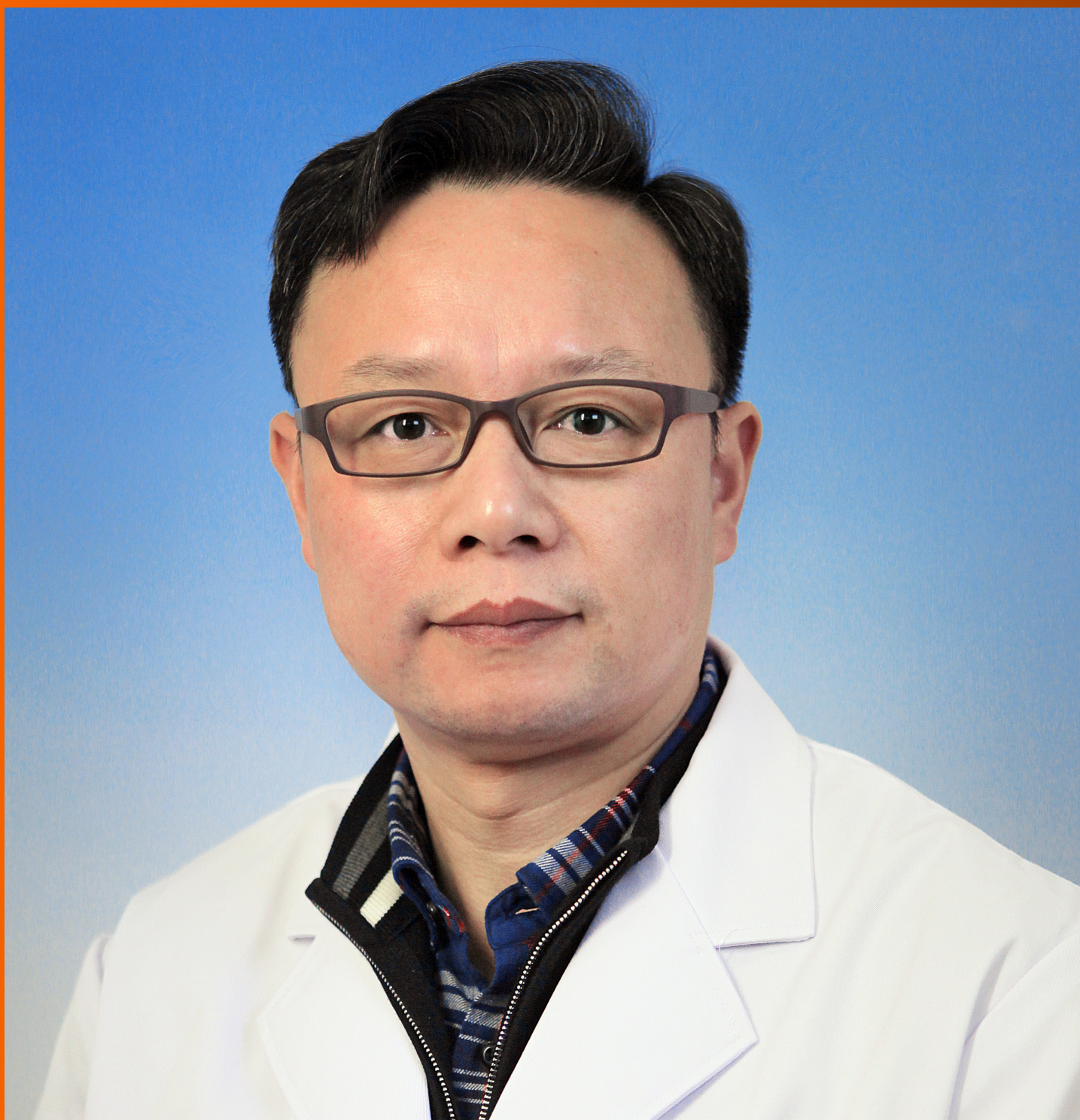


World Journal of *Hepatology*

World J Hepatol 2024 January 27; 16(1): 1-111



EDITORIAL

- 1 Molecular mechanisms underlying SARS-CoV-2 hepatotropism and liver damage
Quarleri J, Delpino MV
- 12 Metabolomics in liver diseases: A novel alternative for liver biopsy?
Tanaka Y

MINIREVIEWS

- 17 Role of fecal microbiota transplant in management of hepatic encephalopathy: Current trends and future directions
Shah YR, Ali H, Tiwari A, Guevara-Lazo D, Nombera-Aznaran N, Pinnam BSM, Gangwani MK, Gopakumar H, Sohail AH, Kanumilli S, Calderon-Martinez E, Krishnamoorthy G, Thakral N, Dahiya DS
- 33 Metabolic disease and the liver: A review
Vargas M, Cardoso Toniasso SC, Riedel PG, Baldin CP, dos Reis FL, Pereira RM, Brum MCB, Joveleviths D, Alvares-da-Silva MR

ORIGINAL ARTICLE

Retrospective Cohort Study

- 41 Direct-acting antivirals failed to reduce the incidence of hepatocellular carcinoma occurrence in hepatitis C virus associated cirrhosis: A real-world study
Tao XM, Zeng MH, Zhao YF, Han JX, Mi YQ, Xu L

Observational Study

- 54 Metabolic puzzle: Exploring liver fibrosis differences in Asian metabolic-associated fatty liver disease subtypes
Shaikh SS, Qazi-Arisar FA, Nafay S, Zaheer S, Shaikh H, Azam Z

Basic Study

- 65 Subcellular distribution of prohibitin 1 in rat liver during liver regeneration and its cellular implication
Sun QJ, Liu T
- 75 Rifaximin on epigenetics and autophagy in animal model of hepatocellular carcinoma secondary to metabolic-dysfunction associated steatotic liver disease
Michalczuk MT, Longo L, Keingeski MB, Basso BS, Guerreiro GTS, Ferrari JT, Vargas JE, Oliveira CP, Uribe-Cruz C, Cerski CTS, Filippi-Chiela E, Alvares-da-Silva MR

META-ANALYSIS

- 91 Sorafenib plus transarterial chemoembolization *vs* sorafenib alone for patients with advanced hepatocellular carcinoma: A systematic review and meta-analysis
Yang HJ, Ye B, Liao JX, Lei L, Chen K

CASE REPORT

- 103** Pylephlebitis-induced acute liver failure: A case report and review of literature

