Title page

Metabolic dysfunction-associated fatty liver disease is associated with greater impairment of lung function than nonalcoholic fatty liver disease

Short title: MAFLD and impaired lung function

Authors' name

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Abbreviations

ANOVA = analysis of variance, BMI = body mass index, BUN = blood urea nitrogen, CI = confidence interval, COPD=chronic obstructive pulmonary disease, DBP = diastolic blood pressure, FEV_1 = forced expiratory volume measured in the first second of exhalation ; FVC= forced vital capacity; FPG = fasting plasma glucose, HDL= high-density lipoprotein, LDL = low-density lipoprotein, NAFLD = non-alcoholic fatty liver disease, non-MD-NAFLD = non-metabolic dysfunction-associated NAFLD, SBP = systolic blood pressure, SD = standard derivation, TC = total cholesterol, TG = triglyceride, HOMA-IR = homeostasis model assessment of insulin resistance, eGFR = estimated glomerular filtration rate, MAFLD = metabolic associated fatty liver disease, NFS = NAFLD fibrosis score,

FIB-4 = fibrosis 4, T2DM = type 2 diabetes mellitus.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions:

Lei Miao, Cheng-Shui Chen and Ming-Hua Zheng designed the study analyzed the data. Li-Sha Guo, Ming-Yang Zhu, Hui Cai, Zhi-Wei Xu, Shuan-Ying Yang and Hai Lin, Zhe Cheng collected the data. Li Yang and Huai Zhang performed statistical analyses. Yu-Ping Li, Qiang-Qiang Shi and Teng-Fei Zhou contributed to writing and proof reading the manuscript. Giovanni Targher and Christopher D. Byrne contributed to writing and proofreading the manuscript. All authors contributed to the manuscript for important intellectual content and approved the final submission.

Abstract

Background/aims: We compared lung function parameters in nonalcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated fatty liver disease (MAFLD), and also examined the association between lung function parameters and fibrosis severity in MAFLD.

Methods: In this cross-sectional study, we randomly recruited 2,543 middle-aged individuals from 25 communities across four cities in China during 2016 and 2020. All participants received a health check-up including measurement of anthropometric parameters, biochemical variables, as well as liver ultrasonography and spirometry. The severity of liver disease was assessed with the fibrosis (FIB)-4 score.

Results: The prevalence of MAFLD and NAFLD was 20.4% (n=519) and 18.4% (n=469), respectively. After adjustment for age, sex, adiposity measures, smoking status and significant alcohol intake, subjects with MAFLD had a significantly lower percent predicted forced vital capacity (FVC: 88.27±17.60% vs. 90.82±16.85%, $P<0.05$) and lower forced expiratory volume in one second (FEV_1: 79.89±17.34 vs. 83.02±16.66%, $P<0.05$) than those with NAFLD. Furthermore, MAFLD with increased FIB-4 score was significantly associated with decreased lung function parameters, i.e. for each 1-point increase in FIB-4, FVC was diminished by -0.507 (95% CI [-0.840, -0.173], P=0.003) and FEV_1 was diminished by -0.439 (95% CI [-0.739, -0.140], P=0.004), after adjustment for sex, age, adiposity measures, smoking status, significant alcohol intake, pre-existing diabetes and other potential confounding factors. The results remained unchanged even when we performed

separate statistical analyses for men and women.

Conclusions: MAFLD is significantly associated with a greater impairment in lung function parameters than NAFLD.

Key words: MAFLD, NAFLD, Lung function, Liver fibrosis score

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) has become one of the most common causes of chronic liver disease, affecting up to ~30% of the world's adults [1]. Convincing evidence indicates that NAFLD is a "multisystem" disease that affects multiple extra-hepatic organ systems, including the respiratory system, cardiovascular system, endocrine system, and other organ systems [2-6]. Jung et al. first reported that NAFLD was associated with decreased lung function [7]. Although decreased lung function is associated with older age, obesity, smoking, and air pollution[8] in recent years, some observational studies have also reported an association between NAFLD and lung function [7, 9-17]. Lonardo et al.[18] also recently proposed that it would be the time to "cross the diaphragm between NAFLD and chronic obstructive pulmonary disease (COPD)". A meta-analysis of six observational studies (133,707 participants of predominantly Asian ethnicity) reported a significant association between NAFLD and impaired lung function [19]. Moreover, it has been reported that individuals with NAFLD had significant reductions in both FVC and FEV_1[20, 21], which worsened with the severity of NAFLD, especially with higher fibrosis stage [9, 16, 22] . A Korean cohort study also showed that the risk for incident NAFLD increased with decreasing quartiles of both FEV_1 (%) and FVC (%), regardless of smoking history, over a mean follow-up of ~6 years [15].

