Originalinvestigations/commentaries

Prevalence of non-alcoholic fatty liver diseases in patient with inflammatory bowel diseases attending Assiut University Hospitals

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Abstract. Background and purpose: Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disorder with hepatic fat deposits. Emerging data have highlighted the co-existence of NAFLD and inflammatory bowel diseases (IBDs); both of which are increasingly prevalent disorders with significant complications. This study was designed to evaluate the frequency of NAFLD among patients with IBDs. Methods: Cross sectional study was conducted on a total of 178 patients with IBDs. All participants were subjected to history taking and clinical evaluation including abdominal ultrasound to assess frequency of non-alcoholic fatty liver disease in those patients. Results: Out of those patients, 49 (27.5%) were found to have NAFLD while the other 129 (72.5%) patients didn't have NAFLD based on ultrasound evaluation. Grade of NAFLD among those patients was; grade 1, grade 2 and grade 3 in 37/49 (75.5%), 6/49 (12.2%) and 6/49 (12.2%) patients, respectively. Both groups of patients with and without NAFLD had insignificant differences as regard baseline data with exception of significantly higher frequency of hypertension among patients with NAFLD. Also, those patients had longer duration of the disease and higher frequency of steroid use. Based on the current study, predictors for NAFLD among patients with IBDs were hypertension, disease duration > 5 years, previous flare and steroid therapy. Conclusion: Patients with IBDs are at risk to develop NAFLD that may progress to serious outcomes. So, patients with IBDs should be regularly screened for NAFLD by simple non-invasive methods as abdominal ultrasound.

Keywords: non-alcoholic fatty liver, inflammatory bowel disease, hepatic steatosis, steatohepatitis, liver echogenicity.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disorders ranging from hepatic steatosis to steatohepatitis (NASH) with associated inflammation and may lead to liver fibrosis along with potential progression to cirrhosis, hepatic failure and hepatocellular carcinoma [1].

Liver biopsy has long been the gold standard to assess NAFLD and to stage liver fibrosis but this procedure is invasive, costly and not very practical for screening. Other non-invasive methods to diagnose fatty liver and liver fibrosis have been used including serum biomarkers, ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) [2].

Inflammatory bowel diseases (IBDs) is an increasingly prevalent intestinal disorder with significant co-morbidities. Elevated transaminases in IBDs patients are frequent, with NAFLD being the most common cause. There are some emerging data suggesting an increase in prevalence of NAFLD in IBDs patients compared to the general population. Some have attributed this to a general increase of metabolic syndrome (MS) or the increasingly successful IBD therapy in achieving remission and improved nutritional status [3].

However, the pathogenesis of NAFLD in the IBDs population may be more complex involving disease-specific risk factors, such as chronic inflammation, drug-induced hepatotoxicity, steroid exposure, malnutrition and gut dysbiosis [4]. So, we designed the current work to assess frequency of NAFLD and its predictors among patients with IBDs.

