BMC Pulmonary Medicine

RESEARCH

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Impact of COPD and sarcopenia on all-cause and respiratory mortality in US adults: NHANES 1999–2018

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Abstract

Background Chronic Obstructive Pulmonary Disease (COPD) and sarcopenia (SAR) are major public health problems in aging societies, as they share common pathophysiological mechanisms and are associated with serious health consequences. We estimated the impact of COPD and SAR on all-cause and respiratory mortalities in the US adult population.

Methods The study analyzed data from the National Health and Nutrition Examination Surveys (NHANES), a representative sample of the US population. Participants aged 20 years or older who had reported whole-body dual X-ray absorptiometry data and data required for the diagnosis of COPD were included. Participants were divided into four groups based on the presence of COPD and SAR.

Results Compared to the COPD−/SAR − group, the COPD−/SAR+, COPD+/SAR−, and COPD+/SAR + groups all demonstrated increased all-cause mortality with Hazard Ratios (HRs) of 1.33 (95% CI 1.20–1.48), 1.51 (95% CI 1.21–1.88), and 1.87 (95% CI 1.32–2.66), respectively. In addition, both the COPD+/SAR − and COPD+/SAR + groups demonstrated increased respiratory mortality with HRs of 5.16 (95% CI 2.96–9.01), and 8.69 (95% CI 3.95–19.1) compared to the COPD−/SAR − group.

Conclusions The coexistence of COPD and SAR additively increased the risk of all-cause and respiratory mortality. Individuals with one of these diseases may need to be treated more carefully to prevent the development of the other disease and thus reduce mortality.

Keywords Chronic obstructive pulmonary disease, Sarcopenia, All-cause mortality, Respiratory mortality, NHANES

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality globally, with a huge and growing economic and social burden [1]. In 2019, there were 212.3 million (200.4-225.1 million) prevalent cases and 16.2 million (15.2–17.2 million) new cases globally, and COPD causes 3.3 million (2.9–3.6 million) deaths [2]. COPD is associated with reduced physical functioning (e.g., decreased exercise, muscle mass and strength) and reduced quality of life, all of which are also closely related to the presence of sarcopenia (SAR), an age-related syndrome characterized by decreased muscle mass, muscle strength, and physical performance [3, 4]. The decline in physical functioning in COPD patients is primarily driven by factors such as breathlessness, chronic inflammation, insufficient oxygen supply, malnutrition, and a sedentary lifestyle. The prevalence of SAR varies across studies and different definitions. It is estimated that 10-16% of older people worldwide suffer from SAR [5]. In addition, SAR is a common comorbid disease that is associated with respiratory disease (including COPD), cardiovascular diseases (CVD), dementia, and diabetes [6]. People with COPD appear to be at higher risk of developing SAR, with prevalence estimated at 21.6% [7], which varies with age, disease severity and BODE (BMI, obstruction, dyspnea and exercise ability) index [8].

Prior studies have indicated that both COPD and SAR are linked to elevated mortality. In 2019, chronic respiratory diseases (CRDs) were the third leading cause of death, accounting for 4 million deaths globally, and among CRDs, COPD has been the leading cause of the global mortality [2]. Individuals with SAR are at increased risk of frailty, functional disability, falls, fractures, metabolic disorders, cognitive impairment, and hospitalization, which can all lead to a higher risk of mortality [5, 9]. Recent studies have shown that SAR was associated with higher mortality, independent of population, definition, and follow-up period [9, 10]. Individuals with SAR also had a higher risk of respiratory disease than those without [11]. To the best of our understanding, there have been no longitudinal studies thus far that have examined the cumulative impact of COPD and SAR on the escalation of respiratory or overall mortalities. Given the widespread occurrence and adverse health consequences associated with these two conditions, exploring the combined effects of their interaction on mortality within the broader population could yield significant insights. Therefore, this research endeavor sought to analyze the influence of COPD and SAR on both all-cause and respiratory mortality utilizing data that is representative at a national level.

Methods

Study design and population

Data was obtained from the National Health and Nutrition Examination Surveys (NHANES), which employed a sophisticated, multistage, probability sampling method to gather nationally representative health-related data. The NHANES is a cross-sectional survey including questions related to health and nutrition, medical, dental, physical measurements, and laboratory analysis with a representative sample of the US population [12], and the NHANES database is publicly available at https://wwwn.cdc.gov/nchs/nhanes/. The NHANES program was approved by the NCHS Ethics Review Board (Approval No. Protocol #98 – 12), and all participants provided informed consent. We acquired baseline data from eight NHANES cycles 1999–2006 and 2011–2018. These baseline data were connected to the mortality data from the National Death Index for the longitudinal study [13]. Participants aged 20 years or older with available skeletal muscle mass, height, COPD diagnosis data, and mortality follow-up data were included in this study. Participants were excluded if they had missing SAR data, mortality follow-up data, COPD-related data, or laboratory and questionnaire data. The questionnaire refers to the "Medical Conditions section" (variable name prefix MCQ, including MCQ160o) of the NHANES questionnaire, which provides self-report and proxy personal interview data on a range of health conditions and medical history (including COPD) [14, 15]. This questionnaire was not developed for this study but is a standardized tool used for NHANES data collection.

