

Perspective

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# Chronic obstructive pulmonary disease (COPD) and metabolic fatty liver syndromes: a dangerous but neglected liaison

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## Abstract

This perspective article aims at addressing the potential commonalities associated with chronic obstructive pulmonary disease (COPD) and the two metabolic fatty liver syndromes: nonalcoholic fatty liver disease (NAFLD) and metabolic (associated) fatty liver disease (MAFLD). To this end, we briefly review the definitions and burdens of COPD and NAFLD and highlight the differences in the diagnostic criteria of NAFLD and MAFLD. We also critically discuss the recent line of research trying to identify an association between COPD and NAFLD. Moreover, among the chief co-morbidities of COPD patients, we identify significant six that exert a major impact on the natural course of COPD: major cardiovascular events, cardiac arrhythmias, metabolic syndrome, obstructive sleep apnea, osteoporosis, and psychodepression. The potential role of NAFLD in each of these COPD co-morbidities is accurately examined based on published studies. We conclude that both COPD and NAFLD/MAFLD are heterogeneous systemic syndromes. While the complex mechanistic links underlying the association of NAFLD/MAFLD with COPD and its co-morbidities remain to be fully elucidated, we highlight that the diagnosis of metabolic fatty liver syndromes in patients with COPD might be clinically relevant, as it might allow identifying a subset of COPD individuals who, being at risk of severe clinical outcomes, would need more comprehensive treatment approaches.



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**Keywords:** Cardiac arrhythmias, heart failure, major cardiovascular events, metabolic syndrome, osteoporosis, psychodepression

## BACKGROUND

The commonalities and similarities shared by the lungs and the liver are impressive. These organs have a dual blood supply and serve similar physiological functions: antigen processing and regulation of energy homeostasis<sup>[1]</sup>. Chronic obstructive pulmonary disease (COPD) and fatty liver syndromes, [i.e., nonalcoholic fatty liver disease (NAFLD) and the more recently defined metabolic-associated fatty liver disease (MAFLD)], rather than discrete nosological entities, are best conceptualized as complex, chronic, systemic, and non-transmissible syndromes exhibiting a high grade of phenotypic variability and poorly predictable clinical courses<sup>[2,3]</sup>.

Despite these commonalities and similarities, the clinical impact of the association of COPD and NAFLD/MAFLD is a relatively under-investigated arena: a PubMed Research of literature conducted on 21 January 2022 (NAFLD[Title/Abstract]) AND (COPD[Title/Abstract]) identified as few as 11 results (theses, cross-references, and other relevant references directly identified by the authors represent the basis of the present perspective article). Although the topic is understudied and probably underrated, we believe that both COPD and NAFLD/MAFLD are associated with systemic chronic inflammation and oxidative stress, with the ensuing risk of accelerated atherogenesis and cancer<sup>[1]</sup>.

On these grounds, this perspective article discusses the evidence calling for more extensive research to ascertain the implications of co-morbid NAFLD/MAFLD among COPD individuals and vice versa.

## COPD

COPD is characterized by chronic respiratory symptoms, particularly progressive exertional dyspnea, which in up to one-third of patients is associated with chronic cough and sputum<sup>[4]</sup>. According to guidelines, the diagnosis should be confirmed by the presence of poorly reversible airflow limitation, i.e., post-bronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>)/forced vital capacity (FVC) ratio < 0.7<sup>[4]</sup>. However, in clinical practice, and even in hospitalized patients, the diagnosis of COPD is mainly based on the presence of chronic respiratory symptoms and/or their exacerbations, smoking habits, age, or previous/ongoing treatment with COPD drugs, particularly inhaled long-acting bronchodilators and/or steroids, or their combination. COPD identifies a heterogeneous group of patients who, while sharing the common denominator of post-bronchodilator airflow limitation, also have variable phenotypical, pathological, and pathophysiological features<sup>[5]</sup>. Consistently, COPD has a complex natural history. This may start in early life and progress slowly, manifesting itself and being diagnosed and treated almost invariably after the age of 40, with cigarette smoking being the strongest risk factor for most subjects from industrialized countries<sup>[5]</sup>. Occupational, environmental, and indoor pollution are major risk factors, particularly in developing countries. Although a large variety of different established and emerging etiologic factors<sup>[6]</sup> embracing genetic determinants (e.g.,  $\alpha$ 1-antitrypsin deficiency), exogenous (smoking, biomass fuels, occupational, or indoor pollutants), infective (viral, and bacterial), or endogenous factors (past infection of the lung, history of asthma and abnormal lung development, and abnormal inflammatory reaction of the airways) interacting throughout the life cycle, no etiological agent is found in a large fraction of spirometrically diagnosed COPD cases<sup>[5,7]</sup>. Additionally, owing to the large variety of concomitant chronic diseases, COPD should best be envisaged as a syndrome rather than a single disease entity<sup>[5,7]</sup> whose variable clinical phenotypes are prone to manifest different natural histories as a function of the variable comorbidity spectrum<sup>[7,8]</sup>. In particular, lung cancer and heart disease are the two most important co-

