Frailty in metabolic syndrome, focusing on nonalcoholic fatty liver disease

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Abstract

In recent years, frailty has been increasingly recognized among researchers of distinct medical specialties worldwide. Frailty comprises a complex of multisystemic physiological decline, reduced physiologic reserve, and vulnerability to stressors. Frail people tend to have a shorter lifespan and greater disability, morbidity and mortality. In the field of hepatology, frailty is identified in nearly 50% of patients who have cirrhosis of any cause. The most predominant cause of chronic liver disease is nonalcoholic fatty liver disease (NAFLD), considered as the hepatic manifestation of the metabolic syndrome (MetS). Although it is viewed as a benign disease, it may progress to nonalcoholic steatohepatitis (NASH), characterized by the additional emergence of inflammation and hepatocyte ballooning, with or without fibrosis. During the progression of NAFLD to NASH and liver cirrhosis, NAFLD patients present sarcopenia along with lower skeletal muscle strength and function. Moreover, aging and the increased prevalence of comorbidities further exacerbate their physical performance. The aforementioned features are strongly associated with the frailty phenotype, implying that the latter could be associated with both MetS and NAFLD. Although it is a relatively new topic of research interest, in this review we aim to provide a synopsis of the current literature dealing with the interplay between frailty and MetS, and to shed more light on the association between NAFLD and frailty. Finally, we discuss the potential pathophysiological mechanisms linking the distinct features of MetS and NAFLD with aspects of the frailty phenotype.

Keywords Frailty, metabolic syndrome, nonalcoholic fatty liver disease, physiologic reserve, sarcopenia

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Introduction

Frailty is characterized by a disruption of homeostasis, which exposes individuals to detrimental health-associated outcomes, such as admissions to hospitals, disability or even death [1],

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while frail people are extremely vulnerable to stressors, both endogenous and exogenous [1]. As a result, the same stressor may have a more severe impact on a frail person than on healthy individuals, concerning both the recovery period following exposure to stressors and the possibly greater mortality [1]. A major contributor to frailty is aging. Aging-associated changes, including lack of appetite, prolonged medication use and social parameters such as poverty and loneliness, could result in anorexia of aging [2]. This in turn can lead to protein-energy undernutrition, cognitive decline, deterioration of body function and sarcopenia, eventually enhancing the frailty circle (Fig. 1) [2]. Moreover, the elderly are more prone to reduced physical activity and to frequent falls, which could also lead to disability and frailty [3]. Notably, inflammaging—a chronic, sterile, low-grade inflammation triggered by genetic susceptibility, central obesity and increased permeability of the gut—contributes to the pathogenesis of age-related diseases, such as metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), cancer, depression, dementia, and sarcopenia, all related to increased morbidity, disability, and frailty [4-9].

In the field of hepatic diseases, nonalcoholic fatty liver disease (NAFLD) has emerged as the predominant cause of chronic liver disease worldwide, affecting approximately one fourth of the global population [10,11]. Its prevalence is increasing along with the growing prevalence of obesity, T2DM and aging, while the disease is considered as the hepatic manifestation of the MetS. Data from the literature suggest that NAFLD comprises a multi-systemic disease, rather than a liver disorder *per se* [11,12]. In NAFLD, the excessive caloric intake, genetic predisposition and the chronic inflammation lead to disruption of the triangle-crosstalk among adipose tissue, skeletal muscle and liver [13]. This in turn, can result in ectopic fat accumulation in skeletal muscle, along with both alterations in muscle composition architecture, defined as myosteatosis, and progressively diminished muscle mass strength and function, defined as sarcopenia [13]. The latter is closely associated with NAFLD and its progression to nonalcoholic steatohepatitis (NASH) and advanced fibrosis [14]. Myokines, such as myostatin and irisin, seem to be implicated in the pathogenesis of sarcopenic obesity [15], imposing a burden on the metabolism, physical activity capacity and quality of life of sarcopenic patients. Aging has been associated with greater susceptibility to NASH, advanced fibrosis and NAFLD-associated hepatocellular carcinoma (HCC), while elderly NAFLD patients, compared to non-NAFLD elderly people, are at higher risk for age-related disorders such as cognitive impairment [16,17]. Some of the aforementioned detrimental effects characterize frail people and could lead to adverse clinical outcomes, namely, more severe tissue injury, end-organ failure, infections and oncogenesis. To this end, patients with NAFLD and/or MetS and frailty may suffer from increased morbidity, a poorer quality of life, more frequent and prolonged hospitalization, and ultimately higher mortality.

