Evaluation of Renal Involvement in Inflammatory Bowel Disease

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Abstract:

Background and Aim: Inflammatory bowel disease (IBD) can develop various extra-intestinal manifestations. Renal manifestations develop in 4%-23% of patients with IBD. The study aimed to evaluate renal impairment in patients with IBD.

Patients and Methods: The study enrolled a total of 60 patients with clinical, laboratory, radiological, and/or histopathological evidence of IBD (group A, included 30 patients with renal impairment (CKD group), and group B, included 30 patients with IBD with normal kidney function (Non-CKD group). All patients were subjected to thorough history taking and full clinical evaluation. In addition, reviewing their medical and endoscopic records to assess the severity of the disease. The following laboratory data were done; complete blood count, liver function tests, kidney function tests (blood urea, serum creatinine), urine analysis, 24-hours urinary proteins or urine ALB/Creat ratio, estimated glomerular filtration by Epi equation C3, C 4, ESR, CRP colonoscopy and ultrasound at the beginning of the study and 3rd and 6th month later as follow up.

Results: Both groups (with/without CKD)had insignificant differences regarding baseline and follow-up after 3- and 6-month data, except for significantly impaired kidney function in the renal affection group. Also, patients with renal impairment had significantly longer duration of disease (4.70 ± 2.72 vs. 3.09 ± 1.98 (years). Predictors of renal impairment in patients with IBD were the age of the patients, longer duration of the disease, and amino salicylate therapy.

Conclusion: patients with IBD are at higher risk for the development of renal affection. The predictors for renal enrolment are younger patients with longer duration of the disease and amino salicylates therapy in patients with inflammatory bowel disease.

Keywords: Renal affection; Inflammatory bowel disease; Amino salicylates.

Introduction:

Extra-intestinal manifestations (EIMs) in inflammatory bowel disorders (IBDs) range in prevalence from 6% to 46%. Contributions from genetic variables, pathogenic agents, circulating bacterial endotoxins, and immune-complex deposition are among the mechanisms that have been proposed (1, 2).

Nearly every organ system may be affected by EIMs (3, 4). The current study evaluated the predictors of renal involvement in IBD patients.

Patients and Methods

Study Design and Setting

A retrospective was done in AL Rajhi Liver Hospital at the Internal Medicine Outpatient Clinic and ICU between December 2020 and December 2021.

Target Populations

The study enrolled 60 patients with clinical, laboratory, radiological, and/or histopathological evidence of IBD.

All patients signed informed consent. The study was approved by Assiut Faculty of Medicine, Institutional Review Board (IRB no: 17101369/ 2021).

Those patients were subdivided based on renal involvement into:

- Group A included 30 patients with renal impairment (CKD group).
- Group B included 30 patients with IBD with normal kidney function (Non-CKD group).

Inclusion Criteria

- Age between 18 and 65 years.
- Patient was diagnosed to have IBD based on clinical, laboratory, radiological, endoscopic, and/or histological data.

Exclusion Criteria

- Age > 65 or < 18 years' old
- Hepatitis C virus, hepatitis B virus
- Known CKD before the diagnosis of IBD
- Acute kidney injury
- Nephrotic Syndrome
- Stones

Methodology

All patients underwent full history taking, clinical evaluation, and disease assessment. Liver tests (transaminases, albumin, and bilirubin), Serum electrolytes included sodium, potassium, calcium, and magnesium, and kidney function tests were done (B Urea, S Creat, Urine analysis, Urine Alb/Creat ratio, C3, C4, eGFR, ESR, CRP)

Imaging and Endoscopy

Plain abdominal radiography could delineate if colitis is present and exclude intestinal obstruction or renal stones. Abdominal ultrasound to assess kidneys, colonic distention, or any possible masses. Sigmoidoscopy, colonoscopy with histopathology. In addition, a renal biopsy in patients with renal involvement may be needed.

