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Neutrophil Gelatinase-Associated Lipocalin as an Early Marker of Contrast-Induced Nephropathy After Coronary Angiography

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Abstract

We investigated whether serum neutrophil gelatinase-associated lipocalin (NGAL) was an early predictive biomarker of contrast-induced nephropathy (CIN) in patients with chronic kidney disease (n = 100) undergoing coronary catheterization. Serum creatinine (SCr) levels were measured at baseline, 24 hours, and 48 hours post procedure. Serum NGAL was measured preprocedure, 4 hours, and 24 hours post procedure. The frequency of CIN was 11%. In patients with CIN, SCr achieved significance only at 48 hours ($P = .006$), whereas serum NGAL increased $\geq$25% from baseline at 24 hours in 7 of 11 patients with CIN ($P = .04$) but did not change in the other 4. However, serum NGAL also rose $\geq$25% in 12 of 89 non-CIN patients. This subgroup could have had "incipient CIN." Serum NGAL delta value at baseline, 24 hours was superior to SCr for early diagnosis of CIN. In conclusion, serum NGAL is an early predictive biomarker for CIN.

Keywords

contrast-induced nephropathy, coronary catheterization, neutrophil gelatinase-associated lipocalin, chronic kidney disease

Introduction

Contrast-induced nephropathy (CIN) was the third most common cause of acute kidney injury (AKI) in hospitalized patients and accounted for 11% of cases of AKI.[1] A large cohort study showed that the risk of developing CIN—defined as a 25% rise in baseline serum creatinine (SCr)—after coronary angiography was 14.5%.[2] Patients with CKD are at higher risk of CIN.[3] The CIN is generally defined as an absolute increase of 0.5 mg/dL (44 μmol/L) or a relative increase of 25% over baseline SCr within 48 hours of exposure to contrast media in the absence of an alternative etiology.[4-6]

The SCr has been considered the standard marker of CIN despite its known limitations, slow rate of change, affected by several factors, for example, age, weight, muscle mass, and various medications.[7,8] Since patients after cardiac catheterization are typically discharged within 24 hours, rarely later than 48 hours, there is a definitive need of reliable biological markers for timing the initial insult and for assessing the duration and severity of AKI, as its early diagnosis will enable timely remedial measures to prevent progression of renal damage.

Both serum cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) have been reported to be superior to SCr for the early diagnosis of CIN in patients who underwent coronary catheterization.[9-12]

The NGAL is a 25-kDa protein covalently bound to gelatinase from neutrophils. Using genomic microarray technology, NGAL has been identified as a potential biomarker of AKI.[13,14] We therefore aimed to evaluate the role of serum NGAL as a new biomarker for early detection of CIN among patients with CKD stages 2 to 4 who underwent coronary angiography with/

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without angioplasty and to determine the frequency of CIN and the risk factors predisposing to CIN in these patients.

Patients and Methods

Study Design

This was a prospective study carried out from October 2008 to November 2009 at Universiti Kebangsaan Malaysia Medical Centre (UKMMC). Patients (n = 100) with stable CKD stages 2 to 4 who underwent coronary angiography with/without angioplasty were enrolled. Patients with AKI, acute myocardial infarction, end-stage kidney disease, and cardiogenic shock were excluded. None of the patients had received nephrotoxic drugs or had been exposed to contrast media since at least 48 hours prior to the study and during the study period.

The CIN was defined as an increase of ≥25% in the baseline SCr within 48 hours of exposure to contrast medium. All patients received intravenous (IV) normal saline at a rate of 1 mL/kg per hour and oral *N*-acetylcysteine (NAC) 600 mg twice daily for 3 days starting from 12 hours preprocedure. Blood samples were collected for SCr and estimated glomerular filtration rate (eGFR) estimation at baseline, 24 hours, and 48 hours after the procedure. Blood samples were collected for serum NGAL estimation at preprocedure, 4 hours, and 24 hours postprocedure.

The protocol was approved by the Medical Research and Ethics Committee of the University. All consecutive patients who gave informed consent were recruited.

