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From NAFLD to MASLD: Meta-analysis and systematic review of NAFLD patients in Turkiye in terms of metabolic profile and MASLD potential

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Abstract

Non-alcoholic Fatty Liver Disease (NAFLD) is both a cause and a consequence of metabolic disturbances. Consequently, the disease term has recently changed to Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Turkiye is one of the leading countries with high incidences of diseases such as diabetes, obesity, metabolic syndrome, and fatty liver. This study aims to identify the metabolic parameters and MASLD potential of NAFLD in Turkiye. All NAFLD studies conducted in Turkiye were systematically searched using the keywords "fatty liver disease" AND " Turkiye " on PubMed, Scopus, and Web of Science databases. A total of 2653 articles were scanned, and 120 studies were eligible for meta-analysis. The metabolic parameters were meta-analyzed from a broad perspective. According to the meta-analysis results, there were significant increases in waist circumferences (mean difference: 10.90, p<0.00001), HOMA-IR (mean difference: 2.13, p<0.00001), aspartate aminotransferase (AST) (mean difference: 17.82, p<0.00001), systolic blood pressure (SBP) (mean difference: 5.86, p<0.00001), and C-reactive protein (CRP) levels (mean difference: 0.95, p<0.00001). These parameters are representative biochemical findings of disturbed glucose metabolism, lipid profile, blood pressure, and acute phase response mechanisms. Furthermore, the analysis of all related parameters commonly found among the articles confirmed these metabolic dysfunctions. NAFLD is a metabolic disease that encompasses multiple pathways related to glucose and lipid metabolism, vascular function, inflammation, and acute phase responses. Additionally, our results suggest that Turkish NAFLD patients identified in previous studies mostly have MASLD. This is the first meta-analysis study indicating changes in metabolism-related parameters with a cumulative meta-analysis of all Turkish NAFLD studies.

Keywords: Diabetes; fatty liver disease; hypertension; inflammation; lipid profile; metabolism.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of ≥5% hepatic steatosis without a competing liver disease such as viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, or alcoholic liver disease, and without the use of steatosis-inducing medications. Non-alcoholic steatohepatitis (NASH)[1] occurs with histopathological findings that cause hepatic damage, fibrosis, cirrhosis, and mortality in a smaller subset of patients with NAFLD.[2] Furthermore, with the participation and agreement of 236 panelists from 56 countries, new medical terms were introduced to the scientific field. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is the new designation for NAFLD and is defined by the detection of liver steatosis (via liver histology, non-invasive biomarkers, or imaging) together with at least one of three criteria: overweight or obesity, type 2 diabetes mellitus, or clinical evidence of metabolic dysfunction such as high waist circumference or abnormal lipid or glycemic profiles. Similarly, the term for nonalcoholic steatohepatitis was changed to "metabolic-associated steatohepatitis" (MASH) to refer to steatohepatitis patients with metabolic dysfunctions.[3,4] Also, diagnostic criteria were updated. In the presence of steatotic liver disease (SLD), the identification of any cardiometabolic risk factor alone would lead to a diagnosis of MASLD, provided no other causes of hepatic steatosis are evident. If additional contributors to steatosis are discovered, it suggests a combination etiology. Specifically, in cases involving alcohol, it is referred to as MASLD with increased alcohol intake (MetALD). In situations where explicit cardiometabolic criteria are absent, other potential causes must be ruled out. If none are found, this is categorized as cryptogenic SLD. However, depending on clinical judgment, it could also be considered as a possible MASLD, warranting periodic reassessment on a case-by-case basis.[4]

NAFLD is a significant burden of health problems that cause chronic liver diseases worldwide. A very recent meta-analysis examined the up-to-date incidence of NAFLD with data from 1,201,807 individuals across 63 studies. According to this global analysis, the incidence of NAFLD was found to be 4,613 per 100,000 person-years, particularly high in men, with a dramatic increase of more than threefold between 2000 and 2015.[5] According to regional results in 2019, NAFLD occurs in 31.29% of the Middle East, 30.45% of South America, 27.37% of Asia, 24.13% of North America, 23.71% of Europe, and 13.48% of Africa.[6] Nearly 30% of the world's population is currently challenged with this health problem.[7]

In America, the number of NAFLD patients, which was 83 million in 2015, is expected to increase to 100.9 million by 2030, a 21% increase, while the prevalence of NASH cases will increase by 63% from 16.52

million to 27.00 million cases.[8] The prevalence of NAFLD is estimated to be 20%–30% in the European Union, and about 3% is NASH. The advanced fibrosis incidence in NASH patients was 67.95 in 1,000 person-years. Liver-specific mortality in the pooled NAFLD versus non-NAFLD incidence rate ratio was found to be 1.94. The adjusted liver-specific mortality hazard ratio for NAFLD patients was 2.60. Although the prevalence of advanced fibrosis among NAFLD patients in the USA and Europe was 10–15%, fibrosis development was found to be lower in the Asia region compared to Western countries.[9] In Turkiye, multi-center prevalence studies are limited in showing the current NAFLD status. However, recent published data pointed to an alarming prevalence of 48.3%, which seems reasonable when compared with the obesity prevalence in Turkiye.[10]

NAFLD is a part of the metabolic syndrome hepatic outcomes and is commonly seen in obese and diabetic patients. Whether NAFLD is a cause or consequence of insulin resistance has been debated for a long time. On the other hand, "lean-NAFLD" can be seen in non-obese subjects, especially in low-income countries or rural areas.[11] This meta-analysis aimed to evaluate all NAFLD cases and their control data in the literature to show the metabolic profile of the disease in Turkiye cumulatively for the first time. The MASLD potential of these patients was discussed according to meta-analysis results.

Materials and Methods

Study Design

To determine the metabolic profile of Turkish NAFLD patients, all NAFLD studies conducted in Turkiye were systematically searched using the keywords "fatty liver disease" and "Turkiye" on PubMed, Scopus, and Web of Science databases. All characteristics and biochemical data were screened and collected for related meta-analysis. Inclusion criteria were established as providing suitable data (using international units) of biochemical parameters for NAFLD-diagnosed patients and a healthy control group.

The parameters of NAFLD diagnosis were generally based on ultrasound screening. Many studies confirmed ultrasound screening results with histopathological examinations after liver biopsy and used elevated liver enzyme levels as inclusion criteria. Exclusion criteria were generally similar across studies, excluding individuals with viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, α1-antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, malignancies, previous abdominal surgery, medication use, and daily alcohol intake exceeding 20 g/day. Several studies also excluded chronic conditions such as coronary artery disease, acute chronic renal failure, hypertension, and diabetes. Some studies set the alcohol intake exclusion limit at 30 or 40 g/day. Detailed information about the inclusion and exclusion criteria of each study was given in Appendix 1.

There were no additional restrictions for individual characteristics. The systematic search continued until July 2023. PRISMA statement guidelines were followed for this meta-analysis. Since this article is a meta-analysis, ethics committee approval is not required.

Statistical Analysis

Cumulative data analysis was conducted to show the metabolic comorbidities of Turkish NAFLD patients. All analysis procedures were performed according to the Cochrane Handbook (cochrane.org/handbook). Mean and standard deviation values of each marker that was cumulatively assessed were entered into the RevMan 5.3 program. Weighted

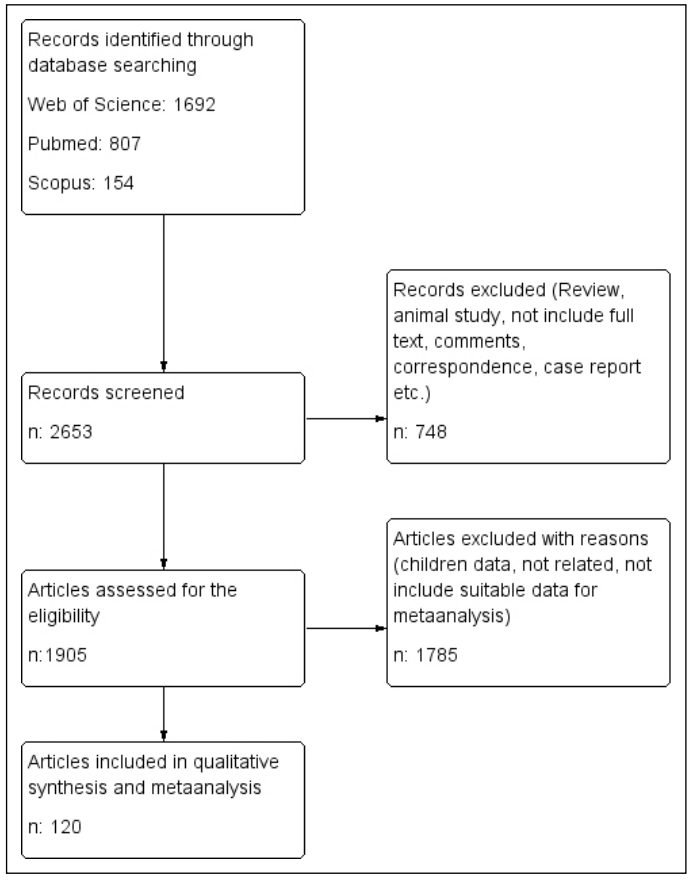

Figure 1. Flow diagram of study selection.

analysis was automatically performed by RevMan 5.3 according to the power of articles. Study power is calculated by RevMan, based on values for effect size magnitude, sample size, the number of studies, and the amount of between-study variability. The I2 was used to measure heterogeneity, which can be seen at the bottom of each figure. I2% values of 0–25, 25–50, 50–75, and 75–100 represent no, low, moderate, and high heterogeneity, respectively. The fixed and random effect models were used according to the heterogeneity tau2 value to combine the results. If the tau2 value is found as 0, the fixed effect model can be used. However, in all our results, the tau2 value was found to be different from 0, which led us to use the random effect model for a better assessment. RevMan 5.3 (Cochrane Collaboration, Copenhagen, 2014) software was used for the meta-analysis, and GraphPad Prism 6 software was used for correlation analysis and visualizing the results.

Results

In total, 2653 articles were scanned. As a result of the screening, 2533 studies were found ineligible for this meta-analysis. The remaining 120 studies were eligible for meta-analysis, and all data on patient and control groups from these studies[10,12–130] were evaluated (Fig. 1).

Obesity-Glucose Metabolism Related Parameters

Data from 14138 NAFLD and 15335 healthy individuals showed that the BMI level is significantly higher in the NAFLD group (Mean difference: 3.48, 95% CI: [3.02, 3.94], $p<0.00001$). Waist circumference in the NAFLD group (n=4650) was increased compared to the control group

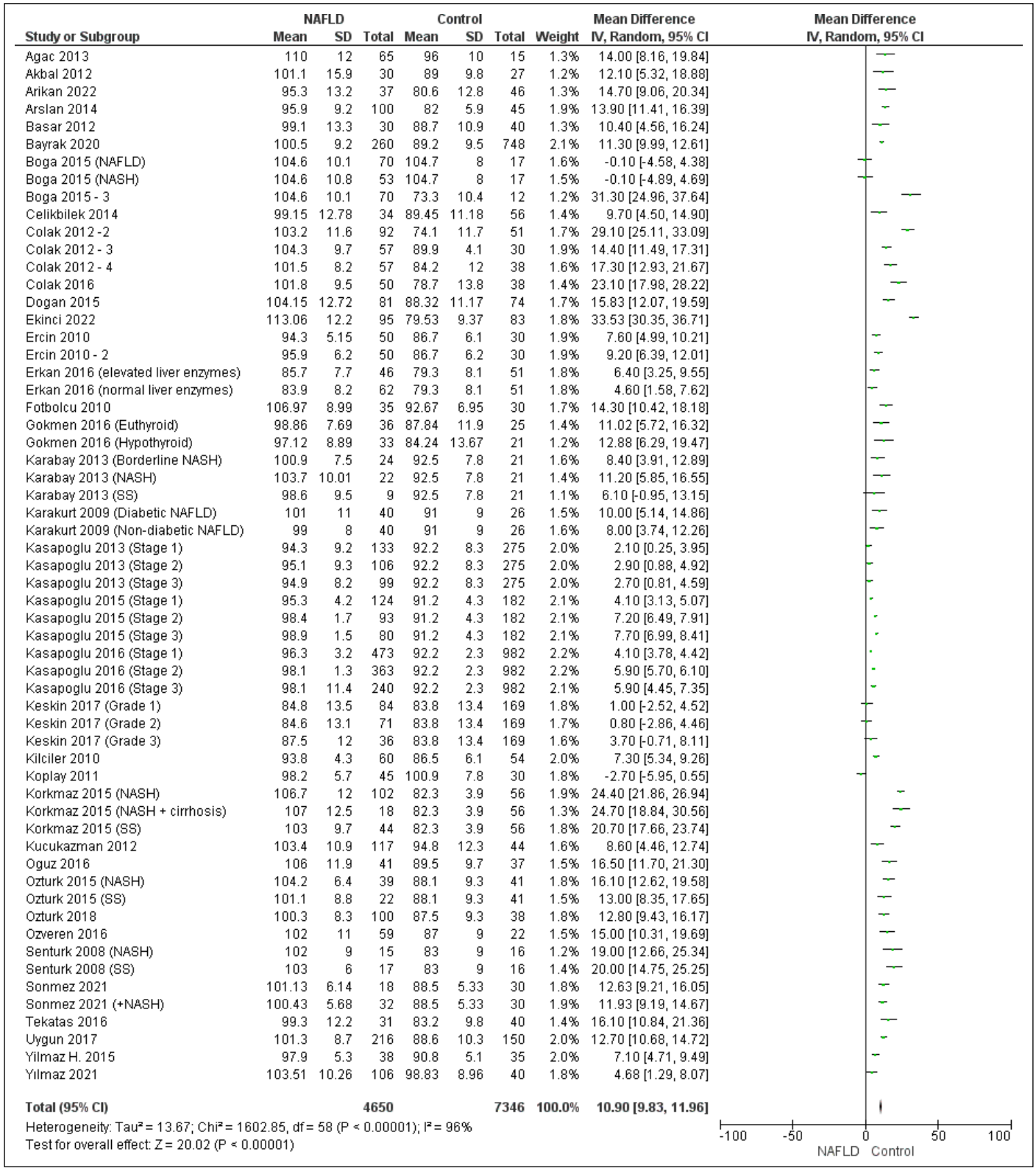

Figure 2. The random effect model of cumulative meta-analysis for waist circumference data obtained from NAFLD and control individuals.

