

The Predictive Utility of the [Tissue Inhibitor of Metalloproteinases-2 * Insulin-like Growth Factor Binding Protein 7] Index for the Detection of Subclinical Kidney Injury in Patients with Inflammatory Bowel Disease

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Abstract

Background	Early detection of renal stress in patients with inflammatory bowel disease (IBD) is crucial to prevent progression to overt kidney injury. The tissue inhibitor of metalloproteinases-2 (TIMP-2) * insulin-like growth factor binding protein 7 (IGFBP7) index has been proposed as a sensitive, non-invasive biomarker for subclinical renal involvement.
Objective	To assess the utility of the TIMP-2 * IGFBP7 index as a marker of renal stress by comparing its levels between patients with IBD and healthy controls.
Methods	A case-control study was conducted at the Department of Chemistry and Biochemistry, College of Medicine, Al-Nahrain University from December 2024 to March 2025, including 60 patients with IBD and 60 age- and sex-matched healthy individuals. Disease activity was assessed using the Mayo Score for ulcerative colitis and the Crohn's disease activity index for Crohn's disease. Serum levels of TIMP-2 and IGFBP7 were measured and compared between groups. Receiver operating characteristic analysis was performed to evaluate discriminative power.
Results	TIMP-2 * IGFBP7 index was significantly higher in patients (0.207 ± 0.1166) compared to controls (0.16 ± 0.11 , $p = 0.0185$). TIMP-2 alone showed a significant elevation, while IGFBP7 index did not differ between groups. Receiver operating characteristic analysis indicated moderate discriminative ability (area under curve = 0.59). Patients with active disease demonstrated higher index levels than those in remission, suggesting a potential association with ongoing intestinal inflammation.
Conclusion	The TIMP-2 * IGFBP7 index is non-invasive marker of early renal stress in patients with IBD. However, its moderate discriminative performance suggests that it should be interpreted in conjunction with other clinical and laboratory parameters.
Keywords	Inflammatory bowel disease, subclinical kidney injury, tissue inhibitor of metalloproteinases-2, insulin-like growth factor binding protein 7, index

List of abbreviations: AKI = Acute kidney injury, AUC = Area under the curve, CKD = Chronic kidney disease, eGFR = Estimated glomerular filtration rate, IBD = Inflammatory bowel disease, IGFBP7 = Insulin-like growth factor binding protein 7, ROC = Receiver operating characteristic, TIMP-2 = Tissue inhibitor of metalloproteinases-2, TIMP-2 * IGFBP7 = The composite index

Introduction

The term inflammatory bowel disease (IBD) refers to the disorder when the gastrointestinal system experiences idiopathic, chronic, recurrent inflammation. Crohn's disease (CD) and ulcerative colitis (UC) are the two most common IBD. While UC only

affects the colon, the CD can affect any part of the gastrointestinal tract, including the mouth and the anus. Nevertheless, CD typically affects the colon and/ or small intestine. IBD significantly increases morbidity and lowers quality of life, typically without altering mortality ⁽¹⁾.

Renal involvement in IBD is often multifactorial. It may result from chronic systemic inflammation, dehydration, drug-induced nephrotoxicity (particularly from amino salicylates or biologics), immune complex deposition, or metabolic disturbances. Importantly, many of these alterations can occur without overt clinical symptoms, leading to subclinical kidney injury that remains undetected by conventional renal biomarkers such as serum creatinine and estimated glomerular filtration rate (eGFR) ^(2,3). These traditional markers reflect glomerular filtration rather than early tubular dysfunction, thus failing to identify renal stress before irreversible damage develops.

In recent years, the focus has shifted toward biomarkers of early tubular cell injury, capable of indicating renal stress before functional loss becomes apparent. Among the most promising are tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7). Both are secreted by renal tubular epithelial cells in response to injury or metabolic stress, where they mediate G1 cell-cycle arrest to prevent propagation of damaged cells ⁽⁴⁾. The TIMP-2*IGFBP7 index, derived from their combined concentrations, has been validated as an early predictive biomarker of acute kidney injury in multiple clinical contexts, including sepsis, critical illness, and cardiac surgery ^(5,6).

