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Association between plasma endothelial microparticles and contrast-induced nephropathy in patients underwent coronary angiography

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Abstract

We aim to investigate the association between plasma endothelial microparticles (EMPs) and contrast-induced nephropathy of patients underwent coronary angiography.

The patients were divided into normal renal function group and renal dysfunction group based on the estimated glomerular filtration rate (eGFR). Among the 180 cases, 117 received determination of EMP and serum creatinine after percutaneous coronary intervention (PCI) and/or coronary angiography. The patients were divided into contrast-induced-nephropathy (CIN) group and non-CIN group. EMPs collection and determination were performed, together with biochemical analysis and digital subtraction angiography (DSA) analysis.

Spearman correlation showed that the expression of EMP was negatively correlated with eGFR ($r = -0.201$, $P < .01$). The serum hypersensitive C-reactive protein (hs-CRP), cystatin C (Cys-C), uric acid (UA) were significantly higher in CIN group than that in the non CIN group. Spearman correlation showed that the expression of EMP was positively correlated with serum interleukin-6 (IL-6, $r = 0.393$, $P < .01$). The expression of EMP was positively correlated with serum hs-CRP ($r = 0.360$, $P < .01$). Logistic regression analysis showed that the levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), eGFR, UA, and Cys-C were correlated with the incidence of contrast induced nephropathy.

In patients with contrast-induced-nephropathy, the plasma EMPs were significantly increased after coronary angiography. The expression of plasma EMPs may play a role in the occurrence of contrast-induced-nephropathy.

Abbreviations: ACEI = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blocker, BMI = body mass index, BUN = serum urea nitrogen, CIN = contrast-induced-nephropathy, CK-MB = creatinine kinase-MB, cTNI = cardiac troponin I, Cys-C = cystatin C, eGFR = estimated glomerular filtration rate, EMPs = endothelial microparticles, hs-CRP = hypersensitive C-reactive protein, IL-6 = interleukin-6, LDL-C = low density lipoprotein cholesterol, NT-proBNP = N-terminal pro-brain natriuretic peptide, PCI = percutaneous coronary intervention, PLT = platelets, ROS = reactive oxygen species, Scr = serum creatinine, TC = total cholesterol, TG = triglyceride, UA = uric acid, WBCs = white blood cells.

Keywords: contrast-induced-nephropathy, endothelial microparticles, estimated glomerular filtration rate

1. Introduction

The incidence of contrast-induced-nephropathy (CIN) is on an increasing trend, which ranks as the third common cause for hospital-acquired acute renal injury.[1] CIN patients show poor prognosis and a high mortality, as well as longer hospitalization duration and higher economic burden.[2] In a retrospective analysis of Mayo Clinic registry, the incidence of CIN was about 3.3% among the patients underwent percutaneous coronary intervention (PCI). The CIN patients showed a 1-year and 5-year mortality of 12.1% and 44.6%, while that for the non-CIN

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XF and JD equally contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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patients was 3.7% and 14.5%, respectively.[3] In a study focused on the complication of CIN and intravascular contrast medium use,[4] there was a significant elevation of hospitalization death in the CIN patients, and the requirements for dialysis showed a marked increase. These led us to investigate the pathogenesis of CIN, together with its early diagnosis and prevention.

To date, the exact mechanism of CIN is still not well defined. Several aspects have been reported to be associated with it, including direct toxicity to the renal tubular epithelial cells caused by contrast, renal hemodynamic imbalance, ischemia or anoxemia in renal medulla, as well as reactive oxygen species (ROS) induced oxidative stress.[5] In recent years, vascular endothelial injury was closely related to the CIN, which may be related to the endothelial apoptosis triggered by contrast-induced cellular toxicity.[6] Meanwhile, iodinated contrast induced anoxia in renal parenchyma may contribute to the generation of ROS, which results in endothelial cell injury and finally triggers in the onset of CIN. Nowadays, some studies have focused on the relationship between inflammation, endothelial injury, and the onset of CIN. However, rare clinical trials have been performed to investigate the roles of contrast in the vascular endothelial cell injury and inflammation.