The current definition of NAFLD requires the exclusion of significant alcohol consumption and other secondary causes of chronic liver disease. More recently, an

international panel of experts has proposed to change the terminology from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD), and also proposed a new set of diagnostic criteria to better define this common liver disease[23-25]. Therefore, MAFLD has been proposed as a more suitable definition to describe the fatty liver disease related to underlying metabolic dysfunction[26-28], and a more accurate definition for identifying those patients, who are at higher risk of developing extra-hepatic complications, such as cardiovascular disease and chronic kidney disease[29, 30].

However, to our knowledge, whether the renaming of NAFLD to MAFLD better identifies patients, who are also at higher risk of impaired lung function, is currently unknown. Therefore, the major aim of this large cross-sectional study was to compare lung function parameters in NAFLD and MAFLD populations, and to examine the association between lung function parameters and fibrosis severity in MAFLD.

2.Materials and Methods

2.1 Study design and data collection

Between the years 2016 and 2020, we have run a non-communicable and chronic disease management national program referred to as 'Identifying Risk Factors and Pathogenesis of Chronic Obstructive Pulmonary Disease (COPD) Based on Clinical bioinformatics Technology and Epidemiology'[31].

The program has randomly recruited a total of 8,375 individuals aged 40 years or older from 25 communities across four cities (Wenzhou, Shanghai, Fuzhou, and Zhengzhou) in Central and Southeast China. In the program, there were 2,960 individuals, who had undergone both spirometry and liver ultrasound examinations. As detailed in **Figure 1**, for the purpose of this study, we excluded participants who meet the following criteria: 1) subjects who had acute or chronic lung diseases, except COPD; 2) those with lung cancers or other extra-pulmonary malignancies; and 3) those missing important clinical and laboratory data. As a consequence of these exclusion criteria, 2,543 adult individuals were included in the final analysis. The research was approved by the Institutional Review Board at each hospital involved in the study (NO. 2016134). All participants signed an informed consent to participate in the study.

At each visit, standardized self-administered questionnaires were administered to collect detailed information on demographic characteristics, alcohol consumption, smoking habit, physical activity, medical history and any clinical symptoms associated with lung diseases.

Serum lipids, liver enzymes, glucose, and other biochemical blood measurements were determined in all participants after an overnight fast, using standard laboratory procedures. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured standing with the

measurement taken horizontal to the floor at the midpoint between the lowest rib and the iliac crest. Hypertension was defined as systolic blood pressure (SBP) ⩾130 mmHg and diastolic blood pressure (DBP) ⩾85 mmHg and/or use of antihypertensive drugs. Type 2 diabetes mellitus (T2DM) was defined by a fasting glucose level ⩾7.0 mmol/L (⩾126 mg/dL) or hemoglobin A1c ⩾6.5% (⩾48 mmol/mol) and/or use of any glucose-lowering agents.

2.2 Criteria for diagnosing NAFLD and MAFLD

Experienced radiologists performed a liver ultrasonography in all participants. These radiologists were blinded to clinical and laboratory details of participants and captured liver images via a standard manner. Diagnosis of hepatic steatosis was mainly based on the increased echogenicity of the liver relative to the echogenicity of the renal cortex or spleen parenchyma[32].

Diagnosis of NAFLD was based on the evidence of hepatic steatosis and exclusion of significant alcohol consumption (defined as ⩾21 drinks/weeks for men and 14 drinks/weeks for women, respectively) and other competing causes for hepatic steatosis, as detailed in **Figure 1**[33].