Measurement of NGAL and Other Variables

The sera for NGAL were first diluted 20-fold using calibrator diluents and then assayed using a commercially available enzyme-linked immunosorbent assay (ELISA) kit from R&D Systems (Minneapolis, Minnesota). Briefly, this is a sandwich monoclonal ELISA designed to measure human Lipocalin-2/NGAL in cell culture supernates, serum, plasma, urine, and saliva. Microplate spectrophotometer reader was used to measure the absorbance at 450 nm with the correction wavelength set at 540 nm.

The SCr levels were measured according to the standard Jaffe method. The eGFR was calculated using the Modification of Diet in Renal Disease equation.[11]

Statistical Analysis

Correlation between any 2 parameters was determined by the Pearson coefficient for normally distributed data and by the Spearman rho test for nonnormally distributed data. Univariate analysis was used to determine the association between risk factors and CIN. Multivariate logistic regression was performed to identify independent risk factors for CIN and predictors for early diagnosis of CIN at 24 hours. We generated receiver–operating characteristic (ROC) curve to describe the performance characteristics of serum NGAL (absolute values) and serum NGAL delta value measured at baseline to 4 hours, 4 to 24 hours, and at baseline to 24 hours post procedure compared to the performance characteristics of SCr delta value measured at baseline and 24 hours post procedure. The area under the curve (AUC) with associated 95% confidence intervals (CIs) served as a measure of the discriminatory capacity of serum NGAL and SCr to predict CIN. SPSS software version 12.0 and MedCalc Version 11.5.1.0 (MedCalc Software, Mariakerke, Belgium) were used for statistical analysis. A $P < .05$ (2-sided) was considered significant.

Results

Baseline Characteristics

Of the 115 patients screened, only 100 completed the study. However, 15 patients dropped out for various reasons—the appointment was postponed in 2 patients—one was due to prolonged international normalized ratio and the other due to anemia secondary to aspirin-induced peptic ulcer disease, and 13 patients withdrew from the study after the blood was taken for the baseline serum NGAL.[15] Their clinical and biochemical characteristics are as shown in Table 1.

Frequency and Risk Factors for CIN

The frequency of CIN was 11% (11 of 100) and 1 patient required dialysis. The risk factors for developing CIN on univariate analysis are presented in Table 2. Multivariate analysis showed that age alone was the independent risk factor for development of CIN ($P = .026$).

Distribution of the Standard Renal Markers and Serum NGAL Levels and Their Correlation

At baseline, the median SCr value was 126 μmol/L (IQR ± 55). At 24 hours after coronary studies, it was 121 μmol/L (IQR ± 55) and was 122 μmol/L (IQR ± 67) at 48 hours after procedure. The mean eGFR at baseline was 50 ± 16 mL/min per 1.73 m^2 and at 24 and 48 hours after the procedure were 52 ± 17 and 49 ± 17 mL/min per 1.73 m^2, respectively.

The median serum NGAL value at baseline was 102 ng/mL (IQR ±85). At 4 and 24 hours after coronary studies, it was 104 (IQR ± 75) and 100 ng/mL (IQR ± 86), respectively. Prior to cardiac catheterization, serum NGAL was significantly correlated with SCr ($r = .420$, $P < .005$) and with eGFR ($r = -.356$, $P < .005$). At baseline (using multiple linear regression), the only predictor for serum NGAL was the SCr (β 0.63, $P < .001$). At 24 hours post coronary studies, there were significant correlations between serum NGAL with SCr and eGFR ($r = .423$, $P < .005$; $r = -.399$, $P < .005$, respectively). Using multiple linear regression analysis, SCr (β 0.589, $P < .001$) was significant predictor of serum NGAL at 24 hours post procedure.

Relationship of the Standard Renal Markers and Serum NGAL Levels With CIN

There were no differences in SCr, eGFR, and serum NGAL at baseline, between those participants who developed CIN and those who did not ($Z = -0.143$, $P = .088$, $P = .287$ and $Z =$

Table 1. Baseline Characteristics and Demographic Data of Patients.

