

Defining the at risk patients for contrast induced nephropathy after coronary angiography; 24-h urine creatinine versus Cockcroft-Gault equation or serum creatinine level

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Background: Definitions of chronic kidney disease (CKD) in many catheterization laboratories have relied on the serum creatinine (Scr) rather than glomerular filtration rate (GFR). Regarding that CKD is the primary predisposing factor for contrast induced nephropathy (CIN), we compared the sensitivity of calculated GFR by 24-h Urine creatinine with Cockcroft-Gault (CG) equation and Scr level to define at risk patients for CIN who were undergone coronary angiography (CAG). **Materials and Methods:** Two hundred fifty four subjects who were candidate for CAG and had normal creatinine level were enrolled. Before CAG, GFR was calculated from a 24-h urine collection, CG equation and a single Scr sample regarding to previously described protocol. Contrast volume used for each case <100 ml. CIN was defined as a 0.5 mg/dL or 25% elevation in the Scr. **Results:** CIN occurred in 10.6%. Baseline GFR, the volume of contrast agent, and diabetes were the independent risk factors for CIN. GFR was less than 60 ml/min/1.73 m² in 28% and 23.2% of patients regarding to 24-h urine creatinine and CG equation, respectively. In CIN prediction, 24-h urine creatinine estimated GFR had 85.2%, 59.3% and CG equation GFR had 78.9%, 81.1% sensitivity and specificity, respectively. **Conclusion:** Although, GFR estimated by CG equation has less sensitivity than GFR calculated from 24-h creatinine in CIN probability, but it is better than Scr alone and because of cost-effectiveness and convenience using of this method, we suggest at least using CG equation for GFR calculation before CIN, especially in diabetic and/or older than 60 years cases.

Keywords: 24-hour urine creatinine, cockcroft-gault equation, contrast induced nephropathy, coronary angiography, glomerular filtration rate, serum creatinine

INTRODUCTION

Contrast induced nephropathy (CIN) is the third most prevalent preventable cause of acute kidney injury in hospitalized patients.^[1] CIN increased mortality and morbidity specially in patients with cardiovascular diseases.^[2] Diabetes mellitus (DM), chronic kidney disease (CKD), severe congestive heart failure (CHF), dehydration, hypotension, type and volume of contrast are risk factors for CIN.^[3]

Patients with renal failure are susceptible for

atherosclerosis, which increased needs for coronary angiography (CAG). Also, many patients with cardiovascular disease have renal failure, or use drugs which could increase the risk of CIN such as angiotensin converting enzyme inhibitors (ACEIs).^[4] The incidence of CIN after CAG reported as zero to 50%.^[5] which was 40% in diabetic patients and 50 to 90% in CKD.^[6]

It seems many patients are at increased risk for CIN and in many of them CAG will be necessary.^[7] So, preventive efforts from CIN should be performed for patients who candidate for CAG. Definition of CKD in many catheterization laboratories have relied on the serum creatinine (Scr) rather than creatinine clearance (Crcl) or glomerular filtration rate (GFR). Because there are many factors in addition to GFR which effect on Scr level, so using Scr alone is not enough to define at risk patients for CIN. The past researches suppose Cockcroft-Gault (CG) equation or nutrition correction instead of Scr alone to determine the risk of CIN.^[8,9]

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In this study, we compared the sensitivity of calculated GFR by 24-h Urine creatinine, CG equation and Scr level to define at risk patients for CIN who were undergone CAG.

MATERIALS AND METHODS

Two hundred fifty four (254) subjects who were candidate for CAG and fulfilled inclusion criteria were enrolled in this prospective study. Nephrotoxic drugs [(such as aminoglycosides, Nonsteroidal anti-inflammatory drugs (NSAIDs)] and drugs which established or unclear nephro-effective (as aminophylline, theophylline, prostaglandin E, ascorbic acid, N-acetyl cysteine and statins) was discontinued from two weeks before procedure.^[3] Also, metformin replaced by insulin in DM cases. During the study if each of exclusion criteria presents in any time, the case was omitted from the study.

