ORIGINAL PAPER

Cystic fibrosis with liver involvement in adults has a benign course. Results from a tertiary referral center cohort

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ABSTRACT

Background: cystic fibrosis liver disease is a poorly understood entity, especially in adults, in terms of its real prevalence, natural history and diagnostic criteria, despite being the most important extrapulmonary cause of mortality. The aim was to evaluate the prevalence, characteristics and potential risk factors of liver disease in adults with cystic fibrosis, according to two diagnostic criteria accepted in the scientific literature.

Methods: patients were recruited in a tertiary referral hospital, and laboratory, ultrasound, non-invasive liver fibrosis tests (AST to Platelet Ratio Index [APRI]; Fibrosis-4 Index [FIB-4]) and transient elastography (Fibroscan®) were performed. The proportion of patients with liver disease according to the Debray and Koh criteria were evaluated.

Results: ninety-five patients were included, 48 (50.5 %) females, with a mean age of 30.4 (28.6-32.2) years. According to the Debray criteria, six (6.3 %) patients presented liver disease. According to the Koh criteria, prevalence increased up to 8.4 %, being statistically different from the 25 % value described in other published series (p = 0.005). Seven (7.5 %) presented ultrasonographic chronic liver disease. Eleven (13 %) presented liver fibrosis according to the APRI score; 95 (100 %) had a normal FIB-4 value. Mean liver stiffness value was 4.4 (4.1-4.7) kPa. FEV1 (OR = 0.16, p 0.05), meconium ileus (OR = 14.16, p 0.002), platelets (Pearson coefficient -0.25, p 0.05) and younger age (Pearson coefficient -0.19, p 0.05) were risk factors.

Conclusions: prevalence and severity of liver disease in adult cystic fibrosis patients were lower than expected. Meconium ileus, platelets, age and respiratory function were confirmed as risk factors associated to cystic fibrosis liver disease.

Keywords: Cystic fibrosis liver disease. Prevalence. Risk factors. Adults.

INTRODUCTION

Cystic fibrosis (CF) is a multisystemic disease with autosomal recessive inheritance, as a consequence of the malfunction of the cystic fibrosis transmembrane regulator (CFTR) protein, present in exocrine tissues of the organism (1). Liver involvement is currently the most important extrapulmonary cause of mortality (2-4). However, despite its importance, it is a poorly understood entity, both in terms of its prevalence and natural history.

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Over the years, the diagnostic criteria for cystic fibrosis liver disease (CFLD) have been modified. Nevertheless, the most accepted to date are those proposed by Debray et al. (5). Recent publications including the use of non-invasive liver fibrosis markers are revolutionizing diagnosis (6-11), improving the detection of affected patients (12,13). Their implementation is recommended by different authors, but they are yet to be included in the clinical practice guidelines of the different societies (14,15).

The prevalence of CFLD has been documented in a variable way over the years, ranging between 17 and 47 % (3,4,12,16-20). However, it varies among different age groups. The numbers vary even more widely in adults and furthermore, a second incidence peak in adulthood, not previously accounted for, seems possible nowadays (4,12).

Given that this pathology has not been thoroughly evaluated in adult patients and the limited number of publications on the subject, this study evaluated the prevalence, characteristics and potential risk factors of liver disease in adults with cystic fibrosis, according to two diagnostic criteria accepted in scientific literature.

METHODS

Patients who attended the CF monographic clinic of the Pneumology Service of Hospital Universitario de La Princesa in Madrid between January 2018 and 2020 were consecutively recruited. Inclusion criteria were as follows: age ≥ 18 years, diagnosis of CF (according to international criteria) (14,21) and maintained follow-up in the aforementioned clinic.

Clinical data was collected from follow-up visits, including physical examination and spirometry values (Datospir 120 Sibelmed spirometer). Three procedures were carried out. First, complete blood count, including liver function parameters and variables to rule out concomitant liver diseases. Two liver fibrosis scores based on serum biomarkers, AST to Platelet Ratio Index (APRI) and Fibrosis-4 Index (FIB-4) were calculated (22,23). Second, abdominal ultrasound (US) (Toshiba Aplio XG ultrasound machine) performed by an experienced sonographer on the same day patients were evaluated in the clinic, after fasting for 6-8 hours. Different US variables were evaluated, according to criteria established by Williams et al. (24). Hepatic steatosis was not considered as a parameter of CFLD but was collected as an independent item. Third, transient elastography (TE) (Fibroscan®, Echosens, Paris, France; version 1.40), carried out by the same sonographer after the ultrasound, following the usual technique. The M probe was used in all patients. Stiffness (kPa), IQR/MED (%) and controlled attenuation parameter (CAP) values (dB/m) were collected as variables. At least ten valid measurements were carried out and the results were considered to be reliable when the IQR/MED was ≤ 30 %. According to the available scientific literature, a cut-off point of 5.5 kPa was used to distinguish degree of fibrosis (F0-1, F ≥ 2) (6,7). Degree of steatosis was also classified (S0: < 248; S1: 248-268; S2: 269-279; S3: ≥ 280) (25).

