

The reliability of estimated glomerular filtration rate in coronary artery bypass grafting

Koroner arter baypas greftlemede tahmini glomerüler filtrasyon hızının güvenilirliği

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ABSTRACT

Background: In this study, we investigated the reliability of the estimated creatinine clearance and glomerular filtration rate in patients undergoing on-pump coronary artery bypass grafting.

Methods: A total of 167 patients (124 males, 43 females; mean age 60.9±9.4 years; range, 35 to 83 years) who underwent on-pump coronary artery bypass grafting in our clinic between January 2009 and January 2011 were enrolled in the study. Demographic characteristics of the patients, creatinine clearance rates measured with 24-hour urine collection, and estimated renal function, and glomerular filtration rates according to the formulas of Cockcroft-Gault, Modification of Diet in Renal Disease-four variables and six variables, Jelliffe-1972, Jelliffe-1973, Mawer, Bjornsson, and Gates of preoperative and postoperative first and fifth-days were retrospectively analyzed.

Results: Among all estimated renal function and glomerular filtration rate equations, the Cockcroft-Gault formula yielded the most significant results for the creatinine clearance rate for all periods.

Conclusion: Our study results suggest that the Cockcroft-Gault equation can be reliably used in the evaluation of kidney functions of patients undergoing coronary artery bypass grafting.

Keywords: Coronary artery bypass grafting; glomerular filtration rate; kidney function tests; reliability.

Kidney dysfunction in the perioperative period of coronary artery bypass grafting (CABG) has been significantly associated with the mortality.^[1-3]

ÖZ

Amaç: Bu çalışmada kardiyopulmoner baypas altında koroner arter baypas greftleme yapılan hastalarda tahmini kreatinin klirensi ve glomerüler filtrasyon hızının güvenilirliği araştırıldı.

Çalışma planı: Kliniğimizde Ocak 2009 - Ocak 2011 tarihleri arasında kardiyopulmoner baypas altında koroner arter baypas greftleme yapılan toplam 167 hasta (124 erkek, 43 kadın; ort. yaş 60.9±9.4 yıl; dağılım 35-83 yıl) çalışmaya alındı. Hastaların demografik özellikleri, 24 saatlik idrar ile ölçülen kreatinin klirensi değerleri ve ameliyat öncesi ve ameliyat sonrası bir ve beşinci günlerde Cockcroft-Gault, Böbrek Hastalığında Diyet Modifikasyonu-dört değişken ve altı değişken, Jelliffe-1972, Jelliffe-1973, Mawer, Bjornsson ve Gates formüllerine göre tahmini böbrek fonksiyonu ve glomerüler filtrasyon hızı retrospektif olarak incelendi.

Bulgular: Tahmini böbrek fonksiyonu ve glomerüler filtrasyon hızı hesaplamaları içerisinde, tüm dönemler için kreatinin klirens hızı için en anlamlı sonuçlar Cockcroft-Gault formülü ile elde edildi.

Sonuç: Çalışma bulgularımız koroner arter baypas greftleme yapılan hastaların böbrek fonksiyonlarının değerlendirmesinde, Cockcroft-Gault eşitliğinin güvenilir bir şekilde kullanılabileceğini göstermektedir.

Anahtar sözcükler: Koroner arter baypas greftleme; glomerüler filtrasyon hızı; böbrek fonksiyon testleri; güvenilirlik.

Timely detection of the dysfunction, particularly in the early postoperative period, can be, therefore, life-saving.^[4,5] The common methods such as blood



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urea nitrogen and creatinine level measurements are usually incapable to meet all the requirements and a standard method of creatinine clearance rate calculation including the collection of all the urine output during a whole day is usually accepted as cumbersome to use.^[6] For these practical reasons, a number of estimated kidney function and glomerular filtration rate (GFR) calculation formulas using different numbers of variables have been developed to date.^[7-14] The predictive values of these equations have been also investigated among different patient populations.^[6] However, the reliability of estimated GFR equations needs to be evaluated for CABG patients, as well. Therefore, in our study, we investigated the reliability of the estimated creatinine clearance and GFR in patients undergoing on-pump CABG.