Inclusion criteria

1. Did not have AKI or CKD presentation:
AKI is defined by an abrupt (within 48 h) absolute increase in the serum creatinine concentration of ≥ 0.3 mg/dL from baseline, or serum creatinine concentration increased ³⁵⁰ percent, or oliguria of less than 0.5 mL/kg per hour for more than six hours.^[10]
CKD is defined based on the presence of either kidney damage or decreased kidney function for three or more months, irrespective of cause. As a routine estimated GFR is used to determined renal function (normal >90 ml/min/1.73 m²). Kidney damage, as defined by structural abnormalities or functional abnormalities other than decreased GFR.^[11]
2. Did not received contrast during last week
3. Did not have any history of contrast sensitivity
4. Did not received diuretics/ACEIs/angiotensin receptor blockers during last 10 days
5. The permission of discontinuing nephrotoxic drugs (such as aminoglycosides, NSAIDs) or drugs which established or unclear nephro-effective (as aminophylline, theophylline, prostaglandin E, ascorbic acid, N-acetyl cysteine and statins).

Exclusive criteria

1. Cardiopulmonary resuscitation (CPR) during CAG
2. Cardiogenic shock
3. Massive bleeding or hemodynamic instability during CAG
4. Acute pulmonary edema
5. Necessary to use renal effective drugs after CAG
6. Incorrect follow up after CAG and did not perform 48 h after CAG samples and tests
7. Contrast volume used more than 100 cc
8. Present of inclusion criteria number 3 or 5 during the study

Before angiography Scr level and 24-h urine creatinine level was checked in all cases. If 24-h urine volume was less than 500 cc or more than 3000 cc or its creatinine level was less than (0.2 × body weight) in males or (0.15 × body weight) in females, the sample define as incorrect collected sample and the case was omitted from the study. Iodixanol (Visipaque®, GE Medical, Inc) was used as contrast in all CAG candidates (the volume of contrast varied in each case by the minimum of need) Contrast volume used for each case <100 ml. After 48 h from angiography Scr level was checked in all cases. CIN was defined as a 25% elevation in the Scr or an absolute increase of 0.5 mg/dl, 48 h after CAG.

GFR before CAG was calculated by 3 ways:

1. Based on Scr; $GFR = \frac{100}{Scr}$
 2. Based on CG equation;
$$GFR = \frac{(140 - Age) \times Weight \times 0.85 (If\ female)}{Scr \times 72}$$
 3. Based on 24-h urine; $GFR = \frac{UCr \times Uvol}{Scr}$
- [Scr: Serum Creatinine (mg/dl), age: years old (years), Ucr: 24-h urine creatinine (mg/dl), Uvol: 24-h Urine Volume (ml/min)]

DM was defined as patients who had history of DM and used specific diabetic treatment, or who had fasting plasma glucose values ≥ 126 mg/dL (7.0 mmol/L) in two times measurement.^[12] Heart failure (systolic) was defined as patients who had ejection fraction lower than 50% in coronary angiography.^[13]

Data were analyzed by SPSS® 16 software with using independent T-test, Chi-square, Pearson correlation, logistic regression. GFR less than 60 ml/min was used to define high risk patients for CIN and sensitivity calculation.

RESULT

Two hundred eighty cases were enrolled in the study but 26 cases omitted because of incorrect follow-up. So, 254 cases remain in. Patient's demographic characteristics report in Table 1 completely. While the Scr was normal (≥ 60 ml/min/1.73 m²) in all subjects, GFR was less than 60 ml/min/1.73 m² in 71 (28%) and 59 (23.2%) of patients regarding to 24-h urine creatinine and CG equation, respectively.

