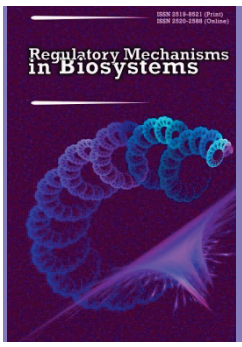

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Assessment of cystatin C and CCL14 as predictive and diagnostic biomarkers for contrast-induced nephropathy

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Contrast-induced nephropathy (CIN) is kidney dysfunction caused by radiocontrast agents, occurring 48–72 hours after their administration. The early prediction of CIN would be valuable in order to limit the damage caused by this condition. The present study aimed to evaluate the serum levels of chemokine (C-C) motif ligand-14 (CCL14), insulin-like growth factor-binding protein-7 (IGFBP7), cystatin C, and creatinine as novel biomarkers that predict contrast-induced nephropathy. This study aimed to assess the predictive value of cystatin C and CCL14 biomarkers for CIN development. The ELISA test was used to quantify serum levels of CCL14, IGFBP7, and cystatin C 2 days after exposure to contrast media in 44 patients with normal renal function before being scheduled to undergo coronary angiography (control group) and 2 days after exposure to contrast media in the contrast-induced nephropathy (CIN) group, and all data were compared. Levels of serum creatinine in CIN and control groups were also compared. The levels of the three biomarkers at 2 days after exposure to contrast media in the CIN group were significantly higher than those in the control group, while the level of serum creatinine was significantly higher than that in the control group. Moreover, the levels of CCL14, IGFBP7, and cystatin C were positively correlated with serum creatinine at 2 days after exposure to contrast media in the CIN group. This study demonstrated that the serum levels of CCL14, IGFBP7, and cystatin C could be potential predictors for CIN.

Keywords: contrast-induced nephropathy; cystatin C; CCL14; chemokine; kidney dysfunction.

Introduction

Contrast-induced nephropathy CIN could be considered a form of acute kidney injury in patients exposed to contrast material. CIN is one of the most common causes of in-hospital acute kidney injury. It is defined as an absolute (an increase in serum creatinine (Scr) by ≥ 0.5mg/dL), or a relative (≥ 25% increase of the creatinine value), increase in serum creatinine levels within 72h of contrast media exposure in the absence of an alternative explanation. The most common causes of CIN are dehydration, diabetes mellitus, hypovolemia, contrast material volume, contrast hyperosmolality, reduced left ventricular ejection fraction, concomitant administration of agents that are toxic to the kidneys (like contrast media), and pre-existing hyperuricemia (Toprak, 2007; Abd-Ulhussein & Rizij, 2019; Shawky Elserafy & Abdelsalam, 2020; Kzar Al-Shukri et al., 2024). CIN is the consequence of a direct toxic effect of contrast media on renal tubular cells. The pathogenic mechanism involves cell cycle arrest, blocking cell division, causing dedifferentiation, and cell apoptosis. Any of these effects will lead to tubular necrosis, which may be followed by acute tubular necrosis and cause acute kidney failure. On the other hand, in contrast nephropathy, cells undergo partial dedifferentiation, preserving their basic function while repairing the lesion caused by the toxic contrast. So, under these assumptions, tissue recovery would predispose a patient to a loss of renal function, meaning it would predispose contrast-induced renal damage, which translates, according to mathematical models of the complex, into CIN (Nikolsky & Sudarsky, 2011; Ewadh et al., 2017; Wacewicz et al., 2017; Shams & Mayrovitz, 2021).

Cystatin C (Cys-C) plasma is an endogenous low-molecular weight (13 kD) protease inhibitor that is not secreted in the urine by renal tubules; rather, it is freely filtered across the glomerular membrane and metabolized in proximal renal tubule cells following megalin-mediated endocytosis (Fujita et al., 2015). Cys-C circulates in the extracellular fluid, whereas Scr circulates in an amount that is three times larger than total body water. As a result, when glomerular filtration rate (GFR) deteriorates, serum Cys-C elevates earlier than Scr (within 24 hours). In comparison with Scr, Cys-C displays earlier fluctuations in serum levels because of its short half-life. It is therefore a more reliable marker of GFR than Scr. However, several conditions may affect its level such as thyroid dysfunction, systemic inflammation, aging, and neoplasia (Kuwabara et al., 2009).