(n=7346) (Mean difference: 10.90 cm, 95% CI: [9.83, 11.96], p<0.00001) (Fig. 2). Data from 6769 NAFLD and 7646 healthy individuals showed that fasting blood glucose levels were higher in the NAFLD group (Mean difference: 12.32 mg/dl, 95% CI: [9.96, 14.69], p<0.00001). HbA1c% values were higher in the NAFLD group (n=1254) than in the control group (n=1327) (Mean difference: 0.52, 95% CI: [0.28, 0.76], p<0.0001).

Study or Subgroup	NAFLD Mean	NAFLD SD	NAFLD Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Akbal 2012	4.5	3.2	30	2.2	1.9	27	0.8%	2.30 [0.95, 3.65]
Akkiz 2021	4.62	6.58	200	1.29	0.32	61	1.1%	3.33 [2.41, 4.25]
Arslan 2014	3.6	3.1	100	0.95	0.36	45	1.3%	2.65 [2.03, 3.27]
Aygun 2008	5.8	4.6	40	1.94	0.88	40	0.8%	3.86 [2.41, 5.31]
Aygun 2014 (elevated liver enzymes)	7.1	1.2	31	1.8	0.2	20	1.4%	5.30 [4.87, 5.73]
Aygun 2014 (normal liver enzymes)	7.9	1.7	20	1.8	0.2	20	1.2%	6.10 [5.35, 6.85]
Boga 2015 (NAFLD)	5.3	3.9	70	3.4	1.4	17	1.0%	1.90 [0.77, 3.03]
Boga 2015 (NASH)	5.9	4.2	53	3.4	1.4	17	0.9%	2.50 [1.19, 3.81]
Boga 2015 - 3	5.2	3.8	70	1.9	1	12	1.0%	3.30 [2.25, 4.35]
Cengiz 2009	3.63	3.24	76	1.6	0.47	24	1.2%	2.03 [1.28, 2.78]
Cetindagli 2017	3.22	1.3	93	1.54	0.47	37	1.4%	1.68 [1.38, 1.98]
Colak 2011	3.2	1.2	60	1.2	0.8	52	1.4%	2.00 [1.63, 2.37]
Colak 2012	2.8	1.86	50	1.35	0.53	28	1.3%	1.45 [0.90, 2.00]
Colak 2012 - 4	4.21	4.1	92	1.35	0.53	51	1.1%	2.86 [2.01, 3.71]
Colak 2016	2.7	1.8	50	0.94	0.5	38	1.3%	1.76 [1.24, 2.28]
Ekinci 2022	7.56	7.95	95	2.48	1.76	83	0.7%	5.08 [3.44, 6.72]
Eminler 2014	5.81	0.88	40	2.04	0.21	40	1.4%	3.77 [3.49, 4.05]
Fotbolcu 2010	3.59	1.51	35	1.28	0.29	30	1.3%	2.31 [1.80, 2.82]
Gokmen 2016 (Euthyroid)	2.62	1.43	36	1.39	0.53	25	1.3%	1.23 [0.72, 1.74]
Gokmen 2016 (Hypothyroid)	2.61	1.3	33	1.34	0.67	21	1.3%	1.27 [0.74, 1.80]
Gulsen 2005	5.58	1.67	71	2.53	1.07	30	1.3%	3.05 [2.50, 3.60]
Kara 2013	3.4	2.3	103	1.5	0.8	57	1.4%	1.90 [1.41, 2.39]
Karabay 2013 (Borderline NASH)	2.7	1.41	24	0.96	0.26	21	1.3%	1.74 [1.17, 2.31]
Karabay 2013 (NASH)	3.98	2.6	22	0.96	0.26	21	1.0%	3.02 [1.93, 4.11]
Karabay 2013 (SS)	1.61	0.93	9	0.96	0.26	21	1.3%	0.65 [0.03, 1.27]
Karakurt 2009 (Diabetic NAFLD)	3.4	2.6	40	1.5	0.9	26	1.1%	1.90 [1.02, 2.78]
Karakurt 2009 (Non-diabetic NAFLD)	1.7	1.2	40	1.5	0.9	26	1.3%	0.20 [-0.31, 0.71]
Karaoğullarından 2023	4.43	5.88	290	1.29	0.38	108	1.2%	3.14 [2.46, 3.82]
Kasapoglu 2013 (Stage 1)	2.1	0.5	133	1.4	0.8	275	1.5%	0.70 [0.57, 0.83]
Kasapoglu 2013 (Stage 2)	2.4	0.4	106	1.4	0.8	275	1.5%	1.00 [0.88, 1.12]
Kasapoglu 2013 (Stage 3)	2.4	0.3	99	1.4	0.8	275	1.5%	1.00 [0.89, 1.11]
Kasapoglu 2015 (Stage 1)	2.6	0.9	124	1.4	0.7	182	1.5%	1.20 [1.01, 1.39]
Kasapoglu 2015 (Stage 2)	3.2	0.9	93	1.4	0.7	182	1.5%	1.80 [1.59, 2.01]
Kasapoglu 2015 (Stage 3)	3.5	1	80	1.4	0.7	182	1.5%	2.10 [1.86, 2.34]
Kasapoglu 2015 - 2 (Stage 1)	2.6	0.9	88	1.5	1.4	136	1.4%	1.10 [0.80, 1.40]
Kasapoglu 2015 - 2 (Stage 2)	3.6	1.1	38	1.5	1.4	136	1.4%	2.10 [1.68, 2.52]
Kasapoglu 2015 - 2 (Stage 3)	3.7	1	24	1.5	1.4	136	1.4%	2.20 [1.74, 2.66]
Kasapoglu 2016 (Stage 1)	2.6	0.9	473	1.5	1.4	982	1.5%	1.10 [0.98, 1.22]
Kasapoglu 2016 (Stage 2)	3.6	1.1	363	1.5	1.4	982	1.5%	2.10 [1.96, 2.24]
Kasapoglu 2016 (Stage 3)	3.7	1	240	1.5	1.4	982	1.5%	2.20 [2.05, 2.35]
Korkmaz 2015 (NASH)	4.9	3.1	102	2.5	1	56	1.3%	2.40 [1.74, 3.06]
Korkmaz 2015 (NASH + cirrhosis)	7.7	3.9	18	2.5	1	56	0.6%	5.20 [3.38, 7.02]
Korkmaz 2015 (SS)	3.8	3.2	44	2.5	1	56	1.1%	1.30 [0.32, 2.28]
Kucukazman 2014	3.45	3.29	154	2.85	2.73	57	1.1%	0.60 [-0.28, 1.48]
Kutlu 2019	4.1	2.8	51	1.6	0.78	30	1.2%	2.50 [1.68, 3.32]
Oral 2019	2.6	1.61	225	1.71	0.77	142	1.5%	0.89 [0.64, 1.14]
Oral 2019 - 2	2.6	1.61	225	1.71	0.77	142	1.5%	0.89 [0.64, 1.14]
Ozturk 2015 (NASH)	4.5	3.2	39	2.1	0.9	41	1.0%	2.40 [1.36, 3.44]
Ozturk 2015 (SS)	3.9	2.4	22	2.1	0.9	41	1.0%	1.80 [0.76, 2.84]
Ozturk 2018	4.5	2.6	100	2.1	0.9	38	1.3%	2.40 [1.82, 2.98]
Ozveren 2016	3.9	2.2	59	1.5	0.5	22	1.3%	2.40 [1.80, 3.00]
Purnak 2012	2.7	0.8	50	2.6	0.88	26	1.4%	0.10 [-0.30, 0.50]
Sapmaz 2016	3.39	3	176	1.95	1.6	90	1.3%	1.44 [0.89, 1.99]
Sargin 2005	3.3	1.5	35	2.1	1.1	34	1.3%	1.20 [0.58, 1.82]
Senates 2011	3.78	2.41	88	1.5	0.8	88	1.3%	2.28 [1.75, 2.81]
Senates 2012	3.7	2.6	97	1.5	0.8	66	1.3%	2.20 [1.65, 2.75]
Senturk 2008 (NASH)	6	2.2	15	2.5	0.4	16	1.0%	3.50 [2.37, 4.63]
Senturk 2008 (SS)	3.9	1.1	17	2.5	0.4	16	1.3%	1.40 [0.84, 1.96]
Tekatas 2016	2.7	3.4	31	0.8	0.7	40	0.9%	1.90 [0.68, 3.12]
Ulaşoğlu 2021	3.9	3.5	175	1.5	0.6	74	1.3%	2.40 [1.86, 2.94]
Uygun 2017	4.6	5.4	216	2.2	1	150	1.2%	2.40 [1.66, 3.14]
Yalniz 2006	7	9.2	37	1.75	0.67	25	0.3%	5.25 [2.27, 8.23]
Yesilova 2005	4.39	0.22	46	2.45	0.28	30	1.5%	1.94 [1.82, 2.06]
Yilmaz Y. 2009	4.7	3.4	40	1.1	0.7	14	1.0%	3.60 [2.48, 4.72]
Yilmaz Y. 2010	3.5	2.2	59	1.4	0.4	77	1.3%	2.10 [1.53, 2.67]
Yilmaz Y. 2010 - 2 (Borderline NASH)	3.8	1.9	17	1.2	0.6	58	1.1%	2.60 [1.68, 3.52]
Yilmaz Y. 2010 - 2 (NASH)	3.3	1.7	26	1.2	0.6	58	1.2%	2.10 [1.43, 2.77]

Mean Difference IV, Random, 95% CI

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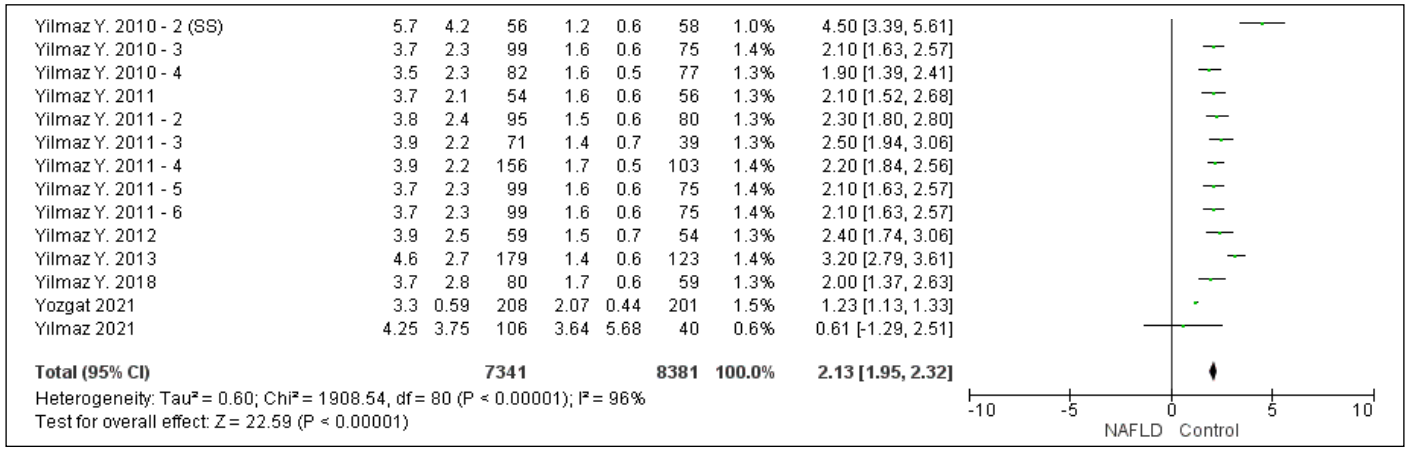

Figure 3. The random effect model of cumulative meta-analysis for HOMA-IR data obtained from NAFLD and control individuals.

