Association analysis of frailty with obstructive sleep apnea syndrome in elderly patients – A Multicenter Cohort Study

Zijun He  
Yan'an University

Xin Xue  
Hospital of Yan'an University

Yinghui Gao  
Peking University International Hospital

Zhang Zuo  
People's Hospital of Ningxia Hui Autonomous Region

Mengxi Li  
Yan'an University

Zhe Zhao  
Department of Cardiology, the Second Medical Center

Libo Zhao  
Department of Cardiology, the Second Medical Center

Xiaofeng Su  
Yan'an University

Mengying Xing  
Yan'an University

Tianjiao Li  
Yan'an University

Kailiang Li  
Health Service Department of the Guard Bureau of the Joint Staff Department

Jiming Han  
Yan'an University

Lin Liu (✉ liulin715@qq.com)  
Chinese PLA General Hospital

Research Article

Keywords: Obstructive sleep apnea syndrome, Senile, Frailty, Incidence, Risk factors, China
Abstract

Objective

We assessed the incidence of frailty and identified the independent risk factors for the occurrence of frailty in elderly patients with obstructive sleep apnea syndrome (OSAS), which aims to provide a reference for the clinical treatment of OSAS and frailty.

Methods

We selected 1006 elderly patients with OSAS diagnosed using polysomnographic (PSG) between January 2015 and October 2017. We divided the patients into the non-frailty group (n = 731) and the frailty group (n = 275) based on the FRAIL scale score, compared the difference between the two groups. Multivariate cox regression analysis was used to identify the factors affecting the onset of frailty among elderly patients with OSAS.

Results

275 patients experienced frailty, yielding an incidence of 27.34%. Multivariate cox regression analysis showed that age (HR = 1.058, 95% CI: 1.043–1.074, P < 0.001), constipation (HR = 1.490, 95% CI: 1.101–2.018, P = 0.010), carotid atherosclerosis (CA) (HR = 1.739, 95% CI: 1.299–2.330, P < 0.001), and renal insufficiency (RI) (HR = 1.878, 95% CI: 1.177–2.996, P = 0.008) are independent risk factors for frailty in elderly patients with OSAS. And platelet count (PLTC) (HR = 0.998, 95% CI: 0.996–1.000, P = 0.040), the mean arterial oxygen saturation (MSaO₂) (HR = 0.950, 95% CI: 0.918–0.984, P = 0.005) are protect factors.

Conclusion

The incidence of frailty among elderly patients with OSAS is relatively high, and it was significantly higher in patients with severe OSAS than in those with mild or moderate OSAS. Age, constipation, CA, and RI are independent risk factors, whereas mean oxygen saturation and platelet count are protective factors for frailty in elderly patients with OSAS.

Introduction

Obstructive sleep apnea syndrome (OSAS) manifests symptoms such as snoring (loud and irregular), nocturnal asphyxia or asphyxia, sleep disturbance, daytime drowsiness, and even cognitive decline and behavioral abnormalities. Among the specific markers of OSAS, the sleep apnea hypopnea index (AHI) is a consistent predictor¹. The incidence of OSAS ranges from 10–15%², and it is higher in the elderly population, making it a common fatal disease³. The onset and progression of OSAS is multifactorial. Studies have shown that OSAS affects the physical and mental health of 24% of adult men and 9% of adult women⁴, and the overall fatality risk in the OSAS population is 5.3 times that in the general
The incidence of OSAS increases with age, with up to 90% and 78% of elderly men and women, respectively, affected by it.

Aging is a global concern, in both developed and developing countries alike, with 1.6% of the global population aged > 85 years. Although life expectancy is increasing, the proportion of frail individuals becoming bedridden and requiring care is also increasing. Frailty refers to functional decline in multiple organ systems and a decline in energy reserves in the elderly. It manifests as physical frailty, cognitive frailty, and psychological frailty, and decreased physical activity is an important clinical manifestation of frailty. The incidence of frailty among individuals aged ≥ 65 years is estimated at 17%, or approximately 120 million people worldwide. Frail patients not only have physical disabilities but also have psychophysiological and social challenges. Thus, they require more social resources than their healthy peers. Frailty impairs the ability to cope with acute stressors, and a study suggested that frailty may be reversible. Another study found that the incidence of frailty in 2011, 2013, and 2015 was 18.7%, 20.6%, and 28.4%, respectively, increasing year by year. Other related studies have shown that people at higher risk of developing OSAS also have a higher risk of developing frailty; in contrast, frail women were more likely to develop OSAS than those without.

