RESEARCH ARTICLE

# Serum interleukin-6 concentration predicts contrast-induced nephropathy in patients undergoing percutaneous coronary intervention

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**ABSTRACT.** ***Background.*** **Contrast media are being widely applied for both diagnostic and therapeutic purposes. This has resulted in increasing incidence of contrast-induced nephropathy (CIN).** ***Methods.*** **We aimed to investigate the value of baseline serum IL-6 concentrations in predicting CIN before the rise of serum creatinine (SCr) in patients undergoing percutaneous coronary intervention. Seventy four Caucasian patients were enrolled. CIN was defined as an increase in SCr concentration of more than 44 μmol/L, or a 25% increase above baseline within 48 hours after contrast administration.** ***Results.*** **CIN developed in 16 out of 74 patients (21.6%). The median concentration of IL-6 was 3.2 pg/mL. The median IL-6 concentration on admission was lower in patients who subsequently did not develop CIN (2.7 pg/mL *versus* 8.3 pg/mL, $p < 0.0001$). Receiver operating characteristics analysis showed a high diagnostic value of baseline SCr and IL-6. The cut-off value to predict CIN for IL-6 was over 4.0 pg/mL (sensitivity 88%, specificity 76%, PPV 50%, NPV 96%). Multivariate logistic regression analysis revealed three independent predictors of CIN: IL-6 (OR 1.43; 95%CI: 1.17-1.76), serum creatinine (OR 1.79; 95%CI: 1.1-3.39), and ejection fraction (OR 0.86; 95%CI: 0.50-0.95).** ***Conclusions.*** **Increased concentrations of IL-6 on admission are associated with subsequent CIN. Our study proposes that IL-6 be added to the list of potential markers that could be used, along with renal function parameters, in clinical practice.**

**Keywords:** interleukin-6, creatinine, contrast-induced nephropathy

Percutaneous coronary intervention (PCI) is a recognized treatment modality of stable coronary artery disease (CAD). Therefore, contrast media are being widely applied for both diagnostic and therapeutic purposes. This has resulted in an increasing incidence of contrast-induced nephropathy (CIN). CIN is generally defined as an increase in serum creatinine (SCr) concentration of > 0.5 mg/dL (> 44 μmol/L) or a 25% increase above baseline within 48 hours of contrast administration [1]. The rate of CIN varies between 12% and 26% depending on the clinical settings. This iatrogenic complication has become the third leading cause of hospital-acquired, acute kidney injury (AKI). It has been a subject of concern to interventional cardiologists because it is associated with increased mortality and morbidity [2]. Despite the use of newer and less nephrotoxic contrast agents, the risk of CIN still remains considerable.

The quest for identifying risk factors and possible biomarkers of CIN is an area of extensive research nowadays. Several new candidates have emerged as possible biomarkers of AKI. These include neutrophil gelatinase-associated lipocalin (NGAL) [3], interleukin-(IL) 18 [4] and kidney injury molecule-1 (KIM-1) [5].

AKI is associated with inflammatory processes, with increased concentrations of IL-1β, IL-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α) [6, 7]. Recent studies have suggested a potential modulating ability of IL-6. The induction of IL-6 expression has been observed in AKI both in human [6] and animal models [8]; yet the role of IL-6 in this process has not been fully established. IL-6 elicits many biological effects, one of which is the initiation of the inflammatory reaction [9, 10]. It is synthesized in response to proinflammatory signals, and its production is also a common response to tissue injury and organ failure [11, 12].

We aimed to investigate the value of baseline serum IL-6 concentrations in predicting CIN before the rise of SCr in patients undergoing PCI. We sought to determine whether serum levels of IL-6 could help identify patients at risk for CIN, potentially optimizing the use of contrast media and periprocedural management.