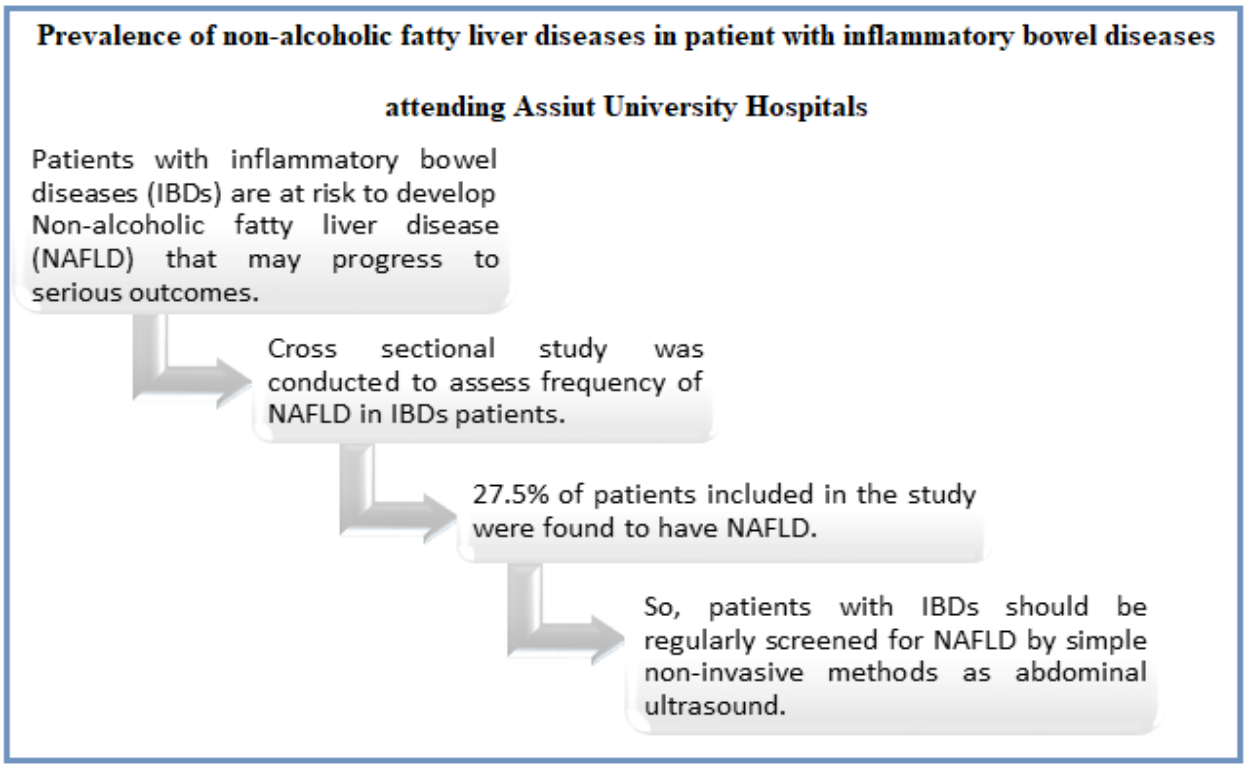

Figure 1. Graphical abstract

Methods

A prospective cross-sectional hospital based study was conducted at IBDs Clinic of Internal Medicine Department in Al Raghy hospital, Assiut University Hospital. Patients with age above of 18 years old and diagnosed to have IBDs; Ulcerative colitis or Crohn's disease (UC or CD) and eligible for biological therapy were recruited in the study. Diagnosis of IBDs was based on clinical, laboratory, radiological, endoscopic and/or histopathological data [5].

Patients with any of the following; diabetes mellitus, secondary cause of NAFLD, mass index exceeded 30 kg/m^2 or alcohol abuse (over 30 and 20 g/day for men and women, respectively) were excluded from the study.

Based on previous reported estimated prevalence of NAFLD in patients with IBDs that was 13.3% [6] in addition to probability error 5% and 80% power on a two-tailed test, a minimum of 178 patients with IBD were needed as an effective sample size for this current issue.

All patients included in the current study were subjected to detailed history taking (age, sex, duration of disease, drug therapy, any previous complications of the IBDs and body mass index) and physical evaluation with strict abdominal and perianal examination. Type of IBD, endoscopic findings and histological findings were recorded.

The results of the following laboratory were collected; liver function tests, complete blood picture, lipid profile and serum creatinine. Also, inflammatory markers were done as erythrocyte sedimentation rate and C-reactive protein

Till now, liver biopsy is considered the gold standard to diagnose NAFLD but secondary to its invasiveness, ultrasonography is a non-invasive test widely adopted for such screening **[7]**. Ultra-sonographic evaluation was performed (after fasting for 8 hours) to assess the presence and severity of NAFLD, using a real-time electronic 3.75 MHz convex-type scanner attached to a high-resolution ultrasound machine (Aplio; Toshiba Medical Systems Corporation, Tochigi, Japan). All the scans were performed by two physicians to avoid inter-observer variability and if there was any mismatching between both of them, the patient was evaluated another senior physician. Those physicians were unaware of the patient's previous medical history or laboratory data.

At enrolment, all subjects underwent abdominal ultrasound examination to estimate the presence and grade of steatosis. Ultrasound diagnosis and grading of steatosis were performed as recently reported by Paige et al [8].