However, despite their proven reliability in acute settings, the role of the TIMP-2*IGFBP7 index in chronic inflammatory diseases such as IBD remains largely unexplored. Given that IBD involves persistent inflammation, oxidative stress, and immune activation, all of which can impair renal tubular integrity this biomarker index may provide valuable insights into

subclinical renal involvement before the appearance of clinically detectable kidney injury.

Therefore, the present study aims to evaluate the predictive utility of the combined TIMP-2*IGFBP7 index for the detection of subclinical kidney injury in patients with IBD compared to healthy controls. Additionally, the study explores associations between hematological parameters (such as anemia and leukocytosis) and electrolyte disturbances with renal stress and systemic disease activity, thereby providing a more comprehensive understanding of the renal consequences of IBD.

Methods

Study design

A case-control study was conducted at the Department of Chemistry and Biochemistry, College of Medicine, Al-Nahrain University, Baghdad, Iraq from December 2024 to March 2025, including 60 IBD patients and 60 healthy controls. Samples were collected from Al-Imamein Al-Kadhimein Medical City and the Gastroenterology and Hepatology Hospital in the Medical City Complex.

Inclusion criteria

Adult patients aged 20–55 years with a firm diagnosis of CD or UC on clinical, endoscopic, and histological basis.

Exclusion criteria

Evidence of pre-existing chronic kidney disease (CKD), autoimmune disease, hypertension, diabetes mellitus, cardiovascular disease, liver disease, pregnancy, thyroid disease, or recent surgery.

Sample preparation and laboratory analysis methods

A total of 2 ml of venous blood was collected from each participant and transferred into gel separator tubes. Blood samples were allowed to clot at room temperature for 20 min and then centrifuged at 2000 xg for 10 min. The

separated serum was aliquoted and stored at -20°C until analysis. Serum levels of TIMP-2 and IGFBP7 were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits supplied by SunLong Biotech Co., Ltd. (TIMP-2: Cat. No. SL1712Hu; IGFBP7: Cat. No. SL3534Hu) according to the manufacturer's instructions.

The TIMP-2*IGFBP7 index was calculated to evaluate the risk of early kidney injury, and eGFR was determined using the CKD Epidemiology Collaboration (CKD-EPI) equation to classify stages of kidney function.

Consent and ethical clearance

The study entailed taking samples of the venous blood of IBD patients and controls. The patients were well educated on the purpose and method of the study and were all presented with informed written consent prior to taking the samples. The study protocol was scrutinized and cleared by the College of Medicine, Al-Nahrain University. The research was conducted in accordance with national and international ethical standards of human subject research to provide protection, confidentiality, and dignity to all concerned.

Statistical analysis

The mean and standard deviation (SD) of the data are shown. The statistical software for the social sciences (SPSS version 25) was used to conduct the statistical analysis. To ascertain the statistical significance between the groups, an unpaired t-test was used. The thresholds of 0.001 and 0.05 were employed to ascertain statistically significant variations.

Results

The demographic characteristics of the study participants are presented in table (1). A total of 120 samples were included in the study, comprising 60 patients diagnosed with IBD and 60 healthy controls. The demographic characteristics of the participants were evaluated by comparing age, body mass index (BMI), and sex between the two groups. As shown in table (1), no statistically significant differences were observed between the IBD and control groups in terms of age (IBD: 37.18 ± 10.72 vs. Control: 39.52 ± 9.64 , $p = 0.21$) or BMI (IBD: 21.9 ± 3.29 vs. Control: 21.93 ± 3.43 , $p = 0.96$). Regarding sex distribution, the IBD group included 20 males (33.3%) and 40 females (66.7%), while the control group included 22 males (36.7%) and 38 females (63.3%). The difference in sex distribution between the two groups was not statistically significant ($p = 0.702$).