In the current review we aim to discuss the implication of frailty with the MetS as well as to shed more light upon the impact of frailty on NAFLD patients.

Evaluation of frailty (Table 1)

The defined frailty phenotype is based on Fried's criteria and consists of 5 components: weakness and poor handgrip strength; slow gait speed; exhaustion; low activity/sedentary behavior; and involuntary weight loss (Fig. 2). However, this phenotype is defined by simple elements and symptoms that may signal an alarm about the potential existence of frailty syndrome; the evaluation of frailty may sometimes be very challenging [18-20]. Beyond Fried's criteria, a plethora of indices that evaluate frailty have been proposed by professional societies worldwide and are comprehensively described in Table 1 [21-24].

Materials and methods

A comprehensive review of the current literature was conducted to investigate the potential association between frailty with MetS and NAFLD. We retrieved the current literature using the PubMed database from the date of inception of the idea of this review until May 2021. We searched for the following terms: "non-alcoholic fatty liver disease" OR "nonalcoholic fatty liver disease" OR "fatty liver disease" OR "NAFLD" OR "non-alcoholic steatohepatitis" OR "nonalcoholic steatohepatitis" OR "metabolic syndrome" OR
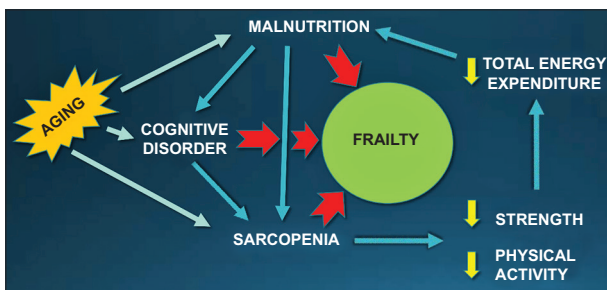

Figure 1 The frailty circle. Aging is a major contributor of the frailty circle. Aging leads to malnutrition, cognitive disorders and loss of muscle mass (sarcopenia). Malnutrition can lead to sarcopenia directly, or through the induction of cognitive disorder. The result of muscle mass loss is a reduction of physical activity and body strength and consequently a decrease in total energy expenditure, loss of appetite and subsequently malnutrition, driving the circle of frailty
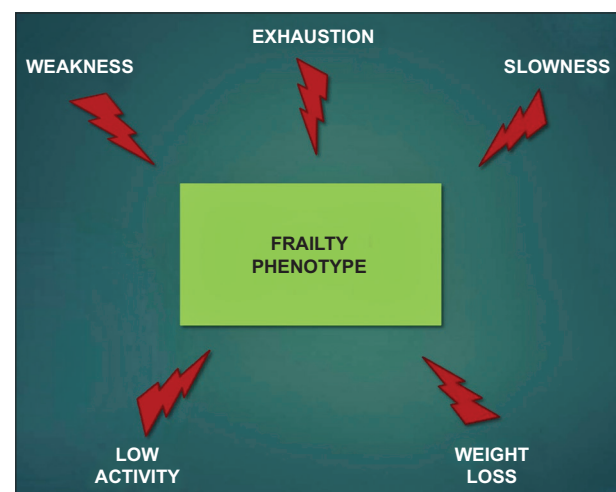
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Figure 2 The defined frailty phenotype consists of 5 components. These 5 components are: weakness and poor handgrip strength, slow gait speed, exhaustion, low activity and sedentary behavior, involuntary weight loss