Although several studies have reported on the risk factors of OSAS or frailty, studies on the incidence of frailty in elderly individuals with OSAS and the risk factors in this population are lacking. We studied the incidence and risk factors of frailty in elderly patients with OSAS. Our results can help determine trends in frailty among patients with OSAS, devise individualized interventions, alleviate frailty, reduce the risk of adverse outcomes, and improve the quality of life.

**Methods**

**Study design and participants**

This study had a multicenter cohort design. We recruited 1,290 elderly patients aged ≥ 60 years with OSAS using PSG at the sleep center of PLA General Hospital (n = 313), the Affiliated Hospital of Gansu University of Traditional Chinese Medicine (n = 112), Peking University People's Hospital (n = 242), Peking University International Hospital (n = 238), Beijing Chaoyang Hospital (n = 337) and 960th Hospital of PLA (n = 48) between January 2015 and October 2017. Exclusions: (1) Incomplete follow-up information; (2) Other diseases cause arterial oxygen saturation (SaO₂) to < 90% at rest; (3) Those with malignant tumors and diseases of their own immune system; (4) Severe cognitive dysfunction, mental illness and acute onset of illness that make it impossible to cooperate with the investigation. (5) CPAP therapy (patients who have maintained regular CPAP therapy (3 months) during the follow-up period or remain on CPAP until the end of follow-up). (6) Patients with confirmed frailty during the baseline period. Finally, 1006 elderly patients with OSAS elderly than 60 years were included. According to the consensus recommendation of Chinese experts, according to the FRAIL scale score, the participants were divided into non-frailty group (n = 731, 72.66%) and frailty group (n = 275, 27.34%), and the age was 63–104
(71.88 ± 7.26) years old. The study is in agreement STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines, and was carried out in accordance with the Declaration of Helsinki. The Ethics Committee of the General Hospital of the People's Liberation Army of Chinese (S2019-352-01) approved the study. All participants have written informed consent. The study graph is shown in the Fig. 1.

Baseline Evaluation

We collected demographic and relevant clinical data for all patients, including sex, age, height, weight, body mass index (BMI; calculated as weight divided by height squared, kg/m$^2$), history of smoking (defined as at least 1 cigarette per day or accumulation for > 6 months)$^{13}$, and history of alcohol consumption (defined as drinking for at least once a week for at least half a year). Sleep parameters including the AHI, oxygen desaturation index (ODI), mean apnea time (MAT), the mean arterial oxygen saturation(MSaO$_2$), and the lowest arterial oxygen saturation(LSaO$_2$) were also recorded.

For blood parameters, blood sample was collected after at least 6 hours of fasting and 4 hours of drinking. Blood parameters included levels of total bilirubin, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatinine (Cre), uric acid (UA), cystatin c (CysC); platelet count (PLTC), red blood cells (RBC), white blood cells (WBC); ratios of uric acid and high-density lipoprotein (UA/HDL), total cholesterol and high-density lipoprotein (TC/HDL), low-density lipoprotein and high-density lipoprotein (LDL/HDL), RBCs and WBCs (RWR), platelets and WBCs (PWR), platelets and mean platelet volume (PLTC/MPV); hemoglobin (HB) levels; and the mean corpuscular hemoglobin concentration (MCHC).

Follow-up

We started the follow-up after all verified data were collected. The starting point of the follow-up was the time when the study subjects were diagnosed with OSA via PSG, and the endpoint was frailty. From the earliest weak time and events, the investigators were trained on telephone follow-up, WeChat follow-up, and hospitalization follow-up to record the clinical symptoms, signs, and other diseases of every follow-up of all selected patients, screen all patients using the FRAIL scale recommended by Chinese expert consensus, and record all patients failed to obtain any information during the follow-up period as lost to follow-up. The follow-up deadline was February 2022. A total of 275 (27.34%) elderly patients with OSA were classified as frail.