Hapshy V, Imburgio S, Sanekommu H, Nightingale B, Taj S, Hossain MA, Patel S

LETTER TO THE EDITOR

- 109** Review on article of effects of tenofovir alafenamide and entecavir in chronic hepatitis B virus patients

Sun YT, Chen QQ

ABOUT COVER

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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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Observational Study

Metabolic puzzle: Exploring liver fibrosis differences in Asian metabolic-associated fatty liver disease subtypes

Sabhita Shabir Shaikh, Fakhar Ali Qazi-Arisar, Saba Nafay, Sidra Zaheer, Hafeezullah Shaikh, Zahid Azam

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Abstract

BACKGROUND

Metabolic-associated fatty liver disease (MAFLD) is a liver condition marked by excessive fat buildup in the absence of heavy alcohol use. It is primarily linked with metabolic issues like insulin resistance, obesity, and abnormal lipid levels, and is often observed with other conditions such as type 2 diabetes and cardiovascular disease. However, whether the subtypes of MAFLD based on the metabolic disorder differentially impact liver fibrosis is not well explicated, especially in the Asian population.

AIM

To compare the severity of liver fibrosis among different MAFLD subtypes.

METHODS

A total of 322 adult patients of either gender with fatty liver on ultrasound were enrolled between January to December 2021. MAFLD was defined as per the Asian Pacific Association for the Study of the Liver guidelines. Fibrosis-4 index (Fib-4) and nonalcoholic fatty liver disease fibrosis score (NFS) were employed to evaluate liver fibrosis.

RESULTS

The mean age was 44.84 ± 11 years. Seventy-two percent of the patients were female. Two hundred and seventy-three patients were classified as having MAFLD, of which 110 (40.3%) carried a single, 129 (47.3%) had two, and 34 (12.5%) had all three metabolic conditions. The cumulative number of metabolic conditions was related to elevated body mass index, triglyceride (TG) levels, and

glycated hemoglobin, lower high-density lipoprotein (HDL) levels, higher liver inflammation (by aspartate aminotransferase and γ -glutamyl transferase), and higher likelihood of fibrosis (by NFS and Fib-4 scores) ($P < 0.05$ for all). The proportion of advanced fibrosis also increased with an increase in the number of metabolic conditions (4.1%, 25.5%, 35.6%, and 44.1% by NFS and 6.1%, 10.9%, 17%, and 26.5% by Fib-4 for no MAFLD and MAFLD with 1, 2, and 3 conditions, respectively). Among MAFLD patients, those with diabetes alone were the eldest and had the highest mean value of NFS score and Fib-4 score ($P < 0.05$), while MAFLD patients diagnosed with lean metabolic dysfunction exhibited the highest levels of TG and alanine aminotransferase but the lowest HDL levels ($P < 0.05$).

CONCLUSION

The study suggests that the severity of liver fibrosis in MAFLD patients is influenced by the number and type of metabolic conditions present. Early identification and management of MAFLD, particularly in patients with multiple metabolic conditions, are crucial to prevent liver-related complications.

Key Words: Metabolic syndrome; Diabetes; Fatty liver disease; Dyslipidemia; Obesity

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Core Tip: This is the first study on the South-Asian population on assessment of fibrosis among metabolic-associated fatty liver disease (MAFLD) patients. The study highlights that as the number of risk factors increases in a patient with MAFLD, it is more likely to have progression of liver fibrosis.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of diseases ranging from benign accumulation of excessive fat in the liver (steatosis) to the inflammation of liver cells [nonalcoholic steatohepatitis (NASH)]. It can lead to advanced fibrosis, cirrhosis, and subsequent hepatocellular carcinoma (HCC). NAFLD is now one of the common indications for liver transplantation from Western data. It is primarily a diagnosis of exclusion that needs to exclude other causes of liver fat accumulation, for instance, alcohol intake above a certain quantity, medications, viral hepatitis, and autoimmune liver disease[1]. The disease progression from benign fatty liver to inflammation and, ultimately, liver fibrosis is linked with the co-existence of diabetes mellitus (DM), obesity, and metabolic syndrome (MS)[2]. This has resulted in the proposal of this terminology change from NAFLD to metabolic-associated fatty liver disease (MAFLD) (metabolic malfunction associated fatty liver disease)[3]. The Asian Pacific Association for the Study of the Liver (APASL) also endorsed this amendment in nomenclature and the development of "diagnostic criteria" for MAFLD, unlike NAFLD, a diagnosis of exclusion[4].

When evaluating fatty liver and fibrosis, liver biopsy remains the gold standard. Due to its invasive nature, various noninvasive diagnostic tools (based on imaging or biomarkers) are now being used. Among them are the NAFLD fibrosis score (NFS) and fibrosis-4 index (Fib-4), endorsed by various guidelines as preference screening panels for predicting advanced fibrosis[4,5]. A strong body of evidence suggests that MAFLD is more effective than NAFLD in identifying significant liver fibrosis[6,7]. However, whether the subtypes of MAFLD differentially influence liver fibrosis is not very well understood, especially in the Asian population. Therefore, given the recent notion of MAFLD, our objective was to compare the severity of liver fibrosis among different MAFLD subtypes.

MATERIALS AND METHODS

This cross-sectional study was conducted at the National Institute of Liver and GI Diseases, located at Dow University Hospital in Karachi, Pakistan. Patients (ranging in age between 18 and 65 years, including both males and females) diagnosed with fatty liver disease between January and December 2021 were included. Those patients with decompensated liver disease, HCC, acute hepatitis, acute-on-chronic liver disease, and other concomitant liver disease (chronic active viral, alcohol, autoimmune, or metabolic liver diseases) were excluded from this study. Pregnant or lactating female patients and patients with concomitant systemic diseases such as tuberculosis, autoimmune disorders, and extra-hepatic malignancies were also excluded.

The demographic, clinical, and laboratory data of the patients were collected and analyzed. The main indications to perform an ultrasound examination were symptoms of dyspepsia and right upper quadrant abdominal pain and an evaluation showing deranged liver function tests. The fatty liver finding was confirmed on ultrasound examination based on the diffuse increased hepatic parenchymal echogenicity or "bright texture of liver parenchyma"[8]. According to the APASL guidelines, MAFLD was defined as the presence of fatty liver in conjunction with at least one of the following three conditions: Overweight/obesity, type 2 DM, or evidence of metabolic dysfunction (MD) such as increased waist circumference or an abnormal lipid or glycemic profile[4]. Fib-4 and NFS were noninvasive tools used to assess liver fibrosis in this population with fatty liver disease. Asian cutoffs for body mass index (BMI) were used to classify the subjects as overweight/obese *vs* lean/normal weight among different MAFLD groups. Figure 1 describes the study flow chart.

