Assessment of estimated GFR and clinical predictors of contrast induced nephropathy among diabetic patients undergoing cardiac catheterization

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Abstract Introduction: Contrast-induced nephropathy is a leading cause of morbidity and mortality in high-risk patients.

Aim: To study different risk predictors of contrast induced nephropathy, among diabetic patients with normal serum creatinine undergoing cardiac catheterization.

Patients and methods: It involved 250 consecutive diabetic patients who underwent either coronary angiography or PCI. All patients were subjected to thorough history taking and clinical examination, measurement of serial serum creatinine levels and creatinine clearance prior to the procedure, 72 h after and after 7 days, coronary angiography or percutaneous coronary intervention, ECG, echocardiography, follow up during the first seventy-two hours for occurrence of contrast-induced nephropathy, follow up one month later for occurrence of major adverse cardiac events.

Results: 58 patients developed CIN with total incidence of 23.2%. CIN was found to be more among the patients who had PCI (40 patients, 69%, P < 0.01). Regarding different predictors of CIN, age, diabetes, ACEIs, anemia, lower LVEF, contrast media volume and lower creatinine clearance, were significantly associated with CIN (P < 0.01). Regarding MACE, only 4 patients had complications, with an incidence of 3.4% vs 1.04% among CIN positive and negative patients, respectively.

Conclusion: Creatinine clearance or estimated GFR are important surrogates for assessment of kidney function among diabetic patients undergoing catheterization despite normal serum creatinine. Modifiable risk predictors of CIN should be corrected as possible. Prophylaxis against CIN should be carried out by adequate hydration to all diabetic patients with calculation of the volume of contrast in relation to CrCl or GFR.

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Key words: CIN; Diabetes; Contrast media
involving the use of radiographic contrast media. Subjects who develop this complication have higher rates of mortality, longer hospital stays and worse long-term outcomes. The occurrence of contrast-induced nephropathy is related to the number of the patients’ co-existing clinical risk factors. Among the many risk factors, pre-existing renal impairment, advancing age, the presence of diabetes mellitus as well as the volume and type of contrast agent administered are the most important. The precise pathophysiological mechanisms responsible for the development of contrast-induced nephropathy are complex and incompletely understood. At present, the only available tool for reducing the risk of developing contrast-induced nephropathy is prevention. This can be achieved by means of adequate peri-procedural hydration, using N-acetyl cysteine as well as the selection of low osmolar or iso-osmolar contrast agents in the least amount possible. Other agents are still being tested for this purpose as well.

2. Aim of study

To study different risk predictors of contrast induced nephropathy, among diabetic patients with normal serum creatinine undergoing cardiac catheterization. To follow up the occurrence of major adverse cardiac events (mortality, reinfarction, stroke, target vessel revascularization) during one month of hospital discharge.

3. Methods

3.1. Study population

The study was conducted on 250 consecutive patients presenting to the Ain Shams University Hospital catheter lab from the period of September 2012 till November 2012 to undergo either coronary angiography or percutaneous coronary intervention. Exclusion criteria were: serum creatinine level ≥1.5 mg/dL, recent exposure to radiographic contrast within forty-eight hours of the study, allergy to radiographic contrast, administration of N-acetyl cysteine, dopamine, mannitol or theophylline during the intended time of the study and patient known to have skeletal muscle disease or myopathy.

3.2. Methods

3.2.1. The suitable patients were subjected to the following

3.2.1.1. Thorough history taking. A full medical history was taken with special emphasis on: the indication of the coronary angiography, history of diabetes mellitus (recognized by the patient giving symptoms suggestive of diabetes mellitus [as polyuria, polydipsia, polyphagia, loss of weight, etc.]) and/or the patient’s receiving treatment for diabetes mellitus, whether it were insulin or oral hypoglycemic drugs), history of pre-existing renal impairment (recognized by symptoms suggestive of the disease as oliguria, pruritus, anorexia, hiccups, peripheral neuropathy, etc.) or by an elevated serum creatinine level, history of allergy to radiographic contrast media, age and sex of the patient (for purpose of calculation of the creatinine clearance level using the Cockcroft–Gault equation).

3.2.1.2. Physical examination. Complete general and local examination with special emphasis on: weight and height of the patient (for purpose of calculation of the creatinine clearance level using the Cockcroft–Gault equation), features and skin complexion (in search for evidence suggestive of pre-existing chronic renal impairment) as: yellow–brown complexion, pallor, itching marks... etc.

3.2.1.3. Twelve-lead surface ECG. To identify evidence of any of the following: an old myocardial infarction, ST-T segment deviations suggestive of ischemia, chamber enlargements, conduction disturbances and rhythm disturbances.

3.2.1.4. Coronary angiography. Coronary angiography was done in the standard fashion after gaining femoral artery access puncture using Seldinger’s technique. The standard coronary views were obtained, which included an average six left coronary and two right coronary artery injections giving sufficient data to enable quantitative angiography. The type of contrast used was Ioversol (Optiray 300) which is low osmolar non ionic contrast media.

3.2.1.5. Assessment of serial serum creatinine levels. A baseline venous sample was withdrawn prior to the procedure as well as two other samples, one of which was collected 72 h after the procedure and the other 7 days after the procedure.

It was assessed using a fully automated analyzer Biolis 24i Premium manufactured by Tokyo Boeki Medical Systems.