morbidities associated with COPD mortality<sup>[9]</sup>. In agreement, COPD is considered the pulmonary chronic component of chronic multi-morbidity<sup>[4,10,11]</sup>, as it is associated in > 90% of the patients<sup>[12]</sup> with at least one concomitant chronic disease mostly due to the same risk factors of all components of multi-morbidity, i.e., aging<sup>[13]</sup>, smoking<sup>[4]</sup>, alcohol consumption, physical inactivity<sup>[14]</sup>, and/or early events, such as prematurity and low birth weight, respiratory infections, (e.g., respiratory syncytial virus), and asthma<sup>[15,16]</sup>.

COPD is associated with high and increasing mortality globally<sup>[9]</sup> and has been projected to become one of the leading causes of mortality worldwide by 2021<sup>[4]</sup>. In Europe, the prevalence of COPD reportedly ranges between 4% and 10% in adults, with an expected increase of disease burden in the near future, mostly among older populations<sup>[4,17]</sup>, and is one of the most frequent causes of hospitalization and in-hospital mortality<sup>[18]</sup>.

The most common and best examined chronic COPD co-morbidities are cardiovascular (arterial hypertension, chronic heart failure, ischemic heart disease, cardiac arrhythmias<sup>[19,20]</sup>, cerebrovascular disease<sup>[21]</sup>), obstructive sleep apnea (OSA)<sup>[22]</sup>, osteoporosis<sup>[23]</sup>, depression<sup>[24]</sup>, metabolic syndrome (MetS) and its individual features (type 2 diabetes and obesity)<sup>[25,26]</sup>, and lung cancer<sup>[27]</sup>.

While the prevalence of individual co-morbidities widely varies across different populations<sup>[28]</sup>, those listed above have been shown to have a direct impact on the clinical course of COPD. Indeed, in COPD, they are associated with an increased risk of exacerbations and hospitalizations<sup>[29,30]</sup>, increased health care costs<sup>[31-33]</sup>, as well as an increased risk of death<sup>[34-36]</sup>. Similar to the co-morbidities of all other chronic diseases, COPD co-morbidities are largely under-diagnosed and under-treated<sup>[37]</sup>, unless actively searched for<sup>[12]</sup>.

Chronic systemic inflammation, a common feature of most of the above co-morbidities, has been hypothesized to be a key factor linking COPD with its co-morbidities<sup>[38,39]</sup>. Interestingly, NAFLD/MAFLD, epidemiologically and clinically prevailing entities in the chronic liver disease (CLD) spectrum, are deemed to be strong risk factors for the future development of chronic cardio-metabolic diseases and other diseases, mainly because they are associated with low-grade chronic inflammation and increased oxidative stress<sup>[40,41]</sup>.

## CHRONIC LIVER DISEASES AND COPD

CLD is an etiologically, clinically, and histologically heterogeneous group of disorders spanning steatosis, steatohepatitis, chronic hepatitis, cirrhosis, and liver cancer. Collectively, CLD accounted for 287,000 deaths in Europe in 2019 (95%CI: 268,000-306,000), and 63,500 (58,916-67,530) of these were due to primary liver cancer<sup>[42]</sup>. These figures, compared to 1990, represent a 25% increase in all liver-related deaths and a 70% increase in deaths due to primary liver cancer<sup>[42]</sup>. Moreover, collectively, CLD ranks second only to ischemic heart disease as the leading cause of years of working life lost in Europe<sup>[42]</sup>.