The study was approved by the Institutional Review Board of Dow University of Health Sciences (IRB-1842). Informed consent was obtained from all eligible participants. The methods employed in this study were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

The statistical analyses were executed using SPSS software version 26.0. Quantitative variables are expressed as the mean \pm SD, while categorical variables are represented as frequencies and percentages. The chi-square test was used to assess categorical variables. The Mann-Whitney *U*-test was applied to compare the difference between two groups, while the Kruskal-Wallis test was performed to evaluate the difference among three groups. A *P* value of 0.05 or less was considered significant.

RESULTS

A total of 322 patients with fatty liver were included, with a mean age of 44.84 ± 11 years. The majority were female (72%). The mean BMI was 29.83 ± 5.53 kg/m², 29.8% had DM, and 9.6% had hypertension.

Out of 322 patients with fatty liver, 273 were classified as having MAFLD. The MAFLD patients were further classified into three categories corresponding to their components of metabolic conditions (*i.e.*, one, two, and three). Out of 273 participants with MAFLD, 110 (40.3%) had a single metabolic condition, 129 (47.3%) had two metabolic conditions, and 34 (12.5%) had all three metabolic conditions (Figure 1).

With the increasing number of metabolic conditions, more patients were diabetic and obese, with the worsening of liver enzymes and lipid profile, as well as increasing hepatic fibrosis scores. With an increase in the cumulative number of metabolic conditions, the patients exhibited a significant elevation in their metabolic parameters such as BMI (28.99 ± 5.19 *vs* 31.63 ± 5.19 *vs* 33.59 ± 4.75 ; $P < 0.001$) and glycated hemoglobin (Hb1Ac) (5.97 ± 1.13 *vs* 6.82 ± 1.86 *vs* 8.22 ± 1.58 , $P < 0.001$). Significant worsening of lipid profile was also noted with the increasing number of metabolic conditions as triglyceride (TG) levels rose (182.45 ± 109.5 *vs* 198.13 ± 98.8 *vs* 221.85 ± 102.38 , $P = 0.002$), while high-density lipoprotein (HDL) levels showed a negative trend among MAFLD patients (41.65 ± 15.08 *vs* 36.05 ± 8.93 *vs* 32.38 ± 6.62 , $P < 0.001$).

As a consequence of these findings, increasing liver inflammation (as reflected by aspartate aminotransferase (AST) 28.62 ± 20.74 *vs* 32.29 ± 23.36 *vs* 40.06 ± 26.74 , $P = 0.021$ and γ -glutamyl transferase 34.93 ± 21.08 *vs* 51.50 ± 36.44 *vs* 65.41 ± 38.02 , $P < 0.001$) and liver fibrosis (reflected by the NFS score -2.59 ± 1.59 *vs* -2.00 ± 1.69 *vs* -1.39 ± 1.60 , $P = 0.002$ and Fib-4 score 0.79 ± 0.45 *vs* 0.94 ± 0.86 *vs* 1.11 ± 0.66 , $P = 0.041$) were seen as the trends of different metabolic categories (Table 1). The proportion of significant fibrosis was also established with the collective number of metabolic conditions. For the NFS score, advanced fibrosis was present in 4.1% of subjects with no fulfilled criteria for MAFLD and in 25.5%, 35.6%, and 44.1% with 1, 2, and 3 MAFLD conditions, respectively, while for the Fib-4 score, advanced fibrosis was present in 6.1% of subjects without MAFLD, and in 10.9%, 17%, and 26.5% with 1, 2, and 3 MAFLD conditions, respectively (Figure 2).

The age of the patients increases somewhat as the number of metabolic diseases increases, with more men afflicted, but these results were not statistically significant across the categories. There was also no significant difference in ALT, platelets, total cholesterol, low-density lipoprotein (LDL) cholesterol, total bilirubin, or alkaline phosphatase levels.

Furthermore, MAFLD patients with a single metabolic condition ($n = 110$, 40.3%) were sub-classified into three categories: Obesity alone ($n = 61$, 55.5%), lean MD ($n = 34$, 30.9%), and DM alone ($n = 15$, 13.6%). Among MAFLD patients with a single metabolic condition, those established with DM alone were the oldest and those with obesity alone were the youngest (mean age 50.73 ± 9.04 for DM *vs* 45.53 ± 10.60 for lean MD and 41.72 ± 10.03 for obesity alone, $P = 0.005$). Similarly significant differences were noted in platelet count, which was within the normal range but the lowest in the DM group (245.40 ± 50.70 *vs* 275.44 ± 81.92 in lean MD *vs* 314.85 ± 97.95 in obesity alone, $P = 0.004$), TG levels, which were the highest in the lean MD group (269.02 ± 120.03 *vs* 176.13 ± 132.33 in DM *vs* 135.75 ± 57.72 in obesity, $P < 0.001$), HDL levels, which were the lowest in the lean MD group (39.96 ± 21.71 *vs* 42.30 ± 8.73 in obesity *vs* 42.50 ± 11.14 in DM, $P = 0.026$), and ALT levels, which were the highest in lean MD (43.94 ± 28.41 *vs* 34.13 ± 19.04 in DM *vs* 33.89 ± 30.47 in obesity, $P = 0.043$). Similarly, diabetic MAFLD had the highest Hb1Ac levels (8.03 ± 1.71 *vs* 5.77 ± 0.48 *vs* 5.56 ± 0.46 , $P < 0.001$) than others (Table 2).

When compared among the three subtypes of MAFLD, the proportion of advanced liver fibrosis was significantly higher among diabetic MAFLD patients according to the NFS score (46.6% *vs* 26.5% for MD alone and 19.7% for obesity alone), whereas patients with lean MD had the highest proportion of advanced fibrosis according to the Fib-4 score (14.7% *vs* 9.8% for obesity alone *vs* 6.7% for DM alone) (Figure 3).