Diagnosis of MAFLD was based on the evidence of hepatic steatosis (on ultrasonography) and presence of at least one of the following three metabolic risk factors: 1) overweight or obesity (i.e., BMI ⩾23 kg/m^2 for Asian people); 2)

established T2DM (according to diagnostic criteria reported above); or 3) metabolic dysregulation, i.e. defined by the presence of at least two of the following seven metabolic risk abnormalities: 1) waist circumference ⩾90 cm for men, and ⩾80 cm for women; 2) blood pressure ⩾130/85 mmHg or drug treatment; 3) triglycerides ⩾ 1.70 mmol/L (⩾150 mg/dL) or drug treatment; 4) high-density lipoprotein (HDL) cholesterol <1.0 mmol/L for men and <1.3 mmol/L for women; 5) prediabetes status (defined as fasting glucose levels between 5.6 and 6.9 mmol/L, or HbA1c between 5.7 and 6.4%); 6) a homeostasis model assessment-estimated insulin resistance (HOMA-IR) score ⩾2.5; and 7) plasma C-reactive protein levels >2 mg/L [24].

Lean subjects with NAFLD, who did not have T2DM or metabolic dysregulation (as reported above), were defined as having non-metabolic dysfunction-associated NAFLD (also abbreviated to non-MD-NAFLD throughout the text)[30].

Fibrosis 4 (FIB-4) score was utilized to non-invasively assess the presence of advanced liver fibrosis and it was calculated according to the following formula: age × AST (IU/L) / [platelet count ($\times 10^9$/L) × ALT (IU/L) $^{0.5}$[34, 35].

2.3 Spirometry

Trained medical personnel, who were blinded to clinical and laboratory details of participants, performed the spirometry, fulfilling the criteria of the American Thoracic Society (ATS)[36]. Forced vital capacity (FVC) and forced expiratory volume in 1 sec

(FEV_1) were recorded and predicted FEV_1 and FVC were calculated for each participant using published prediction equations [37].

2.4 Statistical analysis

Continuous variables were expressed as means ± standard deviation (SD), while categorical variables were expressed as percentages (%) or counts. The one-way analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical variables were used to compare differences between the groups. Separate statistical analyses were also performed by sex. Multivariable linear regression analyses were performed to examine the independence of associations between MAFLD and lung function tests after adjusting for age, sex, adiposity measures, smoking status, presence of significant alcohol intake (i.e. ⩾21 drinks/weeks for men and 14 drinks/weeks for women) and other potential confounding variables. In these analyses, data were expressed as beta coefficients and 95% confidence intervals (CIs). All statistical tests were two-sided and a P-value<0.05 (two-tailed) was considered to be statistically significant. SPSS version 22.0 was used to conduct the statistical analyses.

3. Results

3.1 Subjects characteristics

In total, 2,543 middle-aged Chinese subjects were involved in the study. The clinical and biochemical characteristics, as well as lung function parameters of these

participants are shown in **Table 1**. There were 519 (20.4%) individuals with MAFLD, whereas 469 (18.4%) individuals had NAFLD. Compared to the non-MAFLD group, individuals with MAFLD were younger and had higher levels of serum liver enzymes, white blood cell (WBC) count and total hemoglobin, as well as a significant impairment in lung function parameters, mainly FVC, predicted-FVC (%), and predicted-FEV_1 (%). Moreover, individuals with MAFLD also had a greater prevalence of metabolic syndrome, T2DM, dyslipidemia and hypertension. The two groups of individuals did not significantly differ by sex, smoking status, presence of prior COPD and FEV1/FVC ratio. Similarly, individuals with NAFLD also had a lower FVC, predicted-FVC (%), predicted-FEV1 (%) and a greater prevalence of metabolic syndrome, T2DM, and dyslipidemia compared to the non-MAFLD group. Conversely, there was no statistical difference for FEV1, FEV1/FVC ratio in these two groups of patients.

3.2 Lung function tests between MAFLD and NAFLD non-MD-NAFLD

Table 2 shows the comparison of lung function tests between subjects with NAFLD and different groups of subjects with MAFLD; In this table the differences in lung function tests were adjusted for age, sex, adiposity measures, smoking status and significant alcohol intake (by analysis of covariance). Compared with the NAFLD or non-MD-NAFLD groups, individuals with MAFLD had the lowest values of FVC, predicted-FVC (%), FEV1 and predicted-FEV1 (%). In addition, compared to MAFLD patients without T2DM, those with MAFLD and coexistent T2DM had

lower values of predicted-FVC (%) and predicted-FVC (%). Similarly, lung function tests of patients with MAFLD were worse even after stratification by obesity status (**Table 2**).