Endothelial microparticles (EMP), a marker of vascular endothelial injury, may affect the vascular endothelial injury and mediate the angiogenesis.[7] In a previous study, Buesing et al[8] reported that ectogenic EMP promoted the elevation of proinflammatory factors in pulmonary alveoli such as interleukin -1 (IL-1) and tumor necrosis factor-α (TNF-α), which finally triggered the pulmonary injury. This implied that EMP exerted crucial roles in the inflammation. Meanwhile, Amabile et al[9] showed that in patients with end-stage renal failure, EMP showed a significant increase, which may be closely associated with the endothelial dysfunction and arterial dysfunction. Nevertheless, little is known about the relationship between CIN and the contrast induced endothelial injury, increase of EMP, deterioration of inflammation, as well as the renal injury. In this study, we investigated the expression of EMP in the patients underwent coronary angiography. Meanwhile, we analyzed the correlation between CIN and EMP expression.

2. Materials and methods

2.1. Patients

A total of 180 cases with chest pain presented to our hospital for coronary angiography between November 2017 and November 2018 were included in this study. The exclusion criteria were as follows: those with malignant arrhythmia, aortic dissection; those with hematological disorders including multiple myeloma, hemolytic anemia, aplastic anemia; those with infectious disease; those allergic to the diodone; or those received administration of diodone within 1 week. Each patient signed the informed consent. The study protocols were approved by the Ethical Committee of Second Affiliated Hospital of Dalian Medical University.

2.2. Grouping

The patients were divided into normal renal function group and renal dysfunction group based on the estimated GFR (eGFR) according to the previous description (normal group: $eGFR \geq 90$; renal dysfunction group: $eGFR < 60$ or $60 \leq eGFR < 90$).[10] Among the 180 cases, 117 received determination of EMP and serum creatinine after PCI and/or coronary angiography. The patients were divided into CIN group and non-CIN group. The CIN diagnosis was performed as previously described.[11]

2.3. EMPs collection and determination

Peripheral blood samples (2–3 mL) were obtained from the patients under fasting conditions on day 2 and post-PCI on day 2. The samples were centrifuged at $160 \times g$ for 10 minutes. The obtained platelet-rich plasma was transferred to the Eppendorf tube. The supernatant was centrifuged at $1000 \times g$ for 10 minutes. The PRP was incubated with 2 μL Anti-Human CD42b and 2 μL Anti-Human CD31 for 20 minutes in dark. Finally, the samples were analyzed using flow cytometry.

2.4. Biochemical analysis

The venous blood (3 mL) was obtained from each patient on day 2 under a fasting condition, followed by separation of serum. The blood examination was analyzed using Mindarybc 6800 analyzer. Simens ADVI 2400 analyzer was utilized to determine the concentrations of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), uric acid (UA), serum creatinine (Scr), serum urea nitrogen (BUN), N-terminal pro-brain natriuretic peptide (NT-proBNP), as well as hypersensitive C-reactive protein (hs-CRP). Meanwhile, the serum interleukin-6 (IL-6), cardiac troponin I (cTNI), and creatinine kinase-MB (CK-MB) were determined using commercial kits purchased from Invitrogen.

2.5. Digital subtraction angiography (DSA)

DSA was performed using the Simens Zeego facility according to the manufacturer's instructions. Visipaque (Hengrui Pharmacy, Jiangsu, China) was utilized as the contrast media. The interventional procedures were given by sophisticated physicians.

2.6. Hydration

The hydration was performed as previously described in the patients with eGFR of 60 mL/min1.73 m^2 body surface. For the patients with satisfactory heart function, persistent hydration was given through intravenous injection of isotonic saline solution (1.0 mL/kg/h).