Follow-up

All patients had laboratory data at the time of diagnosis and followed up after three and six months by blood tests and ultrasound.

Results

Baseline data and disease characteristics of the studied patients at the time of diagnosis (Table 1, Figures 1-2)

Patients with Renal involvement group had significant lower mean age in group (29.27 ± 6.83 vs. 37.26 ± 6.83 (years); p< 0.001), longer duration of disease (4.70 ± 2.72 vs. 3.09 ± 1.98 (years); p = 0.01) and higher frequency of patients who used amino salicylates in IBD with CKD group (60% vs. 20%; p < 0.001).

Table 1: Baseline data and disease characteristics of the studied groups

	IBD with CKD group (n= 30)group (A)	**IBD with no-CKD group (n= 30) group (B)**	***P* value**
Age (years)	29.27 ± 6.83	37.26 ± 9.87	< 0.001
Sex			0.09
Male	15 (50%)	9 (30%)	
Female	15 (50%)	21 (70%)	
BMI (kg/m^2)	26.04 ± 3.96	24.83 ± 2.44	0.15
Diarrhea	10 (33.5%)	9 (30%)	0.10
Extra-intestinal manifestations			
Fatigue	7 (23.3%)	5 (16.7%)	0.06
Arthralgia	5 (16.7%)	4 (13.3%)	0.15
Skin manifestations	3 (10%)	4 (13.3%)	0.25
Sclerosing cholangitis	1 (3.3%)	0	0.10
Duration of disease (years)	4.70 ± 2.72	3.09 ± 1.98	0.01

	IBD with CKD group (n= 30)group (A)	**IBD with no-CKD group (n= 30) group (B)**	***P* value**
Type of IBD			0.19
Ulcerative colitis	20 (66.7%)	24 (80%)	
Crohn's disease	10 (33.3%)	6 (20%)	
Therapy			
Amino salicylates	18 (60%)	6 (20%)	< 0.001
Steroid	10 (33.3%)	10 (33.3%)	0.60
Azathioprine	15 (50%)	12 (40%)	0.32
Biological therapy	15 (50%)	14 (46.7%)	0.50
Duration of Amino salicylates therapy (years)	2.11 ± 1.50	1.45 ± 0.50	< 0.001
Activity of the disease			0.94
Mild	17 (56.7%)	18 (60%)	
Moderate	6 (20%)	6 (20%)	
Severe	7 (23.3%)	6 (20%)	

