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Frequency of hepatitis C virus infection in patients with pediatric inflammatory bowel disease: a cross-sectional study

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Abstract

Background Patients with pediatric inflammatory bowel disease (PIBD) are believed to be at higher risk of hepatitis C virus (HCV) infection not only due to using of immunosuppressive drugs but also because of repeated blood transfusion and endoscopic and other invasive procedures used for diagnoses and effective controlling of the disease, so this study aimed to assess the frequency of HCV infection, in patients with PIBD at the New Children's Hospital, Cairo University, and identify the potential risk factors.

Methods This cross-sectional analytic study included 165 IBD patients between 1 and 16 years old of both sexes who were attending the Pediatric Gastroenterology Clinic in the New Children's University Hospital, Cairo University. All patients were screened for anti-HCV antibodies using ELISA. Factors related to IBD (severity, modalities of the treatment, and invasive procedures), to infection (blood transfusion history and family history of hepatitis), and liver enzymes were registered. The risk factors were evaluated by multivariate logistic regression analysis.

Results Present and/or past HCV infection was found in five (3%) of the IBD patients. The multivariate logistic regression to detect independent predictors of HCV +ve antibodies patients had statistically significant value with number of hospital admission related to IBD with *p*-value = 0.002, odd ratio (OR) = 1.467, and confidence interval (CI) = 95% (1.145–1.879) and with number of hospital admission unrelated to IBD with *p*-value = 0.024, *OR* = 0.750, and *CI* 95% (0.585–0.963).

Conclusion The frequency of HCV infection in PIBD patients was 3%. Thus, the frequency of HCV infection in PIBD patients is similar to that in the normal population of the developing countries, and it is strongly related to hospital admission due to IBD or non-IBD causes.

Keywords Hepatitis C virus infection, Inflammatory bowel disease

Background

Pediatric inflammatory bowel disease (PIBD), including Crohn's disease (CD), ulcerative colitis (UC), and unclassified IBD (IBD-U), is a disease characterized by chronic inflammation of the gastrointestinal tract with extraintestinal manifestations involving almost all body systems. It is hypothesized to be a result from an interaction between the immune system and environmental risk factors in a genetically susceptible host [1].

The incidence of pediatric IBD started at ≤ 17 years of age; it can be classified according to the age of onset as

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pediatric onset IBD (< 17 years), early onset IBD (< 10 years), very early onset IBD (< 6 years), infantile onset IBD (0–2 years), and neonatal onset IBD [2].

A recent study estimated that in the pediatric population alone, there are approximately 3.5 million children, aged 1–15 years, chronically infected with HCV. Every year, 1.4 million people die from viral hepatitis-related cirrhosis and hepatobiliary carcinoma [3].

Patients with PIBD are believed to be at an increased risk of hepatitis C virus (HCV) infection not only due to using of immunosuppressive drugs but also because of the elevated frequency of endoscopic, surgical, and transfusion procedures needed to effectively control the disease [4].

This study aimed to detect the frequency of HCV infection and its related risk factors in patients with PIBD in the New Children's University Hospital, Cairo University.

Methods

Study design

It is a single-center cross-sectional analytical study.

Sample size

The sample size was calculated as the following:

Alpha (α) 0.05

Estimated proportion (p) 0.125

Estimated error (d) 0.05

Population size (N) 5000

$$n \geq \frac{NZ^2_{1-\alpha/2}\,p(1-p)}{d^2(N-1)+NZ^2_{1-\alpha/2}\,p(1-p)}$$

Using statistics and sample size calculator version 1.01 with confidence interval 95%, estimated error is 0.05, total sample population 5000 patients at Abo El Rich Clinic with expected 400 IBD patients, and minimal sample size needed is 163. So, the sample size was 165 patients [5, 6].

Study participants

We included one-hundred and sixty-five (165) patients (both sexes) aged 1–16 years who were attending the Pediatric Gastroenterology Clinic in Cairo University Children's Hospital, with established diagnosis of IBD based on classic, clinical, endoscopic, and pathological features, collected by convenient sampling between *January 2019* and *December 2020*.