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## DONORS AND METHODS

### *Study population*

Seventy four Caucasian patients were enrolled in the study. Coronary angiography was performed because of the clinical presentation (worsening of anginal symptoms), and the result of exercise testing. The study conforms to the Declaration of Helsinki. Exclusion criteria were: coexisting autoimmune disorders, acute infectious diseases, chronic inflammatory diseases, chronic kidney disease (CKD) – stage 3 or higher (baseline estimated glomerular filtration rate < 60 mL/min/1.73 $m^2$), known malignant diseases and lack of patient consent to participate. Other exclusion criteria are listed in our previous publication [13].
Coronary angiography was performed using standard protocols and guidelines. Iopromide (a low osmolar, nonionic, iodinated contrast agent) was used. The choice of treatment modality (bare-metal or drug-eluting stent implantation) was at the physician's discretion.

### *IL-6 measurements*

Blood for the IL-6 measurements was drawn from the peripheral vein on admission (12-18 hours before coronary angiography). Serum concentrations of IL-6 were measured using commercial, enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, USA) in duplicate. Measurements for each patient were made with the same kit to avoid inter-kit variability. The intra-assay coefficient of variation (%CV) was 4.2%, the inter-assay coefficient of variation (%CV) was 6.4%, and the sensitivity of the ELISA was: < 0.7 pg/mL.

### *Renal function*

Renal function was assessed using SCr measured: (1) on admission and (2) 48 hours after PCI. The estimated glomerular filtration rate (eGFR) was calculated with a formula developed by the Modification of Diet in Renal Disease Study Group (MDRD) [14]:

$$eGFR = 186.3 \times SCr\ [\mu mol/L]^{-1.154} \times age^{-0.203} \times 0.742 \text{ (if female)}$$

The change in renal function parameters [SCr (2) / SCr (1) and eGFR (2) / eGFR (1)] was also calculated.
CIN was defined as an increase in SCr concentration of more than 44 μmol/L or a 25% increase above baseline within 48 hours after contrast administration [1].
A *post-hoc* analysis was performed to determine potential differences between parameters studied in subjects who developed CIN:
- group 1: 58 patients without CIN;
- group 2: 16 patients with CIN;

## STATISTICAL ANALYSIS

Quantitative data are presented as means ± standard deviations (SD) or medians and interquartile ranges (lower and upper quartiles). Qualitative data are presented as frequencies. The Shapiro-Wilk test was used to determine whether a random sample was normally distributed. The non-parametric Mann-Whitney U-test was used to evaluate differences between the two groups. The relationship between variables studied was evaluated using the Spearman's rank correlation coefficient. Independent variables (all clinical characteristics and laboratory findings) with a p-value ≤ 0.2 in the univariate analysis were entered into the multivariate logistic regression model, using a Wald statistic backward stepwise selection. Multivariate logistic regression analysis was then performed to identify independent predictors of CIN and to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) in order to evaluate the influence of clinical factors and laboratory markers on developing CIN. Receiver operating characteristic (ROC) curves were estimated for IL-6 concentrations. The areas under the ROC curves (AUC) for IL-6 were compared using a nonparametric test. A ROC analysis was planned to identify possible cut-offs to predict CIN. A p-value of < 0.05 was considered to be significant. Statistical analyses were performed using MedCalc for Windows version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium) and STTISTICA version 6.0 (StatSoft Inc, Tulsa, OK, USA).

## RESULTS

Baseline clinical characteristics are presented in *table 1*. The incidence of systemic hypertension, prior myocardial infarction and hypercholesterolemia was high in the study group. CIN developed in 16 out of 74 patients (21.6%). The median concentration of IL-6 was 3.2 pg/mL. Other laboratory findings are listed in *table 2*. The median IL-6 concentration on admission was lower in patients who subsequently did not develop CIN (2.7 pg/mL *versus* 8.3 pg/mL, p < 0.0001) *(figure 1)*. SCr and eGFR on admission was similar in both groups *(figure 2A* and *3A)*. Patients with CIN had higher SCr and lower eGFR 48 hours after PCI *(figures 2B* and *3B*).