C–C motif chemokine ligand-14 belongs to the class of small molecules known as chemokines, which were first discovered as having functions in leukocyte chemotaxis and are presently believed to be implicated in tissue damage and healing processes. The CC chemokine family encompasses C-C motif chemokine ligand 14 (HCC-1). Monocytes are stimulated by CCL14, however chemotaxis is not stimulated. One theory is that injured tubules release CCL14 in response to inflammatory signals (tumor necrosis factor-α and others). A condition like this could trigger additional the inflammatory responses (Luft, 2021). This study aimed to assess the predictive value of the of cystatin C and CCL14 biomarkers for CIN development.

Materials and methods

Study design and settings. A case-control study was conducted at Shahed Al-Mehrab Cardiac Center in Babylon Province-Iraq from July 2023 to January 2024. Demographic and clinical parameters were collected to compare the non-CIN group to the two subgroups of CIN patients. The CIN group, which was comprised of 44 patients diagnosed with post-procedure by increasing level of serum creatinine by 0.5 more than pre procedure of PCI. While the non-CIN group also composed of 44 patients with PCI.

Enrollment criteria. (1) Patients aged 43 years and more; (2) patients presented for elective percutaneous coronary intervention (PCI); (3) allergy to contrast media or severe renal or hepatic impairment and patients who were previously diagnosed with ESRD and those who had received hemodialysis were excluded from our study as shown in the exclusion chart. Eighty eight patients underwent PCI, as shown in Table 1.

Table 1
The age distribution of both groups

Age	Study groups	
	non CIN	CIN
Mean ± SD	57.34 ± 5.24	59.73 ± 6.95
Minimum–maximum	43–65	45–69
P	0.372	

Laboratory investigations. The blood samples were collected at two time points with the first sample collected before contrast infiltration and the other after 48 h. Creatinine serum was measured firstly daily and on the basis of an increasing trend. A CIN was diagnosed depending on the ratio of the maximum increase over 48 h. High risks for the CIN group included factors such as diabetes, anemia, LVF, and genesis drugs.

Blood samples were collected. Serum was subjected to ELISA (1) human serum cystatin C ELISA kit. ElabScience, China. ELISA kit designed for the quantitative measurement of human serum cystatin C; (2) C-C motif chemokine 14 (CCL14) ELISA kits (Human CCL14 Immunoassay) ElabScience ELISA kit designed for the quantitative measurement of human serum CCL14.

Statistics assessment. Statistical analysis was performed using the Statistical Program for Social Science Software IBM Corporation version 19. Results were analyzed and expressed as the mean ± standard deviation (x ± SD) for quantitative variables, whereas qualitative variables were shown as frequencies (number of cases) and their corresponding percentages. Differences between values in the groups were determined using the Tukey test, where the differences were considered significant at $P < 0.05$.

Results

In the present study, quantification of serum levels of cystatin C, CCL14 and IGFBP7 in patients undergoing coronary angiography was performed. The serum level of creatinine, cystatin C and CCL14 was evaluated by market kit according to the manufacturer's guidelines. Table 2 shows the levels of these markers pre and post PCI.

Table 2
The serum levels of creatinine, cystatin C and CCL14 (x ± SD)

Markers		Study groups	
		non CIN	CIN
Creatinine, mg/dL	Pre PCI	1.01 ± 0.15^{a}	1.14 ± 0.21^{ab}
	Post PCI	1.29 ± 0.13^{b}	1.79 ± 0.08^{c}
Cystatin-C, ng/mL	Pre PCI	10.4 ± 1.4^{a}	17.9 ± 1.6^{b}
	Post PCI	13.0 ± 2.2^{a}	20.4 ± 1.8^{c}
CCL14, ng/mL	Pre PCI	213 ± 69^{a}	412 ± 71^{b}
	Post PCI	284 ± 44^{a}	580 ± 101^{c}

Note: different letters indicate selections that significantly differ ($P < 0.05$) from each other according to the results of the Tukey test.