Informed written consent was obtained from all included patients or their legal guardians. Detailed history taking was conducted, including age, residence (urban or rural or slums), onset of IBD, duration and treatment received (steroids, anti-inflammatory, steroid sparing, or biological), number of hospital admissions related and unrelated to IBD, surgery related and unrelated to IBD, endoscopic procedures, family history of hepatitis, and history of blood transfusion.

IBD patients were classified as CD, UC, and IBD-U, using the ESPGHAN "Porto" criteria [7]. The extent of IBD was determined using the pediatric modification of the Montreal classification for IBD (the Paris classification) [8]. Disease activity was calculated by experienced gastroenterologists. The CD activity index was defined using the following scores: < 10, remission; 10–27.5, mild disease activity; 30–37.5, moderate disease activity; and > 40, severe disease activity. The UC disease activity index was defined as follows: < 10, remission; 10–34, mild disease activity; 35–64, moderate disease activity; and > 65, severe disease activity [7].

All patients were evaluated by laboratory tests, including aminotransferase levels (ALT, AST), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GT), total bilirubin, and direct bilirubin. Diagnosis of HCV infection was done by screening PIBD patients using anti-HCV antibodies using ELISA which were detected using Murex anti-HCV (version 4.0). The samples were collected from the patients, while they were on treatment either steroid, steroid sparing, or biological. In Murex, anti-HCV (version 4.0) detects HCV antibodies against NS3, NS4, and NS5 regions of HCV.

Ethical consideration

The study protocol was approved by the Research Ethics Committee of the Pediatric Department, Faculty of Medicine, Cairo University, Egypt (code: Ms-20-2020). The study was conducted in accordance with the Declaration of Helsinki [9].

Statistical analysis

In the present study, data were coded and entered using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, and minimum and maximum in quantitative data and using

frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the nonparametric Mann-Whitney test [10]. For comparing categorical data, chi-square ([2] test was performed. Exact test was used instead when the expected frequency is less than 5 [11]. The receiver operating characteristic (ROC) curve was constructed with area under curve analysis performed to detect best cutoff value of disease duration for detection of HCV. Logistic regression was done to detect independent predictors of HCV [12]. *p*-value less than 0.05 was considered as statistically significant.