**Table 1**
Baseline clinical characteristics

| | **n = 74** |
|---|---|
| Age (years), mean ± SD | 59.3 ± 10.8 |
| Gender, males N (%) | 53 (71.6) |
| Systemic hypertension, N (%) | 47 (63.5) |
| Diabetes mellitus, N (%) | 20 (27.0) |
| Prior myocardial infarction, N (%) | 50 (67.5) |
| Prior PCI, N (%) | 74 (100) |
| Hypercholesterolemia, N (%) | 54 (73.0) |
| CAD severity (CCS functional class) | |
| CCS 2, N (%) | 33 (44.6) |
| CCS 3, N (%) | 41 (55.4) |
| Hospital stay, days (mean ± SD) | 5.7 ± 2.3 |
| Diuretics | 36 (48.6) |
| ACE inhibitors | 48 (64.9) |
| LVEF, % (mean ± SD) | 44.5 ± 12.0 |
| BMI (mean ± SD) | 25.9 ± 2.4 |

SD: standard deviation; CCS: Canadian Cardiovascular Society; PCI: percutaneous coronary intervention; CAD: coronary artery disease; ACE: angiotensin converting enzyme; LVEF: left ventricular ejection fraction; BMI: body mass index.

**Table 2**
Laboratory findings [median (interquartile range)]

| Parameter | n = 74 |
|---|---|
| Interleukin-6 (pg/mL) | 3.2 (1.8-5.6) |
| Leucocytes ($10^3$/mm$^3$) | 7.1 (6.2-8.2) |
| Erythrocytes ($10^6$/mm$^3$) | 4.5 (4.2-4.8) |
| Hemoglobin (mmol/L) | 8.8 (8.2-9.3) |
| Hematocrit (%) | 38 (35-42) |
| Platelets ($10^3$/mm$^3$) | 190 (154-226) |
| SCr (1) on admission (μmol/L) | 79.0 (71.0-84.0) |
| SCr (2) after PCI (μmol/L) | 80.5 (72.0-99.0) |
| SCr (2) / SCr (1) | 1.1 (1.0-1.2) |
| eGFR (1) on admission (mL/min/1.73 m$^2$) | 75.8 (65.2-90.8) |
| eGFR (2) after PCI (mL/min/1.73 m$^2$) | 69.0 (57.0-85.1) |
| eGFR (2) / eGFR (1) | 0.9 (0.8-1.0) |
| Total cholesterol (mmol/L) | 5.2 (4.4-5.9) |
| HDL cholesterol (mmol/L) | 1.3 (1.0-1.6) |
| LDL cholesterol (mmol/L) | 2.7 (1.9-3.4) |
| Triglycerides (mmol/L) | 1.4 (1.1-2.0) |

PCI: percutaneous coronary intervention; SCr: serum creatinine; GFR: glomerular filtration rate; HDL: high density lipoprotein; LDL: low density lipoprotein.

