Rome IV Diagnostic Criteria for Functional Gastrointestinal Disorders in Patients with Chronic Hepatitis C Virus

Alshymaa Hassnine[1]*, Zeinab Saad[1]

[1] Department of Gastroenterology, and Tropical Medicine, Faculty of Medicine, Minia University, Minia, Egypt

*Corresponding Author:
Alshymaa Hassnine, MD
Department of gastroenterology, and tropical Medicine,Minia University, Minia, Egypt.
Tel: 00201092004294
Email: Alshiamaa.Ahmed@mu.edu.eg

Received: 09 Sep. 2021
Accepted: 01 Feb. 2022
Publieshed: 30 Apr. 2022

ABSTRACT

BACKGROUND:
Patients with chronic hepatitis C virus (HCV) usually have different abdominal complaints without any organic lesions. The functional cause of these complaints is claimed in most patients. This study aimed to evaluate functional gastrointestinal disorders (FGIDs) in patients with chronic hepatitis C using Rome IV diagnostic criteria.

METHODS:
This study included 1506 participants (1006 patients with chronic HCV, and 500 controls). All individuals were subjected to taking thorough medical history, basic investigations (complete blood counts, liver and renal functions tests), international normalized ratio (INR), alpha-fetoprotein, HCV RNA PCR (polymerase chain reaction), abdominal ultrasonography, and upper gastrointestinal tract (GIT) endoscopy for patients only), and Rome IV diagnostic questionnaire.

RESULTS:
Patients with HCV had symptoms of FGIDs including functional dyspepsia (FD) ($P=0.009$), early satiety ($P=0.002$), postprandial distress ($P=0.02$), epigastric pain ($P=0.03$), Inflammatory bowel syndrome (IBS) ($P<0.001$), IBS predominant constipation ($P<0.001$), IBS predominant diarrhea ($P<0.001$), and IBS mixed ($P<0.001$). There were multiple factors for the prediction of FD in patients with HCV, including high body mass index (BMI), education level, positive polymerase chain reaction (PCR), and fibrosis stage. Also, there were multiple factors for the prediction of IBS in patients with HCV, including male gender, high BMI, urban residence, education level, positive PCR, and fibrosis stage.

CONCLUSIONS:
FD is a prevalent finding in obese patients with HCV and with higher fibrosis scores. IBS is also prevalent in male patients with HCV.

KEYWORDS:
Rome IV diagnostic criteria, Hepatitis C virus, Functional gastrointestinal disorders, Functional dyspepsia, Irritable bowel syndromes

Please cite this paper as:
Hassnine A, Saad Z. Rome IV diagnostic criteria for functional gastrointestinal disorders in patients with chronic hepatitis C virus. *Middle East J Dig Dis* 2022;14(2):214-221. doi: 10.34172/mejdd.2022.275.

INTRODUCTION

Hepatitis C virus (HCV) is considered as the main cause of chronic liver disease with nearly 71 million chronically infected patients worldwide in 2017.[1,2] The liver is the main site for replication of the virus, but it can be replicated at other extrahepatic sites.[3,4] Dyspepsia is a very common phenomenon in patients with chronic HCV.[5]

Patients with chronic HCV usually have different upper and lower abdominal complaints. Dyspepsia is very common in patients with chronic HCV with different clinical presentations such as epigastric pain and heart burn.[6] Abdominal pain is usually seen in clinical practice in patients with chronic HCV without any organic lesions. The functional cause of these abdominal complaints is claimed in most of patients.[2,7] Various abnormalities in gastrointestinal function and structure have been studied in patients with chronic liver diseases, such as altered gastrointestinal motility, intestinal permeability, and absorption.[8,9]

Functional gastrointestinal disorders (FGIDs) are classified and diagnosed using the Rome criteria. The criteria may change in time as new scientific data emerge.[10,11] The Rome IV diagnostic criteria were released in May 2016. Now, FGIDs are called disorders of gut-brain interaction.[12] The aim of this study was to evaluate FGID in patients with chronic hepatitis C using Rome IV diagnostic criteria.

MATERIALS AND METHODS

This cross-sectional, observational study involved 1090 patients with chronic HCV, in addition to 500 healthy controls matched for age, gender, and educational level. The patients with chronic HCV were selected randomly from the outpatient clinic of the Tropical Medicine Department, Minia University Hospital. The controls were selected randomly from the relatives of the patients and outpatient clinic. Written informed consent was obtained from all subjects (for both participation and publication of the work).

