Supplementary appendix

NAFLD as a metabolic disease in humans: A literature review

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Search strategy

Search string

((("nonalcoholic steatohepatitis"[Title] OR "non-alcoholic steatohepatitis"[Title] OR "non-alcoholic steato-hepatitis"[Title] OR "nonalcoholic steato-hepatitis"[Title] OR NASH[Title] OR "non-alcoholic fatty liver disease"[Title] OR "nonalcoholic fatty liver disease"[Title] OR NAFLD[Title] OR "liver steatosis"[Title] OR "non-alcoholic fatty liver"[Title])

AND

(("global burden"[Title] OR epidemiology[Title] OR prevalence[Title] OR incidence[Title] OR mortality[Title]) OR ("metabolic syndrome"[Title] OR "metabolic risk factor"[Title] OR prediabetes[Title] OR T2D[Title] OR "Type 2 Diabetes"[Title] OR obesity*[Title] OR dyslipidemia*[Title] OR hyperlipidemia*[Title] OR "insulin resistance"[Title] OR predictor[Title] OR pathophysiology[Title] OR hypertension[Title] OR diabetes[Title] OR "insulin sensitivity"[Title] OR "cardiovascular disease"[Title] OR cirrhosis[Title] OR "advanced cirrhosis"[Title/Abstract] OR "advanced fibrosis"[Title/Abstract] OR "stroke"[Title] OR "heart failure"[Title/Abstract] OR "preserved ejection fraction"[Title/Abstract] OR "chronic kidney disease"[Title/Abstract] OR Cancer[Title] OR "liver cancer"[Title/abstract] OR "hepatic cancer"[Title/abstract] OR HCC[Title/Abstract] OR "hepatocellular carcinoma"[Title/Abstract]) OR (diagnosis[Title] OR diagnoses[Title] OR biomarker[Title] OR Fibroscan[Title/abstract] OR markers[Title] OR biopsy[Title]) OR (management[Title] OR treatment[Title] OR drug[Title] OR therapy[Title] OR pharmacotherapy[Title] OR "clinical trial"[Title] OR pharmacological[Title] OR safety[Title] OR efficacy[Title])))

NOT (zebrafish OR transplants OR Hepatitis OR microbiota OR microbiome OR mice OR pediatric OR paediatric OR child OR children OR celiac OR coeliac OR SIBO OR "small intestinal bacterial overgrowth" OR sarcopenia OR Chornobyl OR "Netherton syndrome" OR diet OR gut OR micronutrients OR HIV OR nutraceutical OR curcumin OR "vitamin D" OR "free fatty acid" OR nutrition OR smoking OR HCV OR "Hepatitis C" OR virus OR marmoset OR lung OR thoracic OR epilepsy))

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Diagnosis and monitoring of NAFLD and NASH

The American Diabetes Association (ADA) recommends that patients with type 2 diabetes mellitus (T2DM) be proactively monitored for signs of non-alcoholic fatty liver disease (NAFLD).[1] Therefore, accurate, non-invasive approaches for diagnosis and staging of NAFLD and non-alcoholic steatohepatitis (NASH), particularly for patients with T2DM and/or obesity, are urgently needed. Steatohepatitis is often identified by abdominal ultrasound during routine health checks.[2] Although invasive, costly, and associated with some risks, liver biopsies remain the only definitive technique to determine and then monitor the stage and severity of NAFLD. However, uneven distribution of histological NASH lesions in the liver parenchyma can result in biopsy sampling errors, leading to misdiagnoses and disease staging inaccuracies.[3] Intraoperative liver biopsies have been suggested as a method of screening for NAFLD in patients with increased risk.[4] A prospective observational study in which liver biopsies were taken during laparoscopic cholecystectomy (LC) found a high prevalence of NAFLD; 21.8% of those patients with symptomatic gallstones had asymptomatic NAFLD confirmed by liver biopsy. Singh *et al.* concluded that such screening of patients with gallstone disease undergoing LC may be a potential additional method for early diagnosis of NAFLD.[4]

A number of studies identified have assessed the potential diagnostic value of biomarkers or composites of clinical assessments for NAFLD.[5-7] Commercial biomarker panels (SteatoTest, ActiTest, NashTest-2, and FibroTest) have been validated for diagnosis of NAFLD, NASH, and/or fibrosis, although they have questionable performance in patients with T2DM.[8] The Enhanced Liver Fibrosis (ELF) score (consisting of tissue inhibitor of metalloproteinases 1 [TIMP-1], amino-terminal propeptide of type III procollagen, and hyaluronic acid) is recommended by the UK National Institute for Health and Care Excellence (NICE) for assessment of advanced fibrosis.[9] A wide range of other biomarkers and composite scores incorporating clinical and laboratory assessments have been proposed for detecting fibrosis in patients with NAFLD, including: NAFLD fibrosis score (NFS; a composite of age, hyperglycaemia, BMI, platelet count, albumin level, and aspartate aminotransferase [AST]/alanine aminotransferase [ALT] ratio; mean sensitivity and specificity for significant fibrosis of 65.5% and 82.5%),[10,11] fibrosis-4 index (FIB-4, a composite of age, platelet count, and levels of AST and ALT; mean sensitivity and specificity for significant fibrosis of 64.4% and 70.0%),[11] red cell volume distribution width-to-platelet ratio,[12] a panel comprising variables implicated in fibrogenesis and adipokines in combination with clinical and laboratory parameters,[13] Wisteria floribunda agglutinin-positive Mac-2-binding protein and type 4 collagen 7S,[14] MACK-3 (a composite of AST, homeostatic model assessment of insulin resistance and apoptotic caspase-3 generated cytokeratin-18 fragments),[15] Linköping University-Karolinska Institute (LINKI; based on hyaluronic acid, AST, glucose, and age),[16] and FibroMeter$^{V2G/V3G}$ (fibrosis panel composites of age, sex, AST, platelet count, prothrombin index, alpha-2-macroglobulin, urea and hyaluronic acid or gamma glutamyl-transferase).[17] A study comparing AST–platelet ratio index (APRI), BARD score (comprising BMI, AST/ALT ratio, and presence of T2DM), FIB-4 score, NFS, and FibroMeter in 142 patients with NAFLD reported no significant differences in sensitivity and specificity between scores.[18] Another study concluded that APRI, BARD score, FibroMeter and non-invasive Koeln-Essen index were more accurate in diagnosing advanced fibrosis in NAFLD than Forns' index, S index, Hui model, NFS and FIB-4; stepwise combination of the models performed better than each single scoring system alone.[19] Non-invasive scores for advanced fibrosis (AST/ALT ratio, APRI, FIB-4, and NFS) were assessed in a large cohort of 1157 patients with T2DM and the authors concluded that all scores had

reasonable specificity, but poor sensitivity in this population.[20] These findings are supported by a cross-sectional study in 213 patients with T2DM evaluating a range of clinical scores and biomarkers for NASH (ALT, cytokeratin-18, NashTest 2, the HAIR score [comprising hypertension, ALT, and IR], BARD, and OWLiver) and advanced fibrosis (AST, fragments of propeptide of type III procollagen, FIB-4, APRI, NFS, and FibroTest), reporting that none of the tests had optimal performance.[21] Significantly increased TIMP-1 and -2 levels have been reported in patients with biopsy-confirmed NASH versus age-matched controls and patients with obesity and normal liver enzymes, and TIMP-1 (sensitivity 96.7%, specificity 100%) and TIMP-2 (sensitivity 93.3%, specificity 100%) have been proposed for consideration as non-invasive markers of NASH.[22] Finally, mass spectroscopy profiling of plasma lipids and metabolites in combination with clinical data and the patatin-like phospholipase domain-containing 3 (PNPLA3) genotype has shown promise to accurately identify the risk of NASH in a population of which 83% had morbid obesity; however, the high pretest probability in this patient population limits the usefulness of these findings.[23]