Table 1 The widely-accepted frailty assessment indices and their components

Frailty Assessment Index	Components of each frailty index
Fried's criteria (Frailty Phenotype)	Weakness and poor handgrip strength, slow gait speed, exhaustion, low activity/sedentary behavior and involuntary weight loss
FI	Calculated as the ratio between the number of health deficits of the individual and the total number of health deficits considered for its computation
sFI frailty index	The 5 items of this index are: T2DM, hypertension requiring treatment, functional status, medical history of congestive cardiac failure and chronic obstructive pulmonary disease
G8 score	This score includes age, weight loss, mobility, reduction of food intake, BMI, neuropsychological deficits, comparison with other coeval people and drugs intake
Johns Hopkins Frailty Assessment Calculator	This calculator consists of 5 criteria concerning phenotype, which are low grip strength, involuntary weight loss, low energy consumption, exhaustion, and/or slowed walking speed
ASA Physical Status Classification	Evaluates the patient's physical condition and health status before operations and consists of 5 classes (I to V)
CGA	This assessment concerns components such as fatigue, functional status, comorbidities, cognition, mental health evaluation, nutrition, social support and geriatric syndromes (e.g., dementia, sarcopenia, falls, osteoporosis or spontaneous fractures, polypharmacy, constipation, etc.)
Karnofsky Score and ECOG Performance Status	This score concerns the evaluation of performance status and physical function. Their ranges are 0 to 5 for ECOG and 0 to 100 for Karnofsky score
Mini-COG Assessment	The mini-COG assessment concerns 2 components, which are a simply scored clock drawing test and a 3-item recall test for memory
CISR-G and CCI	Evaluation of comorbidities. Prediction of 10-year survival in patients. CISR-G consists of 14 categories and CCI consists of 17 categories
SOF criteria	These criteria concern: inability to rise from a chair 5 consecutive times without using the arms, poor energy as identified by a negative answer to the question "do you feel full of energy?" on the 30-item Geriatric Depression Scale, weight loss (irrespective of intent to lose weight) of 5% or more between the second and fifth visit (mean time between visits 3.0±0.05 years)
LFI	A tool concerning patients with cirrhosis to objectively measure their physical function. Composed of 3 performance-based tests which are: grip strength, chair stands, and balance
5-Item Frail scale	Fatigue, Resistance, Ambulation, Illness, and Loss of Weight Scores; 0: robust, 1–2: pre-frail and 3–5: frail

FI, frailty index; SFI, simplified 5-item; T2DM, type 2 diabetes mellitus; G8, geriatric 8; BMI, body mass index; ASA, American Society of Anesthesiologists; CGA, comprehensive geriatric assessment; ECOG, eastern cooperative oncology group; mini-COG, mini-cognitive; CISR-G, cumulative illness score rating-geriatrics; CCI, Charlson comorbidity index; SOF, study of osteoporotic fractures; LFI, liver frailty index

"MetS" AND "frailty" OR "frailty syndrome" OR "frail people". We searched only for studies written in the English language. The references of the research articles were scrutinized for relevant studies. For the scope of this review, we only included studies that evaluate the association of MetS or NAFLD with frailty, defined by one of the frailty indices described in Table 1, whereas studies assessing possible associations between components of those indices with MetS or NAFLD were excluded.

Frailty and MetS (Table 2)

Eleven studies fulfilled the aforementioned criteria concerning the association between MetS and frailty.

Concerning MetS, Kane *et al*, based on the US National Health and Nutrition Examination Survey (NHANES), found a positive association between Frailty Index (FI) and MetS (r=0.25) over the lifespan, but this was weakened in older age (>65 years) [25]. Moreover, FI was a predictor of mortality in both age groups, whereas MetS was associated with increased mortality only among the younger group (<65 years) [25]. Similarly, in a cohort study of 1499 community-derived participants aged ≥60 years, individuals with MetS displayed 85% elevated odds for being frail as compared to their non-MetS counterparts, even after adjustment for socioeconomic and lifestyle parameters as well as for laboratory factors, namely fibrogen and high-sensitive C-reactive protein (CRP) [26]. Notably, low grip strength had the strongest association with MetS (odds ratio [OR] 1.67, 95% confidence interval