CFLD was diagnosed according to the criteria established by Debray et al. and by Koh et al. in their respective studies (5,12). Regarding serum liver enzymes, an elevation in at least two of them at least ≥ 2 the upper limit of normality (ULN) was considered as diagnostic.

The study was carried out following the standards specified in the Declaration of Helsinki, the Good Clinical Practice Standards and the International Conference on Harmonisation (ICH) guidelines, and complied with current legislation. The patients who agreed to participate signed an informed consent.

Statistical analysis was performed with the Stata 13.1 statistical software (StataCorp LD, Texas, USA). A sample size calculation was performed assuming that the percentage of CFLD in the reference population is 25 % (3,4,12,16), although the real percentage will be around 10 %, according to our experience in clinical practice. The calculation was performed with an alpha risk of 5 % and a power of 90 %, and with a bilateral test using the arcsine method, determining that 65 patients would be required.

Qualitative variables were expressed as number of patients (percentage). Quantitative variables were described as the mean and 95 % confidence interval (95 % CI), provided they had a normal distribution ($n > 30$ or Shapiro-Wilk test with $p < 0.05$) or as a median (range) (if $n < 30$). The hypothesis testing was performed with a Student's t or Mann-Whitney U test for quantitative variables with or without normal distribution, respectively, and with a Fisher test or X2 for qualitative variables. $p < 0.05$ was considered as statistically significant. The hypothesis testing was carried out with variables related to CFLD assessed according to Koh et al. (12).

RESULTS

Clinical and demographic data of the study cohort are summarized in table 1. Mean values of the different liver function parameters can be seen in table 2. All the patients had a normal physical examination and no patient had received a liver transplant. Four (4.2 %) patients had histological results compatible with CFLD: two of them with "focal biliary fibrosis" and the other two with "multilobular cirrhosis". No liver biopsy was obtained in 91 (95.8 %) patients. Regarding the parameters to rule out concomitant liver disease, ceruloplasmin, alpha-1-antitrypsin and iron profile values were normal in all of the patients. Values regarding immune-globulins and autoantibodies are shown in figure 1. Serologic hepatotropic results were negative in 36 (48 %) patients. The rest of the values correspond to past infections or vaccination: 24 (32 %) patients were anti-HBs positive, five (6.7 %) were IgG anti-HAV positive and ten (13.3 %) patients presented serological results compatible with Epstein-Barr virus (EBV) and cytomegalovirus (CMV) past infections.

On abdominal US, seven (7.5 %) patients presented one or more abnormal parameters suggestive of chronic liver disease. Hepatic steatosis was described in 15 (16 %) patients. Mean APRI value was 0.21 (0.19-0.23). Eleven (13 %) patients presented a value compatible with some degree of fibrosis: nine (9.9 %) with possible fibrosis and two (2.2 %) with likely significant fibrosis. However, 95 (100 %) patients had a normal FIB-4 value. The mean FIB-4 value was 0.47 (0.43-0.52).

Regarding TE, results from 71 patients were obtained. Mean liver stiffness value was 4.4 (4.1-4.7) kPa. All had an IQR/med rate ≤ 30 %. Fifty-eight (81.7 %) patients presented degree

Table 1. *Clinical data of the cohort*

Clinical characteristics n = 95	n (%)/median (95 % CI)
Gender (female)	48 (50.5 %)*
Age (years)	30.4 (28.6-32.2)†
Caucasian	95 (100 %)*
Age at diagnosis < 18 years	81 (90 %)*
Severe genotype	84 (97.7 %)*
BMI (kg/m^2)	22.2 (21.6-22.9)†
History of meconium ileus	4 (4.2 %)*
Pancreatic insufficiency	73 (76.8 %)*
AGT/CFRD	42 (44.2 %)*
FEV1	81.5 (77.9-85)†
Bhalla score	14.8 (13.8-15.9)†
Chronic bronchial infection	81 (87.1 %)*
Lung transplant/waiting list	4 (4.3 %)*
Antibiotic therapy	74 (77.9 %)*
CFTR modulators	14 (14.7 %)*
UDCA	27 (28.4 %)*