All individuals (patients and controls) were subjected to:

1) History taking including personal history (name, gender, age, occupation, educational level, residencial status, and body mass index [BMI] symptomatology), medical history stressing on history of diabetes mellitus (DM), lipid disorders, and drug history.
2) Basic investigations including complete blood count (CBC), liver and renal function tests, international normalized ratio (INR), random blood glucose, alpha-fetoprotein, HCV RNA PCR, and abdominal ultrasonography for patients only.
3) Upper gastrointestinal tract (GIT) endoscopy for patients only.

Rome IV diagnostic questionnaire that was downloaded from the Rome Foundation website (http://www.romecriteria.org/questionnaires/): The purpose of that questionnaire is to know more about the health problems that people sometimes have with their intestines and stomach. The questionnaire will take about 15-20 minutes to be completed.

Of the 1090 patients with chronic HCV who were included in the study; 1077 patients fulfilled the criteria for FGID and underwent upper GIT endoscopy (13 patients refused to do upper endoscopy). About 1006 patients had no abnormality in the upper endoscopy and were diagnosed as having FGID, 17 patients had gastroesophageal reflux disease, 22 patients had gastroesophagitis, peptic ulcer was recorded in 4 patients, and 28 patients had esophageal varcies.

The collected data were inserted, tabulated, and statistically evaluated using SPSS software version 24. Quantitative data were expressed as mean±standard deviation (SD), while qualitative data were expressed as proportions. Comparisons between groups for normally distributed quantitative data were performed by using Mann-Whitney test. Qualitative data were analyzed by chi-square (χ^2) test. Statistical significance was defined as P values less than 0.05.

RESULTS

Sociodemographic data for the two groups are shown in Table 1. There was no statistically significant difference between the two groups in regard to the demographic data. The prevalence of the functional gastrointestinal symptoms between the studied groups is shown in Table 2. There was a statistically significant difference between the two groups in regard to the prevalence of the symptoms of FGIDs in patients with chronic HCV including functional dyspepsia (FD) ($P=0.009$), early satiety ($P=0.002$), postprandial distress ($P=0.02$), epigastric pain ($P=0.03$), inflammatory bowel syndrome (IBS, $P<0.001$), IBS constipation ($P<0.001$), IBS diarrhea ($P<0.001$), and IBS mixed ($P<0.001$). Simple and multiple logistic regression for prediction of risk factors for FD in HCV positive patients are shown in Tables 3 and 4. There were multiple risk factors for the prediction of FD in

Table 1. Sociodemographic data of the studied groups

		Control	Cases	*P* value
		N=500	N=1006	
Age	Range Mean±SD	(27-75) 38.4±9	(19-78) 38.4±12	0.911
BMI	Range Mean±SD	(22-39) 26.3±2.4	(20-39) 26.5±±2.6	0.357
Sex	Male Female	370(74%) 130(26%)	741(73.7%) 265(26.3%)	0.887
Residence	Urban Rural	256(51.2%) 244(48.8%)	512(50.9%) 494(49.1%)	0.911
Education	No Yes	296(59.2%) 204(40.8%)	576(57.3%) 430(42.7%)	0.472

Independent samples T test for parametric quantitative data between the two groups.Chi square test for qualitative data between the two groups.
*: Significant level at P value < 0.05

Table 2. Prevalence of the functional gastrointestinal symptoms between the studied groups

		Control	Cases	*P* value
		n=500	n=1006	
Functional dyspepsia syndrome	No	284 (56.8%)	500 (49.7%)	0.009*
	Yes	216 (43.2%)	506 (51.3%)	
Early satiety	No	268 (53.6%)	452 (44.9%)	0.002*
	Yes	232 (46.4%)	554 (55.1%)	
Post-prandial distress	No	282 (56.4%)	504 (50.1%)	0.021*
	Yes	218 (43.6%)	502 (49.9%)	
Epigastric pain	No	296 (59.2%)	536 (53.3%)	0.030*
	Yes	204 (40.8%)	470 (46.7%)	
IBS	No	198 (39.6%)	290 (28.8%)	<0.001*
	Yes	302 (60.4%)	716 (71.2%)	
IBS (sub types)	No	198 (39.6%)	290 (28.8%)	<0.001*
	Constipation	156 (31.2%)	332 (33%)	
	Diarrhea	77 (15.4%)	144 (14.3%)	
	Mixed	69 (13.8%)	240 (23.9%)	