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

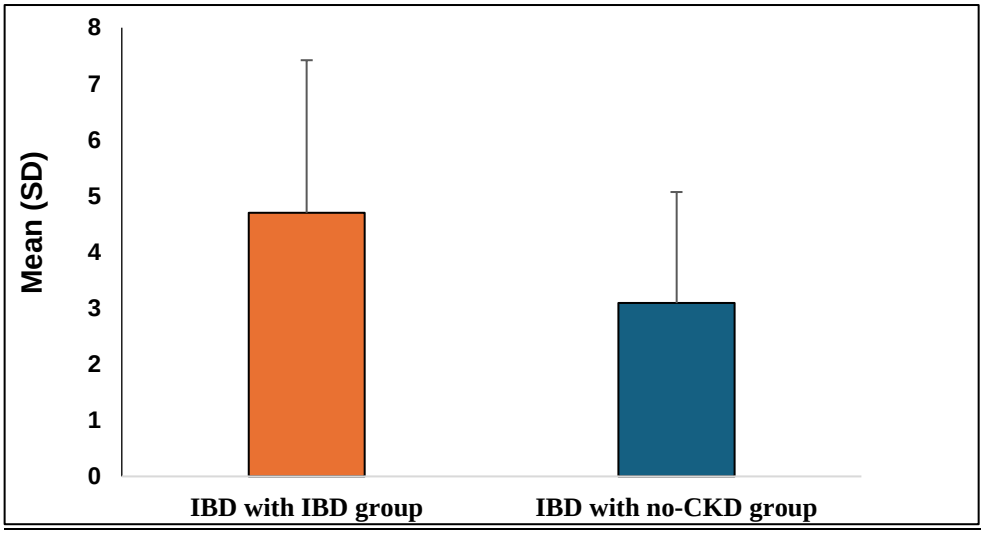

Figure 1: Mean duration of the disease in the two studied groups

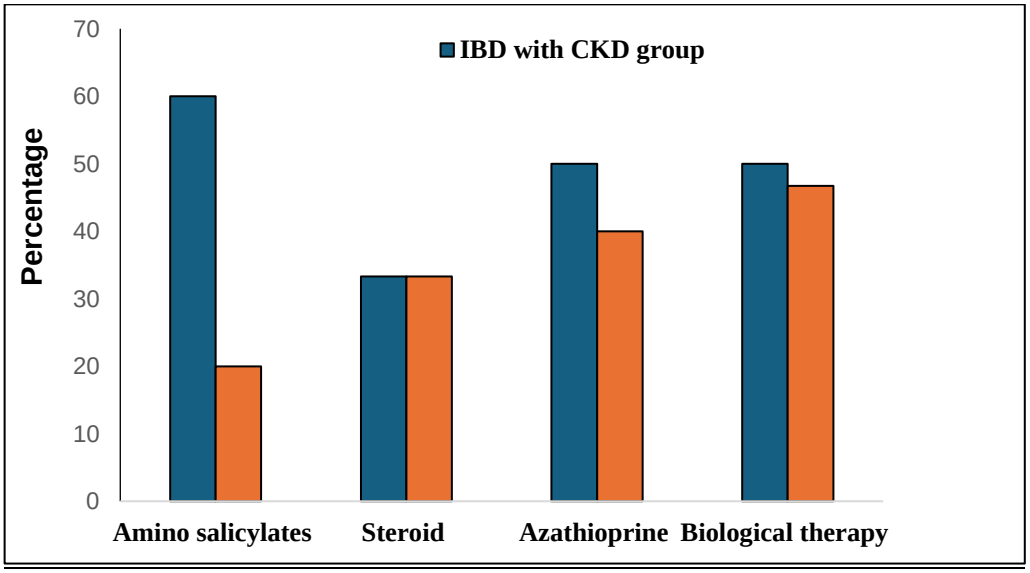

Figure 2: Comparison of the type of therapy in the two studied groups

Baseline laboratory data in the studied groups (Table 2):
Significantly higher creatinine, urea, albumin/creatinine ratio, microscopic hematuria, and albuminuria with significantly lower glomerular filtration rate were noticed in patients with renal impairment.

Table 2: Baseline laboratory data in the studied group

	IBD with CKD group (n= 30) Group (a)	**IBD with no-CKD group (n= 30) Group (B)**	**P value**
Hemoglobin (gm/dl)	11.11 ± 3.90	11.22 ± 1.91	0.78
Leucocytes (10^3/ul)	8.01 ± 2.11	7.84 ± 2.85	0.13
Platelets (10^3/ul)	281.89 ± 59.98	288.37 ± 70.89	0.62
Urea (mg/dl)	33.18 ± 2.34	16.78 ± 1.59	0.01
Creatinine (mg/dl)	2.58 ± .35	.62 ± .15	< 0.001
Albumin/creatinine ratio (mg/g)	2339.86 ± 509.11	7.31 ± 1.154	< 0.001
The number of patients has Proteinuria	25 (83.3%)	0	< 0.001
The number of patients has macroscopic hematuria	7 (23.3%)	5 (16.7%)	0.06
The number of patients has microscopic hematuria	10 (33.3%)	0	0.01
eGFR (ml/minute)	76.01 ± 8.90	101.33 ± 2.33	< 0.001
Decreased eGFR	30 (100%)	0	< 0.001
Total proteins (mg/dl)	75.11 ± 9.27	77.87 ± 9.12	0.56
Albumin (mg/dl)	31.46 ± 6.61	32.68 ± 8.11	0.65
Alanine transaminase (u/L)	34.11 ± 10.55	33.49 ± 2.89	0.23
Aspartate transaminase (u/L)	48.48 ± 6.78	45.45 ± 4.19	0.94
Bilirubin (mmol/l)	12.24 ± 3.53	8.19 ± 4.12	0.37
1st h ESR (ml/h)	60.11 ± 5.98	55.67 ± 3.49	0.08
2nd h ESR (ml/h)	80.98 ± 12.32	89.90 ± 10.34	0.34
C-reactive protein (mg/dl)	23.71 ± 2.11	21.21 ± 3.11	0.99
Stage of CKD			< 0.001
Normal	0	30 (100%)	
Stag I	20 (66.7%)	0	
Stage II	6 (20%)	0	
Stage III	4 (13.3%)	0	
Renal biopsy			
Not done	25 (83.3%)		
Done	5 (16.7%)		
Infected GN	1 (3.3%)		
MPGN	2 (6.7%)		
Tubulo-interstitial nephritis	2 (6.7%)		

