Evaluation of the Impact of Metabolic Syndrome on Fibrosis in Metabolic Dysfunction-Associated Fatty Liver Disease

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ABSTRACT

Background: *Metabolic syndrome (MS) is a condition that consists of several disorders, and the individual impact of these disorders on metabolic dysfunction-associated fatty liver disease (MAFLD) is still not clear in a combined diagnosis of MS. In this study, we aimed to investigate the effect of MS on advanced fibrosis in patients with MAFLD.*

Methods: *We recruited the patients from our gastroenterology out-patient clinic who were being followed up for MAFLD. MAFLD was diagnosed with liver biopsy in all patients. The frequency of MS and other metabolic parameters were also compared between groups with advanced fibrosis and groups in which fibrosis was not as advanced.*

Results: *In total, we enrolled 424 biopsy-proven MAFLD patients to the study. In univariate analysis, individuals with greater age, body mass index (BMI), higher aspartate transaminase (AST), MS, impaired fasting glucose, hypertension, enlarged waist circumference (WC), diabetes mellitus (DM), and women had significantly increased risk for fibrosis. In multivariate analysis, it was found that DM, greater age, higher BMI, and increased AST were seen more commonly in MAFLD patients with advanced fibrosis*

Conclusion: *Greater age, a higher BMI, higher AST and a diagnosis of diabetes were more commonly associated with advanced fibrosis. However, DM was found to be the strongest predictive factor of advanced fibrosis in our cohort (OR: 2.495). Multivariate analyses did not indicate a significantly common occurrence of MS in the advanced fibrosis group, despite its important role in MAFLD pathophysiology.*

Keywords: *Fibrosis, metabolic syndrome, metabolic dysfunction-associated fatty liver disease*

INTRODUCTION

Metabolic dysfunction-associated fatty liver disease (MAFLD) is the most common chronic liver disease that affects nearly a quarter of the global adult population. Previously, the term non-alcoholic fatty liver disease (NAFLD) was routinely used to describe the disease. In time, NAFLD became inadequate to identify the disease. Unlike NAFLD, the term MAFLD centralizes metabolic dysfunction as a significant risk factor for the disease, and includes alcohol consumption as an exacerbating factor. .MAFLD has a chronic progressive course that can cause hepatocellular carcinoma and/or cirrhosis.[1-3]

Disease activity of MAFLD and progression to liver fibrosis are the strongest predictors of an aggressive disease course.[4,5] A biopsy is necessary in the evaluation of disease activity, but some non-invasive scores are also important in predicting activity and fibrosis.[6] However, several factors, such as diabetes mellitus (DM), older age, lipid disorders, obesity, and insulin resistance seem more common in patients with a severe disease, and these factors negatively affect fibrosis progression and play an important role in a worsening disease course.[7-10]

Metabolic syndrome (MS) consists of several metabolic abnormalities. Fatty liver and MS engage with each other in a complicated relationship, and both disorders share common etiologies and are frequently found together.[11,12] However, progression to a severe disease is more commonly seen in fatty liver patients who have accompanying MS.[13]

MS consists of several disorders, of which the individual impact on MAFLD is as yet unclear in a combined diagnosis of MS. In this study, we have aimed to investigate the effect of MS on stages of fibrosis in patients with MAFLD.

METHODS

Patients

We recruited the patients from our gastroenterology out-patient clinic who were being followed up between 2009

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and 2018. The diagnosis was established through evidence of hepatic steatosis by imaging, in addition to 1 of the following 3 criteria: presence of overweight/obesity, a diagnosis of type 2 DM, or evidence of metabolic dysregulation. Liver biopsy was performed on patients who had an elevated aminotransferase level for at least 6 months or who had an existing hepatomegaly and/or splenomegaly without elevated liver function tests. MAFLD patients with a biopsy were enrolled in the study, and the patients without steatosis in liver histology were excluded.