Assessment of SAR, COPD and other covariates

ASM (Appendicular Skeletal Mass) is the sum of the lean body mass of the right and left arms and legs measured using the DXA QDR-4500 Hologic Scanner. SAR was defined according to the Foundation for the National Institutes of Health (FNIH) criteria, using ASM divided by body mass index (BMI) with cutoff points of ≤ 0.789 in men and ≤ 0.512 in women [16]. Additionally, the 2019 European Working Group on Sarcopenia in Older People (EWGSOP2) criteria for SAR, using the ASM/height^2 with cutoff points of ≤ 7.0 kg/m^2 for men and ≤ 5.5 kg/m^2 for women, was used for supplementary analysis [17].

In this study, COPD was diagnosed on the basis of a ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) of less than 0.7 after bronchodilator use, as well as questionnaires to participants and the use of medications related to the treatment of COPD [14].

Demographic variables such as age, gender, ethnicity, educational level, marital status, family income, smoking status and alcohol consumption were self-reported. Family income was divided into three groups according to the poverty income ratio: low (≤ 1.3), medium (> 1.3

to ≤3.5), and high (>3.5) [18]. In addition, smoking status was divided into never smoked (less than 100 cigarettes in lifetime), former smoker (100 cigarettes or more but quit), and current smoker. Alcohol consumption was categorized as never (<12 lifetime drinks), former (≥12 yearly drinks but abstinent last year), current light drinker (≤1 daily drink for women, ≤2 for men), current moderate drinker (2 daily drinks for women, 3 for men), or current heavy drinker (>2 daily drinks for women, >3 for men). Clinical measurements included body mass index (BMI), waist circumference, hemoglobin, total bilirubin, triglycerides, total cholesterol, HDL-cholesterol, HbA1c, urinary albumin creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR). These clinical variables were categorized based on established clinical thresholds, such as BMI categories (underweight, normal weight, overweight, obesity), cholesterol levels (desirable, borderline high, high), and HbA1c levels (normal, prediabetes, diabetes). Medical conditions including diabetes mellitus (DM), hypertension, and cardiovascular disease (CVD), identified by self-report or laboratory/imaging results, were applied in subgroup analyses [19, 20].

According to these definitions, the participants were categorized into four groups based on whether they had COPD and SAR: no COPD or SAR (COPD−/SAR−), with COPD but no SAR (COPD+/SAR−), without COPD but with SAR (COPD−/SAR+), and with both COPD and SAR (COPD+/SAR+).

Outcomes

The primary outcomes of this study were all-cause and respiratory mortalities. The mortality data of the participants until 2019 were retrieved from NHANES dataset. This dataset provided the cause of death based on the International Classification of Diseases-10 (ICD-10) codes and the dates of death of the participants. Respiratory mortality was defined by ICD-10 codes J00-J99 as the cause of death.

Statistical analysis

In accordance with the NHANES analytical guidelines [21], our analysis considered complex sampling designs and sampling weights. Participant characteristics were presented as weighted means with standard error, or median with interquartile range for continuous variables and as frequencies with weighted percentages for categorical variables. Weighted linear regression was used for analyzing continuous data, while the design-adjusted chi-square test was utilized for analyzing categorical data. The Cox proportional hazard model was used to calculate the HR and 95% CI for mortality based on the presence of COPD and SAR: model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, ethnicity, marital status, family income, educational level; model 3 was additionally adjusted for BMI, waist circumference, hemoglobin, triglycerides, total cholesterol, HDL-cholesterol, total bilirubin, HbA1c, smoking status, UACR, eGFR, alcohol user. Additionally, for all-cause and respiratory mortalities, interaction and subgroup analyses by age, sex, DM, hypertension, CVD, and BMI were performed according to model 3. To examine the robustness of our findings, sensitivity analyses were performed by excluding participants who died within two years, and individuals under 40. All analyses were performed using R software version 4.3.1.

Results

Baseline characteristics

In the analyses, we included participants aged 20 years or older, with skeletal muscle and height data, and with data necessary for COPD diagnosis and mortality follow-up, resulting in a total of 80,630 participants screened from the continuous NHANES dataset. We excluded participants who had unavailable SAR data ($n=40114$), those with unavailable mortality data ($n=12354$), those with unavailable COPD data ($n=2450$), and those with unavailable laboratory and questionnaire data ($n=3751$). Therefore, a total of 21,961 participants remained in our cohort for analysis (Fig. 1). Among the 21,961 participants, 19,072 (86.8%) had neither COPD nor SAR (COPD−/SAR−), 2381 (10.8%) had SAR only (COPD−/SAR+), 388 (1.8%) had COPD only (COPD+/SAR−), and 120 (0.5%) had both COPD and SAR (COPD+/ SAR+). Table 1 summarizes the baseline characteristics of the participants in the four groups. The participants in the COPD+/SAR+ group were significantly older than those in the other groups. The BMI, waist circumference, and HbA1c were also significantly higher in the COPD+/SAR+ group than in the other groups (all $p<0.0001$). Participants with both COPD and SAR, compared to those without COPD or SAR, were predominantly male, had lower family income, were predominantly Non-Hispanic White, often had less than 9th-grade education, and were less likely to have never smoked.