While the awareness that prevalence and incidence of the above-mentioned concomitant chronic diseases as well as of their important impact on the outcomes of COPD has increased over time<sup>[28]</sup>, there are few published studies focusing on the relationship between liver diseases and COPD. The most striking - but not surprising - finding is that liver cirrhosis impacts on survival of patients with COPD<sup>[12]</sup>. However, the prevalence of liver cirrhosis among COPD patients is reportedly small<sup>[43]</sup>, and the effect on pulmonary function is predictable considering the clinical manifestations of the disease<sup>[43]</sup>. Of concern, the most authoritative document on COPD<sup>[4]</sup>, which highlights the importance of concomitant chronic diseases and has a separate chapter addressing co-morbidities, does not even mention liver diseases. This highlights the necessity to explore novel paradigms regarding the important role of hepatic conditions associated with COPD.

This apparent lack of interest from the pneumological field reflects our preliminary and incomplete understanding of the effect that most concurrent CLD cases have on respiratory function<sup>[43,44]</sup>, except the portal hepatopulmonary hypertension syndrome and hepatopulmonary syndrome. However, in the last few years, Viglino *et al.* published pioneering papers on the relationship between COPD and NAFLD, the most common chronic liver disease in the general population globally, which has a major impact on morbidity and mortality<sup>[45-48]</sup>.

In the first of their studies, they prospectively examined 111 adult patients with mild-to-severe COPD and, after excluding patients with cancer, significant alcohol consumption, and secondary causes of liver steatosis, assessed the prevalence and predictors of liver steatosis, nonalcoholic steatohepatitis (NASH), and fibrosis using Fibromax and a patented panel of three non-invasive serum biomarkers (SteatoTest for steatosis, NashTest for NASH, and FibroTest for fibrosis; BioPredictive SAS, Paris, France). Their data demonstrate that 41.4% of COPD patients had moderate to severe steatosis (as assessed by SteatoTest  $\geq 0.57$ ), 36.9% had borderline to definite NASH (NashTest  $> 0.25$ ), and 61.3% had fibrosis stage  $\geq$  F0-F1 (FibroTest  $\geq 0.22$ ), suggesting that progressive forms of NAFLD are significantly present in COPD<sup>[47]</sup>. Despite the limitations of the study design, as highlighted by one of us in the accompanying editorial<sup>[1]</sup>, this was the first accurate estimate of the prevalence of NAFLD in COPD patients. In addition, the study described the metabolic abnormalities associated with NAFLD, confirming that NAFLD may indeed be a common co-morbidity in patients with COPD. Considering these results, the authors speculated that NAFLD might further increase the risk of future morbidity and mortality due to co-morbidities in COPD patients<sup>[47]</sup> and, therefore, should be searched for and possibly treated in patients with COPD and vice versa.

This recommendation was confirmed in a more recent intriguing post hoc analysis of one of the pillar studies in the field of COPD, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE)<sup>[49]</sup>. In their analysis, Viglino *et al.*<sup>[50]</sup> measured the density of the liver in the HRCT scans as a marker of liver steatosis. Liver density measured by computed tomography (CT) scan is an imaging proof of liver steatosis, with lower liver densities reflecting more fat infiltration and a liver density of 40 Hounsfield units (HU) corresponding to 30% fat accumulation. The relationship between this measurement and the Fibromax-based markers is unknown, and therefore a direct comparison of the prevalence of steatosis with previous studies could not be made. In addition, because parameters such as alcohol and liver enzymes were not collected in the ECLIPSE study, the results obtained with CT scan density measurement could not be used to assess the prevalence and role of NAFLD, NASH, and fibrosis.

