Risk Factors for Contrast-related Acute Kidney Injury According to Risk, Injury, Failure, Loss, and End-stage Criteria in Patients With Coronary Interventions

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Introduction. Although a series of risk factors for contrast-induced nephropathy are known, data on significance of some of the risk factors such as age, sex, hypercholesterolemia, hyperuricemia, and dose of contrast medium are inconsistent. Our aim was to identify risk factors for contrast-related acute kidney injury (AKI).

Materials and Methods. In this prospective study, 290 consecutive patients with a serum creatinine level lower than 3 mg/dL undergoing percutaneous angiography were analyzed. Contrast-related AKI was evaluated using the risk, injury, failure, loss, and end-stage (RIFLE) criteria, and its correlation with clinical and laboratory data of the patients was analyzed.

Results. Contrast-related AKI was found in 15.5% of the patients, with a maximum RIFLE category (risk in 13.8%, injury in 1.4%, and failure in 0.3%). Serum creatinine level, contrast volume, safe contrast volume factor, diabetes mellitus, and dehydration were significantly associated with contrast-related AKI. Age, sex, and serum uric acid level did not differ significantly between those with and without contrast-related AKI. Multiple logistic regression analysis disclosed diabetes mellitus to be the strongest predictor for being at risk of contrast-related AKI (odds ratio, 5.1; 95% confidence interval, 1.9 to 11.0; \( P = .001 \)), followed by hypercholesterolemia (odds ratio, 4.6; 95% confidence interval, 1.1 to 8.3; \( P = .03 \)), and an estimated glomerular filtration rate lower than 90 mL/min/1.73 m² (odds ratio, 3.0; 95% confidence interval, 1.8 to 5.7; \( P = .003 \)).

Conclusions. Our results indicate that diabetes mellitus, hypercholesterolemia, and underlying chronic kidney disease are the major factors of contrast-related AKI.
initiating the appropriate prophylactic regimens, particularly, in patients with a risk as high as 50% for incidental CIN.6,7

A series of risk factors for CIN have been identified, such as underlying chronic kidney failure, diabetes mellitus (DM), age, female gender, large volume of contrast medium, and heart failure, but significance of some of the factors such as age, gender, hypercholesterolemia, hyperuricemia, and dose of contrast material are controversial.8-11 On the other hand, recently, in a large study carried out on 32 161 patients, it was shown that serum creatinine level increased in patients who were not receiving a contrast medium as often as it did in published series of patients receiving it, making the traditional 25% rise of serum creatinine, a poor diagnostic tool for CIN.12 Considering that CIN is a nephropathy induced by genesis of acute kidney injury (AKI), it has been suggested that the RIFLE criteria be used for the definition of contrast-related AKI until we have more reliable tools for diagnosis of CIN.13 Therefore, in this prospective study, we investigated the risk factors for creatinine-related AKI in 290 consecutive patients admitted to hospital with a serum creatinine level less than 3 mg/dL who underwent coronary artery interventions, using RIFLE criteria to diagnose creatinine-related AKI.

MATERIALS AND METHODS

Patients

Between February and September 2008, we prospectively studied 290 hospitalized patients who underwent coronary artery interventions at Kowsar Hospital, in Shiraz, Iran. The minimum sample size was calculated to be 207 patients, considering a significance level of 0.05, the CIN prevalence of 16%,6 and a precision of 8%. The exclusion criteria were recent exposure to contrast media within 2 days, a serum creatinine level of 3 mg/dL or higher, cardiogenic shock, sepsis, and administration of nephrotoxic agents (aminoglycosides, cyclosporine, tacrolimus, amphotericin B, and non-steroidal anti-inflammatory drugs) within 3 days before the procedures. The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Shiraz University of Medical Sciences. All of the patients provided written informed consent.

A blood sample for measurement of blood urea nitrogen (BUN) and serum levels of creatinine, sodium, potassium, uric acid, and lipids, and a urine sample for urine pH were drawn at admission, after 8 hours overnight fast. Also, follow-up BUN and creatinine levels were measured within 48 hours after cardiac catheterization. Serum creatinine was measured using the Jaffe reaction with adsorbent (picrate) method. Transthoracic echocardiography was done in all of the patients and left ventricular ejection fraction (LVEF) was included. The patients received isotonic saline solution at a rate of 1 mL/kg/h for 6 hours before and 6 hours after angiography. Iodixanol (Visipaque, 320 mg iodine/mL), a nonionic, iso-osmolar (290 mOsm/kg water) contrast medium, was used in all of the patients.

