Relation between serum creatinine and postoperative results of open-heart surgery

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ABSTRACT

الأهداف: التعرف على أثر مستويات مستوى الكرياتينين قبل العملية في المرضى الغير ديال على معدل الوفاة ومعدل المرض بعد العملية.

الطريقة: أجريت دراسة استباقية على مصل الكرياتينين لقياس مستوى قصور وظائف الكلى قبل العملية. اشتملت الدراسة على عدد 1033 مريض أجريت لهم جراحات قلب مفتوح مختلفة مثل عمل توصيلات وريدية وشريانية للشرايين التاجية وعمليات تغيير للصمامات وعمليات جمعت الاثنين في مرضى لا يعانون من قصور في وظائف الكلي ولا يحتاجون غسيل دموي للكلي. أجريت الدراسة في مستشفى الهدا العسكري، الطائف، المملكة العربية السعودية خلال الفترة من مايو 2008م حتى يناير 2012م. تم تحليل البيانات باستخدام اختبار كاي الإحصائي وتحليل الانحدار المتعدد لقياس مستوى خطورة المرض والوفاة المصاحبة لانخفاض مستوى وظائف الكلى.

النتائج: ارتفع معدل الوفاة بعد العملية مع ارتفاع مستوى نسبة الكرياتينين في الدم أعلى من 1.8> مجم/دسلتر $p \leq 0.0005$. وجدنا أن هناك علاقة بين ارتفاع نسبة الكرياتينين عن 1.8مجم/ديسليتر ووجود مضاعفات أو حدوث وفيات بعد اجراء عمليات مختلفة من عمليات جراحات القلب مثل تغيير الصمامات كما هو حادث في عمليات عمل التوصيلات للشرايين التاجية وأيام المكوث في المستشفى وغرفة العناية المركزية.

خاتمة: ارتبط مستوى نسبة الكرياتينين في الدم بمعدل الوفاة والمرض بعد العملية في عمليات القلب المفتوحة. كما أن ارتفاع مستوى الكرياتينين في المرضى الذين لا يعانون من قصور في وظائف الكلي ارتفاع الوفاة والإصابة بعد عمليات القلب.

Objectives: To determine the impact of preoperative serum creatinine level in non-dialyzable patients on postoperative morbidity and mortality.

Methods: This is a prospective study, where serum creatinine was used to give primary assessment on renal function status preoperatively. This study includes 1,033 patients, who underwent coronary artery bypass grafting, or valve(s) operations. The study took place at Al-Hada Military Hospital, Taif, Kingdom of Saudi between May 2008 and January 2012. Data were statistically analyzed using Chi square (χ^2) test and multivariable logistic regression, to evaluate the postoperative morbidity and mortality risks associated with low serum creatinine levels.

Results: Postoperative mortality increased with high serum creatinine level >1.8 mg/dL ($p \leq 0.0005$). Multivariable logistic regression, adjusting for potentially confounding variables demonstrated that a creatinine level of more than 1.8mg/dL was associated with increased risk of re-operation for bleeding, postoperative renal failure, prolonged ventilatory support, ICU stay, and total hospital stay.

Conclusions: Perioperative serum creatinine is strongly related to post operative morbidity and mortality in open heart surgery. High serum creatinine in non-dialyzable patients can predict the increased morbidity and mortality after cardiac operations.

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The relation between preoperative and postoperative renal failure and the adverse outcome in cardiac surgery is well known. Renal function is an important determinant of in-hospital mortality in cardiac surgery, it is known that when it is severe and required dialysis, morbidity and mortality are markedly increased in spite of dialysis is performed and supportive intensive care is taken.[1] There is a lot of information on the effects of renal failure on operative outcome.[1] Through many

studies, little of their assessment of renal function was mostly detected by checking the serum creatinine levels as a diagnostic test. However, use of serum creatinine has been questioned in several reports as it can be normal even when renal function is impaired, and it may underestimate mild-to-moderate renal impairment.[2] On the other side, patients with end-stage renal disease whom undergoing hemodialysis (HD) proved to be at high risk for adverse outcomes after coronary artery bypass grafting(CABG). Coronary artery bypasses grafting surgery aims to improve quality and prolongation of life in patients of ischemic heart disease, however, many studies identified several factors acted as independent predictors of poor outcomes. One of these is renal dysfunction.[3] Patients presenting with a spectrum of preoperative renal dysfunction (RD) has not been well characterized, as the majority of these studies have utilized serum creatinine as the preoperative variable as the determinant for degrees of renal failure.[2] Also, several studies indicate that in advanced RD (end-stage renal disease), there was an increased in morbidity and mortality after CABG surgery. Unfortunately, previous studies used serum creatinine as a dichotomous rather than as a continuous variable, thus, failed to capture the continuum with post-operative risk.[4] Some studies explained the cause of post CABG renal failure as a morbidity, they conclude that progressive hemodilution causes a proportional decrease in the oxygen carrying capacity of the blood which may leads to ischemic injury in susceptible areas of the kidney, also the conduct system used during CPB might generates a large number of emboli of various origins, thereby, increases the risk of renal infarction which end with renal failure in patient with borderline renal impairment preoperative.[4]