Chi-square test for qualitative data between the two groups
* Significant level at *P* value<0.05

patients with chronic HCV, including high BMI, higher level of education, positive PCR, and FIB4 (fibrosis score 4) (≥3.45) with statistically significant *P* values (0.001, 0.026, 0.001, and 0.001, respectively). Simple and multiple logistic regression for the prediction of risk factors for IBS in patients with chronic HCV are shown in Tables 5 and 6. There were multiple risk factors for the prediction of IBS in patients with chronic HCV such as male gender, high BMI, urban residence, higher level of education, positive PCR, and FIB4 (≥3.45) with statistically significant *P* values (0.002, 0.005, 0.001, 0.001, 0.001, and 0.032, respectively). The prevalence of IBS subtypes between the two groups is shown in Table 2. In patients with chronic HCV and IBS, IBS constipation was the most predominant type (33%) followed by IBS mixed (23.9%), and IBS diarrhea (14.3%).

Table 3. Simple logistic regression for the prediction of risk factors for functional dyspepsia in patients with chronic HCV

Variables		Functional dyspepsia		*P*value
		No	Yes	
		n=500	n=506	
Hemoglobin level	Range	(9-16)	(9-16)	0.534
	Mean±SD	12.5±1.2	12.6±1.3	
Platelets	Range	(3.2-3300)	(13-3870)	0.919
	Mean±SD	331±530.3	351.7±562.7	
	Median	208	206	
Alanine transaminase	Range	(12-171)	(10-170)	0.779
	Mean±SD	31.6±22	32.8±22.3	
	Median	23	25	
Bilirubin	Range	(0.5-2)	(0.2-2)	0.163
	Mean±SD	1±0.1	1±0.1	
Albumin	Range	(3-5)	(3-5)	0.874
	Mean±SD	4.4±0.5	4.4±0.5	
International randomized ratio	Range	(1-1.40)	(1-1.40)	0.136
	Mean±SD	1.06±0.09	1.05±0.12	
Creatinine	Range	(0.2-1.5)	(0.1-1.5)	0.242
	Mean±SD	1±0.1	1±0.1	
Alfa fetoprotein	Range	(1-100)	(1-111)	0.649
	Mean±SD	7.7±8.8	7.1±8.6	
	Median	5	5	
Polymerase chain reaction	Range	(0.3-4.2)	(0-5)	<0.001*
	Mean±SD	2±0.7	2.7±0.8	
FIB 4	Range	(0.3-5)	(0.4-5)	0.002*
	Mean±SD	1.6±1	1.9±1.2	
	Median	1	1.2	
FIB 4	F1-F2	462(92.4%)	428(84.6%)	<0.001*
	F3-F4	38(7.6%)	78(15.4%)	
		OR	**95% CI**	***P* value**
High BMI		1.13	1.07-1.19	<0.001*
Education				
No		Ref.		0.006*
Yes		1.43	1.11-1.83	
Positive polymerase chain reaction		3.69	2.98-4.57	<0.001*
FIB 4				
<3.45		Reference		<0.001*
≥3.45		2.22	1.47-3.34	

OR: odds ratio, CI: confidence interval.
* Significant level at *P* value<0.05

Table 4. Multiple logistic regression for prediction of risk factors for functional dyspepsia in chronic HCV patients

Variables	AOR	95% CI	*P* value
High BMI	1.09	1.04-1.15	0.001*
Education			
No	Ref.		0.026*
Yes	1.38	1.04-1.8	
Positive Polymerase chain reaction	3.54	2.86-4.38	<0.001*
FIB 4			
<3.45	Reference		0.001*
≥3.45	2.19	1.39-3.43	

AOR: adjusted odds ratio, CI: confidence interval
* Significant level at *P* value<0.05

Table 5. Simple logistic regression for the prediction of risk factors for IBS in patients with chronic HCV