Clinical Definitions

Diabetic status was determined based on the patient’s history, as either patient required oral hypoglycemic agents or routine injection of insulin, or a fasting blood glucose higher than 126 mg/dL. Hyperuricemia was defined as a serum uric acid level of 7 mg/dL or higher in men and 6.5 mg/dL or higher in women14; hypercholesterolemia, a serum cholesterol level of 200 mg/dL or higher; and hypertriglyceridemia, a serum triglyceride level of 150 mg/dL or higher.15 The BUN-creatinine ratio, which correlates with the state of hydration, was used as an indicator of the patient’s fluid volume status. We used a ratio more than 20 as the cutoff for dehydration. Estimated glomerular filtration rate (GFR) was calculated according to the Modification of Diet in Renal Disease formula.16 Safe contrast volume factor (SCVF) was defined as a factor that must be multiplied by weight and divided by serum creatinine in order to achieve the safe contrast volume (safe contrast volume = SCVF × weight/plasma creatinine). Contrast-related AKI was defined according to the RIFLE criteria,13 within 48 hours after contrast exposure, classified as risk, a 1.5-fold increase in baseline serum creatinine or a 25% or greater decrease in GFR; injury, a 2-fold increase in baseline serum creatinine or a 50% or greater decrease in GFR; failure, a 3-fold increase in baseline serum creatinine, a 75% or greater decrease in GFR, or an absolute serum creatinine of 354 μmol/L or higher with an acute rise of at least 44 μmol/L; and all category, risk or injury or failure.13
Statistical Analyses
Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA). Quantitative data, presented as mean ± standard deviation, were analyzed by the Student t test for comparisons of two groups. Association between categorical variables was analyzed by the chi-square test, and a two-sided 95% confidence interval (CI) was constructed around the point estimate of the odds ratio (OR). We performed multiple logistic regressions with the contrast-related AKI as the dependent variable and the following as potential covariates that were significant in previous analyses: DM, hypercholesterolemia, large contrast volume, dehydration state, a GFR less than 90 mL/min/1.73 m², high serum creatinine level, safe contrast volume factor (SCVF) of 2.5 or higher, and low LVEF as dummy variable. A P value less than .05 was considered significant.

RESULTS
In this prospective study, 290 consecutive patients who were scheduled for coronary angiography or percutaneous coronary intervention participated with a mean age of 57.9 ± 11.7 years (range, 60 years). One hundred and eighty patients (62.3%) were men and 53 (30.3%) were diabetic. Contrast-related AKI occurred in 45 patients (15.5%) within 48 hours of contrast exposure, with a maximum RIFLE category, risk in 40 (13.8%), injury in 4 (1.4%), and failure in 1 (0.3%).

Clinical characteristics and laboratory data of the patients with and without contrast-related AKI are compared in Table 1. Baseline serum creatinine level, contrast volume, SCVF, and BUN-creatinine ratio (indicator of dehydration) were significantly higher and DM was more frequent in patients with AKI compared to those without it (Table 1). As illustrated in Table 2, in univariable analysis, there was a significant correlation between contrast-related AKI with DM (OR, 4.3; 95% CI, 2.2 to 8.7; P = .001), hypercholesterolemia (OR, 2.1; 95% CI, 1.1 to 5.3; P = .04), a SCVF of 2.5 or higher (OR, 3.1; 95% CI, 1.0 to 9.5, P = .05), a baseline serum creatinine level of 1.1 mg/dL or higher (OR, 2.7;
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Table 2. Risk Factor Associated With Acute Kidney Injury*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>*P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>4.3 (2.2 to 8.7)</td>
<td>.001</td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>2.8 (1.1 to 7.6)</td>
<td>.04</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2.1 (1.1 to 5.3)</td>
<td>.04</td>
</tr>
<tr>
<td>Dehydration state</td>
<td>2.3 (1.5 to 8.1)</td>
<td>.03</td>
</tr>
<tr>
<td>eGFR &lt; 90 mL/min</td>
<td>1.8 (1.2 to 3.6)</td>
<td>.005</td>
</tr>
<tr>
<td>Contrast volume ≥ 100 mL</td>
<td>2.7 (1.2 to 6.2)</td>
<td>.02</td>
</tr>
<tr>
<td>SCVF ≥ 2.5</td>
<td>3.1 (1.01 to 9.5)</td>
<td>.05</td>
</tr>
<tr>
<td>Serum creatinine ≥ 1.1 mg/dL</td>
<td>2.7 (1.2 to 7.5)</td>
<td>.004</td>
</tr>
</tbody>
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*LVEF indicates left ventricular ejection fraction; eGFR, estimated glomerular filtration rare; and SCVF, safe contrast volume factor. *It was also significant in favor of risk category.