Non-invasive imaging methods have been assessed for diagnosis and staging of NAFLD, including: transient elastography, supersonic shear imaging, and acoustic radiation force impulse imaging (ARFI),[24-28] magnetic resonance elastography (MRE),[11,29-33] and shear-wave elastography.[11] Doppler ultrasound has been proposed for assessment of fibrosis in patients not suitable for transient elastography.[34] A study comparing detection of advanced fibrosis in patients with NAFLD using ARFI, FIB-4, NFS, and BARD reported inconsistent performance of all the techniques across the range of steatosis severity.[35] A similar study comparing diagnostic measurements of fibrosis grade reported superior diagnostic accuracy of ELF, FibroMeter and liver stiffness measurement (obtained by vibration-controlled transient elastography), over FIB-4 and NFS.[17] In a study of 417 patients with NAFLD from two tertiary care centres in France, ELF and FibroMeter^{V2G} were again found to be superior to FIB-4 and NFS for diagnosis of advanced liver fibrosis, with no significant differences found in diagnostic accuracy between ELF and FibroMeter^{V2G}.[36] In a comparison of shear wave elastography and transient elastography, accuracy was reported to be significantly higher in transient elastography than shear wave elastography for diagnosis of fibrosis stage ≥F2 and ≥F3.[37] Both methods were found to have high reliability, as assessed by intra-operative and inter-operative variability analysis.[37] A retrospective study assessed venous pulsatility index (VPI) for diagnosis of high-risk NAFLD in patients with biopsy-proven NAFLD who underwent duplex Doppler ultrasound assessment of the main portal vein within 1 year of liver biopsy.[38] VPI had higher optimism-corrected area under the curve values than NFS, FIB-4, APRI and BARD, and significantly improved the diagnostic value for high-risk NAFLD when added to any of the other four scoring systems.[38] For patients with obesity undergoing bariatric surgery, visual appearance of liver colour, size, and surface has been reported to accurately identify patients who would benefit from a liver biopsy.[39] Among various imaging modalities, magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) has been recommended as most practical for liver fat quantification in clinical trial settings,[40] and MRE as most accurate in quantifying biomarkers for liver fibrosis.[30,41] FibroScan-AST (FAST) and the MRE combined with FIB-4 (MEFIB) index are discussed in the main manuscript text. FAST has recently shown good performance at identifying patients at risk of progressive NASH (NASH with NAFLD Activity Score ≥4 and fibrosis stage ≥2), with positive predictive values (PPV) of 69–83%.[42] Meanwhile, the MEFIB index demonstrated PPVs of 91–97% for detection of fibrosis stage ≥2.[43]

Insights into the relationship between metabolic dysfunction and NAFLD from genome-wide analyses in recent years

Genome-wide analyses have provided insights into the relationship between metabolic dysfunction and NAFLD in recent years. Mutations that regulate lipid metabolism, glucose metabolism, and the renin–angiotensin system have been implicated in NAFLD onset, steatosis, inflammation, fibrosis, and HCC,[44] particularly PNPLA3 I148M and transmembrane 6 superfamily member 2 (TM6SF2). PNPLA3 I148M (rs738409) is associated with greater risk of NAFLD and T2DM[45] and may be a contributing factor to the development of non-obese NAFLD.[46] A case-control genome-wide association study reported a significant association between *PNPLA3* I148M (rs738409) and cirrhosis in patients with HCC; a 3-fold increased risk of HCC was observed in individuals with the rs738409 mutation.[47] In this study, Hassan *et al.* also identified an additive relationship between *PNPLA3* I148M (rs738409) and presence of diabetes mellitus, in the risk of developing HCC (adjusted odds ratio 19.11).[47] Emerging evidence from recent Mendelian randomization studies (using risk alleles in *PNPLA3*, *TM6SF2*, and other NAFLD-related genetic variants) suggests that genetically driven NAFLD causally increases the risk of developing insulin resistance (IR) and new-onset T2DM.[48-50] A large exome-focused genotyping array study, using the UK Bio-Bank cohort, provides further support for the notion that higher levels of liver fat content (mediated by genotypic variations in *PNPLA3* and *TM6SF2*) increase the risk of incident T2DM.[51] A missense mutation in *PNPLA3* L148M has also been shown to promote cellular triglyceride accumulation in mice.[52]

In hepatic steatosis, insulin receptor substrate (IRS)-2 expression is thought to be downregulated, contributing to hepatic IR. In a recent analysis of mRNA expression in patients with NAFLD and healthy controls, IRS-2 expression was decreased and enzymes involved in gluconeogenesis were upregulated in patients with NAFLD and NASH versus healthy controls, suggesting that selective IR occurs in human hepatocytes during NAFLD.[53] With the progression of NASH to cirrhosis, patients have lower serum triglycerides, low-density lipoprotein and very LDL as a result of decreasing *de novo* lipogenesis capacity, despite consistent hyperinsulinaemia.[54]

Managing NASH by treating liver disease and targeting metabolic risk: Current and emerging strategies – *additional information*

NAFLD has been reported to significantly impact on patients' quality of life, particularly in parameters of physical function versus the general population and in domains such as fatigue, activity, emotions, and worry compared with patients with hepatitis B or C infection.[55,56] Patients with NAFLD experience depression more frequently than the general population, which may be partly as a result of comorbidities such as T2DM and obesity.[56] Patients with NASH have reported a good level of satisfaction with their care, they most commonly reported symptoms of fatigue, having overweight and abdominal discomfort, and they prioritized potential treatments that would impact on their liver status and improve symptoms.[57]

Guidelines

As discussed in the main text, lifestyle modifications consisting of diet, exercise, and weight loss are advocated for patients with NAFLD.[58-60] There are currently no FDA-approved pharmaceutical treatments for patients with NAFLD or NASH; however, some international guidelines do recommend some therapeutic approaches.[9,58-60] To date, none of the treatments assessed in NASH have provided efficacy across the heterogeneous patient population and the lack of simple inexpensive tests to assess treatment response and predictors of likelihood of response is a major challenge for drug development. The European Association for the Study of the Liver (EASL) – European Association for the Study of Diabetes (EASD) – European Association for the Study of Obesity (EASO) Clinical Practice Guidelines for the management of NAFLD (2016)[61] do not recommend any specific therapy for the treatment of NASH. Off-label options, such as insulin sensitizers (e.g. pioglitazone), antioxidants, cytoprotective and lipid-lowering agents, and iron depletion, are suggested as a possibility.[61] Of these, pioglitazone and/or vitamin E are most strongly recommended.[61] The 2018 AASLD[58] and UK NICE[9] guidelines state the benefits of pioglitazone in patients with biopsy-proven NASH with and without T2DM. AASLD,[58] Belgian Association for Study of the Liver (2018),[59] Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease (2017),[60] and NICE[9] guidelines outline the benefits of Vitamin E in non-diabetic, non-cirrhotic adults with biopsy-proven NASH and suggest it as a treatment for NASH. Additionally, the Asia-Pacific[60] and Belgian[59] guidelines endorse liraglutide as a means to improve NASH, mainly through reduction of cardiovascular complications.

