Urinary nephrin and alpha one microglobulin as early renal injury biomarkers in patients with inflammatory bowel disease

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Abstract

Background& aim: Inflammatory bowel disease is an idiopathic disease characterized by severe inflammation of the gastrointestinal tract. Renal affection could occur in 4%-23% of patients with inflammatory bowel disease. The study aimed to assess role of urinary nephrin and alpha one microglobulin as early renal injury biomarkers in patients with inflammatory bowel disease

Patients& Methods: In this study, a total of 90 patients with inflammatory bowel disease were enrolled. All patients were subjected to full history and clinical evaluation with baseline laboratory data. In addition to, urinary nephrin and urinary α 1microglobulin were measured.

Results: A total of 19 (21.1%) patients had renal impairment (RI) while the other 71 (78.9%) patients didn't have RI. We found that both groups had insignificant difference as regard different characteristics with exception of patients with RI had lower mean age (30.16 ± 4.06 vs. 37.97 ± 10.42 (years); p< 0.001) and longer duration of disease (5.74 ± 2.58 vs. 2.77 ± 1.81 (years); p< 0.001). Also, patients with RI had significantly higher urinary nephrin (7.33 ± 0.83 (mg/g); p< 0.001) and urinary α 1microglobulin (7.74 ± 0.25 vs. 4 ± 0.56 (mg/g); p< 0.001). Also, we found that at cutoff point > 6.9 mg/g, urinary nephrin had 98.6% accuracy for prediction of RI in patients with inflammatory bowel disease while at cutoff point > 6.1 mg/g, urinary α 1microglobulin had 94.5% accuracy for prediction of renal impairment in patients with inflammatory bowel disease.

Conclusion: Urinary nephrin and α 1microglobulin are promising biomarkers for early detection of renal impairment in patients with inflammatory bowel disease.

Keywords: Urinary nephrin; α 1microglobulin; inflammatory bowel disease; renal impairment

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Introduction

The gastrointestinal system is affected by the chronic, relapsing disorder known as inflammatory bowel disease (IBD). The two main IBD kinds are ulcerative colitis (UC) and Crohn's disease (CD). The likelihood of IBD incidence has been rising globally, with Western nations having the greatest rates (1, 2).

IBD frequently has extraintestinal symptoms (EIMs), which can occur in 6% to 47% of people, and it can affect almost all organ systems. While certain EIMs may come before IBD, the majority always follows the underlying intestinal illness, and its actions have an impact. There is a significant concordance of EIMs among siblings and first degree relatives with IBD, and it appears that developing one EIM increases the risk of developing others. The skin, eyes, joints, and hepatobiliary tract are the most frequently affected organs (3).

In patients with inflammatory bowel disease (IBD), the renal and urine systems are frequently affected. Their reported incidence ranges from 4% to 23%, and it is higher in patients with more severe and protracted diseases. Additional associations between IBD and renal problems have been described in addition to secondary complications like nephrolithiasis, hydronephrosis, and amyloidosis (4).

Although renal involvement is significant, early detection frequently requires a high index of clinical suspicion, and ongoing monitoring is necessary to reduce consequences and recurrences. Some tubular proteins, such asβ-N-acetyl-D-glucosamidase (β-NAG), α1- microglobulin and β2-microglobulin (β2mGLB), have been found to be accurate indirect indicators of renal tubular disease (3, 4).

A relatively small protein called alpha one microglobulin goes through glomerular filtration, reabsorption, and catabolism in the proximal tubules. Therefore, increased urine 1-microglobulin concentration serves as an indicator of proximal tubule dysfunction. Glomerular filtration barrier-related protein alterations in IBD patients have not been thoroughly studied (5, 6).

Nephrin is an important component of the slit diaphragm, which is required for glomerular function. Nephrin inhibits the filtration of big molecules into the urine space, hence preventing proteinuria. Its detectability in glomerular disorders is well proven, and it has the potential to be used as a noninvasive diagnostic biomarker. The loss of nephrin thus indicates a compromise in the structural and functional viability of podocytes (7).

The study aimed to detect renal impairment early in patients with inflammatory bowel disease who had normal renal function tests, with a focus on glomerular filtration barrier injury and tubular injury and their relationship to disease activity, so that proper precautions could be taken to prevent further renal injury later on.

Patients& Methods

Study setting& design

A cross-sectional hospital-based study was carried out at Assiut University Hospitals' Department of Internal Medicine. It was completed between 2020 and 2021.