3.2.1.6. Assessment of serial creatinine clearance levels. The glomerular filtration rate (GFR) is an index of functioning renal mass and it is the best measure of overall kidney function in health and disease. Normal glomerular filtration rates are 120 ± 25 ml/min for males, and 95 ± 20 ml/min for females. The use of prediction equations to estimate GFR from serum creatinine and other variables (age, sex, race, and body size) is therefore recommended by the National Kidney Foundation for the diagnosis and stratification of chronic kidney diseases. According to this foundation, renal function is moderately decreased if GFR is < 60 ml/min 1.73 m² and severely decreased if GFR is < 30 ml/min 1.73 m². The proposed equations are the Cockroft–Gault formula, as recommended by the American Diabetes Association, and the Modification of Diet in Renal Disease (MDRD) study equation. The more recent MDRD equation seems more accurate, but it has not been validated in diabetic kidney disease. Its superiority over the Cockroft–Gault formula has been mentioned in some, but not all recent reports. A commonly used surrogate marker for estimation of creatinine clearance is the –Gault formula, which in turn estimates GFR in ml/min. It is named after the scientists who first published the formula, and it employs serum creatinine measurements and a patient’s weight to predict the creatinine clearance. The formula, as originally published, is:

$$GFR = (140 – age) \times \text{weight (kg)} / (72 \times \text{serum creatinine})$$

in women, multiplied by 0.85. This formula expects weight to be measured in kilograms and creatinine to be measured in mg/dL, as is standard in the USA.

3.3. End point

The patients were observed during the forty-eight hours of follow up. It has to be noted that the third sample was mostly obtained on an outpatient basis. The primary end point was
the development of contrast-induced nephropathy. Post discharge one month follow up was done to all patients among our study. They were subjected to either clinical visits or phone calls in order to assess the possible occurrence of major adverse cardiac events (mortality, stroke, reinfarction, target vessel revascularization) and occurrence of renal failure and subsequent dialysis.

3.4. Data management

Data were collected, coded, revised and entered into the statistical package for social science (SPSS) version (17) and the following were done. The qualitative data were presented as number and percentages while the quantitative data were presented as mean, standard deviations and ranges. The comparison between two groups with qualitative data was done by using Chi-square test and/or Fisher exact test only when the expected count was less than 5 in any cell. The comparison between two groups with quantitative data was done by using Independent sample t-test. The receiver operating characteristic curve (ROC) was used to assess the cut-off point between two groups with sensitivity, specificity, positive predictive value and negative predictive value. Logistic regression analysis was used to assess the risk factors for CIN with odds ratio. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value of <0.05 was considered significant. P value >0.05 = Non-significant (NS), P value <0.05 = Significant (S) and P value <0.01 = Highly significant (HS).

4. Results

This is a cross sectional study that was conducted on 250 diabetic patients referred to the Ain Shams University Hospital Catheter Lab to undergo either coronary angiography or PCI. They all had serum creatinine levels within the normal range and no history of preexisting renal disease. No preprocedural prophylactic measures against CIN were taken. 158 patients had coronary angiography while 92 patients had PCI, of which 14 primary PCI were done with a successful outcome.

4.1. Baseline demographic characteristics, risk factors and LV systolic function

The age and sex distribution among our study group showed 162 male patients (64.8%) and 88 female patients (35.2%) with age ranging from 40 to 82 years and mean ± SD of 57.73 ± 7.50 years. While the body weight mean ± SD 89.42 ± 10.33 kg and height mean ± SD 166.20 ± 4.39 cm. There were 134 smoker patients (53.6%). 32 patients (12.8%) had a positive family history of ischemic heart disease. They were all type II diabetic patients, 78 patients were receiving oral hypoglycemics, while 158 patients were receiving insulin treatment. No one was on diet regimen with a median duration of eight years. There were 70 hypertensive patients (27%), versus 180 (72%) patients not known to be hypertensive. Patients receiving angiotensin converting enzyme inhibitors were 88 patients. Patients receiving NSAID were eight patients only of the study group. We considered patients having hemoglobin level less than 11 g/dl as anemic patients. They were ten anemic patients among our study group. The mean EF among the patients was 50.52% with the least EF measured 30% and the maximum was 69% (Table 1).

4.2. Baseline S. Creatinine and creatinine clearance

Baseline creatinine clearance was calculated using the Cockroft–Gault equation. The minimum baseline S. Creatinine value during the study was 0.6 and the maximum was 1.4 mg/dl while the mean was 0.87 mg/dl among the study population. After 72 h of contrast administration the maximum S. Creatinine reached 2.5 mg/dl, while the mean was 1.14 mg/dl. The starting mean ± SD baseline creatinine clearance of the patients preprocedural, was 118.64 ml/min ± 34.69 while the minimum CrCl was 49.68 ml/min and the maximum 220.95 ml/min. Creatinine clearance measured using Cockroft–Gault equation 72 h post procedural revealed a mean ± SD of 95.88 ± 36.37 and minimum of 31.37 and maximum of 220.95 as shown in Table 2.

4.3. Volume of contrast in relation to eGFR

The mean amount of contrast used was 165.88 ± 88.88 cc. The minimum amount was 70 cc while the maximum amount used was 400 cc during a primary PCI case. We calculated the volume of contrast in relation to eGFR preprocedural as a predictor of CIN among the study population showing a mean of 1.57 ± 1.09 ml/min.

