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The relationship between nonalcoholic fatty liver disease and frailty: A systematic review and meta-analysis

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ABSTRACT

Background and aim: Frailty is frequently observed in end-stage liver disease of various etiologies, but its role in nonalcoholic fatty liver disease (NAFLD) remains incompletely understood. We aimed to conduct a systematic review and meta-analysis to assess the association and prevalence of frailty in NAFLD.
Methods: A systematic review of PubMed/MEDLINE, EMBASE, Web of Science, and Scopus was performed. The random-effects model was used to estimate the pooled prevalence of frailty. Meta-analyzed odds ratios (OR) were calculated to examine the association between frailty and NAFLD.
Results: Among the initial 430 articles identified, 18 studies were included. Three studies involving 3673 participants had a pooled OR of 2.03 (95% CI: 1.51–2.72; I^2 = 1.1%; $p < 0.0001$) for the association between frailty and NAFLD. The pooled prevalence of frailty in individuals with NAFLD was 23% (95% CI: 13%–38%; I^2 = 93.5%) using the liver frailty index (LFI) and 8% (95% CI: 3%–21%; I^2 = 98.1%) using the Fried frailty index (FFI). NAFLD patients' mean grip strength and balance time were 26.4 kg (95% CI: 23.0–29.8) and 23s (95% CI: 10–35), respectively. Among studies that also included individuals with liver cirrhosis, grip strength was lower in those with cirrhosis vs. the broader population of those with NAFLD.
Conclusions: Our study suggests that frailty is highly prevalent in individuals with NAFLD, with a significantly higher prevalence compared to those without NAFLD. Individuals with NAFLD have more than two-fold increased odds of frailty. Assessing frailty in NAFLD patients enables targeted management to improve outcomes.

1. Introduction

Frailty is a state of vulnerability associated with decreased resilience and poor response to stressors and acute illness [1]. This clinical syndrome is common among elderly individuals and increases the risk of poor health outcomes, such as falls, delirium, disabilities, hospitalizations, and mortality [2,3]. There are various indexes and criteria for assessing frailty. The two most highly documented criteria are the Fried frailty index (FFI) and the Clinical Frailty Scale. The FFI defines frailty by the presence of at least three of the following criteria: unintentional weight loss, self-reported exhaustion, muscle weakness (poor handgrip strength), slow walking speed, and low physical activity [4]. The Clinical Frailty Scale is the proportion of a person's deficits out of the total number of age-related health factors [5]. A recent meta-analysis estimated that the general population's overall prevalence of frailty, defined by FFI and frailty index, amounted to 12%; however, there was a high degree of heterogeneity among the included studies [6]. With an aging population, there is a growing concern for frailty [7,8]. Indeed,

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various studies have demonstrated an apparent correlation between frailty, increased healthcare expenditures, and heightened utilization of medical services [8]. Moreover, multiple studies have confirmed the association of frailty with mortality in diverse settings and subpopulations [9–12].

Previous work has shown that frailty is strongly linked to chronic diseases such as hypertension, congestive heart failure, diabetes mellitus, stroke, chronic obstructive pulmonary disease, rheumatological diseases, and cancer [13–17]. Some studies have suggested that frailty is also associated with chronic liver disease, irrespective of its etiology [18, 19]. The prevalence of frailty varies significantly among individuals with advanced liver disease [20–22], implying that there may exist important heterogeneity across liver disease stages and subtypes. For example, individuals with advanced liver disease frequently exhibit reduced muscle mass, which plays a significant role in exacerbating adverse outcomes and mortality rates [23]. Given the increasing prevalence of nonalcoholic fatty liver disease (NAFLD), it is indeed a concerning and growing public health burden [24–26]. NAFLD affects a significant number of elderly people and is predicted to create a greater burden in the future as the elderly population increases. However, the prevalence of frailty in patients with NAFLD is currently insufficiently characterized, and the potential role of frailty in the association of NAFLD with adverse health outcomes remains incompletely understood.

Considering the high prevalence and burden of NAFLD and its association with frailty as an increasingly important health concern, we performed a systematic review and meta-analysis of studies to elucidate the association between frailty and NAFLD along with its prevalence.

2. Methods

The systematic review and meta-analysis were performed in accordance with the PRISMA guidelines. The study protocol was formally recorded in the *International Prospective Register of Systematic Reviews* (PROSPERO) with the identification number CRD42024499585.

2.1. Literature search

In order to identify relevant publications, systematic searches were conducted on *PubMed/MEDLINE*, *Web of Science* (ISI), *Scopus*, *Embase,* and reference lists of relevant articles on September 18, 2023, for articles in English. No restrictions were imposed on the year of publication. Databases were queried using a combination of *Medical Subject Headings* (MeSH) terms and free-text keywords related to "frailty" and "NAFLD," along with their corresponding expansions. The search query is specified in Supplementary File 1.

2.2. Selection criteria

Studies were included if they [1] were original studies [2]; included humans as study subjects [3]; included individuals with NAFLD; and [4] provided data on frailty indices. Review articles, editorials, case reports, case series, comments, studies with mixed etiology for liver disease (with no subgroup data based on etiology), and non-English publications without English abstracts were excluded.

After removing duplicates, two independent reviewers (PF and SK) assessed the remaining studies based on the predetermined inclusion and exclusion criteria and compiled a list of eligible studies for full-text review. Any conflicts that arose during the review process were effectively resolved through consensus.

2.3. Data extraction

The data from the studies included in the review were collected autonomously by two investigators (PF and MM) utilizing an electronic spreadsheet. The pertinent data extracted from each study, when available, encompassed the authors' names, publication year, study design, country of origin, sample size, age, study population, criteria for diagnosing NAFLD, the severity of chronic liver disease (assessed by the *Model for End-stage Liver Disease-Sodium* [MELD-Na] and *Child-Pugh Score*), duration of follow-up, frailty definition, number of individuals classified as frail, number of females in the sample size, and levels of frailty indices. In addition to these findings, reported summary statistics in the form of coefficient, risk ratio (RR), or odds ratio (OR) were extracted. Furthermore, alongside these results, the associated 95% confidence intervals (CIs), standard deviations (SDs), interquartile range (IQR), and p-values were also acquired, if available. Disagreements were effectively resolved through consensus.

2.4. Quality assessment

The studies included in the analysis were evaluated using the study quality assessment tools developed by the *National Heart, Lung, and Blood Institute* (NHLBI) [27]. Two investigators (PF and MM) independently evaluated the quality of each study based on the criteria determined in the NHLBI assessment tool. Discrepancies regarding quality evaluation were resolved through consensus or—if needed—consultation with a third reviewer (SK). Reviewers employed the NHLBI study rating tools to assess the quality of each study, categorizing them as "good", "fair", or "poor" based on the range of items covered by each tool.

2.5. Statistical analysis

The statistical analyses and visualizations were performed using R version 4.2.2 (R Core Team [2021], Vienna, Austria) using the "meta" package [28]. Random-effects models with inverse-variance weighting were used to determine the pooled prevalence of frailty among individuals with NAFLD, the meta-analyzed association of NAFLD with frailty (represented as a meta-analyzed OR), and mean estimates for frailty markers, including grip strength and balance time.

We used the random-effects model for all analyses due to the expected heterogeneity across the studies and their slightly different frailty measurement techniques. Certain studies included patients with NAFLD-related cirrhosis, while other studies included all NAFLD patients, with cirrhosis or not. For these groups, meta-analyses were conducted both separately and collectively. In order to explore the heterogeneity among the reported prevalence, a subgroup analysis was conducted based on the different indices used to define frailty, namely FFI, liver frailty index (LFI), hospital frailty risk score (HFRS), and deficit index. Studies on grip strength and balance time were further categorized into subgroups based on whether they included only patients with cirrhosis or not.

If the included studies only reported median and range or interquartile range, mean and SD were estimated using methods developed by Luo, Wan, and Shi [29–32]. In studies that only reported median values as summary statistics, mean values were estimated to be equal to the median. The I^2 and tau^2 statistics were employed to evaluate heterogeneity in all meta-analyses. A result was considered statistically significant if its p-value was less than 0.05 and its I^2 value was greater than 50%.

3. Results

3.1. Basic characteristics

Following the execution of database searches, a total of 430 titles were identified. After eliminating duplicate entries, 190 publications were assessed. After evaluating the titles and abstracts, 116 studies were excluded, leaving 74 papers considered appropriate for full-text screening. In the end, 18 studies met the criteria for inclusion. Supplementary File 2 comprises the list of the excluded studies. The process of selecting and excluding studies is outlined in the PRISMA flowchart, depicted in Fig. 1.