Nonetheless, the study provided interesting results. While the prevalence of severe steatosis was not different between COPD patients (4.7%) and control “healthy smokers” and non-smokers (5.2%), in patients with COPD, the lowest liver density quartile compared to the highest liver density quartile was associated with coronary artery disease and stroke, after age and sex adjustment, suggesting that a low liver density (i.e., more severe steatosis) is a risk factor for cardiovascular co-morbidities in the COPD population<sup>[50]</sup>. This finding is in full agreement with a large body of NAFLD literature (such as discussed below). This specific study<sup>[50]</sup> may envisage a novel line of research in as much as CT scan assessed liver density may provide a unique opportunity to evaluate the degree of liver steatosis among the ever-increasing cohort of COPD patients who are undergoing HRCT-scan to better assess COPD (e.g., to characterize emphysema and patient candidacy to lung volume reduction surgery<sup>[51,52]</sup>), to evaluate other co-morbidities (e.g., coronary artery calcifications, pulmonary hypertension, and osteoporosis<sup>[53]</sup>), and for screening of lung cancer. This last objective is undoubtedly reinforced by the recent encouraging results<sup>[54]</sup> and the recommendations issued by the US Preventive Services Task Force<sup>[55]</sup>. This more liberal use of CT scans will provide pneumologists with a unique opportunity to conduct a systematic, non-invasive assessment of liver

steatosis and its pathophysiological and clinical consequences among COPD patients. Similarly, retrospective analysis of large ongoing observational studies in smokers and COPD patients (e.g., COPDgene and SPIROMICS)<sup>[56,57]</sup> that include CT scan and several biomarkers might extend the pivotal observations of Vestbo *et al.*<sup>[49]</sup>.

Considering that both COPD and MAFLD are risk factors for the future development of severe chronic diseases, hospitalizations, and premature mortality, we strongly believe that the co-existence of these two diseases is expected to identify a specific and novel cardio-metabolic “risky” COPD phenotype. Confirmation of our hypothesis would implicate an active search for and management of concomitant diseases through a holistic approach, even though the supporting evidence of its cost-benefit ratio is still elusive.

## NAFLD CO-MORBIDITIES: EPIDEMIOLOGICAL ASSOCIATIONS

NAFLD defines a wide-ranging clinico-pathological spectrum of alcohol-like liver changes spanning from steatosis (i.e., intrahepatocyte fatty changes > 5%) to NASH (i.e., steatosis associated with cellular degeneration and variable amounts of inflammatory and fibrotic changes) to cirrhosis and hepatocellular carcinoma (HCC)<sup>[58]</sup>. By definition, these conditions are histologically identified in individuals who do not have any competing causes of (steatogenic) liver disease, notably including alcohol, and are mutually and bi-directionally associated with MetS and its individual features<sup>[59]</sup>.

The average prevalence of NAFLD is 23.7% (95%CI: 16.1%-33.5%) of the general population in Europe, where it is rapidly becoming a leading cause of liver-related mortality and projected to become the leading cause of end-stage liver disease<sup>[42]</sup>. These impressive epidemiological figures exact high healthcare expenditures owing to direct and indirect costs across European countries and the USA<sup>[60]</sup>.

Similar to COPD, NAFLD is a systemic syndrome rather than a single disease entity. This occurs due to the disease’s pathogenic, pathological, and clinical variability. For example, there are “genetic” and “metabolic” NAFLD types<sup>[61]</sup>; NAFLD is common in the obese, but also a “lean NAFLD” phenotype has been precisely characterized<sup>[62]</sup>. As regards the hepatic spectrum of disease, there is a variability of patho-mechanisms, and a variable susceptibility to disease progression over time, ranging from individuals with mild, stable disease to individuals with rapid fibrosis progression<sup>[63]</sup>. In addition, the mechanisms of development of HCC are incompletely understood<sup>[64]</sup>. Further to this *hepatic spectrum* of disease, some individuals will manifest principally *extra-hepatic manifestations and complications* of NAFLD, which span from cardio-metabolic to certain extra-hepatic cancer types<sup>[65-67]</sup>.

Forty years after the term “NASH” was used for the first time, aimed at giving NAFLD a “positive” definition, namely by using the “metabolic” qualification as opposed to the “negative” nonalcoholic attribute, experts have recently proposed to rename NAFLD as MAFLD [i.e., metabolic (dysfunction) associated fatty liver disease]. Reception of the novel MAFLD nomenclature, although promptly endorsed by many, remains an ongoing process<sup>[68]</sup>. Compared to NAFLD, MAFLD is a shift in the paradigm, emphasizing the major causal role of metabolic dysfunction. Additionally, analysis of the common features shared by both NAFLD and MAFLD, together with the potential changes in epidemiology, pathophysiology, diagnosis, and pharmacotherapy of the newly defined MAFLD, as compared to NAFLD, suggests that, in the future, the broader MAFLD syndrome will likely be increasingly used as a standard to identify subjects at risk of progressive hepatic and extra-hepatic disease<sup>[40,69,70]</sup>.