Diagnostic criteria

Diagnostic criteria for OSAS included (1) sleep-related symptoms (daytime drowsiness, unrecovered energy after waking, fatigue, insomnia, waking up due to breath-holding, wheezing or suffocation at night, habitual snoring and respiratory interruption) and comorbidities such as hypertension, coronary heart disease, stroke, heart failure, atrial fibrillation (AF), type 2 diabetes(T2DM), mood disorders, and cognitive impairment. The diagnosis of OSAS was established if any of the aforementioned sleep-related
symptoms or comorbidities were present and PSG monitoring revealed an AHI ≥ 5 times/h or none of the aforementioned symptoms were present but AHI was ≥ 15 times/h. AHI was measured as the number of apnea and low-breathing events occurring per hour during sleep. OSAS severity was classified as mild (5 ≤ AHI < 15), moderate (15 ≤ AHI < 30), or severe (AHI ≥ 30).

The FRAIL scale includes 5 items: (1) fatigue; (2) Sense of resistance: the upper floor of the stairs is difficult; (3) Free activity decline: can not walk 1 block; (4) Coexistence of multiple diseases: 5 ≥; (5) Weight loss: weight loss within 1 year > 5.0%. In a study, frailty was established when 3 or more of the 5 aforementioned criteria were met; meeting < 3 criteria was classified as pre-frailty and not meeting any criteria was classified as non-frailty14. In this study, meeting ≥ 3 criteria was classified as frailty, and meeting 0–2 criteria was classified as non-frailty14.

We also collected data on clinical history of the following conditions at baseline from the patient's medical records, according to the guidelines: CA15, T2DM16, (RI)17, cardiac insufficiency18, AF19, and constipation20.

**Polysomnography (PSG)**

PSG is the gold standard for the diagnosis of OSAS. All participants underwent a complete PSG (21:00 to 7:00 on the next day) in the sleep laboratory at sleep centers of the participating hospitals (after clinical stabilization during hospitalization). The sleep parameters of all patients were analyzed using the PSG instrument (Compumedics, Melbourne, Australia). PSG evaluation included electroencephalography, electrooculography, electrocardiography, nasal-oral airflow, chest and abdominal wall motion, SaO₂, and body position. Patients were not allowed to consume tea, coffee, sedatives, or hypnotics before monitoring. PSG indicators included all-night AHI, minimum and average SaO₂, and maximum pauses. Sleep tests were analyzed according to the American Society of Sleep Medicine's 2017 guidelines21. The PSG records for each patient were manually analyzed and manually calibrated twice by technically certified and experienced technicians, both blinded to the demographic and clinical characteristics. A professional sleep physician analyzed and interpreted the PSG report.

**Statistical Analysis**

Statistical analysis was performed using SPSS 25.0 statistical software (version 25.0, SPSS Inc., Chicago, Illinois, USA). We first conducted a normality and variance homogeneity test. Normally distributed data are expressed as mean ± standard deviations, and the t test was used. Non-normally distributed data were presented as quartiles [M(P25, P75)]. Discrete data are expressed as proportions, and the chi-square test was used. The risk factors for OSAS were identified using multivariate Cox regression, and \( P < 0.05 \) was considered statistically significant.