The patients were classified according to their creatinine clearance into different groups:

- >90 ml/min indicating normal GFR 196 patients (78.4%).
- 60–89 mild renal impairment, 46 patients (18.4%).
- 30–59 moderate renal impairment; 8 patients (3.2%).
- No patients had CrCl less than 30 ml/min.

4.4. Incidence of CIN among the study group

The definition of contrast induced nephropathy adopted in our study is increase in the serum creatinine ≥0.5 mg/dl from the baseline value within 48–72 h after contrast media

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**Table 1** Baseline demographic characteristics, risk factors and LV EF of the study groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>57.73 ± 7.50</td>
</tr>
<tr>
<td>Males No. (%)</td>
<td>162 (64.8%)</td>
</tr>
<tr>
<td>Females No. (%)</td>
<td>88 (35.2%)</td>
</tr>
<tr>
<td>Mean body weight (kg)</td>
<td>89.42 ± 10.33</td>
</tr>
<tr>
<td>Mean height (cm)</td>
<td>166.20 ± 4.39</td>
</tr>
<tr>
<td>Smoking No. (%)</td>
<td>134 (53.6%)</td>
</tr>
<tr>
<td>Family history No. (%)</td>
<td>32 (12.8%)</td>
</tr>
<tr>
<td>Hypertension No. (%)</td>
<td>70 (27%)</td>
</tr>
<tr>
<td>Median duration of diabetes mellitus (years)</td>
<td>8</td>
</tr>
<tr>
<td>Oral hypoglycemics drugs No. (%)</td>
<td>78 (31.2)</td>
</tr>
<tr>
<td>Insulin no (%)</td>
<td>172 (68.8)</td>
</tr>
<tr>
<td>ACEIs</td>
<td>88 (35.2%)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>8 (3.2%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>LV EF</td>
<td>30–69% (mean: 50.52%)</td>
</tr>
</tbody>
</table>
administration. We found that 58 patients developed CIN with a total incidence of 23.2%. CIN was found to be more among the patients who had PCI, they were 40 patients (69%). It was less among the coronary angiography patients as they were only 18 patients (31%), showing a highly statistically significant $P$ value of less than 0.01 as shown in Table 3.

The occurrence of CIN was even more significant among the patients presenting with acute myocardial infarction requiring primary PCI. There were 14 patients who had primary PCI of which 10 developed CIN, yielding a highly significant relation between having primary PCI and developing CIN showing a highly statistically significant $P$ value $<$0.01.

### 4.5. Different predictors of CIN

#### 4.5.1. Gender

We did not find a correlation between the gender and development of CIN among our study group. A total of 162 male patients were involved, of which only 34 patients developed CIN. A total of 88 female patients were involved, of which only 24 of them developed CIN with incidence of 41.40%, resulting in a non statistically significant $P$ value of 0.26.

#### 4.5.2. Age

We found a strong correlation between increasing age as a predictor of developing CIN. Using the receiver operator characteristic curve analysis we defined a good cut off value of 57 years as a predictor for CIN, patients above this age developed CIN more than those below that age as shown in Fig. 1 with a sensitivity of 73.33% and specificity of 67.74%. Among the 58 patients who developed CIN, 42 patients were above the age of 57 and 16 less than it showing a highly statistically significant $P$ value $<$0.01.

#### 4.5.3. Smoking

We could not find a correlation between smoking as a risk factor for CAD and possible development of CIN. Out of 58 patients who developed CIN, 30 patients were smokers and 28 were not. A $P$ value of 0.7 was considered statistically non significant.

#### 4.5.4. Family history of ischemic heart disease

We did not find a correlation between patients who had positive family history of ischemic heart disease as a risk of CAD, and as a risk predictor for development of CIN among our study group. We found only six patients having a positive family history of ischemic heart disease among all patients who developed CIN. A $P$ value of 0.5 was considered non significant.

#### 4.5.5. Diabetes

All the patients presented in our study were Type II diabetic patients. We intended to see the relation between patients on oral hypoglycemic drugs and those on insulin in relation to CIN occurrence. We found that patients on insulin treatment were significant risk predictor for CIN. Fifty-two patients (89.7%) were on insulin treatment among all the patients who developed CIN, while only six patients were on OHG and developed CIN.

#### 4.5.6. Hypertension

We could not find a correlation between hypertension and development of CIN, with a non significant $P$ value of 0.5. On the contrary patients who were hypertensive, defined as having a systolic blood pressure less than 100 mmHg preprocedural, were a strong risk predictor for development of CIN with a highly statistically significant $P$ value of $<$0.01.

#### 4.5.7. Drugs

Patients who were receiving angiotensin converting enzyme inhibitors either as a treatment of heart failure or as a treatment for hypertension were higher among those who developed CIN. There were 36 patients (62.10%) on regular angiotensin converting enzyme inhibitor treatment who

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**Table 2** Serial measurements of S. Creatinine and CrCl.