Dietary supplements and homeopathic remedies

Marine omega-3 polyunsaturated fatty acids (n-3 PUFA) are precursors to anti-inflammatory mediators and are known to reduce plasma triacylglycerol and fatty acid synthesis.[62] n-3 PUFAs have been evaluated as a dietary supplement in the treatment of NAFLD. Reviews have found several studies reporting reduction in hepatic fat content, inflammatory markers, and liver enzymes after supplementation with n-3 PUFAs such as eicosapentaenoic acid or docosahexaenoic acid.[62,63]

Limonoids have shown anti-inflammatory, anti-oxidative and other beneficial effects.[64] Kelley *et al*. reported that purified limonin glucoside (LG) reduced the inflammatory markers matrix metalloproteinase-9 and tumour necrosis factor α and that the significant reductions found in ALT, alkaline phosphatase, gamma-glutamyl transferase, and complement component 3, were likely liver-specific effects of LG.[65]

Regular consumption of polyphenols may prevent progression of NAFLD to NASH through reduction of *de novo* lipogenesis; increased FA oxidation; and improved insulin sensitivity and adipokine regulation.[66] Rodriguez-Ramiro *et al*. propose the 5' adenosine monophosphate-activated protein kinase/Sirtuin-1 axis as a likely mechanism in polyphenol modulation of metabolism, with further research required to confirm this.[66]

A pilot study investigated the effects of a combination of plant extracts on insulin resistance and hepatic steatosis in 49 patients with NAFLD.[67] The mixture of berberine, tocotrienols and decaffeinated green coffee was reported to improve insulin receptor expression (P<0.05) and significantly reduce hepatic steatosis compared with the placebo group (measured by controlled attenuation parameter during transient elastography, P<0.01).[67]

Acupoint embedding therapy is a modified acupuncture therapy involving insertion of dissolvable sutures at points of acupuncture in order to prolong stimulation.[68] A meta-analysis of the treatment of NAFLD with abnormal transaminase suggested that acupoint embedding alone or as a combination therapy has superior effects on ALT reduction compared to those of conventional methods (P<0.001) and beneficial effects on AST, cholesterol, and trigylcerides.[68] However, there was substantial heterogeneity between the included studies and more rigorous clinical trials are required.[68]

Bariatric surgery

While bariatric surgery is not currently indicated for NAFLD, recent reports suggest that many patients can achieve significant reductions in steatosis and fibrosis after intervention.[69,70] Bariatric surgery has a profound effect on T2DM, with a complete post-surgical resolution reported in 76.8% of patients with morbid obesity in a meta-analysis.[71] A metabolic response is observed immediately post-surgery so is thought to be independent of weight loss, including improved hepatic insulin sensitivity due to post-surgery calorie restriction and improved post-prandial insulin secretion as a result of a rise in GLP-1 that occurs in response to accelerated transport of nutrients into the small intestine.[72] Lassailly *et al*. recently reported encouraging long-term outcomes in a cohort of 180 patients with severe obesity and biopsy-confirmed NASH undergoing bariatric surgery.[73] At 5-year post-surgical follow-up, NASH was resolved without worsening fibrosis in 84% of patients, fibrosis decreased versus baseline in 70.2% and was completely resolved in 56%. Well-designed clinical trials are needed to establish the place of surgical approaches, particularly those that are less invasive, in combination with other lifestyle interventions for patients with NAFLD and obesity.

Table S1. Characteristics of included studies

Number	Source	Study design	Study population	Participants		Objective/intervention	Duration of follow-up	Key finding	Category
				Total N	Male (%)				
1	Aykut 2014[27,a]	Cohort study	Patients with NAFLD	88	56.8	Compare diagnostic performance of FibroMeter™ NAFLD score, NFS, and TE for the detection of liver fibrosis	N/A	Sensitivity/specificity of FibroMeter™ NAFLD score, NFS, and TE for significant fibrosis were 38.6%/86.4%, 52.3%/88.6%, and 75.0%/93.2%, respectively	Diagnosis and biomarkers
2	Chwist 2014[13]	Cohort study	Adult patients with NAFLD	70	57.1	Investigate laboratory variables with potential to predict advanced fibrosis	N/A	Patients with NASH had significantly higher HOMA-IR values and serum levels of visfatin, haptoglobin, and zonulin vs those without NASH	Diagnosis and biomarkers
3	Loomba 2014[32,a]	Cross-sectional study	Patients with NAFLD	117	43.6	Assess the diagnostics accuracy of 2D-MRE, in predicting advanced fibrosis	N/A	MRE is accurate in predicting advanced fibrosis	Diagnosis and biomarkers
4	Di Naso 2015[74]	Observational study	Patients with obesity undergoing bariatric surgery	95	21	Evaluate role of the HSP70 pathway in NAFLD progression	N/A	Negative correlation between NAFLD progression and expression/activation of the HSF1/HSP72 pathway	Association with metabolic risk factors or other diseases
5	Gaharwar 2015[75]	Observational study	Patients with NAFLD from India	70	42.9	Establish risk of MetS and its components	N/A	51.4% of patients had MetS	Association with metabolic risk factors or other diseases
6	Subasi 2015[18,a]	Retrospective analysis	Patients with diagnosed NAFLD	142	53	Compare the diagnostic performance of five non-invasive scores for the assessment of advanced stages of fibrosis	N/A	Different non-invasive scores have similar accuracy for the diagnosis of advanced hepatic fibrosis in NAFLD	Diagnosis and biomarkers
7	Pang 2015[76]	Meta-analysis	Studies estimating the impact of central obesity on NAFLD	45,757	55	Investigate if central obesity is associated with NAFLD	N/A	Central obesity may pose a greater threat to health than general obesity, although both are independently associated with increased risk of NAFLD	Association with metabolic risk factors or other diseases
8	Loomba 2015[77]	RCT	Patients with biopsy-confirmed NASH	50	38	Examine ezetimibe vs placebo in reducing liver fat and liver histology	24 weeks	Ezetimibe did not significantly reduce liver fat in NASH (mean difference –1.3%)	Treatment
9	Al Rifai 2015[78]	Observational study	Adults without known CV disease at the time of enrolment	3976	45	Assess impact of the number of metabolic conditions on inflammation and subclinical atherosclerosis (assessed as CAC)	N/A	NAFLD is associated with increased inflammation and CAC independent of traditional risk factors, obesity and MetS	Association with metabolic risk factors or other diseases