2.7. Statistical analysis

SPSS 23.0 software was used for the data analysis. The measurement data that were normally distributed were presented as mean ± standard deviation. Student t test was used for the comparison of data that were normally distributed. The measurement data that were not normally distributed were presented as median and quartile M (Q1–Q3). The intergroup comparison was performed using Wilcoxon rank test. The numeration data were presented as percentage, and were compared using Chi square test. The correlation analysis was carried out using Spearman analysis. Logistic regression analysis was used to analyze the causal relationship. P value of $<.05$ was considered to be statistically significant.

3. Results

3.1. Patient characteristics

In the renal injury group, significant increase was noticed in the age, serum UA, Cys-C, and NT-proBNP compared with that of

the normal control group ($P < .05$). Patients in the renal injury group showed decline of hemoglobin compared with that of the normal group ($P < .05$). No statistical differences were noticed in the sex, BMI, history of smoking and alcohol, history of diabetes mellitus, coronary heart disease, hypertensive disease, administration of statins, and angiotensin converting enzyme inhibitors/angiotensin receptor blocker (AECI/ARB), as well as the blood examination (e.g., white blood cells [WBCs], platelets [PLT]), TG, TC, LDL-C, cTNI, and CK-MB concentrations between the 2 groups ($P > .05$, Table 1).

3.2. Correlation between EMP expression and serum IL-6 and hs-CRP

In the patients of the renal injury, significant elevation was observed in the serum EMP and hs-CRP compared with that of the normal group ($P < .05$). No statistical differences were noticed in the serum IL-6 between the 2 groups ($P > .05$, Table 2).

3.3. Association between renal injury and plasma EMP, serum hs-CRP, and IL-6

Patients with renal injury were divided into 2 subgroups according to the eGFR. In the patients with an eGFR of <60, the plasma EMP and serum hs-CRP showed significant elevation compared with that with $60 \leq$ eGFR < 90 ($P < .05$). Meanwhile, the serum IL-6 in the patients with eGFR < 60 was significantly higher than that of the patients with $60 \leq$ eGFR < 90 ($P > .05$, Table 3).

Table 1

Clinical features in the normal renal function group and the renal injury group.

	Normal renal function (n = 128)	Renal injury group (n = 52)
Age, yr	62.26 ± 10.04	67.48 ± 10.38*
Male, n (%)	93 (72.66)	38 (73.10)
BMI, kg/m^2	26.11 ± 3.13	25.49 ± 3.11
Smoking history, n (%)	55 (43.00)	21 (40.40)
Drinking alcohol, n (%)	29 (22.70)	9 (17.30)
Diabetes mellitus, n (%)	36 (28.13)	13 (25.00)
Coronary heart disease, n (%)	66 (51.60)	29 (55.80)
Hypertension, n (%)	68 (53.10)	33 (63.50)
Drug administration		
Statins, n (%)	62 (48.40)	28 (53.80)
ACEI/ARB, n (%)	29 (22.70)	18 (34.60)
Biochemical indices		
WBC ($\times 10^9$/L)	6.41 (5.49–7.93)	7.08 (5.65–7.93)
Hb, g/L	142.43 ± 15.22	134.29 ± 18.38*
PLT ($\times 10^9$/L)	211.41 ± 51.88	205.06 ± 47.11
UA, μmol/L	333.37 (275.92–383.45)	409.64 (328.80–468.88)*
Cys-C, mg/L	0.95 (0.85–1.04)	1.20 (1.03–1.59)*
TG, mmol/L	1.38 (1.05–1.89)	1.32 (0.92–1.72)
TC, mmol/L	4.31 (3.47–5.16)	3.85 (3.07–4.96)
LDL-C, mmol/L	2.19 (1.76–2.89)	2.01 (1.58–2.75)
cTNI, μg/L	0.02 (0.02–0.05)	0.02 (0.02–0.07)
CK-MB, μg/L	1.10 (0.60–1.90)	1.10 (0.80–1.68)
NT-proBNP, pg/mL	85.00 (33.00–256.25)	162.50 (49.00–408.00)*

ACEI = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blocker, BMI = body mass index, CK-MB = creatinine kinase-MB, cTNI = cardiac troponin I, Cys-C = cystatin C, Hb = hemoglobin, LDL-C = low density lipoprotein cholesterol, NT-proBNP = N-terminal pro-brain natriuretic peptide, PLT = platelets, TC = total cholesterol, TG = triglyceride, UA = uric acid, WBCs = white blood cells.
* $P < .05$, versus normal renal function group.