Data expressed as mean (SD). *P*-value was significant if < 0.05. CKD: chronic kidney disease; ACR: albumin/creatinine ratio; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; GN: glomerulonephritis; MPGN: membranoproliferative glomerulonephritis

Laboratory data in the studied groups after 3 months (Table 3):
Laboratory data after 3 months are shown in Table 3. Patients with CKD have significantly higher creatinine, urea, and ACR with lower GFR than those without CKD. Other data were comparable between the two groups.

Table 3: Laboratory data in the studied groups after 3 months

	IBD with CKD group (n= 30) Group (A)	**IBD with no-CKD group (n= 30) Group (B)**	***P* value**
Hemoglobin (gm/dl)	11.10 ± 2.88	11.19 ± 1.12	0.78
Leucocytes (10^3/ul)	5.45 ± 2.19	6.01 ± 1.11	0.13
Platelets (10^3/ul)	280.17 ± 59.87	279.78 ± 34.67	0.62
Urea (mg/dl)	30.11 ± 4.78	10.10 ± 2.08	0.01
Creatinine (mg\dl)	1.67 ± .35	.56 ± .23	< 0.001
ACR (mg\g)	1985.56 ± 400.34	6.66 ± 1.11	< 0.001
Proteinuria	27 (90%)	0	< 0.001
Macroscopic hematuria	3 (10%)	1 (3.3%)	0.19
Microscopic hematuria	10 (33.3%)	1 (3.3%)	< 0.001
Active sediment	12 (40%)	2 (6.7%)	< 0.001
eGFR (ml/minute)	77.45 ± 5.55	100.10 ± 2.31	< 0.001
Decrease eGFR	30 (100%)	0	< 0.001
Total proteins (mg/dl)	76.67 ± 9.10	77.11 ± 4.44	0.56
Albumin (mg/dl)	32.13 ± 6.11	33.01 ± 8.09	0.65
ALT (u/L)	32.12 ± 7.66	33.10 ± 5.55	0.23
AST (u/L)	41.23 ± 8.88	42.42 ± 2.65	0.94
Bilirubin (mmol/l)	11.43 ± 1.40	10.11 ± 4.98	0.37
1st h ESR (ml/h)	54.34 ± 3.45	54.33 ± 2.56	0.08
2nd h ESR (ml/h)	70.56 ± 7.67	71.11 ± 4.19	0.34
CRP (mg/dl)	12.45 ± 2.09	10.11 ± 4.33	0.99

Data expressed as mean (SD). *P*-value was significant if < 0.05. CKD: chronic kidney disease; ACR: albumin/creatinine ratio; eGFR: estimated glomerular filtration rate; ALT: alanine transaminase; AST: aspartate transaminase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; GN: glomerulonephritis; MPGN: membranoproliferative glomerulonephritis

Laboratory data in the studied groups after 6 months (Table 4):

Laboratory data after 6 months are shown in Table 4. Up to 90% of those with CKD had proteinuria. Patients with CKD have significantly higher creatinine, urea, and ACR with lower GFR than those without CKD. Other data were comparable between the two groups.