There was significant correlations between GFRs estimated by Scr with GFR measured by 24-h creatinine clearance (Clcr) method ($P < 0.001$, $r = 0.591$) and GFR estimated

by CG equation ($P < 0.001$, $r = 0.726$). The same, there was significant correlation between GFR estimated by CG equation and GFR measurement by 24-h Clcr method ($P < 0.001$, $r = 0.799$, Figure 1).

Mean Scr (mean \pm SD) before angiography was 1 ± 0.21 (mg/dl) and after angiography was 1.05 ± 0.23 (mg/dl) which has significantly difference (P value < 0.001). 27 cases (10.6%) catch CIN.

In patients who complicated by CIN; 17 (63%) cases were male and 10 (37%) cases were female, 7 (25.9%) cases had HF and 20 (74.1%) cases did not have HF (differences were not significant), 9 (33.3%) cases were ≤ 60 years old and 18 (66.7%) cases were >60 years old, 19 (70.4%) cases were diabetic and 8 (29.6%) cases were non-diabetic (differences were significant by P values of 0.001 and < 0.001 , respectively). The mean of consumed contrast volume was 88.7 ± 31.2 ml in cases with CIN versus 71.6 ± 25.4 ml in cases without CIN ($P = 0.001$). GFR estimated by Scr was 102.8 ± 13 ml/min/1.73 m² in CIN group and was 105.1 ± 26.7 ml/min/1.73 m² in non-CIN group ($P = 0.449$). GFR estimated by CG equation was 60.7 ± 22.1 ml/min/1.73 m² in CIN group versus 85.4 ± 33 ml/min/1.73 m² in non-CIN group ($P < 0.001$). GFR measured by 24-h Clcr method was 48.2 ± 21 ml/min/1.73 m² in CIN group against of 78.8 ± 33.2 ml/min/1.73 m² in non-CIN group ($P < 0.001$). The regression analysis was performed to discover independent variables affected CIN so DM, contrast volume and GFR measured by 24-h Clcr method before CAG had significant regression [Table 2].

CIN occurs in 4 (2.2%) patients with GFR measured by 24-h Clcr method ≥ 60 ml/min/1.73 m² and in 23 (32.4%) patients with GFR measured by 24-h Clcr method < 60 , also in 11 (5.6%) cases with GFR estimated by CG equation ≥ 60 and in 16 (27.1%) cases with GFR estimated by CG equation < 60 (P values were < 0.001 in both, Table 3).

Receiver Operating Characteristic (ROC) curves of GFR by 24-h urine Clcr with estimated GFR using CG equation and Scr level shows GFR estimated by Scr has distance from other two GFRs' curves. These distances were prominent in cases more than 60 years old and in cases with diabetes mellitus [Figure 2].

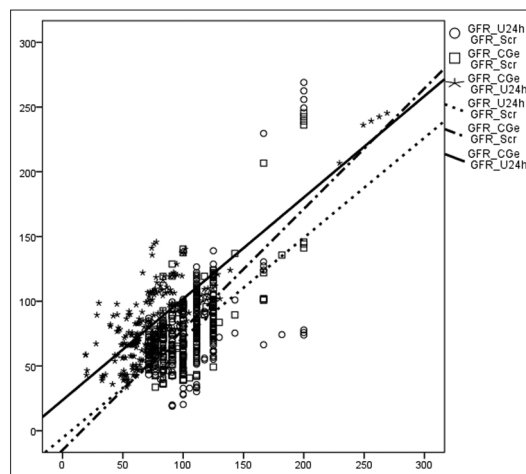


Figure 1: Linear correlation between measured GFR by 24-h Urine Clcr with estimated GFR using CG equation and Scr level