**Results**

**Baseline Characteristics**
A total of 1006 patients with OSAS were included for data analysis, including 262 (24.81%), 310 (24.84%), and 434 (30.65%) with mild, moderate, and severe OSAS, respectively. Height, age, SBP, ODI, MSaO₂, LSaO₂, TC, TG, Cre, CysC, PLTC, RBC, HB, RWR, PWR, PLTC/MPV, and smoking differed significantly across groups ($P < 0.05$). Compared with non-frail patients with OSAS, frail participants tended to be older (76 vs 69 years), had a higher SBP (138 vs 130 mmHg), and tended to be smokers (32.36% vs 20.25%); however, they were also shorter (164.49 vs 166.39 cm; $P < 0.05$). Frail patients scored higher on sleep parameters including ODI (24.10 vs 20.0 events/h) than non-frail patients. In contrast, MSaO₂ (92.70% vs 94.00%) and LSaO₂ (78.00% vs 81.00%) were lower in the frailty group ($P < 0.05$). Cre (73 vs 72 µmol/L) and CysC (0.98 vs 0.93 mg/L) were higher in patients with frailty than in those without ($P < 0.05$). TC (4.15 vs 4.33 mmol/L), TG (1.26 vs 1.43 mmol/L), PLTC (195.00*10^9/L vs 208.00*10^9/L), RBC (4.42*10^12/L vs 4.50*10^12/L), WBC (6.28*10^9/L vs 6.27*10^9/L), HB (137.00 vs 139.00 g/L), RWR (0.69 vs 0.72), PWR (31.07 vs 33.81), PLTC/MPV (18.83 vs 19.93) were lower among patients with frailty than those without ($P < 0.05$)(Table 1).
<table>
<thead>
<tr>
<th></th>
<th>Non-frail group</th>
<th>frail group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 731)</td>
<td>(n = 275)</td>
<td></td>
</tr>
<tr>
<td>Height(cm)</td>
<td>166.39 ± 7.61 a+</td>
<td>164.49 ± 8.33 a+</td>
<td>0.001 *</td>
</tr>
<tr>
<td>Weight(kg)</td>
<td>73.37 ± 12.52 a+</td>
<td>72.59 ± 12.96 a+</td>
<td>0.387</td>
</tr>
<tr>
<td>BMI(kg/m^2)</td>
<td>26.65 ± 4.26 a+</td>
<td>26.87 ± 4.48 a+</td>
<td>0.462</td>
</tr>
<tr>
<td>Age(year)</td>
<td>69.00(66.00, 73.00) b+</td>
<td>76.00(70.00, 82.00) b+</td>
<td>0.000 *</td>
</tr>
<tr>
<td>SBP(mmHg)</td>
<td>130.00(122.00, 140.00) b+</td>
<td>138.00(125.00, 150.00) b+</td>
<td>0.001 *</td>
</tr>
<tr>
<td>DBP(mmHg)</td>
<td>76.00(70.00, 82.00) b+</td>
<td>75.00(70.00, 81.00) b+</td>
<td>0.542</td>
</tr>
<tr>
<td>AHI(events/h)</td>
<td>25.20(14.10, 43.30) b+</td>
<td>28.40(15.50, 45.90) b+</td>
<td>0.098</td>
</tr>
<tr>
<td>ODI(events/h)</td>
<td>20.00(9.90, 39.20) b+</td>
<td>24.10(11.70, 42.90) b+</td>
<td>0.01   *</td>
</tr>
<tr>
<td>MAT(s)</td>
<td>22.00(19.61, 25.03) b+</td>
<td>22.97(19.00, 26.00) b+</td>
<td>0.167</td>
</tr>
<tr>
<td>MSaO₂(%)</td>
<td>94.00(92.00, 95.00) b+</td>
<td>92.70(90.20, 94.80) b+</td>
<td>0.000 *</td>
</tr>
<tr>
<td>LSaO₂(%)</td>
<td>81.00(73.00, 85.00) b+</td>
<td>78.00(69.00, 84.00) b+</td>
<td>0.000 *</td>
</tr>
<tr>
<td>TB(µmol/L)</td>
<td>10.70(8.10, 14.10) b+</td>
<td>10.40(7.90, 14.60) b+</td>
<td>0.703</td>
</tr>
<tr>
<td>TC(mmol/L)</td>
<td>4.33(3.60, 5.00) b+</td>
<td>4.15(3.45, 4.93) b+</td>
<td>0.030 *</td>
</tr>
<tr>
<td>TG(mmol/L)</td>