PATIENTS AND METHODS

A total of 167 patients (124 males, 43 females; mean age 60.9±9.4 years; range, 35 to 83 years) who underwent on-pump CABG surgery in our clinic between January 2009 and January 2011 were enrolled in this study. Preoperative and postoperative first and fifth-day creatinine clearance rates and estimated GFR calculations were retrospectively analyzed. All calculations were made separately for different time periods using different measurement tools. Creatinine clearance rates were accepted as the main standard for the evaluation. We compared the Cockcroft-Gault,^[10] Jelliffe-1972,^[8] Jelliffe-1973,^[9] Mawer,^[7] Bjornsson,^[11] Gates,^[12] Modification of Diet in Renal Disease-four variable (MDRD-4),^[13] and –six variable (MDRD-6)^[14] equations with the main standard tool. These estimated GFR formulas which were originally formed among different patient populations were compared with conventional renal function test results for our heterogeneous patient population in different time periods for clinical feasibility. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The exclusion criteria were as follows: preoperative renal dysfunction, re-operation rates and simultaneous surgical procedures, critical preoperative conditions such as endocarditis, and emergency or salvage operation.

All the operations were performed on-pump and by a single surgical team. Mild hypothermia was used during surgery. Anastomoses were performed under a single aortic cross-clamp. Myocardial protection was achieved via both antegrade and retrograde cold blood cardioplegia.

Statistical analysis

Statistical analysis was performed using IBM SPSS software package version 20.0 (IBM Corporation, Armonk, NY, USA). All data were expressed in mean ± standard deviation or percentage (n, %). For the normality assumptions, the Kolmogorov-Smirnov, Shapiro-Wilk tests, and histograms were used. Parametric variables with normally distributed data were compared among the groups by using repeated measures analysis of variance. Otherwise, the Friedman test was used. The Pearson correlation coefficients (r) were calculated for the normally distributed data; otherwise, the Spearman's correlation coefficients (r) were calculated. The precision values (r²) were calculated after the correlation analyses. The scatter plots of estimated GFR calculations were created for both preoperative and postoperative first and fifth-days. A *p* value of <0.05 was considered statistically significant.

RESULTS

All patients were Caucasian. Sixty patients (36%) had diabetes mellitus, while 99 (59%) had hyperlipidemia (Table 1). There was a significant difference in the preoperative and postoperative blood albumin levels (*p*<0.001) (Table 2). The mean creatinine clearance rate of preoperative and postoperative first, and fifth-days were 80.5±34.1, 103.3±45.2, and 85±33.4 mL•min⁻¹•1.73 m², respectively (Table 2). Among all estimated renal function and glomerular filtration rate equations, the Cockcroft-Gault formula was found to be closest to the standard creatinine clearance rate for all periods [correlation coefficient values (r) for preoperative and postoperative first and fifth-days were 0.648; 0.711; 0.606, respectively (*p*<0.001)] (Tables 3-5). The precision of the Cockcroft-Gault for preoperative and postoperative first and fifth-days were 42.5%; 50.6%; and 36.7%, respectively (*p*<0.001) (Table 3-5). The Bjornsson equation followed the Cockcroft-Gault formula for all periods (Table 3-5). The scatter plots of all estimated renal function and glomerular filtration rate equations showed different distributions of comparisons (Figures 1-3). Overall, precision values were highest in the postoperative first-day measurements, while they reached the lowest state in the postoperative fifth-day (Tables 3-5) (Figures 1-3). Although there were significant differences in the creatinine clearance rates between preoperative and postoperative first and fifth-day measurements (*p*<0.001), there were no statistically significant differences in terms of the estimated GFR calculations (*p*>0.05) (Table 2).