A comparison of baseline characteristics between the excluded and included groups (see Appendix 1) revealed significant differences in multiple key variables. For instance, participants in the excluded group had lower levels of age, BMI, waist circumference, and HbA1c compared to those included in the analysis. Additionally, the excluded group had a different distribution of sex, race, education level, and smoking status. Notably, the excluded group had a higher proportion of Non-Hispanic White participants, were more likely to have less than a 9th-grade education, and had a higher smoking rate. These differences suggest that there may be selection bias between the excluded and included participants, which could potentially affect the generalizability

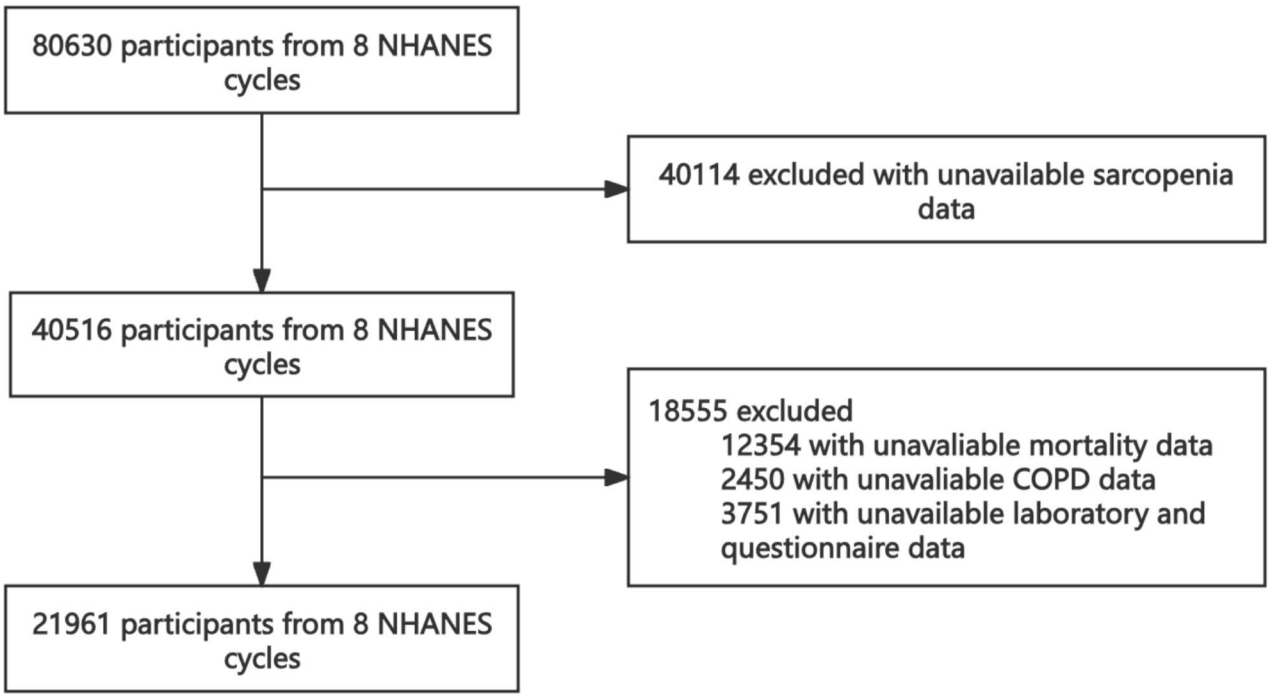

Fig. 1 Flowchart of selection strategy

and interpretation of the study's results. This limitation is addressed in the discussion section.

All-cause and respiratory mortality according to COPD and SAR status

Figure 2 depicts the survival curves of the four groups, demonstrating significant differences in overall and respiratory survival among the groups during the median follow-up duration of 9 years (both log-rank $p < 0.001$). The COPD−/SAR − group had the best survival, whereas the COPD+/SAR + group had the worst survival among all the groups. Table 2 presents the HRs for all-cause and respiratory mortalities according to the COPD and SAR status. An increased risk of all-cause mortality was observed in the COPD−/SAR+ (HR = 1.33, 95% CI 1.20–1.48), COPD+ /SAR− (HR = 1.51, 95% CI 1.21–1.88) and COPD+/SAR+ (HR = 1.87, 95% CI 1.32–2.66) groups than in the COPD−/SAR − group. Compared to the COPD−/SAR − group, both the COPD+/SAR − and COPD+/SAR + groups exhibited an increased risk of respiratory mortality (HR = 5.16, 95% CI 2.96–9.01 and HR = 8.69, 95% CI 3.95–19.1), whereas the COPD−/SAR + group demonstrated no significant difference. The same analyses were performed using the EWGSOP2 criteria. As presented in Appendix 2, participants with COPD, SAR, or both exhibited higher risks of all-cause and respiratory mortalities than those without these conditions. The HRs for all-cause mortality gradually increased in the COPD−/SAR−, COPD+/SAR−, COPD−/SAR+, and COPD+/SAR + groups (p-for-trend < 0.0001), and the HRs for respiratory mortality were gradually increased in the COPD−/SAR−, COPD−/SAR+, COPD+/SAR−, and COPD+/SAR + groups (p-for-trend < 0.001) (Appendix 2).