<td>1.43(1.03, 1.97) b+</td>
<td>1.26(0.97, 1.78) b+</td>
<td>0.007 *</td>
</tr>
<tr>
<td>HDL(mmol/L)</td>
<td>1.11(0.90, 1.38) b+</td>
<td>1.09(0.91, 1.34) b+</td>
<td>0.372</td>
</tr>
<tr>
<td>LDL(mmol/L)</td>
<td>2.37(1.87, 2.94) b+</td>
<td>2.45(1.92, 3.08) b+</td>
<td>0.087</td>
</tr>
<tr>
<td>Cre(µmol/L)</td>
<td>72.00(61.00, 82.19) b+</td>
<td>73.00(63.40, 88.00) b+</td>
<td>0.016 *</td>
</tr>
<tr>
<td>UA(µmol/L)</td>
<td>343.00(301.00, 392.00) b+</td>
<td>345.20(291.00, 390.00) b+</td>
<td>0.817</td>
</tr>
<tr>
<td>CysC(mg/L)</td>
<td>0.93(0.79, 1.09) b+</td>
<td>0.98(0.84, 1.16) b+</td>
<td>0.006 *</td>
</tr>
<tr>
<td>UA/HDL</td>
<td>304.64(230.77, 400.00) b+</td>
<td>308.57(237.41, 389.53) b+</td>
<td>0.550</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>3.81(2.92, 5.02) b+</td>
<td>3.89(2.84, 4.99) b+</td>
<td>0.711</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>2.11(1.56, 2.89) b+</td>
<td>2.22(1.59, 3.10) b+</td>
<td>0.093</td>
</tr>
<tr>
<td></td>
<td>Non-frail group (n = 731)</td>
<td>frail group (n = 275)</td>
<td>P-value</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------</td>
<td>------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>PLTC (10^9/L)</td>
<td>208.00 (172.00, 244.00) b+</td>
<td>195.00 (168.00, 229.60) b+</td>
<td>0.002 *</td>
</tr>
<tr>
<td>RBC (10^12/L)</td>
<td>4.50 (4.22, 4.84) b+</td>
<td>4.42 (4.12, 4.74) b+</td>
<td>0.003 *</td>
</tr>
<tr>
<td>WBC (10^9/L)</td>
<td>6.27 (5.29, 7.26) b+</td>
<td>6.28 (5.35, 7.32) b+</td>
<td>0.422</td>
</tr>
<tr>
<td>HB (g/L)</td>
<td>139.00 (130.00, 147.29) b+</td>
<td>137.00 (125.80, 146.00) b+</td>
<td>0.019 *</td>
</tr>
<tr>
<td>MCHC (g/L)</td>
<td>30.71 (29.70, 31.64) b+</td>
<td>30.89 (29.88, 31.91) b+</td>
<td>0.067</td>
</tr>
<tr>
<td>RWR</td>
<td>0.72 (0.60, 0.87) b+</td>
<td>0.69 (0.58, 0.83) b+</td>
<td>0.016 *</td>
</tr>
<tr>
<td>PWR</td>
<td>33.81 (27.36, 40.43) b+</td>
<td>31.07 (23.81, 38.29) b+</td>
<td>0.000 *</td>
</tr>
<tr>
<td>PLTC/MPV</td>
<td>19.93 (16.34, 24.04) b+</td>
<td>18.83 (15.51, 22.80) b+</td>
<td>0.001 *</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>450 (61.56)</td>
<td>161 (58.55)</td>
<td>0.383</td>
</tr>
<tr>
<td>Smoking, n(%)</td>
<td>148 (20.25)</td>
<td>89 (32.36)</td>
<td>0.000 *</td>
</tr>
<tr>
<td>Drinking, n(%)</td>
<td>81 (11.08)</td>
<td>36 (13.09)</td>
<td>0.375</td>
</tr>
<tr>
<td>CA, n(%)</td>
<td>142 (19.43)</td>
<td>104 (37.81)</td>
<td>0.000 *</td>
</tr>
<tr>
<td>DM, n(%)</td>
<td>154 (21.07)</td>
<td>84 (30.55)</td>
<td>0.002 *</td>
</tr>
<tr>
<td>RI, n(%)</td>
<td>13 (1.78)</td>
<td>22 (8.00)</td>
<td>0.000 *</td>
</tr>
<tr>
<td>Cardiac dysfunction, n(%)</td>
<td>39 (5.34)</td>
<td>23 (8.36)</td>
<td>0.075</td>
</tr>
<tr>
<td>AF, n(%)</td>
<td>52 (7.11)</td>
<td>40 (14.55)</td>
<td>0.000 *</td>
</tr>
<tr>
<td>Constipation, n(%)</td>
<td>79 (10.81)</td>
<td>56 (20.36)</td>
<td>0.000 *</td>
</tr>
</tbody>
</table>