Estimated glomerular filtration rate calculation formulas we used for female patients were as follows:

- Cockcroft-Gault equation:^[10]

$$[(140 - \text{age}) \times \text{weight}] / (72 \times \text{Creatinine}_{\text{Serum}}) \times 0.85]$$
- MDRD-4 equation:^[13]

$$(186 \times \text{Creatinine}_{\text{Serum}}^{-1.154} \times \text{age}^{-0.203} \times 0.742)$$
- MDRD-6 equation:^[14]

$$(170 \times \text{Creatinine}_{\text{Serum}}^{-0.999} \times \text{age}^{-0.176} \times 0.762 \times \text{Urea}_{\text{Serum}}^{-0.170} \times \text{Albumin}_{\text{Serum}}^{0.318})$$
- Jelliffe-1972 equation:^[8]

$$[(80 / \text{Creatinine}_{\text{Serum}}) - 7]$$
- Jelliffe-1973 equation:^[9]

$$[[98 - [0.8 \times (\text{age} - 20)]] / \text{Creatinine}_{\text{Serum}}] \times 0.9]$$
- Mawer equation:^[7]

$$[[[\text{weight} \times [25.3 - (0.175 \times \text{age})] \times [1 - (0.03 \times \text{Creatinine}_{\text{Serum}})]]] / [(14.4 \times \text{Creatinine}_{\text{Serum}}) \times (70 / \text{weight})]$$
- Bjornsson equation:^[11]

$$[[[25 - (0.175 \times \text{age})] \times \text{weight} \times 0.07] / \text{Creatinine}_{\text{Serum}}]$$
- Gates equation:^[12]

$$[(60 \times \text{Creatinine}_{\text{Serum}}^{-1.1}) + (56 - \text{age}) \times (0.3 \times \text{Creatinine}_{\text{Serum}}^{-1.1})]$$

Estimated GFR calculation formulas we used for male patients were as follows:

- Cockcroft-Gault equation:^[10]

$$[(140 - \text{age}) \times \text{weight}] / (72 \times \text{Creatinine}_{\text{Serum}})$$
- MDRD-4 equation:^[13]

$$(186 \times \text{Creatinine}_{\text{Serum}}^{-1.154} \times \text{age}^{-0.203})$$
- MDRD-6 equation:^[14]

$$(170 \times \text{Creatinine}_{\text{Serum}}^{-0.999} \times \text{age}^{-0.176} \times \text{Urea}_{\text{Serum}}^{-0.170} \times \text{Albumin}_{\text{Serum}}^{0.318})$$
- Jelliffe-1972 equation:^[8]

$$[(100 / \text{Creatinine}_{\text{Serum}}) - 12]$$
- Jelliffe-1973 equation:^[9]

$$[[98 - [0.8 \times (\text{age} - 20)]] / \text{Creatinine}_{\text{Serum}}]$$
- Mawer equation:^[7]

$$[[[\text{weight} \times [29.3 - (0.203 \times \text{age})] \times [1 - (0.03 \times \text{Creatinine}_{\text{Serum}})]]] / [(14.4 \times \text{Creatinine}_{\text{Serum}}) \times (70 / \text{weight})]$$
- Bjornsson equation:^[11]

$$[[[27 - (0.173 \times \text{age})] \times \text{weight} \times 0.07] / \text{Creatinine}_{\text{Serum}}]$$
- Gates equation:^[12]

$$[(89.4 \times \text{Creatinine}_{\text{Serum}}^{-1.2}) + (55 - \text{age}) \times (0.447 \times \text{Creatinine}_{\text{Serum}}^{-1.1})]$$

After these calculations were made, all equations were adjusted according to the body surface areas and all units were standardized to mL/min/1.73 m².

Table 1. Patient characteristics and perioperative variables

Variable	n	%	Mean±SD	Min.-Max.
Age (year)			60.9±9.4	35-83
Gender				
Female	43	25.7		
Body mass index (kg/m ²)			27.2±4.3	16.3-42
Body surface area (m ²)			1.9±0.2	1.5-2.3
Hypertension	123	73.7		
Hyperlipidemia	99	59		
Diabetes mellitus	60	36		
Aortic cross clamping time (min)			69.8±29.3	12-155
Total perfusion time (min)			98±3	33-204
Distal bypass			2.5±0.9	1-5
ICU follow-up (hour)			50.7±27.7	10-283
Hospital-stay (day)			9.4±5.4	5-49

SD: Standard deviation; Min.: Minimum; Max.: Maximum; ICU: Intensive care unit.