Results

This cross-sectional study included 165 patients (of both sexes) who were attending the pediatric gastroenterology clinic with established diagnosis of IBD based on classic clinical, endoscopic, and pathological features collecting them by convenient sampling between January 2019 and December 2020. The mean age of the patients at time of enrollment was 8.65 ± 3.53 years. Ninety-seven patients (58.8%) were males, and 68 patients (41.2%) were females. Sixty-five patients (39.3%) were living in urban areas, 58 patients (35.1%) living in rural areas, and 42 patients (25.4%) living in slum areas. One-hundred and seven (64.8%) patients had ulcerative colitis, while thirty-seven (22.4%) patients had Crohn's disease, and twenty-one (12.7%) had IBD unclassified. The mean age of diagnosis was 5.34 ± 3.45 years, and the mean duration of the disease was 3.31 ± 2.44 years. There were 98.8% patients treated with anti-inflammatory drugs (sulfasalazine or mesalazine), while 53.3% were given steroid-sparing drugs (azathioprine), 14.5% using steroids either parenteral methylprednisolone or oral prednisone, and 15.8% received repeated courses of steroids. There were about 12% patients treated with biological treatment (intravenous infliximab or subcutaneous adalimumab). Liver function tests revealed that twenty-four (14.5%) patients had elevated ALT, seventeen (10.3%) patients had elevated AST, and five patients had direct hyperbilirubinemia (Table 1). Patients with +ve HCV were more likely to have elevated AST than patients with − ve HCV with statistically significant difference (*p*-value = 0.036) as presented in Table 2. In our practice, these patients suffered from elevation of liver enzymes, and they were screened routinely for viral hepatitis, autoimmune hepatitis markers, abdominal ultrasound, and meticulous revision of medications doses especially azathioprine. Furthermore, any laboratory abnormalities were detected and managed accordingly and also referred to hepatologist to deal with. There were 12 patients (7.3%) who had surgeries related to IBD (in the form of colostomy and/or ileostomy with peritoneal irrigation, ileal resection and anastomosis, adhesiolysis, and appendectomy), and 43 (26.1%) had other surgeries unrelated to the disease (in the form of tonsillectomy, adenoidectomy, ophthalmic surgeries, and orthopedic surgeries), and the average number of endoscopic procedures was 2.55 ± 2 as most of included IBD patients underwent at least first diagnostic endoscopy with follow-up. Eighty-seven (52.7%) patients with positive family history of HCV infection in first degree relatives. Thirty-nine (23.6%) patients had blood transfusion since their diagnosis as IBD patients. The mean of number of hospital admissions related to IBD was 2.02 ± 5.09 (either due to clinical relapse necessitating parenteral medication, preoperative preparation, carpopedal spasm, severe anemia, and incompliance to oral medications with clinical deterioration or extraintestinal manifestations precludes the normal activity, e.g., arthritis), while the number of hospital admissions unrelated to IBD was *1.09 ± 5.07* (*either* due to pneumonia or urinary tract infection) and 2.02 ± 5.09, while the mean number of hospital admissions unrelated to IBD was 1.09 ± 5.07 (either due to pneumonia or urinary tract infection). There were five patients positive for HCV antibodies: three of them were old cases on treatment, and the other two patients were newly diagnosed by us and were referred to hepatology outpatient clinic for further investigations and follow-up. One patient was in gray zone and negative results using architect. Four of the positive HCV antibody patients were diagnosed as UC, and one patient was diagnosed as IBD-U. The patients with positive HCV Abs were more likely to have more numbers of hospital admissions related or unrelated to IBD than patients with negative HCV Abs with statistically significant difference *p*-value = 0.004 and *p*-value = 0.022, respectively. IBD patients received steroids, and biological treatment was less likely to have HCV +ve antibody than IBD patients who did not receive steroids and biological

Table 1 Liver function tests in studied group

	Mean ± SD	Median
ALT (U/L)	31.48 ± 50.41	21.00 (9.00–510.00)
AST (U/L)	31.95 ± 32.37	25.00 (13.00–302.00)
GGT (U/L)	17.93 ± 18.86	14.00 (7.00–169.00)
Alk. phosphatase (U/L)	217.58 ± 104.09	204.00 (45.00–725.00)
Direct bil. (mg/dl)	0.17 ± 0.26	0.10 (0.00–2.30)
Total bil. (mg/dl)	0.47 ± 0.45	0.40 (0.10–4.00)

Table 2 Comparison between +ve HCV and −ve HCV patients regarding liver function test

	HCV Ab				
	+ve		−ve		*p*-value
	Mean	Median	Mean	Median	
ALT (U/L)	95.20 ± 147.92	23.00 (15–358)	29.49 ± 44.03	21.00 (9–510)	0.324
AST (U/L)	60.20 ± 48.09	34.00 (24–137)	31.07 ± 31.57	25.00 (13–302)	**0.036**
GGT (U/L)	18.00 ± 6.48	15.00 (12–25)	17.92 ± 19.13	13.50 (7–169)	0.270
Alk. phosphatase (U/L)	156.80 ± 60.11	138.00 (81–234)	219.48 ± 104.71	205.50 (45–725)	0.131
Direct bil. (mg/dl)	0.48 ± 0.85	0.10 (0.1–2)	0.16 ± .21	0.10 (0–2.3)	0.623
Total bil. (mg/dl)	1.18 ± 1.59	0.40 (0.3–4)	0.45 ± .36	0.40 (0.1–3.7)	0.258

