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SHORT COMMUNICATION

Age-dependent error in creatinine clearance estimated by Cockcroft–Gault equation for the elderly patients in a Japanese hospital: a cross-sectional study

Mitsuhiro Matsuo[1] · **Fuminori Yamagishi**[2]

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Abstract

The aim of this study is to assess the accuracy of creatinine clearance (CCr) calculated by the Cockcroft–Gault (CG) equation for elderly patients in a Japanese hospital. This study was a retrospective chart review of patients aged ≥ 55 years with a CCr measurement by a 24-h urine collection (24-h) prior to general surgery in our hospital between April 2009 and March 2017. In total, 1028 Japanese patients were included (mean age 73.0 ± 8.9 years). The serum creatinine value was 0.82 ± 0.24 mg/dL. The CCr estimated by CG and measured by 24 h was 64.2 ± 20.9 mL/min and 71.5 ± 21.0 mL/min, respectively. The CG CCr was significantly underestimated in patients aged ≥ 65 years, and the discrepancy exhibited an age-dependent character. The error was reached at 21.7 ± 13.2 mL/min in patients aged ≥ 90 years ($P < 0.001$). The age-dependent errors almost completely disappeared when the modified CG equation was used, in which the term of age in the original CG equation was constantly regarded as 65, if the patient was 65 years or older. Anesthesiologists and intensivists should pay attention to the potential risk of underestimating kidney function when using the CG equation for Japanese elderly patients.

Keywords Aged · Bias · Kidney function · Preoperative evaluation · 24-h urine collection

The correct assessment of renal function in elderly patients is essential for determining the appropriate drug dose and predicting the development of acute kidney injury [1, 2]. The Cockcroft–Gault (CG) equation was originally developed in 1976 to predict the 24-h urinary (24-h) creatinine clearance (CCr) from 249 Caucasian patients aged 18–92 years [3]. One crucial limitation of this widely used equation appears to be that only 17 patients aged ≥ 80 years participated in the study. In addition, the glomerular filtration rate (GFR) is altered by a patient's race even if they have the same serum creatinine concentration [4, 5]. Thus, little is known about the accuracy of the CG equation when used for Japanese elderly patients.

In this study, we performed a retrospective survey of preoperative evaluation in which 24-h CCr was measured prior to general surgery in our hospital, and assessed the concordance of CG CCr with 24-h CCr for elderly patients in a Japanese hospital.

This retrospective cross-sectional study was approved by the ethics committee of Itoigawa General Hospital (no. 2018-06) and conducted in accordance with the principles of the Declaration of Helsinki. We identified all patients aged ≥ 55 years who had participated in a 24-h urine collection within 1 month prior to general surgery at our hospital between April 2009 and May 2017. Patients who declined to participate were excluded. Cardiovascular disease (CVD) included coronary artery disease, heart failure, aortic aneurysms, and cerebrovascular disease. Serum creatinine was measured by an enzymatic method (TBA-c16000, Canon Medical Systems Co., Tochigi). For each patient, creatinine clearance (CCr) was calculated as follows: 24-h CCr (mL/min) = {(urinary creatinine in mg/dL) × (24-h urine volume in mL)}/{(serum creatinine in mg/dL) × 1440}, and the CG equation CCr (mL/min) = {(140 − (age in years))} × (weight in kg)}/{(serum creatinine in mg/dL) × 72} × (0.85 if female) [3].

Statistical comparisons were performed using a paired Student's two-tailed t test. A P value of < 0.05 was

✉ Mitsuhiro Matsuo
matsuo@itoigawa-hp.jp

[1] Department of Anesthesiology, Itoigawa General Hospital, 457-1 Takegahana, Itoigawa, Niigata 941-8502, Japan

[2] Department of Surgery, Itoigawa General Hospital, Itoigawa, Niigata, Japan

considered statistically significant after Bonferroni correction. All statistical analyses were performed using EZR software [6].

In total, 1028 patients for whom a 24-h CCr had been measured prior to an elective surgery were identified. All patients had a Japanese family name. No patients were excluded in this survey. As shown in Table 1, patients were aged 73.0 ± 8.9 years, and 602 (58.6%) were male. Body weight was 56.6 ± 10.7 kg, BMI (body mass index) was 22.7 ± 3.4 kg/m^2, and 25 patients (2.4%) were obese, with a BMI are ≥ 30 kg/m^2. Serum creatinine value was 0.82 ± 0.24 mg/dL. There were no patients who had undergone limb amputation or renal surgery. CG CCr was 64.2 ± 20.9 mL/min, significantly smaller than 24-h CCr (71.5 ± 21.0 mL/min). Six hundred and twenty (60.3%) patients underwent surgery for malignant tumors; 265 of these patients underwent surgery for colorectal cancer. Serum creatinine value and 24-h CCr in patients with malignancy were 0.79 ± 0.21 mg/dL and 72.2 ± 19.6 mL/min, respectively.