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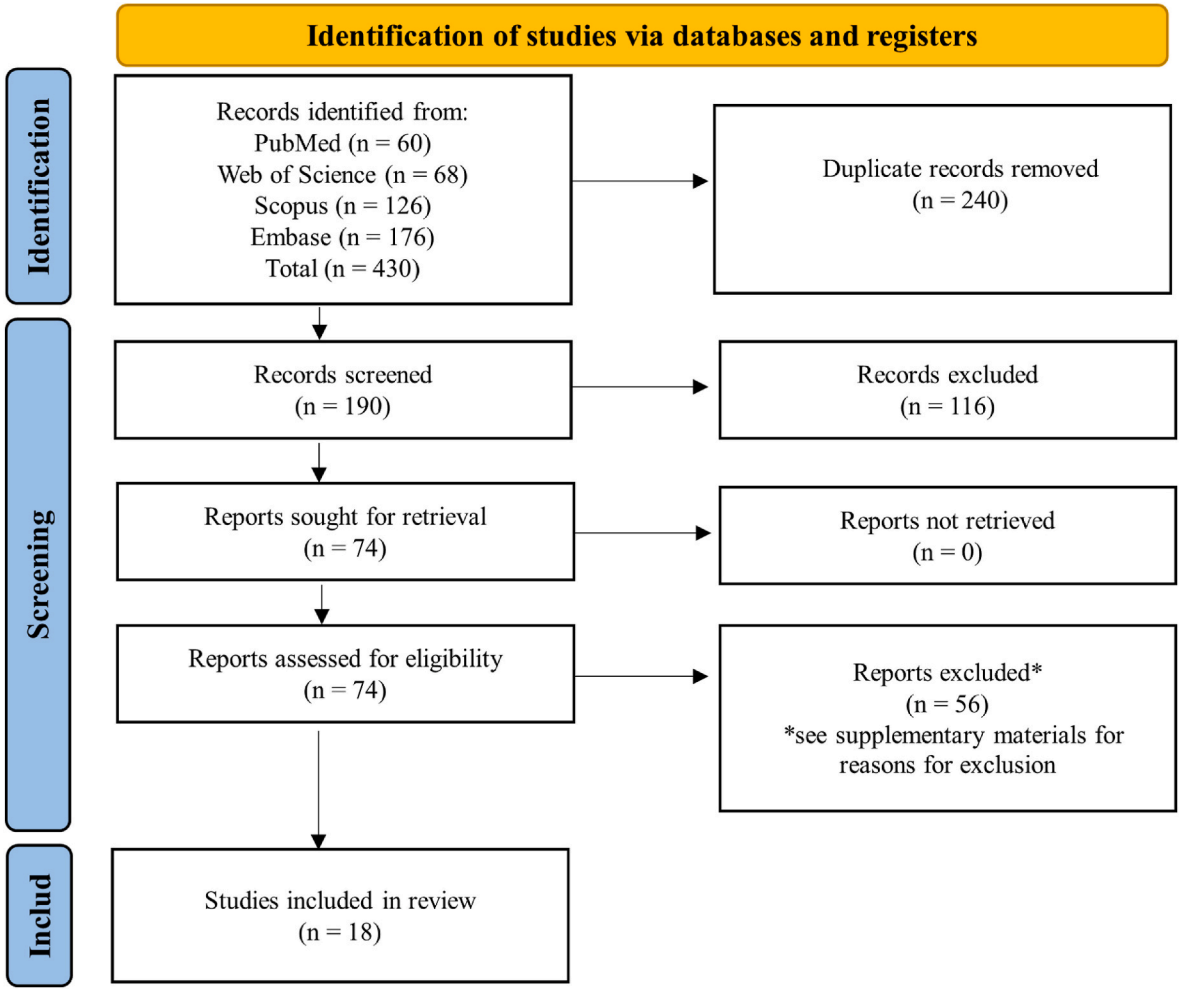

Fig. 1. The PRISMA flowchart.

Table 1 provides a concise overview of the basic characteristics of the included studies. The included papers were published from 2018 to 2023, encompassing a total of 22,339 NAFLD cases from various countries, including the USA, Australia, Belgium, the UK, Ireland, India, Slovakia, Italy, and Chile. Ten studies employed a cohort study design, either prospective or retrospective, while seven studies utilized a cross-sectional design. One study did not disclose the study design [33]. The studies that provided information on the duration of the follow-up reported a range of 6 months–8 years. Diagnostic methods for NAFLD varied across studies, including the fatty liver index, computed tomography (CT) scan, ultrasonography (US), and vibration-controlled transient elastography (VCTE) for assessment of liver stiffness measurement (LSM) and controlled attenuation parameter (CAP). A summary of the findings of the included studies is presented in Table 2.

3.2. Quality assessment

The quality of the included studies was assessed by independent investigators using the NHLBI risk of bias assessment tool (Table 3). According to the investigators' assessment, eight studies were deemed to have "good" quality, while the remaining four were considered to have "fair" quality. Quality assessment was not conducted for conference abstracts.

When evaluating funnel plot asymmetry for the overall frailty prevalence, the rank correlation test (Begg's test) produced a result of z = 1.17 with a p-value of 0.2418, alongside a bias estimate of 26.0000 (standard error [SE] = 22.2111). In the meantime, the linear regression test (Egger's test) revealed a significant heterogeneity with t = −3.06, and a p-value of 0.0084, along with a bias estimate of −9.1717 (SE = 2.9941). The linear regression test also showed multiplicative residual variance (tau^2 = 102.1694). The corresponding funnel plot is provided in Supplementary **Materials**.

3.3. Association of NAFLD with frailty

Eight studies reported a correlation between NAFLD and frailty. Four of these studies utilized LFI to determine the correlation between NAFLD and frailty, while the other four employed FFI. Berry et al. and Wong et al. both reported coefficients to assess the associations between NAFLD and frailty, using the alcohol population as a reference [34,35]. Berry et al. reported a multivariate coefficient of −0.002 (95% CI: −0.11-0.11; p = 0.97), while Wong et al. reported a coefficient of 3.39 (95% CI: 0.78–6.00; p = 0.01). Singh et al. reported a univariate OR of 0.9 (95% CI: 0.3–3.1; p = 0.92) for nonalcoholic steatohepatitis (NASH) to be a predictive factor for frailty [36]. Singh et al. employed an LFI>4.5 to diagnose frailty, which is marginally greater than the LFI ≥4.4 utilized in other studies. Xu et al. also utilized the LFI index and showed a correlation between NAFLD and frailty (LFI ≥4.4), with a multivariable OR of 1.41 (95% CI: 1.00–1.98; p = 0.05) [37]. Of the studies mentioned, the results of Wong et al. were statistically significant, while those of the other studies were not significant. Performing a meta-analysis on these studies was not feasible due to the use of alcoholic reference by Berry et al. and Wong et al., as well as the utilization of an LFI>4.5 by Singh et al. for defining frailty.

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Table 1
Study characteristics of the included studies.

ID	Author, year	Country	Study type	Sample size (F)	Age	Population	NAFLD diagnosis	Chronic liver disease severity	Follow-up
1	Berry, 2022 [31]	USA	Cohort	347		NAFLD cirrhosis			13.1 months
2	Bhanji, 2019 [21]	USA	Cross-sectional	136 [66]	Mean ± SD: 60.2 ± 7.8	NASH cirrhosis		MELD-Na: mean (SD): 15 (6.8)	_
3	Clayton-Chubb, 2023 [35]	Australia	Cross-sectional	2998 (1450)	Mean ± SD: 74.66 ± 3.91	Elderly population with MASLD	FLI ≥60		_
4	Debory, 2020 [37]	USA	Conference abstract (cross-sectional)	200 (0)	median: 55	Cardiovascular disease with NAFLD/HIV⁻	CT scan		_
5	Goffaux, 2023 [57]	Belgium	Conference abstract (cross-sectional)	92 [48]	mean (range): 55 (19–78)	MAFLD			_
6	Koutli, 2020 [58]	UK	Conference abstract (cross-sectional)	92	Mean ± SD: 60 ± 7	NAFLD cirrhosis			_
7	Lai, 2019 [59]	USA	Cohort	177		NASH cirrhosis			381 days
8	Lin, 2021 [60]	USA	Cohort	170		NAFLD cirrhosis			266 days
9	Mohamad, 2019 [30]	USA	Conference abstract	146		NAFL cirrhosis			
10	Naimimohass, 2022 [22]	Ireland	Cross-sectional	109 [55]	Mean ± SD: 56 ± 12	NAFLD	LSM and CAP assessment using VCTE		_
11	Nawaz, 2022 [61]	Ireland	Conference abstract (retrospective cohort)	13830 (8595)	Mean ± SD: NASH without frailty: 62.16 ± 12.10; NASH with frailty: 64.61 ± 11.10	NASH			
12	Peng, 2018 [36]	USA	Conference abstract (cross-sectional)	2412		Elderly population with NAFLD	US		_
13	Singh, 2022 [33]	India	Prospective cohort	12		NASH cirrhosis			6 months
14	Skladany, 2021 [18]	Slovakia	Prospective cohort	105 [49]	median (25–75 percentiles): 62.26 (55.71, 67.13)	NAFLD cirrhosis		MELD-Na: median (25–75 percentiles): 15 [11,19] Child score: median (25–75 percentiles): 8 [7,10]	>6 months
15	Solfrizzi, 2020 [38]	Italy	Prospective cohort	1061 (473)	Mean ± SD 72.39 ± 5.34	Elderly population NFS F0-4			8 years
16	Soto, 2021 [39]	Chile	Prospective cohort	45		MAFLD cirrhosis		MELD ≥12	29.4 months
17	Wong, 2021 [32]	USA	Cohort	60		NASH cirrhosis			
18	Xu, 2021 [34]	USA	Cohort	347		NAFLD cirrhosis		MELD-Na: median (IQR) 21 [17–24]/Child score: median (IQR): 8 [7–10]	13 months