a normally distributed; a + the mean plus or minus the standard deviation (SD); b non-normally distributed; b + Mann-Whitney, median (interquartile range); c chi-square test, n(%); * statistically significant

**BMI** body mass index, **SBP** systolic blood pressure, **DBP** diastolic blood pressure, **AHI** the apnea-hypopnea index, **ODI** the oxygen desaturation index, **MAT** the mean apnea time, **MSaO2** the mean arterial oxygen saturation, **LSaO2** the lowest arterial oxygen saturation, **TB** total bilirubin, **TC** total cholesterol, **TG** triglyceride, **HDL** high-density lipoprotein, **LDL** low-density lipoprotein, **Cre** creatinine, **UA** uric acid, **CysC** cystatin c, **PLTC** platelet count, **RBC** red blood cell count, **WBC** leukocytes count, **HB** hemoglobin, **MCHC** mean corpuscular hemoglobin concentration, **RWR** red blood cell count/white blood cell count, **PWR**
platelet count/white blood cell count, PLTC/MPV platelet count/mean platelet volume, CA carotid atherosclerosis, DM diabetes mellitus, RI renal insufficiency, AF atrial fibrillation

Our study shows that the incidence of frailty was higher among patients with a history of smoking (32.36% vs 20.25%) or drinking (13.09% vs 11.08%), CA (37.81% vs 19.43%), DM (30.55% vs 21.07%), RI (8.00% vs 1.78%), cardiac dysfunction (8.36% vs 5.34%), AF (14.55% vs 7.11%), and constipation (20.36% vs 10.81%).(Fig. 2).

**Incidence of frailty in elderly patients with OSAS**

The incidence of frailty was 27.34% in the total study population. Of these, the incidence of frailty significantly increased with age (13.47% for 60–69 years vs 31.17% for 70–79 years vs 62.33% for 80–104 years). The incidence of frailty tended to increase with increasing OSAS severity: 24.81%, 24.84%, and 30.65% in mild, moderate, and severe OSAS, respectively. Although the incidence of frailty was higher among women than among men (28.86% vs 26.35%), the difference was not significant (Fig. 3). Furthermore, we determined the incidence of debilitation among elderly patients with OSAS with different underlying diseases, as shown in Fig. 4.

**Factors associated with frailty in elderly patients with OSAS**

Multivariate Cox regression analysis considering frailty as the dependent variable revealed that age (hazard ratio [HR], 1.058; 95% confidence interval [CI], 1.043–1.074; \( P < 0.001 \)), constipation (HR, 1.490; 95% CI, 1.101–2.018; \( P = 0.01 \)), CA (HR, 1.739; 95% CI, 1.299–2.330; \( P < 0.001 \)), and renal insufficiency (HR, 1.878; 95% CI, 1.177–2.996; \( P = 0.008 \)) are independent risk factors for frailty in participants after adjustments for height, SBP, TC, TG, Cre, CysC, RBC, PLTC/MPV, and DM. (Table 2).
Table 2
Results of cox regression analysis

<table>
<thead>
<tr>
<th></th>
<th>univariate cox regression analysis</th>
<th>multivariate cox regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR(95%CI)</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.074(1.060 ~ 1.088)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>2.062(1.535 ~ 2.769)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid atherosclerosis</td>
<td>3.146(2.454 ~ 4.034)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>3.682(2.375 ~ 5.709)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.996(0.994 ~ 0.999)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The mean pulse oxygen saturation</td>
<td>0.928(0.899 ~ 0.958)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Discussion

The overall incidence of frailty among elderly patients with OSAS was relatively high, with that among patients with mild, moderate, and severe OSAS being 24.81%, 24.84%, and 30.65%, respectively. Age, constipation, CA, and RI were independent risk factors for frailty in elderly patients with OSAS, and MSaO2 and platelet count are factors preventing the development of frailty in elderly patients with OSAS.

Age is an independent risk factor for frailty, and the risk of developing frailty increases with advancing age. A US study that surveyed 11344 individuals aged ≥ 65 years reported the incidence of frailty at 30.4% and the incidence increased with age; the positivity rate of frailty was 23.9% among patients aged 65–74 years, 28.7% for those aged 75–84 years, and 40.8% among those aged ≥ 85 years22. Another study reported an increasing incidence of frailty and pre-frailty with advancing age23. A study including 970 elderly adults showed that the risk of developing frailty is higher among individuals at medium or high risk of developing OSAS than among those at low risk of developing OSAS (odds ratio [OR]_moderate=1.67, OR_high=3.00). Furthermore, with advancing age, OSAS progressed with the severity of the obstructive event, and the risk of frailty increased11.