Table 3
ROC plot assessment of cystatin C and CCL14 as predictive and diagnostic biomarkers

Biomarkers		AUC	Cut-off value, ng/mL	Sensitivity	Specificity
Cystatin-C, ng/mL	predictive	0.999	15	0.977	1.000
	diagnostic	0.992	17	0.955	0.977
CCL 14, ng/mL	predictive	0.974	323.8	0.955	0.932
	diagnostic	0.980	416.0	0.955	1.000

Discussion

Contrast-induced nephropathy is one of the main concerns in coronary angiography procedures with contrast agents (Liu et al., 2015). CCL14 may be an important marker in the prediction, management, and follow-up of contrast administration while cystatin C represented the highest link with the contrast-induced nephropathy (Prowle et al., 2023).

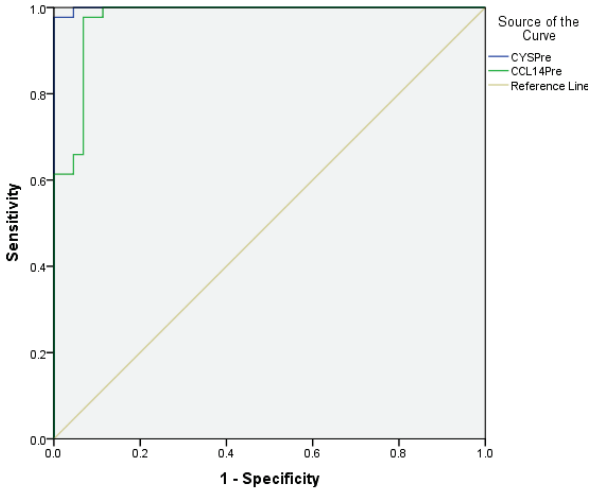

Fig. 1. The ROC plot for cystatin C and CCL14 before PCI

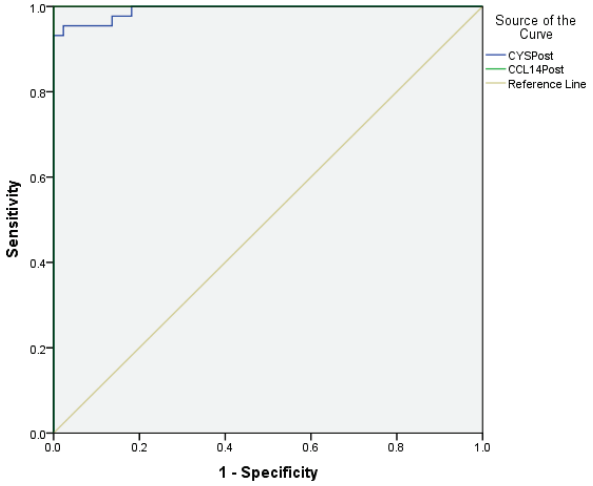

Fig. 2. The ROC plot for cystatin C and CCL14 after PCI

Serum creatinine (SCr) is unreliable in detecting acute changes in kidney function. Even so, changes in SCr are used to estimate acute changes in renal function (but this does not allow us to see the existence of kidney damage) and SCr monitoring remains the cornerstone for CIN diagnosis but it becomes a retrospective, late, insensitive, and misleading measure of kidney damage. Early recognition of CIN can provide better opportunities for preventive interventions. The significant difference between CIN and non-CIN patients in biomarkers serum levels before PCI as presented in Table 2 indicate that they can be used as a predictive markers for getting AKI after contrast media administration at a cutoff value to be specified later by ROC plot (Bhatt et al., 2016; Pierzchała et al., 2022; Yadollahi Fars et al., 2023). The serum level of cystatin C in CIN patients (17.9 ng/mL) was significantly higher ($P < 0.0001$) than that of non-CIN patients (10.4 ng/mL). This result indicated that the serum level of cystatin C can be used as a prediction marker for early detection of suspected CIN patients. It was proposed as established surrogate marker of GFR by a lot of studies like Grubb et al. (2012), Levey et al. (2020), and Ostermann et al. (2023).