No significant differences were observed in gender distribution, education awareness, history of hypertension, blood pressure, and blood levels of cholesterol, LDL, bilirubin, albumin, AST, and alkaline phosphate between these respective

Table 1 Demographic, clinical, and laboratory characteristics of metabolic-associated fatty liver disease patients with different metabolic conditions

Characteristic	Total (n = 322)	No MAFLD (n = 49)	MAFLD (n = 273)			P value			
			Single condition (n = 110; 40.3%)	Two conditions (n = 129; 47.3%)	Three conditions (n = 34; 12.5%)	Overall	Single vs two	Single vs three	Two vs three
Age (yr)	44.84 ± 11	42.69 ± 12	44.13 ± 10.47	45.53 ± 10.80	47.65 ± 10.32	0.332	0.474	0.138	0.321
BMI (kg/m ²)	29.83 ± 5.53	34.38 ± 2.20	28.99 ± 5.19	31.63 ± 5.19	33.59 ± 4.75	< 0.001	< 0.001	< 0.001	0.064
Female gender (%)	232 (72)	32 (65.3)	85 (77.3)	94 (72.9)	21 (61.8)	0.201	0.434	0.073	0.206
Hypertension (%)	31 (9.6)	5 (10.2)	14 (12.7)	12 (9.3)	0 (0.0)	0.086	0.397	0.029	0.065
Diabetes (%)	96 (29.8)	0 (0)	15 (13.6)	47 (36.4)	34 (100)	< 0.001	< 0.001	< 0.001	< 0.001
NFS score	-2.41 ± 1.71	-3.76 ± 1.19	-2.59 ± 1.59	-2.00 ± 1.69	-1.39 ± 1.60	0.002	0.033	< 0.001	0.043
Fib-4 score	0.88 ± 0.67	0.75 ± 0.47	0.79 ± 0.45	0.94 ± 0.86	1.11 ± 0.66	0.041	0.771	0.009	0.031
DBP	85.22 ± 12.07	82.26 ± 11	85.32 ± 13.22	86.34 ± 11.59	84.91 ± 11.80	0.631	0.333	0.643	0.958
SBP	133.86 ± 19.18	129.34 ± 16	133.00 ± 17.73	134.83 ± 20.8	139.56 ± 20.55	0.133	0.148	0.071	0.376
Platelet count	295.77 ± 90.85	305.91 ± 73	293.20 ± 91.20	294.06 ± 92.0	295.97 ± 110.13	0.888	0.644	0.856	0.811
Total cholesterol	183.29 ± 45.18	184.3 ± 47.11	181.03 ± 42.35	182.94 ± 48.3	190.41 ± 39.58	0.375	0.705	0.266	0.161
LDL	124.81 ± 39.85	120.58 ± 38.16	123.85 ± 39.87	126.52 ± 41.3	127.44 ± 37.20	0.859	0.949	0.648	0.573
HDL	38.55 ± 12.08	43.01 ± 11.93	41.65 ± 15.08	36.05 ± 8.93	32.38 ± 6.62	< 0.001	< 0.001	< 0.001	0.038
TG	184.79 ± 101.2	125.57 ± 51.8	182.45 ± 109.5	198.13 ± 98.8	221.85 ± 102.38	0.002	0.022	0.001	0.050
Total bilirubin	0.54 ± 0.37	0.55 ± 0.26	0.53 ± 0.35	0.57 ± 0.43	0.49 ± 0.31	0.284	0.358	0.287	0.157
Direct bilirubin	0.21 ± 0.24	0.21 ± 0.23	0.19 ± 0.09	0.24 ± 0.35	0.18 ± 0.08	0.601	0.417	0.732	0.417
Serum albumin	4.41 ± 0.38	4.51 ± 0.34	4.41 ± 0.37	4.37 ± 0.38	4.40 ± 0.43	0.552	0.305	0.481	0.906
ALT	40.67 ± 31.69	42.2 ± 29	37.03 ± 28.70	42.30 ± 36.49	44.09 ± 24.15	0.058	0.229	0.022	0.097
AST	31.84 ± 22.6	32.22 ± 20	28.62 ± 20.74	32.29 ± 23.36	40.06 ± 26.74	0.021	0.361	0.004	0.040
GGT	46.02 ± 34.77	42.45 ± 43.65	34.93 ± 21.08	51.50 ± 36.44	65.41 ± 38.02	< 0.001	< 0.001	< 0.001	0.016
ALP	110.82 ± 51.76	105.3 ± 40	111.90 ± 59.42	108.22 ± 46.1	125.24 ± 58.81	0.169	0.802	0.089	0.070
HbA1c	6.44 ± 1.65	5.32 ± 0.4	5.97 ± 1.13	6.82 ± 1.86	8.22 ± 1.58	< 0.001	< 0.001	< 0.001	< 0.001

MAFLD: Metabolic associated fatty liver disease; BMI: Body mass index; NFS: Nonalcoholic fatty liver disease fibrosis score; Fib-4: Fibrosis-4 index; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ -glutamyl transferase; ALP: Alkaline phosphatase; HbA1c: Glycated hemoglobin.

Table 2 Comparison of demographic, clinical, and laboratory characteristics among metabolic associated fatty liver disease with a single metabolic condition alone