In detail, the presence of hepatic steatosis was based on the evidence of a bright liver ultra-sonographic pattern with increased liver-kidney contrast. Moreover, the grade of steatosis (mild, moderate, and severe) was evaluated as follows [8]:

- Mild grade (grade I): a slight increase in liver echogenicity, a small liver-kidney contrast, and a persistence of echoes from the portal vein walls.
- Moderate steatosis (grade II): posterior echoes attenuation, great liver-kidney echogenicity difference, and loss of echoes from the walls of the portal vein peripheral branches.
- Severe steatosis (grade III): a large decrease in echoes penetration, large liver-kidney contrast, and loss of echoes from the walls of the portal vein main branches.

Ethical Approval

The current study was applied in accordance with Code of Good Practice and the guidelines of Declaration of Helsinki, 7th revision, 2013 and after being approved by the Medical Ethics Committee of the Faculty of Medicine at Assiut University. The study was registered on *clinicaltrials.gov* with Identifier: NCT04328259

The patients' informed written consent

All participants received a written consent form, the consent was clear and indicated the purpose of the study, and their freedom to participate or withdraw at any time without any obligation. It included their agreement for results publication.

Statistical analysis

Data was collected and analysed using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data were expressed in form of mean ± SD or median (range) while nominal data were expressed in form of frequency (percentage).

*Chi*²-test was used to compare the nominal data of different groups in the study while student t-test was used to compare mean of different two groups. Multivariate regression analysis was used to determine the independent risk factors for prediction of NAFLD among patients with IBD. *P* value was considered significant if < 0.05. The level of confidence was kept at 95% hence a P value <0.05 indicated a significant association.

Results

Out of 178 patients with IBD included in the study, 49 (27.5%) patients had NAFLD while the other 129 (72.5%) patients didn't have NAFLD (based on ultrasound evaluation). Demographic data of studied patients are presented in table 1.

Table 1. Demographic data of studied patients [a].

	N= 178
Age (years)	52.17 ± 9.76
Sex	
Male	148 (83.7%)
Female	30 (16.3%)
Body mass index (kg/m^2)	23.13 ± 3.56
Smoking	65 (36.5%)
Hypertension	55 (30.9%)
Residence	
Rural	128 (71.9%)
Urban	50 (28.1%)
NAFLD [b]	
Yes	49 (27.5%)
No	129 (72.5%)

[a] Data expressed as frequency (percentage) and mean ± SD. [b] NAFLD: non-alcoholic fatty liver disease.

Baseline data of patients with NAFLD compared to those without NAFLD:

It was found that hypertension was frequently present in patients with NAFLD with significant difference between both groups (27 (20.9%) vs. 28 (57.1%); $p< 0.001$). All other baseline data were insignificant (table 2).

Table 2. Baseline data of studied patients based on presence of NAFLD [a].

	Development of NAFLD [b]		*P* value
	No (n= 129)	**Yes (n= 49)**	
Age (years)	51.27 ± 12.31	53.57 ± 11.23	0.25
Sex			0.44
Male	108 (83.7%)	40 (81.6%)	
Female	21 (16.3%)	9 (18.4%)	
Body mass index (kg/m^2)	24.03 ± 2.14	22.67 ± 2.51	0.33
Smoking	49 (38%)	16 (32.7%)	0.31
Hypertension	27 (20.9%)	28 (57.1%)	< **0.001**
Residence			0.38
Rural	94 (72.9%)	34 (69.4%)	
Urban	35 (27.1%)	15 (30.6%)	

[a] Data expressed as frequency (percentage), mean ± SD. [b] NAFLD: non-alcoholic fatty liver disease.

Characteristics of the IBD and baseline laboratory data of patients with NAFLD compared to those without NAFLD:

Patients with NAFLD had significantly longer duration of IBD (5.52 ± 2.25 vs. 4.21 ± 2.51 (years); $p< 0.001$). Also, it was found that patients with NAFLD had significantly higher frequency of previous flare (23 (46.9%) vs. 15 (11.6%); $p< 0.001$) and steroid therapy (38 (77.6%) vs. 69 (53.3%); $p< 0.001$) (table 3).

Table 3. Characteristics of the disease among studied patients based on NAFLD [a].