<table>
<thead>
<tr>
<th></th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of contrast (cc)</td>
<td>70</td>
<td>400</td>
<td>165.88</td>
<td>88.88</td>
</tr>
<tr>
<td>Baseline S. Creatinine mg/dl</td>
<td>0.6</td>
<td>1.4</td>
<td>0.87</td>
<td>0.20</td>
</tr>
<tr>
<td>S. Creatinine day 3 (mg/dl)</td>
<td>0.6</td>
<td>2.5</td>
<td>1.14</td>
<td>0.41</td>
</tr>
<tr>
<td>S. Creatinine day 7 (mg/dl)</td>
<td>0.5</td>
<td>2.3</td>
<td>0.98</td>
<td>0.31</td>
</tr>
<tr>
<td>CrCl day 1 (eGFR)</td>
<td>49.68</td>
<td>220.95</td>
<td>118.64</td>
<td>34.69</td>
</tr>
<tr>
<td>CrCl day 3</td>
<td>31.37</td>
<td>220.95</td>
<td>95.88</td>
<td>36.67</td>
</tr>
<tr>
<td>CrCl day 7</td>
<td>25.92</td>
<td>227.33</td>
<td>108.30</td>
<td>35.89</td>
</tr>
<tr>
<td>Volume of contrast /eGFR</td>
<td>0.41</td>
<td>6.64</td>
<td>1.57</td>
<td>1.09</td>
</tr>
</tbody>
</table>

**Table 3** Incidence of CIN among coronary angiography and PCI patients.

<table>
<thead>
<tr>
<th>Angio/PCI</th>
<th>CIN</th>
<th>Chi-square test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>140</td>
<td>72.90</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>52</td>
<td>27.10</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>100.00</td>
</tr>
</tbody>
</table>
developed CIN while 22 patients (37.9%) were not on ACE treatment and developed CIN. The use of NSAID was limited only to eight patients, four of them developed CIN, they were receiving ibuprofen on regular intervals. They did not show a correlation as a predictor for developing CIN with non statistically significant P value of 0.068.

4.5.8. Anemia

The mean hemoglobin level tends to be lower among the patients who developed CIN which was 12.67 g/dl ± 1.22 SD while among the other group it was 13.53 mg/dl ± 1.07 SD showing a highly statistically significant P value < 0.01. Among the study group we defined anemia as having hemoglobin less than 11 g/dl. We found a total of 10 anemic patients of which 5 developed CIN with a statistically significant P value of 0.04.

4.5.9. Ejection fraction

Patients having a lower ejection fraction tend to have increased risk of CIN compared to those with better ejection fraction with a highly statistically significant P value < 0.01. The mean ejection fraction among patients who developed CIN was 43.45% ± 7.98 while those who did not develop CIN had a mean EF of 52.66% ± 6.91. Patients having EF < 50% were more to develop CIN in comparison to those who were > 50% with a highly statistically significant P value of < 0.01.

4.5.10. Contrast volume

The mean contrast volume used among patients who developed CIN was 240.69 ± 104.86 cc while it was 143.28 ± 69.30 cc among patients who did not. We found a strong correlation between increasing the volume of contrast and increasing the risk of developing CIN. Those patients receiving more than 200 cc of contrast media had a higher incidence (65.5%) among CIN patients in comparison to patients using less than 200 cc of contrast who had an incidence of 34.5% among CIN positive patients.

4.5.11. Creatinine clearance

We calculated the creatinine clearance according to the –Gault equation and we used it as an indirect measure to estimate the glomerular filtration rate and we assumed that it will be more accurate to assess the kidney function using it rather than using the standard S. Creatinine. As we started with patients having normal S. Creatinine, they did not receive any prophylactic measures against CIN. We found that almost eight patients had CrCl less than 60 ml/min indicating a moderate degree of renal impairment. It showed that patients having lower CrCl were higher among the CIN group with a highly statistically significant P value < 0.01 as shown in Tables 4 and 5.

4.6. Volume of contrast in relation to eGFR

In recent studies the Volume of contrast in relation to eGFR was used as independent predictor of CIN. We aimed to find the relation between the increasing ratio of it and the increasing the risk of CIN and to some extent having a cut off value at which we can use and implement in clinical practice. The mean V/eGFR was 2.69 ± 1.35 among patients who developed CIN in comparison to 1.23 ± 0.70 in patients who did not showing a highly statistically significant P value < 0.01. Using the ROC curve we identified a cut off value of 2.7 as a ratio in PCI patients with a specificity of 85.19% and sensitivity of 65% (Fig 2). We could not use this value in coronary angiography patients due to the relative decrease in total amount of contrast used among these patients.

4.7. Risk of CIN in relation to extent of CAD

We found a highly significant correlation, as patients who had more than one vessel treated had a higher risk for developing CIN comparing to those who had only single vessel treated. The increasing number of stents used had a strong correlation with further risk of CIN as patients who had 3 stents or more

Table 4 Serial serum creatinine and CrCl in relation to CIN patients.