Table 2 Associations between frailty with MetS

Author [ref.]	Year/study	Study population	Findings	Frailty assessed by:
Kane *et al* [25]	2017/ Secondary analysis of the US NHANES	8555 individuals	Positive association between FI and MetS especially in aged<65 participants Weaker association in aged≥65 participants	41-Item FI (5 factors of the 46-FI associated with MetS were excluded)
Perez-Tasigchana *et al* [26]	2017/Cohort	1499 community-dwelling individuals aged≥60 years old	Individuals with MetS: ↑risk of frailty vs. non-MetS participants Low grip strength has the strongest association with MetS	Fried's criteria
Viscogliosi *et al* [27]	2016/ Cross-sectional	118 old community-dwelling individuals	Frail people: ↑ likelihood for MetS Mets, but none of its components, was associated with frailty	Fried's criteria
Buchmann *et al* [28]	2019/ Cross-sectional	1486 community-dwelling aged 60-84 years (based on BASE-II study)	Frail people: ↑prevalence of MetS vs. non-frail MetS patients had↑odds for frailty	Modified Fried's criteria
Barzilay *et al* [29]	2007/Cohort	2826 individuals, a subcohort from the Cardiovascular Health Study	MetS was not independently associated with frailty, but with pre-frailty One SD increase at HOMA-IR led to 15% increased hazard for frailty	Fried's criteria
Hao *et al* [34]	2016/ Cross-sectional	767 people aged 90+years from the Project of Longevity and Aging in Dujiangyan.	MetS was not significantly associated with frailty Frailty was related to mortality and this association persisted even after adjusting for MetS	FI: sum of deficits present, divided by the 35 health-related deficits considered.
Hoogendijk *et al* [35]	2017/ Longitudinal cohort	1247 men and women aged ≥65 years of the Longitudinal Aging Study Amsterdam	Presence of MetS was significantly associated with frailty	Fried's criteria
Chao *et al* [30]	2020/Cohort	2862 community-dwelling elderly ≥65 years old	MetS associated with higher risk of frailty/prefrailty Among those ≥80 years of age: association between MetS and frailty/prefrailty disappeared	SOF criteria
Lin *et al* [31]	2015/ Cross-sectional	690 participants age≥50 years old	MetS remarkably led to increased likelihood for frailty MetS strengthened the negative association between EF and frailty	Modified Fried's criteria
Merchant *et al* [32]	2020/ Cross-sectional	722 old adults ≥65 years old	Patients with MetS: ↑ prevalence of frailty compared to participants without MetS	5-item FRAIL scale
Chen *et al* [33]	2021/ Cross-sectional	292 older adults ≥65 years old part of the HOPE cohort	Among MetS patients: frailty associated with polypharmacy, depression, functional impairment and a poorer quality of life	5-item FRAIL scale

NHANES, national health and nutrition examination survey; MetS, metabolic syndrome; FI, frailty index; CSHA, Canadian study of health and aging, women's health initiative-observational study; AD, Alzheimer's disease; VaD, vascular disease; NA, not available; KFACS, Korean frailty and aging cohort study; BMI, body mass index; FMI, fat mass index; TFMI, trunk fat mass index; CERAD, consortium to establish a registry for Alzheimer disease; MMSE, mini-mental state examination; T2DM, type 2 diabetes mellitus; CI, cognitive impairment; SOF, study of osteoporotic fractures; CKD, chronic kidney disease; EF, executive function; FRAIL, fatigue, resistance, ambulation, illness, and loss of weight; HOPE, healthy older people everyday

[CI] 1.25-2.21) [26]. A positive association between the homeostatic model assessment for insulin resistance (HOMA-IR) and frailty was also observed in the same study, with one unit increase of HOMA-IR leading to 15% increased odds for frailty [26]. Interestingly, Viscogliosi *et al* evaluated 118 community-dwelling individuals (mean age 76.1 years) and confirmed that MetS, as an entity, was significantly associated with 53% increased odds for frailty, even after adjustment for demographic parameters, Mini-Mental State Examination test and prevalence of comorbidities [27]. However, none of the specific components of MetS on its own was independently associated with frailty [27]. In addition, a cross-sectional study

with 1486 individuals showed that the prevalence of MetS was higher among prefrail/frail people, whilst it was confirmed that the presence of MetS was related to 50% increased odds for frailty, even after adjustment for confounding factors [28]. However, when the authors associated the components of MetS with frailty, they concluded that the risk for frailty was significantly correlated only with lower levels of high-density lipoprotein cholesterol and increased waist circumference [28]. The aforementioned associations were partially attributed to MetS-mediated chronic low-grade inflammation, as indicated by higher CRP concentration and reduced levels of adiponectin among MetS patients. In contrast, in a relatively old study of 3141 community-dwelling adults aged 69-74 years, a subcohort of participants from the Cardiovascular Health Study, MetS was not significantly associated with frailty, but with prefrailty, defined as having 1 or 2 fewer criteria than frailty. Nonetheless, an increase of HOMA-IR by 1 standard deviation was associated with a 15% higher hazard for frailty [29].