In studies that utilized FFI as an index and examined the relationship between NAFLD and frailty, Clayton-Chubb et al. found that metabolic dysfunction-associated steatotic liver disease (MASLD) is predictive for frailty (using mFFI) and reported a RR of 2.36 (95% CI: 2.16–2.56) in both sexes, a RR of 1.62 (95% CI: 1.47–1.79) in males and 3.17 (95% CI: 2.77–3.62) in females for frailty in individuals with MASLD compared to MASLD [38]. Peng et al., Debory et al., and Solfrizzi et al. all employed a threshold of FFI ≥3 as the diagnostic criteria for frailty and evaluated the association between NAFLD and frailty, which was quantified using ORs [39–41]. The meta-analysis of these studies, which included 3673 cases of NAFLD, yielded a pooled OR of 2.03 (95% CI: 1.51–2.73; I^2 = 1.1%; $p < 0.0001$), indicating a significant association between NAFLD and frailty (Fig. 2).

3.4. Overall frailty prevalence

Various indices were used for diagnosing frailty in the included studies, such as LFI, FFI, deficit index, modified Fried frailty index (mFFI), deficit accumulation frailty (DAF), 6-min walk test (6MWT), gait speed test (GST), self-reported frailty index (SRFI) and HFRS. Among the included studies, 6 employed the FFI criteria to diagnose frailty, while 9 used LFI criteria; one study utilized the deficit index, another used HFRS, and one study did not specify the index employed. The prevalence of frailty ranged from 2.2% to 53.3% across the studies that were included. The highest prevalence reported was by Soto et al., who reported a prevalence of frailty of 53.3% among a population of 45 cases with cirrhosis (caused by NAFLD) [42]. Clayton-Chubb et al. reported the lowest prevalence of frailty, 2.2%, among 2998 elderly individuals with NAFLD using mFFI as a frailty assessment tool [43].

The collective prevalence of frailty, regardless of the specific criteria used for diagnosing frailty, in 21,932 cases of NAFLD, including both cirrhotic and non-cirrhotic, was found to be 16% (95% CI: 9%–27%; I^2 = 99.4%) based on data from 16 studies that reported prevalence (Fig. 3). The subgroup of studies that used LFI criteria to report frailty prevalence consisted of seven studies with 1049 cases of NAFLD. The combined prevalence in this subgroup was 23% (95% CI: 13%–38%; I^2 = 93.5%). The subgroup of studies that employed FFI criteria to establish the prevalence of frailty comprised six studies encompassing 6825

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Table 2
Frailty and performance tests.

ID	Frailty definition	Frail number (%)	Mean/median frailty of participants	Grip strength (kg)	Balance (s)	Other performance tests	Associations
1	LFI ≥4.4						NAFLD with physical frailty: Coefficient (ALD as ref, 95% CI) for univariate models: 0.12 (0.01–0.24) p = 0.04; Coefficient for multivariable model (95% CI): −0.002 (−0.11 to 0.11) p = 0.97
2	deficit index ≥0.25	51 (37.5%)					Patients with NASH had a significantly higher prevalence of frailty compared to patients with ALD (49% vs. 34%; p = 0.0 3)
3	mFFI≥3.5 DAF >0.21	mFFI: 67 (2.2%); DAF:372 (12.4%)		mean (SD):27.55 (9.69); low hand grip strength number: 424 (14.6%)		gait speed (m/s): mean (SD): 1.01 (0.21)	Frailty in MASLD vs. no-MASLD (FLI <30): RR (95% CI) in all: 2.355 (2.164–2.562); RR (95% CI) in males: 1.620 (1.465–1.791); RR (95% CI) in females: 3.166 (2.766–3.623)
4	FFI ≥3	42 (21.0%)					HIV^{-}/NAFLD had 2.6 times [95% CI: 1.2–5.7] higher probability of FRP.
5	LFI> 4.5	4 (4.3%)	LFI: mean (range): 2.98 (1.13–4.71)	mean (range): 31 [8–62]	mean (range): 9.9 (2.1–10)	time for 5 chair stands: mean (range): 8.2 (4.25–24.25)	Frailty was associated with the FIB-4 index (with a mean LFI of 3.72 in case of FIB-4 >2.67 vs 2.8 in case of FIB-4 <1.3 (p = 0.042)).
6	NA	6 (6.7%)					
7	LFI ≥4.5	61 (34.4%)					
8	LFI >4.5 6MWT <250 m GST<0.8 m/s	LFI: 46 (27.1%); 6MWT: 50 (29.4%); GST: 60 (35.3%)					
9	LFI ≥4.5	42 (28.8%)					Frailty did not significantly interact with cirrhosis etiology.
10	FFI ≥3 SRFI ≥0.25	FFI: 4 (3.7%); SRFI: 41 (37.6%)	FFI: median (IQR): 1 [1]; SRFI: median (IQR): 0.18 (0.18); lab-based frailty index: median (IQR): 0.18 (0.12)			TUG (s): median: 7.0 (IQR:1.8); 30STST: median (IQR): 14 [7]	Between F0/F1 and F4 patients a significant increase in SRFI scores (adjusted p = 0.001), a significant decrease in 30STST scores (adjusted p = 0.004), and a significant increase in FI-LAB scores (adjusted p < 0.001) was detected. There were no statistical differences observed between the LSM groupings for either the FFI scores (p = 0.285) or the TUG scores (p = 0.110).
11	HFRS ≥5	6790 (49.1%)	HFRS: mean (SD): 8.51 (2.98)				NASH + frailty and all-cause inpatient mortality: OR: 4.66, 95% CI (2.70–8.05); required intensive care: OR: 4.24, 95%CI (2.86–6.28); longer length of stay [9.5 days versus 4.4 days (p < 0.001)]
12	FFI ≥3	76 (3.2%)					unadjusted OR (95% CI) for frailty for mild, moderate, and severe hepatic steatosis to those with normal hepatic steatosis were 1.49 (0.76–2.91), 1.95 (1.12–3.39) and 1.32 (0.60–2.88); only moderate hepatic steatosis showed a significant association with frailty in the multivariable adjusted model
13	LFI>4.5	5 (41.7%)					NASH as a predictive factor of frailty: univariate OR (95% CI): 0.9 (0.3–3.1) p = 0.92
14	LFI >80th percentile and LFI >4.5	LFI >80th percentile: 14 (13.3%); LFI >4.5: 50 (47.6%)	LFI: median (25–75 percentiles): 4.28 (3.81, 4.87)	median (25–75 percentiles): 23.13 (15.83, 29.86); low hand grip strength number: 67 (63.8%)	median (25–75 percentiles): 30 (24.58, 30)	chair stands (s): median (25–75 percentiles: 0.39 (0.30, 0.48)	
15	FFI ≥3	65 (6.1%)					F3-F4 NFS with physical frailty: independently by age (OR: 1.96, 95% CI: 1.07–3.58); by sex (OR: 2.99, 95% CI: 1.66–5.38); Spearman's ρ coefficients for physical frailty between-groups

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Table 2 (*continued*)

ID	Frailty definition	Frail number (%)	Mean/median frailty of participants	Grip strength (kg)	Balance (s)	Other performance tests	Associations
							comparison, NFS F3-F4 versus NFS F0-F2: 0.11, p < 0.01
16	FFI≥3	24 (53.3%)					
17	LFI≥ 4.5						coefficients for NASH with LFI: multivariable: 3.39 (95% CI: 0.78–6.00) p = 0.01; univariable: 2.48 (95% CI: −0.40–5.37) p = 0.09
18	LFI ≥4.4	32 (9.2%)	LFI median (IQR): 4.1 (3.7–4.6)	median (IQR): 24 [18–31]	median (IQR): 30 [29,30]	chair stands per s: median (IQR): 0.3 (0.2–0.4); able to complete all balance tests: 98%	NAFLD with frailty: multivariable OR (95% CI): 1.41 (1.00–1.98) p = 0.05; univariable OR (95% CI): 1.64 (1.18–2.29) p = 0.003 Frailty and waitlist mortality for NAFLD: univariable sub-HR, (95% CI) 1.08 (0.79–1.49) p = 0.62; multivariable sub-HR, (95%CI) 0.96 (0.69–1.32) p = 0.79

Table 3
NHLBI quality assessment.