Cancer and CVD mortality according to COPD and SAR status

As presented in Appendix 3, participants with COPD, SAR, or both did not exhibit higher risks of CVD mortality compared to those without these conditions in model 3. The *p*-values for all three groups compared to the COPD−/SAR − group were greater than 0.5, indicating no significant differences. For cancer mortality risk, in model 3, there was no significant difference between COPD+/SAR + and COPD−/SAR−, whereas significant differences were found between COPD+/SAR − and COPD−/SAR−, and between COPD−/SAR + and COPD−/SAR−. The reason for these findings may be the small sample size of the COPD+/SAR + group, which could lead to a higher risk of Type II error (false negative results).

Subgroup analyses

The results of the subgroup analyses for all-cause and respiratory mortalities were detailed in Appendix 4 and 5, respectively. In various subgroups, the COPD+/SAR + group showed an increased risk of all-cause mortality and respiratory mortality compared to the COPD−/SAR − group.

Table 1 Characteristics of participants in the NHANES

Variable	Total (*n* = 21961)	COPD-/SAR- (*n* = 19072)	COPD-/SAR+ (*n* = 2381)	COPD+/SAR- (*n* = 388)	COPD+/SAR+ (*n* = 120)	*P* value
Age (years)	42.21(0.19)	41.17(0.20)	50.63(0.42)	54.00(0.63)	60.32(1.37)	**< 0.0001**
Sex, n (%)						**< 0.001**
Female	10,777(49.81)	9399(49.91)	1112(45.82)	215(62.78)	51(43.65)	
Male	11,184(50.19)	9673(50.09)	1269(54.18)	173(37.22)	69(56.35)	
BMI (kg/m^2)	28.00(0.08)	27.55(0.07)	32.92(0.18)	28.02(0.45)	33.78(0.97)	**< 0.0001**
Waist circumference (cm)	95.95(0.20)	94.85(0.20)	107.30(0.42)	99.12(1.09)	113.83(2.42)	**< 0.0001**
Ethnicity, n (%)						**< 0.0001**
Mexican American	4239(8.75)	3195(7.90)	1014(21.22)	15(0.92)	15(2.96)	
Non-Hispanic Black	4354(10.35)	4171(11.09)	100(2.63)	74(7.65)	9(3.65)	
Non-Hispanic White	9627(68.08)	8424(68.49)	873(58.69)	251(82.25)	79(82.43)	
Other Hispanic	1529(6.16)	1296(5.91)	211(10.14)	11(2.14)	11(5.01)	
Other races (Including multiracial)	2212(6.67)	1986(6.61)	183(7.33)	37(7.05)	6(5.96)	
Educational level, n (%)						**< 0.0001**
Less than 9th grade	2280(4.90)	1558(4.00)	643(14.44)	50(7.71)	29(13.82)	
9-11th grade	3101(10.76)	2612(10.31)	392(13.92)	76(18.04)	21(16.19)	
High school graduate	5031(23.84)	4351(23.42)	569(29.03)	87(23.30)	24(24.83)	
College graduate or above	5043(28.52)	4693(29.94)	276(14.65)	62(20.51)	12(9.95)	
Some college or associate degree	6506(31.99)	5858(32.33)	501(27.96)	113(30.44)	34(35.20)	
Family income, n (%)						**< 0.0001**
High	7273(43.47)	6647(44.88)	496(29.41)	105(37.49)	25(23.39)	
Medium	8198(35.13)	7075(34.72)	944(40.20)	134(33.78)	45(38.93)	
Low	6490(21.40)	5350(20.41)	941(30.39)	149(28.73)	50(37.68)	
Marital status, n (%)						**< 0.0001**
Living with partner	1860(8.57)	1699(8.85)	137(6.26)	22(6.18)	2(2.79)	
Married	11,593(55.44)	9903(55.03)	1438(60.54)	190(56.63)	62(48.91)	
Never married	4625(20.81)	4293(21.67)	281(14.27)	38(7.06)	13(13.26)	
Other	3883(15.18)	3177(14.45)	525(18.93)	138(30.13)	43(35.05)	
Alcohol user, n (%)						**< 0.0001**
former	3232(12.28)	2528(11.21)	556(21.32)	109(22.91)	39(29.21)	
heavy	5040(24.49)	4490(24.90)	465(21.25)	70(20.29)	15(13.58)	
moderate	3568(18.36)	3274(18.98)	225(11.12)	58(19.88)	11(9.95)	
mild	7170(34.05)	6354(34.58)	652(28.58)	122(30.34)	42(35.64)	
never	2951(10.83)	2426(10.33)	483(17.74)	29(6.59)	13(11.62)	
Smoking status, n (%)						**< 0.0001**
former	4777(22.03)	3892(21.18)	669(26.64)	147(36.40)	69(53.77)	
never	12,060(53.86)	10,653(54.73)	1326(55.13)	64(17.33)	17(12.37)	
now	5124(24.11)	4527(24.10)	386(18.23)	177(46.27)	34(33.86)	
Hemoglobin (g/L)	14.45(0.02)	14.45(0.02)	14.46(0.05)	14.29(0.11)	14.35(0.22)	0.43
Total bilirubin (mmol/L)	11.46(0.08)	11.53(0.08)	10.76(0.17)	10.73(0.47)	10.87(0.69)	**< 0.0001**
Triglycerides (mmol/L)	1.66(0.02)	1.62(0.02)	2.00(0.05)	2.02(0.20)	2.24(0.23)	**< 0.0001**
Total cholesterol (mmol/L)	5.09(0.01)	5.07(0.01)	5.25(0.03)	5.41(0.09)	5.29(0.14)	**< 0.0001**
HDL-cholesterol (mmol/L)	1.36(0.01)	1.37(0.01)	1.27(0.01)	1.44(0.03)	1.24(0.04)	**< 0.0001**
HbA1c (%)	5.47(0.01)	5.43(0.01)	5.85(0.03)	5.67(0.06)	6.00(0.09)	**< 0.0001**
UACR (mg/g)	5.93(4.03,10.33)	5.77(3.98, 9.91)	8.06(5.14,16.74)	7.16(4.46,13.21)	9.74(4.92,25.45)	**< 0.0001**
eGFR (mL/min/1.73 m^2)	99.25(85.24, 111.82)	99.71(85.86, 111.94)	97.93(81.53, 112.60)	88.98(75.77, 101.03)	88.07(73.23, 97.38)	**< 0.0001**
CVD						**< 0.0001**
no	20,362(94.61)	17,980(95.82)	2022(85.88)	288(78.30)	72(66.90)	
yes	1599(5.39)	1092(4.18)	359(14.12)	100(21.70)	48(33.10)	
DM						**< 0.0001**

