of surgery, patients were transferred to the intensive care unit and managed according to the unit protocol.<sup>17,18</sup>

### Statistical Analysis

Continuous data were expressed as mean  $\pm$  standard deviation, and categorical data as percentages. The Kolmogorov–Smirnov test was used to check for normality of data in the two groups before further analysis. Differences between ORD and control group were compared using  $\chi^2$  test for categorical variables, and the Student *t* test or the Wilcoxon rank sum test, as appropriate, for continuous variables. To reduce the effect of selection bias and potential confounding in this observational study, a propensity score was undertaken.<sup>19</sup> The propensity for ORD was determined without regard of outcomes by the use of a nonparsimonious multiple logistic regression analysis. All the variables listed in Table 1 were included in the analysis. Logistic regression was performed to assess the effect associated with ORD on each end point after adjusting for potentially confounding variables listed in Table 1 and the propensity score. Results are reported as percentages and odds ratios (OR) with 95% confidence interval (CI). All reported *P* values are two-sided, and *P* values of less than .05 were considered to indicate statistical significance. All statistical analysis was performed with SPSS 15.0 (SPSS Inc, Chicago, Ill).

## RESULTS

In the study population of 9159 patients with normal SCr levels, a total of 3675 (40.1%) patients had an eCrCl  $<$  60 mL/min and were classified as having ORD (Figure 1). The mean ( $\pm$  standard deviation) eCrCl was 51.4 (5.8) mL/min versus 73.3 (11.2) mL/min, in the ORD and control patients group, respectively. Baseline characteristics of the study population are shown in Table 1. Patients in the ORD group were older and more often female; they were more likely to have a lower angina functional class, greater prevalence of hypertension, chronic obstructive pulmonary disease, extracardiac arteriopathy, and previous cardiac operations. Patients with ORD were also more likely to have a lower ejection fraction and greater prevalence of New York Heart Association functional class. The prevalence of the off-pump procedure was similar between the two groups.

The overall rate of mortality was 1%. Results from univariate and multivariable logistic analysis are reported in Tables 2 and 3. The ORD was associated with a doubling in the risk of death (53 patients [1.4%] vs 38 patients [0.7%]; OR, 2.1; 95% CI, 1.38–3.19; *P* = .001), PRD (189 patients [5.1%] vs 138 patients [2.5%]; OR, 2.1;

TABLE 1. Baseline characteristics of the patients

Variables	CrCl < 60 mL/min (n = 3675)	CrCl > 60 mL/min (n = 5484)	P value
Age, mean ± SD (y)	70.7 ± 6	59.6 ± 8.3	<.0001
Female	1045 (28.4)	742 (13.5)	<.0001
eCrCl, mean ± SD (mL/min)	51.4 ± 5.8	73.3 ± 11.2	<.0001
CCS 3-4 class	2028 (55.2)	2675 (48.8)	<.0001
NYHA III-IV class	1208 (32.9)	1506 (27.5)	<.0001
Diabetes	523 (14.2)	825 (15)	.296
Hypertension	2525 (68.4)	3443 (62.8)	<.0001
COPD	407 (11.1)	519 (9.5)	.013
Neurologic disease	47 (1.3)	56 (1)	.296
Extracardiac arteriopathy	365 (9.9)	398 (7.3)	<.0001
Previous cardiac surgery	118 (3.2)	121 (2.2)	.004
Critical preoperative state	62 (1.7)	65 (1.2)	.055
Preoperative EF			<.0001
Good	2658 (72.3)	4234 (77.2)	
Fair	845 (23)	1058 (19.3)	
Poor	172 (4.7)	192 (3.5)	
Recent MI	1302 (35.4)	1843 (33.6)	.076
Emergency	71 (1.9)	96 (1.8)	.578
No. grafts performed	2.74 ± 0.79	2.68 ± 0.84	.001
Off-pump surgery	1720 (46.9)	2263 (48.7)	.103

Value are express as n = number of patients and (%) unless specified. *CCS*, Canadian Cardiovascular Society; *COPD*, chronic obstructive pulmonary disease; *eCrCl*, estimated creatinine clearance; *EF*, ejection fraction; *NYHA*, New York Heart Association; *MI*, myocardial infarction; *SD*, standard deviation.