Inclusion criteria

Patients diagnosed to have inflammatory bowel disease (ulcerative colitis or chron's disease)with age more than 18 years and normal kidney function test

Exclusion criteria

Any patient who met one or more of the following criteria was ruled out:

- symptoms of a urinary tract infection
- history of renal disease
- hypertension
- diabetes mellitus
- usage of nonsteroidal anti-inflammatory medications (NSAIDs) or other nephrotoxic medications rather than those used in IBD therapeutic protocol
- recent pregnancy
- Kidney morphological alterations (as detected by ultrasonography)
- patient unwillingness

Sample size calculation

Total coverage sample where any patient fulfilled the inclusion criteria during the study period was recruited in the study. A total of 90 patients who were proven to have IBD were enrolled in the study.

Methodology

Patients were queried about their symptoms (diarrhea with blood or mucus), abdominal discomfort, vomiting, weight loss, fever extraintestinal signs, fistulas, perianal disease (in CD) , and family history of IBD, celiac disease or colorectal illness) ,abdominal cramps and pain in the right lower abdominal quadrant (common in CD or around the umbilicus) or in the lower left quadrant in moderate to severe UC.

Routine laboratory testing included serum urea and creatinine, liver function tests (transaminases, albumin, and bilirubin), and C-reactive protein (CRP). The estimated glomerular filtration rate (eGFR) was determined using CKD - EPI (chronic kidney disease epidemiology collaboration) equation to determine the degree of renal disease and its stage in those patients, and 24-hour urine collection was performed to estimate albuminuria. Renal ultrasonography and Doppler were used to detect the renal resistive index.

Fresh urine samples were collected from patients for urine analysis and detection of the urinary albumin/creatinine ratio. Collect and centrifuge urine at 1000g for approximately 20 minutes, collect the supernatant carefully, store samples at -80°C. for future assay of α1micoalbumin and nephrin by Sandwich ELISA technique .

Outcome

The primary outcome was to evaluate the prevalence of renal impairment in IBD patients, whereas the secondary outcome was to determine the accuracy of the Urinary 1micoalbumin and nephrin in individuals to indicate renal impairment with IBD.

ETHICAL APPROVAL

This work was performed in conformity with the Code of Good Practice and the Declaration of Helsinki, 7th revision, 2013. Also, approval from the Assiut Faculty of Medicine's Institutional Review Board

The degree was acquired. Clinicaltrials.gov was used to register the study. go along with NCT04282577 is the identifier for this study. Patients signed an informed consent form.

Statistical analysis

SPSS (Statistical Package for the Social Sciences, version 20, IBM, Armonk, New York) was used to gather and analyze data. Quantitative data was expressed as the mean ± standard deviation (SD) and compared to the student t test. Nominal data are represented numerically as frequency (%) and compared using Chi2 test.

Urinary nephrin and alpha one microglobulin correlation with other variables was assessed by Pearson correlation . Receiver operator characteristics (ROC) curve were used to evaluate The diagnostic precision of urine nephrin and alpha one microglobulin In the diagnosis of renal impairment . The level of confidence was retained at 95%, hence the P value was 0.05 is considered significant.

Results

The current study recruited a total of 90 patients with IBD. The study aimed to assess role of urinary nephrin and alpha one microglobulin as early renal injury biomarkers in patients with inflammatory bowel disease. Based on the current study, a total of 19 (21.1%) patients had renal impairment (RI) while the other 71 (78.9%) patients didn't have RI.

Baseline data of the studied patients based on renal impairment (table 1):

Patients with RI had significant lower mean age (30.16 ± 4.06 vs. 37.97 ± 10.42 (years); $p< 0.001$) but both groups of patients had insignificant differences as regard mean body mass index (25.07 ± 3.52 vs. 24.67 ± 2.64 (kg/m^2); $p= 0.40$). Patients with RI had significantly longer duration of disease (5.74 ± 2.58 vs. 2.77 ± 1.81 (years); $p< 0.001$). Majority of patients in both groups (52.6% of those with RI and 73.2% of those without RI) had UC with no significant difference between both groups ($p= 0.07$).

As regard activity of the disease; mild, moderate and severe disease present in 21 (29.6%), 24 (33.8%) and 26 (36.6%) patients without RI, respectively and present in 10 (52.6%), 5 (26.3%) and 4 (21.1%) patients with RI, respectively with no significant difference between both groups ($p= 0.16$).