10	Singh 2015[79]	Meta-analysis	Studies including adults with NAFLD and paired liver biopsies ≥1 year apart	411	N/A	Estimating the rates of fibrosis progression in patients with NAFLD	N/A	Liver fibrosis progresses in patients with NAFLD	Association with metabolic risk factors or other diseases
11	Liu 2015[28]	Meta-analysis	Studies assessing ARFI in patients with NAFLD	723	N/A	Evaluate ARFI elastography in detecting hepatic fibrosis in patients with NAFLD	N/A	ARFI elastography was modestly accurate in detecting significant fibrosis in patients with NAFLD	Diagnosis and biomarkers
12	Li 2015[80]	Cohort study	Patients without T2DM from China	4736	66.5	Analyse effects of obesity and NAFLD on T2DM	Median 200.2 weeks	NAFLD could predict risk of T2DM, independent of weight/obesity	Association with metabolic risk factors or other diseases
13	Abdelaziz 2015[22]	Prospective cohort study	Patients with obesity and normal or elevated liver enzymes	90	40	Evaluate TIMPs as non-invasive predictors of NASH	N/A	TIMP-1 and TIMP-2 may be considered non-invasive markers for diagnosis of NASH	Diagnosis and biomarkers
14	Santilli 2015[81]	Cross-sectional study	Patients with familial combined hyperlipidaemia and/or MetS, with or without NAFLD	110	55	Investigate if the advanced glycation end-products pathway is associated with diagnosis of NAFLD with and without MetS	N/A	Activation of the advanced glycation end-products pathway may contribute to progression of both liver and CV disease	Association with metabolic risk factors or other diseases
15	Singh 2015[82]	Retrospective cross-sectional study	Patients diagnosed with fatty liver in India	336	N/A	Compare anthropometric, metabolic, biochemical, ultrasonography, and histological profile of patients with NAFLD with and without IR	N/A	46% of patients with NAFLD did not have IR, of which a third had significant fibrosis despite absence of IR	Association with metabolic risk factors or other diseases
16	VanWagner 2015[83]	Cross-sectional study	Young adults from the USA who underwent CT	2713	41.2	Examining the association between NAFLD and early changes in left ventricular structure	N/A	NAFLD is independently associated with subclinical myocardial remodelling and dysfunction	Association with metabolic risk factors or other diseases
17	Cengiz 2015[12,a]	Cohort study	Adult patients with NAFLD	123	56.1	Investigate the performance of RPR in predicting liver fibrosis vs other non-invasive fibrosis scores	N/A	RPR was able to predict liver fibrosis	Diagnosis and biomarkers
18	Praveenraj 2015[84]	Retrospective analysis	Adults with morbid obesity from India undergoing elective bariatric surgery with concomitant liver biopsy	134	39.3	Determine the prevalence and predictors of NAFLD in Indian patients with morbid obesity	N/A	65.7% of patients had NAFLD, 33.6% had NASH and 31.3% had fibrosis	Burden of disease
19	Vassilatou 2015[85]	Cross-sectional study	Premenopausal women with BMI >25.0 kg/m^2	110	0	Investigate the prevalence of PCOS in premenopausal women with NAFLD who were	N/A	PCOS diagnosed in 43.7% of women with vs 23.1% without NAFLD	Burden of disease

						overweight or had obesity			
20	Carbone 2016[86]	Meta-analysis	Studies in adults with NAFLD receiving GLP-1 receptor agonists or DPP-4i	136	N/A	Evaluate the efficacy of incretin-based therapies	N/A	Significant reduction in serum ALT following GLP-1/DPP-4i treatment (mean reduction of 14.1 IU/L, *P*<0.0001)	Treatment
21	Armstrong 2016[87,b]	RCT	Patients with clinical signs of NASH	52	59.6	Assessing liraglutide vs placebo for patients who are overweight and have clinical evidence of NASH	60 weeks	39% with liraglutide vs 9% with placebo has resolution of NASH at 48-week follow-up (*P*=0.019)	Treatment
22	Cui 2016[33,a]	Cross-sectional analysis	Patients with NAFLD	125	45.6	Head-to-head comparison of MRE vs ARFI for diagnosing fibrosis	N/A	MRE is more accurate than ARFI for diagnosing any fibrosis in NAFLD, especially among patients with obesity	Diagnosis and biomarkers
23	Tang 2016[88]	Meta-analysis	RCTs of anti-diabetic agents in patients with T2DM	961	63	Provide an assessment of the impact of anti-diabetic agents on NAFLD	N/A	Thiazolidinediones and GLP-1 receptor agonists appear to attenuate hepatic fat content	Treatment
24	Lu 2016[89]	Cross-sectional analysis	Adults in China who underwent routine health examinations	1948	66	Investigate the prevalence of and risk factors for NAFLD in a Chinese population	8 years	35.47% of patients were diagnosed with NAFLD at baseline, but it can be reversed with weight loss and control of hyperlipidaemia and hyperglycaemia	Burden of disease
25	Ballestri 2016[90]	Meta-analysis	Prospective studies in patients with diagnosed NAFLD	117,020 (T2DM); 81,411 (MetS)	N/A	Establish risk of T2DM and MetS in patients with NAFLD	260 weeks (T2DM) and 234 weeks (MetS)	NAFLD increases risk of T2DM and MetS	Association with metabolic risk factors or other diseases
26	Li 2016[91]	Meta-analysis	Cohort studies assessing NAFLD risk associated with obesity	381,655	N/A	Investigate the risk of NAFLD associated with obesity	N/A	Patients with obesity have a 3.5-fold increased risk of developing NAFLD vs those without obesity	Association with metabolic risk factors or other diseases
27	Cassinotto 2016[26]	Cohort study	Adult patients with NAFLD who underwent liver biopsy	291	59.1	Compare liver stiffness measurement evaluated by SSI, FibroScan, and ARFI	N/A	FibroScan, ARFI, and especially SSI were all valuable for diagnosis of liver fibrosis in patients with NAFLD	Diagnosis and biomarkers
28	Loomba 2016[31]	Cross-sectional study	Patients with NAFLD	100	44	Compare the diagnostic accuracy of 3D-MRE and 2D-MRE for diagnosing advanced fibrosis	N/A	3D-MRE at 40 Hz has the highest accuracy in diagnosing advanced fibrosis	Diagnosis and biomarkers
29	Ergelen 2016[34]	Cohort study	Patients with NASH	63	61.9	To assess the potential for identifying fibrosis using doppler ultrasound vs TE and liver biopsy	N/A	Doppler ultrasound has moderate sensitivity and specificity, which is lower compared with TE for diagnosis significant fibrosis	Diagnosis and biomarkers
30	Zhou 2016[23]	Cross-sectional study	Patients who underwent liver biopsy because	318	N/A	Investigate whether mass spectrometry-based plasma profiling improves risk estimates	N/A	A score based on mass spectrometry, AST, fasting insulin, and *PNPLA3* genotype is significantly	Diagnosis and biomarkers