Characteristics	Mean/median
Age, years[a]	60.42 ± 8.31
Race—Malay:Chinese:Indian	50 (50%):38 (38%):2 (2%)
Gender—male:female	79 (79%):21(21%)
Smoking history—past:current:nil	43 (43%):9 (9%):48 (48%)
Body mass index, kg/m^{2b}	26.6 kg/m^2 (IQR ± 14.3)
Hyperlipidemia, %	64 (64%)
Diabetes mellitus, %	71 (71%)
Hypertension, %	92 (92%)
Type of procedure	
Coronary angiogram (%)	77 (77%)
Angioplasty (%)	7 (7%)
Coronary angiogram + angioplasty (%)	16 (16%)
Duration of procedure, min[b]	30 (IQR ± 31.5)
Amount of contrast medium, mL[b]	80 (IQR ± 30)
Type of contrast medium	
Iodixanol	68 (68%)
Iohexol	32 (32%)
Antiplatelet agent (%)	96 (96%)
ACEIs/ARBs (%)	56 (56%)
β-Blockers (%)	77 (77%)
Calcium antagonists (%)	35 (35%)
Statins (%)	89 (89%)
Hemoglobin[a] (14.0-17.0 g/dL)	12.71 ±1.53
Hematocrit[b] (39.0-52.0%)	38.1 (IQR ± 6.28)
Cholesterol[b] (<5.7 mmol/L)	4.74 (IQR ± 1.47)
FBS[b] (3.0-6.7 mmol/L)	6.8 (IQR ± 3.57)
Baseline serum creatinine[a] (40-80 μmol/L)	126.5 (IQR ±55)
Baseline eGFR[b], mL/min per 1.73 m^2	50.19 ± 16.16

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; statins, hydroxymethylglutaryl co-enzyme A reductase inhibitors; SD, standard deviation.
[a] Mean ± SD.
[b] Median ± interquartile range (IQR).

Table 2. Risk Factors Significantly Associated With Development of Contrast-Induced Nephropathy (Univariate Analysis).

Parameters	All Participants (n = 100)	CIN (n = 11)	No CIN (n = 89)	*P*
Age, years				
41-49	12 (100%)	0 (0%)	12 (100%)	.011
50-70	77 (77%)	7 (9.1%)	70 (91%)	
>70	11 (11%)	4 (36.3%)	7 (63.6%)	
Gender				
Male	79 (79%)	4 (5.1%)	75 (94.9%)	<.001
Female	21 (21%)	7 (33.3%)	14 (66.7%)	
Race				
Malay	50 (50%)	1 (2%)	49 (98%)	.04
Chinese	38 (38%)	6 (15.8%)	32 (84.2%)	
Indian	12 (12%)	4 (33.3%)	8 (66.7%)	
Diabetes				
Yes	71 (71.0)	11 (15.5%)	60 (84.5%)	.025
No	29 (29.0)	0 (0%)	29 (100%)	
Hemoglobin, g/dL	12.71	11.09	12.91	<.001
Mean ± SD	1.53	1.60	1.40	
Hematocrit, %	38.10	32.56	38.00	.02
Median (IQR)	6.28	5.83	4.18	

Abbreviations: CIN, contrast-induced nephropathy; IQR, interquartile range; SD, standard deviation.

−0.116, $P = .908$, respectively). At 24 and 48 hours post procedure, there was a significant decline in the eGFR in participants who developed CIN ($P = .01$, $P \leq .001$, respectively). The SCr levels in patients who developed CIN started to rise 24 hours post procedure ($Z = -2.76$, $P = .155$) but achieved significance only at 48 hours ($Z = 0.155$, $P = .006$; Figure 1). Serum NGAL at 4 hours was not significantly different from that at baseline ($Z = -0.99$, $P = .32$), while serum NGAL at 24 hours increased ≥25% from the baseline in 7 of 11 patients with CIN ($Z = -1.97$, $P = 0.04$) but did not change in the other 4 of the 11 patients (Figure 2). Serum NGAL also increased by ≥25% in 12 of the non-CIN patients (Fischer exact test = 0.001). These latter patients could well have had "incipient CIN." One of these subsequently developed CIN and was kept in hospital. The rest were discharged with a "stable" SCr 48 hours post coronary studies as our current practice.