Table 1. Demographic characteristics between inflammatory bowel disease and control groups

Variable		IBD N = 60 Mean $\pm$ SD	Control N = 60 Mean $\pm$ SD	P value
Age (yrs)		37.18 $\pm$ 10.72	39.52 $\pm$ 9.64	0.21
BMI (kg/m ²)		21.9 $\pm$ 3.29	21.93 $\pm$ 3.43	0.96
		N (%)	N (%)	
Sex	Male	20 (33.3)	22 (36.7)	0.702
	Female	40 (66.7)	38 (63.3)	

As shown in figure (1), levels of TIMP2 were significantly elevated in the IBD group (113.47 ± 38.32) compared to controls (98.98 ± 38.72), with a p value of 0.04. However, as illustrated in figure (2), there was no significant difference in IGFBP7 levels between

the two groups (1.81 ± 0.74 vs. 1.54 ± 0.74 ; $p = 0.5$). Furthermore, the composite TIMP2*IGFBP7 index, shown in figure (3), was also significantly elevated in the IBD group (0.21 ± 0.17) relative to the control group (0.16 ± 0.11), with a p value of 0.019.

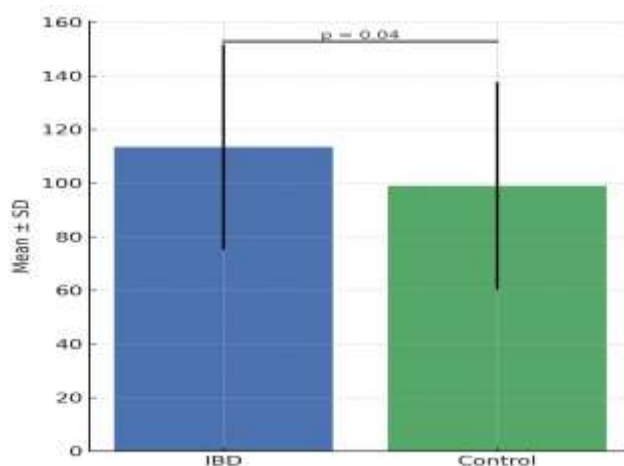


Figure 1. Comparison of TIMP2 between inflammatory bowel disease and control groups

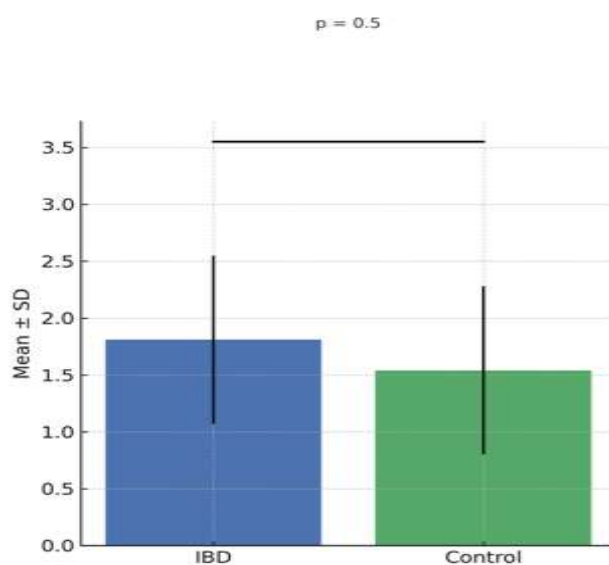


Figure 2. Comparison of IGFBP7 between inflammatory bowel disease and control groups