			of suspected NASH			of NASH vs routine clinical parameters and *PNPLA3* genotype at rs738409		better than clinical or metabolic profiles alone in determining risk of NASH	
31	Lykiardopoulos 2016[16]	Cohort study	Patients with NAFLD	158	74	Develop a novel algorithm for detection of advanced fibrosis based on a combination of serological markers	N/A	Novel LINKI algorithm for detection of advanced fibrosis in NAFLD showed better accuracy than established algorithms	Diagnosis and biomarkers
32	Pan 2017[92,c]	Observational study	Patients who accepted colonoscopy	1793	64.5	Investigate the combined effect of NAFLD and MetS on development of colorectal neoplasm	N/A	NAFLD and MetS are risk factors for colorectal neoplasm and CRC	Association with metabolic risk factors or other diseases
33	Park 2017[30]	Cross-sectional study	Patients undergoing biopsy to assess NAFLD	104	43	Compare the performance of MRE vs TE for diagnosis of fibrosis, and MRI-based proton density fat fraction analysis vs TE-based CAP for diagnosis of steatosis	N/A	MRE was more accurate than TE in identification of liver fibrosis. MRI-based proton density fat fraction is more accurate than CAP in detecting all grades of steatosis in patients with NAFLD	Diagnosis and biomarkers
34	He 2017[6]	Meta-analysis	Studies assessing serum biomarkers in patients with NAFLD	3431	49	Evaluate the diagnostic value of serum biomarkers in the diagnosis of NAFLD and NASH	N/A	Increased serum cytokeratin-18 and FGF21 are associated with NASH, but are not sufficient for diagnosis. A combined biomarker panel may be useful as a diagnostic tool for NASH	Diagnosis and biomarkers
35	Petit 2017[93]	RCT	Patients with T2DM treated with metformin and/or sulfonylurea (or glinides) and/or insulin	68	54	Study impact of liraglutide on liver fat content in patients with uncontrolled T2DM	26 weeks	Liraglutide significantly reduced liver fat content in patients with inadequately controlled T2DM (31% decrease from baseline, $P<0.0001$)	Treatment
36	Yoo 2017[94]	Cross-sectional study	Patients with and without NAFLD who completed a health check-up	320	65	Examining plasma LECT2 levels in the subjects with NAFLD or MetS	N/A	Plasma LECT2 was increased in individuals with NAFLD and those with MetS, but not in those with atherosclerosis	Association with metabolic risk factors or other diseases
37	Tokita 2017[95]	Observational study	Individuals who had annual health checks in Japan	2408	64	Investigate if NAFLD diagnosed by ultrasonography could predict risk of T2DM	520 weeks	NAFLD was a significant predictor for future T2DM, especially in women	Association with metabolic risk factors or other diseases
38	Musso 2017[96]	Meta-analysis	RCTs assessing thiazolidinedione therapy in biopsy-confirmed NASH	516	N/A	Evaluate the association between thiazolidinedione therapy and advanced liver fibrosis in NASH	N/A	Pioglitazone use significantly improves advanced fibrosis in NASH, even in patients without T2DM	Treatment
39	Dulai 2017[97]	Meta-analysis	Adult patients with NAFLD	1495	54	Quantify the fibrosis stage-specific relative risk of all-cause mortality and liver-	N/A	The risk of liver-related mortality increases exponentially with increase in fibrosis stage	Burden of disease

						related mortality for NAFLD			
40	Caussy 2017[98]	Cross-sectional analysis	Patients with NAFLD-cirrhosis and their first-degree relatives	203	28	Assess the risk of advanced fibrosis in first-degree relatives of patients with NAFLD-cirrhosis	N/A	First-degree relatives of patients with NAFLD-cirrhosis have a 12x higher risk of advanced fibrosis	Burden of disease
41	Zhang 2017[99]	Cross-sectional study	Steel company employees aged ≥20 years from China	10,069	63	Exploring the effects of obesity on the association between uric acid, MetS, and NAFLD	N/A	Obesity and elevated uric acid have a pronounced synergistic effect on the development of NAFLD and hypertriglyceridaemia	Association with metabolic risk factors or other diseases
42	Dong 2017[100]	Meta-analysis	Patients with NAFLD or NASH established by liver biopsy or imaging	329	N/A	Evaluate the efficacy and safety of GLP-1 receptor agonists	N/A	GLP-1 receptor agonists significantly reduced steatosis, lobular inflammation, hepatocellular ballooning and fibrosis vs baseline	Treatment
43	Jaruvongvanich 2017[10]	Meta-analysis	Studies assessing the association between NFS and mortality in patients with NAFLD	5033	52.1	Investigate the role of NFS for prediction of mortality from NAFLD	Median 60–174 months	High NFS is associated with increased risk of mortality among patients with NAFLD	Diagnosis and biomarkers
44	Yip 2017[7]	Cross-sectional study	Patients with NAFLD and healthy participants without NAFLD	922	42	Develop and validate a laboratory parameter-based machine learning model to detect NAFLD	N/A	NAFLD ridge score was a simple and predictive score for excluding NAFLD in general population	Diagnosis and biomarkers
45	Feng 2017[101]	RCT	Patients with T2DM and NAFLD from China	87	69	Comparing the effects of gliclazide, liraglutide, and metformin on hepatic fat	24 weeks	Hepatic fat content was significantly reduced in all three treatment groups vs baseline (P<0.001)	Treatment
46	Dai 2017[102]	Meta-analysis	Patients with T2DM	N/A	N/A	Establish pooled prevalence of NAFLD in patients with T2DM	N/A	59.67% pooled prevalence of NAFLD in patients with T2DM	Burden of disease
47	Friedrich-Rust 2017[103]	Prospective cohort study	Patients undergoing elective coronary angiography	505	78	Evaluate the association between the presence and severity of CAD and NAFLD	N/A	CAD is frequently associated with presence of NAFLD	Association with metabolic risk factors or other diseases
48	Lee 2017[25]	Cohort study	Patients with NAFLD	94	43.6	Head-to-head comparison of the diagnostic performances of TE, ARFI, and SSI for staging fibrosis and identify clinical, anthropometric, biochemical, and histological features that might affect LSM	N/A	LSM methods had similar diagnostic performance for staging fibrosis in patients with NAFLD. Pre-LSM anthropometric evaluation may help predict the reliability of SSI	Diagnosis and biomarkers
49	Xiao 2017[11]	Meta-analysis	Patients with diagnosed NAFLD, viral	13,294	54	Compare the diagnostic performance of seven non-invasive scores for	N/A	MRE and SWE may have the highest diagnostic accuracy for staging fibrosis in patients with NAFLD. NFS	Diagnosis and biomarkers