Consistently, among 2862 community-dwelling elderly people (≥65 years) the presence of MetS (OR 2.53, 95%CI 1.78-3.6), age (OR 1.05, 95%CI 1.03-1.06) or chronic kidney disease (CKD) (OR 1.42, 95%CI 1.11-1.83) was associated with a significantly higher risk of frailty/prefrailty phenotype [30]. Moreover, among patients with CKD, the presence of MetS was significantly associated with a progressively higher risk of frailty/prefrailty (for CKD stage ≥3 and for stage ≥3b, OR 6.4, 95%CI 2.48-16.5 and 12.4, 95%CI 3.87-23.2, respectively), whereas among those aged ≥80 years, a nonsignificant association between MetS and frailty/prefrailty was identified (P=0.329) [30]. Notably, Lin *et al* investigated whether MetS could moderate the association of cognition with frailty in middle and old age [31], evaluating episodic memory and executive function by a confirmatory factor analysis of cognitive tests [31]. Structural equation modeling demonstrated that MetS was strongly associated with a greater likelihood of frailty [31].

Finally, 2 recent studies, both based on the Healthy Older People Everyday (HOPE) Study, confirmed that the prevalence of frailty was markedly higher among patients with MetS compared to participants without MetS (7.2% vs. 4.5%, P=0.015) [32], while Chen *et al* showed that, among MetS patients, frailty was significantly associated with polypharmacy, depression, functional impairment, and a poorer quality of life [33].

Nonetheless, there is a smaller body of literature not linking Mets with frailty. Among more elderly people (aged 90+ years), Hao *et al* investigated the relationship between frailty and MetS and evaluated their impact on mortality [34]. FI was not significantly correlated with MetS, nor with its components. In the multivariate Cox proportional hazard model, adjusted for age, sex and education, the FI score was related closely to mortality (hazard ratio [HR] 1.03, 95%CI 1.02-1.04), while this positive association persisted even after adjustment for MetS [34].

Similarly, Hoogendijk *et al* investigated the associations of MetS with 19-year all-cause mortality in older adults (55-84 years) [35]. In a model adjusted for age, sex and educational level, the hazard of mortality was significantly higher in people with MetS (HR 1.23, 95%CI 1.08-1.40), whilst after adjustment for frailty, the association of MetS with mortality decreased, but remained statistically significant (HR 1.15, 95%CI 1.01-1.31). Interestingly, the elevated hazard was mainly attributed to the presence of chronic diseases such as cardiovascular disease (CVD) and T2DM (HR 1.12, 95%CI 1.01-1.28), rather than to the physical frailty [35].

Frailty and NAFLD (Table 3)

Seven studies were eligible for the investigation of the NAFLD–frailty interplay. Bhanji *et al*, in their retrospective study, included 265 patients suffering from NAFLD or alcoholic liver disease (ALD) evaluated for liver transplantation (LT) [36]. Although NAFLD patients had a lower prevalence of sarcopenia, they had a significantly greater prevalence of frailty compared to their ALD counterparts [36], while no significant differences in body mass index (BMI), age or sex were observed when they compared frail to non-frail patients from each subgroup [36]. Intriguingly, in NASH patients the duration of hospitalization was positively correlated with their FI, leading to 2.7 more days of hospitalization in a multivariate linear regression model. No similar association was detected among ALD patients [36]. Furthermore, frailty was remarkably associated with an increased risk of delisting among NASH, but not ALD patients [36]. In contrast, sarcopenia was markedly related to a higher likelihood of delisting and poor waitlist survival only in patients with ALD [36]. Consistently, Linge *et al* confirmed that, although sarcopenia was less prevalent in NAFLD compared to non-NAFLD patients, the former had either a similar prevalence of poor function, assessed by low hand grip strength and a similar number of falls during the last year, or an even higher prevalence of inadequate function, as evaluated by slow walking pace and no capacity for stair climbing [37].