The presence of impaired renal function potentially results in several physiologic abnormalities that could contribute to adverse operative outcome.[5] Indeed, the absence of renal function depending on serum creatinine clearance has been well documented to be associated with relatively high morbidity and mortality after surgery, including cardiac surgery.[5] However, in non-dialyzable patients or those not known renal impairment patients, we depends on serum creatinine as pre-operative simple test assessment for kidney function, and we did not go for further investigation if it is within the range between low and high normal levels. Therefore, we investigate more about the relation between serum creatinine pre-operative and the postoperative morbidity and mortality.[6] The purpose of this study was to test the hypothesis that serum creatinine concentration of 1.4-1.8 mg/dl has a relationship with adverse outcome after open-heart surgery.

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Methods. This is a prospectively study of 1033 patients underwent open-heart surgery (coronary artery bypass grafting, valve surgery or both), at Al-Hada Military Hospital, Armed Forces Hospital, Taif, Saudi Arabia between May 2008 and January 2012. The research was conducted in full accordance with ethical principles of Helsinki Declaration. Our study was ethically approved by the Postgraduate Training and Research Centre (PTRC), Armed Forces Hospitals, Taif, Saudi Arabia.

Data were collected for all patients according to the following manner: Preoperative (age, gender, diabetes mellitus, hypertension and history of smoking), degree of dyspnea, previous cardiac surgery, heart failure, myocardial infarction, established renal failure, peripheral vascular disease, cerebrovascular disease, and chronic obstructive airway disease. Full laboratory data such as serum creatinine and hepatitis markers, and electrocardiogram (ECG). Abdominal ultrasound for patients with creatinine >1.8 to exclude renal pathology in need for hemodialysis, and echo cardiography. Preoperative risk factors as preoperative serum creatinine was searched and documented for all patients and according we classified patients into 3 categories patients with normal serum creatinine <1.3, patients with serum creatinine (>1.4 and <1.8) and patients with creatinine >1.8 and not in need for renal support in the form of hemodialysis, or medical treatment, or dietary adjustment. All operations were performed with systematic hypothermia (30°C) and cold, blood, ante-grade and intermittent blood cardioplegia. Cardiopulmonary bypass flow rates were recorded between 1.8 and 2.0 liter per min^{-1} m^{-2}, mean arterial pressure was maintained between 40 and 80 mm Hg.

Postoperative manners were hours of commencing ventilation, reopening due to bleeding, new onset for atrial fibrillation, inotropes, or intra-aortic balloon pump (IABP, central nervous system (CNS), renal, pulmonary, and gastroenterology (GIT) complications, wound infection (superficial or deep), hospital stay, and mortality.

We assessed neurological status of the patients postoperatively and investigated any neurological abnormality by computed tomographic scan. We

assessed the cardiac function post-operative through cardiac index (CI) and echo cardiograph, and considered low cardiac output if patient was in need for cardiac inotropes for more than 24 hours, after surgery.

Exclusion criteria. Patients with other concomitant surgical procedure were excluded from our study such as carotid endarterectomises, aortic procedures, transplantation, and congenital abnormalities. Patients with established renal impairment on regular or intermittent renal hemodialysis, patients with liver disease, ascites and/or hepatitis C positive. Postoperative bleeding in redo cases. Leg wound delayed healing and/or infection in patients with peripheral vascular disease

Statistical analysis. Chi square (x^2) test was used to evaluate potential confounders of the relationship between serum creatinine level and operative morbidity and mortality. A variable was considered a potential confounder if it was related to the level of serum creatinine and postoperative morbidity and mortality with a p value of ≤2.0. To adjust potential confounding effect of other risk factors, we used multi-variable logistic regression to evaluate operative mortality and morbidity risk associated with high serum creatinine levels. The potential confounders included age, gender, ejection fraction, New York Heart Association function class, preoperative diabetes, peripheral and cerebral vascular disease, hypertension, congestive heart failure, myocardial infarction, chronic obstructive pulmonary disease, and smoking. The odds ratio for mortality for each of the identified risk factors was then calculated. The statistical analyses were performed with the use of Strata versions 8.