Author, year	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	Quality rating (good, (fair, poor)
Berry, 2022	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	Fair
Bhanji, 2019	Y	Y	Y	Y	NA	N	Y	Y	Y	N	Y	N	Y	Y	Fair
Clayton-Chubb, 2023	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Good
Lai, 2019	Y	Y	Y	Y	NA	Y	Y	Y	Y	N	Y	Y	Y	Y	Good
Lin, 2021	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good
Naimimohass, 2022	Y	Y	Y	Y	NA	Y	NA	Y	Y	N	Y	Y	Y	Y	Fair
Singh, 2022	Y	Y	Y	Y	NA	Y	Y	Y	Y	N	Y	Y	Y	Y	Good
Skladany, 2021	Y	Y	Y	Y	NA	Y	Y	Y	Y	N	Y	Y	Y	Y	Good
Solfrizzi, 2020	Y	Y	Y	Y	NA	Y	Y	Y	Y	N	Y	Y	Y	Y	Good
Soto, 2021	Y	Y	Y	Y	NA	Y	Y	Y	Y	N	Y	Y	Y	Y	Good
Wong, 2021	Y	Y	Y	Y	NA	Y	NA	Y	Y	N	Y	Y	Y	Y	Fair
Xu, 2021	Y	Y	Y	Y	NA	Y	Y	Y	Y	N	Y	Y	Y	Y	Good

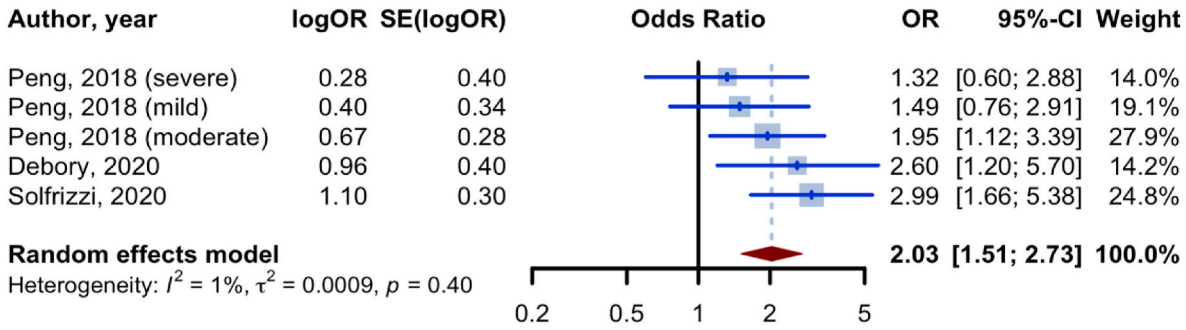

Fig. 2. NAFLD and frailty association.

cases of NAFLD. The overall prevalence rate in this specific subgroup was 8% (95% CI: 3%–21%; I^2 = 98.1%). One study utilized the deficit index to analyze 136 cases of NAFLD, while another study employed the HFRS index to examine 13,830 cases of NAFLD. Prevalence estimates for these studies were 38% (95% CI: 30%–46%) and 49% (95% CI: 48%–50%), respectively. The prevalence of frailty in an individual study, which did not specify the specific frailty index used, was 6.5% (95% CI: 3%–14%). Based on the frailty index, the test for subgroup differences was statistically significant (p ≤ 0.0001).

To further analyze the variability seen in frailty prevalence across the studies, we performed a mixed-effects meta-regression analysis (multivariate analysis), including factors of gender (female percentage), age, and body mass index (BMI). The results for testing moderators, as presented in Table 4, had a p-value of 0.0037. This shows that the moderators considered in the model (female percentage, age, and BMI) play a significant role in accounting for the variability in frailty prevalence. The notable negative estimate for the female percentage variable indicates that gender plays a crucial role, with females exhibiting a lower prevalence of frailty in comparison to males. Age is also an important factor, as a notable negative estimate suggests that frailty diminishes with increasing age in NAFLD populations. The relationship between BMI and the prevalence of frailty is positive, although it is not statistically significant. Fig. 4 also displays the bubble plots for these covariates when examined individually.

3.5. Frailty prevalence in the cirrhotic population of NAFLD patients

Nine studies reported the prevalence of frailty among NAFLD patients with cirrhosis. The studies encompassed a collective of 1230 patients diagnosed with cirrhosis with NAFLD etiology. The combined prevalence of frailty in these nine studies was 28% (95% CI: 18%–41%; I^2 = 92.8%) (Fig. 5). Out of these nine studies, six studies utilized LFI to

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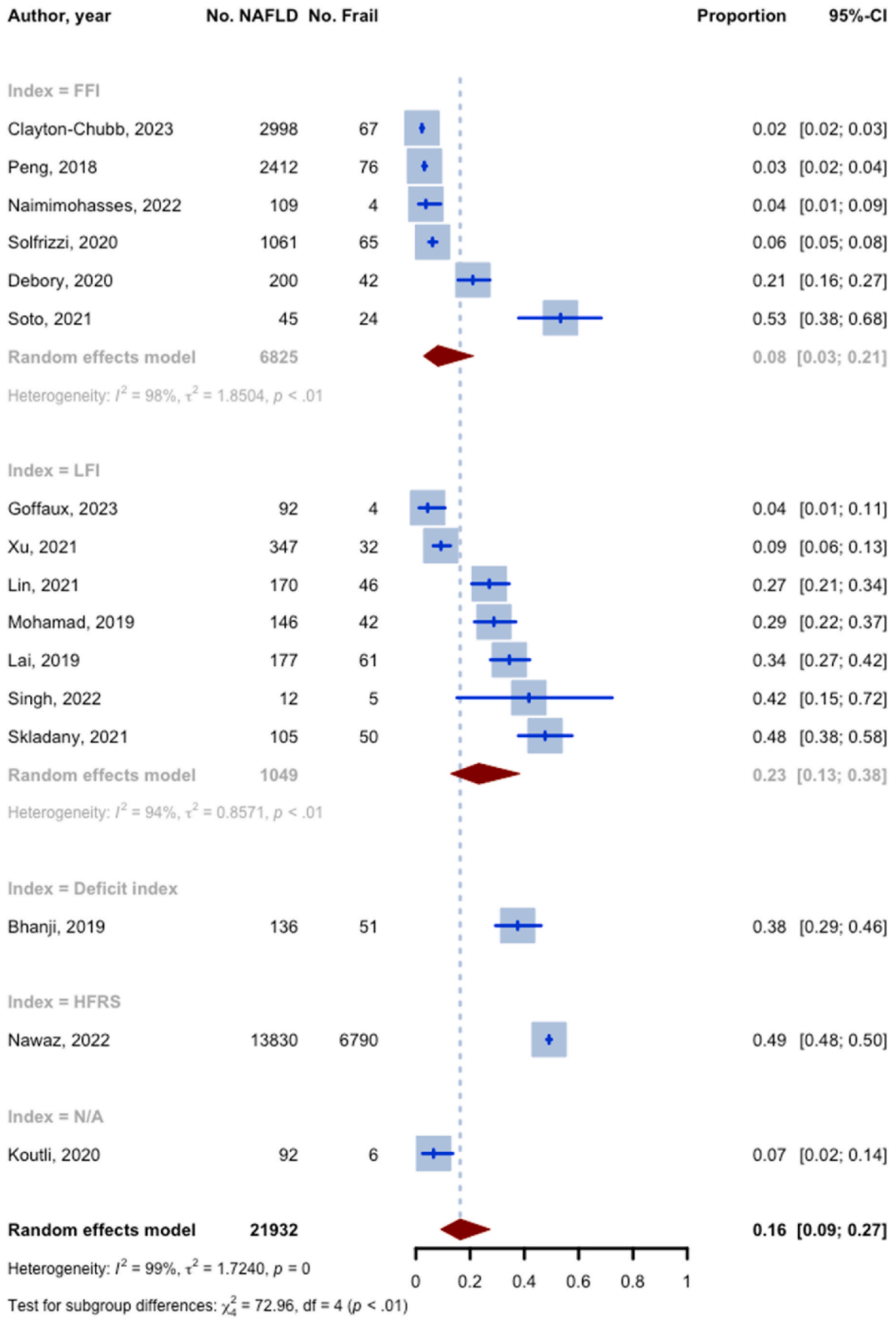

Fig. 3. Overall frailty prevalence.