Variables		IBS		*P* value
		No	Yes	
		N = 290	N = 716	
Hemoglobin level	Range	(9-16)	(9-16)	0.086
	Mean ± SD	12.7 ± 1.4	12.5 ± 1.2	
Platelets	Range	(100-3200)	(3.2-3870)	0.064
	Mean ± SD	348.7 ± 505.3	338.4 ± 562.8	
	Median	210	204.5	
Alanine transaminase	Range	(12-121)	(10-171)	0.001*
	Mean ± SD	32.6 ± 17.5	32 ± 23.8	
	Median	28	23	
Bilirubin	Range	(0.9-2)	(0.2-2)	0.642
	Mean ± SD	1 ± 0.1	1 ± 0.1	
Albumin	Range	(3-5)	(3-5)	0.087
	Mean ± SD	4.4 ± 0.5	4.4 ± 0.5	
International randomized ratio	Range	(1-1.4)	(1-1.4)	0.115
	Mean ± SD	1.05 ± 0.09	1.04 ± 0.11	
Creatinine	Range	(0.7-1.4)	(0.1-1.5)	0.158
	Mean ± SD	1 ± 0.1	1 ± 0.1	
Polymerase chain reaction	Range	(0-3.3)	(0.6-5)	< 0.001*
	Mean ± SD	1.7 ± 0.7	2.6 ± 0.7	
FIB 4	Range	(0.3-4)	(0.3-5)	0.169
	Mean ± SD	1.6 ± 1	1.7 ± 1.1	
	Median	1	1.1	
FIB 4	< 3.45	268 (92.4%)	622 (86.9%)	0.013*
	≥ 3.45	22 (7.6%)	94 (13.1%)	
		OR	**95% CI**	***P* value**
Gender				
Female		Ref.		
Male		1.53	1.13-2.06	0.006*
High BMI		1.15	1.08-1.22	< 0.001*
Residence				
Rural		Ref.		
Urban		1.93	1.46-2.55	< 0.001*
Education				
No		Ref.		
Yes		2.89	2.13-3.9	< 0.001*
Chronic disease				
No		Ref.		
DM		0.87	0.56-1.36	0.543
HTN		0.16	0.05-0.5	0.002*
Positive PCR		5.94	4.57-7.72	< 0.001*
FIB 4				
< 3.45		Reference		
≥ 3.45		1.84	1.13-2.99	0.014*

OR: odds ratio, CI: Confidence Interval
* Significant level at *P* value < 0.05

Table 6. Multiple logistic regression for the prediction of risk factors for IBS in patients with chronic HCV

Variables	AOR	95% CI	*P* value
Gender			
Female	Ref.		0.002*
Male	1.82	1.23-2.68	
High BMI	1.11	1.03-1.19	0.005*
Residence			
Rural	Ref.		<0.001*
Urban	2.09	1.48-2.95	
Education			
No	Ref.		<0.001*
Yes	4.29	2.92-6.29	
Positive polymerase chain reaction	6.37	4.83-8.41	<0.001*
FIB 4			
<3.45	Reference		0.033*
≥3.45	1.92	1.06-3.5	

OR: odds ratio, CI: Confidence Interval
* Significant level at *P* value<0.05

DISCUSSION

Patients with chronic hepatitis C usually have different abdominal complaints. Dyspepsia is very frequent in HCV patients with different presentations such as epigastric pain and heart burn.[6] Abdominal pain is seen frequently in clinical practice in patients with chronic HCV without any organic cause. The current study was designed to evaluate FGIDs in patients with chronic hepatitis C. In the present study, we evaluated the presence of FD in patients with chronic HCV. Our data showed that there was a significant difference in FD between the patients with chronic HCV, and the controls. The percentage of FD according to Rome IV criteria was significantly higher in patients with chronic HCV than normal controls (51.3% vs. 43.2%, respectively). Regarding FD subtypes, postprandial distress syndrome (PDS) was more predominant than epigastric pain syndrome (EPS). In addition, there were multiple risk factors for the prediction of FD in patients with chronic HCV, including high BMI, higher level of education, positive PCR, and FIB4 (≥3.45). FD is more prevalent in obese patients with chronic HCV who had high education levels and higher fibrosis scores. Our results are in accordance with the report by Grassi and colleagues[13] who reported the presence of FD in about 28.8 % of the patients with chronic liver diseases. About 71.2 % had an organic cause of dyspepsia, such as gastroesophageal reflux disease, gallbladder stones, and ulcers. The most important factors that predict the presence of FD were fibrosis scores and BMI, while age, gender, smoking, and residential status were not significantly associated. Also, our results were in agreement with Aro and colleagues[14] who found that PDS in Sweden was more prevalent than EPS, and obesity was predictive for FD. Mohamed et al[15] reported the same result. They found that the percentage of patients with FD according to Rome III criteria were significantly higher in patients with chronic HCV than controls (65.9%, and 28.7%, respectively). Regarding FD subtypes, the PDS subtype was more predominant than the EPS in both groups. The study included 251 patients infected with HCV. 187 patients showed the criteria of FD and underwent upper GIT endoscopy. About 166 patients had normal endoscopic findings and were diagnosed as having FD. Similar results were obtained from the study of Ahmed et al[16] which included 266 patients with chronic HCV and 170 normal healthy controls. Upper GIT endoscopy was performed for all patients to exclude any organic causes. The prevalence of FD was significantly higher in patients with chronic HCV than the controls (67.8% vs. 32.4%, respectively). PDS subtype was more prevalent than EPS subtype. Also, elevated ALT levels and high fibrosis scores were