Table 1: Demographic characteristics of assessed patients

Gender	Male (%)	140 (55.1)
	Female (%)	114 (44.9)
Age (year)	Mean (SD)	56.6 (11.9)
Weight (kg)	Mean (SD)	72.3 (13.2)
Disease	DM (%)	57 (22.4)
	HF (%)	60 (23.6)
	DM+HF (%)	12 (4.7)
GFR (ml/min) (Mean (SD) based on)	Scr	104.9 (25.6)
	24-h Ucr	75.5 (33.4)
	CG equation	82.8 (32.8)

DM = Diabetes Mellitus, HF = Heart failure, Scr = Serum creatinine, 24-h Ucr = 24-h Urine creatinine, CG equation = Cockcroft Gualt equation

Table 2: Comparative analysis between contrast induced nephropathy subgroups by studied variables

Variable		Contrast induced nephropathy		P value (regression')
		Positive(%)	Negative(%)	
Gender	Male	17 (63)	123 (54.2)	0.420
	Female	10 (37)	104 (45.8)	
Age (year)	≤ 60	9 (33.3)	155 (68.3)	0.001(r: ns*)
	> 60	18 (66.7)	72 (31.7)	
DM	Positive	19 (70.4)	38 (16.7)	< 0.001 (r = 13.9*)
	Negative	8 (29.6)	189 (83.3)	
HF	Positive	7 (25.9)	53 (23.3)	0.811
	Negative	20 (74.1)	174 (76.7)	
Contrast volume (ml)		88.7 ± 31.2	71.6 ± 25.4	0.001 (r= 1.02*)
GFR by Scr (ml/min)		102.8 ± 13	105.1 ± 26.7	0.449
GFR by CG equation (ml/min)		60.7 ± 22.1	85.4 ± 33	< 0.001 (r: ns*)
GFR by 24-h Ucr (ml/min)		48.2 ± 21	78.8 ± 33.2	< 0.001 (r = -0.92*)

DM = Diabetes Mellitus, HF = Heart failure, Scr = Serum creatinine, 24-h Ucr = 24-h Urine creatinine, CG equation = Cockcroft Gualt equation, NS = Not significant; *Coefficients of regression analysis to defined independence factors affect CIN

GFR measured by 24-h Clcr method had 85.2% sensitivity, 78.9% specificity, 32.4% and 87.8% positive and negative predictive values and 79.52% accuracy in predicting

probability of contrast induced nephropathy. GFR estimated by CG equation had 59.3% sensitivity, 81.1% specificity, 27.1% and 94.4% positive and negative predictive values and 78.74% accuracy in predicting probability of contrast induced nephropathy. Complete information of diagnostic values is mentioned in Tables 4.

Table 3: Comparison of contrast induced nephropathy prevalence

variable		Contrast induced nephropathy		Total	P value
		Positive(%)	Negative		
GFR by 24-h Ucr (ml/min)	≥60	4 (2.2)	179 (97.8)	183 (100)	<0.001
	<60	23 (32.4)	48 (67.6)	71 (100)	
GFR by CG equation (ml/min)	≥60	11 (5.6)	184 (94.4)	195 (100)	<0.001
	<60	16 (27.1)	43 (72.9)	59 (100)	

24-h Ucr = 24-h Urine creatinine, CG equation = Cockcroft Gault equation GFR calculated based on serum creatinine in all cases was more than 60 ml/min/1.73 m²

DISCUSSION

CIN has economic and clinical complications such as increased duration of hospitalization, dialysis need and mortality and morbidity risk. CIN prevalence were reported varies from 0 to 50% (up to 40% in diabetic patients and 50 to 90% in CKD)^[6] by different mentioned factors.^[5] In Cuvate