Insulin levels were also higher in the NAFLD group (n=3194) compared to the control group (n=1881) (Mean difference: 6.73, 95% CI: [5.94, 7.53], p<0.00001). The HOMA-IR values showed a significant increase in the NAFLD group (n=7341) compared to the control group (n=8381) (Mean difference: 2.13, 95% CI: [1.95, 2.32], p<0.00001) (Fig. 3).

Liver Function Parameters

AST values of the NAFLD group (n=9357) were higher than those of the control group (n=11080) (mean difference: 17.82 IU/L, 95% CI: [15.47, 20.17], p<0.00001) (Fig. 4). Similarly, ALT levels in the NAFLD group (n=12535) were increased compared to the healthy group (n=14434) (mean difference: 35.11 IU/L, 95% CI: [31.27, 38.95], p<0.00001). Increased ALP levels were observed in NAFLD patients (n=2615) compared to healthy controls (n=4452) (mean difference: 12.10 IU/L, 95% CI: [8.38, 15.83], p<0.00001). GGT levels in the NAFLD group (n=5756) were higher than in the control group (n=7634) (mean difference: 21.73, 95% CI: [19.35, 24.10], p<0.00001). No significant difference was found in total bilirubin levels between the NAFLD group (n=830) and control group (n=735) (mean difference: 0.07, 95% CI: [-0.01, 0.16], p=0.10). Similarly, albumin levels showed no significant difference between groups (NAFLD group n=1994, control group n=1752) (mean difference: -0.02, 95% CI: [-0.09, 0.05], p=0.55).

Hyperlipidemia Related Parameters

Increased levels of triglycerides were found in NAFLD patients (n=9052) compared to healthy individuals (n=10489) (Mean difference: 49.34 mg/dl, 95% CI: [44.24, 54.44], p<0.00001). HDL levels of the NAFLD group (n=9097) were lower than those of the control group (n=10522) (Mean difference: -2.59 mg/dl, 95% CI: [-3.86, -1.32], p<0.0001). LDL levels of the NAFLD group (n=8695) were higher than those of the control group (n=10249) (Mean difference: 13.52, 95% CI: [10.94, 16.10], p<0.00001). Total cholesterol levels of NAFLD patients (n=8823) were also increased compared to controls (n=9699) (Mean difference: 22.59, 95% CI: [18.94, 26.24], p<0.00001).

Blood Pressure Parameters

Systolic blood pressure (SBP) was higher in NAFLD patients (n=3778) compared to controls (n=2987) (mean difference: 5.86 mmHg, 95% CI: [5.39, 8.14], p<0.00001) (Fig. 5). Diastolic blood pressure was also increased in NAFLD patients (n=3778) compared to controls (n=2987) (mean difference: 3.83 mmHg, 95% CI: [2.55, 5.11], p<0.00001).

Acute Phase Reactants

CRP values of the NAFLD group (n=3765) were higher than those of the control group (n=5859) (Mean difference: 0.95 mg/L, 95% CI: [0.72, 1.19], p<0.00001) (Fig. 6. ESR was prolonged in the NAFLD group (n=786) compared to the healthy group (n=482) (mean difference: 2.35 mm/hr, 95% CI: [0.47, 4.23], p<0.01). Ferritin levels in NAFLD patients (n=1921) were increased compared to the control group (n= 3812) (Mean difference: 45.63 ng/mL, 95% CI: [32.72, 58.54], p<0.00001). Hemoglobin levels were also higher in the NAFLD group (n=398) than in the control group (n=780) (Mean difference: 0.28, %95 CI: [0.12, 0.43], p=0.0004). Serum creatinine levels of NAFLD patients (n=2650) were higher than those of healthy controls (n=2479) (mean difference: 0.07 mg/dL, 95% CI: [0.05, 0.09], p<0.00001).

Correlation Results

Correlation analysis indicated that obesity and glucose metabolism parameters such as fasting blood glucose, waist circumference, insulin, and HOMA-IR levels were associated with liver function, as evidenced by increases in ALT, AST, and GGT enzyme levels. Fasting blood glucose correlated with AST (p<0.0001, r=0.401), ALT (p<0.0001, r=0.276), and GGT (p=0.018, r=0.245). Waist circumference levels were found to be correlated with AST (p<0.0001, r=0.371), ALT (p<0.0001, r=0.368), and ALP (p=0.04, r=0.50). Similarly, insulin/HOMA-IR levels correlated with AST (p=0.001/p<0.0001, r=0.342/0.760), ALT (p<0.0001/p<0.0001, r=0.369/0.710), and GGT levels (p=0.017/p<0.0001, r=0.289/0.495).

Discussion

Our meta-analysis showed that Turkish NAFLD patients have glucose metabolism disorders, hyperlipidemia, and impaired liver functions compared to the control group. Blood pressure values were elevated in NAFLD patients. Furthermore, CRP, ESR, Ferritin, Hemoglobin, and Creatinine levels, which were determined as acute phase reactants, were elevated in NAFLD patients in Turkiye. These results suggest that NAFLD patients in Turkiye carry a high risk of metabolic dysfunction and that Turkish NAFLD patients detected in previous studies might mostly have MASLD.

Study or Subgroup	NAFLD Mean	NAFLD SD	NAFLD Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Acikel 2009 (Grade 1)	31.9	35.8	100	48.6	90.9	140	0.7%	-16.70 [-33.31, -0.09]
Acikel 2009 (Grade 2-3)	34.5	35.6	115	48.6	90.9	140	0.7%	-14.10 [-30.50, 2.30]
Akbal 2012	62.7	24.5	30	22.8	6	27	0.9%	39.90 [30.85, 48.95]
Akbal 2016	54.3	49.8	24	20.8	4.1	22	0.6%	33.50 [13.50, 53.50]
Akkiz 2021	32.04	19.5	200	21.6	7.15	61	1.0%	10.44 [7.20, 13.68]
Aktas 2011	44	19	91	24	9	81	1.0%	20.00 [15.63, 24.37]
Akyildiz 2009	49.9	21	37	23.5	10	104	0.9%	26.40 [19.37, 33.43]
Arslan 2014	38.7	25.2	100	19.3	4.8	45	1.0%	19.40 [14.27, 24.53]
Aygun 2008	44.9	27.8	31	17.5	4.3	20	0.9%	27.40 [17.43, 37.37]
Aygun 2014 (elevated liver enzymes)	22.9	8.3	20	17.5	4.3	20	1.0%	5.40 [1.30, 9.50]
Aygun 2014 (normal liver enzymes)	49.4	28.7	40	24.9	14.1	40	0.9%	24.50 [14.59, 34.41]
Basar 2012	38.4	18.6	30	23.7	10.5	40	0.9%	14.70 [7.29, 22.11]
Baskol 2005	57.83	45.81	23	22.78	8.97	23	0.6%	35.05 [15.97, 54.13]
Bayrak 2020	23.7	14.7	260	18.4	6.8	748	1.0%	5.30 [3.45, 7.15]
Bekler 2015	25.7	6.9	32	25.2	7.4	22	1.0%	0.50 [-3.41, 4.41]
Bilgir 2014	37.6	19.6	53	22	3.3	45	1.0%	15.60 [10.24, 20.96]
Boga 2015 (NAFLD)	61.8	27.8	70	57.2	20.1	17	0.8%	4.60 [-6.96, 16.16]
Boga 2015 (NASH)	63.3	29.9	53	57.2	20.1	17	0.8%	6.10 [-6.39, 18.59]
Boga 2015 - 2	53.5	54.9158	66	18	8.7333	35	0.8%	35.50 [21.94, 49.06]
Boga 2015 - 3	61.8	27.8	70	18.7	5.5	12	0.9%	43.10 [35.88, 50.32]
Cengiz 2015	40	4.16	57	20	0.73	57	1.0%	20.00 [18.90, 21.10]
Cengiz 2016	48.91	28.03	69	21.3	6.44	69	0.9%	27.61 [20.82, 34.40]
Colak 2011	62.9	5.7	60	20.2	1.3	52	1.0%	42.70 [41.22, 44.18]
Colak 2012	39.9	21.9	50	20.9	5	28	0.9%	19.00 [12.65, 25.35]
Colak 2012 -2	54.2	46.3	92	18.7	4.2	51	0.9%	35.50 [25.97, 45.03]
Colak 2012 - 3	41.1	20.7	57	25.7	7.3	30	0.9%	15.40 [9.42, 21.38]
Colak 2012 - 4	42.1	22.1	57	18.7	5.5	38	0.9%	23.40 [17.40, 29.40]
Colak 2016	39.7	21.1	50	20.2	6.1	38	0.9%	19.50 [13.34, 25.66]
Delik 2020	45.78	32.98	248	22.85	8.43	81	1.0%	22.93 [18.43, 27.43]
Demirag 2007	26.4	13.3	237	20.3	8.1	201	1.0%	6.10 [4.07, 8.13]
Ekinci 2022	26.56	14.7	95	16.32	4.78	83	1.0%	10.24 [7.11, 13.37]
Eminler 2014	51.5	7.54	40	20.2	1.23	40	1.0%	31.30 [28.93, 33.67]
Emre 2015	82	35	75	76	35	111	0.8%	6.00 [-4.25, 16.25]
Eren 2012	46	13	91	22	11	74	1.0%	24.00 [20.34, 27.66]
Fotbolcu 2010	33.23	13.33	35	23.07	5.82	30	1.0%	10.16 [5.28, 15.04]
Gulsen 2005	50.04	14.64	71	24.13	4.75	30	1.0%	25.91 [22.10, 29.72]
Kara 2013	48	20	103	22	5	57	1.0%	26.00 [21.93, 30.07]
Karabay 2013 (Borderline NASH)	38.2	15.5	24	25.4	8.8	21	0.9%	12.80 [5.55, 20.05]
Karabay 2013 (NASH)	45.2	26.9	22	25.4	8.8	21	0.8%	19.80 [7.95, 31.65]
Karabay 2013 (SS)	39.5	21.5	9	25.4	8.8	21	0.7%	14.10 [-0.44, 28.64]
Karaoğullarından 2023	37.12	25.21	290	20.4	8.64	108	1.0%	16.72 [13.39, 20.05]
Kargili 2006	27.6	16.2	33	20.8	10.1	28	0.9%	6.80 [0.13, 13.47]
Kasapoglu 2013 (Stage 1)	19.8	9.2	133	18.8	7.6	275	1.0%	1.00 [-0.80, 2.80]
Kasapoglu 2013 (Stage 2)	20.3	11.4	106	18.8	7.6	275	1.0%	1.50 [-0.85, 3.85]
Kasapoglu 2013 (Stage 3)	22.2	11.1	99	18.8	7.6	275	1.0%	3.40 [1.04, 5.76]
Kasapoglu 2015 (Stage 1)	19.1	9.1	124	17.5	7.9	182	1.0%	1.60 [-0.37, 3.57]
Kasapoglu 2015 (Stage 2)	22.4	9.4	93	17.5	7.9	182	1.0%	4.90 [2.67, 7.13]
Kasapoglu 2015 (Stage 3)	24.2	9.1	80	17.5	7.9	182	1.0%	6.70 [4.40, 9.00]
Kasapoglu 2015 - 2 (Stage 1)	20.3	9.7	88	19.2	7.7	136	1.0%	1.10 [-1.30, 3.50]
Kasapoglu 2015 - 2 (Stage 2)	22.6	12.5	38	19.2	7.7	136	1.0%	3.40 [-0.78, 7.58]
Kasapoglu 2015 - 2 (Stage 3)	24.2	13.7	24	19.2	7.7	136	1.0%	5.00 [-0.63, 10.63]
Kasapoglu 2016 (Stage 1)	19.2	9.2	473	18.5	7.6	982	1.0%	0.70 [-0.26, 1.66]
Kasapoglu 2016 (Stage 2)	25.3	11.4	363	18.5	7.6	982	1.0%	6.80 [5.53, 8.07]
Kasapoglu 2016 (Stage 3)	30.2	11.1	240	18.5	7.6	982	1.0%	11.70 [10.22, 13.18]
Keskin 2017 (Grade 1)	33	25	84	30	17	169	0.9%	3.00 [-2.93, 8.93]
Keskin 2017 (Grade 2)	33	25	71	30	17	169	0.9%	3.00 [-3.35, 9.35]
Keskin 2017 (Grade 3)	36	22	36	30	17	169	0.9%	6.00 [-1.63, 13.63]
Koplay 2011	28.6	12.8	45	19.1	3.9	30	1.0%	9.50 [5.51, 13.49]
Korkmaz 2015 (NASH)	50.1	14.3	102	20.6	5.7	56	1.0%	29.50 [26.35, 32.65]
Korkmaz 2015 (NASH + cirrhosis)	64.2	16	18	20.6	5.7	56	0.9%	43.60 [36.06, 51.14]
Korkmaz 2015 (SS)	37.1	9.8	44	20.6	5.7	56	1.0%	16.50 [13.24, 19.76]
Kucukazman 2012	34.5	18.1	154	22.5	6.5	57	1.0%	12.00 [8.68, 15.32]
Kucukazman 2014	35	17.3	117	22.4	7.7	44	1.0%	12.60 [8.73, 16.47]
Kutlu 2019	22.9	10.5	51	20.4	10.2	30	1.0%	2.50 [-2.15, 7.15]
Oral 2019	18.48	5.66	225	16.99	4.6	142	1.0%	1.49 [0.43, 2.55]
Oral 2019 - 2	18.48	5.66	225	16.99	4.6	142	1.0%	1.49 [0.43, 2.55]
Ozturk 2015 (NASH)	70.4	47	39	21	4.4	41	0.7%	49.40 [34.59, 64.21]
Ozturk 2015 (SS)	46.6	16.8	22	21	4.4	41	0.9%	25.60 [18.45, 32.75]
Ozturk 2018	53.9	37.2	100	20.5	4.6	38	0.9%	33.40 [25.96, 40.84]
Ozveren 2014	26.8	12.3	59	20.5	3.8	22	1.0%	6.30 [2.78, 9.82]
Ozveren 2016	21	12	59	21	4	22	1.0%	0.00 [-3.49, 3.49]