CI: confidence interval; BMI: body mass index; AGT: abnormal glucose tolerance; CFRD: cystic fibrosis related diabetes; FEV1: forced expiratory volume in one second; CFTR: cystic fibrosis transmembrane regulator; UDCA: ursodeoxycholic acid. *n (%). †Mean (95 % CI).

Table 2. *Liver function parameters*

Variable	Value Mean (95 % CI)	Patients with altered values n (%)
AST (U/l)	21.2 (19.3-23.1)	2 (2.2 %)*
ALT (U/l)	23.7 (20.8-26.6)	11 (12.1 %)*
GGT (U/l)	24 (17.2-30.8)	5 (5.5 %)*
ALP (U/l)	92.7 (84.5-100.9)	17 (18.7 %)*
Total bilirubin (mg/dl)	0.5 (0.4-0.5)	4 (4.4 %)*
Albumin (g/dl)	4.5 (4.4-4.6)	2 (2.2 %)†
Platelet count (109/l)	288 (274.3-301.7)	1 (1.1 %)†
INR	1.03 (1.01-1.05)	0

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; INR: international normalized ratio. *Above the upper limit of normal (ULN). †Below the lower limit of normal (LLN).

F0-1 and 13 (18.3 %) degree F2. The mean CAP value was 209.2 (195.4-223) (dB/m). Fifty-nine (83.1 %) patients presented a degree of steatosis of S0, whilst six (8.5 %) patients presented degree S1, one (1.4 %) degree S2 and five (7 %) patients degree S3.

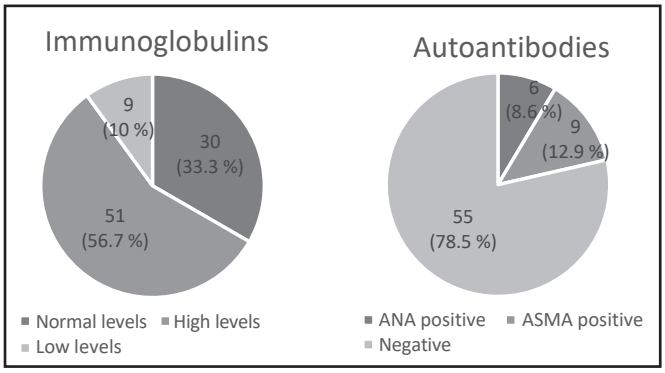

Fig. 1. *Values obtained by the patients in blood counts regarding the study of autoimmunity.*

According to the criteria by Debray et al. (5), only six (6.3 %) patients presented liver disease. The prevalence according to the criteria of Koh et al. (12) was eight (8.4 %), being statistically different from the 25 % value described in other published series (p 0.005). The possible relationships of different factors with the fact of presenting CFLD were analyzed, as shown in table 3.

DISCUSSION

The finding of a lower prevalence of liver disease in CF patients was surprising with respect to other reported studies, although with some variability, the prevalence values are between 17 and 47 % (3,4,12,16-20). However, not only was there a frequency low, but the involvement was relatively benign, with no data in patients suggesting terminal decompensated cirrhosis. These findings support what had been reported about the insufficient knowledge of this entity, even today.

Despite the low general prevalence of CFLD, the use of non-invasive liver fibrosis tests led to an increase in its detection, which reinforces the usefulness of including these markers in routine clinical practice. However, more studies are needed to establish adequate and universal cut-off points, as in other liver diseases, to safely incorporate their use.

Different reasons could explain the variability of prevalence values among the different published studies, including ours. One of the most determining factors is the fact that clinical characteristics and study designs in the existing scientific literature are very different from one another, thereby hindering a comparison between them. Our cohort should only be compared with similar Caucasian or Spanish cohorts (with previously reported prevalence values of 4.5 and 21 %) (17,26), as the values of other published studies may have been influenced by the particular genetic characteristics of the population in each territory (27,28).