The ROC Curve Analysis

The ROC curves were constructed to test the ability of serum NGAL compared to SCr to predict CIN. The results are given in Table 3. The AUC for SCr (absolute value) at 24 hours was 0.632 (95% CI: 0.52-0.72; $P = .155$). The AUC for delta value at baseline 24 hours was 0.747 (95% CI: 0.65-0.82; $P = .008$). The AUC for serum NGAL (absolute value) was 0.683 (95% CI: 0.50-0.86; $P = .049$). The AUC for delta at baseline 4 hours was 0.646 (95% CI: 0.54-0.73; $P = .116$). The AUC for delta at 4 to 24 hours was 0.704 (95% CI: 0.60-0.79; $P = .028$) and for delta at baseline 24 hours was 0.845 (CI: 0.75-0.91: $P < .001$; Figure 3). The cutoff values for serum NGAL at different time points were chosen and positive and negative predictive values were determined as presented in Table 3. After contrast medium exposure, serum NGAL (absolute value at 24 hours) with cutoff value set at 91.8 ng/mL had sensitivity and specificity of 72.7% and 45%, respectively. While with cutoff 17.7 ng/mL for delta value of serum NGAL measured at baseline 24 hours, the sensitivity and specificity were 72.7% and 76.4%, respectively, for early detection of CIN (Figure 4).

Independent Predictors of CIN

Using multivariate logistic regression analysis, among variables, which included age, SCr, and serum NGAL measured as delta value at baseline-24 hours. Only, serum NGAL levels (odds ratio [OR] = 6.53, 95% CI: 1.30-32.64; $P = .02$) and advanced age (OR = 1.14, 95% CI: 1.01-1.2: $P = .03$) were independent predictors for the development of CIN. Whereas SCr at the same time point did not predict CIN (OR = 1.08, 95% CI: 0.21-5.45, $P = .92$).

Serum NGAL Levels and Relationship With CKD Stages

Serum NGAL was significantly higher at baseline in 6 patients, 2 had CKD stage 3, and the remaining 4 had CKD

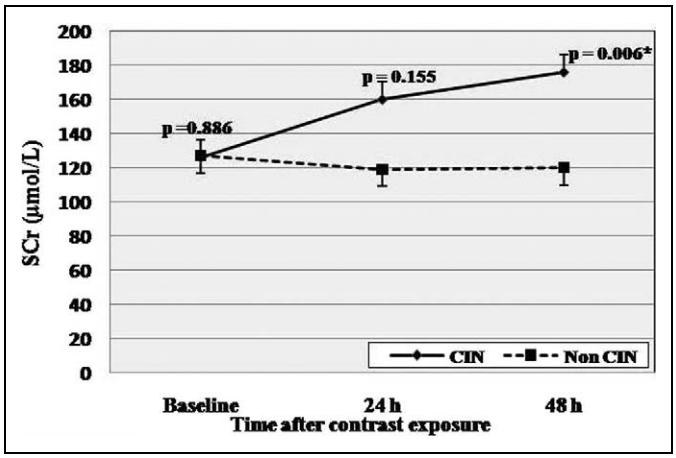

Figure 1. Median serum creatinine (SCr) measurements obtained at various time points following contrast exposure. Contrast-induced nephropathy (CIN) defined as a 25% increase in SCr from baseline. The asterisks indicates statistically significant difference between patients with CIN and those without.

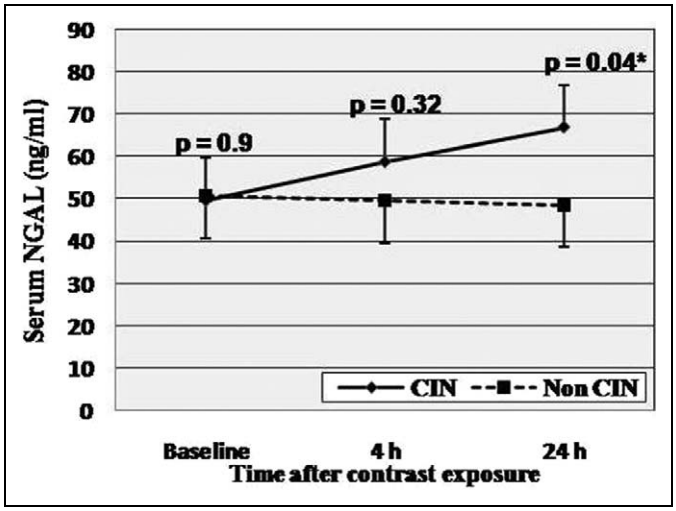

Figure 2. Median serum neutrophil gelatinase-associated lipocalin (NGAL) measurements obtained at various time points following contrast exposure. Contrast-induced nephropathy (CIN) defined as a 25% increase in serum creatinine from baseline. The asterisks indicates statistically significant difference between patients with CIN and those without.