Mean Difference IV, Random, 95% CI

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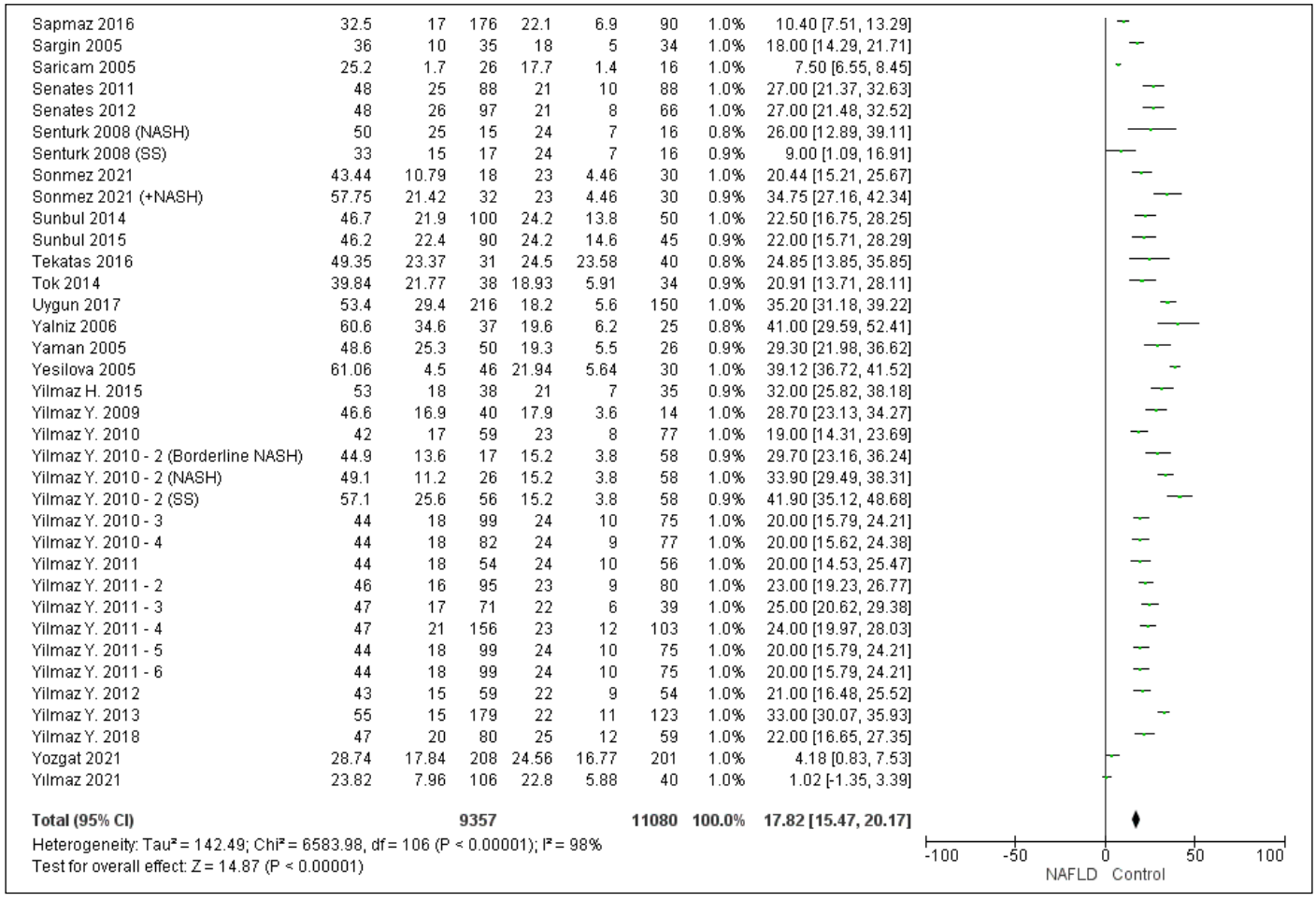

Figure 4. The random effect model of cumulative meta-analysis for AST data obtained from NAFLD and control individuals.

The pathogenesis of NAFLD, specifically whether NAFLD precedes insulin resistance or vice versa, has been debated for a long time. Diacylglycerol is recognized as a key factor of lipid-induced insulin resistance in the liver. Elevated diacylglycerol activates protein kinase C, which phosphorylates and inhibits the insulin receptor, thereby impairing glucose metabolism in NAFLD primarily through this mechanism.[131]

The global prevalence of NAFLD is 30%,[7] and a 2016 meta-analysis reported a pooled analysis for NASH prevalence at 59.10% among biopsied NAFLD patients. According to comorbidity analysis, the prevalence of obesity was 51.34%/81.83%, diabetes was 22.51%/43.63%, hyperlipidemia was 69.16%/72.13%, hypertriglyceridemia was 40.74%/83.33%, hypertension was 39.34%/67.97%, and metabolic syndrome was 42.54%/70.65% among NAFLD/NASH patients worldwide. These results indicate that the prevalence of comorbidities rises with the development of NASH compared to NAFLD without steatohepatitis.[8] However, a 2023 meta-analysis showed that the incidence of NAFLD was higher among those with obesity, diabetes, hyperlipidemia, and metabolic syndrome, though the differences were not significant. Only tobacco use status showed significant incidence differences among patient characteristics.[5]

A single-center study investigating Turkiye's NAFLD profile revealed that 90.4% of NAFLD patients had biopsy-proven NASH, and simple steatosis was rare (9.6%). The clinical outcomes indicated that significant fibrosis was present in 6.4%, advanced fibrosis in 32.6%, and cirrhosis in 61% of patients. Overweight (32.6%), obesity (61%), diabetes (33.5%), and metabolic syndrome (63%) were frequently seen comorbidities in these patients. This may be because this hospital is a tertiary referral center, and Fibroscan is commonly used to indicate biopsy.[9] These results provide evidence that NAFLD/NASH is an epidemic in Turkiye. A study conducted in five different centers in the East-Southeastern Anatolia Regions of Turkiye showed that 85% were overweight, 37% were obese, 18% had type 2 diabetes mellitus, and 80.6% had hyperlipidemia. According to multivariate regression analysis, age, diabetes, and aspartate aminotransferase were related to the severity of the disease.[24]

Is It "Non-Alcoholic Fatty Liver Disease" or "Metabolic Dysfunction Associated Steatotic Liver Disease"?

Our results show that NAFLD is not solely a liver-based disease; it is both a cause and consequence of metabolic disturbances. Insulin resistance and glucose metabolism-related parameters support this hypothesis. After many critical meetings, authorities agreed that MASLD is a more appropriate overarching term. This new designation integrates the current understanding of patient heterogeneity encompassed by the acronym NAFLD and offers terminology suggestions that more accurately reflect the pathogenesis. It is believed that this new term will accelerate the transition to novel treatments and will facilitate sub-phenotyping efforts of the disease with future studies.[4,132,133]

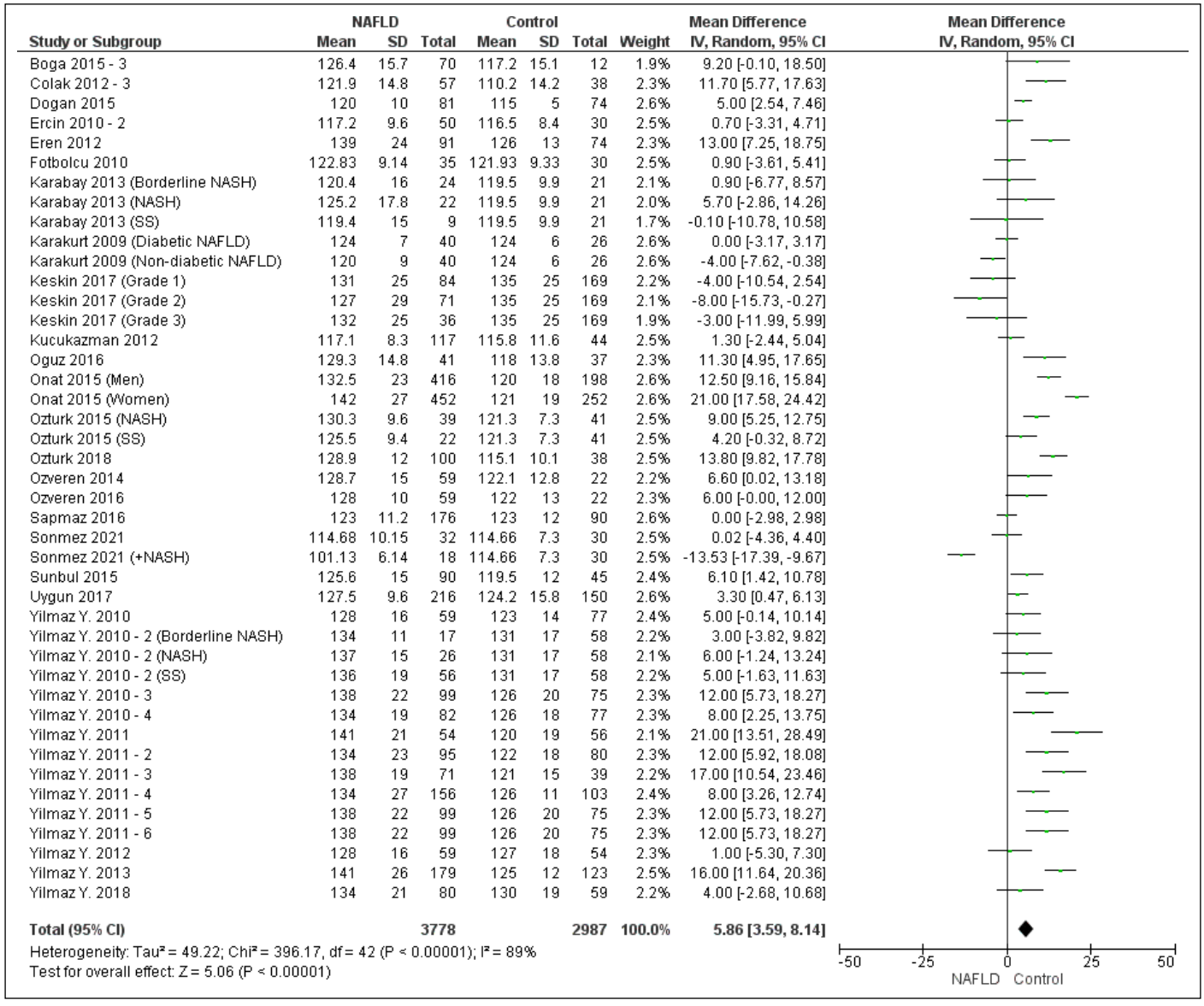

Figure 5. The random effect model of cumulative meta-analysis for Systolic Blood Pressure (SBP) data obtained from NAFLD and control individuals.

A recent meta-analysis involving cohorts from the USA, Japan, and Turkiye revealed negative implications of type 2 diabetes in relation to NAFLD. The study found that participants with type 2 diabetes had a significantly elevated risk of hepatic decompensation at 1, 3, and 5 years compared to those without type 2 diabetes. After considering various confounding factors, it was determined that type 2 diabetes and glycated hemoglobin were independent predictors of hepatic decompensation. Furthermore, even after adjusting for baseline liver stiffness assessed by magnetic resonance elastography, the association between type 2 diabetes and hepatic decompensation remained consistent. Notably, type 2 diabetes emerged as an independent predictor of hepatocellular carcinoma development.[134]

Another recent meta-analysis aimed to explore the relationship between the triglyceride and glucose (TyG) index, calculated as fasting triglyceride divided by fasting glucose, and the risk of NAFLD. The results revealed a positive and linear association between the TyG index and the risk of NAFLD. Each additional unit of the TyG index was associated with a higher risk of NAFLD, with a summary odds ratio (OR) of 2.84.[135]

The findings of our meta-analysis, combined with results from other studies, emphasize the importance of assessing metabolic parameters in understanding the development and prognosis of NAFLD. This highlights the need for countries with a high incidence of NAFLD, such as Turkiye, to focus on developing metabolic approaches for the treatment and monitoring of these conditions. By emphasizing metabolic factors, healthcare professionals can better manage and address the challenges posed by NAFLD.