Table 4: Laboratory data in studied groups after 6 months

	IBD with CKD group (n= 30) Group (A)	**IBD with no-CKD group (n= 30) Group (B)**	***P* value**
Hemoglobin (gm/dl)	11.89 ± 2.88	11.55 ± 1.31	0.21
Leucocytes (10^3/ul)	6.01 ± 2.11	7.24 ± 2.09	0.39
Platelets (10^3/ul)	240.34 ± 59.87	250.67 ± 50.11	0.54
Urea (mg/dl)	32.23 ± 4.11	12.89 ± 3.33	0.02
Creatinine (mg\dl)	1.45 ± 0.35	0.76 ± 0.11	< 0.001
ACR (mg\g)	1700.12 ± 400.34	4.50 ± 0.45	< 0.001
Proteinuria	27 (90%)	0	< 0.001
Macroscopic hematuria	3 (13.3%)	1 (3.3%)	0.19
Microscopic hematuria	12 (40%)	2 (6.7%)	< 0.001
Active sediment	12 (40%)	2 (6.7%)	< 0.001
eGFR (ml/minute)	72.40 ± 5.15	101.34 ± 4.33	< 0.001
Decrease eGFR	30 (100%)	0	< 0.001
Total proteins (mg/dl)	72.98 ± 15.56	74.56 ± 4.11	0.45

	IBD with CKD group (n= 30) Group (A)	IBD with no-CKD group (n= 30) Group (B)	*P* value
Albumin (mg/dl)	31.13 ± 4.44	33.11 ± 7.45	0.19
ALT (u/L)	32.89 ± 7.11	34.56 ± 8.12	0.38
AST (u/L)	34.45 ± 8.90	42.11 ± 2.91	0.09
Bilirubin (mmol/l)	12.12 ± 1.23	10.23 ± 4.11	0.11
1st h ESR (ml/h)	34.45 ± 9.87	31.32 ± 5.78	0.56
2nd h ESR (ml/h)	55.56 ± 10.23	50.11 ± 4.67	0.17
CRP (mg/dl)	10.14 ± 2.11	9.09 ± 2.25	0.79

Data expressed as mean (SD). *P*-value was significant if < 0.05. CKD: chronic kidney disease; ACR: albumin/creatinine ratio; eGFR: estimated glomerular filtration rate; ALT: alanine transaminase; AST: aspartate transaminase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; GN: glomerulonephritis; MPGN: membranoproliferative glomerulonephritis

Predictors of renal affection (Table 5):

Predictors of renal disease in patients with IBD were age, disease duration, and amino salicylate therapy

Table 5: Predictors of renal affection in inflammatory bowel disease

Variables	Odds ratio	95%confidence interval	*P* value
Age of diagnosis	3.11	3.01-6.67	< 0.001
Duration of disease	2.22	1.98-4.19	< 0.001
5-amino salicylic acid	2.45	1.56-5.01	< 0.001

P-value was significant if < 0.05

Discussion

Our study was done on 60 patients diagnosed with IBD in AUH from 2020 to 2021, divided into groups A (IBD with CKD group) and B (IBD with no CKD group). All enrolled patients underwent clinical, laboratory, radiological, and colonoscopic evaluation. Many previous reports estimated renal affection was between 6% to 46% of all patients with IBD (5-7). This wide range may be attributed to definitions of renal impairment in different studies, study design, sample size, and the studied populations.

