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The Role of IGFBP-7 in Predicting Contrast-Induced Acute Kidney Injury

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Abstract
Background: Acute kidney injury (AKI) is a significant complication associated with the administration of contrast media, leading to increased morbidity and healthcare costs. Insulin-like growth factor binding protein-7 (IGFBP-7) has emerged as a potential biomarker for predicting AKI. This study aims to evaluate the role of IGFBP-7 in predicting contrast-induced AKI (CI-AKI). **Methods:** ELISA test was used to quantify serum levels of Cr and IGFBP7. Serum levels of Cr and IGFBP-7 were measured pre- and post- two days of contrast exposure. Statistical analyses included sensitivity, specificity, and receiver operating characteristic (ROC) curves to assess the predictive power of IGFBP-7 and IGFBP-7/Cr. **Results:** A total of 938 patients were enrolled, with a reported incidence of CI-AKI at 4.7%. Elevated levels of IGFBP-7 and IGFBP-7/Cr were significantly associated with the development of AKI ($p < 0.001$). ROC curve analysis revealed an area under the curve (AUC) of 0.997 and 0.947 respectively, indicating good predictive accuracy. The optimal cutoff level for IGFBP-7 and IGFBP-7/Cr was determined to be 1.807 ng/mL and 0.1492 respectively, with a sensitivity of 97% and 90% and specificity of 99% and 97% respectively. **Conclusions:** Our findings suggest that IGFBP-7 and IGFBP-7/Cr is a promising biomarker for the early prediction of contrast-induced acute kidney injury. Implementing routine measurement of IGFBP-7 may enhance the clinical management of patients at risk for CI-AKI, allowing for timely interventions to mitigate renal damage. Further prospective studies are warranted to validate these results and establish clinical guidelines for its use.

Key Word: CI-AKI, PCI, IGFBP-7, Cardiac disease, Kidney Injury, ROC curve

Introduction

Acute kidney injury (AKI) is a complex heterogeneous clinical syndrome with a broad range of clinical presentations and varying trajectories and outcomes. It is often multifactorial with overlapping contributors, including hypervolemia, hemodynamic instability, inflammation, nephrotoxin exposure and potential obstruction. AKI has a major impact on morbidity, mortality, and health care resource utilization. The incidence of AKI is particularly high in patients with cardiovascular disease caused by advanced age and presence of comorbidities that increase the likelihood of chronic kidney disease (CKD), and performance of cardiovascular procedures (e.g., coronary angiography, percutaneous coronary intervention [PCI], or cardiac surgery)(1–3)

Contrast-induced acute kidney injury (CI-AKI) is characterized by a rapid decline in renal function, leading to increased morbidity, prolonged hospital stays, and higher healthcare costs. The incidence of CI-AKI can range from 0.5% to 20% in high-risk populations, making early identification and intervention crucial for improving patient outcomes.(4,5)

Current methods for diagnosing AKI primarily rely on serum creatinine levels and urea; however, these traditional markers often detect renal injury only after significant damage has occurred. As a result, there is a pressing need for reliable early biomarkers that can predict the onset of AKI before irreversible damage ensues. Insulin-like growth factor binding protein-7 (IGFBP-7) has emerged as a promising candidate in this regard. Recent studies have indicated that elevated levels of IGFBP-7 are associated with renal injury and may serve as an early indicator of AKI.

IGFBP-7 is highly expressed in liver, kidney, bone and muscle, and the expression level is higher in renal tubules. The molecular weight of IGFBP-7 is 29.1 kda. IGFBP-7 plays a quite important role in kidney, and the main use of IGFBP-7 is the early predictive and prognostic marker for AKI. The diagnostic performance of IGFBP-7 as biomarkers of AKI was first described in Sapphire study(6,7)

Aim of Study: This study aims to analyze the role of IGFBP-7 and IGFBP-7/Cr in predicting CI-AKI, By establishing a correlation between IGFBP-7 levels and the development of CI-AKI, we hope to provide insights that could enhance early detection strategies, ultimately leading to improved clinical management and outcomes for patients at risk of renal injury. Our findings could pave the way for integrating IGFBP-7 measurement into routine clinical practice, offering a valuable tool for nephrologists and radiologists alike in mitigating the impact of CI-AKI.

Material and Methods

I. 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-AKI group to the two subgroups of CI-AKI patients. The CI-AKI group, which was comprised of 44 patients diagnosed with post-procedure by increasing level of serum creatinine by 0.5 than pre procedure of PCI. While the non-AKI group also composed of 44 patients with PCI

II. Enrollment criteria:

1) Patients aged 45 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 had received hemodialysis were excluded from our study as shown in the exclusion chart.

III. 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 based on an increasing trend. A CI-AKI was diagnosed depending on the ratio of the maximum increase over 48 h.

IV. Blood samples were collected: Serum was subjected to ELISA

1. Human serum IGFBP-7 ELISA kit. ElabScience, China. ELISA kit designed for the quantitative measurement of human serum IGFBP-7

V. 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 (± SD) for quantitative variables, whereas qualitative variables were shown as frequencies (number of cases) and their corresponding percentages. Results represented as P value, mean, standard deviation, and confidence interval. A probability value (P-value) less than or equal to 0.05 was considered significant, and highly significant if it was less than 0.05.