In our study, younger age was a statistically proven risk factor, supporting what has been classically considered (2,3,29). However, young and therefore, potentially more severe patients may have been lost for follow-up and consequently, not included due to its transversal design. This survival bias may have affected the prevalence of adult cohorts such as ours.

Table 3. *Possible risk factors related with CFLD*

Variables	No CFLD	CFLD	Pearson correlation/OR	p
Age (years)‡	29.1 (19-60)	23.7 (18.7-36.6)	-0.19*	0.05
BMI (kg/m^2)‡	21.7 (16.2-33.3)	21.5 (19.2-27)	< 0.001*	0.93
Gender (male)§	41 (47.1 %)	6 (75 %)	3.06 (0.65-14.41)†	0.15
Severe genotype§	77 (97.5 %)	7 (100 %)	-	1
UDCA therapy§	24 (27.6 %)	3 (37.5 %)	1.51 (0.38-5.88)†	0.68
Antibiotic therapy§	67 (77 %)	7 (87.5 %)	1.98 (0.25-15.25)†	0.68
Platelet count (10^9/l)‡	288.5 (149-464)	238 (178-280)	-0.25*	0.005
Albumin (g/dl)‡	4.55 (2.9-5.2)	4.50 (4.3-4.9)	0.004*	0.8
Bilirubin (mg/dl)‡	0.39 (0.14-1.67)	0.54 (0.22-0.84)	0.05*	0.23
FEV1‡	82 (40-122)	93 (55-108)	0.16*	0.05
Meconium ileus§	2 (2.3 %)	2 (25 %)	14.16 (2.10-97.25)†	0.002
Pancreatic insufficiency§	65 (74.7 %)	8 (100 %)	-	0.19
AGT/CFRD§	18 (20.7 %)	1 (12.5 %)	0.57 (0.07-4.36)†	*1*

CFLD: cystic fibrosis liver disease; BMI: body mass index; AGT: abnormal glucose tolerance; CFRD: cystic fibrosis related diabetes; FEV1: forced expiratory volume in one second; UDCA: ursodeoxycholic acid. *Pearson correlation. †Odds ratio. ‡Mean (95 % CI). §n (%).

The existence of a second incidence peak in adulthood is increasingly reported, due to the appearance of lesions other than classic fibrosis, such as non-cirrhotic portal hypertension (12,16,30). These lesions may not be appropriately detected without a targeted search for them (for example, with biopsy), thereby leading to an underestimation in studies like ours.

However, the most determining factor when comparing prevalence is the heterogeneity in the defining criteria of CFLD. The different studies select different parameters, sometimes in a very unequal way. We strictly applied the most accepted criteria (5,12), but this may have limited the number of diagnosed patients compared to other studies carried out with less stringent specifications. The phenotypic classification proposed by other authors (31) is perhaps more practical for routine clinical practice. However, it seems less useful whenever the frequency of advanced liver disease is low, as occurred in our cohort.

Hepatic steatosis was ultrasonographically detected in a lower percentage than in other published series (16 % as compared to 25-67 %) (18,31) but there was a good agreement with the results of TE (16.9 % CAP ≥ S1). Following criteria commonly used in the literature, it was not considered as suggestive of liver involvement (3,5,12,18,32). However, some studies include it as a CFLD parameter and therefore, the prevalence described in those studies increases (16).

Considering steatosis as part of the CFLD spectrum is controversial. Some of the factors involved in non-alcoholic fatty liver disease (NAFLD) are also present in CF patients (such as chronic antibiotic therapy or insulin resistance). However, very few have shown a causal relationship with steatosis in CF (18,32). Steatosis is modified with CFTR modulators, suggesting it is related to CFTR protein dysfunction (33). On the other hand, the causal relationship between altered intestinal permeability and the development of liver disease (within the intestine-liver axis theory) may also explain CFLD pathogenesis (34).

Forced expiratory volume in one second (FEV1) values presented a statistically significant inverse relationship with the presence of CFLD. Different studies have shown similar results to ours (18), while others have demonstrated an association between poor respiratory function and the presence of CFLD (16,19). Although respiratory and hepatic functions are mutually dependent on each other, many other factors must play a role in this interrelation and are yet to be adequately investigated.