Table 3 Comparison between +ve HCV and −ve HCV patients as regards

Treatment modality		+ve HCV		−ve HCV		*p*-value
		No.	Percentage	No.	Percentage	
Anti-inflammatory		5	3.1%	158	96.9%	1
Steroid sparing		4	4.5%	84	95.5%	0.373
Biological		3	15.0%	17	85.0%	**0.013**
Steroids		4	8.0%	46	92.0%	**0.030**
Steroids details	**No**	1	0.9%	114	99.1%	**0.019**
	Once	1	4.2%	23	95.8%	
	Repeated	3	11.5%	23	88.5%	

treatment with statistically significant difference with *p*-value = 0.030, 0.013, respectively (Table 3). Patients with −ve HCV were more likely to have history of surgery related to IBD, blood transfusion, and advanced grade of activity than patients with + ve HCV with statistically significant difference with *p*-value = 0.043, 0.011, and 0.001, respectively (Table 4). Multivariate logistic regression to detect independent predictors of HCV +ve had statistically significant value with number of *hospital admission* related to IBD with *p*-value = 0.002, odd ratio (OR) = 1.467, and confidence interval (CI) = 95% (1.145–1.879) and with number of hospital admission unrelated to IBD with *p*-value = 0.024, *OR* = 0.750, and *CI* = 95% (0.585–0.963) (Table 5).

ROC curve analysis for duration of IBD in years and HCV acquisition shows that 4.1 years or more is the cut-off point with the highest a specificity (*75.6%*) and with a sensitivity of *60%*, and this shows statistically significant *p-value = 0.002* (Fig. 1).

Discussion

In this study, the frequency of HCV infection in PIBD patients was 3% (5/165 patients), while the estimated worldwide prevalence was 2.5% of the population (177.5 million infected adults); this ranges from 1.3% in the Americas to 2.9% in Africa [13].

The prevalence of HCV infection in children and adolescents has been reported to vary from 0.05–0.36% in the USA and Europe to 1.8–5.8% in certain developing countries [14]. However, these reports likely underestimate the true prevalence since current ascertainment practices enable only a small fraction of children expected to be infected with HCV to be identified [15]. Thus, the frequency of HCV infection is similar to that in the normal population; this result is in agreement with the Indian study conducted by Harsh and his colleagues in 2017 [16]. On contrary, Huang with his colleagues in 2014 and Szántó and his colleagues in 2020 reported that none of the patients of inflammatory bowel disease had hepatitis C virus infection [4, 17]. A multicentric study conducted by Martinelli and his colleagues in 2020 revealed that the HCV prevalence is much more higher in the IBD patients than in the normal population [18]. This might be attributed to different factors including duration of disease, time of HCV screening, severity of disease, and frequency of hospital admission.

The mean age of the patients in the present study was 8.65 ± 3.53 years, while Ashton and his collegues in 2019 reported in their study that the mean age of the IBD

Table 4 Comparison between +ve HCV patients and −ve HCV patients (surgical history, family history, blood transfusion history, type of IBD, and disease activity

		HCV Ab				*p*-value
		+ve		−ve		
		No.	%	No.	%	
Surgery-related to IBD		2	16.7%	10	83.3%	**0.043**
Surgery unrelated to IBD		1	2.3%	42	97.7%	1
Family history of hepatitis		3	3.4%	84	96.6%	1
Blood transfusion history		4	10.3%	35	89.7%	**0.011**
		HCV Ab				*p*-value
		+ve		**−ve**		
		No.	%	**No.**	%	
Subtypes	**UC**	4	3.7%	103	96.3%	0.502
	CD	0	0.0%	37	100.0%	
	IBD-U	1	4.8%	20	95.2%	
PCDAI (IBD activity)	**Severe**	0	0.0%	1	100.0%	**0.001**
	Moderate	1	33.3%	2	76.7%%	
	Clinical remission	0	0.0%	42	100.0%	
PUCAI (IBD activity)	**Severe**	0	0.0%	2	100.0%	0.102
	Moderate	3	11.1%	24	88..9%	
	Clinical remission	1	1.1%	89	98.9%	