3.3 Relation between lung function tests and fibrosis severity

Table 3 shows the lung function tests stratified by increasing quartiles of FIB-4 score among subjects with MAFLD or NAFLD. The mean values of most lung function tests progressively decreased across FIB-4 quartiles both in subjects with NAFLD and in those with MAFLD.

Table 4 shows the unadjusted and adjusted changes in lung function tests for 1-point increase in FIB-4 score amongst patients with MAFLD. In univariable linear regression analyses (unadjusted model 1), the severity of liver fibrosis (as assessed by FIB4 score) was inversely related to FVC, $FEV_{1,}$ and predicted-FVC (%). As the FIB-4 score increased by one point, FVC (%) was diminished by -6.441 (95% CI [-12.032, -0.851]; P=0.024), FVC was diminished by -0.748 (95% CI [-1.002, -0.495]; P<0.001) and FEV1 was diminished by -0.587 (95% CI [-0.796, -0.378]; P<0.001), respectively.

As also shown in **Table 4**, these results remained unchanged in multivariable regression models adjusting for sex, age, prior COPD, smoking status and significant alcohol intake (adjusted models 2), as well as in regression models additionally

adjusting for adiposity measures, blood pressure, WBC count, total hemoglobin, serum transaminases, fasting glucose, and plasma lipid profile (adjusted models 3). For instance, in adjusted model 2, we found that each point increase in FIB-4 score was associated with a significant reduction in both FVC (-0.507 [-0.840, -0.173], P=0.003) and FEV_1 (-0.439 [-0.739, -0.140], P=0.004).

3.4 Lung function tests between MAFLD and NAFLD non-MD-NAFLD subjects, stratified by sex

Notably, the aforementioned results remained essentially unchanged even when we performed separate statistical analyses by sex. As shown in **supplementary Table S1, Table S2, Table S3**, and **Table S4**, we found that the trends in impairment of lung function parameters were essentially comparable in men and women with MAFLD, but the impairment in lung function parameters appeared to be greater in men with MAFLD (than in women with MAFLD), after adjusting for age ≥65 years, pre-existing COPD, smoking status, significant alcohol intake, adiposity measures, and other potential confounding factors (**Table S4**, adjusted model 3).

4.Discussion

The main findings of this large cross-sectional study were that both MAFLD and NAFLD were significantly associated with decreased lung function tests (i.e., FVC and FEV_1) in Chinese middle-aged individuals after adjustment for multiple potential

confounding factors, but the observed reduction in these lung function parameters appeared to be significantly greater in subjects with MAFLD than in those with NAFLD. Furthermore, the significant reduction in FEV1 and FVC in subjects with MAFLD increased progressively with the severity of liver fibrosis, as assessed non-invasively by FIB-4 score.

To the best of our knowledge, this is the first observational study that aimed to compare lung function parameters in NAFLD and MAFLD populations, and that examined the association between lung function parameters and MAFLD fibrosis severity (as assessed non-invasively by FIB-4 score). As summarized in **supplementary Table 5**, previous observational studies reported that NAFLD was associated with impaired lung function tests [9, 12, 19-21, 38], and that this association worsened with the histological severity of NAFLD, especially with higher fibrosis stage [16]. Moreover, some studies have shown a significant association between NAFLD and the presence of COPD or chronic restrictive pulmonary diseases [12, 15, 17]. Although most of the aforementioned studies were cross-sectional and NAFLD was diagnosed by ultrasonography, they support the existence of an association between NAFLD and COPD.

The precise pathogenic mechanisms underpinning the association between MAFLD and reduced lung function tests remain poorly understood to date. Both the lung and the liver are two highly vascularized organs with a dual blood supply, and both are

involved in antigen processing and are master regulators of energy homeostasis[18]. Thus, it might be hypothesized that MAFLD and its associated metabolic disorders (principally obesity and T2DM) may promote systemic chronic inflammation, increased oxidative stress, greater insulin resistance, and lipotoxicity [10, 39, 40], which may induce lung function impairment in the long-term, possibly through activation of bronchial inflammation, lung fibrosis and hypotrophy of airway respiratory muscles. As low-grade chronic inflammation is associated with both impaired lung function and NAFLD [41, 42], some studies have shown that increased plasma C-reactive protein concentrations are associated with impaired lung function [43-45]. In turn, impaired lung function may also promote greater insulin resistance, oxidative stress, and low-grade chronic inflammation, all of which may contribute to NAFLD progression[46, 47]. Nevertheless, future prospective cohort studies are required to better elucidate the direction of the relationship between impaired lung function and fatty liver disease.