Our meta-analysis has for the first time indicated the overall metabolic profile and MASLD potential of NAFLD patients in Turkiye. While acknowledging the limitations of our work due to the quality of the studies and data in the literature, we recognize several specific constraints. Some limitations stem from the characteristics of the fatty liver patients, the design of the studies, and the procedures of the centers where they were performed, affecting the determination of the disease or patients' states and introducing heterogeneity. High statistical heterogeneity of the data was observed. Additionally, we

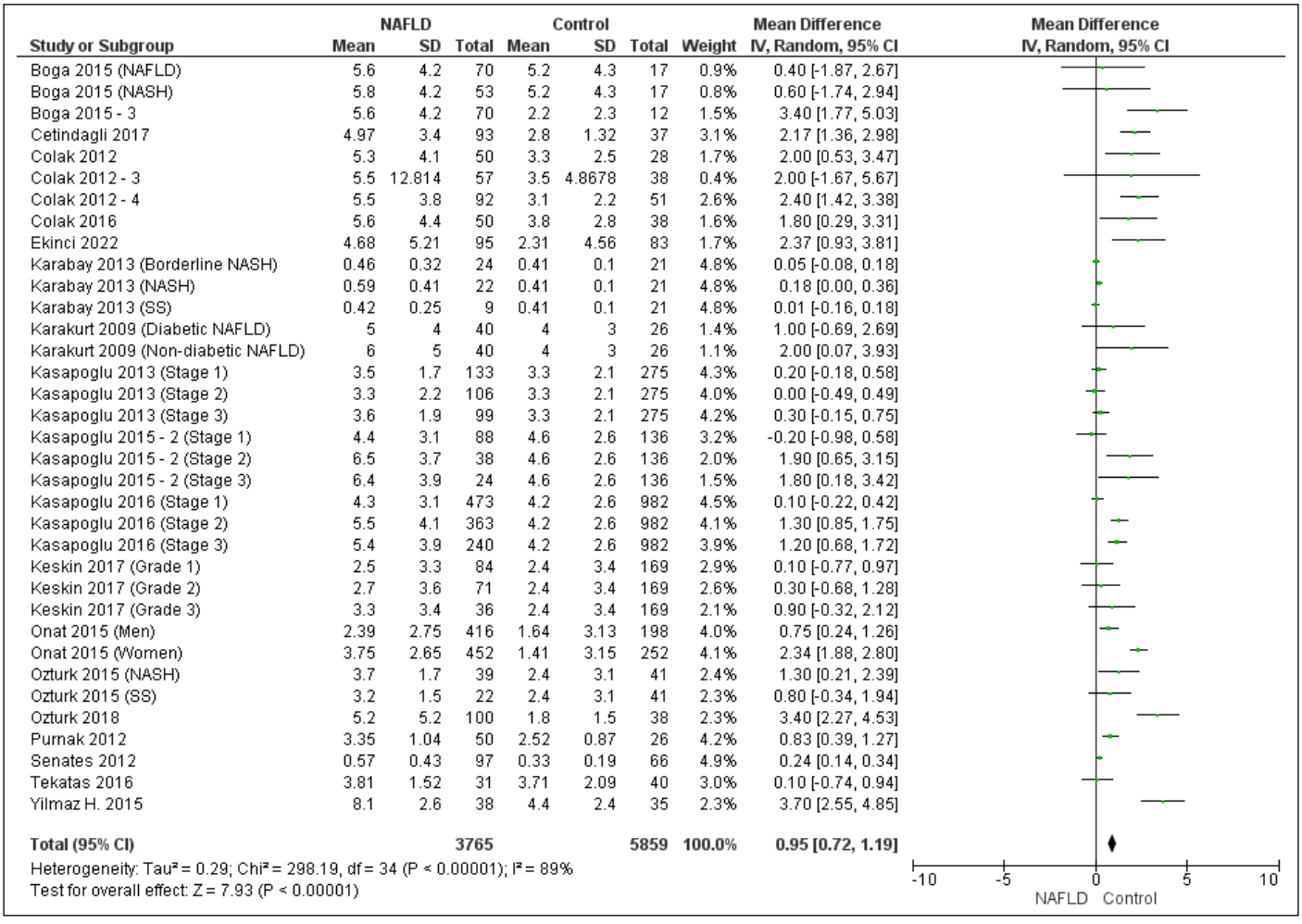

Figure 6. The random effect model of cumulative meta-analysis for CRP data obtained from NAFLD and control individuals.

did not include comorbidity or disease severity status (in terms of liver fibrosis) in our analysis due to the limited amount of studies and the heterogeneity among these studies. Our primary goal was to analyze the metabolic profile of the patients cumulatively, and we acknowledge that further studies and meta-analyses are needed to assess the effects of disease stages on the metabolic profile. It would also be beneficial to evaluate these in future studies due to changes in terminology and disease diagnosis.

We are aware of the risk of bias among studies, particularly those using the same cohort in studies conducted by the same group within a close time period. Although inclusion and exclusion criteria were mainly similar among studies, some excluded specific chronic diseases that could affect the biochemical profiles of selected patients. We accepted this heterogeneity as a limitation of our meta-analysis. However, we believe that our meta-analysis provides a comprehensive overview with a significant amount of data, specifically from Turkiye. These bias risks and limitations might have a minor impact given the extensive dataset.

Given the recency of the MASLD terminology, there are not many studies targeting exact MASLD patients according to specific diagnostic criteria for MASLD. Therefore, our study couldn't distinctly show the MSFLD and NAFLD difference or the MASLD profile of Turkiye. We acknowledge these limitations in the ongoing debate,[136] yet our results support the notion that many patients included in our meta-analysis might have MASLD, according to our cumulative results.

Conclusion

In conclusion, NAFLD is a metabolic disease that involves multiple pathways related to glucose and lipid metabolism, vascular function, inflammation, and acute phase responses. This was demonstrated through the cumulative meta-analysis of all Turkish NAFLD studies to date. These cumulative results are important for defining the metabolic profile of NAFLD patients in Turkiye and could serve as a valuable reference for many countries in Europe, Asia, and the Middle East. Additionally, the new term MASLD could be more appropriate, reflecting the related metabolic outcomes assessed cumulatively in our meta-analysis.

Author Contributions: Concept – SA, NY; Design – SA, NY; Supervision – NY; Data Collection and/or Processing – SA, NY; Analysis and/or Interpretation – SA, NY; Literature Search – SA, NY; Writing – SA; Critical Reviews – NY.

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Appendix 1. Inclusion and exclusion criteria of studies

Author, date	Inclusion criteria and diagnosis	Exclusion criteria
Acikel, 2009	Ultrasonographic findings were used to define NAFLD. grade 0, no steatosis; grade 1 steatosis, presence of hepatorenal con trast and bright liver; grade 2 steatosis, disturbed con tours of intrahepatic vessels and diaphragm or enhanced echogenicity; grade 3 steatosis, disappearance of dia phragm and intrahepatic contours or severely enhanced echogenity.	Patients with coronary angiography, history of percutaneous coronary intervention surgical revascularization. Chronic alcohol consumption (>20 g/day), serum hepatitis B antigen or anti hepatitis C viral antibody positivity, known etiologies of liver disease, systemic diseases causing fatty liver, use of drugs inducing fatty liver disease (steroids, estrogens, amiodarone, tamoxifen, or other chemotherapeutic agents within the previous 6 months).
Agac, 2013	Ultrasonographic findings were used to define NAFLD. grade 0, no steatosis; grade 1 steatosis, presence of hepatorenal con trast and bright liver; grade 2 steatosis, disturbed con tours of intrahepatic vessels and diaphragm or enhanced echogenicity; grade 3 steatosis, disappearance of dia phragm and intrahepatic contours or severely enhanced echogenity.	Patients without known coronary artery disease documented in a previous coronary angiography or without a history of percutaneous coronary intervention surgical revascularization.
Akbal, 2012	Ultrasonographic findings were used to define NAFLD. grade 0, no steatosis; grade 1 steatosis, presence of hepatorenal con trast and bright liver; grade 2 steatosis, disturbed con tours of intrahepatic vessels and diaphragm or enhanced echogenicity; grade 3 steatosis, disappearance of dia phragm and intrahepatic contours or severely enhanced echogenity.	Hepatitis B, C, cytomegalovirus, Epstein Barr infections, monogram specific autoantibodies, alcohol consumption, diabetes mellitus, intolerance fasting glucose, medication (diabetic drugs, blood pressure lowering medication, and statins), and hereditary defects (iron and copper storage diseases and alpha 1 antitrypsin deficiency).
Akbal, 2016	Ultrasonographic findings were used to define NAFLD. grade 0, no steatosis; grade 1 steatosis, presence of hepatorenal con trast and bright liver; grade 2 steatosis, disturbed con tours of intrahepatic vessels and diaphragm or enhanced echogenicity; grade 3 steatosis, disappearance of dia phragm and intrahepatic contours or severely enhanced echogenity.	Any amount of alcohol consumption or history of alcohol consumption. Viral hepatitis markers (Hepatitis B surface antigen, anti HCV antibody, cytomegalovirus, Epstein–Barr virus), anti nuclear antibody, anti liver kidney antibody, serum copper, and ceruloplasmin levels were positive.
Aktas, 2011	Ultrasonography guided liver biopsies under conscious sedation using a 16 gauge Hepafix needle. Biopsy specimens stained with hematoxylin eosin and Masson trichrome. Experienced pathologist blinded to clinical data scored the liver biopsies according to the National Institute of Diabetes and Digestive and Kidney Diseases NASH Clinical Research Network scoring system.	Viral hepatitis, hemochromatosis, Wilson disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, α1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, or malignancies. Medication use: estrogens, amiodarone, steroids, tamoxifen, and lipid lowering agents. Daily alcohol intake exceeding 20 g/day, previous abdominal surgery.
Akyildiz, 2009	NAFLD diagnosis by liver biopsy and clinical findings. Histopathologic reexamination by a blinded pathologist according to NAFLD study group definitions. Blood collection and DNA obtained from patients and healthy controls. Stratification of NAFLD into NASH, probable NASH, and steatosis groups based on NAFLD Activity Score (NAS) by histopathologic examination.	Alcohol consumption greater than 20 g/day. Presence of HBV, HCV, or HIV infection. Receiving hepatotoxic drugs. Coexisting chronic liver diseases (hereditary metabolic liver, autoimmune liver disease, etc.). Pregnancy, organ transplantation, chemotherapy. Presence of systemic infection and/or autoimmune disease. Having malignancy.
Akyuz, 2014	NAFLD diagnosis based on evidence of steatosis grade 1 or higher on liver ultrasound. Absent to low alcohol consumption. Evidence of NAFLD on liver biopsy.	Specific conditions leading to hepatic steatosis (viral hepatitis, drug induced liver disease, total parenteral nutrition, autoimmune hepatitis, and metabolic/genetic liver diseases).
Arslan, 2014	NAFLD diagnosis based on biochemical, radiological, and histological criteria.	Exclusion of other forms of liver disease, including autoimmune, drug induced, and metabolic liver diseases. Hepatitis excluded by examining necessary indicators such as serum HBsAg, HCV, and Anti Hbs levels, and further diagnostic tests if needed.