Table 2

Comparison of EMP, IL-6, and hs-CRP between the 2 groups.

	Normal renal function (n = 128)	Renal injury group (n = 52)
EMP, count/μL	356.67 (229.67–618.77)	490.66 (347.84–933.44)*
IL-6, pg/dL	6.24 (3.12–12.08)	6.81 (4.00–11.25)
hs-CRP, mg/L	0.94 (0.22–3.57)	1.73 (0.67–5.91)*

EMPs = endothelial microparticles, hs-CRP = hypersensitive C-reactive protein, IL-6 = interleukin-6.
* $P < .05$, versus normal renal function group.

3.4. Correlation analysis between EMP expression and eGFR

Regression analysis revealed that there was negative correlation between EMP expression and eGFR (Fig. 1).

3.5. Comparison of CIN incidence in the patients underwent coronary angiography

A total of 117 cases received determination of serum creatinine after PCI, among which 6 (5.1%) showed CIN. In the patients with eGFR of ≥90, the CIN incidence was about 2.6%, while that in the patients with $60 \leq$ eGFR < 90 and eGFR < 60 was 6.6% and 22.2%, respectively. There were significant differences in the CIN incidences among the 3 settings ($P < .05$, Fig. 2).

3.6. Comparison of plasma EMP, serum hs-CRP, and IL-6 between CIN group and non-CIN group

Significant differences were noticed in the hydration between the CIN group and non-CIN group ($P < .05$). The hs-CRP, Cys-C, and UA in the CIN group were significantly higher than that of the non-CIN group ($P < .05$). There were no statistical differences between the age, sex, body mass index (BMI), history of smoking and alcohol, history of diabetes mellitus, hypertensive disease, administration of statins, and AECI/ARB, as well as the WBC, HGB, PLT, BUN, TG, TC, LDL-C, cTNI, CK-MB, NT-proBNP, Scr, and IL-6 concentrations between the 2 groups ($P > .05$, Table 4).

3.7. Comparison of EMP before and after PCI

In the CIN group, the serum EMP level changes before and after PCI showed significant elevation compared with that of the non-CIN group ($P < .05$). No statistical differences were noticed in the baseline EMP between the 2 groups ($P > .05$, Table 5).

Table 3

Renal injury severity, EMP, IL-6, and hs-CRP.

	60 ≤ eGFR < 90 (n = 42)	eGFR < 60 (n = 10)
EMP (count/μL)	469.03 (256.29–753.68)	1163.33 (466.06–2145.72)*
IL-6, pg/dL	6.78 (3.96–12.13)	7.54 (5.10–10.50)
hs-CRP, mg/L	1.32 (0.55–3.04)	7.22 (0.85–8.71)*

EMPs = endothelial microparticles, eGFR = estimated glomerular filtration rate, hs-CRP = hypersensitive C-reactive protein, IL-6 = interleukin-6.
* $P < .05$, versus those with $60 \leq$ eGFR < 90.

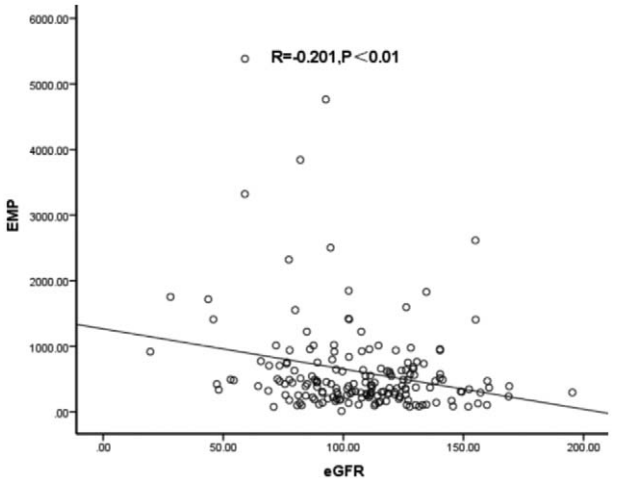

Figure 1. Correlation analysis between EMP and eGFR. eGFR = estimated glomerular filtration rate, EMP = endothelial microparticle.