<table>
<thead>
<tr>
<th>CIN</th>
<th>Independent t-test</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative Mean SD</td>
<td>Positive Mean SD</td>
<td>T</td>
</tr>
<tr>
<td>S. Creatinine day 1</td>
<td>0.82 0.17</td>
<td>1.00 0.24</td>
<td>-6.048</td>
</tr>
<tr>
<td>S. Creatinine day 3</td>
<td>0.97 0.24</td>
<td>1.69 0.39</td>
<td>-16.861</td>
</tr>
<tr>
<td>S. Creatinine day 7</td>
<td>0.86 0.16</td>
<td>1.35 0.38</td>
<td>-14.024</td>
</tr>
<tr>
<td>CrCl 1</td>
<td>125.63 32.34</td>
<td>95.50 32.29</td>
<td>6.219</td>
</tr>
<tr>
<td>CrCl 3</td>
<td>108.04 32.00</td>
<td>55.63 17.17</td>
<td>11.932</td>
</tr>
<tr>
<td>CrCl 7</td>
<td>119.49 30.99</td>
<td>71.62 24.71</td>
<td>10.761</td>
</tr>
</tbody>
</table>

Figure 1 ROC curve showing cutoff value of 57 years as a predictor for CIN.
had more risk than who had 2 stents or less. After we did a univariate analysis, we found that risk predictors of CIN were older patients who had PCI and received larger amounts of contrast media, and hypotensive patients. In addition to those patients receiving ACE, patients receiving NSAID, lower EF were also at a higher risk. Patients having greater extent of CAD revealed by multivessel affection and increased number of vessels treated and stents used were also significant predictors of CIN. We intended to do a multivariate analysis among different predictors as shown in Table 6 revealing that patients who were hypotensive and anemic, had no correlation as a predictor of CIN.

### 4.8. Morbidity and mortality

Follow up of MACE for one month among patients presented in our study was done either by clinical appointments or phone calls upon which detailed history was taken regarding these possible complications. We found only 4 patients who had complications, with an incidence of 3.4% vs 1.04% among CIN positive and negative patients, respectively, as shown in Table 7.

We found that CIN was regressive in 34 patients (58.6%). After one week we found that 24 patients still had an increase in serum creatinine ≥1.5 mg/dl.

### 5. Discussion

Contrast induced nephropathy is most commonly defined as a rise in the serum creatinine level of at least 0.5 mg/dL within 48–72 h of contrast medium administration. The incidence of CIN in the general population has been calculated to be <2%. In high-risk patients, i.e., patients with chronic renal impairment, diabetes mellitus, congestive heart failure, and older age, the incidence has been calculated to be >20–30%.

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**Table 5** Relation between preprocedural creatinine clearance at day one and CIN.

<table>
<thead>
<tr>
<th>CrCl preprocedure</th>
<th>CIN</th>
<th>Chi-square test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>Positive</td>
</tr>
<tr>
<td>≥60 (ml/min)</td>
<td>192</td>
<td>100.00</td>
<td>50</td>
</tr>
<tr>
<td>&lt;60 (ml/min)</td>
<td>0</td>
<td>0.00</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>100.00</td>
<td>58</td>
</tr>
</tbody>
</table>

**Table 6** Logistic regression analysis for prediction of CIN.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Std. error</th>
<th>P</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary angiography /PCI</td>
<td>1.9195</td>
<td>0.3722</td>
<td>&lt;0.0001</td>
<td>6.8177</td>
<td>3.29–14.141</td>
</tr>
<tr>
<td>Age &gt;57</td>
<td>1.5259</td>
<td>0.3757</td>
<td>&lt;0.0001</td>
<td>4.5991</td>
<td>2.20–9.61</td>
</tr>
<tr>
<td>Treatment of Diabetes (insulin)</td>
<td>1.4931</td>
<td>0.468</td>
<td>0.0014</td>
<td>4.4511</td>
<td>1.78–11.14</td>
</tr>
<tr>
<td>Hypotension SBP &lt;100 mmHg</td>
<td>20.6234</td>
<td>2180.794</td>
<td>0.9925</td>
<td>0.0000</td>
<td>0.00–0.00</td>
</tr>
<tr>
<td>ACE</td>
<td>1.5844</td>
<td>0.3601</td>
<td>&lt;0.0001</td>
<td>4.8765</td>
<td>2.42–9.88</td>
</tr>
<tr>
<td>Anemia HGB &lt;11</td>
<td>0.9919</td>
<td>0.7834</td>
<td>0.2055</td>
<td>2.6964</td>
<td>0.58–12.52</td>
</tr>
<tr>
<td>Contrast volume ≥200 cc</td>
<td>2.0218</td>
<td>0.3719</td>
<td>&lt;0.0001</td>
<td>7.5521</td>
<td>3.64–15.65</td>
</tr>
<tr>
<td>V/eGFR ≥2.7</td>
<td>2.9957</td>
<td>0.547</td>
<td>&lt;0.0001</td>
<td>20</td>
<td>6.85–58.44</td>
</tr>
<tr>
<td>Number of vessels treated</td>
<td>2.0794</td>
<td>0.4515</td>
<td>&lt;0.0001</td>
<td>8</td>
<td>3.30–19.38</td>
</tr>
<tr>
<td>Number of stents</td>
<td>1.9915</td>
<td>0.4708</td>
<td>&lt;0.0001</td>
<td>7.3262</td>
<td>2.91–18.43</td>
</tr>
</tbody>
</table>

**Figure 2** Cut-off point, sensitivity, specificity, for V/eGFR in prediction of CIN patients.
In this cross sectional study, we studied 250 diabetic patients taken consecutively with no history of pre-existing renal disease who had normal serum creatinine. They were subjected to cardiac catheterization, 158 patients had coronary angiography while 92 patients had PCI of which 14 patients presented with acute myocardial infarction and required primary intervention. They all received low osmolar, non ionic contrast media. We adopted a single definition of CIN which is increase in baseline S. Creatinine value ≥0.5 mg/dl after 48–72 of contrast administration.