Table 1 (continued)

Variable	Total (*n* = 21961)	COPD-/SAR- (*n* = 19072)	COPD-/SAR+ (*n* = 2381)	COPD+/SAR- (*n* = 388)	COPD+/SAR+ (*n* = 120)	*P* value
no	19,331(91.37)	17,140(92.65)	1786(78.63)	328(87.89)	77(63.60)	
yes	2630(8.63)	1932(7.35)	595(21.37)	60(12.11)	43(36.40)	
Hypertension						**< 0.0001**
no	14,451(69.95)	13,091(72.17)	1167(51.57)	161(47.99)	32(27.33)	
yes	7510(30.05)	5981(27.83)	1214(48.43)	227(52.01)	88(72.67)	
Follow-up time (month)	135.00(64.00,201.00)	156.00(65.00,203.00)	105.00(60.00,189.00)	99.00(63.00,179.00)	91.00(45.00,142.00)	< 0.0001

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; SAR, sarcopenia; BMI, body mass index; UACR, urinary albumin creatinine ratio; eGFR, estimated glomerular filtration rate

Categorical variables are expressed as frequencies with weighted percentages, and continuous variables are expressed as weighted mean with standard error, or median with interquartile range

Values in **bold** are statistically significant

Sensitivity analyses

Sensitivity analysis was performed by excluding the participants who died within two years (Appendix 6). The number of participants who died within two years was 244. Compared to the COPD−/SAR− group, the COPD-/SAR+, COPD+/SAR− and COPD+/SAR+ groups exhibited an increased risk of all-cause mortality with HRs of 1.31 (95% CI 1.17–1.48), 1.46 (95% CI 1.14–1.87), and 1.78 (95% CI 1.26–2.52) respectively (p-for-trend < 0.0001). Regarding the respiratory mortality, COPD+/SAR− and COPD+/SAR+ groups demonstrated a significantly higher risk of respiratory mortality than those without either of the diseases with HRs of 4.54 (95% CI 2.48–8.33), and 7.21 (95% CI 3.43–15.12) respectively (p-for-trend < 0.0001), whereas the risk of respiratory mortality in the SAR-only group was not significant. Sensitivity analysis performed by excluding the participants who were younger than 40 years of age also demonstrated similar results (Appendix 7). The Appendix 8 and 9, display the results of Kaplan-Meier sensitivity tests by excluding the participants who died within two years, demonstrating significant differences in overall and respiratory-related survival among the four groups ($p < 0.0001$). The Appendix 10 and 11, display the results of Kaplan-Meier sensitivity tests by excluding the participants who were younger than 40 years of age, demonstrating significant differences in overall and respiratory-related survival among the four groups ($p < 0.0001$). The results of these two Kaplan-Meier sensitivity test methods were consistent with Fig. 2, where the COPD−/SAR− group had the best survival, while the COPD+/SAR+ group had the worst survival among all the groups.