Characteristic	Obesity alone (n = 61)	Lean MD (n = 34)	DM alone (n = 15)	P value			
				Overall	Obesity vs lean MD	Obesity vs DM	Lean MD vs DM
Age (yr)	41.72 ± 10.03	45.53 ± 10.60	50.73 ± 9.04	0.005	0.082	0.002	0.116
BMI (kg/m ²)	32.33 ± 4.66	24.86 ± 1.63	24.81 ± 1.58	< 0.001	< 0.001	< 0.001	0.965
Female Gender (%)	51 (83.6)	23 (67.6)	11 (73.3)	0.191	0.072	0.358	0.691
Hypertension (%)	8 (13.1)	6 (17.6)	0 (0.0)	0.230	0.551	0.138	0.082
NFS score	-2.86 ± 1.74	-2.50 ± 1.40	-1.61 ± 0.81	0.017	0.309	0.005	0.054
Fib-4 score	0.68 ± 0.35	0.92 ± 0.56	0.95 ± 0.48	0.027	0.050	0.017	0.761
DBP	84.26 ± 15.41	87.03 ± 10.43	85.73 ± 8.61	0.499	0.262	0.548	0.728
SBP	131.03 ± 17.46	135.82 ± 19.94	134.60 ± 12.89	0.306	0.255	0.181	0.828
Platelet count	314.85 ± 97.95	275.44 ± 81.92	245.40 ± 50.70	0.004	0.032	0.002	0.298
Total cholesterol	176.91 ± 37.71	190.97 ± 49.33	175.00 ± 41.93	0.336	0.160	0.879	0.313
LDL	120.53 ± 35.87	126.76 ± 44.83	130.73 ± 44.80	0.626	0.473	0.433	0.688
HDL	42.50 ± 11.14	39.96 ± 21.71	42.30 ± 8.73	0.026	0.010	0.678	0.079
TG	135.75 ± 57.72	269.02 ± 120.03	176.13 ± 132.33	< 0.001	< 0.001	0.213	0.001
Total bilirubin	0.52 ± 0.43	0.55 ± 0.24	0.50 ± 0.22	0.171	0.055	0.698	0.467
Direct bilirubin	0.19 ± 0.10	0.18 ± 0.08	0.20 ± 0.09	0.613	0.480	0.549	0.424
Serum albumin	4.41 ± 0.34	4.40 ± 0.33	4.44 ± 0.59	0.731	0.779	0.526	0.428
ALT	33.89 ± 30.47	43.94 ± 28.41	34.13 ± 19.04	0.043	0.016	0.264	0.288
AST	25.75 ± 15.38	34.76 ± 29.26	26.33 ± 13.60	0.086	0.025	0.724	0.302
GGT	32.32 ± 21.22	37.85 ± 20.37	39.15 ± 22.28	0.139	0.083	0.169	0.849
ALP	113.61 ± 68.86	107.03 ± 39.59	116.00 ± 58.23	0.948	0.880	0.734	0.888
HbA1c	5.56 ± 0.46	5.77 ± 0.48	8.03 ± 1.71	< 0.001	0.006	< 0.001	< 0.001

MD: Metabolic dysfunction; DM: Diabetes mellitus; BMI: Body mass index; NFS: Nonalcoholic fatty liver disease fibrosis score; Fib-4: Fibrosis-4 index; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ -glutamyl transferase; ALP: Alkaline phosphatase; HbA1c: Glycated hemoglobin.

three groups.

DISCUSSION

The present study provides valuable insights into the progression of MAFLD and its subtypes in the Pakistani population. Our findings demonstrated that as the cumulative number of metabolic conditions increased, there was a corresponding escalation in the NFS and Fib-4 scores. This trend aligns with the work of Yamamura *et al*[6], which also reported that patients with multiple metabolic conditions exhibited a higher risk of advanced fibrosis.

In our study, around 60% of patients had more than one metabolic condition, which is comparable to a recent study of the NHANES III database in which more than 70% of all patients with MAFLD had more than one metabolic condition. Additionally, having more than one metabolic condition was associated with abnormal liver function tests and kidney diseases[9]. The same study found that there were an increasing number of metabolic conditions in the higher age group. In our study, there was only a non-significant association between older age and comorbidities. This may be attributed to the different demographic spectra in our population (North American *vs* Southeast Asian). Recent meta-analytical evidence lends further credence, delineating the clinical characteristics of NAFLD in Asian populations. It demonstrates that the pooled mean age of NAFLD patients was 52.07 years (95%CI: 51.28-52.85), which contrasts with a notably younger mean age of 42.66 years (95%CI: 32.23-53.11) observed in patients from Southeast Asia, indicating regional age-related disparities among NAFLD patients[10].

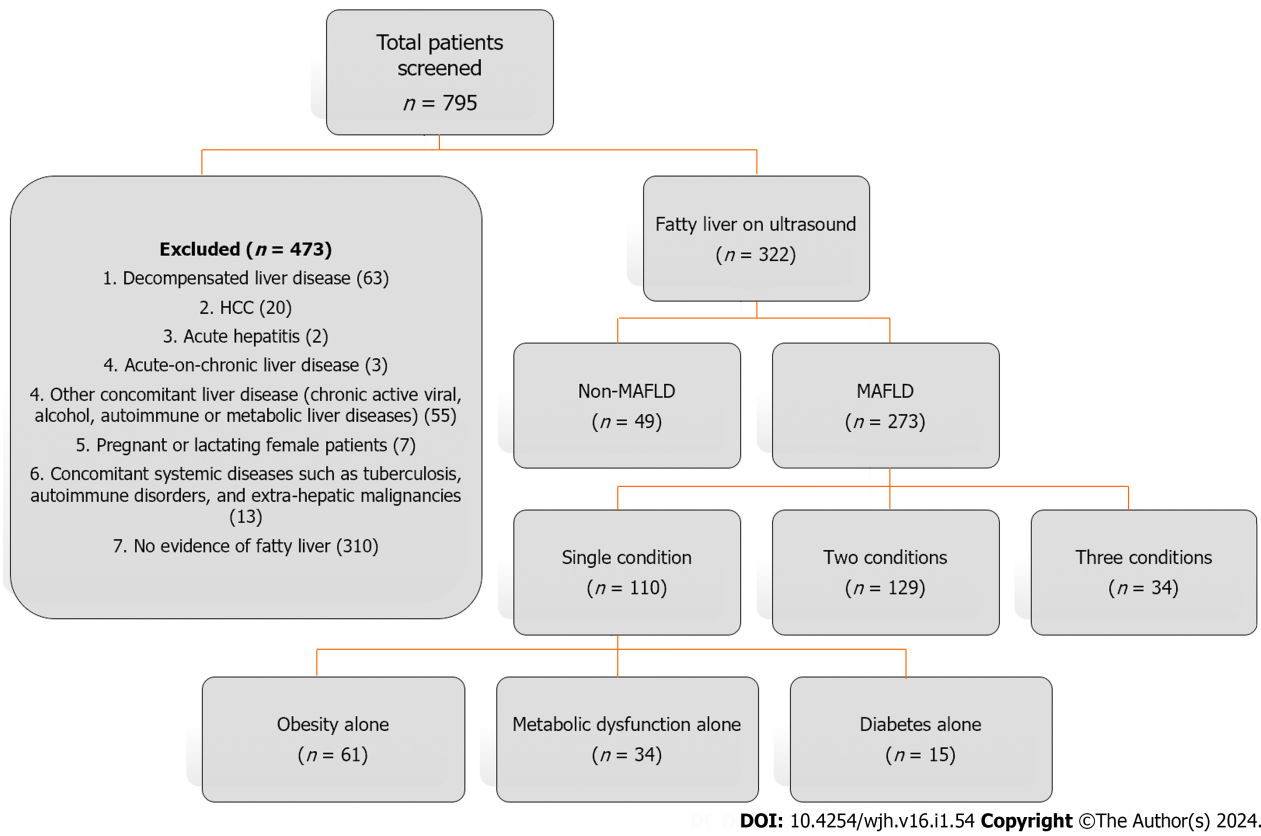


Figure 1 Flow chart of sample selection. HCC: Hepatocellular carcinoma; MAFLD: Metabolic-associated fatty liver disease.