	Development of NAFLD [b]		*P* value
	No (n= 129)	**Yes (n= 49)**	
Disease duration (years)	4.21 ± 2.51	5.52 ± 2.25	< **0.001**
Previous flare	15 (11.6%)	23 (46.9%)	< **0.001**
Type of IBD			0.07
Ulcerative colitis	99 (76.7%)	43 (87.8%)	
Crohn's disease	30 (23.3%)	6 (12.2%)	
Steroid & thiopurine & 5-ASA therapy [c]	72 (55.8%)	15 (67.4%)	**0.01**
Thiopurine & 5-ASA therapy	38 (29.5%)	10 (20.4%)	0.87

Biological therapy	19 (14.7%)	6 (12.2%)	0.37

[a] Data expressed as frequency (percentage), mean ± SD. [b] NAFLD: non-alcoholic fatty liver disease. [c] 5-ASA: Aminosalicylic acid.

Both groups had insignificant differences as regard baseline laboratory date (p> 0.05) with exception of significantly higher alanine transaminase (37.59 ± 11.56 vs. 30.27 ± 16.25 (u/l); p< 0.001) and aspartate transaminase (53.88 ± 15.67 vs. 45.53 ± 26.97 (u/l); p< 0.001) (table 4).

Table 4. Baseline laboratory data in studied patients based on development of NAFLD [a].

	Development of NAFLD [b]		*P* value
	No (n= 129)	**Yes (n= 49)**	
Haemoglobin (g/dl)	11.06 ± 1.91	10.71 ± 1.69	0.26
Leucocytes (10^3/ul)	6.34 ± 2.44	6.86 ± 2.48	0.20
Platelets (10^3/ul)	294.79 ± 110.72	295.80 ± 119.34	0.95
Bilirubin (mmol/l)	8.11 ± 1.95	8.16 ± 3.24	0.89
Alanine transaminase (u/l)	30.27 ± 16.25	37.59 ± 11.56	**< 0.001**
Aspartate transaminase (u/l)	45.53 ± 26.97	53.88 ± 15.67	**0.04**
Serum albumin (g/dl)	33.45 ± 2.34	32.23 ± 1.90	0.09
Serum creatinine (mg/dl)	0.81 ± 0.29	0.85 ± 0.27	0.41
Random blood sugar (mg/dl)	99.95 ± 6.42	101.11 ± 3.33	0.87
Cholesterol (mg/dl)	169.18 ± 32.34	169.40 ± 24.27	0.96
Low density lipoproteins (mg/dl)	105.36 ± 26.67	106.18 ± 22.74	0.84
High density lipoproteins (mg/dl)	48.09 ± 7.46	49.22 ± 8.15	0.37
Triglycerides (mg/dl)	132.41 ± 41.23	125.57 ± 39.73	0.31
ESR (ml/hour)[c]	59.46 ± 29.03	58.08 ± 24.67	0.76
C-reactive protein (mg/dl)	11.83 ± 9.45	11.51 ± 5.67	0.87

[a] Data expressed as mean ± SD. [b] NAFLD: non-alcoholic fatty liver disease; [c] ESR: erythrocyte sedimentation rate.

Grade of NAFLD based on severity of the disease:

It was found that 26/49 (53%) patients with NAFLD have mild/moderate disease severity while 23 (47%) patients with NAFLD had severe disease with statistically insignificant difference between groups with different degrees of diseases severity (*p*=0.55) (table 5).

Table 5. Grade of NAFLD based on severity of the disease [a].

	Severity of the disease		*P* value
	Mild/moderate (n= 26)	**Severe (n= 23)**	
Grade of NAFLD [b]			0.55

Grad-I	21 (80.7%)	16 (69.6%)	
Grade-II	3 (11.5%)	3 (13%)	
Grade-III	2 (7.7%)	4 (17.4%)	

[a] Data expressed as frequency (percentage), mean ± SD. [b] NAFLD: non-alcoholic fatty liver disease

Predictors of development of NAFLD among patients with IBD:

Based on the current study, predictors for NAFLD among patients with IBD were hypertension (odd's ratio (OR)= 6.77, 95% confidence interval (CI)=2.93-15.62, *P*< 0.001), disease duration > 5 years (OR= 2.61, 95%CI= 1.14-5.96, *p*= 0.02), previous flare (OR= 6.17, 95%CI= 2.53-15.04, *p*< 0.001) and steroid therapy (OR= 3.10, 95%CI= 1.27-7.55, *p*= 0.01) (table 6).

Table 6. Predictors of development of NAFLD among patients with IBD.