3.8. Correlation between EMP expression and IL-6 and hs-CRP

EMP was positively correlated with IL-6 ($r = 0.393$, $P < .01$, Fig. 3A). Meanwhile, a positive correlation was noticed between EMP expression and hs-CRP ($r = 0.360$, $P < .01$, Fig. 3B).

3.9. Risk factor analysis for CIN

Logistic regression analysis was performed using EMP, Cys-C, NT-proBNP, eGFR, Scr, UA, BUN, hydration, dose of contrast, age, sex, BMI, history of smoking, diabetes mellitus, and administration of statins and ACEI/ARB as the independent variables. Our data showed that eGFR was identified as the risk factors for CIN (Table 6).

4. Discussion

EMP plays important roles in predicting the prognosis of patients with renal diseases. In a previous study, Lau et al[12] analyzed the expression of EMP and the renal function in 160 patients with atrial fibrillation, which indicated that EMP expression was correlated with the renal function in these patients. With the decrease of the eGFR, the EMP expression showed gradual elevation. Meanwhile, the EMP expression was negatively correlated with the severity of renal injury. Moreover, Eyre et al[13] reported that TNF-α could simulate the generation of EMP in the human umbilical vein endothelial cells, which then

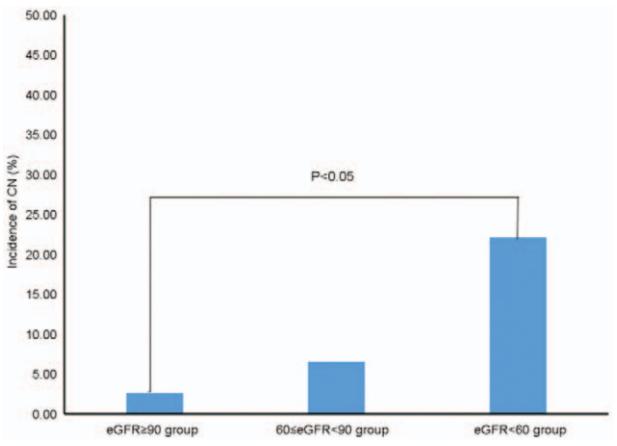

Figure 2. CIN incidence in the patients underwent coronary angiography. CIN = contrast-induced-nephropathy.

Table 4

Comparison of clinical features in the non-CIN group and CIN group.