Results

The serum level of Creatinine, IGFBP-7 and IGFBP-7/Cr were evaluated by markers kit according to the manufacturer's guidelines. Table 1 was shown the levels of these markers pre and post PCI.

Table 1: the Serum Levels of Creatinine, IGFBP-7 and IGFBP-7/Cr

Markers		Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
				Lower Bound	Upper Bound		
Cr Pre PCI mg/dl	Non-AKI	1.0152	0.1551	0.9681	1.0624	0.8400	1.6200
	CI-AKI	1.1439	0.2139	1.0788	1.2089	0.8100	1.6500
Cr Post PCI mg/dl	Non-AKI	1.2930	0.1251	1.2549	1.3310	1.0400	1.5000
	CI-AKI	1.7895	0.0839	1.7640	1.8151	1.6800	1.9500
IGFBP-7 pre-PCI ng/ml	Non-AKI	1.0734	0.1692	1.0220	1.1249	0.8111	1.4123

	CI-AKI	2.1660	0.2694	2.0840	2.2479	1.8021	2.6489
IGFBP-7 post PCI ng/ml	Non-AKI	1.3259	0.2356	1.2542	1.3975	0.9992	1.8033
	CI-AKI	2.4684	0.3737	2.3548	2.5821	1.9002	3.0170
IGFBP-7/Cr Pre PCI	Non-AKI	0.1055	0.0270	0.0973	0.1137	0.0199	0.1681
	CI-AKI	0.1946	0.0351	0.1840	0.2053	0.1245	0.2524
IGFBP-7/Cr Post PCI	Non-AKI	0.1026	0.0273	0.0943	0.1108	0.0077	0.1503
	CI-AKI	0.1389	0.0259	0.1311	0.1468	0.1026	0.1714

Creatinine is a widely used marker of kidney function, but its levels may not rise until later stages of kidney injury. The use of ratios in biomarker analysis for contrast-induced acute kidney injury (CI-AKI) offers several advantages, primarily due to their ability to integrate multiple physiological parameters into a single, interpretable metric. This approach enhances the predictive accuracy and clinical utility of biomarkers, facilitating early detection and intervention in CI-AKI.(8–10)

The serum level of IGFBP-7 in CI-AKI patients (2.166 ng/ml) was significantly higher ($p<0.001$) than that of non-AKI patients (1.073 ng/ml). This result indicated that the serum level of IGFBP-7 can be used as a prediction marker for early detection of suspected CI-AKI patients. This result come in accordance with many studies which have been proposed as diagnostic tools for predicting AKI, diagnosing AKI, and estimating AKI severity in a laboratory test called NephroCheck (11–13) .

The serum level of IGFBP-7 in CI-AKI patients (2.468 ng/ml) was significantly higher ($p<0.001$) than that of non-AKI patients (1.325 ng/ml). This result indicated that the serum level of IGFBP-7 can be used as a diagnostic marker for diagnosis of CI-AKI patients. IGFBP-7 is predominantly expressed in cells derived from proximal convoluted tubules, Wang et al demonstrated that the overexpression of IGFBP-7 significantly induced cell cycle arrest at the G1-G0 phases and promoted apoptosis(14–16).

It appears from table (2) and figure (1) that the area under the ROC curve (AUC) of **IGFBP-7** was **0.997**. The cut-off Ct value chosen was **1.807 ng/ml,** it has a sensitivity of **97%** and specificity of **90%**, it was appeared to has optimal sensitivity to predict CIN and optimal specificity to exclude those who are not in the risk of getting CI-AKI

It appears from table (2) and figure (1) that the area under the ROC curve (AUC) of **IGFBP-7/Cr** was **0.947**. The cut-off Ct value chosen was **0.1492,** it has a sensitivity of **99**% and specificity of **97%**, it was appeared to has optimal sensitivity to predict CIN and optimal specificity to exclude those who are not in the risk of getting CI-AKI.

Table2: ROC plot assessment of IGFBP-7 and IGFBP-7/Cr as predictive markers

Markers		AUC	Cut-off value	sensitivity	specificity
IGFBP-7	Predictive	0.997	1.807 ng/mL	97%	90%
IGFBP-7/Cr	Predictive	0.947	0.1492	99%	97%