Table 3. Characteristics of biomarker test post cardiac catheterization for early detection of CIN.

Value	AUC (95% CI)	P value	Cut off value	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Serum creatinine (µmol/L)							
-24 h Post CM exposure (absolute value)	0.632 (0.52 -0.72)	0.155	130	54.5 (23.4 - 83.3)	62.9 (52.0 - 72.9)	15.4 (5.9 - 30.5)	91.8 (81.8 - 97.3)
-48 h Post CM exposure (absolute value)	0.755 (0.65 - 0.83)	0.003	164	63.6 (30.8 - 89.1)	77.5 (67.4 - 85.7)	25 (10.9 - 46.7)	94.5 (86.6 - 98.5)
-Delta1: 24 h-0	0.747 (0.65 - 0.82)	0.008	15	54.5 (23.4 - 83.3)	78.6 (68.7 - 86.6)	23 (9.1 - 45.6)	93.3 (85.1 - 97.8)
-Delta2: 24-4 h	0.826 (0.73 -0.89)	0.0001	21	63.6 (30.8 - 89.1)	91.0 (83.1 - 96.0)	46 (20.5 - 74.3)	95 (88.4-98.7)
-Delta3: 48 h-0	0.985 (0.93 - 0.99)	0.0001	29	72.7 (39.0 - 94.0)	95.5 (88.9 - 98.8)	66 (34.9 - 90.1)	96 (90.4 - 99.3)
Serum NGAL (ng/ml)							
-24 h Post CM exposure (absolute value)	0.683 (0.50 - 0.86)	0.049	91.8	72.7 (39.0 - 94.0)	45 (35.4 - 57.0)	16 (6.4 - 26.2)	93.1 (81.3 - 98.6)
-Delta1: 4 h-0	0.646 (0.54 - 0.73)	0.116	9.4	63.6 (30.8 - 89.1)	74.1 (63.8 - 82.9)	25 (9.7 - 42.7)	94.3 (86.0 - 98.4)
-Delta 2: 24 h-4 h	0.704 (0.60 - 0.79)	.028	13	63.6 (30.8 - 89.1)	80.9 (72.5 - 89.4)	30 (12.9 - 50.5)	94.7 (87.2 - 98.6)
-Delta 3: 24 h-0	0.845 (0.75 - 0.91)	<0.001	17.7	72.7 (39.0 - 94.0)	76.4 (66.2 - 84.8)	33 (14.7 - 54.2)	95.8 (88.1 - 99.1)

Abbreviations: AUC, area under curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; CM, contrast medium.

stage 4. The median serum NGAL was 265.6 ng/mL (IQR $\pm$ 279.8) in those patients with CKD stage 3 versus 543.8 ng/mL (IQR $\pm$ 307.2) in those patients with CKD stage 4. The mean eGFR was 41 $\pm$ 8 mL/min per 1.73 m^2 for those patients with CKD stage 3 versus 20 $\pm$ 4 mL/min per 1.73 m^2 for those patients with CKD stage 4. There was a significant correlation between serum NGAL and eGFR at baseline ($r = -.829$, $P = .042$).

Discussion

The CIN is a significant complication of coronary catheterization in renal-impaired patients. The risk of CIN is significantly increased in proportion to the severity of the underlying renal impairment.[3,16] Other reported risk factors for CIN include diabetes mellitus, older age, increased dose of contrast agent, congestive heart failure, preprocedural hypovolemia, and the concurrent use of nephrotoxic drugs.[2,17] Recently, several