Table 1 Characteristics of patients in whom a 24-h CCr was measured prior to general surgery in this study

	Total (n = 1028)
Patients	
Age (years)	73.0 ± 8.9
Gender, male	602 (58.6)
Height (cm)	157.7 ± 9.7
Weight (kg)	56.6 ± 10.7
BMI (kg/m^2)	22.7 ± 3.4
Serum creatinine (mg/dL)	0.82 ± 0.24
24-h CCr (mL/min)	71.5 ± 21.0
CG CCr (mL/min)	64.2 ± 20.9
Comorbidity	
HTN	610 (59.3)
Dyslipidemia	302 (29.4)
DM	170 (16.5)
History of CVD	164 (16.0)
Operative indication	
Malignancy	620 (60.3)
Hernia	217 (21.1)
Cholecystolithiasis	89 (8.7)
Peritonitis	26 (2.5)
Bowel obstruction	16 (1.6)
Stoma	14 (1.4)
Others	46 (4.5)
Types of malignancy (n = 620)	
Colorectal cancer	265 (42.7)
Gastric cancer	152 (24.5)
Breast cancer	88 (14.2)
Liver cancer	48 (7.7)
Pancreatic cancer	17 (2.7)
Cholangiocarcinoma	17 (2.7)
Esophageal cancer	11 (1.8)
Thyroid cancer	10 (1.6)
Duodenal cancer	4 (0.6)
Others	8 (1.3)

Data presented as mean ± SD or median number (%)

BMI body mass index, *CCr* creatinine clearance, *CG* Cockcroft–Gault, *CVD* cardiovascular disease, *DM* diabetes mellitus

The CG CCr and 24-h CCr in each individual were shown as mean ± SD (Fig. 1a). The CG CCr was significantly underestimated in patients aged ≥ 65 years, and the discrepancy exhibited an age-dependent character. The error was reached at 21.7 ± 13.2 mL/min in patients aged ≥ 90 years (P < 0.001).

Next, we tried to modify the CG equation to minimize the error occurring in elderly subjects. We hypothesized that the equation term of "140 minus age" in the CG equation caused the difference in patients with an age of ≥ 65 years. Therefore, in our modified equation, the age term in the original

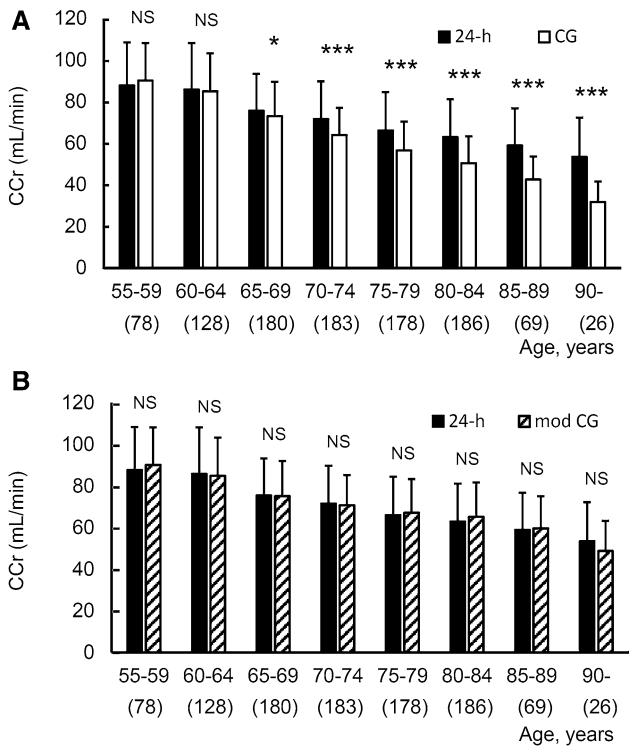

Fig. 1 Effect of age on discrepancy in creatinine clearance (CCr) between 24-h urine collection and Cockcroft–Gault (CG) equation. The 24-h estimated CCr using original CG (**a**) and modified CG (**b**) are shown as mean ± SD, respectively. A number of patients are indicated in parentheses. In the modified equation, the age term in the original CG equation was constantly regarded as 65 if the patients was 65 years or older. Numbers of patients in each group are indicated in parentheses. *< 0.05, ***< 0.001 after Bonferroni correction. *NS* not significant

CG equation was constantly regarded as 65 if the patients was 65 years or older. When we used the modified CG equation, the errors almost completely disappeared in patients aged ≥ 65 years (Fig. 1b).