DISCUSSION

Acute kidney failure (AKF) is one of the major complications which increases the mortality rates after CABG.^[11,15] Preoperative renal dysfunction was accepted as an independent predictor of long-term mortality after cardiac surgery.^[16,17] Besides, close monitoring for early detection and prevention of AKF is of utmost importance in CABG perioperatively.^[18] Although GFR measurement with urinary or plasma clearance of a standard marker such as inulin is accepted as the gold standard, it is not cost-effective in the daily clinical practice.^[16] On the other hand, the creatinine clearance rate calculation via collecting urine output during a whole day can be accepted as the clinical standard.^[18] In the present study, we preferred to use creatinine clearance rate measurements as the

main standard in parallel with some recent literature study findings.^[16] However, it is challenging to use it routinely for all patients. Another disadvantage of this technique is the risk of late detection and intervention. Blood urea nitrogen and creatinine levels can be used, but not enough to evaluate glomerular filtration rates alone. For this reason, estimated creatinine clearance and GFR equations were developed.^[7-14] These equations are usually evaluated and used for overall patient populations.^[6] In particular, in CABG patients, there are a number of major alterations in blood measures, including plasma albumin levels after on-pump surgery.^[18,19] Cardiopulmonary bypass circuit and the oxygenator membrane itself may also induce a high amount of cytokines to release, increasing the membrane permeability.^[19,20] Therefore, off-pump

Table 2. Renal function tests, estimated creatinine clearance and glomerular filtration rates, and related variables

	Preoperative		Postoperative 1 st day		Postoperative 5 th day		p
	Mean±SD	Min.-Max.	Mean±SD	Min.-Max.	Mean±SD	Min.-Max.	
Blood urea nitrogen (mg/dL)	40.8±12.4	13-84	48.3±18.7	14-118	46.5±30.5	15-235	<0.001*
Blood creatinine (mg/dL)	1±0.2	0.6-2	1±0.4	0.5-3.4	1±0.4	0.5-3.8	0.165
Blood albumin (g/dL)	3.8±0.4	1.1-4.9	2.6±0.3	1.6-3.5	2.8±0.4	1.4-3.9	<0.001*
Creatinine clearance rate†	80.5±34.1	19.6-257	103.3±45.2	14.5-263.6	85±33.4	19.6-192.4	<0.001*
Cockcroft-Gault formula‡	84±24.9	31.5-193	88.1±33.7	21.6-200	86.4±27.4	21.2-159.8	0.349
Bjornsson equation†	88.4±25.4	34.1-199	92.6±34.4	22.7-203.6	91±27.9	22.9-165	0.354
Mawer equation†	98.1±40.7	25.1-259.7	102.3±49.3	19.9-267.9	100.9±42.9	17.6-217	0.558
Gates equation†	82.7±21.3	38.6-178	87.8±32.4	19.9-193.3	85.4±24.6	25.2-175	0.198
MDRD-4 variable equation†	67.6±21.4	30.3-248.1	62.9±31.5	16.5-341.2	62±17.6	17.8-132.7	0.098
MDRD-6 variable equation†	79±18.4	37.1-160	83.6±29	19.7-184.5	81.5±21.6	25.8-157	0.192
Jelliffe-1972 equation†	66.3±16	33.3-127	70.1±24.5	19.2-164.7	68.3±18.7	23.9-134	0.186
Jelliffe-1973 equation†	87.4±18.5	39-163.4	91.7±28.4	17.4-154.7	90.1±22	33-154.7	0.237

SD: Standard deviation; Min.: Minimum; Max.: Maximum; MDRD: Modification of Diet in Renal Disease; * Statistically significant; † mL•min⁻¹•1.73 m²; ‡ Adjusted to body surface area (mL•min⁻¹•1.73 m²).

Table 3. Preoperative correlation measurements between creatinine clearance rates and estimated equations*

Rank	Equation	CC (r)	Precision (r ²)	<i>p</i>
1	Cockcroft and Gault ^[10]	0.652	0.425	<0.001
2	Bjornsson ^[11]	0.646	0.417	<0.001
3	Mawer ^[7]	0.602	0.362	<0.001
4	Jelliffe-1973 ^[9]	0.567	0.321	<0.001
5	Gates ^[12]	0.555	0.308	<0.001
6	MDRD-4 variable ^[13]	0.549	0.301	<0.001
7	MDRD-6 variable ^[14]	0.546	0.298	<0.001
8	Jelliffe-1972 ^[8]	0.479	0.229	<0.001