Clinical and Laboratory Data

A detailed anamnesis was taken and a physical examination performed of all patients. Clinical, anthropometric, and laboratory data were collected retrospectively from the hospital's electronic database and hardcopy patient files. After a 12-hour fasting period, the patients' aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet, albumin, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, plasma glucose concentration, and insulin levels were measured and recorded. Body mass index (BMI) was calculated with weight in kilograms and height in meters; patients with BMI ≥30 were defined as obese. Waist circumference (WC) was measured around the waist at the midpoint between the lower costal border and the iliac crest at the end of normal expiration, while hip circumference was measured at the maximum circumference around the buttocks. Arterial tension was measured using a brachial sphygmomanometer while the patient was in the sitting position.

MS was defined by the presence of at least 3 of the following metabolic abnormalities[14]: (1) WC >102 cm for men and >88 cm for women; (2) systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg and/or patient was under a tension-lowering agent due to a previous hypertension diagnosis; (3) either DM previously diagnosed and under treatment or an impaired fasting glucose (IFG); (4) triglyceride levels >150 mg/dL; (5) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women.

Liver biopsies were examined by a single gastroenterology-specific pathologist in our university hospital. Steatosis, ballooning, lobular inflammation, and fibrosis stages were determined according to the Kleiner classification.[15] Steatosis was ascribed when over 5% of hepatocytes contained fat droplets. Stage 0 indicates the absence of fibrosis (F0); stage 1 indicates perisinusoidal or periportal fibrosis (F1); stage 2 indicates perisinusoidal and portal or periportal fibrosis (F2); stage 3 indicates septal and bridging fibrosis (F3); and stage 4 indicates cirrhosis (F4). Advanced fibrosis was defined as F3 or F4 fibrosis. The grade of activity was defined based on the total lobular inflammation and ballooning.

Statistical Analysis

The dataset contained both continuous and categorical variables. The normality of the continuous variables was investigated using QQ and PP plots, Kolmogorov–Smirnov tests, boxplots, and skewness and kurtosis values.

The measurements were expressed as either mean ± standard deviation or median and interquartile range (IQR), depending on their distributions. Categorical variables were expressed in frequencies and percentages. The significance of the difference between groups with advanced fibrosis and those with fibrosis that was not as advanced, was tested using either the Student's *t*-test or the Mann–Whitney *U*-test with respect to the continuous variables, and using Fisher's exact test with respect to the categorical variables. All analyses were two-sided and performed with an alpha level of 0.05.

The study was approved by the local ethics committee (Approval Date: January 3, 2020, Approval Number: 09.2020.25). All procedures followed were in accordance with the ethical standards of the concerned committee on human experimentation and with the Declaration of Helsinki 1975, as revised in 2008.

RESULTS

The demographic, anthropometric, and clinical data of 424 biopsy-proven MAFLD patients are summarized in Table 1. In our study, the patients' mean age was 46.31 ± 10.51; 47.6% of patients were female. The mean BMI was 31.61 ± 5.14 kg/m², 36.6% of patients were diabetic, and 65.8% had MS. All patients were diagnosed with MAFLD based on histopathology, and 70 patients (16.5%) had advanced fibrosis.

With the univariate analysis, the risk for fibrosis was shown to be significantly increased with older age, higher BMI, higher AST, MS, IFG, hypertension, enlarged WC, DM, and in women (Table 2). The results of the reduced multivariable model show that for each 1-unit increase in age, the odds of having fibrosis were increased by a factor of

Table 1. General Characteristics of Patients With Biopsy-Proven Metabolic Dysfunction-Associated Fatty Liver Disease With and Without Advanced Fibrosis