	Non-CIN group (n = 111)	CIN group (n = 6)
Male, n (%)	81 (73.00)	3 (50.00)
Age, yr	67.00 (59.00–72.00)	65.00 (45.75–80.25)
BMI, kg/m^2	25.83 (23.66–27.46)	24.85 (23.95–26.09)
Smoking history, n (%)	53 (47.70)	2 (33.30)
Drinking alcohol, n (%)	24 (21.60)	1 (16.70)
Hypertension, n (%)	65 (58.60)	5 (83.30)
Diabetes mellitus, n (%)	37 (33.30)	1 (16.70)
Hydration, n (%)	8 (7.20)	2 (33.30)*
Contrast dosage, mL	120.00 (60.00–160.00)	135.00 (97.50–160)
Drug administration		
Statins, n (%)	57 (51.40)	3 (50.00)
ACEI/ARB, n (%)	31 (27.90)	2 (33.30)
Biochemical indices		
WBC ($\times 10^9$/L)	6.91 (5.38–8.08)	7.62 (6.34–9.90)
Hb, g/L	138.17 ± 17.11	132.67 ± 15.91
PLT ($\times 10^9$/L)	207.78 ± 52.90	198.67 ± 19.75
UA, μmol/L	356.75 ± 87.47	503.82 ± 176.55*
BUN, μmol/L	5.44 (4.61–6.91)	6.23 (5.44–11.34)
TG, mmol/L	1.35 (0.99–1.84)	1.18 (1.05–3.98)
TC, mmol/L	4.04 (3.34–5.03)	4.55 (2.93–5.77)
LDL-C, mmol/L	2.15 (1.75–2.86)	2.38 (1.89–3.28)
cTNI, μg/L	0.02 (0.02–0.31)	0.05 (0.02–0.20)
CK-MB, μg/L	1.20 (0.70–2.10)	1.05 (0.35–1.93)
NT-proBNP, pg/mL	140 (50.00–354.00)	563.50 (117.75–5491.00)
eGFR, mL/min1.73m^2	106.99 ± 30.17	79.59 ± 24.07*
Scr, μmol/L	70.02 (58.78–81.76)	84.23 (66.40–115.60)
Cys-C, mg/L	1.00 (0.90–1.14)	1.48 (1.18–2.41)*
IL-6, pg/dL	8.00 (3.98–12.90)	14.50 (9.30–21.13)
hs-CRP, mg/L	1.39 (0.51–4.75)	6.80 (3.93–10.89)*

ACEI = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blocker, BMI = body mass index, BUN = serum urea nitrogen, cTNI = cardiac troponin I, CK-MB = creatinine kinase-MB, CIN = contrast-induced-nephropathy, Cys-C = cystatin C, eGFR = estimated glomerular filtration rate, Hb = hemoglobin, hs-CRP = hypersensitive C-reactive protein, IL-6 = interleukin-6, LDL-C = low density lipoprotein cholesterol, NT-proBNP = N-terminal pro-brain natriuretic peptide, PLT = platelets, Scr = serum creatinine, TC = total cholesterol, TG = triglyceride, UA = uric acid, WBCs = white blood cells.

* $P < .05$ versus non-CIN group.

Table 5

Comparison of EMP in non-CIN and CIN groups before and after PCI.

	Non-CIN group (n = 111)	CIN group (n = 6)
Baseline EMP (count/μL)	466.16 (293.64–837.88)	549.81 (417.14–870.88)
Postoperative EMP (count/μL)	444.50 (287.02–765.02)	724.10 (558.79–1156.99)*
ΔEMP (count/μL)	0.00 (-298.20–222.55)	237.55 (99.23–318.43)*

CIN = contrast-induced-nephropathy, EMPs = endothelial microparticles, PCI = percutaneous coronary intervention.

* $P < .05$ versus non-CIN group.