Appendix 1 (cont). Inclusion and exclusion criteria of studies

Author, date	Inclusion criteria and diagnosis	Exclusion criteria
Ayaz, 2014	Ultrasonography performed on all patients. Liver echogenicity recorded based on the absence of steatosis (Grade 0) or grades 1 to 3 for mild to severe fatty infiltration.	Presence of a known cardiovascular disease, acute chronic renal failure, malignancy, thyroid disease, hepatitis, regular alcohol consumption, or active smoking and pregnancy. Exclusion of patients with certain metabolic disorders, including Wilson disease, lipodystrophy, starvation, parenteral nutrition, abetalipoproteinemia, and inborn errors of metabolism. Exclusion of patients receiving medications, including amiodarone, methotrexate, tamoxifen, and corticosteroids.
Aygun, 2016	NAFLD patients admitted with incidentally found elevation of liver enzymes or with a fatty liver seen on ultrasound screening. Detailed clinical and laboratory evaluation, including liver enzymes, hepatitis markers, autoantibodies, ferritin, and ceruloplasmin. Upper abdominal ultrasonography. Definite diagnosis of NAFLD by histopathological examination after liver biopsy. Grading of histopathologic findings for steatohepatitis.	Alcohol consumption more than 40 g/week. Previous or current malignant disease. Any known pancreas disease, adrenal or pituitary disease. Chronic drug or hormone use. Gastrointestinal surgery.
Aygun, 2008	NAFLD patients admitted with elevated liver enzymes and fatty liver on ultrasound screening. Diagnosis confirmed by histopathological examination after liver biopsy.	Alcohol consumption >40 g/week, previous/current malignant disease, pancreas disease, adrenal/pituitary disease, chronic drug/hormone use, gastrointestinal surgery.
Bahcecioglu, 2006	Diagnosed NAFLD by biopsy. The pathological samples (paraffin blocks) from patients diagnosed with NAFLD in the 5 centers were sent to a single center, and evaluated by an expert pathologist; stage 1: zone 3 peri venular, perisinusoidal or pericellular fibrosis, focal or extensive; stage 2: as for stage 1 plus focal or extensive portal fibrosis; stage 3: bridging fibrosis, focal or extensive portal fibrosis, and stage 4: cir rhosis with or without residual perisinusoidal fibrosis.	Alcohol consumption >20 g/day, diseases mimicking NAFLD, vitamin E intake, antioxidant use, ursodeoxycholic acid treatment in the last 6 months, specific drug use, severe cardiac deficiency, coronary artery disease, renal failure, need for antihyperlipidemic drug use, psychiatric disorders leading to inadaptability, liver cirrhosis.
Basar, 2012	NAFLD patients were diagnosed with elevated liver enzymes and grade 2 3 liver steatosis on ultrasonography.	Viral hepatitis, autoimmune hepatitis, alcohol consumption, glucose metabolism disorders, medications (anti diabetic, antihypertensive, statins), hereditary diseases.
Baskol, 2005	NAFLD diagnosed by ultrasonography and confirmed by histopathological examination.	Possible ethanol ingestion, history of gastrointestinal surgical procedures, protein malnutrition, corticosteroid use.
Bekler, 2015	Diagnosed with hepatosteatosis using abdominal ultrasonography.	Previous coronary artery disease, congestive heart failure, known or history of valvular heart disease, pulmonary disease, pulmonary hypertension, left bundle branch block, rhythm other than sinus, pericarditis, chronic alcohol consumption (>20 g/day), serum hepatitis B antigen or anti hepatitis C viral antibody positivity.
Bilgin, 2011	NAFLD patients assessed by liver biopsies.	Viral hepatitis, Wilson's disease, α1 antitrypsin deficiency, autoimmune hepatitis, genetic hemochromatosis, use of steatogenic drugs, history of ischemic heart disease, cerebrovascular diseases, chronic renal failure, autoimmune disorders, malignancies.
Bilgir, 2014	Hepatic ultrasonography performed by a radiologist to assess NAFLD.	History of drug use, gastrointestinal surgical operation, alcoholic liver disease, viral hepatitis (B, C, D, TORCH), cholestatic liver disease, hemochromatosis, liver disease secondary to drug use, Wilson's disease, α1 antitrypsin deficiency, history of alcohol intake >20 g/day.
Boga, 2015	Elevated ALT and AST levels for at least 6 months with steatosis on ultrasonography. Liver biopsies performed.	Hepatotoxic drugs, hormone replacement therapy, herbal products, alcohol consumption >20 g/d, viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α1 antitrypsin deficiency, biliary disease, malignancies, known coronary artery disease, angina, myocardial infarction.

Appendix 1 (cont). Inclusion and exclusion criteria of studies

Author, date	Inclusion criteria and diagnosis	Exclusion criteria
Celebi, 2015	Persistently (at least for 6 months) elevated aminotransferases, ultrasonographic presence of bright liver without any other liver or biliary tract disease, and liver histology compatible with a diagnosis of NAFLD.	Alcohol consumption ≥20 g/day in the previous year, a positive test for hepatitis B surface antigen, hepatitis C antibody, and other causes of liver disease, serum creatinine >133 μmol/L, presence of T2D, hypertension, morbid obesity [body mass index (BMI) ≥40 kg/m^2], any acute or chronic inflammatory disease as determined by a leukocyte count >10,000/mm^3 or clinical signs of infection, and history of major diseases such as generalized inflammation or advanced malignant diseases, exposure to occupational hepatotoxins or drugs known to be steatogenic or to affect glucose, and lipid metabolism.
Celikbilek, 2013	18 years or older, persistently elevated (for at least 6 months) aminotransferases, ultrasonographic presence of hyperechogenic liver and 4 liver histology with a diagnosis of NASH without cirrhosis obtained no more than 6 months.	A history of any level of alcohol consumption; hypertension, any other form of chronic liver disease; use of any medications thought to cause or affect NAFLD; abnormal thyroid function tests; plasma fasting glucose 126 mg/dl or antidiabetic drug use; any medication that can interfere with platelet function (e.g. aspirin); heart failure; valvular heart disease; chronic obstructive pulmonary disease; peripheral and cerebral vascular disease; hematologic disorders; acute or chronic infection; history of cancer; chronic kidney diseases; and documented coronary artery disease (CAD).
Celikbilek, 2014	NAFLD was diagnosed by abdominal ultrasonography. All ultrasonographic examinations were performed by the same experienced radiologist, who was blinded to the research design, using a commercially avail able US scanner.	Patients with malignancies, chronic kidney or heart disease, diabetes mellitus, hyperlipidemia, hypertension, thyroid disease, anemia, pregnancy, morbid obesity, smoking habits or use of drugs known to cause fatty liver, history of alcohol consumption, bile duct dilatation, hepatic mass, hepatitis, viral or autoim mune liver disease, liver cirrhosis, or hepatic surgery were excluded.
Celikbilek, 2018	NAFLD was diagnosed by abdominal ultrasonography. All ultrasonographic examinations were performed by the same experienced radiologist, who was blinded to the research design, using a commercially avail able US scanner.	Participants with malignancies, chronic renal, hepatic, or cardiovascular disease, thyroid disease, a history of dementia, psychiatric and/or central nervous system disorders (such as traumatic brain injury, multiple sclerosis, etc.), pregnancy, or morbid obesity, and those who were current smokers or used drugs known to cause fatty liver, or who had vitamin B12 or folate deficiency and/ or memory problems in daily life, were excluded from the study.
Cengiz, 2009	Steatosis on liver ultrasound. Liver biopsies evaluated by a pathologist.	>120 g alcohol intake per week, diabetes, hepatitis C virus, hepatitis B virus, HIV, miscellaneous causes of liver disease, use of antidiabetics, steroids, other steroid inducing medicines.
Cengiz, 2015	Elevated liver enzymes and hepatosteatosis on ultrasonography without other causes. Histopathologically confirmed NASH.	Viral hepatitis, sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α1 antitrypsin deficiency, malignancy, drug induced liver disease, impaired nutritional condition, altered lipid metabolism, alcohol consumption >20 g/day (men) or >10 g/day (women), hormone replacement therapy, steatogenic drugs.
Cengiz, 2016	NAFLD based on continuously elevated serum aminotransferase levels and diffusely hyperechogenic liver on image studies, confirmed by biopsy.	Alcohol consumption >20 g/day (men) or >10 g/day (women), viral hepatitis infections, parenteral nutrition use, drugs inducing steatosis, infectious diseases, known liver disorders, chronic renal diseases, collagen vascular diseases, malignancies.
Cetindagli, 2017	NAFLD diagnosed with ultrasound and/or liver biopsy, elevated liver enzymes for ≥6 months without other hepatic or bile duct disease.	History of alcohol intake >40 g/week, positive viral serology or autoimmune panel, abnormal copper metabolism, hepatotoxin exposure, drugs affecting lipid or glucose metabolism, cardiovascular disease, diabetes mellitus, hypertension, hyperlipidemia, rheumatic disease, chronic infection, primary immunodeficiency syndrome, immunosuppressive drug intake, renal impairment, thyroid disease, chronic obstructive pulmonary disease, malignancy.
Colak, 2011	NAFLD diagnosed based on persistently raised ALT level (>1.5 times upper normal limit for 6 months or more) using liver ultrasound.	Viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha 1 antitrypsin deficiency, malignancies, medication use.
Colak, 2012	Patients with ALT elevations for at least 6 months, followed up for hepatosteatosis on ultrasonography. Liver biopsy performed for NAFLD diagnosis.	Daily alcohol intake exceeding 20 g/day, previous abdominal surgery.

Appendix 1 (cont). Inclusion and exclusion criteria of studies

Author, date	Inclusion criteria and diagnosis	Exclusion criteria
Colak, 2012/2	NAFLD diagnosed based on persistently elevated ALT level using liver ultrasound.	Viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha 1 antitrypsin deficiency, malignancies, medication use.
Colak, 2012/3	Patients admitted with high transaminase levels and NAFLD diagnosis in histopathological evaluation. ALT elevations for at least 6 months, followed up for hepatosteatosis on ultrasonography. Liver biopsy performed for NAFLD diagnosis.	Hepatotoxic drugs, hormone replacement therapy, herbal products, alcohol consumption more than 20g/day, viral serology, autoimmune markers, iron status, ceruloplasmin, serum and 24 hour urinary copper, alpha 1 antitrypsin levels, thyroid functions, eye examination.
Colak, 2012/4	Patients attending clinic with ALT elevations for at least 6 months. Ultrasonography guided liver biopsy performed for NAFLD diagnosis.	Daily alcohol intake exceeding 20 g/day, viral hepatitis, autoimmune hepatitis, Wilson's disease, hemochromatosis, alpha 1 antitrypsin deficiency, biliary disease, malignancies.
Colak, 2016	Patients evaluated in the gastroenterology clinic within the last 1 year with high transaminase levels and diagnosed with NAFLD histopathologically. ALT elevations for at least 6 months, hepatosteatosis on ultrasonography, and liver biopsy performed.	Hepatotoxic drug use, hormone replacement therapy, herbal products, alcohol use more than 20 g/day, viral serology, autoimmune markers, iron status, ceruloplasmin, serum and 24 hour urinary copper, alpha 1 antitrypsin levels, thyroid functions, Kayser Fleischer rings.
Demirag, 2007	Ultrasonographic diagnosis of NAFLD.	Diabetes mellitus, viral hepatitis, significant alcohol intake, signs/symptoms/laboratory abnormalities of metabolic liver diseases.
Dogan, 2015	NAFLD diagnosed by abdominal US with increased echogenicity.	History of alcohol consumption, bile duct dilatation, hepatic mass, hepatitis, viral or autoimmune liver disease, liver cirrhosis, hepatic surgery.
Emre, 2015	Liver ultrasound scan was performed to assess fatty liver disease.	Diagnosis of diabetes mellitus or HbA1c >6.5%. Hepatitis B or C infection. Alcohol consumption >30 g/day. Chronic liver or systemic disease. Conditions associated with FLD (polycystic ovarian syndrome, obstructive sleep apnea syndrome, hypothyroidism, hypogonadism, and duodeno pancreatic resection). Conditions confounding STR interpretation on electrocardiograms (left bundle branch block, pacing, preexcitation).
Eminler, 2014	Fatty liver was detected by ultrasonography, and the diagnosis was confirmed with liver biopsy.	Patients with etiological causes that can lead to high levels of liver enzymes, including (viral and autoimmune hepatitis, Wilson's disease, α1 antitrypsin deficiency, storage diseases or drug use) and those with malignancy, adrenal or hypophysis disease or undergoing gastrointestinal operation were excluded from the study.
Ercin, 2010	Persistently elevated aminotransferases for at least 6 months. Ultrasonographic presence of bright liver without any other liver or biliary tract disease. Liver histology compatible with a diagnosis of NASH or SS.	History of alcohol consumption ≥40 g/week. BMI ≥30 kg/m². Positive serum markers of viral, autoimmune, or celiac disease. Abnormal copper metabolism or thyroid function tests. Overt diabetes mellitus. Hypertension. Serum total cholesterol ≥250 mg/dL. Serum triglycerides ≥400 mg/dL. Exposure to occupational hepatotoxins or drugs known to be steatogenic or affect glucose metabolism.
Ercin, 2010/2	Persistently elevated aminotransferases for at least 6 months. Ultrasonographic presence of bright liver without any other liver or biliary tract disease. Liver histology compatible with a diagnosis of NASH or SS.	History of alcohol consumption ≥40 g/week. BMI ≥35 kg/m². Positive serum markers of viral, autoimmune, or celiac disease. Abnormal copper metabolism or thyroid function test results. Diabetes mellitus. Serum total cholesterol ≥250 mg/dL. Serum triglycerides ≥400 mg/dL. Exposure to occupational hepatotoxins or drugs known to be steatogenic or affect glucose and lipid metabolism.
Ercin, 2016	Persistently elevated liver enzymes (aminotransferases). Liver biopsy confirmed NAFLD.	Hepatitis B and C infection and other causes of liver disease (autoimmune liver disease, Wilson's disease, hemochromatosis, α1 antitrypsin deficiency, etc.). Alcohol intake >20 g per day. Medication use known to increase fat deposition in the liver. Subjects with hypertension and/or type 2 diabetes mellitus (T2DM).
Eren, 2012	Liver biopsy confirmed NAFLD. Persistent abnormality in liver tests, dyslipidemia, or history of liver steatosis. Daily alcohol intake lower than 20 mg.	Chronic viral hepatitis, autoimmune hepatitis, hereditary hemochromatosis, Wilson's disease, drug induced liver disease. Clinical or imaging evidence of decompensated cirrhosis.