Results. Sixty-eight percent of the patients underwent isolated CABG procedures, 18% underwent isolated valve operation, and 14% underwent combined CABG and valve procedures. Emergency operations were performed within 24 hours of the diagnosis. The median age of the patients was 65 years. The median serum creatinine level was 1.4 mg/dL with lower quartile of 0.7 mg/dL and upper quartile of 2.3 mg/dL. The overall mortality was 3.8%.The preoperative demographics, risk factors, and clinical presentation of the study group is presented in **Table 1**. Patients with a serum creatinine level of more than 1.8 mg/dl had a greater number of comorbidities and risk factors, diabetic 30%, hypertension 61%. Higher levels of serum creatinine were associated with a higher incidence of postoperative complications and prolonged ICU stay 20% in those with serum levels between 1.4 and 1.8, 27% in those with serum level more than 1.8, ventilatory support 23% and 33%, and hospital stay 24% and 29% respectively (**Table 2**). Thus, the highest prevalence of complications was seen in those patients with serum creatinine level more than 1.8 mg/dL. There was no association between preoperative serum creatinine levels and infection in the form of saphenous vein harvest site infections 4.4 % and deep sterna wound infection 3.3%. In multi-variable analysis adjusting for potential confounders. Patients with a serum creatinine level more than 1.4 mg/dL had a significantly increased risk for renal failure and need for hemodialysis as it was 2.1% in those with serum creatinine <1.3 mg/dl, 4.8% in those with serum level between 1.4 mg/dl and 1.8 mg/dl and increased to 6.3% in those with serum level more than 1.8 mg/dl, also postoperative atrial fibrillation and re-exploration for bleeding, occurrence of post operative pneumonia, sepsis and myocardial infarction (**Table 3**). Patients with a serum creatinine level of more than 1.8 mg/dL also had an increased risk of death, low cardiac output. Odds ratio and 95% confidence for post operative outcomes after adjusting for confounders in patients with high normal serum levels of creatinine showed that OR of death and renal failure are 2.0 for those with serum creatinine more than 1.8 mg/dl (p=0.002), OR for ventilator support more than one day is 2.5 (p=0.0001), OR for length of hospital stay is 1.9 (p=0.0001), and OR for ICU stay for more than 3 days is 1.7 (p=0.0001).

Discussion. We found in this study that high serum creatinine level for patient not known to have any renal insufficiency preoperatively increase the postoperative morbidity and mortality after open-heart surgery. By using multi-variable analysis and adjusting for these risk factors, we noticed that mortality and new onset of renal failure that might need for hemodialysis have a high prevalence postoperatively in patients who had high normal levels of serum creatinine, also there were high prevalence of longer length of hospital stay, ICU stay, ventilator support, developing myocardial infarction, new AF, pneumonia and re-exploration for bleeding. The findings of the current study are consistent with those Weerasinghe et al who did a study on 1427 patients who had no known pre-existing renal disease and who were undergoing first-time CABG with cardiopulmonary bypass. They divided their patients on the basis of preoperative serum creatinine level into 3 groups as follows: <1.4 mg/dl, 1.4-1.69 mg/dl and ≥1.7 mg/dl,[7] which is similar to our study design that showed mild elevation of 1.4-1.69 mg/dl. In the preoperative results, the serum creatinine level significantly increases the need for mechanical renal support, the duration of special care, total postoperative stay, and in-hospital

Table 1 - The preoperative demographics, risk factors, and clinical presentation of the study group. Percentages of patients in strata of serum creatinine level and postoperative outcome.