Table 3. Risk Factors Associated With Acute Kidney Injury in Multi Logistic Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>5.1 (1.9 to 11.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>4.6 (1.1 to 8.3)</td>
<td>.03</td>
</tr>
<tr>
<td>eGFR &lt; 90 mL/min</td>
<td>3.0 (1.8 to 5.7)</td>
<td>.003</td>
</tr>
</tbody>
</table>

*It was also significant in favor of risk category.

95% CI, 1.2 to 7.5; *P = .004), and a maximum safe contrast volume higher than 100 mL (OR, 2.7; 95% CI, 1.2 to 6.2; *P = .02). The frequency of contrast-related AKI was 27.6% (18 of 65 patients) in diabetic patients with a baseline serum creatinine level higher than 1.1 mg/dL compared to 26.0% (6 of 23) in those with a baseline creatinine of 1.1 mg/dL or lower (*P = .18).

Results of the multiple logistic regression analysis are shown in Table 3, which disclosed DM to be the strongest predictor for being at risk of contrast-related AKI (OR, 5.1; 95% CI, 1.9 to 11.0; *P = .001), followed by hypercholesterolemia (OR, 4.6; 95% CI, 1.1 to 8.3; *P = .03), and an estimated GFR lower than 90 mL/min/1.73 m² (OR, 3.0; 95% CI, 1.8 to 5.7; *P = .003).

DISCUSSION

Although, the recently proposed the RIFLE criteria have been validated in numerous studies, to date, they have not been used for identification of predisposing factors to contrast-related AKI. In this study, we investigated for the first time the risk factors for contrast-related AKI on the basis of the RIFLE criteria. However, most of our patients with contrast-related AKI were in the risk category, and due to the small number of patients with the injury and failure, possibly originating from preventive hydration therapy as well as the fact that our study population were low-risk patients (serum creatinine, < 3 mg/dL), it was impossible to reach conclusive results in the injury and failure categories, necessitating larger studies to clarify the issue in these categories.

Identifying patients at a high risk of contrast-related AKI after cardiac catheterization is of utmost importance for its prevention as well as prognostic implications. Numerous studies have attempted to identify factors that may affect the incidence of CIN, and various risk factors have been proposed. In this study, DM was found to be the strongest predictor of being at risk of contrast-related AKI. Due to diminished nitric oxide-dependent renal vasodilatation and reduced outer renal medullary oxygenation, patients with DM are at a higher risk of CIN. In the previously published series, it has been shown that the incidence of CIN is as low as 2% in patients without DM and azotemia, while it is 16% in diabetic patients with preserved kidney function, and 38% in patients with azotemia due to DM. Parfrey and colleagues showed that none of their 85 patients with DM and normal kidney function developed clinically significant CIN. In our study, the frequency of contrast-related AKI was not significantly higher in diabetic patients with kidney dysfunction, which means DM was a significant risk factor of contrast-related AKI irrespective of kidney function.

In few experimental studies, it has been shown that hypercholesterolemia aggravates CIN via the reduced production of nitric oxide and also hypercholesterolemia-induced renal vasoconstriction and increased resistive index in renal blood flow with a consequent fall in GFR following contrast media injection. However, some studies carried out in humans did not show any significant correlation between hypercholesterolemia and occurrence of CIN. On the contrary, we found that hypercholesterolemia was the second strongest predictor of the risk for the contrast-related AKI.