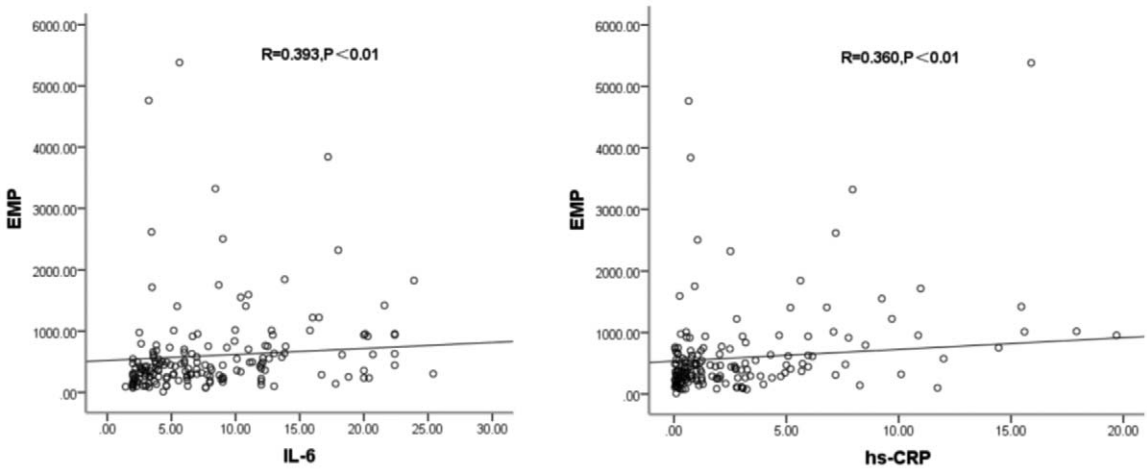

Figure 3. Correlation analysis between EMP and IL-6 (A) and hs-CRP (B). EMP = endothelial microparticles, hs-CRP = hypersensitive C-reactive protein, IL-6 = interleukin-6.

up-regulated the generation of IL-6 and monocyte chemoattractant protein-1 excreted by podocytes. Meanwhile, the EMP could lead to deterioration of renal injury through inducing the secretion of inflammatory factors. In this study, patients with renal injury showed significant elevation of plasma EMP and serum hs-CRP. Meanwhile, the plasma EMP and serum hs-CRP in the group with eGFR of <60 showed significant elevation compared with those with $60 \leq$ eGFR < 90. There was a negative correlation between EMP expression and eGFR ($r = -2.01$, $P < .01$), which was similar with the recent studies. This may be related to the glycation end products mediated endothelial nitric oxide inhibition, increase of circulating lignan, which then resulted in endothelial dysfunction and release of endothelial granules. Moreover, in cases of renal injury, there might be occurrence of stress reaction, and massive generation of glycation end products, lipopolysaccharide, and proinflammatory factors (e.g., IL-1 and TNF-α), which then triggered the endothelial injury and generation of endothelial granules.[14] Therefore, there was a correlation between EMP and renal insufficiency, while the patients with renal insufficiency showed elevation of plasma EMP, especially in those with severe injuries.

Table 6

Univariate regression analysis of CIN.

	CIN		
Variables	**OR**	**95% CI**	***P* value**
Baseline EMP	1.00	0.99–1.00	.779
Cys-C	0.07	0.01–0.33	.000
NT-proBNP	1.00	0.99–1.00	.000
eGFR	1.03	1.00–1.06	.004
Scr	0.98	0.95–1.00	.088
UA	0.99	0.98–0.99	.005
BUN	0.786	0.61–1.01	.060
Hydration	5.667	0.91–35.23	.063
Contrast dosage	0.996	0.98–1.01	.540
Age	1.013	0.94–1.09	.740
Gender	0.37	0.07–1.94	.240
BMI	1.106	0.84–1.46	.470
Smoking history	0.547	0.10–3.11	.500
Hypertension	0.538	0.40–31.3	.260
Diabetes mellitus	0.4	0.05–3.55	.411
Statins	0.947	0.18–4.90	.949
ACEI/ARB	1.29	0.23–7.40	.775

ARB = angiotensin receptor blocker, ACEI = angiotensin converting enzyme inhibitors, BMI = body mass index, BUN = serum urea nitrogen, CI = confidential interval, CIN = contrast-induced-nephropathy, Cys-C = cystatin C, eGFR = estimated glomerular filtration rate, EMPs = endothelial microparticles, NT-proBNP = N-terminal pro-brain natriuretic peptide, OR = odds ratio, Scr = serum creatinine, UA = uric acid.

Hydration is considered as an important measure for preventing CIN. In a previous study, Akyuz et al[15] included 90 cases with type II diabetes mellitus to investigate the effects of hydration on CIN incidence. The data showed that hydration could reduce the incidence of CIN. In this study, there were significant differences between the hydration of CIN and non-CIN groups. Interestingly, the incidence of hydration in the CIN group was significantly higher than that of the non-CIN group, which may be related to the fact that only populations with eGFR < 60 received hydration. Meanwhile, the incidence of CIN in the renal injury patients was also high and the sample size was relatively small. In a recent study, Wang et al[19] showed that patients underwent coronary angiography presented significant elevation of serum Cys-C levels at postoperative 24 hours compared with the baseline level, while the Scr levels showed significant elevation at postoperative 48 hours. This indicated that Cys-C could serve as a marker for the early detection of CIN, and its concentration change was superior to that of Scr. In the previous study,[16] the pathogenesis of CIN was correlated to the baseline renal function of the patients. This was similar with the lower eGFR in the CIN groups. On this basis, it was suitable to conclude that patients with severe renal injury opted to develop CIN.