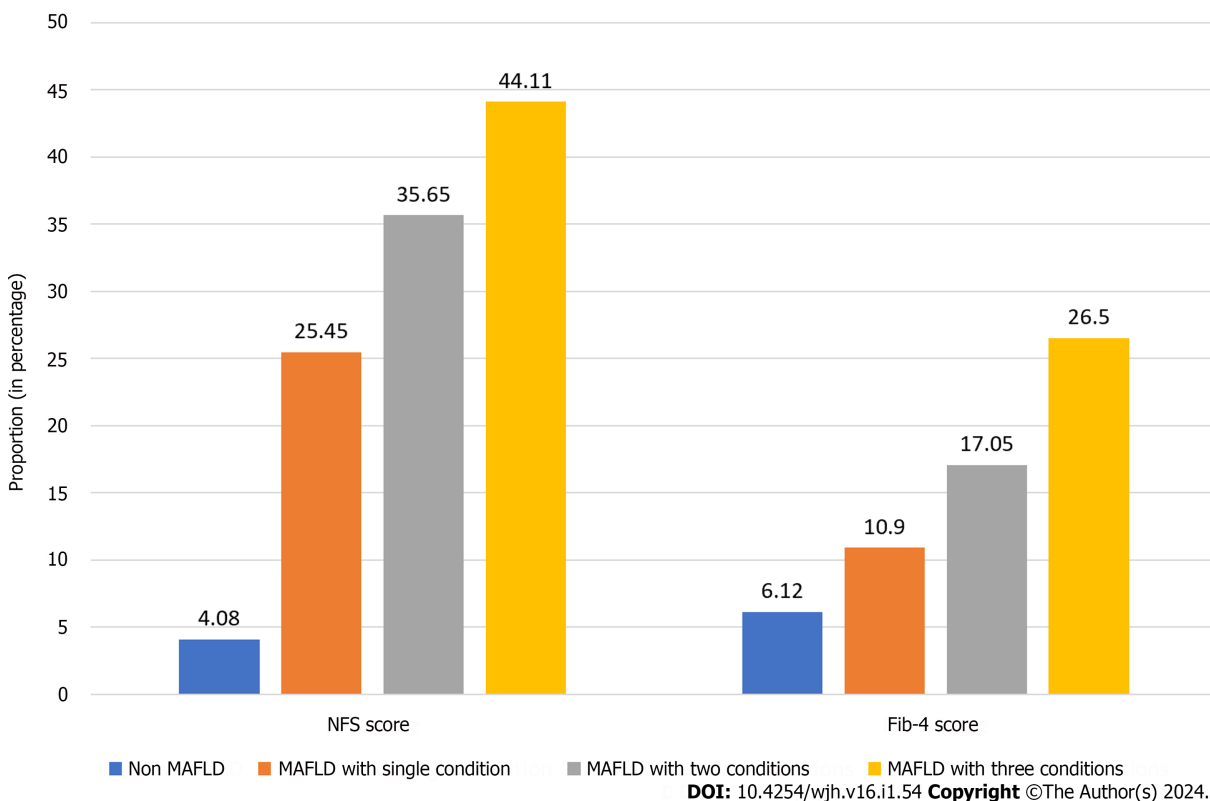


Figure 2 Proportion of advanced liver fibrosis in relation to the cumulative number of metabolic conditions. Fib-4: Fibrosis-4 index; NFS: Nonalcoholic fatty liver disease fibrosis score; MAFLD: Metabolic-associated fatty liver disease.

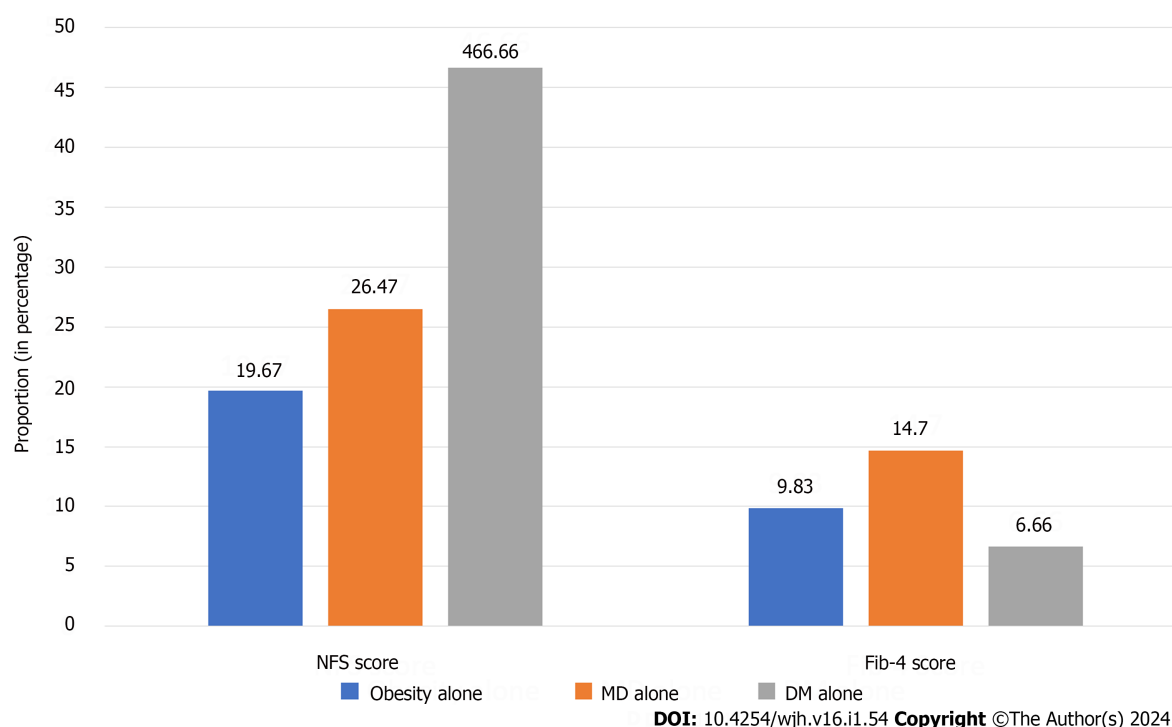


Figure 3 Proportion of advanced liver fibrosis in patients with single metabolic conditions. Fib-4: Fibrosis-4 index; NFS: Nonalcoholic fatty liver disease fibrosis score; MD: Metabolic dysfunction; DM: Diabetes mellitus.