			hepatitis, and other diseases			the diagnosis of liver fibrosis in NAFLD		and FIB-4 may offer the best diagnostic performance for advanced fibrosis	
50	Wongjarupong 2017[104]	Meta-analysis	Patients with iCCA or eCCA	5067 (iCCA); 4035 (eCCA); 129,111 (controls)	N/A	Determine a potential association between NAFLD and CCA, stratifying by its subtypes; iCCA and eCCA	N/A	NAFLD may potentially increase the risk of CCA development and the magnitude of NAFLD on CCA risk is greater for iCCA than eCCA subtype	Association with metabolic risk factors or other diseases
51	Costa-Silva 2018[29]	Observational study	Adult patients with NAFLD and healthy volunteers	90	25.6	Evaluate MRE in diagnosing and staging hepatic fibrosis and in distinguishing simple steatosis from NASH	N/A	MRE was effective in detecting/staging fibrosis in NAFLD. Patients with NAFLD and inflammation without fibrosis have greater liver stiffness than those with simple steatosis	Diagnosis and biomarkers
52	Kamarajah 2018[24]	Longitudinal study	Patients with NAFLD in Asia	113	50	Determine the value of repeated LSM in NAFLD	Median 37 months	Repeat LSM can predict liver-related complications and may identify patients at risk of CV events	Diagnosis and biomarkers
53	Joo 2018[35]	Cross-sectional analysis	Patients with NAFLD	315	51	Assess the potential for non-invasive tests to predict advanced fibrosis in patients with NAFLD	N/A	Steatosis severity may affect the diagnostic performances of non-invasive fibrosis tests in patients with NAFLD	Diagnosis and biomarkers
54	Romero-Ibarguengoitia 2018[105]	Cross-sectional study	Normoglycaemic subjects	137	30	Addressing relationships between obesity, NAFLD, and family history of obesity	N/A	Family history of obesity results in alterations in the regulation of key metabolic pathways and predicts inflammation, IR, obesity, and NAFLD	Association with metabolic risk factors or other diseases
55	Ooi 2018[39]	Prospective cohort study	Patients with obesity undergoing bariatric surgery	152	24	Evaluate the diagnostic accuracy and reproducibility of a simple intraoperative visual liver score to stratify the risk of NASH and NAFLD in obesity	N/A	Liver appearance can be a useful and reliable tool for NAFLD risk stratification and identification of patients who would benefit from liver biopsy	Diagnosis and biomarkers
56	Alexander 2018[106]	Case-cohort study	Patients with NAFLD and risk of stroke from the USA	1589	45	Assess the relationship between NAFLD, hepatic biomarkers and incident ischaemic stroke	5.8 years	NAFLD was inversely associated with stroke risk in men, but not women	Diagnosis and biomarkers
57	Harrison 2018[107]	RCT	Patients aged 18–75 years with biopsy-confirmed non-alcoholic steatohepatitis	82	42	Assessing the safety and efficacy of NGM282 in non-alcoholic steatohepatitis	4 weeks	Both doses (3 and 6 mg) of NGM282 were well tolerated and 74% and 79% of these doses, respectively, achieved at least a 5% reduction in absolute liver fat content from baseline	Treatment
58	Kabir 2018[108]	Observational study	Patients with T2DM from Bangladesh	258	56.9	Determine the prevalence of NAFLD and identify	N/A	64.7% of patients had fatty liver	Burden of disease

						predisposing factors for T2DM and NAFLD			
59	Boursier 2018[15]	Retrospective analysis	Patients with NAFLD	846	37.9	Develop a new blood test for NASH and advanced fibrosis	N/A	MACK-3 provided excellent accuracy for the diagnosis of fibrotic NASH	Diagnosis and biomarkers
60	Lu 2018[109]	Meta-analysis	Studies in patients with diagnosed NAFLD	11,043	N/A	Comparison between non-obese and obese NAFLD	N/A	Obesity can predict a worse long-term prognosis for patients with NAFLD	Association with metabolic risk factors or other diseases
61	Friedman 2018[110]	RCT	Adults with histological evidence of NASH	289	47	Evaluate cenicriviroc for treatment of NASH with liver fibrosis	52 weeks	Similar proportion of patients achieved hepatic histological improvement with cenicriviroc vs placebo	Treatment
62	Chalasani 2018[111]	RCT	Patients with clinical and laboratory criteria consistent with NAFLD	70	44	Evaluate the efficacy of NS-0200 (leucine–metformin–sildenafil fixed-dose combination) in reducing hepatic steatosis	16 weeks	High-dose NS-0200 significantly reduced hepatic fat by 15.7% in patients with NAFLD and elevated ALT (P<0.005)	Treatment
63	Zhou 2018[112]	Meta-analysis	Patients with T2DM	8346	N/A	Assessing the association between NAFLD and CV disease in patients with T2DM	N/A	NAFLD increases the risk of CV disease in populations with comparable T2DM profiles	Association with metabolic risk factors or other diseases
64	Strey 2018[113]	Retrospective observational study	Patients with morbid obesity undergoing bariatric surgery	219	21	Effect of T2DM and insulin therapy on NAFLD	N/A	T2DM was an independent risk factor for severe steatosis and severe fibrosis	Association with metabolic risk factors or other diseases
65	Golabi 2018[114]	Observational study	Liver transplant candidates and recipients with primary diagnosis of NASH or CC	198,467	61.1	Assess clinical presentation and outcomes for liver transplant candidates with NASH vs CC	N/A	Outcomes of patients receiving a liver transplant for CC or NASH were similar to those of patients with other chronic liver diseases	Treatment
66	Kuchay 2018[115]	RCT	Patients with documented NAFLD and uncontrolled T2DM from India	42	60	Examine the effect of empagliflozin on liver fat	12 weeks	Liver fat was significantly decreased with empagliflozin vs standard T2DM treatment (mean difference 4.0%; P<0.0001)	Treatment
67	Eriksson 2018[116]	RCT	Patients with T2DM and NAFLD	84	70	Investigate the effects of dapagliflozin and omega-3 carboxylic acids on liver fat content	12 weeks	Combination of dapagliflozin and carboxylic acids significantly reduced liver fat content vs placebo (21% decrease, P=0.046)	Treatment
68	Harrison 2018[117]	RCT	Adults with NASH and advanced fibrosis	30	56.7	Determine change in liver stiffness using iron-corrected MRI, MRE and shear-wave ultrasonic elastography in patients receiving either 4-month treatment with GR-MD-02 or placebo	17–19 weeks	No significant difference between GR-MD-02 and placebo groups by MRI, MRE, or LSM	Diagnosis and biomarkers
69	Stine 2018[118]	Meta-analysis	Studies in patients with	168,571	N/A	Characterize the pooled risk of HCC	N/A	Patients with NASH have a higher risk of HCC compared	Association with metabolic