Appendix 1 (cont). Inclusion and exclusion criteria of studies

Author, date	Inclusion criteria and diagnosis	Exclusion criteria
Erkan, 2016	Presence of hepatosteatosis on USG. BMI of 18.5–25 kg/m^2. Negative markers for metabolic, autoimmune, and viral liver diseases.	Presence of diabetes mellitus or impaired glucose tolerance. Positive markers for metabolic, autoimmune, and viral liver diseases (HBV, HCV, autoimmune hepatitis). Use of drugs that lead to hepatic steatosis. Excessive consumption of ethanol (>20 g/day). Presence of chronic liver disease, biliary tract dilatation, and hepatic nodule and mass on USG.
Fotbolcu, 2010	Abdominal ultrasound showing fatty infiltration in the liver. Scoring system applied based on hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring criteria.	Established diagnosis of hypertension, diabetes mellitus, renal failure (stage 4 and 5 kidney disease), valvular insufficiency or stenosis, congenital heart disease, atrial fibrillation. Severe left ventricular systolic dysfunction. Coronary artery disease, familial hypercholesterolemia. Aortic disease. Smoking. Alcohol consumption >200 g/week. Evidence of hepatitis B or C. Hepatotoxic medications.
Fotbolcu, 2010/2	Abdominal ultrasound showing fatty infiltration in the liver. Scoring system applied based on hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring criteria.	Established diagnosis of hypertension, diabetes mellitus, renal failure (stage 4 and 5 kidney disease), valvular insufficiency or stenosis, congenital heart disease, atrial fibrillation. Severe left ventricular systolic dysfunction. Coronary artery disease, familial hypercholesterolemia. Aortic disease. Smoking. Alcohol consumption >200 g/week. Evidence of hepatitis B or C. Hepatotoxic medications.
Gokmen, 2016	The presence of qualitative steatosis was determined using a standard 2D abdominal ultrasonography (USG). NAFLD was characterized by the presence of hepatic brightness, hepatorenal echo contrast, deep attenuation and vascular blurring on USG.	Patients meeting the following criteria were excluded: chronic liver and kidney disease, viral hepatitis, diabetes mellitus, undergoing corticosteroid treatment, malignancy, alcohol consumption greater than 20 g/d, and pregnancy.
Gulsen, 2005	NAFLD diagnosis based on chronic hypertransaminasemia (>6 months). Bright liver evidence at ultrasound. Liver biopsy.	Subjects with a history of diabetes mellitus, hypertension, pancreatic and vascular diseases, intake of vitamin B6, vitamin B12 and/or folic acid supplements, and smoking. Alcohol consumption >20 g per day. Chronic viral hepatitis, hepatocellular carcinoma, and other forms of chronic liver diseases. Positive antihuman immunodeficiency antibodies.
Kara, 2013	Elevated aminotransferase levels for at least 6 months. Hyperechoic liver on ultrasound without any other liver or gall bladder pathology. Presence of SS or NASH on liver biopsy.	Positive serum viral markers, autoimmune hepatitis, Celiac disease, abnormal copper and thyroid function tests. Environmental hepatotoxins, and drug usage. Chronic viral hepatitis or chronic liver disease. Previous or current malignant disease. Hepatotoxic drug use. Alcohol consumption >20 g/day.
Karabay, 2013	Elevated alanine transaminase levels for at least 6 months. US guided liver biopsy showing hepatosteatosis.	History of hepatotoxic drugs or herbal supplements. Alcohol consumption >20 g/day. Viral hepatitis or chronic liver disease. Postmenopausal women. Drug use (estrogens, amiodarone, diltiazem, steroids, tamoxifen).
Karakurt, 2009	Hepatic ultrasonography showing hepatic steatosis.	Previous or current malignant disease. Known pancreas disease, adrenal or pituitary disease. Acute or chronic liver diseases, cerebrovascular event. Gastrointestinal surgery. History of alcohol use. Positive for hepatitis B or C.
Kargili, 2006	Diagnosis of fatty liver based on ultrasonographic findings.	Chronic viral hepatitis, hepatocellular carcinoma, and other forms of chronic liver diseases. Positive
Kasapoglu, 2013	All patients underwent liver ultrasonography, fatty liver graded 0–3. Liver steatosis scored on a scale of 0 to 3.	Significant history of alcohol use (>30 g daily for men, >20 g daily for women), positive results for hepatitis B surface antigen or anti hepatitis C virus antibody, autoimmune hepatitis, Wilson's disease, haemochromatosis, any chronic liver disease, malignancies, diabetes mellitus, thyroid disease, or renal disease.
Kasapoglu, 2015	All subjects underwent liver ultrasonography, fatty liver graded 0–3. Liver steatosis scored on a scale of 0–3.	Significant history of alcohol use (>30 g for males and >20 g for females), BMI ≥30 kg/m^2, positive results for HBsAg or anti HCV, autoimmune hepatitis, Wilson's disease, hemochromatosis, any known chronic liver disease, hypertension, malignancies, diabetes mellitus, thyroid disease, atherosclerotic heart disease, or renal disease.

Appendix 1 (cont). Inclusion and exclusion criteria of studies

Author, date	Inclusion criteria and diagnosis	Exclusion criteria
Kasapoglu, 2015/2	All patients underwent liver ultrasonography, fatty liver graded 0–3. Liver steatosis scored on a scale of 0–3.	Significant history of alcohol use (>30 g for males and >20 g for females), positive results for HBsAg or anti HCV, autoimmune hepatitis, Wilson's disease, hemochromatosis, any chronic liver disease, malignancies, and diabetes mellitus.
Kasapoglu, 2016	All subjects underwent liver ultrasonography, fatty liver graded 0–3. Liver steatosis scored on a scale of 0 3.	Significant history of alcohol use (>30 g for males, >20 g for females), BMI >30 kg/m^2, positive results for HBsAg or anti HCV, autoimmune hepatitis, Wilson's disease, haemochromatosis, any known chronic liver disease, malignancies, diabetes mellitus, thyroid disease, atherosclerotic heart disease, or renal disease.
Keskin, 2017	Diagnosis of NAFLD based on characteristic sonographic features.	Exclusion criteria: treatment with thrombolytic drugs in the previous 24 hours, active infections, recent major surgical procedure or trauma, neoplastic disease, end stage renal and liver failure, previously proven systemic inflammatory disease, history of alcohol intake more than 30 g/day in men and more than 20 g/day in women.
Kilciler, 2010	Inclusion criteria: persistently elevated aminotransferases, ultrasonographic presence of hyperechogenic liver.	Exclusion criteria: history of alcohol consumption (40 g/wk), obesity (BMI ≥30 kg/m^2), positive blood markers of viral, autoimmune, or celiac disease, abnormal copper metabolism or thyroid function tests, overt diabetes mellitus, total cholesterol (TC) ≥6.47 mmol/L, triglycerides (TG) ≥4.52 mmol/L.
Koplay, 2011	Diagnoses of NAFLD through abdominal ultrasonography (US).	Excluded patients with diabetes mellitus, known liver disease, malignant disease, active infections, drug induced fatty liver, positive hepatitis B and C tests, and biliary disease.
Korkmaz, 2015	Liver tissue samples obtained by biopsy. Fibrosis staged on a five point scale. Steatosis graded 1–3.	
Kucukazman, 2014	Liver ultrasonography performed to assess the degree of steatosis. Steatosis scored on a scale of 0 3.	
Kutlu, 2019	Diagnosis of NAFLD based on increased echogenicity via ultrasound.	Chronic diseases such as diabetes mellitus or hypertension, postmenopausal women, pregnant women, patients on steroid treatment, patients diagnosed with malignancy, and obese patients with a body mass index (BMI) >30 were excluded.
Oguz, 2016	Patients observed at the gastroenterology outpatient clinic. Liver ultrasound examinations were performed to assess the degree of steatosis.	Coronary artery disease, positive treadmill exercise test result, diabetes mellitus, BMI >35 kg/m^2, bundle branch block, paced rhythm, atrial fibrillation, Q waves, left ventricular hypertrophy, significant valvular heart disease, congenital heart disease, aortic aneurysm, systemic diseases affecting the aorta, severe obstructive pulmonary disease, chronic renal disease, treatment with certain medications, history of abdominal surgery, history or suspicion of viral hepatitis, and daily alcohol intake exceeding 20 g/day.
Onat, 2015	Not clear.	Not clear.
Oral, 2019	NAFLD diagnosed by liver biopsy. Liver histology evaluated by an experienced liver pathologist.	Presence of any other chronic liver disease, HIV infection, diabetes mellitus, heart failure, valvular disease, asthma, chronic obstructive pulmonary disease, peripheral and cerebral vascular disease, hematological disorders, acute or chronic infections, cancer history involving liver transplantation, previous exposure to drugs associated with fatty liver.
Oral, 2019 2	Candidates underwent ultrasonography, CT, and MRI evaluation. Preoperative liver biopsy performed for evidence of moderate or severe fatty liver.	Cirrhosis, diabetes mellitus, cardiovascular diseases, asthma, hematologic problems, infections, previous cancer history of liver transplantation, drug induced hepatosteatosis.
Ozturk, 2015	Inclusion criteria for NAFLD: age ≥40 and ≤20 years, persistently elevated aminotransferases, ultrasonographic presence of bright liver, evidence of NAFLD on liver biopsy.	Previous cardiovascular disease, morbid obesity (BMI >40 kg/m^2), diabetes mellitus, hypertension, total cholesterol ≥250 mg/dl, triglycerides ≥400 mg/dl, chronic renal failure, infections (presence of certain antibodies), inflammatory disorders, other known causes of chronic liver diseases, alcohol consumption >140 g/week, exposure to occupational hepatotoxins or drugs.

Appendix 1 (cont). Inclusion and exclusion criteria of studies

Author, date	Inclusion criteria and diagnosis	Exclusion criteria
Ozturk, 2018	Patients with fatty liver on sonography and persistently elevated liver function tests for at least 6 months underwent liver biopsy.	Any liver disease other than NAFLD, positive serologic tests for hepatitis B, hepatitis C, and HIV, history of alcohol intake (>20 g/day), diabetes mellitus, hypertension, cardiovascular disease, pancreatic disease or surgery.
Ozveren, 2014	All patients admitted to the Gastroenterology Clinic with NAFLD and the Cardiology Department for general health examination.	<10 g/dl hemoglobin, diseases interfering with the autonomic nervous system, cardiovascular diseases, neurological diseases, chronic obstructive pulmonary disease, smokers.
Ozveren, 2016	Liver ultrasonography performed by a single experienced radiologist. Diagnosis of NAFLD based on characteristic ultrasonographic features.	Any other liver disease (viral, alcohol or drug related hepatitis, cirrhosis, hemochromatosis, autoimmune hepatitis), previous diagnosis of ischemic heart disease, heart failure, diabetes mellitus, clinical hypertension, valvular heart disease.
Purnak, 2012	Diagnosis of NAFLD based on clinical, biochemical, and radiological findings.	Other causes of hepatic dysfunction (viral hepatitis, Wilson's disease, hemochromatosis, autoimmune hepatitis), history of alcohol consumption >10 g/day.
Sapmaz, 2016	Hepatic USG scans performed for all participants. Diagnosis of NAFLD based on known criteria.	History of chronic alcohol consumption, chronic liver disease, seropositivity of hepatitis B or C virus, history of cardiovascular disease, cerebrovascular disease, peripheral vascular disease.
Sargin, 2005	Elevated serum aminotransferase levels for longer than 6 months and bright liver on ultrasound scan.	Presence of hepatitis B, hepatitis C, Epstein Barr virus infection, non organ specific autoantibodies, hereditary defects, alcohol consumption >20 g/d, use of certain medications, jejunoileal bypass or extensive small bowel resection, total parenteral nutrition, malignancy, hypo hyperthyroid disease, pregnancy, other known liver diseases like cirrhosis and diabetes.
Saricam, 2005	The hepatosteatosis cases were diagnosed ultrasonographically and confir med by biopsy No alcohol consumption or consumption of less than 20 g/day.	Presence of anti HCV negativity, HBs Ag nega tivity, and negativity of specific autoantibodies for autoimmune liver disease. Drug intake (glucocorticoids, estrogens, ta moxifen, amiodarone, perhexiline) leading to he patosteatosis. Total parenteral nutrition, rapid we ight loss, massive intestinal resection, gastro pathy, and Wilson's disease, which cause hepatos teatosis. Diabetes mellitus (fasting blood glucose <126 mg/dl).
Senates, 2011	Evidence of steatosis grade 1 or higher on liver ultrasound; absent to low alcohol consumption; evidence of NAFLD on liver biopsy.	Inflammatory diseases, anemia, viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, a 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, malignancies. Subjects using estrogens, amiodarone, steroids, tamoxifen, lipid lowering agents, daily alcohol intake exceeding 20 grams/day, previous abdominal surgery.
Senates, 2012	Evidence of steatosis grade 1 or higher on liver ultrasound; absent to low alcohol consumption; evidence of NAFLD on liver biopsy.	Inflammatory diseases, anemia, viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, a 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, malignancies. Subjects using estrogens, amiodarone, steroids, tamoxifen, lipid lowering agents, daily alcohol intake exceeding 20 grams/day, previous abdominal surgery.
Senturk, 2008	The diagnosis of simple steatosis or NASH was based on the histological evaluation of liver biopsy samples.At ultrasonographic examination, the following four findings were tested: (i) diffuse hyperechoic echo texture, (ii) increased liver echo texture compared with the kidneys, (iii) vascular blurring and (iv) deep attenuation.	Alcohol intake of more than 20 g/day, viral hepatitis, autoimmune liver disease, Wilson disease, a1 antitrypsin deficiency.
Sertoglu, 2014	Inclusion criteria were: persistently (at least 6 months) elevated aminotransferases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], ultrasonographic presence of bright liver without any other liver or biliary tract disease and liver histology compatible with a diagnosis of NAFLD.	≥20 g/day in the last year, a positive test for hepatitis B surface antigen, hepatitis C antibody and other causes of liver disease, presence of T2DM, hypertension, morbid obesity (body mass index: BMI ≥40 kg/m^2), and any other major diseases, including generalized inflammation or advanced malignant diseases, exposure to occupational hepatotoxins or drugs known to be steatogenic or to affect glucose and lipid metabolism.