In the present study, we found an age-dependency of underestimation in the CG equation compared with measured CCr from the 24-h urine collection in the Japanese elderly patients. To minimize the discrepancy caused by age, we proposed a modified CG equation in which the age term in the original CG equation was constantly regarded as 65 if the patient was 65 years or older. This is a pilot study to provide a simple modification method of the CG equation for elderly patients to predict 24-h CCr.

Age is the one of the most important variables used in current and historical equations for estimation of the GFR from serum creatinine [7]. The underestimation trend of the original CG equation in elderly patients was observed in this study and is supported by the other previous reports [8–11]. These observations indicate that the original CG equation is inadequate for representing CCr in old people aged ≥ 65 years and a modification of the equation is warranted with regard to age.

Body weight is another important variable in estimating CCr in several equations [7]. The use of actual body weight in calculating CCr for patients with BMI ≥ 30 kg/m^2 resulted in a substantial and statistically significant difference [9, 10]. On the other hand, patients with a mean BMI of 27.3 showed that a better concordance with the equation was obtained with actual body weight than with ideal body weight [11]. These observations indicate that a BMI of ≥ 30 kg/m^2 is a potential factor affecting the error in CG CCr estimation. Although we did not modify the CG equation with regard to body weight, because the number of obesity patients was very small (2.4%) in our Japanese cohorts, the possibility that a BMI of ≥ 30 kg/m^2 is a significant variable in obese cohorts cannot be ruled out. Other potential factors that interfere the estimation of CG equation includes gender and kidney function itself.

According to the original article by Cockcroft and Gault, a 15% reduction of CCr in female patients is not based on statistical evidence but just experience [3]. In addition, a study showed that CG CCr and measured GFR correlation was reduced in outside the range 50–120 mL/min [12].

The creatinine clearance, shown in mL/min, is well described to exceed the true GFR by approximately 10–40%, since this is the fraction of urinary creatinine that is derived from tubular secretion [13]. To estimate more accurate GFR, the Modification of Diet in Renal Disease (MDRD) study equation [14] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [5], which are normalized to body surface area for standardized values, has been established. However, drug-dosing guidelines have historically been developed using the Cockcroft–Gault equation to estimate kidney function [15], and now in Japan, creatinine clearance values are more frequently used than estimated GFR as renal function in the package inserts of prescription drugs [16]. Thus, a better understanding of properties of CG CCr is needed to predict pharmacokinetics and subsequently to take a full advantage of the drug therapy.

There are some types of chemical methods to measure creatinine in routine clinical laboratories [17], and the method to use also affects interpretation of creatinine value. For instance, serum creatinine measured by means of the alkaline picrate (Jaffe method) is tend to be overestimated than enzymatic method, because the Jaffe method is less specific to creatinine than the enzymatic method [8]. On the other hand, the MDRD and CKD-EPI equations significantly overestimated creatinine clearance in individuals aged ≥ 70 years, possibly due to their reduced muscle mass and subsequent lowering serum creatinine [18]. Thus, when concomitantly use creatinine value measured by enzymatic method and estimation equations for elderly patient, CG equation would supposed to additively overestimate CCr. Interestingly, however, the present study showed underestimation of CCr by CG equation, suggesting that factor of age is critically important to modify the CG equation in elderly patients.

A major limitation of this study is that it was retrospectively performed, using preoperative data. All patients were scheduled to undergo general surgery, indicating that they had been stable in their medical status to undergo general anesthesia and surgery. There is a possibility that such a population may be different from those needing a strict estimation of kidney function, such as critically ill patients. Moreover, 60.3% of our patients had malignancy. Although CCr in patients with malignancy was comparable to that in patients without malignancy in this study, cachexia is often observed in patients with malignancy and affects the creatinine value because of the systemic muscle loss. Since ethnicity is incorporated into several equations for estimating GFR [4, 5], it should be noted that this study was performed in a single Japanese hospital.

In conclusion, we found an age-dependency in the discrepancy in CG CCr compared with the measured CCr from a 24-h urine collection in Japanese patients. The dependency was diminished using our modified CG equation, but further validation studies are needed. Anesthesiologists and intensivists should pay attention to the potential risk of underestimating CCr when using the CG equation for Japanese elderly patients.

Author contributions MM designed and performed the research; preparing manuscript was supervised by YF.

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