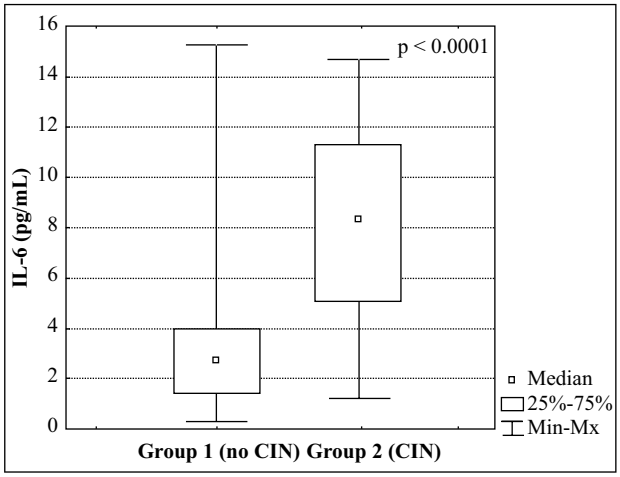


**Figure 1**
Median concentrations of interleukin-6.
CIN: contrast-induced nephropathy.

ROC analysis showed a high diagnostic value of baseline SCr and IL-6. The comparison of AUC for IL-6 and SCr showed a trend towards a better diagnostic value of baseline IL-6 (p = 0.1) *(figure 4)*. We found a significant correlation between IL-6 concentrations and SCr after PCI (Spearman R = 0.23; p = 0.05), and between IL-6 concentrations and the change in SCr [Scr (2)/SCr (1)] (Spearman R = 0.42; p = 0.0002). There was no correlation between IL-6 and SCr before PCI (Spearman R = - 0.08; p = 0.5). Univariate analysis revealed six potential predictors of CIN. These were: age (OR: 1.70; 95%CI: 0.93-2.60; p = 0.09), SCr (OR: 2.39; 95%CI: 1.75-2.93; p = 0.02), diabetes mellitus (OR: 1.45; 95%CI: 1.00-2.13; p = 0.05), IL-6 (OR: 1.51; 95%CI: 1.12-1.79; p = 0.002), female gender (OR: 1.02; 95%CI: 0.93-1.30; p = 0.18) and ejection fraction (OR: 0.87; 95%CI: 0.63-0.99; p = 0.045). Three variables were independently associated with the development of CIN *(figure 5)*. A rise in SCr and IL-6 concentrations increased the risk of CIN, whereas a higher ejection fraction decreased that risk. However age, diabetes mellitus and female gender, did not reach statistical significance in multivariate analysis.

## DISCUSSION

Serum creatinine is an unreliable indicator during acute changes in kidney function [15]. SCr levels can vary widely with age, gender, muscle mass and metabolism, medication and hydration status. Therefore, using only baseline SCr measurements in patients without advanced CKD seems futile. In the quest to find risk markers of CIN, we analyzed the predictive value of serum IL-6 in patients with normal baseline SCr levels. The results of our study show that patients who subsequently developed CIN had increased concentrations of IL-6 on admission. Multivariate logistic regression revealed that baseline IL-6 level was one of three independent predictors of CIN. For every 1 pg/mL increase in baseline IL-6, the risk for CIN increased by 43%. Given the multifactorial nature of CIN, ROC analysis confirmed a high negative predictive value of IL-6 measurements before PCI with a cut-off point at 4.0 pg/mL. Moreover, admission IL-6 concentrations were significantly associated with the change in renal function parameters (increase in SCr).

Data are accumulating that AKI may affect both the production and clearance of cytokines. Development of renal injury mediated by IL-6 is related to alterations in endothelial permeability, induction of mesangial cell proliferation, and increased fibronectin expression. [16-19]. Hoke *et al.* demonstrated in animal models that early AKI is characterized by increased serum levels of IL-6 and IL-8 [20]. IL-6 may affect structural renal cells. In diseased kidneys, IL-6 synthesis is up-regulated in proliferating mesangial and/or the damaged tubular cells [21, 22]. Accumulating evidence now exists that increased renal expression and urinary levels of IL-6 correlate with mesangial proliferation or the degree of tubulointerstitial damage [21-24]. A recent report has indicated that urinary levels of IL-6 in patients undergoing renal transplantation are predictive of the development of sustained, acute renal failure [25]. Experimental renal ischemia/reperfusion also results in a significant and sustained increase in the expression of the IL-6 gene [26]. Patel *et al.* investigated the effects of renal ischemia/reperfusion on the degree of renal injury, dysfunction and inflammation in IL-6 knock-out (IL-6$^{-/-}$) mice [27]. They found that pro-inflammatory cytokines (TNF-α and IL-1β) in renal tissues were significantly attenuated in IL-6$^{-/-}$ mice to levels seen in wild-type mice. IL-6$^{-/-}$ mice demonstrated reduced histological evidence of tubular injury. The authors proposed that endogenous IL-6 enhances the degree of renal injury, dysfunction and inflammation caused by ischemia/reperfusion of the kidney by promoting the expression of adhesion molecules and subsequent oxidative and nitrosative stress.

Some authors have reported that increased serum IL-6 predicts subsequent AKI. In a secondary analysis of the