CIN among the study group was found to be 23% which is considered to be relatively high. We can contribute this high incidence to all patients being type 2 diabetics, having no prophylaxis against CIN although having multiple risk factors. Larger amounts of contrast used especially among patients having PCI and complex intervention in addition to those having primary PCI. Although patients presented with normal S. Creatinine we found 21% having procedural impairment in their eGFR with 8 patients below 60 ml/min and 46 patients having eGFR between 60 and 90 ml/min.

This is similar to what was reached by Wang et al. who conducted their study on 114 diabetic patients undergoing elective PCI through radial approach and found it to be 18.4%. This high incidence could be related to some of their patients who already had elevated baseline S. Creatinine >1.5 mg/dl.

On the contrary, El Etriby et al. who studied the frequency and predictors of CIN among 169 type 2 diabetic patients in an Egyptian cohort undergoing cardiac catheterization found that overall incidence of CIN was 8.87%, with an incidence of CIN among patients with normal S. Creatinine 3.33% and among those who had preexisting renal disease 22.44%. This relatively low overall incidence could be attributed to giving hydration intravenously to all patients undergoing cardiac catheterization and excluding those having primary PCI. All their patients who developed CIN had CrCl <55 ml/min even though patients who had normal baseline S. Creatinine and developed CIN. Another study was conducted by Eric et al. who found the incidence of CIN 7.3% among a total of 3036 patients, with normal baseline S. Creatinine <1.5 undergoing PCI. Although the same type of contrast was used, which was low osmolar non ionic, this low incidence could be contributed to having only 1090 diabetic patients among their study (35.9%). These patients had only elective PCI with preprocedural hydration. On the same side Yong et al. found an incidence of 9% of CIN among their study of 277 consecutive patients undergoing primary PCI, they used low osmolar non ionic contrast and iso-osmolar non ionic contrast and preprocedure hydration was carried out among all the patients.

We studied the age as a risk predictor of CIN and we found that older patients >57 years were at higher risk of developing CIN (OR 4.5; 95% CI 2.2–9.6) with P value <0.01 using multivariate analysis. The same was reached by Eric et al. as he found that age was a significant independent risk predictor for CIN (odds ratio 6.4; 95% CI, 1.01–13.3) with a statistically significant P value = 0.042. That was concordant with Yong et al. who found almost the same result with patients older than 65 years were significantly associated with CIN. Same results were reached by El Etriby et al. who found that patients were older among CIN group mean ± SD 62.1 ± 5.5 vs 55.9 ± 7.7 with a highly significant P value <0.01. This can be contributed to older patients who usually have multiple comorbidities, longer diabetes duration, decrease in renal mass and perfusion and function, and concomitant extent of coronary artery disease, more difficult vascular access, preexisting renal impairment despite normal serum creatinine.

In our study we could not have a correlation between female gender and development of CIN showing a non significant P value of 0.261. This could be attributed to the small sample size of the study. That was against Eric et al. who studied 3036 patients and found that female gender was a highly significant predictor for CIN (OR, 2.0; 95% CI, 1.5–2.7; p = 0.001), they contributed this to the fact that usually they have lower eGFR despite normal S. Creatinine value. As regards using the ejection fraction as risk predictor of CIN we found in our study that patients having lower ejection fraction mean ± SD 43.45 ± 7.98% were among the patients who developed CIN, with a highly significant P value <0.01. We considered EF of 50% as a cutoff value using ROC curve analysis. Patients below that figure showed a highly significant predictor of CIN (OR, 5.398; 95% CI, 3.134–9.164; P value <0.01) which was concordant with a study by Eric et al. who found that abnormal LV EF <50% was a significant risk predictor for development of CIN (OR, 1.02; 95% CI, 1.01–1.04; P value = 0.01). We can contribute this to LV dysfunction results in low effective intravascular volume leading to renal hypoperfusion, in addition to concomitant use of ACE and diuretics among this population. The same was reached by El Etriby et al. who concluded in their study that patients who presented with congestive heart failure had been at risk to develop CIN with a highly significant P value <0.01. They did not take into consideration the actual ejection fraction of the patients; instead they considered the clinical symptoms and signs of congestive heart failure.

In the context of assessing anemia as a risk predictor of CIN, we could not find by multivariate logistic regression analysis a correlation between anemia and CIN, defined by hemoglobin level less than 11 g/dl with a P value of 0.2. It could be due to the small sample size and due to not taking into consideration the hematocrit level of the patients, in addition to the fact that anemia was a significant risk in patients who already had moderate renal impairment as stated by Mehran et al. On the contrary Eric et al. found that anemia with hemoglobin less than 11 g/dl was a significant risk predictor of CIN (OR1.5; 95% CI, 1.01–2.2; P value = 0.044). Mehran and Nikolsky found that lower baseline hematocrit was identified as an independent predictor of CIN regardless of the presence or absence of chronic kidney disease, each 3% decrease in baseline hematocrit resulted in a significant increase in the odds of CIN in patients with and without chronic kidney disease (11% and 23%, respectively).