Constipation is an important risk factor for frailty in elderly patients with OSAS. Related studies have shown that it is strongly associated with frailty; the incidence of chronic constipation varies with the state of frailty. The incidence of chronic constipation in healthy individuals is 4.4%, whereas it is 18.5% in the frail population and 10.7% overall24. Another study attributed this association to the association between constipation and malnutrition, as malnutrition in turn is strongly associated with frailty25. The study
found that the overall incidence of functional constipation in the elderly population was 26.8% and that among women and men was 32.4% and 21.8%, respectively. The incidence of functional constipation in the frail population was 41.7%, whereas it was 33.9% and 24.2% in the pre-frail and healthy populations, respectively. Another study reported that increasing severity of frailty is associated with increasing incidence of frailty (6.5%, 25.8%, and 67.7% among healthy, pre-frail, and frail individuals, respectively).

Imbalance in the gut microbiota is also an important factor contributing to chronic constipation. A domestic study performed 16-S rRNA microbiome sequencing, metagenome sequencing, and histological analysis of stool samples from patients with chronic constipation. The incidence of Prevora-9 bacteria was lower and E. coli is higher in constipation compared to healthy people. As previously mentioned, debilitating physical manifestations are usually characterized by the presence of sarcopenia. One of the significant changes in body composition was defined as the loss of skeletal muscle mass and strength. Increasing evidence suggests that the gut microbiota may play a role in this phenomenon, possibly by affecting muscle protein synthesis or through the action of microbiota-dependent metabolites.

Our study found that atherosclerosis is a risk factor for frailty in old age, which is consistent with the findings of other studies. In theory, changes in arterial stiffness may be affecting body composition and cardiovascular risk factors. Sampaio et al. suggest that blood flow to muscles decreases with age, which is associated with the severity of atherosclerosis. Atherosclerosis and frailty have similar pathophysiological mechanisms that may be related to inflammation, endothelial dysfunction, and hormone levels, suggesting a potential correlation between the two. Atherosclerosis can reduce physical activity, affect psychological state, and social life, thereby accelerating the onset of frailty. Both are interrelated and affect each other.

Studies have shown that patients with chronic kidney disease have a higher incidence of frailty. Regardless of dialysis administration, frail patients with chronic kidney disease have a reduced quality of life. Regardless of age, sex, or comorbidities, hospitalization rates and mortality rates increased accordingly. Other studies have also shown that frailty is common among patients with advanced chronic kidney disease, with an incidence up to 73% in patients on maintenance hemodialysis; in contrast, in the general population aged ≥ 65 years, the incidence is approximately 10%. One review suggested that the incidence of frailty in patients with chronic kidney disease is remarkably high and increases with increasing frailty severity. Several pathophysiological processes associated with chronic kidney disease may notably affect skeletal muscle function, resulting in impaired physical performance that leads to physical frailty. Chronic kidney disease leads to loss of body protein mass and energy reserves, which are associated with mitochondrial dysfunction and disorders of muscle protein synthesis. The superposition of physiological and psychological factors leads to a decrease in the body's functional reserves, resulting in a decrease in resistance to stressors and resulting in frailty onset and progression.

Our findings show that platelet counts are a protective factor for the development of frailty in elderly patients with OSAS. A study showed that for individuals within a wide age range and particularly among
the elderly, the platelet count gradually decreases with aging\textsuperscript{41}. Another study found that thromboplastin and hormone metalloproteinase (ADAM10) levels may be associated with mild cognitive impairment (MCI) and physical frailty, with platelet ADAM10 levels decreasing under conditions of MCI and physical frailty\textsuperscript{42}. Therefore, we can hypothesize that a higher platelet count within the normal range is associated with a lower the risk of frailty in elderly patients with OSAS, and the specific underlying pathophysiology needs further exploration.