95% CI, 1.68-2.27;  $P < .0001$ ), and need for dialysis (30 patients [0.8%] vs 22 patients [0.4%]; OR, 2; 95% CI, 1.18-3.58;  $P = .014$ ). There was a significant difference between ORD and the control patients group in the risk of stroke (35 patients [1%] vs 18 patients [0.3%]; OR, 2.9; 95% CI, 1.65-5.16;  $P < .0001$ ), arrhythmia (1046 patients [28.5%] vs 1163 patients [21.2%]; OR, 1.48; 95% CI, 1.34-1.63;  $P < .0001$ ), and hospital stay > 7 days. After adjusting for confounding variables listed in Table 1, as well as propensity score, the ORD remained an important predictor of mortality (OR, 1.72; 95% CI, 1.12-2.64; C-statistic, 0.78), PRD (OR, 1.9; 95% CI, 1.53-2.41; C statistic, 0.84), need for dialysis (OR, 1.82; 95% CI, 1.01-3.2; C-statistic, 0.77), stroke (OR, 2.6; 95% CI, 1.47-4.67; C statistic, 0.8), arrhythmia (OR, 1.42; 95% CI, 1.28-1.57; C statistic, 0.81). The ORD was not significantly associated with increased risk of postoperative MI in either univariate or multivariable analysis. The median length of hospital stay was 6 days (interquartile range, 5 to 8). The rate of hospital stay > 7 days was higher in the ORD group (1337 patients [36.4%] vs 1344 patients [24.5%]; OR, 1.76; 95% CI, 1.61-1.93;  $P < .0001$ ) and at multivariable analysis, the ORD group was confirmed to be a predictor of length of stay > 7 days (OR, 1.65; 95% CI, 1.5-1.81; C statistic, 0.82). When modeled as univariate continuous variable, a curvilinear relationship was seen between the estimated probability of death and eCrCl; a similar relationship was observed between eCrCl and the estimated probability of PRD (Figure 2).

## DISCUSSION

Our study demonstrates that ORD, defined as an impairment of glomerular filtration rate (eCrCl < 60 mL/min) with normal SCr level, is a mortality and morbidity risk factor in patients undergoing CABG. Specifically, we found that ORD was associated with doubling in the risk of death, PRD, and dialysis. Moreover, ORD increased the risk of stroke, arrhythmia, and length of hospital stay > 7 days. We observed no significant relationship between ORD and the risk of postoperative MI.

Earlier studies, as well as the most common risk stratifications, rely on SCr as a screening test for estimating renal reserve in predicting adverse outcomes in cardiac surgery.<sup>1,20-22</sup> The accuracy of SCr as indicator of renal disease is limited because it depends on several nonrenal factors, as well as filtration creatinine; therefore SCr levels may remain within the normal range when renal function is significantly impaired. The National Kidney Foundation published clinical guidelines on evaluation, classification, and risk stratification in chronic renal failure, identifying the GFR as the best measure of overall kidney function.<sup>13</sup> Chronic kidney disease was defined as GFR < 60 mL/min/1.73 m<sup>2</sup> for more than 3 months with or without kidney damage. This cutoff represents loss of half or more of the adult level of normal kidney function.<sup>13</sup> However, because practical limitations exist in measuring GFR directly, eCrCl was considered as an alternative measure of renal function that estimates GFR.<sup>7,13,16</sup> An increased risk of postoperative mortality and morbidity with decreased estimated GFR