The degree of liver fibrosis varies across MAFLD subtypes[11], with an increased risk of liver-related death as fibrosis progresses[12]. Hence, we further classified the MAFLD into subtypes according to the type of metabolic conditions. Interestingly, the sub-classification of MAFLD based on individual metabolic conditions revealed distinct profiles. Diabetic MAFLD patients tended to be older, have higher TG levels, and exhibit more pronounced fibrosis compared to those with other MAFLD subtypes, echoing the finding of Chhabra *et al*[13] that diabetes is a strong predictor of advanced fibrosis in MAFLD. Studies have consistently shown a higher proportion of advanced liver fibrosis in diabetic MAFLD patients compared to other MAFLD subtypes[9,14]. The relationship between DM, MAFLD, and advanced fibrosis is likely a multifactorial chronic process, with insulin resistance and older age playing significant roles[15,16]. This relationship is reflected in the Fib-4 and NFS scores, which incorporate age as a variable, leading to higher scores in older individuals. These findings underscore the importance of considering diabetes as a risk factor for advanced fibrosis in MAFLD patients, particularly among older individuals. Early identification and management of diabetes and MAFLD are crucial to prevent liver-related complications and improve patient outcomes.

Elevated TG, ALT, and AST levels in lean MAFLD indicate that lean MAFLD has clinical implications and is associated with liver inflammation or injury. Lean MAFLD patients have a more detrimental metabolic profile compared to lean non-MAFLD patients[17]. Lean MAFLD is independently associated with an increased risk of overall mortality [hazard ratio (HR): 1.296; 95%CI: 1.064-1.578][18], as well as liver-specific mortality (HR: 2.84; 95%CI: 2.72-2.97) as compared to other MAFLD subtypes[19]. Furthermore, this impact was also observed in post-liver transplant, as lean NASH patients have worse post-liver transplant overall survival compared to non-lean NASH (HR: 0.17; 95%CI: 0.03-0.86, $P = 0.0142$) [20]. These findings highlight the importance of recognizing lean MAFLD as a distinct clinical entity with significant adverse health outcomes. Early identification and management of lean MAFLD are crucial to prevent liver-related complications and improve patient outcomes.

On the other hand, individuals with obesity as the sole metabolic condition presented with a younger age and less severe fibrosis, suggesting a potential protective effect of youth or a longer disease trajectory before significant fibrosis develops, which has been suggested by Yang *et al*[21].

Our study did not find statistically significant differences in ALT, total cholesterol, LDL, bilirubin, or alkaline phosphatase levels across the MAFLD subtypes, which diverges from the findings of Wong *et al*[22], who reported dyslipidemia and elevated liver enzymes as common features in MAFLD patients. This discrepancy could be attributed to the genetic or dietary factors unique to our study population, underlining the complexity of MAFLD phenotypes as noted by Eslam *et al*[23].

The diagnostic performance of Fib-4 and NFS for advanced fibrosis can be influenced by various factors, including age, DM, and BMI. In particular, the inclusion of overweight or obesity as a criterion for MAFLD has impacted the BMI component in NFS, leading to differences in the sensitivity and specificity of the two scores in identifying advanced fibrosis. A recent study found that although the overall performance of Fib-4 and NFS in diagnosing liver fibrosis was similar between lean and non-lean individuals, the sensitivity and specificity of NFS varied according to BMI quartile ranges. Specifically, NFS was found to be less sensitive in lean individuals compared to Fib-4[24]. Another study found that the diagnostic ability of NFS was lower among individuals with diabetes compared to Fib-4 [area under the receiver

operating characteristic curve (AUROC) 0.717 *vs* 0.809; $P = 0.002$]. This suggests that NFS may not be as effective in identifying advanced fibrosis in patients with diabetes[25]. A recent study also found that Fib-4 was superior to NFS in accurately classifying non-obese NAFLD patients with F2–4 fibrosis (AUROC 81.5% *vs* 73.7%, $P < 0.001$). This suggests that Fib-4 may be a better choice for diagnosing advanced fibrosis in this patient population[26]. Overall, the evidence suggests that Fib-4 may be a more reliable tool for diagnosing advanced fibrosis than NFS, particularly in lean individuals and patients with diabetes. Further research is needed to confirm these findings and to determine the optimal use of both scores in clinical practice.

The strengths of this study are multifaceted, encompassing stringent participant selection, methodological robustness, ethical integrity, and analytical rigor. First, the study employed rigorous inclusion and exclusion criteria, ensuring a well-defined study population that accurately represented the target demographic for MAFLD. This strategic participant selection minimized confounding variables, thereby enhancing the validity of the findings. Second, the adoption of a cross-sectional study design facilitated the examination of the prevalence and association patterns of liver fibrosis with metabolic conditions at a specific point in time. Moreover, this is the first study on the South Asian population to highlight the importance of subtyping MAFLD, validating previous reports from the Western world that the severity of liver fibrosis varies across the MAFLD subtypes and is linked with mortality in fatty liver disease[27,28]. The ample sample size of 322 patients provided sufficient statistical power to the findings. The subclassification of MAFLD patients based on the presence of metabolic conditions permitted a nuanced analysis of the data. Lastly, the real-world clinical setting at Dow University Hospital ensured that the research findings were applicable and relevant to clinical practice, enhancing the external validity and generalizability of the study.