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Table 4
Multiple meta-regression analyses of covariates for frailty prevalence in the NAFLD population.

Multivariate analysis					
Variable	Estimate	SE	P-value	CI.lower bound	CI.upper bound
Intercept	46.4476	14.6578	0.0015	17.7188	75.1763
Female	−99.2679	35.1846	0.0048	−168.2285	−30.3073
Age	−0.1952	0.0598	0.0011	−0.3123	−0.0781
BMI	0.3739	0.2154	0.0825	−0.0482	0.7961

identify frailty. The combined prevalence of frailty in these studies, which included 957 cases of NAFLD with liver cirrhosis, was 28% (95% CI: 18%–42%; I^2 = 93.4%). Only one study provided information on the prevalence of frailty based on the FFI criteria. This study included 45 cases and reported a prevalence of 53% (95% CI: 39%–67%). One study using the deficit index for frailty encompassed 136 cases and documented a prevalence of 37.5% (95% CI: 30%–46%). Another study did not explicitly state the particular frailty index employed and reported a prevalence of 6.5% (95% CI: 3%–14%). The statistical analysis revealed a significant difference between the subgroups (LFI subgroup vs. FFI subgroup vs. deficit index subgroup vs. N/A subgroup), as indicated by a p-value of <0.0001.

The univariate meta-regression using a mixed-effects model indicated that age did not significantly impact frailty in patients with cirrhosis, yielding an estimate of −0.0031 (95% CI: −0.1727 - 0.1666; p = 0.9719). The estimated residual heterogeneity I^2 value was 94.09%, suggesting a considerable degree of variability that the model did not account for. The test for residual heterogeneity yielded a p-value of < 0.0001, indicating that heterogeneity is statistically significant.

The univariate meta-regression results for BMI indicated an estimate of −0.0139 (95% CI: −0.4318 - 0.4040; p = 0.9481), implying an insignificant association between BMI and frailty in patients with cirrhosis. The residual I^2 value of 96.15% suggests a notable degree of heterogeneity. The p-value of less than 0.0001 from the test for residual heterogeneity showed significant residual variability.

3.6. Frailty prevalence in the MAFLD/NASH population (cirrhotic and non-cirrhotic)

Seven studies reported the prevalence of frailty in patients with metabolic dysfunction-associated fatty liver disease (MAFLD) or NASH, regardless of having cirrhosis. The studies included a total of 20,702 patients. The overall prevalence of frailty in these studies was 7.4% (95% CI: 3.0%–17.4%; I^2 = 99.7%) (Fig. 6). Among the mentioned studies, five studies employed FFI as the diagnostic criteria for identifying frailty. The aggregate prevalence of frailty in these studies, encompassing 6780 patients, was 5.2% (95% CI: 2.4%–10.6%; I^2 = 97.3%). One study provided data on the prevalence of frailty using the LFI criteria. This study encompassed a total of 92 cases, with a combined prevalence of 4.4% (95% CI: 1.6%–11.0%). The prevalence of frailty using the HFRS criteria in one study encompassing a total of 13,830 cases was 49% (95% CI: 48%–50%). The statistical analysis of the subgroup difference (LFI subgroup vs. FFI subgroup vs. HFRS subgroup) did yield a significant result, as indicated by a p-value of <0.0001.

The univariate meta-regression employing a mixed-effects model revealed that age had an insignificant effect on frailty, with an estimate of −0.0709 (95% CI: −0.2104-0.0687; p = 0.3196). The estimated residual heterogeneity I^2 value was 99.03%, indicating a significant level of variability that the model failed to address. The test for residual heterogeneity produced a p-value of < 0.0001, suggesting that heterogeneity is statistically significant.

The univariate meta-regression results for BMI showed an estimate of −0.2022 (95% CI: −0.2702 to −0.1342; p < 0.0001), suggesting a significant association between BMI and frailty. The residual I^2 value of 0.00% indicates an insignificant level of heterogeneity. The p-value of 0.2743 from the test for residual heterogeneity indicated minimal residual variability.

The proportion of females was also an insignificant factor in frailty among NAFLD patients. The model results showed that the proportion of females had an estimate of −0.8658 (95% CI: −6.1603 to 4.4287, p = 0.7486), indicating a statistically insignificant effect of gender on frailty and underscoring the lack of significant differences in frailty outcomes between male and female patients. The mixed-effects model yielded a

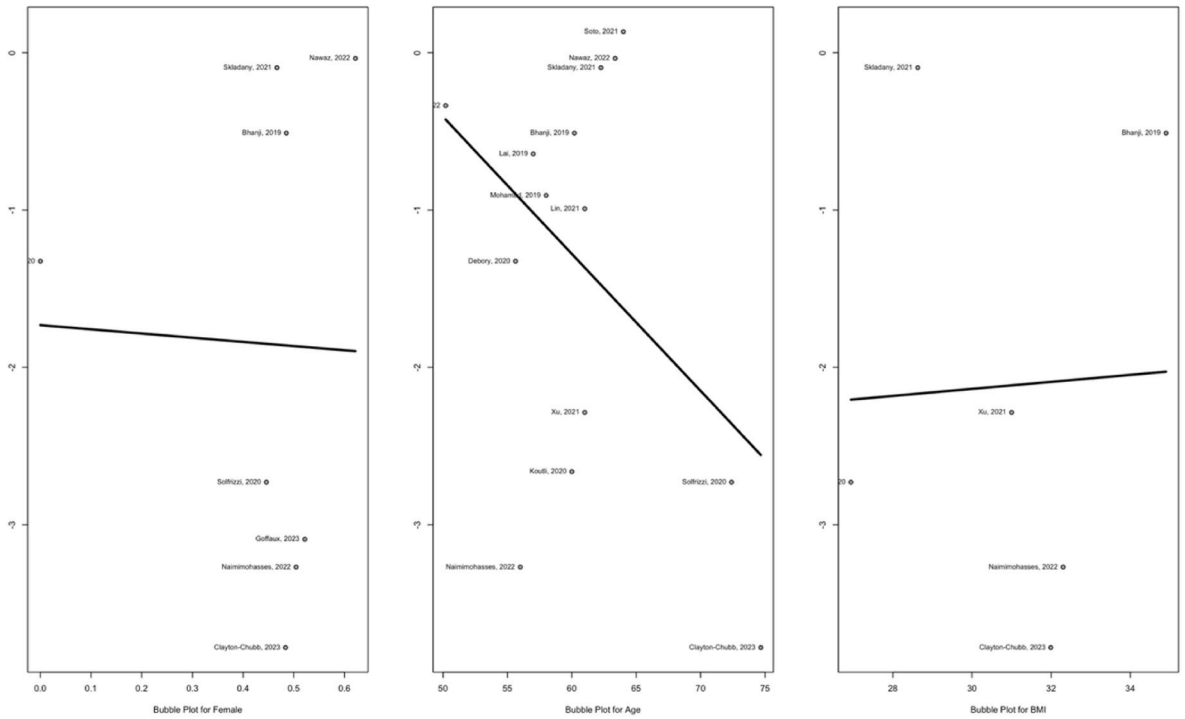

Fig. 4. Bubble plots for meta-regression analyses of covariates for frailty prevalence in the NAFLD population.