In the current study, patients with CKD had a significantly lower mean age (29.27 ± 6.83 vs. 37.26 ± 6.83 (years); $p< 0.001$). This was consistent with the study of Lewis et al., who found that patients with IBD in the CKD group had a lower mean age (8). An important finding in the current study was that patients with CKD had significantly longer duration of disease (4.70 ± 2.72 vs. 3.09 ± 1.98 (years); $p= 0.01$). In agreement with the current study, a study by Lewis et al retrospectively examined 251 admitted patients with IBD and found a higher 15.9% frequency of renal insufficiency, two-thirds of whom had chronic (9).

We observed that almost all patients in both groups had UC, with no significant difference between groups. Similarly, a case-control study in the United States discovered renal damage in 40 of 251 IBD patients (15.9%). Although more CD patients had kidney disease than UC patients, the rates were not substantially different (18.0% vs 12.0%) (8).

Park et al., on the other hand, disagreed with our findings and claimed that patients with CD were considerably more likely to develop ESRD than individuals with UC and CD without CKD, regardless of age, gender, or comorbidities. However, among CD patients, the risk of ESRD was higher in those who were younger, metabolically fit, and had not been diagnosed with diabetes, hypertension, or dyslipidemia (10).

In disagreement with the current study, an Austrian retrospective cohort study, Primas et al found renal damage in 11 of 775 IBD patients (2.0%). All of the individuals in that study had CD. Two of the 11 individuals with renal disease required hemodialysis regularly. This disparity in our study could be related to a different

population, selection bias (they only recruited patients with CD), and a smaller sample size (11).

In the present research, both groups had minor differences in treatment regimens (p> 0.05), except for a higher frequency of patients using amino salicylates in the IBD with CKD group (60% vs. 20%; p 0.001). Most patients (56.7% in the IBD with CKD group and 60% in the non-IBD with CKD group) had modest disease activity, with no significant difference between the two groups (p= 0.94). This was consistent with several earlier investigations that found 5-ASA nephrotoxic (12-14).

In consistent with our results, Khalifa et al. reported that the predictors of renal disease in individuals with inflammatory bowel disease were younger age of diagnosis (OR= 5.67), longer disease duration (OR= 2.10), and a family history of CKD (OR= 2.10). They discovered that the usage of 5-ASA was not a predictor of CKD in IBD patients (15). Also, **Vajravelu et al.** stated that persons with IBD stated that common IBD medications such as azathioprine and methotrexate are not associated with lower eGFR compared to not using those medications (16).

Several studies have been conducted to investigate various IBD medicinal therapy and their relationship with renal damage, particularly the 5-ASA medicines. Although there were exceptions, most kidney diseases developed within the first year of using a 5-ASA, and kidney disease does not appear to be dose dependent (17). Other studies have argued against the role of 5-ASA usage in causing kidney disease (18). So, currently, there is no clear agreement in the literature about the nephrotoxic effect of different therapies in causing CKD in patients with IBD.

The main findings in the current study were that predictors of renal impairment in patients with inflammatory bowel disease were age of the patients (odds ratio (OR)= 3.11), longer duration of the disease (OR= 2.22), and amino salicylate therapy (OR= 2.45). In accordance with the current study, Lewis et al. stated that young patients with IBD are at risk of developing RI (8). The study's limitations included a small sample size, no long-term follow-up of those patients, and the study was conducted in a single tertiary center, so the patients with IBD used in our study may not be representative of the IBD population as a whole, as these patients may be in other centers. Only five patients had a renal biopsy, while the remaining patients refused. Subnephrotic range proteinuria is present, and a renal biopsy is required. We did not evaluate any potential biomarkers for early identification of CKD in IBD patients. More research is needed to evaluate these points.

The study's strengths include discussing important issues frequently found in clinical practice. Assessment of renal impairment in patients with IBD. We enrolled a control group in the study that enabled us to perform multivariate regression analysis and determine possible risk factors for the development of renal impairment in patients with IBD.

Conclusion

Patients with IBD are vulnerable to developing chronic kidney disease. Younger age, longer duration of IBD, and therapy with aminoacylate are considered for renal affection in such patients. It's recommended that such a study be performed on many patients to confirm these findings.

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