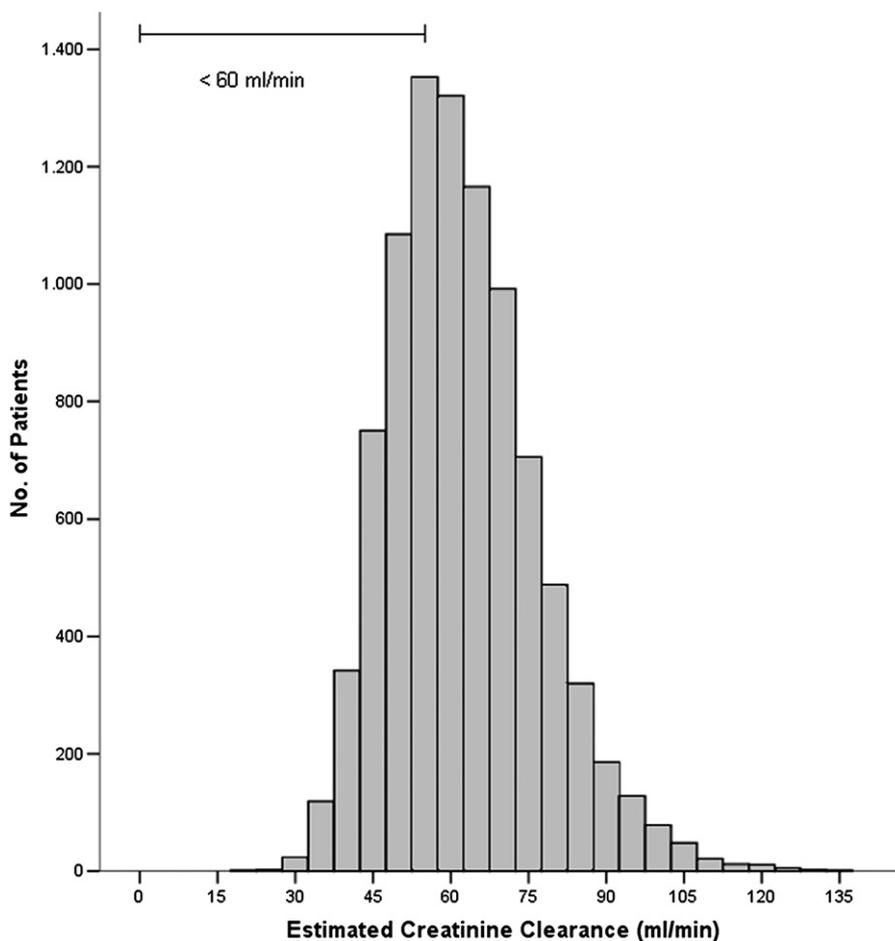


FIGURE 1. Distribution of estimated creatinine clearance among patients in the study.

has been previously described among patients undergoing cardiac surgery.<sup>9-12</sup> However, only sub-analysis of a few studies have focused on patients with normal range SCr levels and reduced renal function.<sup>5,11</sup> Wang and colleagues<sup>5</sup> revealed that among 4603 patients with normal plasma creatinine levels undergoing cardiac surgery, 28% had an estimated CrCl < 60 mL/min that was associated with increased risk of mortality, renal failure requiring dialysis, and major morbidity including cardiovascular, respira-

tory, neurologic, and infectious events.<sup>5</sup> In Wijeyesundera and colleagues,<sup>11</sup> 13% of individual with normal SCr were found to have ORD; in comparison with patients with normal renal function, patients with ORD experienced more than 3-fold increased risk of mortality and renal replacement therapy.<sup>11</sup> Both these studies were focused on

TABLE 2. Clinical outcomes

Outcomes	CrCl < 60 mL/min (n = 3675)	CrCl > 60 mL/min (n = 5484)	P value
Mortality	53 (1.4)	38 (0.7)	.001
Renal dysfunction	189 (5.1)	138 (2.5)	<.0001
Dialysis	30 (0.8)	22 (0.4)	.014
MI	99 (2.7)	129 (2.4)	.337
Stroke, n (%)	35 (1)	18 (0.3)	<.0001
Arrhythmia, n (%)	1046 (28.5)	1163 (21.2)	<.0001
Hospital stay > 7 days, n (%)	1337 (36.4)	1344 (24.5)	<.0001

Results are expressed as n = number of patients and (%). CrCl, Creatinine clearance; MI, myocardial infarction.

TABLE 3. Observed and adjusted ORs of postoperative adverse outcomes after CABG, according to presence or absence of occult renal dysfunction

Outcomes	OR	
	Crude (95% CI)	Adjusted* (95% CI)
Mortality	2.1 (1.38-3.19)	1.72 (1.12-2.64)
Renal dysfunction	2.1 (1.68-2.27)	1.9 (1.53-2.41)
Dialysis	2 (1.18-3.58)	1.82 (1.01-3.2)
MI	1.15 (0.88-1.5)	1.1 (0.84-1.44)
Stroke	2.9 (1.65-5.16)	2.6 (1.47-4.67)
Arrhythmia	1.48 (1.34-1.63)	1.42 (1.28-1.57)
Hospital stay (> 7 days)	1.76 (1.61-1.93)	1.65 (1.5-1.81)

CABG, Coronary artery bypass grafting; CI, confidence interval; OR, odds ratio; MI, myocardial infarct. \*Adjusted for baseline characteristics listed in Table 1 and propensity score.