Patient's characteristics	Serum creatinine (mg/dL)			Operative death		
	>1.8	1.4-1.8	<1.3	All patients	Yes	No
No. of patients	153	382	498	1033	39	994
Percentages of all patients	15	37	48	100	3.8	96.2
Demographics (%)						
Female	40	32	30	32	42	31
Age >65 years	27	23	23	25	40	23
Serum creatinine (mg/dL)						
Level >1.8				15	29	14
Level 1.4-1.8				37	16	20
Level <1.3				48	55	66
Risk factors						
EF <30%	7	7	8	7	16	7
NYHA functional class IV	21	17	17	18	36	17
Previous cardiac surgery	17	16	16	16	36	15
Diabetes mellitus	30	26	28	28	34	27
PVD	17	13	11	13	29	12
Cerebral vascular disease	16	12	10	11	23	11
Systemic hypertension	61	60	57	58	70	58
CHF	40	32	35	35	57	34
Previous MI	55	51	47	49	67	49
COPD	11	10	10	10	15	10
Smoking history	63	64	64	64	64	64
Clinical presentation						
Elective operation	58	66	70	67	41	68
Emergency operation	42	34	30	33	59	32
Intraoperative procedure						
CABG	68	67	67	68	52	68
Valve(s)	14	16	19	18	14	18
CABG and valve	17	15	14	14	34	14
Bilateral ITA usage	73	77	82	79	49	80
Median pump time (>120 min)	34	28	29	30	68	21
Median cross clamp time (>90 min)	30	26	24	25	47	24

EF - ejection fraction, NYHA - New York Heart Association, PVD - peripheral vascular disease, CHF - congestive heart failure, MI - myocardial infarction, COPD - chronic obstructive pulmonary disease, CABG - coronary artery bypass grafting, ITA - internal thoracic artery. Cerebral vascular disease includes any patient with a previous cerebral vascular accident, transient ischemic attack, or carotid stenosis.

Table 2 - Patients in strata of preoperative creatinine with postoperative outcomes after coronary artery bypass grafting (CABG) and/or valve surgery.

Outcome	Creatinine (mg/dL)			
	>1.8	1.4-1.8	<1.3	*P*-value*
CVA/TIA	5.2	3.5	3.9	0.11
Renal failure	6.3	4.8	2.1	≤0.0005
Pneumonia	4.3	3.8	2.8	0.07
Sepsis	3.5	2.9	2.2	0.11
Myocardial infarction	4.3	2.8	2.4	0.02
Low cardiac output	14.7	10.4	7.6	≤0.0005
New atrial fibrillation	34	32	27.0	≤0.0005
Re-exploration for bleeding	7.4	4.0	4.4	0.001
Deep sternal wound infection	3.3	3.3	2.0	0.06
Leg infection	4.4	4.1	3.8	0.83
ICU stay >3 days	27	20.0	14.0	≤0.0005
Ventilatory support >1 day	33	23.0	14.0	≤0.0005
Hospital stay >10 days	29	24.0	15.0	≤0.0005

Values are presented as percentage.
CVA - cerebrovascular accident, TIA - transient ischemic attack, ICU - intensive care unit. *Chi square (χ^2) test was used to calculate the *p*-values.

mortality. As the preoperative serum creatinine level increases (≥1.7 mg/dl), effects were more pronounced.[7] They also showed that no significant difference in the outcome between the use of cardioplegia or cross clamp fibrillation for myocardial protection. In our study, we noticed that one third or more of our patients with serum creatinine of >1.8 mg/dl underwent median cross clamp time (>90 min) and median pump time (>120 min); and those constitute 47% and 68% respectively of the total mortality, which means that long bypass machine and cross clamping time play a role in the postoperative mortality in those with high normal levels of serum creatinine,[7] and still we included the variant types of open heart surgery not only CABG. Ascione et al[8] found that patients with pre-operative non-dialysis dependent renal insufficiency who underwent off pump coronary artery bypass surgery had less in hospital morbidity especially acute renal failure. This findings support our findings related to the relation between

Table 3 - Odds ratio and 95% confidence interval for postoperative outcomes after adjustments for confounders in patients with high serum creatinine levels.

Outcome	Creatinine (mg/dL)			
	>1.8 OR (CI)	*P*-value	1.4-1.8 OR (CI)	*P*-value
Death	2.0 (1.3-3.0)	0.002	1.1 (0.8-1.6)	0.6
CVA/TIA	1.1 (0.7-1.6)	0.7	0.8 (0.5-1.1)	0.1
Renal failure	2.0 (1.3-3.2)	0.002	1.9 (1.3-2.7)	0.001
Pneumonia	1.1 (0.7-1.8)	0.6	1.1 (0.8-1.5)	0.7
Sepsis	0.2 (0.7-2.0)	0.5	1.1 (0.76-1.7)	0.5
MI	1.5 (0.9-2.3)	0.1	1.0 (0.7-1.4)	0.9
Low cardiac output	1.6 (1.2-2.1)	0.001	1.2 (1.0-1.5)	0.1
New AF	1.4 (1.2-1.7)	0.0001	1.3 (1.2-1.5)	0.0001
Re-exploration for bleeding	1.4 (1.0-2.1)	0.04	0.8 (0.6-1.1)	0.3
Deep sternal wound infection	1.7 (0.8-3.6)	0.2	1.5 (0.9-2.5)	0.1
Leg infection	1.1 (0.5-2.2)	0.8	1.0 (0.7-1.6)	0.8
ICU >3 days	1.7 (1.4-2.1)	0.0001	1.3 (1.1-1.6)	0.006
Ventilatory support >1 day	2.5 (2.0-3.1)	0.0001	1.5 (1.2-1.7)	0.0001
Length of stay >10 days	1.9 (1.5-2.4)	0.0001	1.6 (1.3-1.8)	0.0001