Table 5 Multivariate logistic regression to detect independent predictors of HCV +ve

		p-value	OR	95% CI	
				Lower	**Upper**
HCV +ve	**No. of hospital admissions related to IBD**	**0.002**	1.467	1.145	1.879
	No. of hospital admissions unrelated to IBD	**0.024**	0.750	0.585	0.963

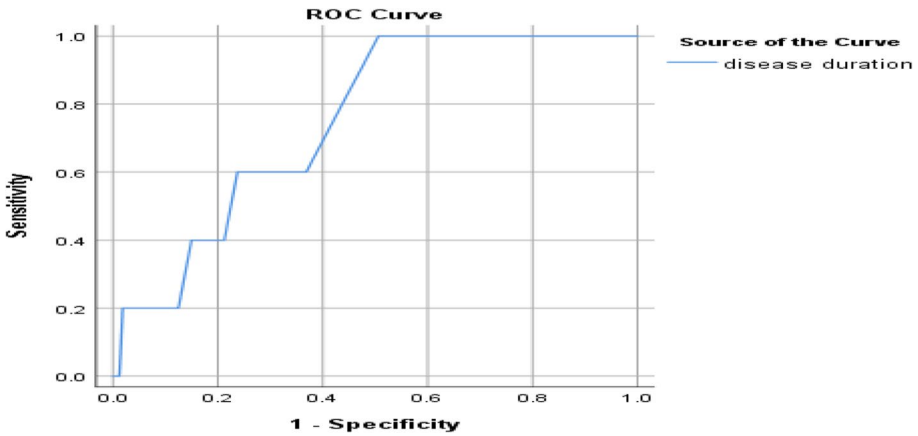

Fig. 1 ROC curve between duration of IBD in years and HCV acquisition

patients was 13.6 years, and it was 6 years in the study of Tse and his collegues in 2021 [19, 20].

In the present study, the mean age of diagnosis was 5.34 ± 3.45 years, while it was lower than other study of Ledder and his colleagues in 2020 about appraisal of the PIBD-classes criteria, who reported that age of diagnosis was 13 ± 3 years [21] and was 10.2 ± 4.1 years in the study of Velasco Rodríguez-Belvís and his collegues in 2020 [22].

Meanwhile, the mean duration of the disease was 3.31 ± 2.44 years in our study, and Mosli and Saadah in 2021 reported in their study that the mean duration of the disease of PIBD patients was 2.1 ± 2.4 years [23] together with another study of Shawihdi and his collegues in 2021 who reported that the mean duration of the disease was 109.5 months (5–540 months) [24].

Regarding the disease classification in our study, the majority of the patients were diagnosed as UC (64.8%), while 22.4% patients had CD, and 12.7% had IBD unclassified.

This is in agreement with the study of Clough and his colleagues in 2021 who reported that 66.7% were diagnosed with UC, 29.8% with CD, and 3.5% with IBD-U [25] and an Egyptian study of El-Shabrawi and his colleagues in 2020 who had different percentages as it revealed that the most of the cases (50%) had UC, (22.9%) had CD, and (27.1%) had IBD-U [6], together with the study of Hussein and his colleagues in 2020 who reported that out of 18 children diagnosed as IBD, 15 of them were diagnosed as ulcerative colitis (UC) and 3 of them diagnosed as Crohn's disease (CD) [26] and also the study of Esmat and his colleagues in 2014 who found that among 157 patients, 135 patients were diagnosed with UC (86% of the total) and 22 patients with CD (14% of the total) [27]. This is in contrary to the study of Koumaki and his colleagues in 2021 reporting mucocutaneous manifestations in patients with inflammatory bowel disease, who reported that 441 (54.7%) patients had Crohn's disease, 352 (43.7%) had ulcerative colitis, and 13 (1.6%) had IBD unclassified (IBD-U) [28]. As regards the PUCAI scoring of the UC patients, most of the patients (91.3%) were in clinical remission during the enrollment, only 2.2% had the disease in the severe form, and 6.5% had moderate disease form. This might be attributed that most of patients were controlled by the treatment. In the present study following the results of Esmat and his colleagues in 2014 who reported that most of the patients (66%) had mild disease, 17% had the disease in the severe form, and 52% had moderate disease form. This is unlike the study of Loras sand his colleagues in 2009 which revealed that 53% of the patients had moderate disease activity and 24% had the severe form, and regarding the course of the disease, the majority of them had a relapsing course (75%) [29]. While the PCDAI scoring of the CD patients, there were two (1.7%) patients who had severe disease, twenty-seven (22.6%) had moderate form and ninety, 75.6% of patients were in clinical remission.