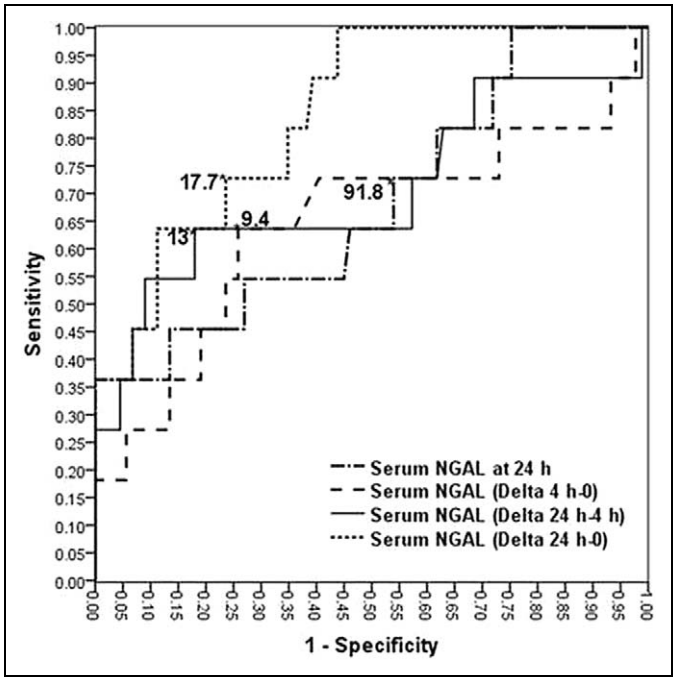

Figure 3. The receiver–operating characteristic (ROC) curve of serum neutrophil gelatinase-associated lipocalin (NGAL) of absolute values measured at 24 hours and delta values measured at different time points at baseline to 4 hours, 4 to 24 hours, and at baseline to 24 hours, considering contrast-induced nephropathy (CIN) as status variable. The area under the curve (AUC) for absolute value was 0.683 (95% confidence interval [CI]: 0.50-0.86), for delta value at baseline to 4 hours was 0.646 (95% CI: 0.54-0.73) while for delta value at 4 to 24 hours was 0.704 (95% CI: 0.60-0.79), and for delta value at baseline to 24 hours was 0.845 (95% CI: 0.75-0.91). For serum NGAL (absolute value) the sensitivity and specificity were optimal at 91.8 ng/mL, for serum NGAL delta value at baseline to 4 hours, the sensitivity and specificity were optimal at 9.4 ng/mL, for delta at 4 to 24 hours the sensitivity and specificity were optimal at 13 ng/mL, and for serum NGAL delta value at baseline to 24 hours, the sensitivity and specificity were optimal at the 17.7 ng/mL.

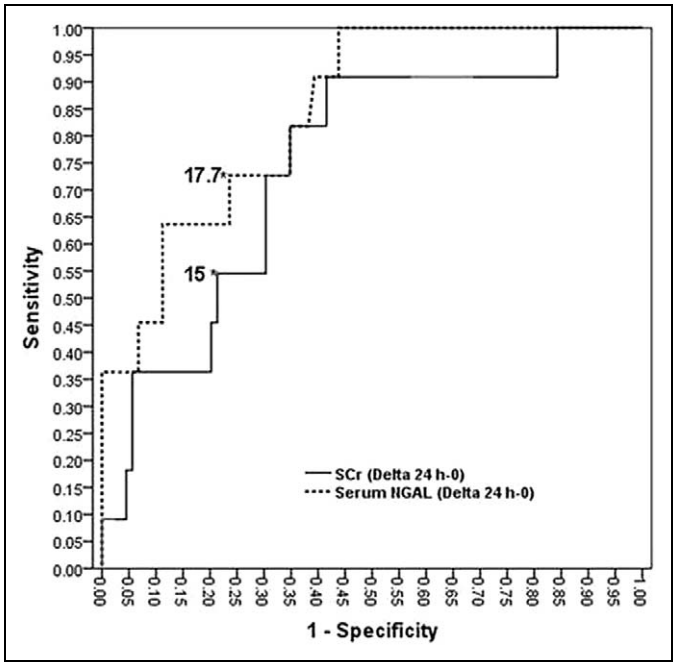

Figure 4. The receiver–operating characteristic (ROC) curve of serum creatinine (SCr) delta value at baseline to 24 hours, and serum neutrophil gelatinase-associated lipocalin (serum NGAL) delta value at baseline to 24 hours, considering contrast-induced nephropathy (CIN) as status variable. The area under the curve for SCr was 0.747 (95% CI: 0.65-0.82,) and for serum NGAL was 0.845 (95% CI: 0.75-0.91). The area for delta value at baseline to 24 hours value of serum NGAL ($P < .001$) was superior to that of SCr area at the same time point ($P = .008$). The best cutoff value for serum NGAL measured as delta value at baseline to 24 hours value to predict the CIN was found to be 17.7 with a sensitivity 72.7% and specificity 76.4%, whereas the best cutoff value for SCr measured as delta value at baseline - 24 h was 15 μmol/L with a sensitivity 54.5% and specificity 78.6%.