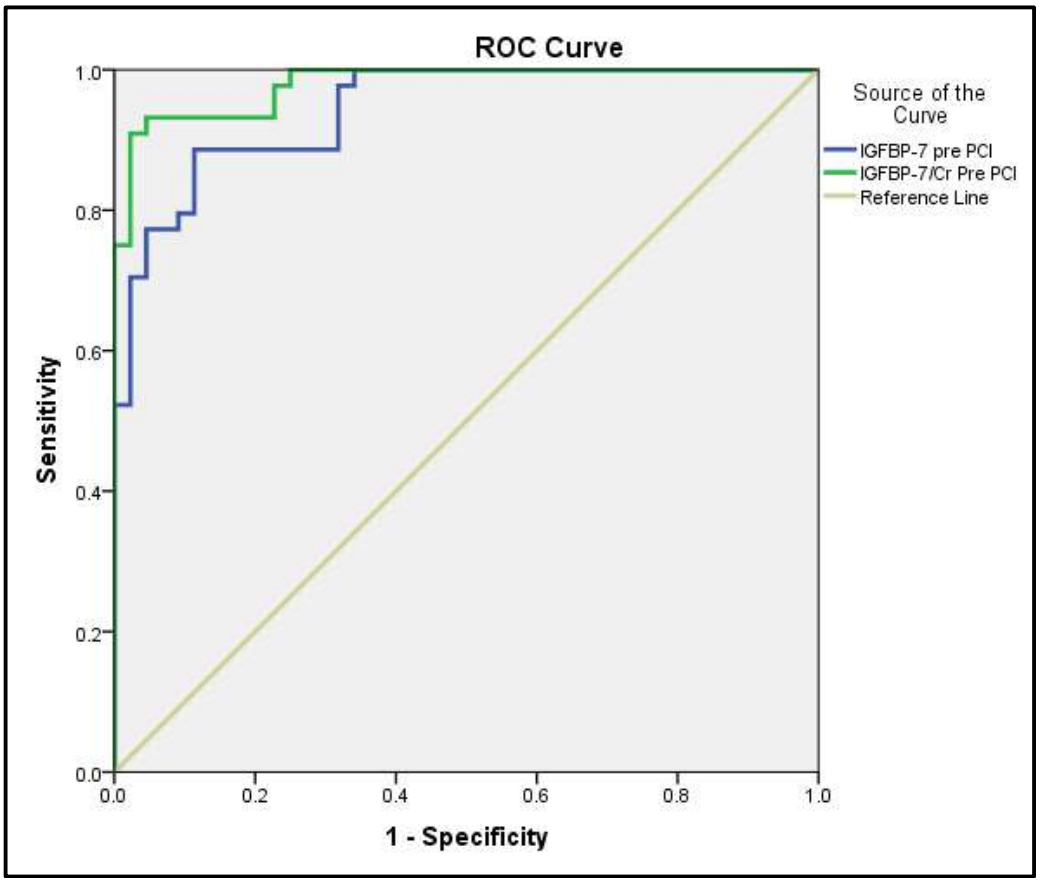

Figure (1): The ROC Plot for IGFBP-7 and IGFBP-7/Cr before PCI

Discussion

The role of Insulin-like Growth Factor Binding Protein 7 (IGFBP-7) in predicting Contrast-Induced Acute Kidney Injury (CI-AKI) is increasingly recognized due to its potential as a biomarker for early detection and risk stratification. IGFBP-7, when combined with TIMP-2, has been shown to significantly improve the prediction of CI-AKI. In a study involving cardiac patients, the product of IGFBP-7 and TIMP-2 concentrations in urine was found to be a reliable indicator of CI-AKI risk(17). This combination outperformed the individual biomarkers, highlighting the synergistic effect of using both markers together.

The ability of IGFBP-7 to predict CI-AKI early is crucial, as it allows for timely intervention. In pediatric patients, urinary levels of IGFBP-7 and TIMP-2 increased significantly within hours of contrast medium administration, providing a window for preventive measures(18,19). This rapid response is advantageous over traditional markers like serum creatinine, which often lag actual kidney damage.

IGFBP-7 is involved in cell cycle regulation, which is a key mechanism in the pathogenesis of AKI. It acts by inducing G1 cell cycle arrest, thereby protecting renal cells from further damage. This mechanism underpins its role as a biomarker, as elevated levels of IGFBP-7 reflect early cellular responses to nephrotoxic insults(20) .

The clinical utility of IGFBP-7 extends beyond prediction to include risk stratification and management of CI-AKI. By identifying high-risk patients, clinicians can implement strategies such as hydration and avoidance of nephrotoxic agents to mitigate the risk of kidney injury. This proactive approach is essential in settings like cardiac surgery, where the risk of AKI is heightened(21).

Furthermore, integrating IGFBP-7 measurement into clinical practice could improve patient management. Unlike traditional biomarkers, which often respond to substantial renal damage, IGFBP-7 can provide an early warning signal, facilitating timely interventions such as hydration protocols or adjustments in contrast media usage(4). This proactive approach could lead to improved patient outcomes and reduced healthcare costs associated with severe AKI(22-24).

Conclusion

The elevation of serum IGFBP-7 levels in CI-AKI patients highlights its potential as a novel biomarker for early detection and risk assessment. Future research should focus on validating these findings and establishing standardized cutoff values for clinical use.

Ethical approval:

The local ethics committee in University of Babylon reviewed and approved of the study protocol and consent form according to the document number (Ref. 444, 7.8.2023).

Conflict of interest

No potential conflict of interest relevant to this manuscript was reported.

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