Recently, an international panel of experts proposed the change in name and definition of NAFLD to MAFLD[48]. However, the criteria for diagnosing MAFLD and NAFLD are distinct and, to the best of our knowledge, there is currently no research related to MAFLD and lung function. Thus, given the emerging worldwide epidemic of this metabolic liver disease, it is important to ascertain if the newly proposed definition of MAFLD is able to better identify subjects with impaired lung function compared to the “old” NAFLD definition.

In our study, we were able to make some key observations. Firstly, both MAFLD and NAFLD definitions were associated with a significant reduction in lung function parameters in Chinese people, but this reduction was significantly greater in patients with MAFLD than in those with NAFLD. Secondly, patients with MAFLD and T2DM (or overweight/obesity) had decreased lung function parameters compared with their counterparts without T2DM or overweight/obesity. Thirdly, patients with MAFLD and increased FIB-4 score had worse lung function parameters, even after adjusting for sex, age, smoking status, significant alcohol intake, BMI, pre-existing T2DM and other potential confounding factors. Fourthly, patients with non-MD-NAFLD had the best lung function parameters compared with the MAFLD and NAFLD groups. Since patients with MAFLD have various metabolic conditions (especially overweight/obesity and T2DM) that may adversely affect lung function, it is clinically important to manage and control the underlying metabolic disorders related to MAFLD.

Our study has some important limitations that should be mentioned. Firstly, we used liver ultrasonography and FIB-4 score for non-invasively diagnosing and staging NAFLD or MAFLD. Secondly, our participants recruited from community hospitals are mostly middle-aged and elderly populations, which may have contributed to worse lung function compared to the normal population. Thirdly, the cross-sectional design of the study does not allow any temporal and causal inferences about the observed

significant associations between decreased lung function volumes and MAFLD or MAFLD-related liver fibrosis. Finally, these findings should be also confirmed in different ethnic groups.

In conclusion, the results of our study show that both MAFLD and NAFLD are associated with significant reductions of FEV1 and FVC in a large hospital-based cohort of Chinese middle-aged individuals. Reductions in lung volumes appear to be significantly greater in subjects with MAFLD than in those with NAFLD. Reduced lung function parameters are also associated with higher FIB-4 scores in MAFLD. We suggest that future prospective and mechanistic studies are needed to decipher the existing but complex links between MAFLD and impaired lung function.

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Table legends

Table 1. Main clinical and biochemical characteristics and lung function tests in subjects with and without MAFLD and in those with and without NAFLD.

Table 2. Comparison of lung function parameters between different groups of subjects with MAFLD or NAFLD.

Note:

* P <0.05 for MAFLD vs. NAFLD;

# P<0.05 for NAFLD vs. Non-MD-NAFLD;

&P<0.05 for MAFLD vs. Non-MD-NAFLD;

$ P<0.05 for comparison among the NAFLD, MAFLD and Non-MD-NAFLD.

Table 3. Lung function tests according to increasing FIB-4 quartiles in subjects with MAFLD or NAFLD

Table 4 Changes in each lung function test for 1-point increase in FIB-4 score in patients with MAFLD**.**

Supplementary Table 1. Comparison of main clinical and biochemical

characteristics and lung function tests in men with and without MAFLD and in men with and without NAFLD.

Supplementary Table 2. Comparison of main clinical and biochemical characteristics and lung function tests in women with and without MAFLD and in women with and without NAFLD.

Supplementary Table 3. Lung function tests stratified by increasing FIB-4 quartiles in men and women with MAFLD.

Supplementary Table 4. Changes in each lung function test for 1-point increase in FIB-4 score in men and women with MAFLD (n=519).

Supplementary Table 5. Published studies investigating the association between lung function parameters and NAFLD.

Figure legends

Figure 1. Flow-chart for the subject recruitment.