Predictors	**Odd's ratio**	**95% confidence interval**	***P* value**
Hypertension	6.77	2.93-15.62	< 0.001
Disease duration (>years)	2.61	1.14-5.96	0.02
Previous flare	6.17	2.53-15.04	< 0.001
Steroid therapy	3.10	1.27-7.55	0.01
Abnormal ALT	1.23	0.81-2.22	0.09
Abnormal AST	1.44	0.56-2.88	0.20

Discussion

The study enrolled 178 patients with IBDs based on clinical, laboratory, endoscopic and histopathological data. Out of those patients; it was found that 49 (27.5%) patients were found to have NAFLD. Grade of NAFLD among those patients was; grade 1, grade 2 and grade 3 in 37/49 (75.5%), 6/49 (12.2%) and 6/49 (12.2%) patients, respectively.

In line with the current study; cross-sectional studies reported a prevalence of NAFLD in IBDs ranging between 6.2% and 40% (6, 9-13). This discrepancy is largely owed to different definitions and diagnostic tools adopted for NAFLD and limited reported data about prevalence of NAFLD in patients with IBD [9].

Several studies evaluated NAFLD in IBDs using ultrasonography, which has an 85% (95%CI: 79.5%-88.9%) sensitivity and 94% (95%CI: 87.2%-97%) specificity for NAFLD. A one year, single centre nested case controlled study analysed 928 IBD patients who had any abdominal imaging and found 7.2% had NAFLD. All included patients did not have clinically significant alcohol consumption to minimize confounding appearance of hepatic steatosis on imaging [10].

Several studies have used liver enzymes derangements to detect NAFLD in IBD, which have poor predictive value to exclude NAFLD. A one-year prospective analysis of 200 UC patients found 40% with abnormal liver enzymes, with liver biopsy revealing NAFLD in 11.2% of these patients [11].

A five-year prospective study of IBDs (401 UC, 385 CD) showed 15.3% had abnormal liver enzymes. Ultrasonography of these patients revealed 40.8% had NAFLD, representing 6.2% of all patients. These two studies are also limited by lack of evaluation on relevant confounding factors [12]. Another study demonstrated a higher prevalence (28%) of ultra-sonographic NAFLD in IBD patients compared with non-IBD (20%). Moreover, patients with NAFLD were younger within IBD than non-IBD group [13].

In the current study, we found that both groups of patients based on development of NAFLD had insignificant differences as regard baseline data with exception of significantly higher frequency of hypertension among patients with NAFLD. Also, in the current study mean age of patients with NAFLD was 53.57 (years) and majority (81.6%) of them was males.

In study of Bessissow *et al.* 321 consecutive patients were observed for a median of 3.2 years. A total of 108 (33.6%) patients developed NAFLD. The authors found no significant differences between those with NAFLD and those without NAFLD as regard sex and HTN

but age and BMI of NAFLD were significantly higher. This discrepancy with our study may be due different sample size and studied population [14].

Another study enrolled 302 patients with IBD, 145 (48%) patients were found to have NAFLD. The authors found that both groups of patients based on development of NAFLD had insignificant differences as regard sex and smoking with significantly higher frequency of HTN among NAFLD group. In contrast to our study, they found patients with NAFLD had significantly higher age and BMI [15].

In the current study, patients with NAFLD had significantly longer duration of IBD. Also, it was found that patients with NAFLD had significantly higher frequency of previous flare and steroid therapy. The most frequent type of IBD among both groups was UC (76.7% of those without NAFLD and 87.8% of those with NAFLD) followed by CD (23.3% of those without NAFLD and 12.2% of those with NAFLD) with no significant differences between both groups.

In agreement with the current study, Bessissow *et al*. found that duration of IBD was significantly higher among those patients who developed NAFLD (9.3 vs. 6.5 (years); *p*= 0.02). Also, they found higher frequency of active disease and CD was reported among NAFLD group. In contrast, they stated that both groups had insignificant difference as regard different lines of therapy [14].

Another study found that 157 (52%) of the CD patients had no NAFLD, while mild NAFLD was diagnosed in 54 (18%), moderate NAFLD in 50 (16%), and severe NAFLD in 41 (14%) of the patients. In UC patients, corresponding results were 85 (56%), 30 (20%), 25 (16%), and 13 (8%) [15].