authors have reported the use of risk scores to predict CIN in patients undergoing coronary catheterization.[18-20] So, that renoprotective measures can be put in place preexposure to contrast medium. Fu et al[18] developed a risk score to predict CIN in the elderly patients undergoing percutaneous coronary intervention (PCI). Raposeiras et al[19] found that patients with myocardial infarction and normal kidney function with high level of Global Registry of Acute Coronary Events risk score (>140) are at higher risk of developing CIN. Elbasan et al[20] reported that the SYNTAX score which devised to grade the complexity of coronary artery disease[21] was associated with CIN in patients with ST-elevation myocardial infarction treated with PCI.

Despite the preventive measures taken, the frequency of CIN in our patients undergoing coronary contrast medium studies was 11%. This was essentially similar to that reported in our previous UKMMC study, in the same group that received similar prophylaxis 14.3% (UKMMC project, unpublished data, 2006). The reported frequencies of CIN in similar patient populations given similar prophylaxis have ranged from 4% to 8%.[22,23] Indeed, our earlier study by Zainuddin et al[24] reported a frequency of CIN of only 2.9% in a similar CKD cohort in whom both IV normal saline and IV NAC were used as prophylaxis. Whereas the control group who received only IV normal saline had a frequency of CIN of 20%.

Our results show that oral NAC has no beneficial effects in prevention of CIN in patients with CKD undergoing coronary angiography. These findings are consistent with those reported by O'Sullivan et al,[25] Goldenberg et al,[26] and Seyon et al.[27] However, several meta-analyses have shown that oral NAC could prevent CIN in patients undergoing cardiac catheterization.[28-32]

We found that an increasing age was an independent risk factor for CIN. This finding concurs with the literature.[33] Possible reasons that may account for the high frequency of CIN in elderly patients include atherosclerotic vasculopathy with superimposed calcification of their blood vessels that may require greater amounts of contrast media and the presence of renovascular disease.[34,35] Previous randomized controlled trials have found male gender to be an independent

risk factor for CIN.[3] Our study showed the contrary despite their smaller numbers (female:male = 21:79), females were at a higher risk of CIN compared to males. These females were elderly, postmenopausal, diabetic, and dyslipidemic, that is, they had multiple traditional cardiovascular risks in addition to CKD.

We also found that of the 3 major races, Indian ethnicity predisposed to CIN. All the Indian patients were females and older than 60 years. Diabetes mellitus and hypertension are known major risks of developing CIN.[2,36] In our study, all the patients with CIN were elderly individuals and diabetic. Although diabetes mellitus was a significant risk for CIN in the univariate analysis, it was not an independent risk predictor. Our results are thus in agreement with those reported by Rihal et al[37] and Weisberg et al.[38] Rihal et al[37] have reported that all patients with CKD (SCr >176 μmol/L), regardless of diabetic status, have a similarly high risk of CIN after coronary intervention. However, in the absence of CKD, diabetes mellitus became a significant risk factor.[37] Similar to other studies anemia and low hematocrit were found to be independent risk factors for CIN.[39,40] Anemia probably aggravates renal ischemia when patients with renal impairment are exposed to radiocontrast media that are nephrotoxic.

Our study also showed no differences between the type of contrast medium and the development of CIN. Our experience has been consistently different from other reported studies which found that iso-osmolar agents were less likely to cause CIN in high-risk patients than low-osmolar, nonionic contrast media.[41,42] In fact, Zainuddin et al[24] in an earlier study at our center showed that the type of contrast medium did not impact on CIN. The volume of contrast has also been reported to be a major risk factor for the development of CIN.[2,37] However, the volume of contrast media in our study was not associated with the development of CIN.