Furthermore, since frailty measured at a single time point is already considered as a predictive factor of mortality for cirrhotic patients, Lai *et al*, in a large multicenter study from the USA evaluating cirrhotic patients listed for LT, showed that NAFLD compared to non-NAFLD cirrhotic patients were significantly more likely to experience worsening of frailty over time [38]. To this end, they assigned the patients to 4 categories according to their alterations of fatty liver index (FLI), an accurate predictor of hepatic steatosis based on BMI, waist circumference, triglycerides and γ-glutamyl transferase [38]. The authors found that FLI was associated with significantly greater waitlist mortality, since an 0.1 unit increase in FLI at 3 months led to an 85% increased hazard for death at waitlist [38].

De Vincentis *et al*, based on the InCHIANTI study, investigated the relation between 4 noninvasive liver fibrosis scores—2 general scores: Fibrosis-4 (FIB-4), and aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT), as well as 2 NAFLD-specific scores: NAFLD fibrosis score (NFS) and BARD score (BMI ≥28 kg/m^2 = 1 point, AST/ALT ratio ≥0.8 = 2 points, and T2DM = 1 point)—and health outcomes regarding disability and mortality in 962 randomly selected community-dwelling individuals aged ≥65 years, with a mean follow up of 95.7 months [39]. The prevalence

Table 3 Associations between frailty and NAFLD

Author [ref.]	Year/study	Study population	Findings	Frailty assessed by:
Bhanji *et al* [36]	2019/ Retrospective	265 individuals	NAFLD vs. ALD: ↓prevalence of sarcopenia but↑prevalence of frailty NAFLD: positive correlation between LOS and FI NAFLD: ↑delisting risk	7-point Clinical Frailty Scale
Linge *et al* [37]	2021/ Retrospective	10,019 individuals (based on UK biobank)	NAFLD vs. non-NAFLD individuals: ↓prevalence of sarcopenia but↑prevalence of not adequate function evaluated by slow walking pace and no capacity of stair climbing NAFLD vs. non-NAFLD: similar hand grip strength and number of falls at the last year	Low hand grip strength, Slow walking pace, No stair climbing, More than one fall last year
Lai *et al* [38]	2020/Prospective	1093 cirrhotic patients	NAFLD vs. non-NAFLD cirrhotic patients: ↑possibility to experience worsening of frailty over time and↑risk of waitlist mortality	Grip strength, Timed chair stands, Balance testing
De Vincentis *et al* [39]	2019/Prospective population-based	962 individuals aged ≥65 years	↑NFS was associated with ↑prevalence of sarcopenia and frailty ↑BARD was associated with ↑prevalence of sarcopenia ↑NFS was associated with ↑overall and cardiovascular-related mortality ↑BARD was associated with ↑overall mortality High-risk NFS patients, had↑incidence of disability at 6 years	Fried's criteria
Solfrizzi *et al* [40]	2020/Longitudinal	1061 individuals aged ≥65 years	F3 and F4 NFS participants had ↑prevalence of physical frailty vs. F0-F2 NFS counterparts Among frail people, F3 and F4 NFS participants had↑hazard for dementia in a long time period vs. F0-F2.	Modified Fried's criteria (for frailty), Mini-Mental State Examination, Babcock Story Recall Test (for dementia)
Skladany *et al* [42]	2021/ Retrospective	385 patients	Similar prevalence of frailty in NAFLD vs. ALD patients NAFLD patients: more sensitive to the increase of LFI	LFI
Lin *et al* [43]	2021/ Ambispective cohort study	517 patients	Patients with NAFLD and ALD-related cirrhosis had worse frailty metrics by all frailty assessment tools vs. other etiologies of cirrhosis	LFI, 6-minute walk test, gait speed test

NAFLD, nonalcoholic fatty liver disease; ALD, alcoholic liver disease; LOS, length of stay; FI, frailty index; T2DM, type 2 diabetes mellitus; ALT, alanine aminotransferase; gGT, gamma-glutamyl transferase; NFS, NAFLD fibrosis score; LFI, liver frailty index; NA, not applicable

of both sarcopenia and frailty was remarkably associated with higher NFS classes, whereas the prevalence of sarcopenia, but not frailty, was greater in high BARD categories [39]. In addition, intermediate and high-risk NFS classes were markedly associated with higher overall and cardiovascular-related mortality in a model adjusted for demographic and clinico-epidemiological factors, whilst an increased hazard only for overall mortality was detected in the high-risk BARD category [39]. Accordingly, patients classified as high-risk according to NFS and BARD scores had a higher incidence of disability at 6 years in univariate analysis, whereas only the association for NFS remained significant in the adjusted multivariate model [39].