	All Patients (n = 424)	Patients Without Advanced Fibrosis (F ≤ 2) (n = 354)	Patients With Advanced Fibrosis (F > 2) (n = 70)
Sex			
Female (n, %)	202 (47.6%)	160 (45.2%)	42 (60.0%)
Male (n, %)	222 (52.4%)	194 (54.8%)	28 (40.0%)
Age (years) (mean ± SD)	46.31 ± 10.51	45.50 ± 10.38	50.41 ± 10.22
Height (cm) (mean ± SD)	164.46 ± 9.70	165.04 ± 9.56	161.53 ± 9.92
Weight (kg) (mean ± SD)	85.29 ± 14.01	84.85 ± 13.01	87.49 ± 18.19
Body mass index (kg/m^2) (mean ± SD)	31.61 ± 5.14	31.24 ± 4.91	33.47 ± 5.88
Waist circumference (cm) (mean ± SD)	103.83 ± 10.34	103.34 ± 10.01	106.36 ± 11.66
Hip circumference (cm) (mean ± SD)	109.03 ± 10.68	108.82 ± 10.35	110.15 ±12.27
Diabetes mellitus (n, %) (mean ± SD)	155 (36.6%)	112 (31.6%)	43 (61.4%)
AST (IU/L) (median, min-max)	42.0 (15.0-302.0)	41.0 (15.0-302.0)	48.0 (17.0-247.0)
ALT (IU/L) (median, min-max)	66.0 (12.0-483.0)	66.0 (12.0-343.0)	65.0 (12.0-483.0)
Total cholesterol (mM) (mean ± SD)	213.08 ± 46.18	212.69 ± 46.14	215.02 ± 46.72
HDL cholesterol (mM)	45.39 ± 10.93	45.03 ± 10.58	47.24 ± 12.47
LDL cholesterol (mM) (mean ± SD)	134.87 ± 40.44	135.43 ± 40.67	132.06 ± 39.39
Triglycerides (mM) (median, min-max)	189.39 ± 108.60	191.62 ± 112.07	178.10 ± 88.83
Waist circumference >102 cm for men, >88 cm for women (n, %)	328 (77.4%)	266 (75.1%)	62 (88.6%)
Hypertension (n, %)	228 (53.8%)	181 (51.1%)	47 (67.1%)
IFG (n, %)	257 (60.6%)	204 (57.6%)	53 (75.7%)
Triglyceride > 150 mg/dL (n, %)	256 (60.4%)	214 (60.5%)	42 (60.0%)
HDL cholesterol <40 mg/dL for men and <50 mg/dL for women (n, %)	209 (49.3%)	174 (49.2%)	35 (50.0%)
Metabolic syndrome (n, %)	279 (65.8%)	225 (63.6%)	54 (77.1%)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein. Data are presented as means and SD, counts, or medians and interquartile ranges, as appropriate.

1.046 in the presence of other variables (BMI, AST, DM) (OR: 1.046, 95% CI: 1.015-1.078). For each 1-unit increase in BMI, the odds of fibrosis were increased by a factor of 1.061 in the presence of other variables (age, AST, DM) (OR: 1.061, 95% CI: 1.009-1.115). Similarly, for a unit of increase in the AST, the odds of fibrosis were increased by a factor of 1.011, adjusted for other variables (age, BMI, DM) (OR: 1.011, 95% CI: 1.004-1.019). When adjusted for age, BMI, and AST, patients with DM were 2.495 times more likely (OR: 2.495, 95% CI: 1.425-4.418), to be at risk for fibrosis than patients without DM, and the group was statistically significant (P = .001). As seen from the results, although MS and some of its subgroups were statistically significant in the univariate model, they were not included in the reduced model (Table 2).

DISCUSSION

MAFLD pathogenesis and the factors associated with the activity of the disease are not clear yet. Metabolic disorders, lifestyle, and nutrition play an important role in the occurrence and progression of fatty liver. In this study, we found that DM, older age, higher BMI, and increased AST were more common in MAFLD patients with advanced fibrosis; in this context, these factors are assessable as a risk factor for advanced disease and advanced fibrosis in MAFLD.