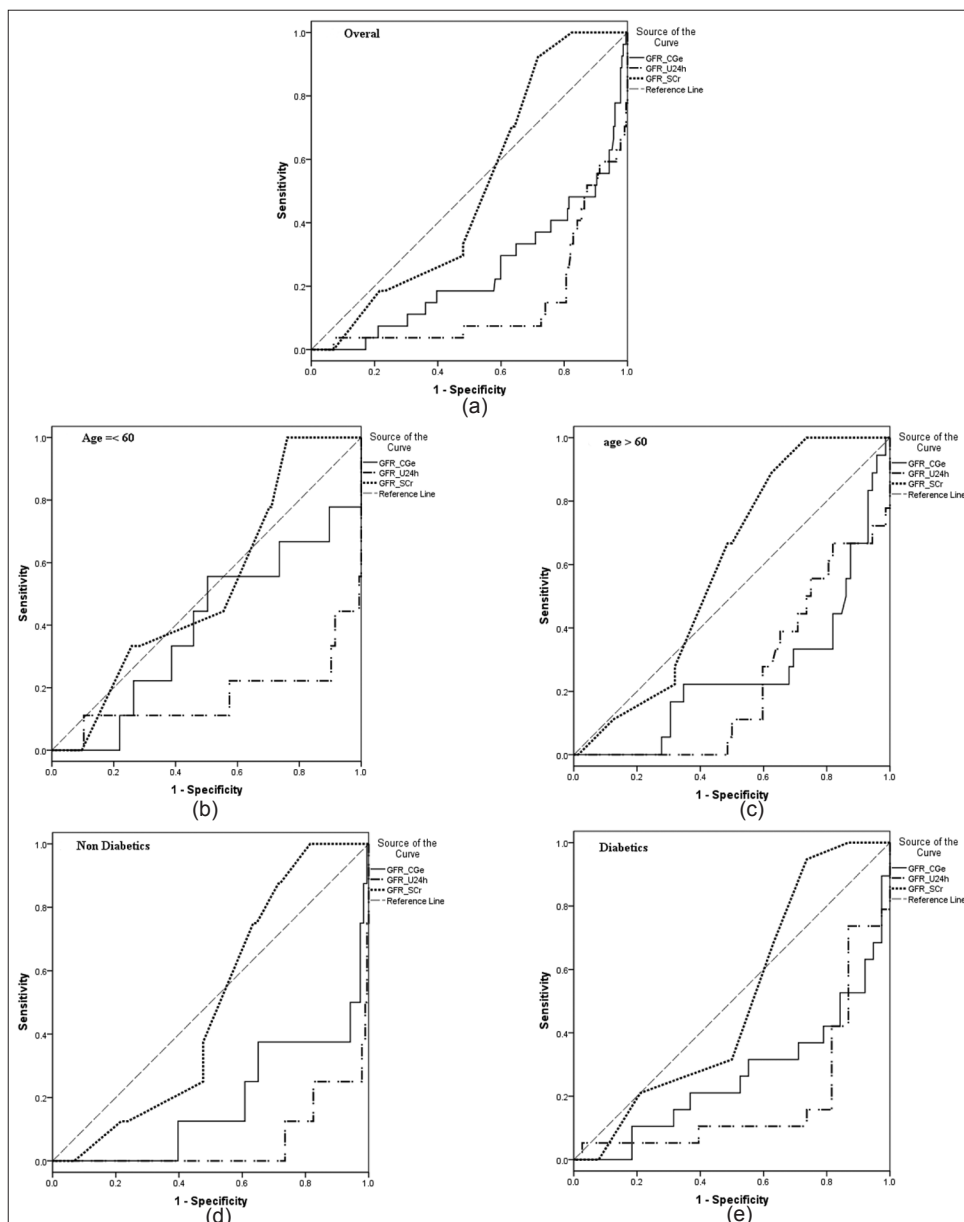


Figure 2: Receiver Operating Characteristic (ROC) curves of GFR by 24-h Urine Clcr with estimated GFR using CG equation and Scr level. A: Overall, B: in cases ≤ 60 years old, C: in cases > 60 years old, D: in cases without diabetes mellitus, E: in cases with diabetes mellitus

Table 4: Comparison of diagnostic values of GFRs calculated by 24-h urine creatinine and CG equation to predict probability contrast induced nephropathy