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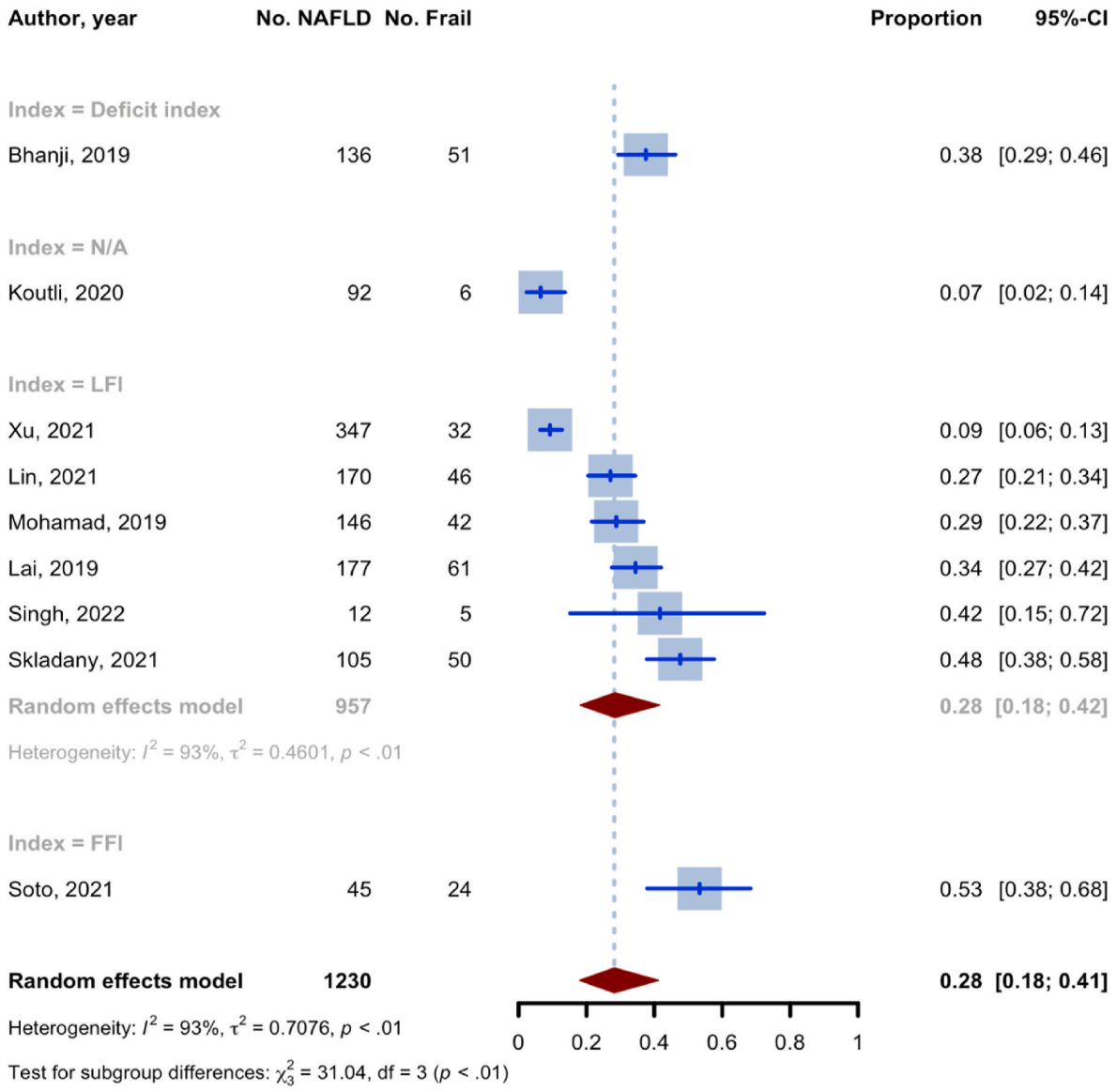

Fig. 5. Frailty prevalence in the cirrhotic population of NAFLD patients.

residual I^2 value of 98.77%, indicating considerable heterogeneity that the model failed to address. The test for residual heterogeneity revealed a p-value of less than 0.0001, suggesting significant unexplained variability, with gender serving as a moderator.

3.7. Frailty measures

Four studies reported handgrip strength as an indicator of maximum voluntary muscle strength, while three studies reported balance time as a measure of frailty robustness in individuals with NAFLD. The combined mean grip strength of 3542 cases of NAFLD was 26.4 kg (95% CI: 23.0–29.8; I^2 = 95.2%) (Fig. 7). The combined grip strength for the subgroup of studies, which included a population of 452 cases of liver cirrhosis caused by NAFLD, was 24 (95% CI: 23–25; I^2 = 34.2%). The subgroup of studies encompassing all patients with NAFLD, irrespective of the presence of liver cirrhosis, involved a total population of 3090 cases of NAFLD. The combined grip strength for this subgroup was 29 (95% CI: 26–32; I^2 = 88.8%). Test for subgroup differences was statistically significant (p = 0.0048), showing a significantly lower grip strength in patients with liver cirrhosis caused by NAFLD.

The univariate meta-regression using a mixed-effects model indicated that age had a significant impact on frailty, with an estimate of 0.2761 (95% CI: 0.0842–0.4681; p = 0.0048), underscoring the role of age as a predictor. The estimated residual heterogeneity I^2 value was 56.48%, suggesting a moderate level of variability that the model did not account for. The test for residual heterogeneity (QE) yielded a p-value of 0.1295, indicating that heterogeneity is not statistically significant, suggesting that the residual heterogeneity is probably within the anticipated range.

The univariate meta-regression results for BMI indicated an estimate of 1.2962 (95% CI: 0.0171–2.5752; p = 0.0470), implying that a higher BMI is significantly linked to increased frailty. The residual I^2 value of 88.83% suggests a significant level of heterogeneity that the model did not account for. The p-value of 0.0028 from the test for residual heterogeneity (QE) also showed considerable residual variability.

The female percentage variable is also an important factor in frailty among NAFLD patients. The model results indicated that the female coefficient had a notable estimate of 135.6731 (95% CI: 41.9731–229.3732; p = 0.0045), highlighting a statistically significant effect of gender on frailty and emphasizing the significant disparity in frailty outcomes between male and female patients. Yet, the mixed-effects model produced a residual I^2 value of 85.43%, which suggests

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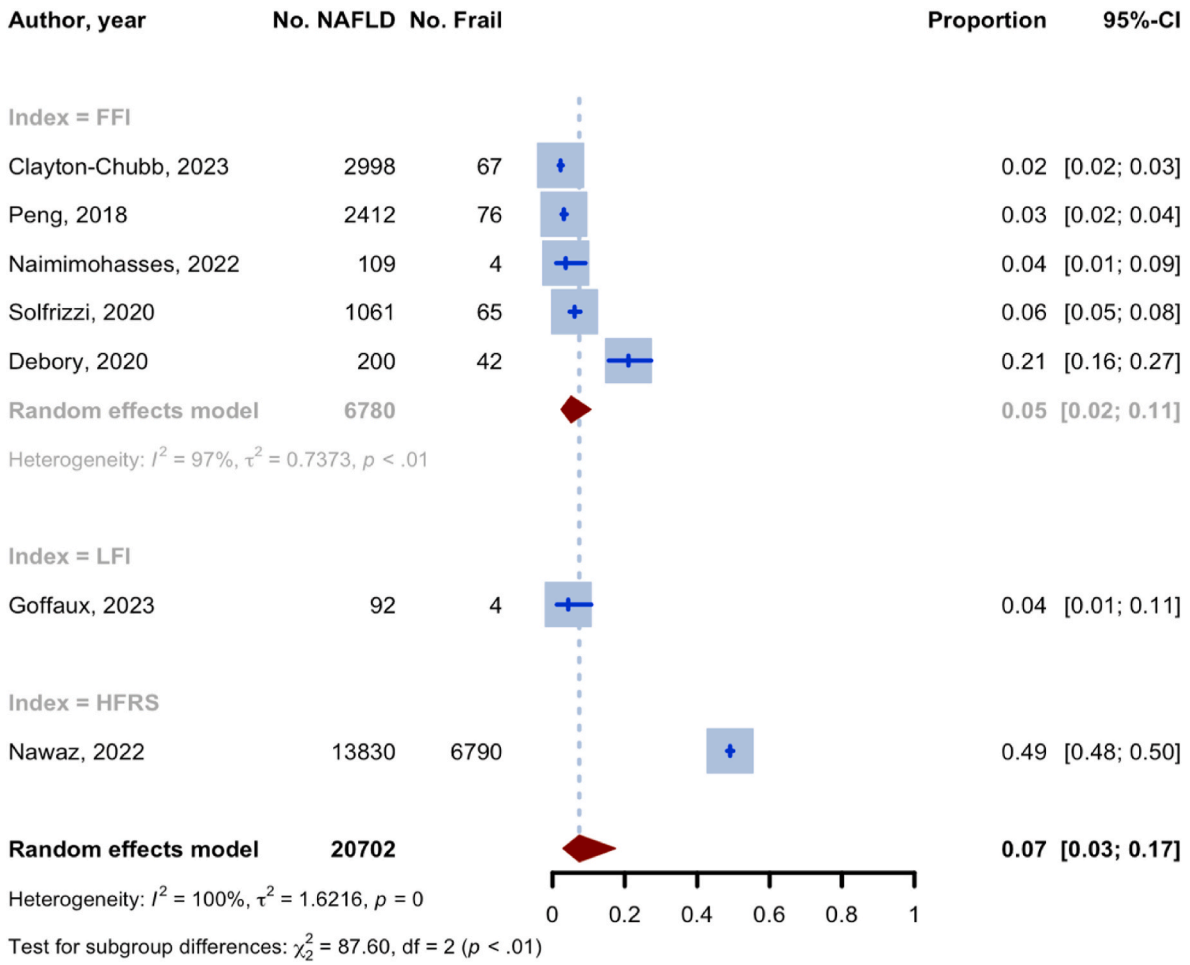

Fig. 6. Frailty prevalence in the MAFLD/NASH population (cirrhotic and non-cirrhotic).

significant heterogeneity that the model did not account for. The test for residual heterogeneity (QE) showed a p-value of 0.0088, indicating a notable unexplained variability with gender acting as a moderator.