Our study has several limitations, its transversal design being the most significant one. Although it was carried out in a reference hospital, it is a single-center study. Therefore, although the sample size is adequate, the recruitment of patients from only one location may have an impact on the applicability of our results to wider populations. On the other hand, it was conducted in a clinical practice setting. Therefore, our observations may be more suitable for application in real-life practice. Our study is one of a few based exclusively on adult patients. Available studies of Spanish cohorts are even more infrequent and encompass all digestive comorbidities (17,26), whereas our study is specific to liver involvement.

We can conclude that the prevalence and severity of CFLD in our cohort of adult patients were lower than expected. Universally accepted diagnostic criteria should be established for a better characterization of the disease. Meconium ileus, younger age, platelet count and respiratory function were confirmed as factors associated to CFLD.

REFERENCES

1. Elborn JS. Cystic fibrosis. Lancet 2016;388(10059):2519-31. DOI: 10.1016/S0140-6736(16)00576-6
2. Ooi CY, Durie PR. Cystic fibrosis from the gastroenterologist's perspective. Nat Rev Gastroenterol Hepatol 2016;13(3):175-85. DOI: 10.1038/nrgastro.2015.226
3. Colombo C, Battezzati PM, Crosignani A, et al. Liver disease in cystic fibrosis: a prospective study on incidence, risk factors, and outcome. Hepatology 2002;36(6):1374-82. DOI: 10.1002/hep.1840360613
4. Sakiani S, Kleiner DE, Heller T, et al. Hepatic manifestations of cystic fibrosis. Clin Liver Dis 2019;23(2):263-77. DOI: 10.1016/j.cld.2018.12.008
5. Debray D, Kelly D, Houwen R, et al. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. J Cyst Fibros 2011;10(Suppl 2):S29-S36. DOI: 10.1016/S1569-1993(11)60006-4
6. Rath T, Menéndez Menéndez K, Kügler M, et al. TIMP-1/-2 and transient elastography allow non-invasive diagnosis of cystic fibrosis associated liver disease. Dig Liver Dis 2012;44:780-7. DOI: 10.1016/j.dld.2012.04.008
7. Lewindon PJ, Puertolas-López MV, Ramm LE, et al. Accuracy of transient elastography data combined with APRI in detection and staging of liver disease in pediatric patients with cystic fibrosis. Clin Gastroenterol Hepatol 2019;17(12):2561-9.e5. DOI: 10.1016/j.cgh.2019.03.015
8. Kitson MT, Kemp WW, Iser DM, et al. Utility of transient elastography in the non-invasive evaluation of cystic fibrosis liver disease. Liver Int 2013;33(5):698-705. DOI: 10.1111/liv.12113
9. Sadler MD, Crotty P, Fatovich L, et al. Noninvasive methods, including transient elastography, for the detection of liver disease in adults with cystic fibrosis. Can J Gastroenterol Hepatol 2015;29(3):139-44. DOI: 10.1155/2015/138530
10. Leung DH, Khan M, Minard CG, et al. Aspartate aminotransferase to platelet ratio and fibrosis-4 as biomarkers in biopsy-validated pediatric cystic fibrosis liver disease. Hepatology 2015;62(5):1576-83. DOI: 10.1002/hep.28016
11. Lam S, Nettel-Aguirre A, Van Biervliet S, et al. Transient elastography in the evaluation of cystic fibrosis-associated liver disease: systematic review and meta-analysis. J Can Assoc Gastroenterol 2019;2(2):71-80. DOI: 10.1093/jcag/gwy029
12. Koh C, Sakiani S, Surana P, et al. Adult onset cystic fibrosis liver disease: diagnosis and characterization of an underappreciated entity. Hepatology 2017;66(2):591-601. DOI: 10.1002/hep.29217
13. Alexopoulou A, Pouriki S, Vasilieva L, et al. Evaluation of noninvasive markers for the diagnosis of cystic fibrosis liver disease. Scand J Gastroenterol 2018;53(12):1547-52. DOI: 10.1080/00365521.2018.1534986
14. Castellani C, Duff AJA, Bell SC, et al. ECFS best practice guidelines: the 2018 revision. J Cyst Fibros 2018;17(2):153-78. DOI: 10.1016/j.jcf.2018.02.006