Discussion

COPD and SAR have high prevalence rates globally and represent a significant public health burden. To the best of our knowledge, this is the first longitudinal study to assess the impacts of COPD and SAR on all-cause and respiratory mortality using the FNIH and EWGSOP2 criteria for assessing low muscle mass. In this study, which was based on a population-based survey, we showed that the coexistence of COPD and SAR exhibited the highest risk of overall and respiratory mortality, with an HR higher than those for each condition alone.

It has been reported that the global prevalence of COPD is 10.3% [1], and the prevalence of SAR is 10-16% [5]. People with COPD appear to be at higher risk of developing SAR, with the prevalence estimated at 21.6% [7]. In this study, the prevalence of COPD is 2.3%, SAR prevalence is 11.4%, and the prevalence of SAR in the COPD population is estimated at 23.6%. Compared to the reported statistics, the COPD prevalence in this study is relatively low, while the SAR prevalence and the prevalence of SAR in the COPD population are close to the reported figures. This suggests that COPD is a significantly underestimated disease.

The results of the present study demonstrated that the coexistence of COPD and SAR nearly doubled the risk of all-cause mortality (HR = 1.87, 95% CI 1.32–2.66) and more than eight times the risk of respiratory mortality (HR = 8.69, 95% CI 3.95–19.14) by using FNIH criteria, and the results obtained using the EWGSOP2 criteria are similar (Table 2 and Appendix 2). When we analyzed the impact of COPD-only and SAR-only on mortality, the risks of all-cause mortality were both significantly increased regardless of the diagnostic criteria used, which was in line with the results of earlier studies [1, 9, 22, 23]. Respiratory mortality was significantly higher in the COPD+/SAR- and COPD+/SAR+ groups compared to the COPD-/SAR- group, whereas there was no significant difference in the SAR-only group. In contrast, according to the EWGSOP2 criteria, the presence of COPD and SAR, either in combination or in isolation, caused a significant increase in respiratory mortality (Appendix 2). We performed the same analysis by excluding the participants who died within two years or were younger than 40 years of age and observed consistent results (Appendix 6 and 7). In addition, we also performed subgroup analyses. In various subgroups, the COPD+/SAR+ group