Decreased MSaO\textsubscript{2} due to nocturnal hypoxia may be a cause of frailty in elderly patients with OSAS, which is consistent with the findings of Mariam El Assar et al\textsuperscript{43}, who hypothesized that decreased expression of genes associated with oxidative stress or hypoxia response is strongly associated with frailty; that is, a reduced gene expression implies a longer hypoxia time, which in turn increases frailty risk. In contrast, actively resolving hypoxia and reducing hypoxia time reduces frailty risk. Elderly patients with OSAS experience repeated post-collapse ventilation of the upper respiratory tract, which results in repeated hypoxia and reoxygenation that increases oxidative stress, which in turn may lead to an increased risk of frailty in elderly patients with OSAS. Thus, the higher the average oxygen saturation, the lower the risk of developing frailty in elderly patients with OSAS.

**Study limitations**

Our study has merits and some limitations. First, we studied the incidence and influencing factors of frailty in elderly patients with OSAS, but excluded a healthy control group; Second, all study subjects consisted of Chinese patients and, as a result, selection biases may occur; Finally, due to the relative complexity of medication in elderly patients, we did not explore the effect of medication on the occurrence of frail in elderly patients. However, these limitations do not affect the value of our research, and we will further improve it in future research.

**Conclusion**

The proportion of underlying conditions in patients with frailty was also relatively high, which greatly reduced the quality of life in the elderly population. Of those, advanced age, constipation, and CA are independent risk factors, and platelet count and average oxygen saturation are protective factors for the development of frailty in elderly patients with OSAS. Therefore, dietary regulation, moderate exercise, and effective treatment of OSAS may help in early prevention and treatment of frailty and improve its prognosis.

**Abbreviations**

(OSAS) obstructive sleep apnea syndrome

(PSG) polysomnographic
(CA) carotid atherosclerosis

(RI) renal insufficiency

(PLTC) platelet count

(MSaO$_2$) mean arterial oxygen saturation

(AHI) sleep apnea hypopnea index

(BMI) body mass index

(ODI) oxygen desaturation index

(MAT) mean apnea time

(LSaO$_2$) lowest arterial oxygen saturation

(TC) total cholesterol

(TG) triglyceride

(HDL) high-density lipoprotein

(LDL) low-density lipoprotein

(Cre) creatinine

(UA) uric acid

(CysC) cystatin c

(RBC) red blood cells

(WBC) white blood cells

(UA/HDL) ratios of uric acid and high-density lipoprotein

(TC/HDL) total cholesterol and high-density lipoprotein

(LDL/HDL) low-density lipoprotein and high-density lipoprotein

(RWR) RBCs and WBCs

(PWR) platelets and WBCs

(PLTC/MPV) platelets and mean platelet volume
(HB) hemoglobin
(MCHC) the mean corpuscular hemoglobin concentration
(AF) atrial fibrillation
(DM) diabetes mellitus

Declarations

Disclosure Statement

The study is in agreement STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines and was carried out in accordance with the Declaration of Helsinki. The Ethics Committee of the General Hospital of the People's Liberation Army of Chinese (S2019-352-01) approved the study. All participants have written informed consent.

Consent for publication:

Not applicable.

Availability of data and materials:

Our data may not be shared directly, because it is our teamwork; informed consent should be attained from all the team members. Our data or material may be available after contacting the corresponding author or first author.

Competing interests:

All authors have seen and approved this manuscript. All other authors report no conflicts of interest.

Funding:

This study was supported by Military Health Care Project (22BJZ52, 23BJZ27); Youth Program for Military Medicine of Chinese PLA General Hospital (QNC19054); The PLA General Hospital Joint Logistic Support Equipment Project(LB20211A010013). Military experimental animal special research project (SYDW_KY[2021]04). The funders had not directly role in the design, data collection, analysis, interpretation or writing of the manuscript.

Authors’ contributions:

Zijun He, Xin Xue, Yinghui Gao, ZuoZhang, Zhe Zhao, Libo Zhao, Xiaofeng Su, Mengxi Li, Mengying Xing, Tianjiao Li and Fengfeng Fang collected the data. Zijun He analyzed the data and wrote the manuscript draft, Kailiang Li, Jiming Han and Lin Liu designed this study. All authors have read and approved the manuscript.
Acknowledgements:

Not applicable.

References


**Figures**
Figure 1

Study flowchart
Figure 2

Prevalence of different underlying diseases in frailty and non-frailty.

Figure 3

Incidence of frailty in total study population, male and female, different age groups, and Severity of OSAS.
Figure 4

Incidence of frailty in different underlying diseases.