DM was found to be more common in the advanced fibrosis group, and it was statically significant in the multivariate analysis (OR: 2.495, 95% CI, 1.425-4.418). Impaired glucose tolerance and DM were more commonly seen in

Table 2. The estimated coefficients in the univariate logistic regression and reduced multivariable logistic regression with descriptors and the clinical demographic data

	Univariate analyses (Logistic regression)			Multivariable analysis (Logistic regression)		
	Coef	OR (95% CI)	*P*	Coef	OR (95% CI)	*P*
Age	0.048	1.049 (1.022-1.078)	.0004*	0.045	1.046 (1.015-1.078)	.003*
BMI	0.077	1.080 (1.030-1.132)	.0013*	0.059	1.061 (1.009-1.115)	.020*
Grade of activity ≥ 2	1.548	4.701 (1.402-29.256)	.0354*			
AST	0.0088	1.009 (1.002-1.015)	.0078*	0.011	1.011 (1.004-1.019)	.002*
ALT	0.0025	1.042 (0.998-1.007)	.2790			
LDL	–0.002	0.998 (0.991-1.004)	.5227			
Metabolic Syndrome	0.660	1.935 (1.086-3.620)	.0306*			
IFG	0.830	2.292 (1.301-4.224)	.0055*			
HDL Cholesterol <40 mg/dl for men and <50 mg/dl for women	0.034	1.034 (0.618-1.730)	.897			
Triglyceride > 150 mg/dl	–0.019	0.981 (0.584-1.670)	.944			
Hypertension	0.669	1.953 (1.149-3.402)	.0152*			
Waist Circumference >102 cm for men, >88cm for women	0.942	2.564 (1.247-5.988)	.0172*			
Diabetes Mellitus	1.236	3.441 (2.036-5.908)	<.001*	0.914	2.495 (1.425-4.418)	.001*
Sex	0.598	1.819 (1.084-3.091)	.0247*			

*$P < 0.05$ accepted as statistically significant.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, Body Mass Index; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein.

fatty liver, and vice versa. DM increases the disease progression and activity of fatty liver with an unknown etiology.[16] On the other hand, DM is also an independent risk factor and predictor of progressive fibrosis. DM was seen more commonly in patients with fatty liver and advanced fibrosis, and patients with DM also showed greater progression to fibrosis.[17-19] In line with the current literature, we found diabetes to be both more common in the advanced fibrosis group and predictive of fibrosis in patients diagnosed with MAFLD.

MAFLD is a chronic disease of the liver, and fibrosis progresses over time through a chronic inflammatory process. Fibrosis also progresses with the duration and severity of inflammation; in other words, elderly patients with fatty liver have a high probability of progressing to an advanced fibrosis such as an aggressive steatohepatitis.[20] We also found that older age is a prognostic factor for advanced fibrosis in MAFLD.

BMI was shown to have a positive correlation with advanced fibrosis, and increased BMI is a predictor of advanced fibrosis. To put it differently, an increase in BMI also predicts advanced fibrosis in fatty liver. The effect of obesity and increased BMI on fibrosis is controversial in the current literature. In one study, the prevalence of advanced fibrosis increased in obese patients with fatty liver.[21] In contrast, 540 patients with biopsy-proven

fatty liver enrolled in another study, and BMI was not described as a predictive factor for advanced fibrosis. However, the obese patients in the study were younger than the patients who were not obese. Because age is a well-known predictor of fibrosis, it may have been a confounding factor in the comparison of advanced fibrosis between both groups.[22] In addition to these studies, a meta-analysis that included 11 043 patients with biopsy-proven and non-biopsy-proven fatty liver from 13 studies found no correlation between advanced liver fibrosis and obesity.[23] In our study, all patients were biopsy-proven, and the difference to the meta-analysis may be for this reason. It is obvious that further studies are needed to clarify the effect of BMI and obesity on fibrosis progression in MAFLD.

AST is an indirect indicator of both hepatitis and severe disease. We found AST to be higher in the advanced fibrosis group. In a previous study, AST elevation was not found to be significant in fibrosis progression; however, the AST/ALT ratio was increased in fibrosis.[24] Another study revealed similar results: In the univariate analysis, AST was found to be higher in the advanced fibrosis group but was not significantly higher in the multivariate analysis.[7] In a previous study, AST was higher in the advanced fibrosis group of patients with fatty liver, in furtherance to our study.[25] An AST increase is not clearly associated with advanced fibrosis in the current literature; although our study also reveals a significant elevation in the advanced fibrosis group, this finding does not have a strong impact (OR: 1.011).