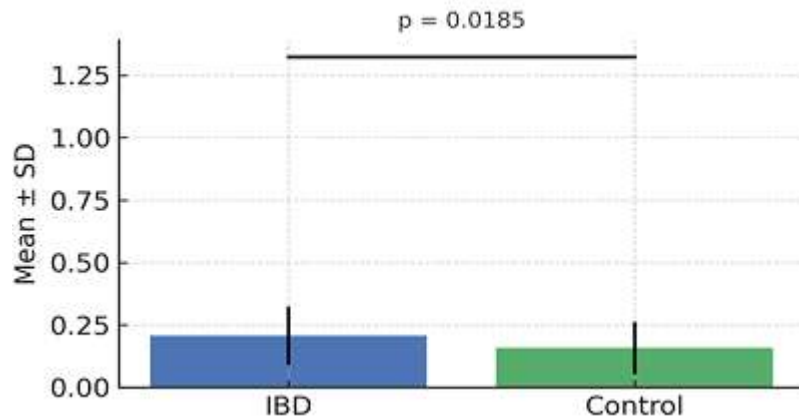


Figure 3. Comparison of (TIMP2*IGFBP7) Index between inflammatory bowel disease and control groups

Table (2) summarizes the receiver operating characteristic (ROC) analysis conducted to evaluate the diagnostic performance of TIMP2, IGFBP7, and the composite TIMP2*IGFBP7 index in distinguishing IBD patients from healthy controls. The area under the curve (AUC) values were used to assess the discriminatory ability of each biomarker. TIMP2 alone demonstrated the highest diagnostic performance, with an AUC of 0.636. The

composite TIMP2*IGFBP7 index showed an AUC of 0.59. At an optimal cut-off value of 0.183, the composite index showed a sensitivity of 63.0% and a specificity of 60.0%, with a positive likelihood ratio (LR+) of 1.58 and a negative likelihood ratio (LR-) of 0.62. IGFBP7 had the lowest AUC at 0.573, indicating limited diagnostic utility when used individually (Figure 4).

Table 2. ROC Analysis Summary of Biomarkers

Biomarker	AUC	Optimal cut-off	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
TIMP2 (ng/ml)	0.636	106.2	60.0	58.0	1.43	0.69
IGFBP7 (ng/ml)	0.573	1.67	56.0	54.0	1.22	0.81
TIMP2*IGFBP7 Index	0.59	0.183	63.0	60.0	1.58	0.62