We firmly believe that the diagnosis of NAFLD/MAFLD in any given COPD patient has a potentially strong biological and clinical impact, given that NAFLD is a definite risk factor for the development of many of the above-described COPD cardiovascular co-morbidities. For example, tipping the balance in favor of a strong physiological impact of MAFLD on COPD course, Miao *et al.*<sup>[71]</sup>, by evaluating as many as 2543 Chinese adults undergoing health check-up examinations, found that, after adjusting for confounding factors (age, sex, adiposity, smoking, and alcohol) and compared to those with NAFLD, individuals with MAFLD had a significantly lower predicted FVC (FVC:  $88.27 \pm 17.60\%$  vs.  $90.82 \pm 16.85\%$ ,  $P < 0.05$ ) and FEV<sub>1</sub> ( $79.89 \pm 17.34$  vs.  $83.02 \pm 16.66\%$ ,  $P < 0.05$ ). As expected, the most advanced MAFLD forms were associated with more severe spirometric findings such that, for each one-point increase in the non-invasive fibrosis biomarker FIB-4, FVC diminished by 0.507 [95% confidence interval (CI): -0.840 to -0.173,  $P < 0.003$ ], and FEV by 0.439 (95%CI: -0.739 to -0.140,  $P < 0.004$ ). Interestingly, statistical analysis conducted separately by sex yielded unchanged results<sup>[71]</sup>.

To illustrate our thesis further, here we discuss NAFLD's major role in modulating the risk of six among the most common and clinically relevant COPD co-morbidities: major cardiovascular events, cardiac arrhythmias, MetS, OSA, osteoporosis, and psychodepression. Collectively, these COPD systemic co-morbidities are major modifiers of both quality of life and reduced life expectancy among COPD patients, thus supporting the potential role of NAFLD in the clinical course of COPD patients.

### Major cardiovascular events

A consistent line of research has identified NAFLD as a strong risk factor for fatal and non-fatal cardiovascular events. The best evidence for this was recently published by Mantovani *et al.*<sup>[65]</sup>. In their updated meta-analysis of 36 longitudinal studies (with a median 6.5-year follow-up) with aggregate data on 5,802,226 middle-aged individuals NAFLD (diagnosed histologically, with imaging techniques, or based on International Classification of Diseases (ICD) codes, in the absence of competing causes of steatosis, notably including alcohol either  $>20$  g/day for either sex, or  $> 30$  g/day for men and  $> 20$  g/day for women) was associated with a moderately increased risk of fatal or non-fatal cardiovascular disease (CVD) events [pooled random-effects hazard ratio (HR): 1.45, 95%CI: 1.31-1.61;  $I^2 = 86.18\%$ ]. This risk markedly increased in parallel with the stage of liver fibrosis (pooled random-effects HR 2.50, 95%CI 1.68-3.72;  $I^2 = 73.84\%$ ), was independent of confounding factors (age, sex, adiposity measures, diabetes, and other common cardio-metabolic risk factors), and was not modified by sensitivity analyses. Given that the proportion of concurrent COPD among these NAFLD individuals is unknown, more studies are necessary to identify the additive risk on cardiovascular morbidity and mortality resulting from the association of both NAFLD and COPD in the same individuals.

### Cardiac arrhythmias

Interestingly, NAFLD is also inherently associated with the risk of cardiomyopathy and cardiac arrhythmias - and particularly atrial fibrillation (AF)<sup>[72]</sup> - which are also common among COPD patients. Supporting this notion, Gong *et al.*<sup>[73]</sup>, in their meta-analytic review of 19 published studies totaling 7,012,960 adult participants, found that NAFLD (diagnosed based on the ICD code, liver biopsy, imaging techniques, or fatty liver index in the absence of competing causes of CLD, notably including significant alcohol consumption) was independently associated with higher risks of AF [Odds ratios (OR): 1.71, 95%CI: 1.14-2.57; HR: 1.12, 95%CI: 1.11-1.13], prolonged QT interval (OR: 2.86, 95%CI: 1.64-4.99), premature atrial/ventricular contraction (OR: 2.53, 95%CI: 1.70-3.78), and heart block (OR 2.65, 95%CI: 1.88-3.72). Completing the spectrum of cardiovascular manifestations, NAFLD is reportedly associated with an increased risk of heart failure (HF) independent of confounding clinical and demographic factors. In agreement, Fudim *et al.*<sup>[74]</sup>, retrospectively evaluating a cohort of Medicare beneficiaries, observed that, over a mean 14.3-month follow-up, patients with baseline NAFLD had a significantly higher risk of new-onset