MS was found to be significantly higher in the advanced fibrosis group in the univariate analysis, but this significance was not seen in the multivariate analysis. Several subitems of MS were also found to be significantly higher in the advanced fibrosis group, but again, none of them were found to be significantly higher in the multivariate analysis (Table 2). MS and fatty liver have a bidirectional relationship; MS increases the risk of fatty liver, and vice versa. However, the impact of MS on liver fibrosis is not clear in fatty liver. MS was found to increase the progression of fibrosis in a single study,[26] but patients who had a diagnosis of DM had been excluded. Because DM is one of the most important factors regarding both disease course and fibrosis progression in fatty liver, we did not exclude patients with DM. In our cohort, 36.6% of patients were diabetic, a difference between the 2 studies which may have caused the adversity. Moreover, in several studies, no relationship was found between MS and fibrosis, which is similar to our result.[27-30]

The retrospective design was the main limitation of our study. There is no doubt that the impact of MS on fibrosis progression would be more accurately evaluated through a prospective study with repetitive biopsies on the same patients, following up the factors that affect the disease course. However, 89.4% of our cohort and 97.1% of patients with advanced fibrosis had been diagnosed with a severe disease; for this reason, studies with a more balanced cohort would contribute to a better understanding of the topic.

CONCLUSION

Our study sheds light on the common factors affecting fibrosis in a real-life cohort that included a considerable number of MAFLD patients. Older age, higher BMI, higher AST and a diagnosis of diabetes were shown to be more common in advanced fibrosis patients. However, DM was revealed as the strongest predictive factor of advanced fibrosis in our cohort (OR: 2.495). In multivariate analyses, MS was not found to be significantly more common in the advanced fibrosis group, despite its important role in MAFLD pathophysiology. Prospectively designed studies with repetitive biopsies are needed to more accurately evaluate the effect of MS on advanced fibrosis.

Ethics Committee Approval: The study was approved by the local ethics committee (Approval Date: 03 January 2020, Approval Number: 09.2020.25).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

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REFERENCES

1. Cengiz Seval G. The natural course of non-alcoholic fatty liver disease. Hepatol Forum. 2020:20-24. [CrossRef]

2. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol. 2020;73(1): 202-209. [CrossRef]