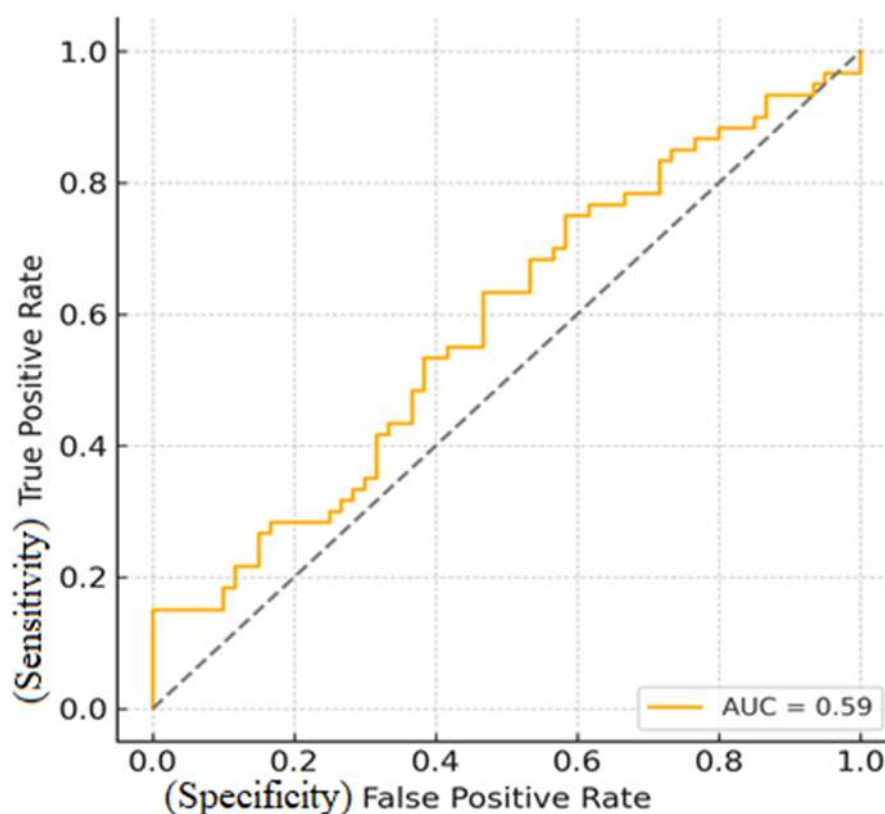


Figure 5. ROC curve for TIMP2*IGFBP7 index

Discussion

Early detection of renal stress in IBD is essential, as conventional renal tests may not identify early tubular injury. The biomarkers TIMP-2 and IGFBP7 represent sensitive indicators of renal epithelial cell cycle arrest and early kidney damage ^(7,8). The combined TIMP-2*IGFBP7 index has demonstrated higher diagnostic sensitivity than individual markers in identifying subclinical tubular injury ⁽⁹⁻¹¹⁾.

Significant elevation of TIMP-2 and the composite index in IBD patients compared with controls confirms the diagnostic potential of this biomarker panel for detecting renal stress before overt dysfunction occurs ^(7,10). This observation supports previous evidence emphasizing the importance of including early tubular stress markers in kidney injury assessment protocols ^(10,12).

IBD involves chronic intestinal inflammation with systemic immune activation and oxidative stress that can extend to renal tissue ⁽¹³⁻¹⁵⁾. Persistent inflammatory mediators contribute

to metabolic stress and microvascular injury, promoting subtle renal impairment even during clinical remission ^(17,18). Psychological burden and reduced quality of life have also been linked to disease activity and systemic inflammatory status, further amplifying renal vulnerability ⁽¹⁶⁾.

Epidemiological analyses have shown a higher incidence of acute kidney injury among IBD patients compared with non-IBD populations, emphasizing the need for early nephrological evaluation ⁽¹⁷⁾.

ROC analysis showed moderate diagnostic performance of the TIMP-2*IGFBP7 index (AUC = 0.59), exceeding that of individual biomarkers TIMP-2 (AUC = 0.636) and IGFBP7 (AUC = 0.573). This result agrees with previous multicenter evaluations demonstrating consistent predictive ability of the index for early kidney injury across inflammatory and critical settings ⁽¹⁸⁾.

Persistent systemic inflammation in IBD may contribute to ongoing immune activation and

the development of extra intestinal manifestations, even in patients receiving treatment⁽¹⁹⁾. Continued biomarker monitoring is therefore necessary to detect early renal changes and prevent progression to irreversible damage.

In conclusion, patients with IBD exhibited significant elevations in TIMP-2 and the composite TIMP-2*IGFBP7 index, indicating the presence of subclinical renal stress despite preserved conventional renal function. The TIMP-2/IGFBP7 index may serve as a potential non-invasive biomarker for the early detection of renal involvement in patients with IBD. However, its moderate diagnostic performance suggests that it should be interpreted in conjunction with conventional clinical and laboratory parameters. Further large-scale prospective studies are warranted to validate its clinical utility and establish its role in routine IBD management.

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Author contribution

Abduljabar: Sample collection, laboratory investigations, ELISA assays, statistical analysis, data interpretation, and manuscript drafting. Dr. Abbas: Study design, supervised the methodology, reviewed the interpretation of findings, and contributed to the critical revision of the manuscript. Dr. Al-Shammaa: Clinical diagnosis, patients recruitment according to the study criteria.

Conflict of interest

Authors declare that there is no conflicts of interest for this research.

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