Based on the current study, predictors for NAFLD among patients with IBD were hypertension (OR= 6.77, 95%CI=2.93-15.62, P< 0.001), disease duration > 5 years (OR= 2.61, 95% CI= 1.14-5.96, p= 0.02), previous flare (OR= 6.17, 95% CI= 2.53-15.04, p< 0.001) and steroid therapy (OR= 3.10, 95% CI= 1.27-7.55, p= 0.01).

A one year, single centre nested case controlled study analysed 928 IBD patients who had any abdominal imaging and found 7.2% had NAFLD. Mean age, age at diagnosis, body mass index (BMI) and prevalence of MS were greater in NAFLD patients. Risk factors for NAFLD in IBD were small bowel surgery (OR = 3.7, 95% CI: 1.5-9.3, P = 0.005), hypertension (OR = 3.5, 95% CI: 1.5-8.1, P = 0.004) obesity (OR = 2.1, 95% CI: 1.05-4, P = 0.035) and steroid use at imaging (OR = 3.7, 95% CI: 1.5-9.3, P = 0.005) [10].

Also, NAFLD development was predicted by active disease (HR = 1.58, 95% CI: 1.07-2.33), longer disease duration (HR = 1.12, 95% CI: 1.03-1.23) and prior IBD-related surgery (HR = 1.34, 95% CI: 1.04-1.74). Anti-tumour necrosis factor alpha (Anti-TNFα) therapy trended toward predisposing to NAFLD (HR = 1.69, 95% CI: 0.99-2.9, *P* = 0.056). There was no association between the incident of NAFLD and steroids use [14].

Development of NAFLD was predicted by disease-specific factors including disease activity and duration, and prior surgery. IBD activity has been linked to alteration of gut microbiota. On the same line, NAFLD is associated with increased intestine permeability and small bowel bacterial overgrowth. As such, alteration of gut microbiota may act as a pathogenetic trait d'union between IBD and NAFLD [16].

Duration of IBD was another independent predictor of development of NAFLD. Longer disease duration exposes patients to multiple risk factors for NAFLD, including chronic relapsing inflammation, metabolic comorbidities and hepatotoxic drugs. This finding is in line with previous cross-sectional reports employing imaging and most likely represents a surrogate marker of the severity of the disease, with a more active inflammatory condition. Those patients will also tend to be exposed to hepatotoxic medications repeatedly [10].

Hoffmann *et al*. stated that age, dyslipidemia and BMI in CD patients and BMI and hypertension in UC patients were identified as risk factors in the mixed logistic regression model. Also, in CD patients, higher Harvey Bradshaw Index (HBI), endoscopic disease activity, history of bowel resection(s), and use of azathioprine were risk factors for NAFLD. In UC patients, endoscopic disease activity was significantly associated with NAFLD in the mixed logistic regression model [15].

This study has several strengths, including the longitudinal design, which allowed us to capture dynamic changes, and the well-defined study population. Also, ultrasound examination of every patient was assessed by two physicians to avoid inter-observer variability and if there was any mismatching between both of them, the patient was evaluated another senior physician.

Conclusion

Patients with longer duration of IBDs (> 5 years) should be screened for presence of NAFLD that may progress to serious outcome. Usage of ultrasound is a non-invasive simple tool for detection of NAFLD in such patients. Future studies with the usage of laboratory markers of NAFLD are highly recommended.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mohamed AA Abozaid, Essam Abdelmohsen and Alshymaa Abdelhakam Ahmed. The first draft of the manuscript was written by Shereen MM Abdel Aziz and Hossam Mahmoud Abdelwahab and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations' section

The authors have no relevant financial or non-financial interests to disclose.

Data availability statement: Data will be available at a reasonable request.

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Ethical Approval

The current study was applied in accordance with Code of Good Practice and the guidelines of Declaration of Helsinki, 7th revision, 2013 and after being approved by the Medical Ethics Committee of the Faculty of Medicine at Assiut University. The study was registered on *clinicaltrials.gov* with Identifier: NCT04328259

The patients' informed written consent

All participants received a written consent form, the consent was clear and indicated the purpose of the study, and their freedom to participate or withdraw at any time without any obligation. It included their agreement for results publication.

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