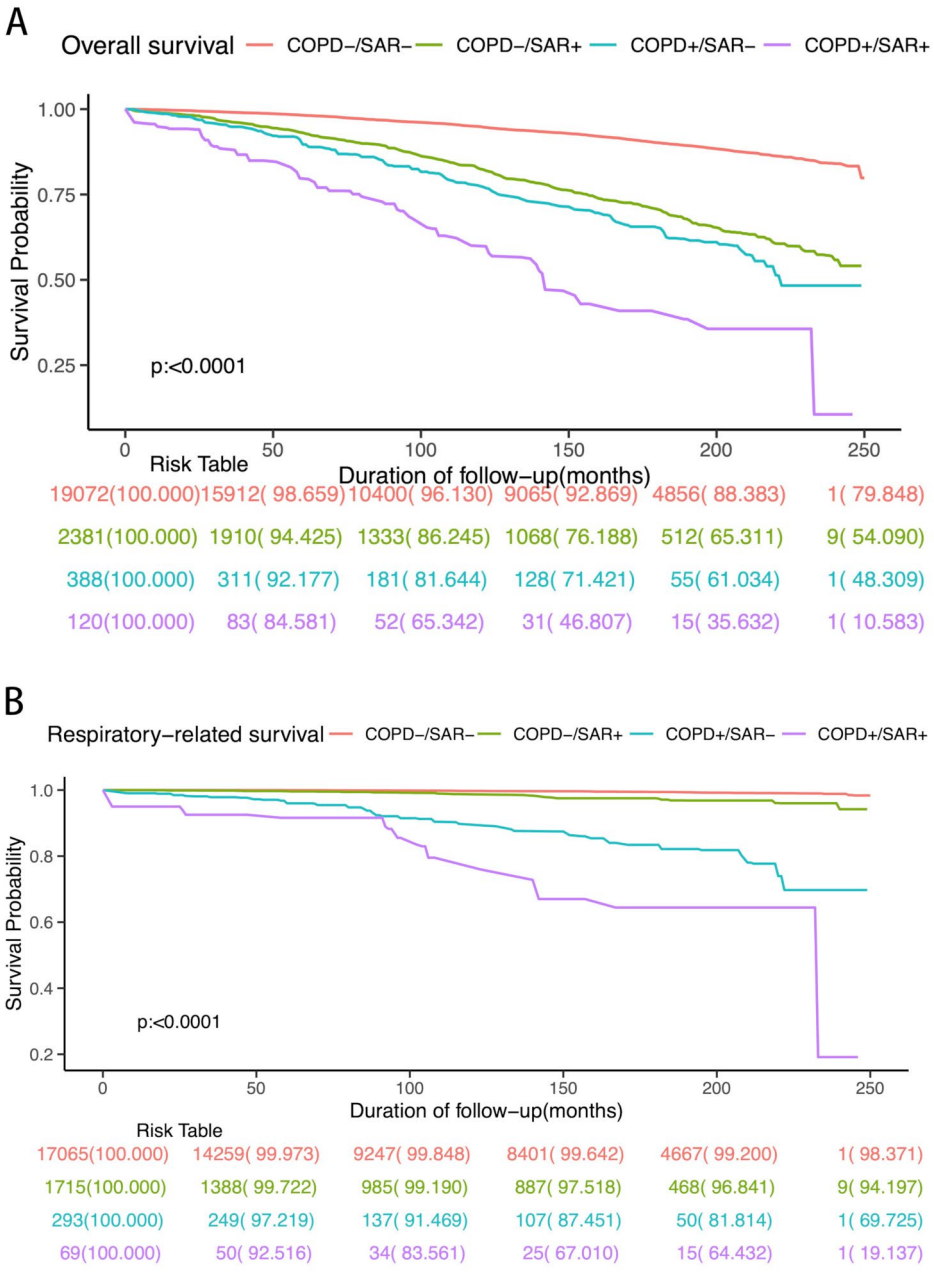

Fig. 2 (**A**) Overall survival and (**B**) Respiratory-related survival according to COPD and SAR status. Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; SAR, sarcopenia

showed an association with increased all-cause and respiratory mortalities compared to the COPD-/SAR- group (Appendix 4 and 5).

Multiple studies have demonstrated a strong and intricate connection between COPD and SAR. Oxidative stress is believed to play a significant role in COPD [24–26]. Studies have demonstrated a link between oxidative stress and severity of COPD, which can result in medical comorbidities and impaired muscle function [27–29]. Moreover, muscle dysfunction in COPD, particularly affecting respiratory muscles, seems to be more severely impaired in patients with SAR [30]. Furthermore, advanced glycation end products (AGEs) also play an important role in the development of COPD and SAR. Major AGEs include hydroimidazolone, glucosepane, pentosidine and Nε-carboxymethyl-lysine. AGEs levels are elevated in COPD patients and strongly correlate with disease severity. This suggests that AGEs may serve as a marker to predict the severity of COPD [31]. Accumulation of AGEs also affects lung tissue and

Table 2 Association of COPD/SAR with all-cause and respiratory mortality using the FNIH criteria

Character	Crude model		Model 1		Model 2		Model 3	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
All-cause mortality								
COPD-/SAR-	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
COPD-/SAR+	3.48(3.12, 3.89)	< 0.0001	1.39(1.25, 1.55)	< 0.0001	1.34(1.21, 1.48)	< 0.0001	1.33(1.20, 1.48)	< 0.0001
COPD+/SAR-	4.47(3.57, 5.60)	< 0.0001	2.27(1.81, 2.84)	< 0.0001	1.94(1.57, 2.38)	< 0.0001	1.51(1.21, 1.88)	< 0.001
COPD+/SAR+	9.28(6.33, 13.60)	< 0.0001	2.62(1.92, 3.57)	< 0.0001	2.24(1.64, 3.07)	< 0.0001	1.87(1.32, 2.66)	< 0.001
p for trend		< 0.0001		< 0.0001		< 0.0001		< 0.0001
Respiratory mortality								
COPD-/SAR-	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
COPD-/SAR+	4.38(2.76, 6.95)	< 0.0001	1.39(0.86, 2.27)	0.18	1.26(0.74, 2.13)	0.39	1.82(0.91, 3.63)	0.09
COPD+/SAR-	33.61(21.68, 52.12)	< 0.0001	12.12(7.25, 20.25)	< 0.0001	9.54(5.66,16.08)	< 0.0001	5.16(2.96, 9.01)	< 0.0001
COPD+/SAR+	74.51(38.40, 144.57)	< 0.0001	12.37(6.36, 24.06)	< 0.0001	10.95(5.38,22.28)	< 0.0001	8.69(3.95, 19.14)	< 0.0001
p for trend		< 0.0001		< 0.0001		< 0.0001		< 0.0001

Abbreviations: HR, hazard ratio; CI, confidence interval

Crude model

Model 1: Age, sex

Model 2: Age, sex, ethnicity, marital, family income, educational level

Model 3: Age, sex, ethnicity, marital, family income, educational level, BMI, waist circumference, hemoglobin, TG, total cholesterol, HDL, Total bilirubin, HbA1c, smoke, UACR, eGFR, alcohol use

promotes the development of chronic bronchitis or emphysema [32]. In addition, AGEs have been associated with skeletal muscle dysfunction, where increased levels increase cross-linking of proteins within the muscle, thereby interfering with the muscle's ability to contract [33, 34]. Although these biomarkers may play a significant role in the pathogenesis of both COPD and SAR, their clinical applicability and the techniques for measuring them warrant further investigation. Future research could focus on directly measuring nitric oxide (NO) and AGEs to gain a deeper understanding of their role in the interplay between COPD and SAR. Such studies may offer more precise insights and provide guidance for the integrated management of both conditions. Recent studies have shown that SAR was more common in patients with higher COPD severity (GOLD stages III-IV), with a prevalence of 37.6%, and in milder patients (GOLD stages I-II), with a prevalence of 19.1%. In addition, COPD patients with SAR typically have poorer daily physical abilities, less daily activity, more dyspnea with daily activities, and a higher risk of death [6, 35].