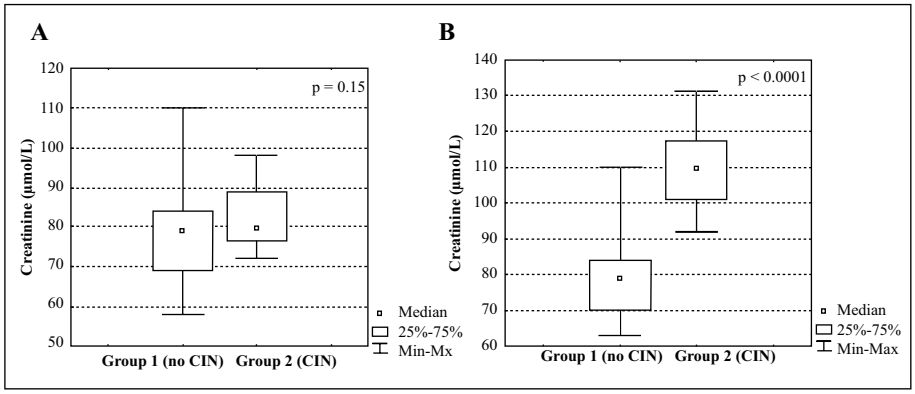


**Figure 2**
Median concentrations of serum creatinine on admission (**A**) and 48 hours after percutaneous coronary intervention (**B**). CIN: contrast-induced nephropathy; SCr: serum creatinine.

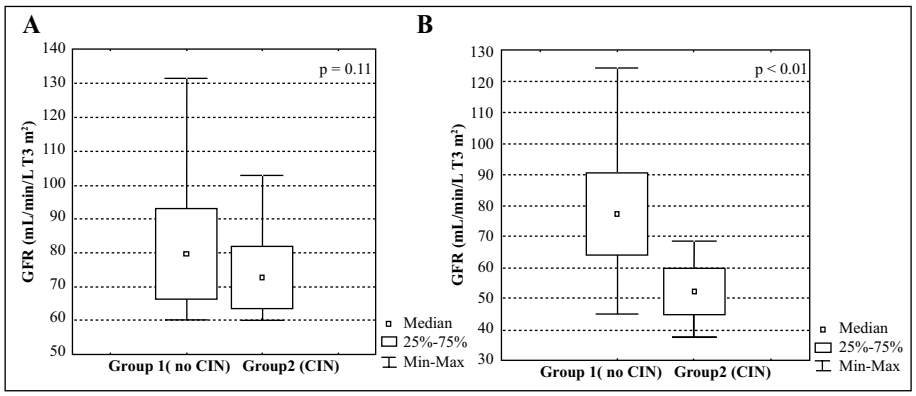


**Figure 3**
Median glomerular filtration rate on admission (**A**) and 48 hours after percutaneous coronary intervention (**B**). CIN: contrast-induced nephropathy; GFR: glomerular filtration rate.

PROWESS clinical trial of activated protein C for the treatment of severe sepsis, Chawla *et al.* demonstrated that baseline IL-6 levels were predictive of AKI [28]. The authors reported that for every 10-fold increase in baseline IL-6, the risk of AKI increased by 16%. Moreover, baseline IL-6 was an independent risk factor for AKI and the need for hemofiltration. Liu *et al.* analyzed biological and clinical predictors of AKI in subjects with acute lung injury [29]. They reported that IL-6 levels were independently associated with AKI after adjustment for demographics, interventions, and severity of illness. Nevertheless, these two studies were conducted in critically ill patients with sepsis and acute lung injury. In those studies, AKI may have contributed to high concentrations of IL-6, or may have resulted from the severity of illness and proinflammatory state. In contrast, Liu *et al.* also studied the role of cytokine release as a biomarker of AKI in children undergoing cardiac surgery [30]. They found that IL-6 levels at two and 12 hours after cardiopulmonary bypass (CPB), and IL-8 levels at two, 12 and 24 hours were associated with the development of AKI using the Wilcoxon rank-sum test, and after adjustment for age, gender, race, and prior cardiac surgery in multivariate logistic regression analysis.

However, we studied the predictive role of IL-6 in stable clinical settings (patients with stable CAD undergoing coronary angiography). Our findings are similar to those observed in critically ill patients reported by other authors [29, 30]. This research indicates that IL-6 measured on admission could identify a subset of patients at risk for CIN.

Of note, the route of administration also plays an important role, with contrast agents being more nephrotoxic when administered intra-arterially due to the fact that the intrarenal concentration of contrast agent is much higher after intra-arterial rather than intravenous injection [31]. Therefore, further studies are required to investigate the role of IL-6 in developing CIN after intravenous contrast medium administration.