HF in adjusted analyses [adjusted HR (95%CI), 1.23 (1.18-1.29)], and the risk of HF was stronger for HF with preserved ejection fraction [adjusted HR (95%CI): 1.24 (1.14-1.34)] than with HF with reduced ejection fraction [adjusted HR (95%CI): 1.09 (0.98-1.2)]. Based on their comprehensive analysis of the published evidence, Mantovani *et al.*<sup>[75]</sup> recently concluded that “*there is a strong association between NAFLD and increased risk of new-onset HF, regardless of the presence or absence of T2D and other co-existing cardiometabolic risk factors. The magnitude of this risk increases with the severity of liver disease in NAFLD (especially with higher fibrosis stage)*”. Again, specific studies should prospectively evaluate the predicted unfavorable interaction of concurrent NAFLD and COPD in increasing the risk of HF.

### Metabolic syndrome

The relationship between NAFLD and MetS is close, mutual, and bi-directional, as supported by several lines of evidence (reviewed in Ref.<sup>[59]</sup>). For example, Zhang *et al.*<sup>[76]</sup>, using a simplified Bayesian network analysis constructed to infer the reciprocal causality, identified mutual associations between NAFLD (steatosis was diagnosed with ultrasonography) and MetS in a Chinese population. Based on a prospective large-scale health check-up database, they found that, in reciprocal causality, the effect of MetS on NAFLD was higher than that of NAFLD on MetS. This study, together with others, has led to the conclusion that NAFLD is more than “*the hepatic manifestation of metabolic syndrome*” but may also serve as the precursor of MetS<sup>[77-79]</sup>. Confirming this notion, a meta-analytic study conducted by Ballestri *et al.*<sup>[80]</sup> on 20 published studies found that NAFLD was associated with an increased risk of incident MetS over a median five-year follow-up period (range, 3-14.7 years) with a pooled relative risk of 1.80 (95%CI: 1.72-1.89). The risk varied based on the technique used to capture NAFLD ranging from 1.80 (95%CI: 1.72-1.89) for alanine aminotransferase (last vs. first quartile or quintile) to 3.22 (95%CI: 3.05-3.41) for ultrasonography. Intermediate values of risk were associated with NAFLD diagnosed with GGT [1.98 (95%CI: 1.89-2.07)]<sup>[80]</sup>. The risk of progression from NAFLD at baseline to incident type 2 diabetes (T2D) in the medium term is also substantial. Mantovani *et al.*<sup>[66]</sup> conducted a meta-analysis of 33 studies totaling 501,022 individuals (30.8% with NAFLD), and, among these, 27,953 cases had incident diabetes over a median of five-year follow-up. This study has two findings: Firstly, NAFLD patients had a higher risk of incident diabetes (HR: 2.19, 95%CI: 1.93-2.48;  $I^2 = 91.2\%$ ). Secondly, the risk of incident diabetes was higher among those with more “severe” NAFLD (HR: 2.69, 95%CI: 2.08-3.49;  $I^2 = 69\%$ ) and also markedly increased across the severity of liver fibrosis stages (HR: 3.42, 95%CI: 2.29-5.11;  $I^2 = 44.6\%$ ). Interestingly, all risks were independent of confounding factors (age, sex, adiposity measures, and other common metabolic risk factors), sensitivity analyses did not alter these findings, and no significant publication bias was disclosed<sup>[66]</sup>. These findings are clinically relevant given that both T2D and MetS are definite risk factors for the fibrotic progression of NAFLD and its transformation to HCC in a proportion of cases<sup>[81,82]</sup>. Specific studies should investigate the role, if any, of concurrent COPD in modulating this mutual association of progressive NAFLD forms with the MetS.