Appendix 1 (cont). Inclusion and exclusion criteria of studies

Author, date	Inclusion criteria and diagnosis	Exclusion criteria
Sunbul, 2014	Evidence of steatosis grade 1 or higher on liver ultrasound; absent to low alcohol consumption; evidence of NAFLD on liver biopsy.	Viral B and C hepatitis, Wilson's disease, a1 antitrypsin deficiency, autoimmune hepatitis, genetic hemochromatosis, use of steatogenic drugs. History of ischemic heart disease, cerebrovascular diseases, chronic renal failure, autoimmune disorders, malignancies.
Sunbul, 2015	Evidence of steatosis grade 1 or higher on liver ultrasound; absent to low alcohol consumption; evidence of NAFLD on liver biopsy.	Viral B and C hepatitis, Wilson's disease, a1 antitrypsin deficiency, autoimmune hepatitis, genetic hemochromatosis, use of steatogenic drugs. History of ischemic heart disease, cerebrovascular disease, chronic renal failure, autoimmune disorder, malignancy.
Tekatas, 2016	Adult (>18 years) patients found to have steatosis on abdominal ultrasonography and a diagnosis of steatosis made by liver biopsy after exclusion of other liver diseases.	Concurrent alcohol consumption, pregnancy, systemic diseases (cardiovascular disease, renal failure, cerebrovascular disease, severe coronary artery disease, uncontrolled hypertension, malignancy, receiving oncologic treatment, major operation in the last 2 months, patients receiving parenteral nutrition, patients using drugs that might be hepatotoxic. Excessive alcohol consumption for longer than 1 year at any time in their lifetime (>20 g/day for women, >30 g/day for men).
Tok, 2014	Liver biopsies containing at least 6 por tal tracts were considered adequate. METAVIR stages were used in evaluating the fibrosis staging. F0, F1 was termed "no/minimal fibrosis" and F2, F3, F4 were termed "significant fibrosis"	Previous antiviral ther apy for patients co infected with other viral hepatitis and HIV or liver transplantation, clini cally overt cirrhosis, Wilson disease, hemochro matosis, alcohol abuse, autoimmune or choles tatic liver disease were the exclusion criterion.
Turkay, 2012	Abdominal ultrasound was carried out using a 5 MHz curvilinear probe by a trained operator who was blinded to all clinical and laboratory characteristics of participants. The findings of hepatic steatosis at sonography include increased echogenicity and sound attenuation. The sever ity of fatty liver was determined by measuring the liver/ kidney echogenicity ratio (hepatorenal index).	Excess alcohol intake (≥20 g/d for males, 10 g/d for females), viral hepatitis, other causes of chronic liver disease.
Uygun, 2017	Liver histology. Individuals with persistently elevated ALT levels above the upper limits (>40 U/l) and a liver bright pattern in transabdominal ultrasound.	Evidence of other chronic liver diseases, including viral hepatitis B and C, autoimmune hepatitis, hemochromatosis, primary biliary cirrhosis, Wilson's disease, α1 antitrypsin deficiency. Alcohol consumption more than 140 g/week, exposure to occupational hepatotoxins or drugs.
Yalniz, 2006	Presence of steatosis (>10%), lobular inflammation, and ballooning degeneration (with or without fibrosis) on liver biopsy. Intake of less than 20 g of ethanol per day, confirmed by the physician and family members.	Other liver diseases such as alcoholic liver disease, viral hepatitis, autoimmune hepatitis, drug induced liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, biliary obstruction, celiac disease, and metabolic liver diseases.
Yaman, 2005	The diagnosis of NAFLD in subjects with chronic hypertransaminasemia was based on the following criteria: exclusion of any other putative cause of chronic liver disease, evidence of bright liver at ultrasound scan, and liver biopsy.	History of diabetes mellitus, hypertension, pancreatic and vascular diseases, intake of vitamin B6, vitamin B12, and/or folic acid supplements, and smoking. Patients consuming more than 20 g of alcohol per day.
Yesilova, 2005	Chronic hypertransaminasemia (>6 months). Exclusion of any other putative cause of chronic liver disease. Evidence of bright liver at ultrasound scan. Liver biopsy.	Gastrointestinal bypass surgery, diabetes mellitus, hypertension, pancreatic and vascular diseases, smoking, and current use of statins or fibrate. Patients consuming more than 20 g of alcohol per day.
Yilmaz Y., 2009	Ultrasonographic evidence of steatosis grade 1 or higher. An experienced pathologist blinded to clinical data scored the liver biopsies according to the NIDDK NASH Clinical Research Network scoring system.	Viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, a 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, diabetes mellitus, impaired renal function, malignancies. Known diabetes with fasting plasma glucose level ≥110 mg/dl. Medication use: estrogens, amiodarone, steroids, tamoxifen, herbal supplements, statins, or other lipid lowering drugs. Daily alcohol consumption exceeding 20 g/day, previous abdominal surgery.

Appendix 1 (cont). Inclusion and exclusion criteria of studies

Author, date	Inclusion criteria and diagnosis	Exclusion criteria
Yilmaz Y., 2010	Ultrasonographic evidence of steatosis grade 1 or higher. An experienced pathologist blinded to clinical data scored the liver biopsies according to the NIDDK NASH Clinical Research Network scoring system.	Viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, malignancies. Medication use: estrogens, amiodarone, steroids, tamoxifen, lipid lowering agents. Daily alcohol consumption exceeding 20 g/day, previous abdominal surgery.
Yilmaz Y., 2010/2	Ultrasonographic evidence of steatosis grade 1 or higher. An experienced pathologist blinded to clinical data scored the liver biopsies according to the NIDDK NASH Clinical Research Network scoring system.	Viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, malignancies. Medication use: estrogens, amiodarone, steroids, tamoxifen, lipid lowering agents. Daily alcohol consumption exceeding 20g/day, previous abdominal surgery.
Yilmaz Y., 2010/3	Ultrasonographic evidence of steatosis grade 1 or higher. An experienced pathologist blinded to clinical data scored the liver biopsies according to the NIDDK NASH Clinical Research Network scoring system.	Viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, malignancies. Medication use: estrogens, amiodarone, steroids, tamoxifen, lipid lowering agents. Daily alcohol consumption exceeding 20 g/day, previous abdominal surgery.
Yilmaz Y., 2010/4	Ultrasonographic evidence of steatosis grade 1 or higher. An experienced pathologist blinded to clinical data scored the liver biopsies according to the NIDDK NASH Clinical Research Network scoring system.	Viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, malignancies. Medication use: estrogens, amiodarone, steroids, tamoxifen, lipid lowering agents. Daily alcohol consumption exceeding 20 g/day, previous abdominal surgery.
Yilmaz Y., 2011	Ultrasonographic evidence of steatosis grade 1 or higher. An experienced pathologist blinded to clinical data scored the liver biopsies according to the NIDDK NASH Clinical Research Network scoring system.	Viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, malignancies. Medication use: estrogens, amiodarone, steroids, tamoxifen, lipid lowering agents. Daily alcohol consumption exceeding 20 g/day, previous abdominal surgery.
Yilmaz Y., 2011/2	Ultrasonographic evidence of steatosis grade 1 or higher. Absent to low alcohol consumption (<20 g/day). Evidence of NAFLD on liver biopsy. Experienced pathologist for liver biopsy scoring.	Viral B and C hepatitis, Wilson's disease, α1 antitrypsin deficiency, autoimmune hepatitis, genetic hemochromatosis, use of steatogenic drugs. Major comorbidities: ischemic heart disease, cerebrovascular diseases, autoimmune disorders, malignancies, and chronic renal insufficiency.
Yilmaz Y., 2011/3	NAFLD patients consecutively seen in specialized outpatient clinics in the past 12 months. Ultrasonographic evidence of steatosis grade 1 or higher. Experienced pathologist for liver biopsy scoring.	Viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, malignancies. Medication use: estrogens, amiodarone, steroids, tamoxifen, lipid lowering agents. Daily alcohol consumption exceeding 20 g/day, previous abdominal surgery.
Yilmaz Y., 2011/4	All NAFLD patients with ultrasonographic evidence of steatosis grade 1 or higher. Experienced pathologist for liver biopsy scoring.	Viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, malignancies. Medication use: estrogens, amiodarone, steroids, tamoxifen, lipid lowering agents. Daily alcohol consumption exceeding 20 g/day, previous abdominal surgery.
Yilmaz Y., 2011/5	NAFLD patients consecutively seen at specialized outpatient clinics in the past 12 months. Ultrasonographic evidence of steatosis grade 1 or higher. Experienced pathologist for	Viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, malignancies.

Appendix 1 (cont). Inclusion and exclusion criteria of studies

Author, date	Inclusion criteria and diagnosis	Exclusion criteria
	liver biopsy scoring.	Medication use: estrogens, amiodarone, steroids, tamoxifen, lipid lowering agents. Daily alcohol consumption exceeding 20 g/day, previous abdominal surgery.
Yilmaz Y., 2011/6	Fatty liver on ultrasound with persistent elevations of liver function tests for 6 months. Fatty liver on ultrasound with hepatomegaly and/or splenomegaly even in the absence of elevations of liver function tests. NAFLD patients consecutively seen at specialized outpatient clinics in the past 12 months. Ultrasonographic evidence of steatosis grade 1 or higher. Experienced pathologist for liver biopsy scoring.	Viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, alpha 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, malignancies. Medication use: estrogens, amiodarone, steroids, tamoxifen, lipid lowering agents. Daily alcohol intake exceeding 20 g/day, previous intestinal surgery.
Yilmaz Y., 2012	Biopsy proven NAFLD, >18 years of age, gave written informed consent, and had serum samples available for syndecan 1 measurements. Experienced pathologist blinded to clinical data for liver biopsy scoring.	Overt cardiovascular disease, daily alcohol consumption >20 g, seropositivity for hepatitis B or C, intake of any drug which may cause fatty liver, any severe acute or chronic illness, and severe end organ dysfunction.
Yilmaz Y., 2013	NAFLD patients with >5% macrovesicular steatosis as evaluated by light microscopic examination.	Chronic viral hepatitis, autoimmune hepatitis, hereditary hemochromatosis, Wilson's disease, drug induced liver disease, or presenting with clinical or imaging evidence of decompensated cirrhosis, daily alcohol consumption >20 g.
Yilmaz Y., 2018	Turkish patients with biopsy proven NAFLD selected by ultrasound guided liver biopsy. Liver biopsies scored by a single pathologist.	Viral or autoimmune hepatitis, significant alcohol consumption (>20 g/day), use of steatogenic medications, hereditary disorder associated with hepatic fat accumulation. Excluded patients with a history of abdominal surgery, impaired kidney function, ischemic heart or cerebrovascular disease, or malignancies.
Yilmaz H., 2015	NASH diagnosis based on liver biopsy. Exclusion of other causes of chronic liver disease (alcohol intake >20 g/day, viral hepatitis, autoimmune hepatitis, or medications).	Age younger than 18 years. History of oral and/or parenteral corticosteroids or other treatment affecting serum cytokine levels in the past 6 months. History of malignancy, alcohol consumption, chronic inflammatory disease, liver diseases with other etiology, autoimmune diseases, metabolic diseases, hemochromatosis, or drug induced diseases.