Thirty-two (45.1%), 29 (40.8%), 29 (40.8%) and 32 (45.1%) patients of those without RI and 11 (57.9%), 5 (26.3%), 11 (57.9%) and 11 (57.9%) patients of those with RI received amino salicylates, steroid, azathioprine and biological therapy, respectively.

Table 1: Baseline data of the studied patients based on renal impairment

	Renal impairment		
	No (n=71)	Yes (n= 19)	*P* value
Age (years)	37.97 ± 10.42	30.16 ± 4.06	< **0.001**
Sex			0.31
Male	33 (46.5%)	7 (36.8%)	
Female	38 (53.5%)	12 (63.2%)	
BMI (kg/m^2)	25.07 ± 3.52	24.67 ± 2.64	0.40
Duration of disease (year)	2.77 ± 1.81	5.74 ± 2.58	< **0.001**
Type of IBD			0.07
Ulcerative colitis	52 (73.2%)	10 (52.6%)	
Crohn's disease	19 (26.8%)	9 (47.4%)	
Therapy			
Amino salicylates	36 (50.7%)	11 (57.9%)	0.38
Steroid	29 (40.8%)	5 (26.3%)	0.18
Azathioprine	29 (40.8%)	11 (57.9%)	0.14
Biological therapy	32 (45.1%)	11 (57.9%)	0.23
Activity of the disease			0.16
Mild	21 (29.6%)	10 (52.6%)	
Moderate	24 (33.8%)	5 (26.3%)	
Severe	26 (36.6%)	4 (21.1%)	

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. **BMI**: body mass index; **IBD**: inflammatory bowel disease

Baseline laboratory data in studied patients based on RI (table 2):

Both groups of patients with or without RI had insignificant differences as regard baseline laboratory data with exception of significantly higher albumin/creatinine ratio among those patients with RI (2339.86 ± 509.11 vs. 7.31 ± 1.154; $p< 0.001$). Patients with RI had significantly higher urinary nephrin (7.33 ± 0.83 (mg/g); $p< 0.001$) and urinary α 1microglobulin (7.74 ± 0.25 vs. 4 ± 0.56 (mg/g); $p< 0.001$) in comparison to those without RI.

Table 2: Baseline laboratory data in studied patients based on RI

	Renal impairment		
	No (n=71)	Yes (n= 19)	*P* value
Hemoglobin (gm/dl)	11.36 ± 2.35	11.71 ± 1.99	0.56
MCV (fl)	80.53 ± 12.28	81.84 ± 6.99	0.65
MCH (pg)	28.82 ± 7.78	26.65 ± 3.23	0.23
RDW (%)	15.46 ± 2.93	15.41 ± 2.09	0.94
Leucocytes (10^3/ul)	7.20 ± 2.78	7.84 ± 2.85	0.37
Platelets (10^3/ul)	336.14 ± 104.90	288.37 ± 104.57	0.08

Urea (mg/dl)	4.65 ± 2	5.24 ± 1.47	0.34
Creatinine (mmol/l)	58.32 ± 22.75	62.95 ± 15.81	0.30
ACR	7.31 ± 1.154	2339.86 ± 509.11	< **0.001**
Calcium (mg/dl)	8.67 ± 0.74	8.66 ± 0.57	0.94
Phosphorous (mmol/l)	3.80 ± 0.87	3.62 ± 0.77	0.39
Parathermone (pg/ml)	32.96 ± 4.35	45.72 ± 5.56	0.06
Total proteins (mg/dl)	65.69 ± 9.27	65.04 ± 10.05	0.78
Albumin (mg/dl)	36.46 ± 6.61	38.68 ± 8.01	0.21
ALT (u/L)	24.11 ± 3.45	20.24 ± 3.33	0.17
AST (u/L)	24.48 ± 2.22	21.98 ± 1.01	0.34
Bilirubin (mmol/l)	12.24 ± 1.98	11.09 ± 2.19	0.13
1st h ESR (ml/h)	42.90 ± 12.21	45.89 ± 9.23	0.62
2nd h ESR (ml/h)	67 ± 12.98	68.09 ± 15.58	0.92
CRP (mg/dl)	22.71 ± 2.91	21.21 ± 3.33	0.95
Fecal calprotectin	656.17 ± 123.45	644.17 ± 109.40	0.90
Resistive index	0.65 ± 0.10	0.71 ± 0.12	0.76
Urinary nephrin (mg/g)	3.92 ± 0.72	7.33 ± 0.83	< **0.001**
Urinary α 1microglobulin (mg/g)	4 ± 0.56	7.74 ± 0.25	< **0.001**