The combined mean balance time of 544 cases of NAFLD was 22.5 s (95% CI: 10–35; I^2 = 100.0%) (Fig. 7). The combined balance time for the subgroup of studies, which included a population of 452 cases of liver cirrhosis caused by NAFLD, was 29 (95% CI: 27–30; I^2 = 93.4%). The only study that included 92 patients with NAFLD, regardless of the presence of liver cirrhosis, reported a balance time of 9.9 s (95% CI: 9.6–10.2). The test for subgroup differences yielded a statistically significant result ($p < 0.0001$), indicating a significantly longer balance time in patients with liver cirrhosis caused by NAFLD.

4. Discussion

We conducted this systematic review and meta-analysis of 18 eligible studies investigating the association between frailty and NAFLD. In these included studies, frailty was assessed through various scales that included different constructs and were designed for distinct objectives. In the meta-analysis of the studies that reported an association between frailty and NAFLD, the pooled OR was 2.03 (95% CI: 1.51–2.73; $p < 0.0001$). The combined prevalence of frailty in NAFLD patients using LFI and FFI was 23% (95% CI: 13%–38%; I^2 = 93.5%) and 8% (95% CI: 3%–21%; I^2 = 98.1%), respectively. Frailty was associated with disease progression in most studies, showing a correlation with the fibrosis stage.

Frailty syndrome is delineated as a syndrome of multiple etiologies distinguished by diminished muscular power and strength as well as decreased physiological function [44]. Studies have indicated a significant correlation between frailty and various chronic and metabolic diseases [45–47]. The concept of frailty has also gained significant attention in the field of NAFLD spectrum due to the aging population and the rapidly growing burden of NAFLD [48]. Elderly patients with NAFLD are more likely to experience advanced liver fibrosis and cirrhosis, as well as higher rates of hospitalization and mortality [49]. Frailty is a significant condition that physicians encounter when managing NAFLD, irrespective of the specific clinical context.

Multiple mechanisms contribute to the development of frailty in individuals with NAFLD. NAFLD is closely associated with metabolic dysfunction that can contribute to the development of frailty by promoting muscle wasting and impaired energy metabolism [50,51]. In NAFLD, the combination of increased caloric consumption, genetic susceptibility, and chronic low-grade inflammation results in the disturbance of the interplay among adipose tissue, skeletal muscle, and liver. Consequently, this can lead to ectopic fat accumulation within the skeletal muscle, resulting in changes in muscle composition architecture, known as myosteatosis, as well as a gradual reduction in muscle mass, strength, and function, referred to as sarcopenia [52,53]. Overall, these changes promote muscle wasting and impaired muscle regeneration, eventually advancing frailty [54].

Also, insulin resistance and elevated body mass index (BMI) may represent additional potentially exacerbating factors linked to the heightened prevalence of frailty among individuals with NAFLD [50,55,56]. Furthermore, a reduction in muscle mass and the development of sarcopenia, which are characteristic manifestations of frailty, have been linked to an increased likelihood of severe fibrosis associated with

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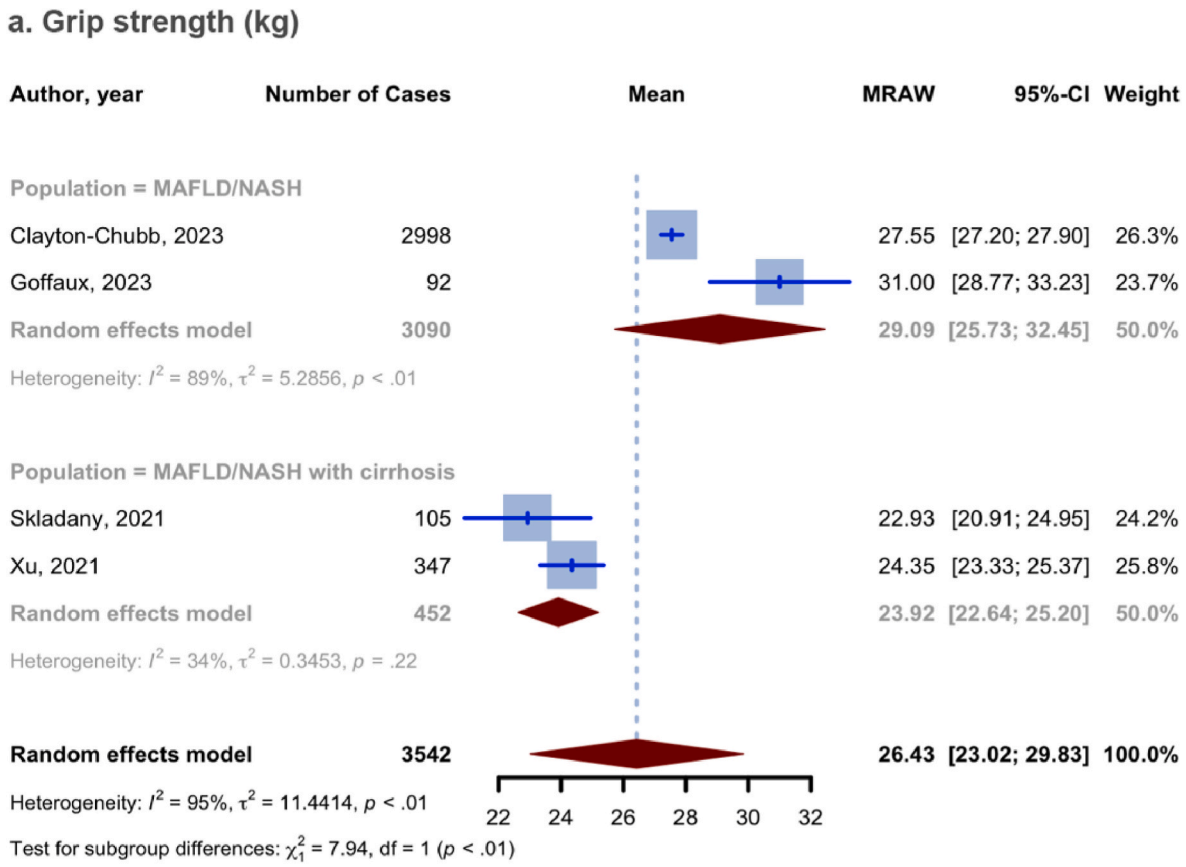

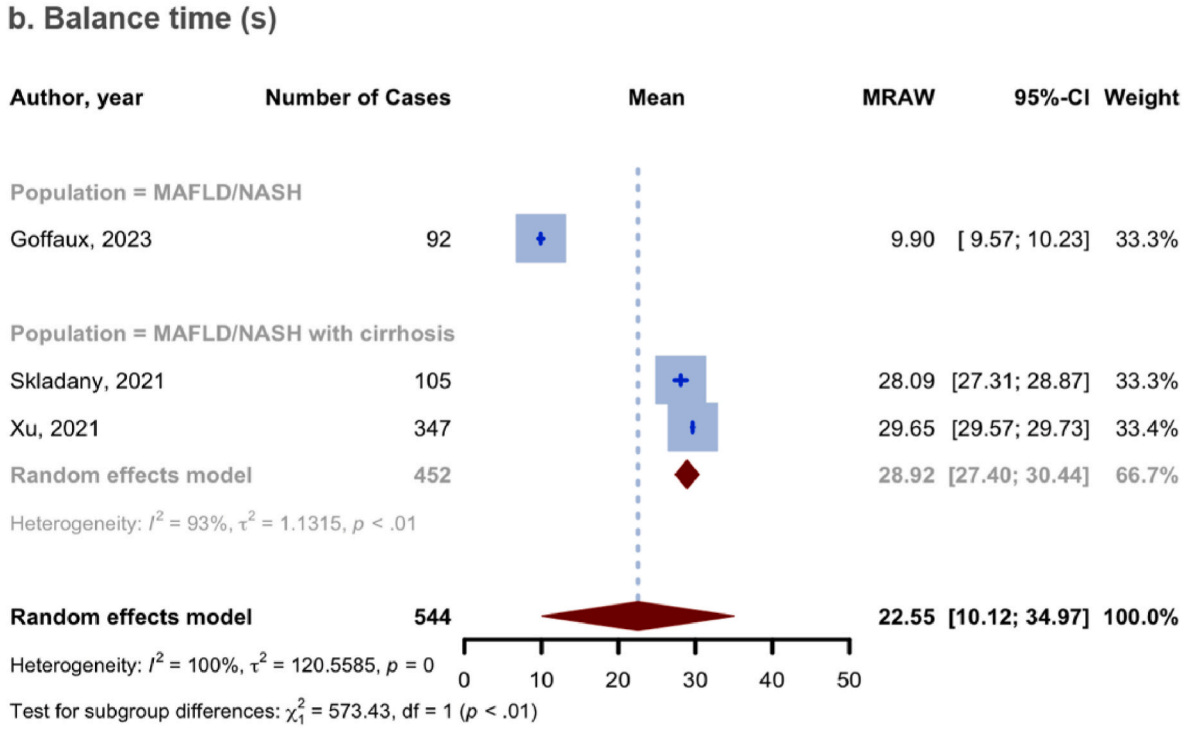

Fig. 7. Grip strength (a) and balance time (b) meta-analyses.