The serum level of CCL14 in CIN patients (412 ng/mL) was significantly higher ($P < 0.0001$) than that of non-CIN patients (213 ng/mL). This result indicated that the serum level of CCL14 can be used as a prediction marker for early diagnosis of CIN patients. This result came in accordance with Rossiter et al. (2024), who stated that elevation of serum level of CCL14 is associated with AKI and explore their potential in aiding diagnosis, understanding the pathophysiology and directing therapy. The significant difference between CIN and non-CIN patients in bio-

markers serum levels after PCI as presented in Table 2 indicate that they can be used as a diagnostic marker for patients getting AKI after contrast media administration at a cutoff value to be specified later by ROC plot.

The serum level of cystatin C in CIN patients (20.3 ng/mL) was significantly higher ($P < 0.0001$) than that of non-CIN patients (13.0 ng/mL). This result indicated that the serum level of cystatin C can be used a diagnostic marker for diagnosis of CIN patients. The previous data demonstrate that sCysC is a sensitive marker for the identification of renal injury in the absence of a diagnostic increase in sCr. The glomeruli freely filter CysC, which is then reabsorbed and nearly entirely catabolized in the proximal renal tubules. The GFR determines the sCysC, and no external factor, such as sex, age, diet, and weight, has a substantial impact on it. Thus, CysC was a suitable endogenous indicator for the early detection of deviations in glomerular filtration rate (GFR) and damage to the epithelial cells in the renal tubules (Chen et al., 2020; Hidayati et al., 2021).

The serum level of CCL14 in CIN patients (580.6 ng/mL) was significantly higher ($P < 0.0001$) than that of non-CIN patients (284.5 ng/mL). This result indicated that the serum level of CCL14 can be used as a diagnostic marker for diagnosis of CIN patients. This result came in accordance with Rossiter et al. (2024), who stated that elevation of serum level of CCL14 is associated with AKI and explore their potential in aiding diagnosis, understanding the pathophysiology and directing therapy (Chen et al., 2023; Qian et al., 2023). To evaluate the feasibility and diagnostics with prediction ability of the studied biomarkers (CCL14 and cystatin-C) and assessing its possible use in a clinical setting, the ROC curve was implicated and AUC determined. The larger the area under the ROC curve, the higher the diagnostic value. For cut-off value, values exceeding the cut-off are positive cases, while those below the cut-off are negative cases. Cystatin C appears from Table 3 and Figure 1 to have an area under the ROC curve (AUC) of 0.999. The cut-off Ct value chosen was 14.8 ng/mL, it has a sensitivity of 0.977 and specificity of 0.977, it appeared to have optimal sensitivity to predict CIN and optimal specificity to exclude those who are not at risk of getting CIN.

CCL14 appears from Table 3 and Figure 1 to have an area under the ROC curve (AUC) of 0.974. The cut-off Ct value chosen was 323.8 ng/mL, it has a sensitivity of 0.955 and specificity of 0.932, it appeared to have optimal sensitivity to predict CIN with optimal specificity to exclude those who are not at risk of getting CIN. Cystatin C appears from Table 3 and Figure 2 to have an area under the ROC curve (AUC) of 0.992 . The cut-off value chosen was 17 ng/mL, it has a sensitivity of 0.955 and specificity of 0.977, it appeared to have maximum sensitivity to diagnose CIN and maximum specificity to exclude non-CIN. CCL14 appears from Table 3 and Figure 2 to have an area under the ROC curve (AUC) of 0.980. The cut-off value chosen was 416 ng/mL, it has a sensitivity of 0.955 and specificity of 1.000, it appeared to have maximum sensitivity to diagnose CIN with maximum specificity to exclude those who are non-CIN.

Conclusion

CCL14 and cystatin C are significantly elevated with PCI-induced contrast nephropathy. Serum concentrations of these markers play a role in early identification of patients with PCI-induced contrast nephropathy before the detection of changes in eGFR. Serum CCL14 and cystatin C can act as predictors for the contrast-induced nephropathy.

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