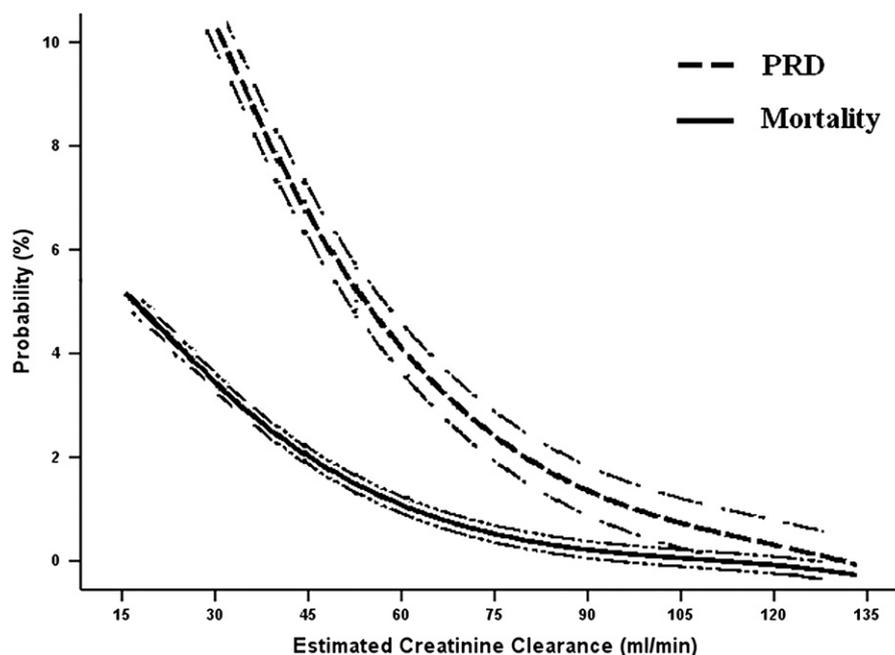


FIGURE 2. Probability of death and postoperative renal dysfunction (PRD) according to preoperative estimated creatinine clearance.

a nonselective population of patient with either ischemic or valvular heart disease, which could be a significant bias in retrospective studies. Furthermore, the aim of these studies was to investigate the accuracy of eCrCl in predicting outcomes in several categories of risk (normal, mild, moderate, and severe renal dysfunction), including patients with high SCr creatinine levels. The risk associated with ORD was investigated in a rather limited sample size. Our study was based on a large homogenous group of patients with normal SCr levels undergoing isolated CABG, confirming the greater sensitivity of eCrCl in predicting renal dysfunction, and adverse postoperative outcomes.

Among 9159 patients with normal SCr levels undergoing CABG, approximately 40% had an eCrCl < 60 mL/min, suggestive of ORD. This differs from previous reports that found an incidence of ORD ranging from 6% to 28%.<sup>5,11,23</sup> A possible explanation could be the different definition of normal range for SCr level. We defined SCr levels normal range between 30 and 130  $\mu\text{mol}$  (0.34-1.47 mg/dL) and these limits represent the 97.5 percentile of the distribution of SCr levels in healthy male and female volunteers.<sup>8</sup> In the other studies, the normal range for SCr was defined as < 100  $\mu\text{mol/L}$  (1.1 mg/dL).<sup>5,11,23</sup>

The association between ORD and adverse outcomes in patients after CABG may have several explanations. In our study, patients in the ORD group had a higher prevalence of hypertension, diabetes, recent MI, left ventricular dysfunction, extracardiac arteriopathy, and chronic obstructive pulmonary disease, which are well-known cardiovascular risk factors for adverse events in CABG. The presence of nontraditional risk factors in renal dysfunction, such as ane-

mia, abnormal calcium/phosphate metabolism, extracellular fluid volume overload, electrolyte imbalance, oxidative stress, inflammation, condition promoting coagulation, and the effects of toxic metabolites might break up a delicate homeostasis leading to increased risk of acute renal failure and atrial fibrillation, which are strongly associated with mortality.<sup>14,24,25</sup> These hypotheses raise the question of whether ORD is a marker or a risk factor for worse outcomes after CABG. However, in our study, we demonstrated that ORD remained a predictor of mortality and morbidity after multivariable analysis adjusting for baseline characteristics and propensity score. Furthermore, we found that the eCrCl formula was very sensitive in identifying and unmasking a consistent group of patients considered “normal” from a renal point of view.

### Limitations

This study has several limitations. It is based on the retrospective analysis of our large institutional observational prospectively collected database, and we are unable to account for the influence of any residual unmeasured factors that could affect the adverse outcomes. Furthermore, we do not have the specific details on the intraoperative and postoperative management of these patients.

Mortality in coronary artery bypass grafting is a very infrequent event, and our data reflect this trend. In our study, the overall mortality in patients with normal creatinine levels was 1%, but double in patients with ORD. We strongly believe that this association is not only statistically significant but also clinically important.

The Cockcroft-Gault equation was developed to estimate CrCl rather than GFR; it may overestimate renal function, especially in the elderly and obese patients as compared with 24 hours urine collection samples. Finally, we do not have information regarding the role of nephropathy induced by contrast medium administered before serum creatinine was measured.

## CONCLUSIONS

Our study shows that ORD, defined as normal creatinine level with impaired renal function is associated with increased mortality and postoperative morbidity in patients undergoing CABG. An accurate assessment of renal function by estimation of creatinine clearance, in addition to serum creatinine might identify higher risk patients and provide a better risk stratification that can help optimize therapeutic strategies in these patients.

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