* Equations are ranked according to correlation values; CC: Correlation coefficient; MDRD: Modification of Diet in Renal Disease.

surgery is accepted superior to on-pump surgery in terms of the risk of acute kidney injury and failure.^[19,20] Under these circumstances, estimated GFR calculations in on-pump CABG patients need to have special concerns. First, the majority of our CABG candidates suffered from several comorbidities such as diabetes mellitus, hypertension, and hyperlipidemia. It makes the first main difference between these patients and healthy population. Second, cardiopulmonary bypass itself was the major factor which affected

renal functions in the early postoperative period. Perfusion also affected electrolyte and body fluid balances, resulting in body weight changes, eventually, estimated GFR equations. For these reasons, we made all calculations separately for different time periods using separate measurement tools. As we expected, creatinine clearance rates and blood urea nitrogen differed postoperatively compared to the baseline values. Besides, blood creatinine levels did not differ significantly in the perioperative period.

Table 4. Postoperative first day correlation measurements between creatinine clearance rates and estimated equations*

Rank	Equation	CC (r)	Precision (r ²)	<i>p</i>
1	Cockcroft and Gault ^[10]	0.711	0.506	<0.001
2	Bjornsson ^[11]	0.709	0.503	<0.001
3	MDRD-4 variable ^[13]	0.696	0.484	<0.001
4	Jelliffe-1972 ^[8]	0.694	0.482	<0.001
5	Mawer ^[7]	0.681	0.464	<0.001
6	Gates ^[12]	0.635	0.403	<0.001
7	MDRD-6 variable ^[14]	0.616	0.379	<0.001
8	Jelliffe-1973 ^[9]	0.608	0.370	<0.001

* Equations are ranked according to correlation values; CC: Correlation coefficient; MDRD: Modification of Diet in Renal Disease.

Table 5. Postoperative fifth day correlation measurements between creatinine clearance rates and estimated equations*

Rank	Equation	CC (r)	Precision (r ²)	<i>p</i>
1	Cockcroft and Gault ^[10]	0.606	0.367	<0.001
2	Bjornsson ^[11]	0.597	0.356	<0.001
3	Gates ^[12]	0.560	0.314	<0.001
4	MDRD-6 variable ^[14]	0.541	0.293	<0.001
5	Mawer ^[7]	0.528	0.279	<0.001
6	MDRD-4 variable ^[13]	0.494	0.244	<0.001
7	Jelliffe-1972 ^[8]	0.493	0.243	<0.001
8	Jelliffe-1973 ^[9]	0.487	0.237	<0.001

* Equations are ranked according to correlation values; CC: Correlation coefficient; MDRD: Modification of Diet in Renal Disease.