This study has several limitations. First, it focused exclusively on the US population, limiting the generalizability of the findings to other populations. However, due to the complex multistage probability sampling methodology employed in NHANES, which ensures nationally representative health-related data, the results of this study still provide valuable insights for future research in different populations. Second, despite thorough adjustments for potential factors related to mortality, some residual biases remain that could not be fully accounted for. Third, the NHANES dataset lacks longitudinal data on COPD and muscle-related factors, preventing an evaluation of changes in COPD and SAR over time. Additionally, a potential limitation arises from the differences between participants included in the analysis and those excluded, which may introduce selection bias. As outlined in the baseline characteristics table, significant differences were observed in variables such as age, BMI, waist circumference, HbA1c levels, sex, race, education, and smoking status between the included and excluded groups. These disparities suggest that the excluded participants may not be fully representative of the broader population, which could impact the generalizability of our findings. For instance, the excluded group had a higher proportion of non-Hispanic White participants, higher smoking rates, and lower educational attainment—factors that could influence outcomes related to COPD and SAR. While efforts were made to adjust for these variables in our analysis, it is important to consider these differences when interpreting the results. Another limitation is the inability to assess muscle strength, as the necessary variables were not included in the NHANES dataset. This restricted our ability to fully explore the relationship between SAR and other health outcomes, particularly in terms of muscle function. One of the most significant limitations was the small number of individuals with both COPD and SAR—only 0.5% of the sample (120 individuals out of 21,961 respondents)—as well as those with SAR alone (1.8% of the sample). This small sample size likely reduced the statistical power of our analysis and may limit the robustness and generalizability of our findings. Finally, while COPD was diagnosed using a ratio of FEV1 to FVC of less than 0.7 after bronchodilator use, combined with participant questionnaires and medication data, the relatively small number

of participants diagnosed solely through spirometry data led to significant missing lung function data. This missing data made it challenging to classify disease severity in a meaningful way, which has been acknowledged as a limitation in the manuscript. However, our study had some strengths. First, this study included a large number of participants. Second, this study utilized a longitudinal study design and had a relatively long follow-up period. In addition, this study provided information about various potential confounders in the analysis. Furthermore, using a sample from the community, following standardized data collection procedures, and ensuring thorough follow-up for deaths could enhance the credibility of our study findings. Substantially consistent results were observed using two different SAR criteria, FNIH and EWGSOP2, and in sensitivity analyses that excluded participants who died within two years and were younger than 40 years.

The clinical implications of this study highlight the effect of COPD and SAR on increasing the risk of overall and respiratory mortality. This finding suggests that clinicians should be vigilant in monitoring both conditions simultaneously, as the coexistence of COPD and SAR may exacerbate patient outcomes. Early identification and management of sarcopenia in COPD patients, through interventions such as physical rehabilitation and nutritional support, could be key strategies to reduce mortality risk. Future research should focus on exploring the underlying mechanisms linking COPD and SAR, as well as investigating the effectiveness of integrated care approaches to address both conditions. Randomized controlled trials are needed to test specific interventions targeting the prevention and treatment of SAR in COPD patients, with the aim of improving survival rates and quality of life.

Conclusion

In conclusion, the combination of COPD and SAR cumulatively increased the risk of overall and respiratory mortalities compared with having each condition separately. These findings suggest that closely monitoring and taking preventive actions to address the progression of either COPD or SAR are crucial strategies for reducing the risk of death in patients with these conditions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03675-0.

Supplementary Material 1

Author contributions

The authors contributed to the paper as follows: Conception and design: HF, QLS, SQL. Methodology: JX, QYZ. Data curation: JX, QYZ. Formal analysis: JX, QYZ. Original draft: JX, QYZ, XYM. Critical revision of manuscript: YHM, HN, SQL, HF, QLS. All authors reviewed the results and approved the final version of the manuscript.

Funding

This study was supported by the Key Research and Development Project of Sichuan Province (Grant number: 2022YFS0261); and the National Key Research and Development Program of China (Grant number: 2022YFC3601503).

Data availability

Availability of data and materialsAll data used in this study are anonymized and available at NHANES official website (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx).

Declarations

Ethics approval and consent to participate

This study was approved by the NCHS Research Ethics Review Board (ERB) and all participants provided written informed consent. The details of the NCHS Research Ethics Review Board Approval can be found on the NHANES website (https://www.cdc.gov/nchs/nhanes/irba98.htm).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Role of the funding sources

The funding sources had no influence of the planning, conduct or reporting of the study.

Received: 1 September 2024 / Accepted: 18 April 2025
Published online: 09 May 2025

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