Data expressed as mean (SD). *P* value was significant if < 0.05. **RI**: renal impairment; **MCV**: mean corpuscular volume; **MCH**: mean corpuscular hemoglobin; **RDW**: red cell distribution width; **ACR**: albumin/creatinine ratio; **ALT**: alanine transaminase; AST: aspartate transaminase; **ESR**: erythrocyte sedimentation rate; **CRP**: C-reactive protein

Correlation of urinary nephrin and α 1microglobulin with other variables (table 3):

It was found that duration of the disease had positive significant correlation with urinary nephrin (r= 0.34, p< 0.001) and urinary α 1microglobulin (r= 0.39, p< 0.001). All other correlations were insignificant.

Table 3: Correlation of urinary nephrin and α 1microglobulin with other variables

	Urinary nephrin	**Urinary α 1microglobulin**
Age (years)	-0.23 (0.16)	-0.14 (0.16)
Body mass index (kg/m^2)	-0.02 (0.79)	0.05 (0.61)
Duration of the disease (years)	**0.34 (< 0.001)**	**0.39 (< 0.001)**
Hemoglobin (gm/dl)	-0.03 (0.98)	0.11 (0.28)
MCV (fl)	0.02 (0.80)	0.03 (0.71)
MCH (pg)	-0.06 (0.54)	-0.08 (0.44)
RDW (%)	0.04 (0.66)	-0.06 (0.95)
Leucocytes (10^3/ul)	0.05 (0.59)	0.06 (0.58)
Platelets (10^3/ul)	-0.01 (0.86)	-0.08 (0.43)
Urea (mg/dl)	0.05 (0.60)	-0.01 (0.91)

Creatinine (mmol/l)	-0.09 (0.37)	-0.02 (0.80)
ACR	0.18 (0.09)	0.16 (0.12)
Calcium (mg/dl)	0.03 (0.97)	-0.03 (0.73)
Phosphorous (mmol/l)	-0.10 (0.33)	-0.11 (0.91)
Parathermone (pg/ml)	0.09 (0.36)	0.26 (0.78)
Total proteins (mg/dl)	-0.04 (0.97)	0.01 (0.92)
Albumin (mg/dl)	0.02 (0.82)	0.10 (0.33)
ALT (u/L)	-0.25 (0.14)	-0.17 (0.16)
AST (u/L)	-0.15 (0.13)	-0.13 (0.20)
Bilirubin (mmol/l)	-0.05 (0.61)	-0.15 (0.13)
1st h ESR (ml/h)	0.06 (0.57)	-0.07 (0.50)
2nd h ESR (ml/h)	0.04 (0.66)	-0.11 (0.29)
CRP (mg/dl)	-0.04 (0.70)	-0.04 (0.71)
Fecal calprotectin	0.01(0.92)	-0.07 (0.49)

Data expressed as *r* (*p*) where *r* indicates to strength of correlation while *p* indicates to significance of correlation and was significant if < 0.05. **RI**: renal impairment; **MCV**: mean corpuscular volume; **MCH**: mean corpuscular hemoglobin; **RDW**: red cell distribution width; **ACR**: albumin/creatinine ratio; **ALT**: alanine transaminase; AST: aspartate transaminase; **ESR**: erythrocyte sedimentation rate; **CRP**: C-reactive protein

Accuracy of urinary nephrin and α 1microglobulin in prediction of RI in patients with IBD (table 4, figure 1):

At cutoff point > 6.9 mg/g, urinary nephrin had 98.6% accuracy for prediction of RI in patients with IBD with area under curve (AUC) was 0.98 while at cutoff point > 6.1 mg/g, urinary α 1microglobulin had 94.5% accuracy for prediction of RI in patients with IBD with AUC was 0.97.