In addition, the association of liver fibrosis, as assessed by NFS, with the prevalence of physical frailty and the risk of developing dementia was assessed in 1061 adults aged >65 years from the Italian Longitudinal Study on Aging [40]. Participants classified as having advanced fibrosis or cirrhosis (fibrosis F3/F4, i.e., NFS >0.676) had a higher prevalence of physical frailty as compared to their counterparts with no advanced fibrosis/cirrhosis (fibrosis F0-F2, i.e., NFS <-1.455) [40]. Notably,

this relation was independent of age [40]. Moreover, among frail people, those with NFS score F3/F4 had a significantly greater hazard for dementia over a long period, as indicated in a multivariable model adjusted for clinical and laboratory parameters [40]. Recently, Xu *et al*, analyzing data from cirrhotic patients awaiting LT, showed that NAFLD patients had a higher median liver frailty index (LFI) compared to their non-NAFLD counterparts [41]. Moreover, the prevalence of frailty was higher in the NAFLD group of patients [41]. Nonetheless, in the multivariate analysis, adjusted for age, model for end-stage liver disease-sodium score and ascites, only ALD and other causes of liver disease were independently associated with frailty, whereas NAFLD was marginally correlated with frailty (P=0.05). Furthermore, the underlying etiology of cirrhosis was not significantly associated with waitlist mortality during a median follow up of 13 months [41].

Notably, Skladany *et al*, based on a registry of hospitalized patients with decompensated cirrhosis or curable HCC since 2014, evaluated 280 ALD and 105 NAFLD patients with at least 6 months of follow up. Although the prevalence of frailty as assessed by the LFI was similar among the 2 groups, NAFLD

patients had a higher risk for death or LT and displayed higher all-cause mortality (HR 1.88, 95%CI 1.32-2.67) compared to their ALD counterparts [42].

Lastly, in a cohort study of 517 LT candidates who participated in a prehabilitation program, NAFLD and ALD patients had significantly greater frailty metrics, assessed by LFI, 6-min walk test and gait speed, compared to patients with autoimmune hepatitis or viral hepatitis-related liver disease. The authors showed that prehabilitation led to improved frailty metrics in LT candidates and was associated with a survival advantage [43].

Potential underlying mechanisms of association between MetS and NAFLD with frailty

Since experimental data derived from animal studies are lacking, it is understandable that we cannot describe the specific underlying pathogenetic mechanisms concerning the possible association of MetS and NAFLD with frailty. Nevertheless, we shall offer some assumptions about that intriguing interplay. Metabolic dysregulation refers to a wide variety of alterations in lipid and glucose metabolism, including insulin resistance or T2DM, obesity and MetS, strongly related with NAFLD and its progression to NASH. Frailty syndrome seems to be closely related to metabolic diseases and MetS [25], and those findings were only partially attributable to the consequences of T2DM, namely macro- and microangiopathy, peripheral nervous system dysfunction and visual disorders. Importantly, the decreased insulin sensitivity provokes a proinflammatory catabolic state, during which muscle mass and strength are reduced, leading to sarcopenia, while the insulin resistance-mediated accumulation of lipid droplets into skeletal muscle, along with lower lean muscle mass, could explain the deterioration of physical activity [44], the loss of strength and ultimately the frailty. It seems that visceral adiposity and elevated intramuscular lipid droplet accumulation further favor that muscle mass catabolism [45,46]. Moreover, T2DM is a major risk factor for CVDs [47], which, in turn, are strongly associated with frailty, since they negatively affect self-caring capacity and independence, leading to a burdened quality of life.