OR - odds ratio, CI - confidence interval, CVA - cerebral vascular accident, TIA - transient ischemic attack, MI - myocardial infarction, AF - atrial fibrillation, ICU - intensive care unit. The reference groups are patients with a normal serum creatinine (<1.3 mg/dL).

cross clamp time, pump time, and postoperative morbidity, and increase incidence of renal failure. We could explain this relation due to the ischemic injury which could happened for kidneys or due to the effect of micro emboli from conduct system of cardiopulmonary bypass machine. Litmathe et al[9] retrospectively analyzed 2511 patients undergoing isolated CABG between 2004 and 2007 with a preoperative serum creatinine of ≤2.2 mg/dL. They studied 592 patients with preoperative serum creatinine between 1.4 and 2.2 mg/dl, and 1919 patients with <1.4 mg/dl, which means that they had a mild renal dysfunction group. They analyzed the perioperative risk factors for postoperative renal dialysis (PRD) by multivariate regression analysis. They concluded that preoperative mild renal dysfunction is an important predictor of outcome after CABG. Thus, PRD dramatically increases mortality, morbidity, and length of hospital stay. Holzmann et al,[10] did similar study but they assessed the renal function by creatinine clearance. Six thousand seven hundred eleven consecutive patients without dialysis-dependent renal insufficiency undergoing a first isolated CABG were included. Preoperative serum creatinine concentrations and creatinine clearance were calculated using the Cockroft-Gault formula and they foun it was related to the mortality within 30 days postoperatively[10] and they stated that moderate and severe renal insufficiency independently increase the risk of early death after CABG. They indicate that calculating creatinine clearance is a better predictor of early mortality postoperatively than serum creatinine concentration.[10] We did not assess the creatinine clearance as we aimed to estimate the serum creatinine as a simple routine test used for all patients preoperatively, but they included only the moderate to severe renal insufficiency not the mild renal dysfunction. Beside, they have more patients and included only CABG patients. Our study was an observational and retrospective in nature, that restricting us to identify and analyze all the potential confounders. Hospital complications and mortality could not be assessed due to lack of follow up data in the hospital records. We rely on the serum creatinine alone for our patients as they had not any history of renal insufficiency, and those patients might had occult renal impairment which was responsible of this significant relation between high serum creatinine and postoperative morbidity and mortality. Thus, we recommend preoperative calculation of creatinine clearance as well as serum creatinine especially in patients with high creatinine even there was no history of renal insufficiency or ultrasound finding as Holzmann et al[10] suggested. to identify patients requiring special type of procedure if possible like off-pump versus on-pump, or hemodynamic control during cardiopulmonary by pass or in need for special intensive care like blood pressure control and drug adjustment according to creatinine clearance.

In this study, we use serum creatinine as a single renal parameter as preoperative assessment in an open heart surgery not only in CABG, which is the same with other studies and we found that high serum creatinine level in non-dialyzable patients has a significant

relation to the number of postoperative complications. In addition, serum creatinine >1.8 mg/dL increased the length of hospitalization and mortality. These findings were independent of patient age and gender. However, this study was limited by relying on a single parameter in assessing renal function status and we put in our consideration that serum creatinine levels may be affected by different causes such as chronic congestive heart failure, hepatic insufficiency, nutritional status, dehydration, using dye during coronary artery angiography, preoperative, and systemic illness.

In conclusion, serum creatinine as an isolated factor had a good relation with post open-heart surgery mortality and morbidity; however, the cause of the high level of serum creatinine. It can be added to other preoperative predictors to enhance risk stratification models for all patients undergoing cardiac surgery not only CABG surgery.[11,12]

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Ethical Consent

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.