	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)	Accuracy (95%CI)
GFR by 24-h Ucr (ml/min)	85.2% (65.4-95.1)	78.9% (72.8-83.9)	32.4% (22-44.7)	87.8% (94.1-99.3)	79.52% (74.5-84.4)
GFR by CG equation (ml/min)	59.3% (39-77)	81.1% (75.2-85.8)	27.1% (16.7-40.5)	94.4% (89.9-97)	78.74% (73.7-83.7)

24-h Ucr = 24-h urine creatinine, CG equation = Cockcroft Gault equation

country, Ghani *et al.* fined 5.52% CIN from 247 cases,^[14] Valente *et al.* report 10.8%,^[15] and Kim report 13%^[8] CIN's in their research. Also, in other CIN reported as 13% and 20% in non-diabetic and diabetic patients, respectively.^[16] In-hospital CIN developed in 72 (8.3%) patients, in Mager *et al.* report^[17] and 5.2% in Worasuwannarak and Pornratanarangi's report.^[18] The same as these researches in our study CIN prevalence was 10.6%.

There was wide variation in risk factors, which contributes with CIN. There were age over 75 years old, DM, CHF, pulmonary edema history, contrast volume, serum creatinine over 1.5 mg/dl and GFR less than 60 ml/min/1.73 m² as risk factors for CIN in Rihale and Baret studies.^[19,20] Beckris confirmed them and added dehydration as a CIN's risk factor.^[21] Kim *et al.* report left ventricular ejection fraction less than 40%, GFR less than 60 ml/min/1.73 m², serum reactive protein C more than 0.5 mg/dl and contrast volume consumption more than 250 cc as CIN's independent risk factors.^[8] Basal Scr level, shock, female gender, DM were CIN's risk factors in report of Ghani *et al.*^[11] Renal underlying disease, hemodynamic instability, dyslipidemia, hypotension after angiography were risk factors for CIN in Valente *et al.* research.^[22] In the same pattern in our study, independent risk factors for CIN were basal GFR, DM, and contrast volume [Table 3].

National kidney foundation define a single system for chronic renal disorders classification, based on GFR during 2002 and suggest to use CG equation or modification of diet in renal disease (MDRD) for GFR estimation.^[23] This real despite of limitations in these equations (as over estimation of GFR in CG equation and did not use body surface area, the same as GFR estimation in MDRD equation), but also it is better for determining CKD staging rather than Scr level alone.

Similarly in our study, ROC curves in Figure 2 shows GFRs' based on CG equation and 24-h Clcr method have similar pattern than to GFR based on Scr, especially in subgroups of age and DM. So, sensitivity and specificity of both GFRs based on CG equation and 24-h urine Clcr seems more similar than to GFR estimated by Scr, especially in patients over 60 years old or DM. According to Table 4, it was cleared that, CG equation is better than Scr alone for GFR estimation. Although, this equation has less sensitivity than

GFR, calculated from 24-h creatinine in CIN probability, but 24-h urine collection needs more time and it is more expensive than estimating GFR using equations, so CG equation seems more convenience as it is cost effective as a simple method for physicians in their practice, especially in cases over 60 years old or DM. On the other hand, using GFR based on CG equation could revealed at least 28% of cases with GFR < 60 ml/min/1.73 m² and high risk for CIN more than using Scr alone or GFR based on Scr.

CONCLUSION

GFR by 24-h urine Clcr is more accurate way to estimate GFR in patients who candidate for CAG, but it needs more time, cost and hospitalization. While using CG equation for GFR calculation to assess CIN's risk in patients is more applicable than Scr level alone. Although, estimating the GFR using this equation has less sensitivity than GFR calculated from 24-h creatinine in CIN probability, but because of cost-effectiveness, we suggest using CG equation for GFR calculation before CIN, to choose patients who need more attention for preventive support, especially in cases over 60 years old or DM.

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