significantly higher in patients with FD than in patients without FD, and the most predictors of FD were fibrosis score and BMI. These findings indicate that patients with chronic HCV may have meal-related disorders, which may be needed further investigations of gastric neuromuscular function and gastric emptying studies.[17] These symptoms may be explained by the increase in the portal blood flow and volume changes of the liver after the meal, which may result in the stretch of the capsule, more congestion,[18] and subsequently lead to vagal stimulation, which may result in symptoms of postprandial fullness, nausea, and pain.[19] In our study, we assessed the presence of IBS symptoms in patients with chronic HCV. Our data showed that the prevalence of IBS was significantly higher in patients with chronic HCV (71.1%) than the controls. Regarding IBS subtypes, IBS with constipation was the most predominant type, in addition, there were multiple risk factors for the prediction of IBS in patients with chronic HCV in the form of the male gender, high BMI, urban residence, higher level of education, positive PCR, and FIB4 (≥3.45). Similar results were reported by Fouad and colleagues[20] who included 258 patients with chronic HCV, 36 patients with chronic HBV, and 160 healthy control in their study. All individuals were administered a questionnaire of IBS according to Rome III criteria. They noted that the prevalence of IBS was significantly higher in patients with chronic HCV (66%) than patients with chronic hepatitis B and normal controls. While there was no significant difference between the patients with chronic hepatitis B and normal controls, IBS with constipation was the most predominant type (51%) followed by mixed IBS (43%), in addition, the prevalence of IBS was significantly higher in female patients than male patients (91%) and in HCV patients with a high fibrosis score. These finding indicate that the association between HCV and IBS whether is due to infectious changes, psychological factors, or motor dysfunctions remains to be further studied.[21]

Thus, in summary, FGIDs, including FD and IBS, are a prevalent finding in patients with chronic HCV, and their pattern of presentations are similar to that of the general population. IBS with constipation and mixed IBS are the predominant types. Obese patients with chronic HCV with higher fibrosis scores and a high level of education are more likely to have FD.

ETHICAL APPROVAL

Local Ethics Committee for human subject research reviewed and approved the study protocol and consent forms (Approval No 23-2019).

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

REFERENCES

1. Saito YA, Schoenfeld P, Locke GR 3rd. The epidemiology of irritable bowel syndrome in North America: a systematic review. *Am J Gastroenterol* 2002;97(8):1910-5. doi: 10.1111/j.1572-0241.2002.05913.x
2. Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Functional esophageal disorders. *Gastroenterology* 2016;150(6):1368-79. doi: 10.1053/j.gastro.2016.02.012
3. Zignego AL, Ferri C, Pileri SA, Caini P, Bianchi FB. Extrahepatic manifestations of hepatitis C virus infection: a general overview and guidelines for a clinical approach. *Dig Liver Dis* 2007;39(1):2-17. doi: 10.1016/j.dld.2006.06.008
4. Carreño V, Bartolomé J, Castillo I, Quiroga JA. New perspectives in occult hepatitis C virus infection. *World J Gastroenterol* 2012;18(23):2887-94. doi: 10.3748/wjg.v18.i23.2887
5. Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. *Gastroenterology* 2016;150(6):1380-92. doi: 10.1053/j.gastro.2016.02.011
6. Ahlawat SK, Richard Locke G, Weaver AL, Farmer SA, Yawn BP, Talley NJ. Dyspepsia consulters and patterns of management: a population-based study. *Aliment Pharmacol Ther* 2005;22(3):251-9. doi: 10.1111/j.1365-2036.2005.02525.x
7. Lehman EM, Wilson ML. Epidemic hepatitis C virus infection in Egypt: estimates of past incidence and future morbidity and mortality. *J Viral Hepat* 2009;16(9):650-8. doi: 10.1111/j.1365-2893.2009.01115.x
8. Drossman DA, Hasler WL. Rome IV-functional GI disorders: disorders of gut-brain interaction. *Gastroenterology* 2016;150(6):1257-61. doi: 10.1053/j.gastro.2016.03.035
9. Kalaitzakis E, Simrén M, Olsson R, Henfridsson P, Hugosson I, Bengtsson M, et al. Gastrointestinal symptoms in patients with liver cirrhosis: associations with nutritional status and health-related quality of life. *Scand J Gastroenterol* 2006;41(12):1464-72. doi: 10.1080/00365520600825117
10. Keefer L, Drossman DA, Guthrie E, Simrén M, Tillisch K, Olden K, et al. Centrally mediated