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NAFLD, particularly among younger adults with NAFLD [57].

Our systematic review shows that across the spectrum of NAFLD, the prevalence of frailty increases with disease advancement and progression. To describe more precisely, the incidence of frailty was found to be greater in cirrhotic patients compared to those with NASH. Also, one of the included studies has found an association between a higher fatty liver index score, indicating a greater likelihood of having fatty liver disease, and an increased risk of frailty [48]. A study conducted by Naimimohasses et al. revealed a significant increase in SRFI scores between F0/F1 patients and F4 patients. There was also a significant decrease in 30STST scores between F0/F1 patients and F4 patients. Additionally, there was a significant increase in laboratory frailty index (FI-lab) scores between both F0/F1 patients and F4 patients, as well as F0/F1 patients and F2/F3 patients [22]. Another study showed a higher prevalence of frailty in individuals with NAFLD, particularly in those with advanced fibrosis, described by a high liver elasticity compatible with an F4 stage [58]. Therefore, early detection and subsequently appropriate management of NAFLD enable timely interventions to prevent or slow down the progression of frailty in individuals with NAFLD, potentially improving overall health outcomes and quality of life.

Our meta-analysis has also elucidated that individuals diagnosed with liver cirrhosis caused by NAFLD exhibit a statistically significant decrease in grip strength and an extended duration of balance time. Liver cirrhosis has the potential to induce muscle wasting and debilitation, thereby influencing grip strength. In addition, it can impede the body's efficacy in upholding equilibrium, consequently prolonging the balance duration. Moreover, this ailment may lead to diminished engagement in physical exertion, contributing to decreased muscle strength and balance. More specifically, one study showed that the performance of patients with advanced cirrhosis with impaired cognition was lower than that of other cirrhotic patients in all three components of the LFI, including hand grip strength, chair stands, and balance. Further, this study clarified that NAFLD is associated with cognitive impairment; chronically impaired cognition status can lead to inadequate nutrition, insufficient calorie intake, and poor dietary quality, potentially leading to muscle wasting and decreased physical activity, which can contribute to the exacerbation of physical frailty [59].

An important issue in frailty studies is that there is inconsistency in the qualitative/quantitative description of frailty. In these reviewed studies, various indicators and criteria have been used to define and assess frailty, including the FFI, deficit index, LFI, frailty-related phenotype (FRP), and HFRS. Frailty results in our comprehensive meta-analysis exhibited significant differences contingent upon the particular type of index that was employed in the various studies conducted. In our meta-analysis, NAFLD showed a stronger correlation with frailty when using the FFI compared to the LFI. Then, it is indispensable to consider the variations between different frailty indexes when interpreting and comparing findings across studies. Frailty is a complex and multidimensional concept, and researchers have put forth diverse definitions and criteria. The measurement of frailty can vary across different assessment tools, scales, and criteria, leading to inconsistent application and potentially inappropriate recommendations in clinical practice and making it challenging to establish standardized guidelines. Therefore, a single universally agreed-upon definition may be unlikely [8]. Then, it is essential to consider the specific context and purpose when applying a frailty definition.

The sensitivity and specificity of various non-invasive methods for diagnosing NAFLD vary significantly. VCTE has demonstrated an AUC of 0.85 for advanced fibrosis, while the FIB-4 showed lower AUCs of 0.76 [60]. Imaging techniques such as magnetic resonance elastography (MRE) exhibited high accuracy, with AUCs reaching 0.93, while ultrasound and CT had AUCs of 0.82 [61]. Additionally, the FLI and other biochemical markers have shown promise, particularly when combined with clinical data, enhancing diagnostic accuracy for NAFLD [62]. While the inclusion of studies with diverse diagnostic methods introduces some variability, this approach is consistent with the methodology of similar published systematic reviews and meta-analyses [63–66]. The inclusion of studies with diverse diagnostic methods, while introducing some variability, enhances the comprehensiveness and robustness of this study's findings and provides valuable insights for clinical practice.

Clinicians must consider the potential interplay between NAFLD and frailty and its clinical significance, especially in the elderly, as part of comprehensive patient management. As we mentioned above, NAFLD can contribute to the progression of frailty in individuals. The presence of liver disease, especially advanced fibrosis or cirrhosis, can lead to complications such as muscle wasting, reduced physical function, and increased vulnerability. This can further worsen the frailty status of individuals. On the other hand, the presence of sarcopenia and myosteatosis as distinctive features of frailty are associated with an increased risk of disease progression and mortality in NAFLD patients [67]. Additionally, they are associated with prolonged hospitalization and an increased susceptibility to perioperative bacterial infections following liver transplantation in cirrhotic patients [68]. A study conducted by Skladany et al. (2021) indicated that the influence of frailty on mortality seems to be stronger in patients with NAFLD compared to those with alcoholic liver disease (ALD) [18].

Altogether, by incorporating frailty identification, evaluation, and management into routine NAFLD management, we can improve patient outcomes, optimize treatment strategies, and potentially reduce the risk of complications associated with frailty and NAFLD. Considering the results of the present study, screening for frailty in patients with NAFLD, particularly in older patients and those with end-stage liver disease, is indeed required for early identification, comorbidity management, personalized treatment plans, and interventions, and consequently could improve the overall survival of these patients.

Our review used a comprehensive search strategy, supplemented by precise study selection and quality assessment, to elucidate the correlation between NAFLD and frailty. To the best of our knowledge, our study is the first systematic review and meta-analysis on the association of NAFLD and frailty. However, our study had several limitations. There was heterogeneity among the studies included, with differences in inclusion criteria and representativeness potentially leading to selection bias, as well as variations in the frailty measurement and NAFLD definition, conformity of frailty criteria, and study settings. Frailty is a complex condition influenced by multiple factors; thus, we faced challenges in adequately adjusting for potential confounding variables, such as comorbidities and lifestyle factors. The meta-analysis was constrained by a lack of data for some indexes and variations in the assessment tools used for frailty and NAFLD across different studies.

Further research employing more rigorous and standardized methods for assessing frailty based on longitudinal designs is crucial to deepen our understanding of the relationship between frailty and NAFLD, guide the development of specific treatment recommendations, and identify specific therapy targets for frail individuals with NAFLD.

5. Conclusion

In conclusion, the present study supports the correlation between NAFLD and frailty syndrome and confirmed frailty exhibits a higher prevalence among individuals afflicted with NAFLD compared to the general population. In addition, the prevalence of frailty increases with disease advancement and progression across the spectrum of NAFLD. Also, it seems that NAFLD showed a stronger correlation with frailty when using the FFI compared to the LFI. More precise and standardized assessments of frailty, based on longitudinal designs, are required to improve understanding of the relationship between frailty and NAFLD. This will enable the better management of NAFLD in frail individuals, as well as potential targets for therapy. Ultimately, these findings will contribute to developing specific recommendations for managing NAFLD in frail adults.

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Contributors

SK conducted the systematic literature search, reviewed all titles and abstracts, selected eligible articles, extracted the data from individual articles, verified the data, and drafted and co-wrote the article. MM extracted the data from individual articles, planned and performed the statistical analyses, verified the data, and drafted and co-wrote the article. PF reviewed all titles and abstracts, selected eligible articles, extracted the data from individual articles, and edited the article. AH verified the data, and drafted and co-wrote the article. AS contributed to the interpretation of the results, and drafting and editing of the article. MSK conceived the study, verified the data, and planned and contributed to the analyses, the interpretation of the results, and drafting and editing of the article. All authors had full access to the data and had final responsibility for the decision to submit for publication.

Data sharing

Data extracted from original articles are all included in the article and supplementary materials. Analytic code are available upon reasonable request to be used for meta-analyses of summary statistics or umbrella reviews. Proposals should be directed to drshafikuchay@gmail.com.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2025.103187.

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