## CONCLUSION

In conclusion, providing patients protection from the development and progression of CIN still remains a challenge for interventional cardiologists. Increased concentrations of IL-6 on admission are associated with subsequent CIN. Our study proposes that IL-6 be to the list of potential markers that could be used, along with SCr and eGFR, in clinical practice. The combination of inflammatory markers and clinical risk factors may have an important and additive value in predictive models for

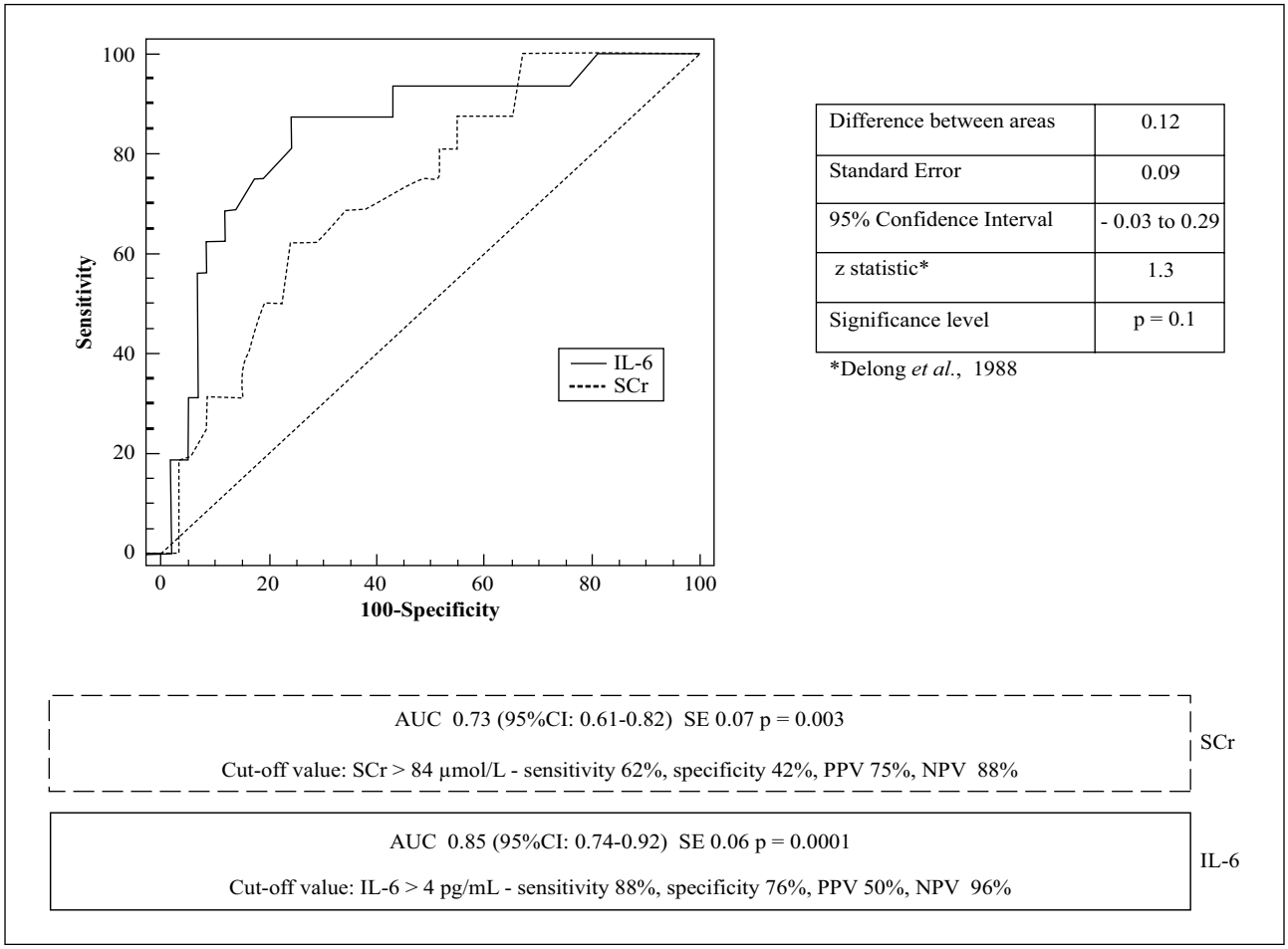


**Figure 4**

Comparison of area under the ROC curves for IL-6 and SCr.
AUC: area under the curve; CI: confidence interval; SE: standard error; PPV: positive predictive value; NPV: negative predictive value; SCr: serum creatinine.