disorders of gastrointestinal pain. *Gastroenterology* 2016;150(6):1408-19.doi:10.1053/j.gastro.2016.02.034
11. Quigley EM, Barbara G, Feinle-Bisset C. The intestinal microenvironment functional gastrointestinl disorders. In: Drossman DA, Chang LC, Kellow J, Tack J, Whitehead WE, The Rome IV Committees, eds. *Rome IV Functional Gastrointestinal Disorders–Disorders of Gut-Brain Interaction*. Vol 1. Raleigh, NC: The Rome Foundation; 2016. p. 179-247.
12. Sperber AD, Francisconi C, Fukudo S. Multicultural aspects of functional gastrointestinal disorders. In: Drossman DA, Chang LC, Kellow J, Tack J, Whitehead WE, The Rome IV Committees, eds. *Rome IV Functional Gastrointestinal Disorders–Disorders of Gut-Brain Interaction*. Vol 1. Raleigh, NC: The Rome Foundation; 2016.
13. Grassi M, Albiani B, De Matteis A, Fontana M, Lucchetta MC, Raffa S. [Prevalence of dyspepsia in liver cirrhosis: a clinical and epidemiological investigation]. *Minerva Med* 2001;92(1):7-12.
14. Aro P, Talley NJ, Ronkainen J, Storskrubb T, Vieth M, Johansson SE, et al. Anxiety is associated with uninvestigated and functional dyspepsia (Rome III criteria) in a Swedish population-based study. *Gastroenterology* 2009;137(1):94-100. doi: 10.1053/j.gastro.2009.03.039
15. Mohamed HI, Mokarib HA, Saad ZM, Abd El Ghany WM. The prevalence of functional dyspepsia using Rome III questionnaire among chronic hepatitis C patients. *BMC Gastroenterol* 2016;16:32. doi: 10.1186/s12876-016-0443-2
16. Ahmed O, Sameer A, Imoto A, Kojima Y, Higuchi K. Functional dyspepsia identified by Rome IV criteria in patients with chronic hepatitis C: is it rare? *Gastroenterology* 2018;154(6 Suppl 1):S-959. doi: 10.1016/s0016-5085(18)33233-5
17. Madrid AM, Cumsille F, Defilippi C. Altered small bowel motility in patients with liver cirrhosis depends on severity of liver disease. *Dig Dis Sci* 1997;42(4):738-42. doi: 10.1023/a:1018899611006
18. Barbaro B, Manfredi R, Bombardieri G, Vecchio FM, Palazzoni G, Mancini AP, et al. Correlation of MRI liver volume and doppler sonographic portal hemodynamics with histologic findings in patients with chronic hepatitis C. *J Clin Ultrasound* 2000;28(9):461-8. doi: 10.1002/1097-0096(200011/12)28:9<461::aid-jcu3>3.0.co;2-5
19. Rathgaber S, Rex DK. Right upper quadrant abdominal pain. Diagnosis in patients without evident gallstones. *Postgrad Med* 1993;94(2):153-61.
20. Fouad YM, Makhlouf MM, Khalaf H, Mostafa Z, Abdel Raheem E, Meneasi W. Is irritable bowel syndrome associated with chronic hepatitis C? *J Gastroenterol Hepatol* 2010;25(7):1285-8. doi: 10.1111/j.1440-1746.2010.06311.x
21. Drossman DA, Morris CB, Hu Y, Toner BB, Diamant N, Leserman J, et al. A prospective assessment of bowel habit in irritable bowel syndrome in women: defining an alternator. *Gastroenterology* 2005;128(3):580-9. doi: 10.1053/j.gastro.2004.12.006