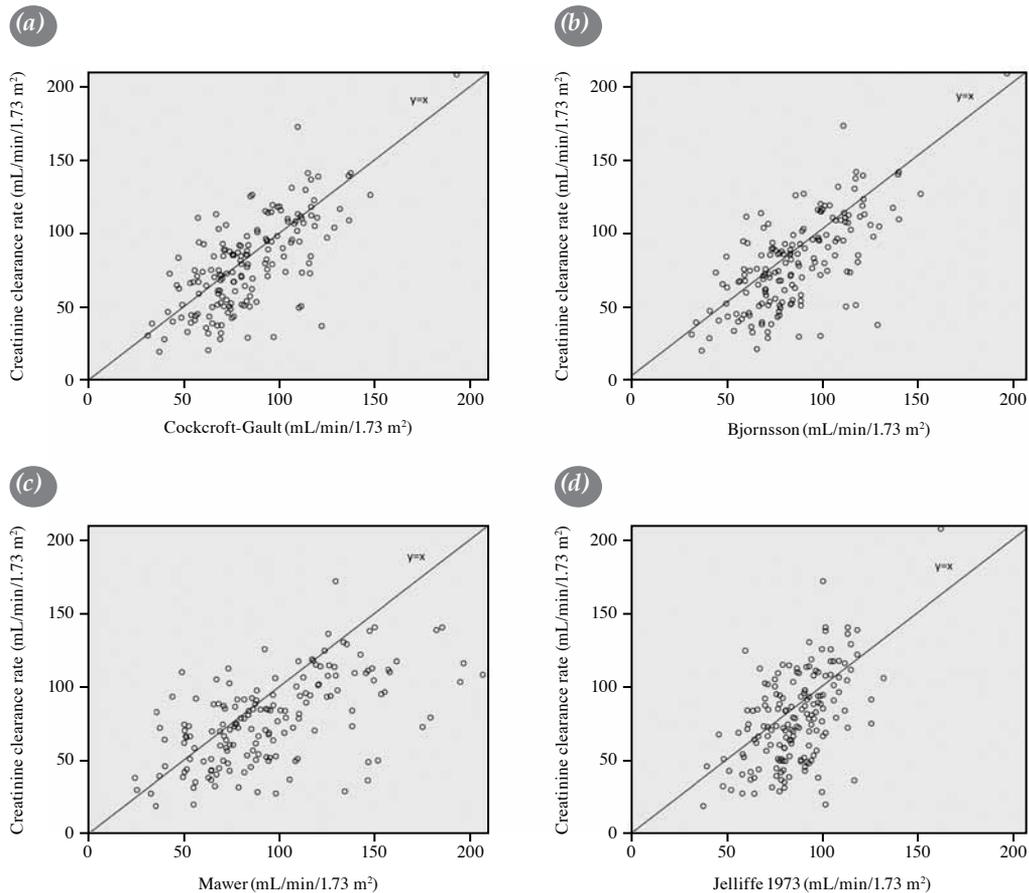


Figure 1. Scatter plots of preoperative comparisons between CCR vs top four estimated renal function equations according to precision values.* **(a)** CCR vs Cockcroft-Gault; **(b)** CCR vs. Bjornsson; **(c)** CCR vs Mawer; **(d)** CCR vs Jelliffe-1973.

CCR: Creatinine clearance rate; * All equations were adjusted to the body surface area (mL/min/1.73 m²) before comparison.

This finding can be interpreted as the lack of precision of conventional renal function tests reflecting the real glomerular filtration rates. After the estimated kidney function and glomerular filtration rate equation measurements were done, we adjusted all units according to the body surface areas. We did not use the race variable of MDRD formulas, as there was no black patient in our study. Consistent with the literature findings, correlation analyses showed us the Cockcroft-Gault formula had higher correlation coefficient and precision values for all the time periods perioperatively, compared to other equations.^[6] Of note, among all time periods, the Cockcroft-Gault equation had the highest precision in the postoperative first-day with 50.6% ($p < 0.001$). There were some literature findings suggesting that MDRD-4 formula was a more accurate measurement tool in predicting the long-term survival after cardiac surgery^[16,17] and Cockcroft-Gault equation might result in an overestimated GFR in patients with

end-stage kidney failure, particularly.^[17] Furthermore, studies including a heterogeneous group of cardiac and vascular patients^[17] were not consistent with our findings. We included a more homogenous patient population - only CABG patients. We also excluded patients with end-stage renal dysfunction and critical preoperative conditions. Cardiac risk scoring systems such as EuroSCORE-II utilize the Cockcroft-Gault equation for the evaluation of renal functions as well as in the risk prediction.^[21] This also encourages that using the Cockcroft-Gault equation can be helpful in our daily clinical practice. In our study, the Bjornsson equation followed the Cockcroft-Gault formula with precision values of preoperative and postoperative first and fifth-day as 0.417; 0.503; 0.367, respectively ($p < 0.001$). In contrast with the literature, we did not find MDRD-6 formula as precisely described.^[6] This can be attributed to the impact of blood albumin levels in terms of postoperative changes after perfusion. We also