In our study we found that hypotension defined as having systolic blood pressure <100 mmHg was a non significant predictor of CIN using multivariate analysis with a non-significant P value of 0.9. On the contrary Eric et al. found that systolic hypotension with blood pressure <100 mmHg was a significant predictor (OR, 1.5; 95% CI 1.01–2.2; p = 0.004). It is well known that hypotension results in marked renal hypoperfusion augmenting the toxic effect of contrast and increasing medullary ischemia. We can conclude that the difference in the results was related to the small sample size among our study.

Among our study we found that diabetic patients receiving insulin therapy were at high risk for development of CIN by
using multivariate analysis which showed a highly significant statistically $P$ value of 0.0014 (OR, 4.45; 95% CI 1.78–11.14). The same was reached by Eric et al. who showed that diabetics on insulin therapy were at highest risk compared to diabetics on oral hypoglycemic $P$ value of 0.001 due to relatively longer duration of diabetes and they were associated with more multivessel disease affection and decrease in their renal function.

We calculated volume of contrast in relation to eGFR as a predictor of CIN, we found a ratio $> 2.7$ as fair discrimination and as a predictor for CIN using ROC curve analysis. We used it as an independent predictor of CIN with odds ratio of 20; 95% CI 6.85–58.44, $P$ value $< 0.01$ with a sensitivity of 65% and specificity of 85% among diabetic patients with normal serum creatinine undergoing PCI. We calculated eGFR using the –Gault equation instead of using the MDRD equation. Almost the same result was conducted by Tan et al. who studied the volume of contrast in relation to creatinine clearance as a predictor of CIN in patients undergoing PCI. Ratios were obtained from 1140 consecutive patients undergoing unselective PCI. ROC curve analysis indicated that a V/CrCl ratio of 2.62 was a fair discriminator for CIN (odds ratio: 2.20; 95% confidence interval: 1.00–4.81, $P < 0.05$). The same was reached by Yong et al. who found that a V/eGFR ratio $> 2.39$ remained significantly associated with CIN odds ratio 4.24, 95% confidence interval 1.23–14.66; $P < 0.05$ and is an independent predictor of CIN after primary PCI in patients with STEMI showing a sensitivity of 72% and sensitivity of 80% in detecting CIN. The eGFR in their study was calculated using MDRD equation. All the figures were relatively close to each other, and this could be explained by using almost close volume of contrast, and the mean eGFR of the patients was close to each other giving us almost the same cut off value.

On the contrary Wang et al. found a higher cut off value as he retrospectively investigated clinical factors associated with the development of CIN in 114 diabetic patients who had undergone elective PCI through radial approach. Stepwise regression analysis showed that the V/eGFR ratio was a significant independent predictor for the development of CIN ($P = 0.001$). At a cut-off point of $> 3.1$, the V/eGFR ratio exhibited 71% sensitivity and 70% specificity for detecting CIN. This higher cutoff value could be contributed to the different route of access used leading to a larger amount of contrast among their study in association with the lower eGFR and using the MDRD equation, they also used this value as an early predictor of rise in serum creatinine after 24 h of contrast administration.

It is noted that the increasing volume of contrast administered is a significant risk predictor of CIN. We found in our study that the volume of contrast was among CIN positive and negative patients, respectively (240.69 ± 104.86) ml vs. (143.28 ± 69.30) ml, with a highly significant $P$ value $< 0.01$. We also found that patients receiving high contrast volume $\geq 200$ ce, were at a higher risk of developing CIN with a significant $P$ value $< 0.01$ (OR 7.5; 95% CI 3.64–15.65). This was coincordant with what El Etriby et al. found as increasing volume of contrast was a significant risk predictor among PCI patients (285 ± 63.9 vs 139.1 ± 46.6) with a $P$ value $< 0.01$. The same was reached by Wang et al. who found a larger amount of contrast among patients with CIN (253 ± 75 ml vs 211 ± 71 ml) with a significant $P$ value of 0.017.

While we calculated the preprocedural creatinine clearance of the patients using the –Gault equation to give us a better overall assessment of kidney function we found that 21% of the patients had renal impairment although having normal baseline S. Creatinine $< 1.5$ mg/dl. We found that 3.2% had moderate renal impairment with CrCl $30–59$ ml/min and 18.4% had mild renal impairment with CrCl $60–89$ ml/min. On the same lines Mujtaba et al. who assessed renal insufficiency in patients with normal S. Creatinine undergoing Coronary Angiography in a Pakistani cohort found that among total 693 patients 34.1% patients had eGFR $< 80$ ml/min using the –Gault equation. They showed a significant correlation between increasing age and female gender with decreases in eGFR despite normal S. Creatinine with a $P$ value of $< 0.01$.

In our study patients with preprocedural decrease in creatinine clearance were more among the CIN patients (95.50 ± 32.29) ml/min vs (125.63 ± 32.34) ml/min, $P < 0.01$. We used a CrCl of 60 ml/min as cut off value showing a significant risk predictor for CIN. This shows that it will be of great practice to assess kidney function prior to any procedure by calculating the CrCl of the patient.