The SCr levels in all our patients who developed CIN increased to ≥25% from baseline only at 48 hours. This is consistent with those reported by other studies that SCr only peaks at 48 to 72 hours following AKI.[43,44] This indicates that SCr is an insensitive and late marker for acute renal dysfunction.[45] In contrast, NGAL promptly increases after nephrotoxic and ischemic injury in the human kidney cortical tubules.[13] Mishra et al[14] suggested that NGAL could serve as a novel biomarker for the early detection of AKI.

Our study showed that serum NGAL rose predictably as anticipated at 24 hours post procedure in those who developed CIN. We believe that the 24 hours time point is more clinically relevant, practical, and cost-efficient as most patients who undergo coronary contrast studies are discharged after 24 hours if their SCr is stable. With the available results of serum NGAL at 24 hours, medical officers can then objectively decide which patients can be safely discharged and which can be retained for a further 24 hours when SCr rise should be evident in those developing CIN. This corroborates with the findings of many other workers.[9,10]

Of note, the serum NGAL at 4 hours did not change significantly in our study. This may be due to the fact that all our patients had received a standard protocol of hydration and prophylactic oral NAC from 12 hours preinsult. The NAC was continued for 12 hours post procedure. Whereas Bachorzewska-Gajewska et al[10] had reported that both serum and urine NGAL values increased at 2 to 4 and 4 to 12 hours, respectively, after contrast exposure while no significant changes in SCr occurred at 24 and 48 hours. The serum NGAL increased ≥25% from baseline at 24 hours in 7 of the 11 patients with CIN, but did not change in the other 4. It also increased in 12 of the 89 non-CIN patients, 1 of whom subsequently developed CIN while the rest were discharged 48 hours post coronary study. We postulated that those patients may well have had mild or early CIN post discharge based on their SCr levels. Unfortunately, our study did not extend to post discharge follow-up, so this postulate remains conjectural.

The discriminatory capacity of serum NGAL for delta values at baseline 24 hours as an early predictive biomarker for CIN was significantly superior than that for the SCr at the same time point and for the serum NGAL (absolute value at 24 hours). Affected patients can then be detained in hospital while the rest can be safely discharged home.

In the present study, serum NGAL levels were independent predictors for the development of CIN whereby an increase of 6 ng/mL in serum NGAL (delta baseline 24 hours) increased this risk by 53%. Increasing age was also independent risk predictor for CIN whereby an increase in age by 1 year increased the risk of developing CIN by 14%. The SCr levels at the same time point were not significant predictors of CIN.

Serum NGAL was significantly higher at baseline in 6 of our patients with CKD. Two of them had CKD stage 3 and the remaining 4 had CKD stage 4. There was a significant correlation between their serum NGAL, SCr, and eGFR at baseline. Other studies have shown that an unprovoked elevation in serum NGAL may reflect the severity of the underlying CKD and may predict a higher risk of CKD progression.[46,47] Bolignano et al[46] reported that in patients with CKD, serum NGAL closely reflects the severity of renal impairment and represents a strong and independent risk marker for progression of CKD. Mitsnefes et al[47] reported that in children with CKD stages 2 to 4, serum NGAL levels correlated inversely with the GFR. At lower values of GFR, serum NGAL performed better than cystatin C as a marker of CKD severity.[47] However, whether the elevated NGAL of advancing CKD stages represents ongoing active renal tubular inflammation or damage or reflect certain renal causes has not been adequately addressed to date since not all patients with CKD in both our and other CIN studies have an elevated baseline serum NGAL. If this were the case, then NGAL would not have been considered an early biomarker for AKI or in this case, CIN.

Our study has several limitations. The number of patients is relatively small and due to budget constraints we could not obtain more frequent blood samples for serum NGAL assay.

In conclusion, our study demonstrated that despite prophylactic measures, the frequency of CIN remained high. Older

patients with CKD are at increased risk of CIN. Since SCr levels in patients with CIN rose significantly only at 48 hours after contrast exposure, CIN may be missed with the current practice of high patient turnover times of 36 to 48 hours for elective investigations. Whereas serum NGAL rose within 24 hours after contrast media exposure and is thus a better biomarker for the earlier diagnosis of CIN.

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Author's Note

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Declaration of Conflicting Interests

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