			NASH without cirrhosis					with other aetiologies of liver disease	risk factors or other diseases
70	Hu 2018[119]	Cohort study	Middle-aged and elderly patients with and without NAFLD	984	67.5	Investigate the correlation between CAP and MetS and its components	N/A	CAP values are closely correlated with MetS and its components in middle-aged and elderly patients with NAFLD	Association with metabolic risk factors or other diseases
71	Ogawa 2018[14]	Cohort study	Patients with NAFLD from Japan	165	58	Investigate the usefulness of liver fibrosis markers, clinical scoring systems, and elastography for the staging of liver fibrosis	N/A	Serum WFA^+-M2BP and type IV collagen 7S together increased the sensitivity and negative predictive value for the diagnosis of liver fibrosis	Diagnosis and biomarkers
72	Wijarnpreecha 2018[120]	Meta-analysis	Adult patients with and without NAFLD	280,645	N/A	Investigate the association between NAFLD and diastolic cardiac dysfunction	N/A	A significant association between diastolic cardiac dysfunction and NAFLD was observed	Association with metabolic risk factors or other diseases
73	Loomba 2018[121]	RCT	Patients with biopsy-confirmed NASH	126	35	Evaluate GS-0976 (acetyl-coenzyme A carboxylase inhibitor) on liver fat and stiffness	12 weeks	Significantly greater decrease in liver fat with GS-0976 20 mg vs placebo (P=0.004)	Treatment
74	Herath 2019[122]	Cohort study	Patients with T2DM in Sri Lanka	233	47	Investigate the prevalence of NAFLD	N/A	Use of pioglitazone, higher BMI, and waist circumference were independently and significantly associated with NAFLD	Association with metabolic risk factors or other diseases
75	Lin 2019[123]	Retrospective analysis	Patients with biopsy-confirmed NASH from Taiwan	10	70	Investigate progression of NASH in patients receiving paired liver biopsies	Median 20.5 months	60% of patients had disease progression on second biopsy	Burden of disease
76	Feng 2019[5]	Cohort study	Patients with NAFLD and healthy volunteers	171	N/A	Integration of clinical and laboratory NAFLD indicators (BMI, ALT, AST and uric acid) in a non-invasive diagnostic formula for NAFLD	N/A	The proposed formula demonstrated both high sensitivity and specificity, with accuracy significantly higher than FibroScan	Diagnosis and biomarkers
77	Chen 2019[124]	Meta-analysis	Population-based studies in subjects with or without NAFLD followed up with colonoscopy	124,206	N/A	Determine association between NAFLD and risk of incident and recurrence of CRA/CRC	N/A	NAFLD was associated with increased incident of CRA/CRC	Association with metabolic risk factors or other diseases
78	Feng 2019[125]	RCT	Patients with T2DM and NAFLD from China	85	69	Comparing the effects of gliclazide, liraglutide and metformin on weight, BMI and body composition	24 weeks	Liraglutide and metformin provided greater weight loss, reductions in body fat mass, and better blood glucose control vs gliclazide	Treatment
79	Yang 2019[19]	Cohort study	Patients with NAFLD	453	59	Evaluate the diagnostic performance of clinical non-invasive fibrosis models in NAFLD, to provide an optimal	N/A	APRI, BARD, FibroMeter NAFLD and NIKEI had better diagnostic accuracy, and could be preferred for diagnosing NAFLD fibrosis	Diagnosis and biomarkers

						diagnostic method for advanced fibrosis			
80	Traussnigg 2019[126]	RCT	Patients with NAFLD, with or without diabetes	198	62	Assess the efficacy of two doses of norursodeoxycholic acid vs placebo for the treatment of NAFLD	4 weeks	Norursodeoxycholic acid at 1500 mg resulted in a significant reduction of serum ALT within 12 weeks of treatment when compared with placebo	Treatment
81	Staufer 2019[17]	RCT	Patients with NAFLD with or without NASH	186	57	Compare the diagnostic accuracy of several widely available non-invasive tests for fibrosis	N/A	Proprietary fibrosis panels and VCTE show superior diagnostic accuracy for non-invasive diagnosis of fibrosis stage in NAFLD as compared to FIB-4 and NFS	Diagnosis and biomarkers
82	Pockros 2019[127]	RCT	Patients with NASH	84	39	To evaluate how statins can regulate lipoprotein metabolism with OCA treatment in patients with NASH	N/A	OCA-induced increases in LDLc in patients with NASH were mitigated with atorvastatin	Treatment
83	Singh 2020[4]	Prospective observational	Patients who underwent LC for symptomatic gallstones	101	25	To identify the prevalence of asymptomatic NAFLD or NASH in liver biopsy and also to identify the association of hypercholesterolemia with NAFLD in patients undergoing LC	N/A	Dyslipidaemia was present in 49.5% of patients. There was no association between NAFLD and serum cholesterol, triglycerides or LDLc (*P*=0.428, 0.848, 0.371, respectively). NAFLD was confirmed in liver biopsy in 21.8% of patients	Association with metabolic risk factors or other diseases
84	Harrison 2019[128]	RCT	Patients with NASH and hepatic fat fraction of at least 10%	84	45	To assess the safety and efficacy of resmetirom in patients with NASH	2 weeks	Resmetirom-treated patients showed a relative reduction of hepatic fat compared with placebo at Week 12 (LS mean difference –22.5%, *P*<0.0001) and Week 36 (LS mean difference –28.8%, *P*<0.0001)	Treatment
85	Guillaume 2019[36]	Cohort study	Patients with NAFLD	417	59	To compare ELF and FibroMeter^{V2G} for the non-invasive diagnosis of liver fibrosis in NAFLD	N/A	The diagnostic accuracy of FibroMeter^{V2G} and ELF test is not significantly different in a population of patients with NAFLD from tertiary care centres	Diagnosis and biomarkers
86	Cossiga 2019[67]	RCT	Patients with NAFLD	49	66	To evaluate the effects of Berberis aristata, Elaeis guineensis and decaffeinated green coffee on the improvement of glycaemic profile in patients with NAFLD	6 months	Patients treated with plant extracts displayed a significant reduction of serum glucose *(P*<0.001), insulin levels (*P*<0.01), HOMA-IR (*P*<0.001), and CAP value (*P*<0.01) compared with placebo	Treatment
87	Dai 2020[68]	Meta-analysis	Adult patients with NAFLD with abnormal liver	1349	N/A	To evaluate the effectiveness and safety of acupoint embedding	N/A	There was substantial heterogeneity between the included studies and more	Treatment