We found that patients on chronic use of ACE inhibitors as either a treatment of heart failure or to control hypertension had a highly significant correlation with $P$ value $< 0.001$ (OR = 4.8, 95% CI 2.42–9.88). This could be due to the decrease in renal perfusion by vasoconstriction of the afferent arteriole. The same was reached by Barış et al. who studied the effects of chronic usage of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on contrast-induced nephropathy in low-risk patients among 295 patients. CIN occurrence was significantly higher in RAAS than no RAAS group (17.5% vs. 7.4%, $p = 0.01$). Chronic RAAS blocker administration was an independent predictor of CIN ($OR = 2.69; 95\% CI: 1.025–7.067; p = 0.04$). Also, Umruddin et al. found that the odds ratio for development of CIN with respect to ACEI or ARB use was 2.68 (95% confidence interval, 1.51–4.76 $p < 0.001$). They concluded that it is reasonable to discontinue their use 48 h prior to exposure to radiocontrast agents, especially in patients with multiple risk factors.

We tried to find a relation between the extent of coronary artery disease as a risk predictor of CIN. We found that patients who had more multivessel affection on their coronary angiogram were at higher risk of CIN especially those who had more than one vessel treated (OR 8, 95%CI 3.3–19.38, $P < 0.01$) and those who had three or more stents used (OR 7.32, 95% CI 2.91–18.43, $P < 0.01$). The same was reached by Wang et al. who found that the number of treated vessels and the number of stents used were higher among the CIN group, he assumed that such patients required longer time of operation, larger volume of contrast and advised to have staged PCI among patients who were at the highest risk.

On the contrary Yong et al. did not find a relation between the number of stents used and number of vessels treated as a risk predictor for CIN among their study on primary PCI patients with a non-significant $P$ value of 0.37 and 0.309, respectively. This could be related to treating only the culprit lesion and usually requiring lesser number of stents used during primary PCI than elective cases.

Regarding our follow up, we could not find that CIN alone caused mortality in this cohort of patients. We found that no patients had renal failure or subsequent need of dialysis, two
patients had stroke, and one patient had reinfarction while one patient died. The incidence of complication was higher among patients who developed CIN 3.4% vs 1.04%. We found that one week after the procedure CIN was regressive in 34 patients (58.6%), and 24 patients still had increase in S. Creatinine being ≥1.5 mg/dl, we can assume that the rate of CIN regression would be higher if we had in addition another S. Creatinine sample after one month.

Eric et al. found that the mortality rate was significantly higher in CIN (+) patients compared to CIN (−) patients (14.5% vs 1.1%) at 1 month and (17.8% vs 2.2%) at 6 months. We can contribute these different statistical results to the large number of CIN cases (222 patients) that were followed up for more extended period of time reaching up to 6 months.

6. Summary

Contrast-induced nephropathy is a potentially avoidable complication caused during procedures involving the use of radiographic contrast media. All subjects, especially the high-risk ones should be subjected to available preventive protocols prior to and after such procedures. The current study was done to evaluate different clinical risk predictors of contrast induced nephropathy among diabetic patients not known to have pre-existing renal disease and presenting with normal S. creatinine, undergoing cardiac catheterization. The current study was conducted on 250 patients presenting to the Cath Lab at Ain Shams University Hospitals to undergo coronary angiography or percutaneous coronary intervention for different indications in the period between September 2012 and November 2012. All patients were subjected to proper history taking, thorough clinical examination, standard twelve-lead surface ECG and coronary angiography or percutaneous coronary intervention. Three venous samples were withdrawn from all patients before the procedure, 72 h after the procedure and after 7 days. Different risk factors: Age, sex, CrCl, ejection fraction, volume of contrast, hypotension, hypertension, anemia, number of vessels affected, number of vessels treated, number of stents used, the use of NSAID and ACE. The current study found that it is of utmost importance to depend on creatinine clearance or estimated GFR as a surrogate for assessment of kidney function among patients undergoing catheterization despite normal serum creatinine. It was, however, concluded that patients with diabetes were among the high risk patients for development of CIN, despite normal kidney function. All modifiable risk predictors of CIN should be determined prior to any procedure of contrast administration especially among those undergoing cardiac catheterization and should be corrected as possible. Prophylaxis against CIN should be carried out by adequate hydration to all diabetic patients undergoing catheterization with adequate assessment of patient risk score and calculation of the volume of contrast in relation to estimated GFR or CrCl keeping in mind the different cut off values predicted by different studies.

7. Conclusion

Risk assessment should be done to all patients undergoing cardiac catheterization even though they had normal serum creatinine. It is of utmost importance to assess patient kidney function by either calculating creatinine clearance or estimated GFR. All efforts should be done to correct all modifiable risk predictors of CIN such as contrast volume, anemia and hypertension and withdrawal of nephrotoxic medications prior to the procedure. It is of value to use the volume in contrast in relation to CrCl as a predictor of CIN. Subgroups of patients with normal baseline Cr undergoing PCI are at risk of developing CIN. Age, female gender, insulin dependent diabetes mellitus, presence of hypotension, anemia and low LVEF are predictors of CIN. Prophylaxis may be considered in these patients.

8. Recommendations

Preventive hydration, should be undertaken for all patients undergoing any procedure involving the use of intravenous contrast media.

Conflict of interest

Not only serum creatinine should be taken as a reference for contrast induced nephropathy. Diabetic patients are at high risk for developing contrast induced nephropathy. Subjects who develop this complication have higher rates of mortality, longer hospital stays and worse long-term outcomes. So, other parameters such as creatinine clearance or estimated GFR should be taken into consideration as a surrogate for assessment of kidney function among patients undergoing catheterization despite normal serum creatinine.

References