Several factors have been reported to be associated with the pathogenesis of CIN, including the CIN risk factor evaluation including hypotension, intra-aortic balloon pump, congestive heart failure, age of >75 years, anemia, diabetes mellitus, contrast dosage, baseline creatinine and creatinine clearance rate, as well as the combination of diabetes mellitus and renal insufficiency.[11,17,18] Serum Cys-C level after coronary angiography could reflect the changes of serum eGFR, while its sensitivity was superior to the serum Scr as Scr was affected by

several factors such as age, sex, and diets. Previously, Wang et al[19] showed that CIN pathogenesis was associated with age, female individuals, contrast dosage, and exposure time. Additionally, there was a potential link between elevation of Cys-C and CIN pathogenesis. The elevation of Cys-C and contrast application contributed to the sensitivity and specificity of the CIN prediction. In this study, logistic regression was performed to identify the risk factors of CIN, which indicated that eGFR (odds ratio [OR] = 1.03, 95% confidence interval [CI], 1.00–1.06, $P = .004$) was the risk factors for the pathogenesis of CIN. Our data showed that the Cys-C concentration in the CIN group showed significant elevation before coronary angiography. But the Cys-C concentrations before coronary angiography cannot be predictable for the pathogenesis of CIN (OR = 0.07, 95% CI, 0.01–0.33, $P < .01$).

Previously, Cao et al[20] showed that the circulating EMP was remarkably elevated in the patients underwent PCI after infusion of contrast media, which implied the endothelial injury mediated by the media and the subsequent elevation of EMP in the peripheral blood. In this study, we compared the EMP changes before and after PCI in the CIN and non-CIN groups. Our data showed that there was a significant change in the EMP after PCI compared with the baseline level in the CIN group. Whereas, no statistical differences were noticed in the EMP after PCI compared with the baseline level in the non-CIN group. This demonstrated that EMP may involve in the pathogenesis of CIN. Before coronary angiography, there were no statistical differences in the EMP in both groups. Upon infusion of contrast media, several aspects may occur including renal medulla ischemia and anoxia. Meanwhile, it may activate the ROS generation, which then led to imbalance of oxidation/anti-oxidation and the oxidative stress injury in the renal tissues. Furthermore, ROS may mediate the vascular endothelial injury through cellular signaling transmission and the subsequent massive release of EMP, which then deteriorated the renal injury and the pathogenesis of CIN.

There are some limitations in this study. Firstly, the sample size was not large as we only included 6 cases in the CIN group. The fasting serum creatinine was used to calculate the eGFR, and there might be technical errors as the serum creatinine was only tested once. All the patients received creatinine monitor about 2 days after PCI, and no multiple-point monitoring was set in this study. Thus, we cannot determine the changes of EMP, renal function, hs-CRP, and IL-6 in a dynamic manner, and then the peak time of the serum creatinine elevation was missed together with the lower estimation of the CIN. Secondly, we utilized flow cytometry to determine the EMP, however, there was a lack of standardization and consensus.

In summary, EMP expression was associated with renal injury, and those with severe renal injury showed a higher incidence of CIN. For the CIN patients, the postoperative EMP expression was significantly higher than that of the baseline level. Meanwhile, the EMP expression was positively correlated to the inflammatory mediators such as hs-CRP and IL-6. This implied that in the presence of contrast media, the vascular endothelial cells may present injury, together with increased release of EMP and the subsequent inflammation. This process may finally responsible for the pathogenesis of CIN. However, the exact mechanism is not well defined, and in the future, further studies are required to fully illustrate the mechanism.

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