Table 4: Accuracy of urinary nephrin and α 1microglobulin in prediction of RI in patients with IBD

	Urinary nephrin	**α 1microglobulin**
Sensitivity	95%	95%
Specificity	100%	94.4%
Positive predictive value	100%	81.6%
Negative predictive value	98.6%	98.7%
Accuracy	98.9	94.5%
Cutoff point	> 6.9	> 6.1
Area under curve	0.98	0.97
P value	< 0.001	< 0.001

P value was significant if < 0.05. **RI:** renal impairment; **IBD:** inflammatory bowel disease

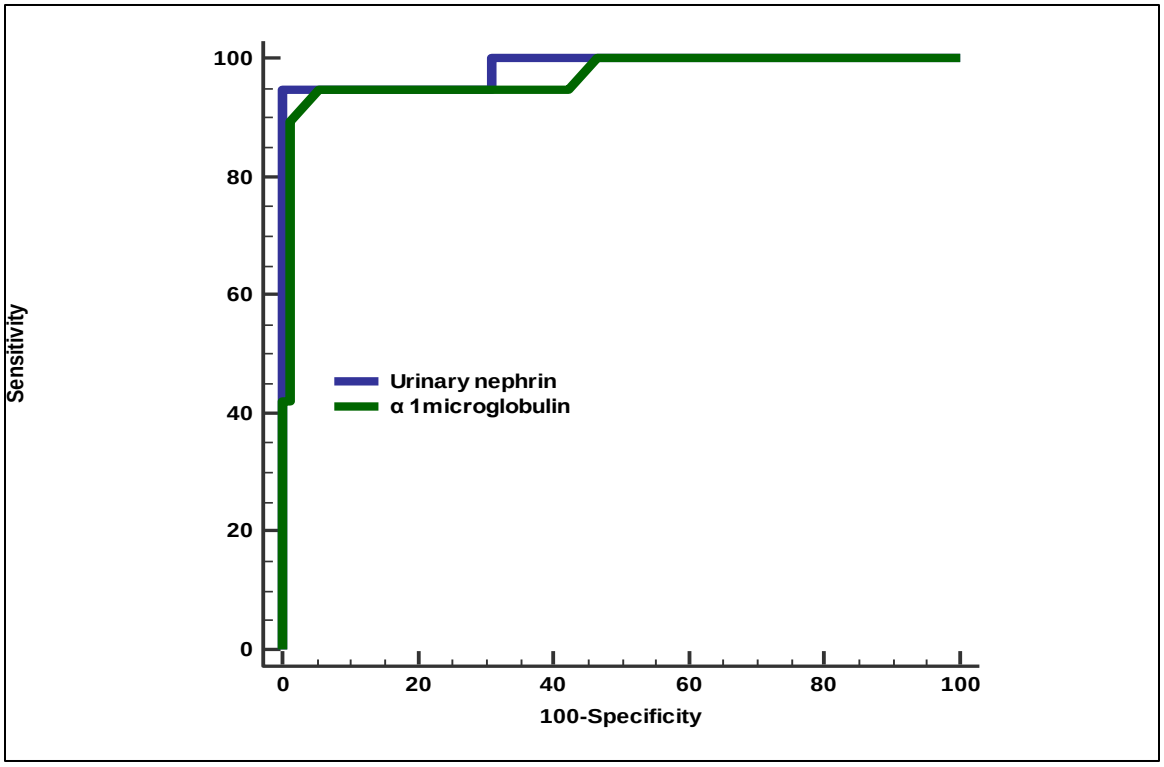

Figure 1: Accuracy of urinary nephrin and α 1microglobulin in prediction of RI in patients with IBD. **RI:** renal impairment; **IBD:** inflammatory bowel disease

Discussion

Kidney disease has been considered as an extraintestinal manifestation in both Crohn's disease and ulcerative colitis. The most common kidney diseases in inflammatory bowel disease patients include Nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis, and amyloidosis(8)

Several biomarkers have been used to detect kidney injury early, but none of them have been proven to be genuinely specific for renal injury. Early detection and intervention in kidney damage reduces mortality advancing harm and lower the risk of complications and death. New biomarkers including urinary nephrin and alpha one microglobulin. can be utilized to predict early renal damage in IBD patients (6, 9).

The current study recruited a total of 90 patients with IBD. The study aimed to assess role of urinary nephrin and alpha one microglobulin as early renal injury biomarkers in patients with inflammatory bowel disease. Based on the current study, a total of 19 (21.1%) patients had renal impairment (RI) while the other 71 (78.9%) patients didn't have RI.

This finding was consistent with earlier findings that estimated renal affection ranged from 6% to 46% of all IBD patients (5, 10, 11). This broad range may be related to varying definitions of renal impairment. studies, study design, sample size and the examined populations.