Concerning NAFLD, we can assume that, since frailty is thought to represent the overall end-manifestation of deficits and comorbidities a patient may acquire, NAFLD patients who display a high prevalence of comorbidities such as T2DM, CVD, arterial hypertension or CKD should have a higher rate of frailty. Moreover, the higher prevalence of frailty among cirrhotic NAFLD compared to non-NAFLD cirrhotic patients could be attributed to the typically greater age of the former, as the physiologic reserve declines with age [36,42]. Insulin resistance and high BMI may be additional potentially burdening factors associated with the increased prevalence of frailty among NAFLD patients. As we outlined previously, insulin resistance, but also obesity, favor an inflammatory environment with elevated levels of cytokines, namely interleukin-6 and tumor necrosis factor-α, higher levels of

which facilitate increased muscle breakdown and subsequent decreased muscle mass and strength [48]. To this end, upon muscle mass decline, lower levels of glucose are taken up by the muscle cells, driving higher insulin secretion and further exacerbating the insulin resistance, thus promoting a vicious cycle of muscle loss and glucose intolerance [49]. Moreover, decreased muscle mass and sarcopenia, distinctive features of frailty, have been associated with a higher risk of NAFLD-associated severe fibrosis, regardless of BMI and insulin resistance, especially in younger NAFLD patients [50]. Concurrently, lower muscle mass is strongly linked to frailty, since it is related with falls, functional decline, disabilities and increased mortality in older age, indicating an additional plausible explanation for the NAFLD-frailty interplay.

Thus, in our view, the potential interplay between NAFLD and frailty could be attributed to a broad base of causes. The overall biological frailty resulting from the higher age of NAFLD patients compared to their non-NAFLD counterparts, along with the greater prevalence of major comorbidities that detrimentally affect the functional status of NAFLD patients, could lead to a deficit-acquired phenotype, higher morbidity, and worse outcomes for patients on the waiting list for LT. Furthermore, the development of sarcopenic obesity, as well as the progression of NASH and fibrosis along with a potential at-risk genetic predisposition, may further aggravate the overall disease burden, rendering NAFLD patients even more vulnerable to stressors and ultimately frail. We should point out, however, that it is still unclear whether NAFLD is independently associated with frailty, or whether that link is due to the comorbidities that NAFLD patients may have; thus, more studies, including patients with chronic liver diseases and incorporating adjustment for age and prevalence of comorbidities, are a necessity.

Concluding remarks

Since patients with MetS seem to have a higher prevalence of frailty regardless of demographic parameters, the global epidemic spread of obesity and T2DM, 2 major components of the MetS, raises some concern, considering the vast pool of people who could potentially suffer from frailty and its complications. Besides MetS, frailty phenotype as the end-manifestation of an individual's accumulation of deficits is strongly related to other comorbidities, such as CVD, T2DM and CKD, that ultimately result in a hypo-nutritional status and hormonal dysregulation. As the prevalence of those comorbidities is higher among NAFLD as compared to non-NAFLD patients, it is expected that the former would have a higher likelihood of being frail. To this end, they may have a prolonged hospitalization period that makes them even more vulnerable to intra-hospital complications, as well as imposing a higher financial burden on national healthcare systems.

Moreover, NASH compared to ALD patients seem to display a higher risk of delisting, while being on the LT waiting list, since frailty modifies the patients' health status and could be associated with poorer waitlist survival. In clinical practice,

the evaluation of frailty seems to be especially important in patients awaiting LT. For instance, a frail NAFLD patient may have a greater hazard for waitlist mortality than a non-frail NAFLD one, even though the latter may be older. Therefore, beyond the comorbidities, modification of the distinctive features associated with frailty syndrome, such as sarcopenia, malnutrition, cognitive disorders and reduced physical activity, could have a beneficial impact on NASH candidates for LT. These interventions could lead to a shorter hospital stay, thus preventing hospital-acquired complications and reducing the hospitalization cost.

Whereas at first glance frailty may seem a consequence of NAFLD, further research studies are necessary to evaluate the physical and performance status of NAFLD patients, ideally on a longitudinal basis as well as comparing them with their non-NAFLD counterparts. Since the potential association between NAFLD and frailty has been recently evaluated, assessments of the potential independent contribution of NAFLD to frailty remain scarce. We should bear in mind that frailty screening in patients with NAFLD, focusing on older patients and those with end-stage liver disease, could be critical for early identification and optimized management of the comorbidities, personalized medical care, and eventually better survival of those patients.

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