### Obstructive sleep apnea

OSA describes repeated episodes of partial/total loss of respiratory airflow, which occur while sleeping and are associated with upper airway collapse in inspiration, strenuous breathing. And ominous cardio-metabolic consequences<sup>[83]</sup>. Musso *et al.*<sup>[84]</sup>, by submitting 18 cross-sectional studies overall totaling 2183 participants to a meta-analytic review, showed that pooled ORs of OSA for the presence of NAFLD (diagnosed with histology, imaging, and altered liver enzymes) were 2.01 (95%CI: 1.36-2.97), 2.99 (1.79-4.99), 2.36 (1.46-3.82), and 2.60 (1.88-3.61), respectively. Pooled ORs of OSA for NASH, fibrosis-any stage, or advanced fibrosis in biopsy-proven NAFLD patients were 2.37 (1.59-3.51), 2.16 (1.45-3.20), and 2.30 (1.21-4.38), respectively. These findings remained unaltered after correction for confounding factors [age, sex, and body mass index (BMI)] indicating that OSA was associated with an increased risk of NAFLD, NASH, and hepatic fibrosis<sup>[84]</sup>. Although this study suggests that patients with OSA should best be screened

for NAFLD and NASH, it fails to analyze the patho-mechanisms underlying these associations. Bringing these findings further, Sundaram *et al.*, in a selected cohort of 36 adolescents with NAFLD and 14 lean controls, demonstrated that nocturnal hypoxia was a trigger for localized hepatic oxidative stress, an important factor associated with the progression of NASH and liver fibrosis in obese pediatric patients<sup>[85]</sup>. This study agrees with the finding that, in adults, OSA is indeed associated with NASH and advanced liver histology<sup>[86]</sup>. The evidence discussed above supports the notion that NAFLD forms with more advanced fibrosis are exposed to increased cardiovascular risk<sup>[65]</sup>. In this connection, OSA may trigger a vicious cycle leading to increased CVD risk via progressive liver fibrosis. Bettini *et al.*<sup>[87]</sup> cross-sectionally studied the relationships among OSA severity, steatosis extent in NAFLD, and cardiovascular risk in a cohort of 110 adult patients aged 18-65 years with OSA. The data show that the degree of steatosis in patients with NAFLD was significantly correlated with the severity of OSA, carotid intima-media thickness measurements, ICAM-1, and Lp(a), underscoring the need to screen for NAFLD in patients with OSA to ensure prompt risk stratification and intensive management approaches<sup>[87]</sup>.

### Osteoporosis

Although chronic inflammation, a definite feature of NAFLD, is a major risk factor for osteoporosis, and some studies have supported the association between low bone mineral density (BMD) and NAFLD, collectively, the data regarding this association are conflicting thus far. Upala *et al.*<sup>[88]</sup>, therefore, conducted a meta-analytic review of eleven observational studies articles involving 1276 participants (638 with NAFLD) to ascertain the association between NAFLD and BMD in adults ( $\geq 18$  years of age). These individuals had no other cause of liver disease, osteoporosis, or pathological bone disease at baseline. The main meta-analysis failed to demonstrate any significant difference in BMD between NAFLD patients and controls; of all variables analyzed, BMI had the strongest and most significant predictive effect on the difference in BMD<sup>[88]</sup>. Given that these authors concluded that further studies were required to fully show this relationship, Mantovani *et al.*<sup>[89]</sup> repeated a meta-analytic study in children or adolescents in whom NAFLD was diagnosed by either imaging or histology, and BMD Z-score was measured by dual-energy X-ray absorptiometry. Based on eight (observational cross-sectional or case-control) studies enrolling 632 children and adolescents (mean age, 12.8 years), 357 of whom had NAFLD; they were able to show significant differences in whole-body or lumbar BMD Z-scores between children/adolescents with and without NAFLD ( $n = 6$  studies; pooled WMD: -0.48; 95%CI: 0.74 to -0.21;  $I^2 = 55.5\%$ ), as well as between those with biopsy-proven NASH and those with no-NASH ( $n = 4$  studies; pooled WMD: -0.27; 95%CI: -0.40 to -0.13;  $I^2 = 0\%$ ). The aforementioned WMDs in BMD Z-scores were independent of confounding factors (age, sex, race/ethnicity, and BMI); findings were not modified by sensitivity analyses, and no evidence of significant publication bias was detected. These authors concluded that the presence and severity of NAFLD were significantly associated with reduced whole-body BMD Z-scores in children and adolescents<sup>[89]</sup>. However, given the observational design of the original studies submitted to a meta-analytic evaluation, causality remains unproven. Additionally, specific studies should be designed and conducted to explore the triangular association of reduced BMD, COPD, and NAFLD in adults.