A retrospective cohort study in Austria discovered renal damage in 11 of 775 IBD patients (2.0%). All of the individuals in that study had CD. Two of the 11 patients with renal disease required regular hemodialysis. This disparity in our study could be attributed to a distinct population, selection bias (they only recruited patients' CD), and varying sample size (12).

In the current investigation, we discovered that patients with RI had a significantly lower mean age (30.16 4.06 vs. 37.97 10.42 (years); p 0.001) and a longer duration of disease (5.74 2.58 vs. 2.77 1.81 (years); p 0.001), but Other baseline data showed no significant differences between groups. Furthermore,There were no significant differences between the groups in terms of activity and disease therapy.

In consistent with the current study, Lewis and colleagues investigated 251 hospitalized patients with IBD and discovered a greater 15.9% frequency of renal insufficiency, with two-thirds of them were chronic. There was no statistically significant difference in frequency between CD and UC patients. Furthermore, patients with RI had considerably longer disease duration. (13). Also, the findings of Primas et al. agreed with those of the current investigation. (14)

The finding that the relation between IBD and CKD weakens with age is demonstrated by Park et al.'s study, which found that being younger than 40 increased the risk of ESRD compared to being 40 or older. The mechanism of decreasing strength of connection between IBD and CKD in the growing age shown in both our study and Park's study is questionable (15).

In agreement with the current study, Vajravelu et al. reported that for people with IBD, common IBD drugs such as 5-ASAs, azathioprine, and methotrexate are not related with reduced eGFR who compared to not receiving those drugs. These findings have significant consequences for clinical practice. Since physicians frequently check the renal function of patients taking 5-ASAs to avoid nephrotoxicity (16).

There are also numerous research looking into various IBD drugs and their link to renal damage, particularly the 5-ASA drugs. The majority of kidney illness usually occurs within the first year of utilizing a 5-ASA, with certain exceptions and the kidney disease appears to be dosage independent (17). Other studies have argued against the role of 5-ASA use in the development of renal disease (18) .so , at present there is no strong agreement in the literature about the nephrotoxic effect of various therapies. in causing RI in IBD patients.

Urinary markers such as alpha-1-microglobulin [alpha-1-M] and N-acetyl-betaD-glucosaminidase [NAG] were used as a non-invasive method to measure renal function in IBD patients. These tubular Enzymes were discovered to be a sensitive and specific screening marker for renal disease in IBD patients . However, they are not yet available as a screening tool and could not identify the precise pattern of renal involvement (4, 19).

In a cross-sectional research, 33.6% of individuals with normal albuminuria had increased -1 microglobulin levels in their urine. This is explained by tubular injury prior to microalbuminuria, which is considerably more sensitive and earlier urine biomarker (20). Furthermore, nephrin is a biomarker of early glomerular injury and linked to podocyte injury. Alteration of nephrine in podocytes in diabetic nephropathy may result in NephrInuria in normoalbuminuric patients before microalbuminuria (21).

We found patients with RI had significantly higher urinary nephrin (7.33 ± 0.83 (mg/g); $p< 0.001$) and urinary α 1microglobulin (7.74 ± 0.25 vs. 4 ± 0.56 (mg/g); $p< 0.001$) in comparison to those without RI. Also, at cutoff point > 6.9 mg/g, urinary nephrin had 98.6% accuracy for prediction of RI in patients with IBD with AUC was 0.98 while at cutoff point > 6.1 mg/g, urinary α 1microglobulin had 94.5% accuracy for prediction of RI in patients with IBD with AUC was 0.97.

To our knowledge, this is the first reported study that determine a cutoff point for urinary α 1microglobulin and nephrin for prediction of RI in patients with IBDs. And yet, there are some limitations in the current study included relatively small sample size and no long term follow of those patients.

Furthermore, the study was conducted in a single tertiary hospital, therefore the IBD patients included in our study may not be representative of the IBD population as a whole. because these patients may reflect patients with a more severe course that necessitates hospitalization than those whose condition is successfully managed with simply an outpatient care .

CONCLUSION:

Renal impairment screening in individuals with inflammatory bowel disease should be done on a frequent basis in patients who have risk factors. Urinary nephrin and 1microglobulin are promising new indicators for the early diagnosis of renal disease in IBD patients . Future multi centers studies to confirm such findings with a large-scale research and a highier number of patients is recommended .

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