3. Demitas CO, Yilmaz Y. Metabolic-associated Fatty Liver Disease: time to integrate ground-breaking new terminology to our clinical practice? Hepatol Forum. 2020;3(1):79-81. [CrossRef]
4. Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology. 2015;61(5):1547-1554. [CrossRef]
5. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients With nonalcoholic fatty liver disease. Gastroenterology. 2015;149(2):389-397.e10. [CrossRef]
6. Kaya E, Bakir A, Eren F, Yilmaz Y. The utility of noninvasive scores in non-alcoholic fatty liver disease patients with normal and elevated serum transaminases. Hepatol Forum. 2020;1(1):8-13. [CrossRef]
7. Labenz C, Huber Y, Kalliga E, et al. Predictors of advanced fibrosis in non-cirrhotic non-alcoholic fatty liver disease in Germany. Aliment Pharmacol Ther. 2018;48(10):1109-1116. [CrossRef]
8. Tada T, Toyoda H, Sone Y, et al. Type 2 diabetes mellitus is a risk factor for progression of liver fibrosis in middle-aged patients with non-alcoholic fatty liver disease. J Gastroenterol Hepatol. 2019;34(11):2011-2018. [CrossRef]
9. Kim Y, Chang Y, Cho YK, et al. Obesity and weight gain are associated With progression of fibrosis in patients With nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2019;17(3):543-550.e2. [CrossRef]
10. Fujii H, Imajo K, Yoneda M, et al. HOMA-IR: an independent predictor of advanced liver fibrosis in nondiabetic non-alcoholic fatty liver disease. J Gastroenterol Hepatol. 2019;34(8):1390-1395. [CrossRef]
11. Sookoian S, Pirola CJ. Nonalcoholic fatty liver disease and metabolic syndrome: shared genetic basis of pathogenesis. Hepatology. 2016;64(5):1417-1420. [CrossRef])
12. Yilmaz Y, Senates E, Ayyildiz T, et al. Characterization of nonalcoholic fatty liver disease unrelated to the metabolic syndrome. Eur J Clin Invest. 2012;42(4):411-418. [CrossRef]
13. Xu ZJ, Shi JP, Yu DR, et al. Evaluating the relationship Between metabolic syndrome and liver biopsy-proven non-alcoholic steatohepatitis in China: A multicenter cross-sectional study design. Adv Ther. 2016;33(11):2069-2081. [CrossRef]
14. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment Panel III). JAMA. 2001;285(19):2486-2497. [CrossRef]
15. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41(6):1313-1321. [CrossRef]
16. Nakahara T, Hyogo H, Yoneda M, et al. Type 2 diabetes mellitus is associated with the fibrosis severity in patients with nonalcoholic fatty liver disease in a large retrospective cohort of Japanese patients. J Gastroenterol. 2014;49(11):1477-1484. [CrossRef]
17. McPherson S, Hardy T, Henderson E, et al. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol. 2015;62(5):1148-1155. [CrossRef]
18. Goh GB, Pagadala MR, Dasarathy J, et al. Clinical spectrum of non-alcoholic fatty liver disease in diabetic and non-diabetic patients. BBA Clin. 2015;3:141-145. [CrossRef]
19. Hossain N, Afendy A, Stepanova M, et al. Independent predictors of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterological Assoc. 2009;7(11):1224-1229.e2. [CrossRef]
20. Noureddin M, Yates KP, Vaughn IA, et al. Clinical and histological determinants of nonalcoholic steatohepatitis and advanced fibrosis in elderly patients. Hepatology. 2013;58(5):1644-1654. [CrossRef]
21. Leung JC, Loong TC, Wei JL, et al. Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. Hepatology. 2017;65(1):54-64. [CrossRef]
22. Honda Y, Yoneda M, Kessoku T, et al. Characteristics of non-obese non-alcoholic fatty liver disease: effect of genetic and environmental factors. Hepatol Res. 2016;46(10):1011-1018. [CrossRef]
23. Lu F.B., Hu E.D., Xu L.M. , et al. The relationship between obesity and the severity of non-alcoholic fatty liver disease: systematic review and meta-analysis. Expert Rev Gastroenterol Hepatol. 2018;12(5):491-502. [CrossRef]
24. Pattnaik K, Bhuyan P, Singh A, et al. Biopsy proven fibrosis in non-alcoholic fatty liver disease: an analysis of risk factors. J Clin Exp Hepatol. 2018;8(4):367-374. [CrossRef]
25. Seko Y, Yamaguchi K, Mizuno N, et al. Combination of PNPLA3 and TLL1 polymorphism can predict advanced fibrosis in Japanese patients with nonalcoholic fatty liver disease. J Gastroenterol. 2018;53(3):438-448. [CrossRef]
26. Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology. 2003;37(4):917-923. [CrossRef]
27. Adams LA, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. J Hepatol. 2005;42(1):132-138 [CrossRef]
28. Ryan MC, Wilson AM, Slavin J, et al. Associations between liver histology and severity of the metabolic syndrome in subjects with nonalcoholic fatty liver disease. Diabetes Care. 2005;28(5):1222-1224. [CrossRef]
29. Pais R, Charlotte F, Fedchuk L, et al. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. J Hepatol. 2013;59(3):550-556. [CrossRef]
30. Ballestri S, Nascimbeni F, Romagnoli D, Lonardo A. The independent predictors of non-alcoholic steatohepatitis and its individual histological features: insulin resistance, serum uric acid, metabolic syndrome, alanine aminotransferase and serum total cholesterol are a clue to pathogenesis and candidate targets for treatment. Hepatol Res. 2016;46(11):1074-1087. [CrossRef]