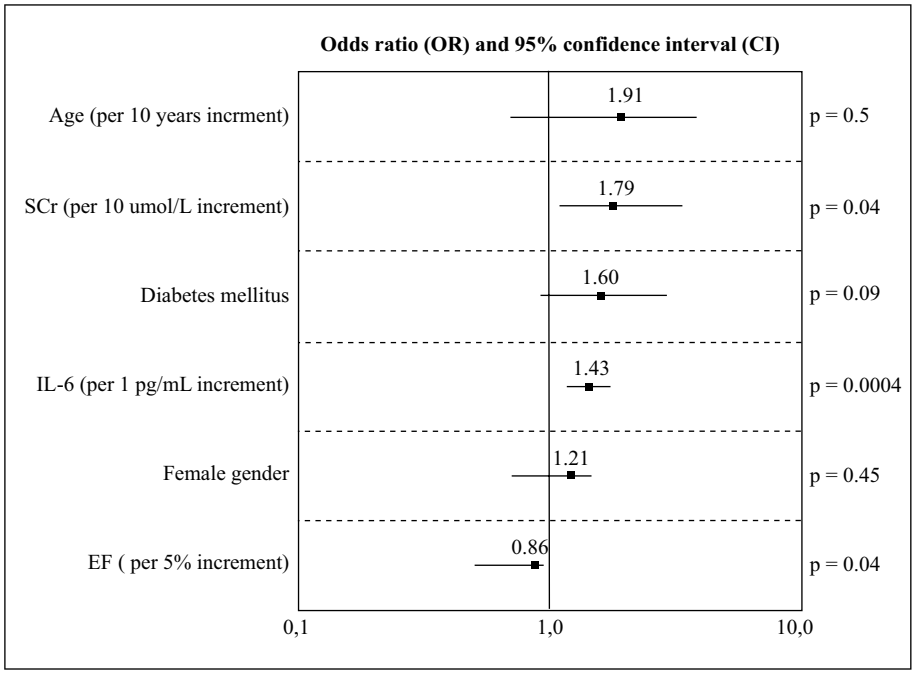


**Figure 5**

Independent predictors of contrast-induced nephropathy.
SCr: serum creatinine; EF: ejection fraction; OR: odds ratio; CI: confidence interval.

CIN. It is therefore our hypothesis that elevated concentrations of inflammatory markers could identify a subset of patients with normal baseline SCr, who are at risk of CIN, thus allowing for timely institution of a variety of therapeutic interventions.

It should be noted that our study has some limitations. Renal function parameters were measured before and after the procedure, whereas IL-6 concentrations were measured only once. A relatively small number of patients could have rendered some differences insignificant between the study groups. Further, large-scale studies are required to investigate the time-course release of IL-6 in patients undergoing diagnostic or therapeutic procedures with the use of contrast media, its association with the development of CIN, and its effect on clinical outcomes.

eGFR calculation is subject to limitations due to the formula used. Although the rise in SCr occurs within the first 24 h after exposure to contrast media in 80% of the patients, the time limit used in the present study (SCr increase within 48 hours after contrast administration) might have resulted in a slight underestimation of CIN.

The incidence of CIN was relatively high in the low-risk patients analyzed in our study. One possible explanation for this phenomenon is that no specific preventive measures such as volume supplementation [32, 33], bicarbonate [33, 34], N-acetylcysteine [35, 36] administration were employed because of the low risk of developing CIN. The other reason may be the relatively high rate of diuretic [37] and ACE inhibitor use [38, 39], which may alter renal perfusion. However, there is some contradictory evidence suggesting that ACE inhibitors may have anti-inflammatory and renoprotective effects [40, 41]. Clearly, the available data are conflicting, and further, large-scale, randomized trials are needed to determine the association between ACE inhibitor use and the development of CIN.

***Disclosure.*** *None of the authors has any conflict of interest to disclose.*

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