Some studies indicate that a preexisting kidney disease is the greatest independent predictor of CIN, which might be due to decreased vasodilator response, and its severity (measured by serum creatinine level) directly correlates with the incidence of CIN. Moore and colleagues...
and also Barrett and coworkers reported that the incidence of CIN increased from 4% to 20%, as the baseline serum creatinine level increased from 1.2 mg/dL to 2.9 mg/dL.\textsuperscript{26,27} Similarly, the cutoff of baseline serum creatinine as a risk factor of contrast-related AKI in this study was 1.1 mg/dL, and higher serum creatinine levels were seen significantly more frequently in patients at risk of contrast-related AKI than those without it. Another major risk factor for CIN has been shown to be an estimated GFR less than 60 mL/min.\textsuperscript{6} However, in the present study, a GFR less than 90 mL/min was found significantly more frequently in patients with contrast-related AKI than those without it. On the basis of our findings, it seems that any degree of kidney failure must be sought and preventive measures undertaken for those with abnormal serum creatinine or GFR levels for minimizing the risk of contrast-related AKI.

In most studies, it has been shown that a low LVEF (< 49%) is an independent risk factor for CIN,\textsuperscript{28,29} as a result of neurohormonal vasoconstrictive stimuli and impaired nitric oxide-dependent renal vasodilatation, which might compromise the medullary oxygenation.\textsuperscript{25} Similarly, in our study population, an LVEF less than 40% was a significant risk factor for contrast-related AKI.

Decreased effective circulating volume and reduced renal perfusion aggravates renal vasoconstriction after administration of a contrast medium.\textsuperscript{30} Lautin and associates failed to show a significant correlation between low effective circulating volume and CIN, when a BUN-creatinine ratio higher than 15 was considered as the cutoff point for diagnosis of dehydration.\textsuperscript{8} However, in our study, the patient’s state of hydration had a significant correlation with the risk for contrast-related AKI, when a BUN/creatinine ratio higher than 20 was used to define low circulating volume status.

Some reports have suggested a positive relationship between the dose of contrast medium and CIN,\textsuperscript{10,11} whereas other studies have claimed that increasing the dose does not increase the risk of contrast-related AKI.\textsuperscript{1,31} In our study, a contrast volume of 100 mL or higher was the best cutoff point to show the increasing risk of contrast-related AKI. On the other hand, the incidence of contrast-related AKI can be minimized by careful restriction of the amount of contrast material in accordance with the degree of azotemia. Thus, we re-evaluated the Cigarroa and colleagues’ formula\textsuperscript{32} as contrast volume = 5 × weight/serum creatinine that had been utilized many years for calculating the maximum amounts of contrast media that could be given safely. We found that this level is very high and the risk of contrast-related AKI was significantly higher with lower levels of contrast volume, and in our patients, the best limit for SCVF with lower risk of contrast-related AKI was 2.5.

In the previously published series, data regarding significance of advanced age and gender of the patients as risk factors of CIN are inconsistent; our data in agreement with findings of Lautin and colleagues,\textsuperscript{8} and in contrast to those of McCullough and coworkers\textsuperscript{9} did not disclose any significant difference between age and gender of patients with and without of the risk of contrast-related AKI.

Some studies suggest that tubular obstruction by uric acid plays a role in the pathogenesis of CIN,\textsuperscript{31,33} but this was not substantiated in a multivariable analysis.\textsuperscript{34} This discrepancy might have arisen from the point that most of the series that blame uric acid as a predisposing factor to CIN have been carried out in patients who had underlying chronic kidney failure and a GFR less than 60 mL/min, as well as decreased effective circulating volume, all of which are associated with concomitant hyperuricemia.\textsuperscript{35} However, our study was on patients that a significant number of whom had normal kidney function and showed no significant correlation between serum uric acid and risk factors of contrast-related AKI. Our study had some limitation; we included a small population admitted to a single center. Our findings should be confirmed and application of the risk score be validated in a large multicenter trial.

**CONCLUSIONS**

We conclude that DM was the strongest predictor of contrast-related AKI, followed by hypercholestrolemia and underlying chronic kidney failure. Even mild chronic kidney dysfunction, as a GFR less than 90 mL/min, was a risk factor of contrast-related AKI. Otherwise, in univariable analysis, patients with left ventricular dysfunction, dehydration, and high contrast volume were at the risk of contrast-related AKI. Thus, in patients who undergo contrast study, very low volume of
contrast must be considered. These findings need more investigation with higher-scale multicenter studies to clarify risk factors of contrast-related AKI.

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CONFLICT OF INTEREST
None declared.

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