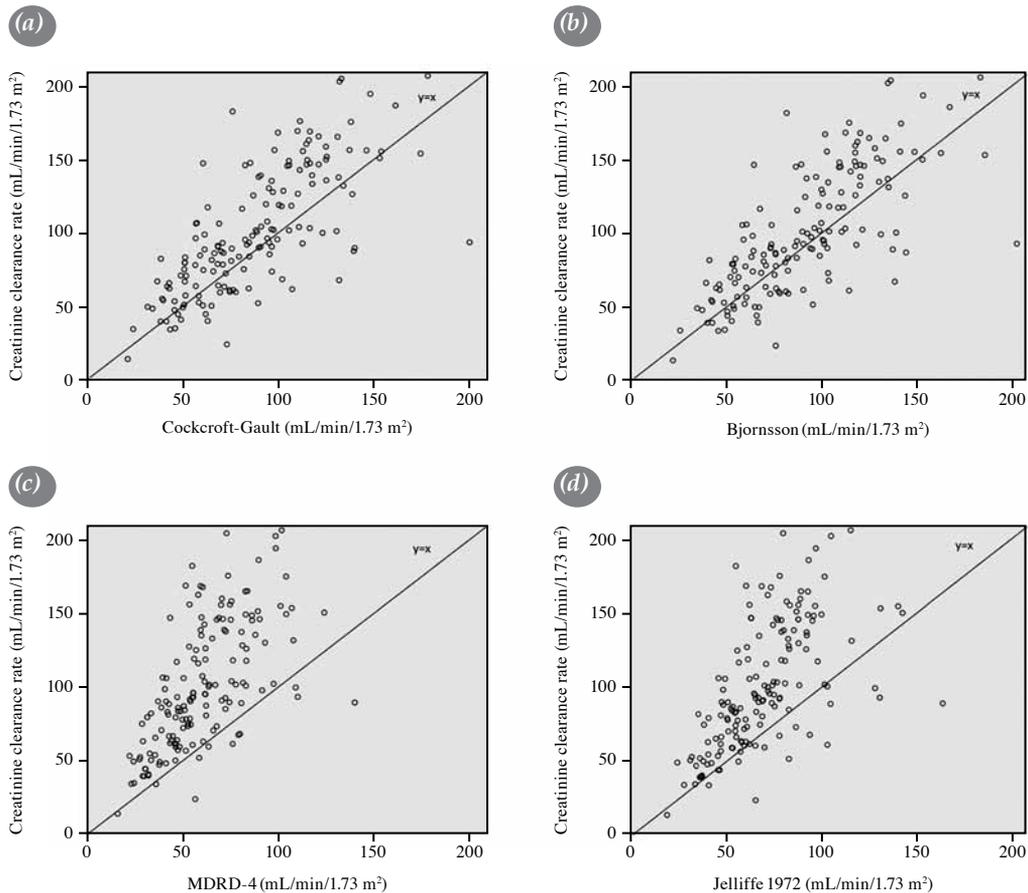


Figure 2. Scatter plots of postoperative first day comparisons between CCR vs top four estimated renal function equations according to precision values.* **(a)** CCR vs Cockcroft-Gault; **(b)** CCR vs Bjornsson; **(c)** CCR vs MDRD-4 variable; **(d)** CCR vs Jelliffe-1972.

CCR: Creatinine clearance rate; MDRD: Modification of Diet in Renal Disease; * All equations were adjusted to the body surface area (mL/min/1.73m²) before comparison.

found that blood albumin levels were significantly different between preoperative and postoperative first and fifth-day measurements ($p < 0.001$). The scatter plots of all estimated renal function and glomerular filtration rate equations showed many different distributions. Overall, precision values were the highest in the postoperative first-day measurements. Furthermore, we observed a significant difference between preoperative and postoperative first and fifth-day measurements in terms of creatinine clearance rate ($p < 0.001$). However, we were unable to find significant differences between the time groups of estimated GFR equations ($p > 0.05$). Therefore, we should remember that predictive capabilities of estimated calculation formulas are still suboptimal compared to conventional standard methods.^[6] Besides, the Cockcroft-Gault formula was also reported as the best predictor of early and late mortality after CABG compared to the other estimated renal function measurements.^[22] This finding

also supports the clinical use of the Cockcroft-Gault equation as a clinical practical evaluation method of kidney functions after CABG. Kidney dysfunctions still play an important role in the prediction of mortality and morbidity of CABG patients.^[23-25] Therefore, practical and precise methods for the evaluation of glomerular filtration rates still stays as indispensable tools in our daily practices.