			aminotransferases			alone or in combination for NAFLD with abnormal transaminase		rigorous clinical trials are required	
88	Leong 2020[37]	Prospective study	Patients with NAFLD scheduled for liver biopsy	100	46	To compare the accuracy of TE and pSWE to diagnose fibrosis stage in NAFLD and to study the intra-observer and inter-observer variability	N/A	Transient elastography was significantly better than pSWE for the diagnosis of fibrosis stage ≥F2 and ≥F3. Both TE and pSWE had excellent intra-observer and inter-observer variability	Diagnosis and biomarkers
89	Sinha 2020[129]	Prospective, cross-sectional and control-matched study	Patients with NAFLD	120	55	To investigate and compare the clinical characteristics, metabolic associations and cardiovascular risk factors among patients having NAFLD with or without obesity	N/A	The components of MetS such as systolic blood pressure, diastolic blood pressure, fasting blood sugar and serum triglyceride were comparable among patients with lean and obese NAFLD	Association with metabolic risk factors or other diseases
90	Baikpour 2020[38]	Retrospective study	Patients with biopsy-proven NAFLD who underwent duplex Doppler ultrasound assessment of the main portal vein within 1 year of liver biopsy	123	N/A	To assess the accuracy of portal vein pulsatility for non-invasive diagnosis of high-risk NAFLD compared with NFS, FIB-4, BARD score, and APRI	N/A	Venous pulsatility index had the highest optimism-corrected AUC; addition of venous pulsatility index to any of the four scoring systems significantly improved the diagnostic value of the score for high-risk NAFLD	Diagnosis and biomarkers
91	Jarvis 2020[130]	Meta-analysis	Patients with NAFLD	N/A	N/A	To synthesize evidence on metabolic risk factors and prognostic value for liver disease outcomes in populations at risk of or diagnosed with NAFLD	N/A	T2DM is associated with a greater than 2-fold increase in the risk of developing severe liver disease	Association with metabolic risk factors or other diseases
92	Ye 2020[131]	Meta-analysis	Patients with non-obese or lean NAFLD	N/A	N/A	To characterize prevalence, incidence, and long-term outcomes of non-obese or lean NAFLD at a global level	N/A	Overall, around 40% of the global NAFLD population was classified as non-obese and almost a fifth was lean. Both non-obese and lean groups had substantial long-term liver and non-liver comorbidities	Burden of disease
93	Kogiso 2020[132]	Observational retrospective	Patients with NAFLD	365	51	To evaluate the long-term outcomes of mortality and HCC within Japanese patients with NAFLD	Median 7.1 years	The rates of liver-related and non-liver-related deaths and HCC development were significantly prominent in patients with advanced fibrosis	Burden of disease
94	Al-Qarni 2020[133]	Observational Study	Patients with obesity and NAFLD who underwent bariatric surgery	26	42	Evaluate the expression of four candidate NAFLD biomarkers, assessing the applicability to classify and treat the disease	N/A	COL1A1 (P=0.03) and PNPLA3 (P=0.03) protein levels significantly increased amongst patients with fibrosis-stage NAFLD	Diagnosis and biomarkers

								compared with patients with steatosis-stage NAFLD	
95	Cevik Saldiran 2020[134]	RCT	Patients with NAFLD	31	39	Examine the effectiveness of adding WBV exercises to aerobic training in terms of metabolic features and quality of life	N/A	Insulin resistance was markedly reduced (−2.36; 95% CI: −4.96 to −0.24; *P*=0.049) with addition of WBV. WBV did not provide further benefits in metabolic properties or quality of life	Treatment

Abbreviations: ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; AUC, area under curve; BARD, body mass index, AST–to–ALT ratio, diabetes mellitus; BMI, body mass index; CAC, coronary artery calcium; CAD, coronary artery disease; CAP, controlled attenuation parameter; CC, cryptogenic cirrhosis; CCA, cholangiocarcinoma; COL1A1, collagen type 1 alpha 1; CRA, colorectal adenoma; CRC, colorectal cancer; CT, computed tomography; CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; eCCA, extrahepatic CCA; ELF, enhanced liver fibrosis; FGF, fibroblast growth factor; FIB-4, fibrosis-4 index; GLP-1, glucagon-like peptide-1; GR-MD-02, galactoarabino-rhamnogalaturonate; HCC, hepatocellular carcinoma; HOMA-IR, homeostatic model assessment of insulin resistance; HSF, heat shock factor, HSP, heat shock protein; iCCA, intrahepatic CCA; IR, insulin resistance; LC, laparoscopic cholecystectomy; LDLc, low-density lipoprotein cholesterol; LECT2, leukocyte cell-derived chemotaxin-2; LINKI, Linköping University-Karolinska Institute; LS, least squares; LSM, liver stiffness measurement; MACK-3, hoMa, Ast, CK18 composite; MetS, metabolic syndrome; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; N/A, not applicable; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NFS, NAFLD fibrosis score; NIKEI, non-invasive Koeln-Essen index; OCA, obeticholic acid; PCOS, polycystic ovary syndrome; PNPLA3, patatin-like phospholipase domain-containing 3; pSWE, point shear wave elastography; RCT, randomized controlled trial; RPR, red cell volume distribution width-to-platelet ratio; SSI, supersonic shear imaging; SWE, shear wave elastography; T2DM, type 2 diabetes mellitus; TE, transient elastography; TIMP, tissue inhibitor of metalloproteinase; VCTE, vibration-controlled transient elastography; WBV, whole-body vibration; WFA^+-M2BP, *Wisteria floribunda* agglutinin-positive Mac-2-binding protein.

[a]Reference contained within Xiao (2017) meta-analysis.
[b]Reference contained within Dong (2017) meta-analysis.
[c]Reference contained within Chen (2019) meta-analysis.

Abbreviations

AASLD, American Association for Study of Liver Diseases

ACC, acetyl-CoA carboxylase

ALT, alanine aminotransferase

APRI, AST-to-platelet ratio index

ARFI, acoustic radiation force impulse

AST, aspartate aminotransferase

AUC, area under the curve

BARD, body mass index, AST–to–ALT ratio, diabetes mellitus

BID, twice daily

BMI, body mass index

CAD, coronary artery disease

CI, confidence interval

COL1A1, collagen type 1 alpha 1

CRA, colorectal adenoma

CRC, colorectal cancer

CV, cardiovascular

DAG, diacylglycerol

DNL, *de novo* lipogenesis

ELF, enhanced liver fibrosis

FAST, FibroScan-AST

FDA, Food and Drug Administration

FGF, fibroblast growth factor

FIB-4, fibrosis-4 index

FPG, fasting plasma glucose

FXR, farnesoid X receptor

GGT, gamma glutamyl-transferase

GLP-1, glucagon-like peptide-1

HCC, hepatocellular carcinoma

HOMA-IR, homeostatic model assessment of insulin resistance

HR, hazard ratio

hsCRP, high-sensitivity C-reactive protein

HSF, heat shock factor

HSP, heat shock protein

IR, insulin resistance

LECT2, leukocyte cell-derived chemotaxin-2

LC, laparoscopic cholecystectomy

LDL, low-density lipoprotein

LDLc, low-density lipoprotein cholesterol

LINKI, Linköping University-Karolinska Institute

LS, least squares

LSM, liver stiffness measurement

MACK-3, hoMa, Ast, CK18

MAFLD, metabolic dysfunction-associated fatty liver disease

MEFIB, MRE combined with FIB-4

MetS, metabolic syndrome

MRE, magnetic resonance elastography

NAFLD, non-alcoholic fatty liver disease

NASH, non-alcoholic steatohepatitis

NFS, NAFLD fibrosis score

NIKEI, non-invasive Koeln-Essen index

OCA, obeticholic acid

OR, odds ratio

PKC, protein kinase C

PNPLA3, patatin-like phospholipase domain-containing 3

PPAR, peroxisome proliferator-activated receptor

PPV, positive predictive value

pSWE, point shear wave elastography

RR, relative risk

SGLT, sodium-glucose co-transporter

SWE, shear wave elastography

T2DM, type 2 diabetes mellitus

TAG, triacylglycerol

TIMP, tissue inhibitor of metalloproteinase

UA, uric acid

VCTE, vibration-controlled transient elastography

VLDL, very low-density lipoprotein

WFA^+-M2BP, *Wisteria floribunda* agglutinin-positive Mac-2-binding protein

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