### Depression

The observation that poor diet, inadequate physical activity, and sedentary behavior are shared features of both NAFLD and psycho-depression<sup>[90]</sup> supports the rationale for conducting specific studies evaluating the association linking the latter to NAFLD in a proportion of cases. Gu *et al.*, based on the analysis of seven published articles (most of which were cross-sectional), found that NAFLD patients had a significantly increased risk of depression (pooled OR = 1.13, 95%CI: 1.03-1.24,  $P = 0.007$ )<sup>[91]</sup>. Similarly, patients with depression also had a significantly increased risk of developing NAFLD (pooled OR = 1.46, 95%CI: 1.15-1.85,  $P = 0.002$ )<sup>[89]</sup>. Given the important clinical implications for the treatment of depression as both a cause and a consequence of NAFLD, this meta-analysis calls for prospective longitudinal studies to ascertain the

cause-effect relationships. Moreover, COPD individuals with NAFLD are expected to be prone to an increased risk of depression, which remains to be ascertained with well-conducted prospective studies.

## RESEARCH AGENDA

COPD and MetS are commonly associated in clinical studies, and patients are unaware of this double morbidity<sup>[92]</sup>. COPD and NAFLD/MAFLD are both complex syndromes with systemic manifestations whose co-morbidities extend far from the primarily affected organs, the lungs and liver, respectively. However, studies conducted on NAFLD patients have thus far neglected to define the proportion of patients who had concurrent COPD. From the side of COPD, which is often associated with cardio-metabolic co-morbidities, there is limited evidence to confirm/reject the notion that concurrent NAFLD carries, as it is logical to postulate, an increased risk of fatal and non-fatal cardiovascular events, HF, and metabolic complications. Of concern, chronic hypoxia and smoking, two definite pathophysiological features of COPD, both have the potential to trigger hepatic fibrogenesis, thereby promoting the development of progressive NAFLD forms<sup>[93]</sup>. These, in turn, are burdened with the highest risks of cardio-metabolic complications, therefore perpetuating a dangerous vicious cycle of progressive liver disease associated with COPD complications. Finally, the complex mechanistic links underlying the association of NAFLD, COPD, and its co-morbidities and complications must be fully elucidated. These include, among others, those molecular links associating NAFLD with accelerated atherogenesis and increased risk of cardiovascular disease such as systemic and hepatic metabolic derangements; intestinal dysbiosis; perturbed cellular and sub-cellular pathways; adipokines and pro-inflammatory cytokines; NAFLD-related liver inflammation, fibrosis and hepatocyte injury; and chronic hypoxia<sup>[94]</sup>.

## CONCLUSIONS

We critically discuss the grounds supporting the ominous and neglected association of COPD with metabolic fatty liver syndromes: our analysis calls for filling in research gaps. To accomplish these investigation priorities, we advocate more systematic collaboration between COPD physicians and NAFLD clinicians aimed at conducting systematic surveys exploring NAFLD features among those with COPD as well as COPD among NAFLD patients. In this regard, two elements of novelty are predicted to immensely facilitate such studies: the recent proposal to adopt the more descriptive MAFLD nomenclature (which, at variance with NAFLD, does not request liver biopsy or the exclusion of competing causes of steatosis)<sup>[40]</sup>, together with the increased availability of liver imaging studies among COPD individuals submitted to CT scans in the setting of lung cancer screenings<sup>[55]</sup>.

## DECLARATIONS

### Authors' contributions

Conceived the study design, performed bibliographic research and wrote the first drafts of the manuscript: Lonardo A, Beghe B, Fabbri L M

Revised the first drafts of the manuscript and addressed Reviewers' comments: Lonardo A, Beghe B, Fabbri L M

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for Publication

Not applicable.

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