On the other hand, there are some limitations to this study. We used creatinine clearance rate measurements as the main standard for the evaluation in our study, as these tools are more practical and cost-effective compared to inulin clearance measurements, which is accepted as the gold standard. In addition, estimated GFR formulas which were compared in our study were originally described for different patient populations, but not specifically for the perioperative evaluation of CABG patients. Finally, our study was a single-center

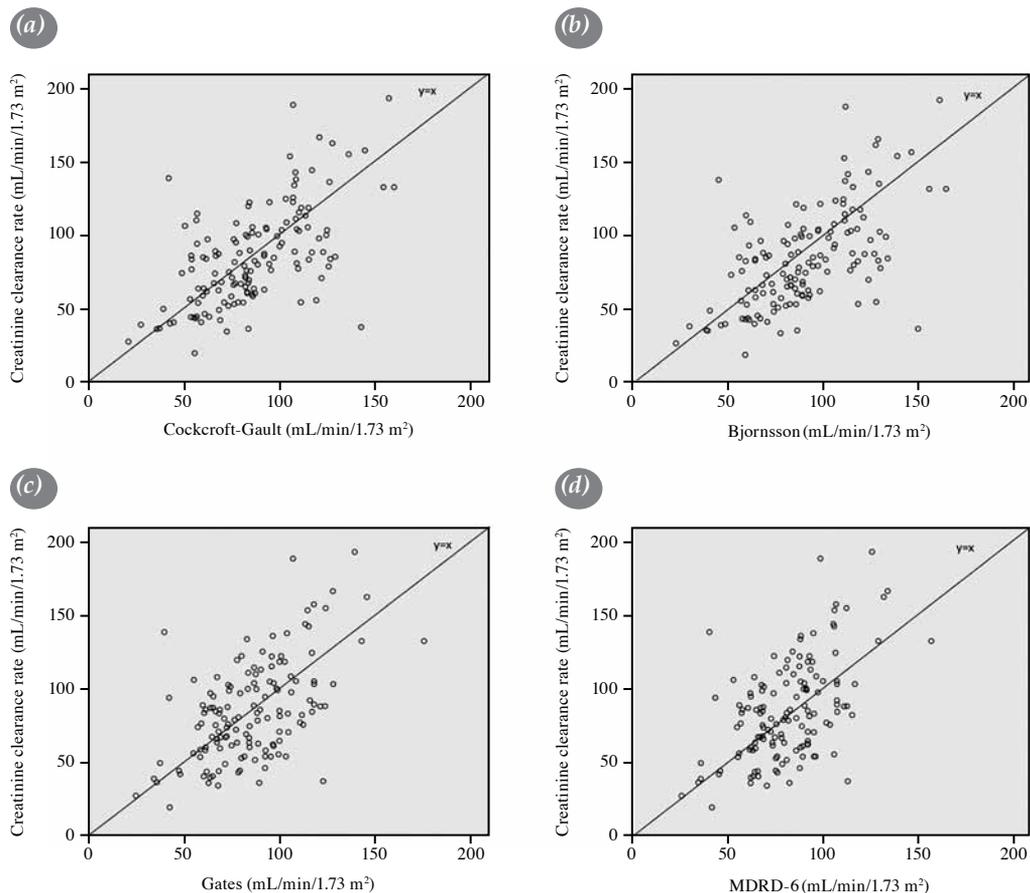


Figure 3. Scatter plots of postoperative fifth comparisons between CCR vs top four estimated renal function equations according to precision values.* **(a)** CCR vs Cockcroft-Gault; **(b)** CCR vs Bjornsson; **(c)** CCR vs Gates; **(d)** CCR vs MDRD-6 variables.

CCR: Creatinine clearance rate; MDRD: Modification of Diet in Renal Disease; * All equations were adjusted to the body surface area (mL/min/1.73 m²) before comparison.

and retrospective study. Therefore, further multi-center and prospective studies with a larger sample size are required to confirm our findings.

In conclusion, although the efficacy of estimated glomerular filtration rate calculations is still suboptimal, they can be used instead of simple blood urea nitrogen and blood creatinine measurements. They are also more practical than standard creatinine clearance rate measurements by collecting whole 24-hour urine output. In the evaluation of renal functions of patients undergoing coronary artery bypass grafting surgery, the Cockcroft-Gault equation can be more reliably used for the calculation of estimated kidney functions, compared to the formulas.

Declaration of conflicting interests

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