Regarding the risk factors, our study revealed that the patients with positive HCV Abs were more likely to have more number of hospital admissions related or unrelated to IBD than patients with negative HCV Abs with statistically significant difference.

While there was not statistically significant difference between patients with positive HCV Abs and patients with negative HCV Abs as regards age, residence, weight, duration of the disease, and number of endoscopic procedure, the lack of association with endoscopic procedures suggests the existence of adequate preventive measures in centers attending to these patients.

Moreover, patients with −ve HCV were more likely to have history of surgery related to IBD, blood transfusion, and advanced grade of activity than patients with +ve HCV with statistically significant difference

Unlikely, the multicenter Spanish study of Loras and his colleagues (2009) who assessed the factors related to hepatitis B and C in inflammatory bowel disease patients and reported that transfusions and antibiotic use was significantly related to HCV infection [29].

While in the study of Huang and his colleagues (2014), potential risk factors for HCV were not analyzed due to the limited number of HCV-positive patients in the study [4].

Moreover, it was noticed that IBD patients who received steroid and biological treatment were less likely to had HCV +ve antibody than IBD patients who did not receive them. Also, those patients who had repeated courses of steroids were less likely to had positive HCV antibody than patients who did not receive repeated courses of steroids.

This may be explained by the altered immune status of the patients who were already on immunomodulatory and/or anti-TNFα therapy.

These results are in agreement with the Italian study of Losurdo and his colleagues in 2020 which included chronic viral hepatitis in inflammatory bowel disease patients who reported that the patients with HCV +ve antibody were less frequently exposed to infliximab, while no differences were found with other biologic or immunomodulatory drugs [30].

This is not in agreement with the study of Loras and his colleagues (2009) who reported much higher incidence of using steroids (73%) among negative HCV infection patients and (84%) among positive patients and also (79%) of negative patients and (87%) of the positive patients were on immunosuppressive therapy [29].

Conclusion

The frequency of HCV infection in PIBD patients in the current study in the New Children's University Hospital, Cairo University, was 3% similar to the prevalence of HCV infection in children and adolescents of normal population varying from 1.8 to 5.8% in certain developing countries with estimated prevalence in the USA and Europe 0.05–0.36% .Risk factors of HCV infection were number of hospital admission

whether related or unrelated to IBD, while history of operations, blood transfusion history and severity of the disease, corticosteroid, and biological therapy used for treatment were not related to HCV infection in the current study.

Study limitations

It should be considered that IBD patients receiving steroids and immunosuppressive medications with any elevation of liver enzymes should be screened for HCV RNA PCR.

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Authors' contributions
EB collected the data, ST analyzed and interpreted the data, AEE supervised and revised the work, and AA contributes in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Research Ethics Committee, Faculty of Medicine, Cairo University, registration no.: approval code: MS-20-2020. This study was approved by the Ethical Research Committee of Faculty of Medicine Cairo University in Egypt. The ethics committee reference number is not available. A verbal consent was taken from the legal guardians of all patients accepting to participate in our research work. Written approval was taken from ER for asking patients by questionnaire. Also, the study was approved by Ethics Committee of Cairo University Children Hospital. The study has been performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975 and its later amendments. All methods were carried out in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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