The present study, while contributing valuable insights into the long-term implications of MAFLD subtypes on hepatic fibrosis, is not without its limitations that merit acknowledgment. First, the study's design was observational, precluding any assertions of causality between MAFLD subtypes and the progression of hepatic fibrosis. Second, the reliance on existing clinical datasets limits the scope to fully capture the nuances of patients' longitudinal metabolic changes and their direct impact on liver pathology. Another constraint is the study's dependence on non-invasive markers of hepatic fibrosis, which, while clinically relevant, cannot substitute for the histopathological assessment through liver biopsy or transient elastography, the gold standard for fibrosis evaluation. The use of surrogate endpoints, therefore, necessitates cautious interpretation of the findings. However, Fib-4 and NFS are widely used and endorsed by various guidelines for screening MAFLD patients for advanced fibrosis, and they are superior to other scores like aspartate aminotransferase to platelet ratio index (APRI) and BMI, AST/ALT ratio, and diabetes mellitus (BARD)[29,30]. Even though, they may not be as effective due to limitations by risk factors like age and BMI scores[1]. Lastly, the study's geographic and demographic concentration may restrict the generalizability of the findings across different populations and ethnicities.

These limitations highlight areas for future research, emphasizing the need for prospective studies, using a longitudinal study design, larger sample size with a more diverse demographic distribution, integration of transient elastography with existing non-invasive markers like NFS and Fib-4, and comparative analyses juxtaposing patients with MAFLD against control groups without MD, to delineate the specific contributory pathways leading to fibrosis within the context of MS.

CONCLUSION

This research has rigorously demonstrated that the severity of liver fibrosis in MAFLD patients is influenced by the number and type of metabolic conditions present. Early identification and management of MAFLD, particularly in patients with multiple metabolic conditions, are crucial to prevent liver-related complications.

ARTICLE HIGHLIGHTS

Research background

Metabolic-associated fatty liver disease (MAFLD) is a medical condition characterized by the presence of fatty liver along with overweight/obesity and/or diabetes and/or metabolic dysfunction. However, whether the subtypes of MAFLD based on the metabolic disorder differentially impact on liver fibrosis is not well explicated, especially in the Asian population.

Research motivation

Different subgroups of MAFLD present distinct clinical spectra and risks of advanced liver fibrosis, which can influence their treatment strategies. Metabolic syndrome is related to higher deaths in nonalcoholic fatty liver disease (NAFLD) patients. Moreover, the high fibrotic burden in fatty liver disease is associated with a higher risk of development of hepatocellular carcinoma, liver-related mortality, and cardiovascular disease. Hence, it is worth classifying the MAFLD patients depending on the number of metabolic conditions at the beginning. This helps to stratify patients with MAFLD according to the long-term risk of significant liver fibrosis.

Research objectives

To compare the severity of liver fibrosis among different MAFLD subtypes.

Research methods

This was a cross-sectional investigation carried out at the National Institute of Liver and GI Diseases, located at Dow University Hospital in Karachi, Pakistan. All patients aged between 18 and 65 years, irrespective of gender, who were diagnosed with fatty liver between January and December 2021 were included. Patients with decompensated liver disease, hepatocellular carcinoma, acute hepatitis, acute-on-chronic liver disease, and other concomitant liver disease (chronic active viral, alcohol, autoimmune, or metabolic liver diseases) were excluded. Pregnant or lactating female patients and patients with concomitant systemic diseases such as tuberculosis, autoimmune disorders, and extra-hepatic malignancies were also excluded from the study. MAFLD was defined according to the Asia Pacific Association for the Study of the Liver guidelines, and fibrosis-4 index (Fib-4) and NAFLD fibrosis score (NFS) were used to assess liver fibrosis. Asian cutoffs were used for body mass index to classify the subjects into overweight/obese *vs* lean/normal weight MAFLD groups.

Research results

Out of 322 patients with fatty liver, 273 were classified as having MAFLD. The MAFLD patients were segregated into three categories according to their number of metabolic conditions (*i.e.*, one, two, and three). Out of 273 participants with MAFLD, 110 (40.3%) carried a single metabolic condition, 129 (47.3%) had two metabolic conditions, and 34 (12.5%) had all the three metabolic conditions. The proportion of significant fibrosis increased with the cumulative number of metabolic conditions. For the NFS score, advanced fibrosis was 4.1%, 25.5%, 35.6%, and 44.1% for no MAFLD and MAFLD with 1, 2, and 3 conditions, respectively, while for Fib-4 score, the proportion of advanced fibrosis was 6.1%, 10.9%, 17%, and 26.5% for no MAFLD and MAFLD with 1, 2, and 3 conditions, respectively. Furthermore, MAFLD patients with a single metabolic condition ($n = 110$, 40.3%) were sub-classified into three categories: Obesity alone ($n = 61$, 55.5%), lean metabolic dysfunction (MD) ($n = 34$, 30.9%), and diabetes mellitus (DM) alone ($n = 15$, 13.6%). When compared among the three subtypes of MAFLD, the proportion of advanced liver fibrosis was significantly higher among diabetic MAFLD patients according to the NFS score (46.6% *vs* 26.5% for MD alone and 19.7% for obesity alone), whereas patients with lean MD had the highest proportion of advanced fibrosis according to the Fib-4 score (14.7% *vs* 9.8% for obesity alone *vs* 6.7% for DM alone).

Research conclusions

The increased number of metabolic conditions increases the likelihood of fibrosis in patients with MAFLD. The severity of liver fibrosis varies among different subtypes of MAFLD. Patients with diabetes and MAFLD have the highest risk of developing fibrosis.

Research perspectives

The direction of future research in this area involves several key questions that need to be addressed. Investigating the specific diagnostic markers for different subgroups within MAFLD, such as those with obesity, lean individuals, and those with type 2 diabetes. Further exploration is needed regarding the pathogenesis of MAFLD/metabolic dysfunction-associated steatohepatitis (MASH). By conducting thorough investigations into these areas, researchers can gain a better understanding of the complexities surrounding non-alcoholic fatty liver disease and its associated MD. Future research should focus on identifying effective pharmacotherapeutic interventions for MAFLD/MASH, as there is currently no approved treatment for this condition.

FOOTNOTES

Author contributions: Shaikh SS designed the research study; Shaikh SS and Nafay S participated in the data acquisition; Shaikh SS and Zaheer S participated in the analysis and interpretation of the data; Shaikh SS and Qazi-Arisar FA drafted the initial manuscript; Qazi-Arisar FA, Shaikh H, and Azam Z revised the article critically for important intellectual content.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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