15. Cystic Fibrosis Foundation. Liver Disease Clinical Care Guidelines. Accessed: March 12th, 2021. Available from: https://www.cff.org/Care/Clinical-Care-Guidelines/Other-CF-Related-Conditions-Clinical-Care-Guidelines/Liver-Disease-Clinical-Care-Guidelines/
16. Toledano MB, Mukherjee SK, Howell J, et al. The emerging burden of liver disease in cystic fibrosis patients: a UK nationwide study. PLoS One 2019;14(4):e0212779. DOI: 10.1371/journal.pone.0212779
17. Pérez-Aguilar F, Ferrer-Calvete J, Nicolás D, et al. Digestive alterations in cystic fibrosis. Retrospective study of a series of 46 adult patients. Gastroenterol Hepatol 1999;22:72-8.
18. Lindblad A, Glaumann H, Strandvik B. Natural history of liver disease in cystic fibrosis. Hepatology 1999;30(5):1151-8. DOI: 10.1002/hep.510300527
19. Chryssostalis A, Hubert D, Coste J, et al. Liver disease in adult patients with cystic fibrosis: a frequent and independent prognostic factor associated with death or lung transplantation. J Hepatol 2011;55(6):1377-82. DOI: 10.1016/j.jhep.2011.03.028
20. Sokol RJ, Durie PR. Recommendations for management of liver and biliary tract disease in cystic fibrosis. J Pediatr Gastroenterol Nutr 1999;28(Suppl. 1). DOI: 10.1097/00005176-199900001-00001
21. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr 2017;181:S4-S15.e1. DOI: 10.1016/j.jpeds.2016.09.064
22. Loaeza-del-Castillo A, Paz-Pineda F, Oviedo-Cárdenas E, et al. AST to Platelet Ratio Index (APRI) for the noninvasive evaluation of liver fibrosis. Ann Hepatol 2008;7(4):350-7. DOI: 10.1016/s1665-2681(19)31836-8
23. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43(6):1317-25. DOI: 10.1002/hep.21178
24. Williams SGJ, Evanson JE, Barrett N, et al. An ultrasound scoring system for the diagnosis of liver disease in cystic fibrosis. J Hepatol 1995;22(5):513-21. DOI: 10.1016/0168-8278(95)80444-7
25. Karlas T, Petroff D, Sasso M, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol 2017;66:1022-30. DOI: 10.1016/j.jhep.2016.12.022
26. Modolell I, Álvarez A, Guarner L, et al. Gastrointestinal, liver, and pancreatic involvement in adult patients with cystic fibrosis. Pancreas 2001;22(4):395-9. DOI: 10.1097/00006676-200105000-00010
27. Buu MMC, Sanders LM, Mayo JA, et al. Assessing differences in mortality rates and risk factors between Hispanic and non-Hispanic patients with cystic fibrosis in California. Chest 2016;149(2):380-9. DOI: 10.1378/chest.14-2189
28. Villaverde-Hueso A, Sánchez-Díaz G, Molina-Cabrero FJ, et al. Mortality due to cystic fibrosis over a 36-year period in Spain: time trends and geographic variations. Int J Environ Res Public Health 2019;16(1). DOI: 10.3390/ijerph16010119
29. Lamireau T, Monnereau S, Martin S, et al. Epidemiology of liver disease in cystic fibrosis: a longitudinal study. J Hepatol 2004;41(6):920-5. DOI: 10.1016/j.jhep.2004.08.006
30. Boëlle P, Debray D, Guillot L, et al. Cystic fibrosis liver disease: outcomes and risk factors in a large cohort of French patients. Hepatology 2019;69(4):1648-56. DOI: 10.1002/HEP.30148
31. Flass T, Narkewicz MR. Cirrhosis and other liver disease in cystic fibrosis. J Cyst Fibros 2013;12(2):116-4. DOI: 10.1016/j.jcf.2012.11.010
32. Ayoub F, Trillo-Álvarez C, Morelli G, et al. Risk factors for hepatic steatosis in adults with cystic fibrosis: similarities to non-alcoholic fatty liver disease. World J Hepatol 2018;10(1):34-40. DOI: 10.4254/wjh.v10.i1.34
33. Kutney K, Donnola SB D, Flask CA, et al. Lumacaftor/ivacaftor therapy is associated with reduced hepatic steatosis in cystic fibrosis patients. World J Hepatol 2019;11(12):761-72. DOI: 10.4254/WJH.V11.I12.761
34. Fiorotto R, Strazzabosco M. Pathophysiology of cystic fibrosis liver disease: a channelopathy leading to alterations in innate immunity and in microbiota. CMGH 2019;8(2):197-207. DOI: 10.1016/j.jcmgh.2019.04.013