Metabolic syndrome prevalence in patients with obstructive sleep apnea syndrome and chronic obstructive pulmonary disease: Relationship with systemic inflammation

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Abstract

Objectives: Metabolic syndrome (MetS) is frequent in both chronic obstructive pulmonary disease (COPD) and Obstructive sleep apnea (OSA). The aim of this study was to assess the frequency of MetS and the status of systemic inflammation in overlap syndrome.

Methods: A total of 151 consecutive COPD patients were recruited in this cross-sectional study. Spirometry and polysomnography were done in all patients. The MetS was defined according to the criteria of the International Diabetes Federation. Anthropometry, metabolic parameters and inflammatory biomarkers: IL-6, TNF-α, leptin, resistin and adiponectin were recorded.

Results: OSA was present in 19.2% COPD patients. Subjects with overlap syndrome had higher neck and waist circumference compared to those with COPD alone. Significant differences in levels of blood pressure, lipid metabolic and glucose metabolic were found between two groups with overlap and COPD, as well as inflammatory biomarkers. Prevalence of MetS was increased in overlap group. Multivariate logistic regression showed that BMI, systolic BP when fall asleep and recumbent angiotens levels as significant independent predictors of the presence of Mets in overlap syndrome.

Conclusion: This study shows that MetS is frequent in patients with overlap. Overlap syndrome indicates a higher cardiometabolic risk and higher levels of systemic inflammatory.

KEYWORDS
cardiometabolic risk, chronic obstructive pulmonary disease, inflammatory profile, insulin resistance, metabolic syndrome, obstructive sleep apnea
1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD), which is characterized by both airway inflammation and systemic inflammation, is a complex and progressive disease and a growing global epidemic especially in developing countries. It is prone to the viewpoint that systemic inflammation maybe complicated in the pathogenesis of majority comorbidity of COPD. Obstructive sleep apnea (OSA) is characterized by repeated episodes of complete or partial upper airway obstruction during sleep, which results in interruptions of breathing during sleep, recurring episodes of hypoxemia, sleep fragmentation and daytime sleepiness. It has been recognized that OSA is complicated by COPD and noted in polysomnography (PSG) studies of COPD patients. The underlying mechanisms of COPD patient running high risk of OSA include many factors as follows: alveolar hypoventilation, airway obstruction, hyperinflation, respiratory muscle dysfunction, blunted ventilatory responses to hypoxia and hypercapnia. Their coexistence, which is denominated as “overlap syndrome (OS)”, has a prevalence of 0.5%~1% in the population over 40 years, and is known to have a greater degree of hypoxemia and hypercapnia than OSA or COPD alone, and furthermore intensifies pronounced inflammatory activation which may play an important role in the development and progression of metabolic dysfunction.

Metabolic syndrome (MetS) is a complex of interrelated disorders associated with abdominal obesity, elevated blood glucose, arterial hypertension and dyslipidemia [elevated triglycerides and low levels of high-density lipoprotein (HDL) cholesterol]. Metabolic syndrome may induce atherosclerotic cardiovascular disease and increase the risk of developing type 2 diabetes.

Previously studies reported that MetS is more prevalent in COPD patients than in people with normal lung function, underlying the mechanisms of obesity (especially neck obesity), physical inactivity, cigarette smoking, corticosteroid use (by promoting central obesity and fluid retention with associated upper airway narrowing), as well as inflammation and oxidative stress, and hypoxia. OSA is associated with multiple systemic complications such as cardiovascular morbidities, hypertension, obesity, dyslipidemia, insulin resistance (IR), diabetes and metabolic syndrome. Potential mechanisms through which OSA induces metabolic disturbances may include hypoxia, sympathetic activation and systemic inflammation, involving the activation of inflammatory pathway, imbalance of lipid synthesis and lipid clearance, and the imbalance of glucose and insulin regulating hormones, such as interleukin (IL) -6, tumor necrosis factor alpha (TNF-α), leptin and adiponectin. It is well known that systemic inflammation plays a key role in both COPD and OSA. There will be a more severe or an “overlapped” systemic/multiple organic inflammation and oxidative stress in overlap syndrome with no exactly clear mechanism which may play an important role in the development and progression of metabolic dysfunction.

Metabolic syndrome associated with COPD and OSA alone have been largely studied in the population, but few studies have been conducted in overlap syndrome patients. Based on a large cohort study of MetS, there are comprehensive indexes to evaluate cardiometabolic status in COPD and OSA alone including fasting lipid profile, blood glucose (BG), Fasting insulin, HgbA1C, blood pressure and renin-angiotensin-aldosterone (RAAS). So we measured above-mentioned indexes in patients with COPD combined with OSA. Also, low-grade inflammation, a hallmark of COPD, OSA and MetS, is included in development and progression of atherosclerosis. Therefore, we assess inflammatory markers (TNF-α, IL-6, leptin, resistin and adiponectin) in COPD patients with OSA and those without OSA. The purpose of the study was to evaluate the metabolic abnormalities, the level of systemic inflammation and to identify the cardiometabolic risk factors in subjects with COPD overlapped with OSA.

2 | METHODOLOGY

About 151 consecutive COPD patients were enrolled from Jan 2014 to Jun 2015 in this cross-sectional study. Patients requiring hospital admission, those who refused to participate in the study were excluded. The ethical and methodological aspects of the investigation were approved by the corresponding ethics committees and all participants signed an informed consent. The diagnosis was made based on the Global initiative for chronic obstructive lung disease (GOLD) criteria. Inclusion criteria were a diagnosis of COPD patient over 40-year-old, disease during stable state (no exacerbations and no medication change.
in the preceding 6 weeks), while exclusion criteria were considered the presence of respiratory diseases other than COPD such as interstitial pneumonia, tuberculosis, neoplasm, bronchial asthma, thoracic or abdominal surgery and pleural disease.

We recorded for each of the participants the demographic characteristics. Blood pressure, weight, height, neck and waist circumference (WC) were measured. Venous blood samples were obtained for analysis of glucose, glycated hemoglobin, plasma insulin, triglycerides, cholesterol [total, HDL, low-density lipoprotein (LDL)], resistin, angiotensin and aldosterone, 25 Hydroxylated Vitamin D, IL-6, TNF-α, leptin, adiponectin. Urine was obtained for measurement of microalbumin. Patients also underwent pulmonary function tests and overnight polysomnography study.

The MetS was assessed according to the 2006 consensus definition by the International Diabetes Federation: abdominal obesity characterized by the presence of waist circumference(WC) ≥94 cm for men and ≥80 cm for women, plus any 2 or more of the following criteria: (1) Fasting blood glucose (FBG) ≥5.6 mmol/L, or previously diagnosed type 2 diabetes; (2) systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or treatment for diagnosed hypertension; (3) HDL cholesterol <1.03 mmol/L in male and <1.29 mmol/L in female or specific treatment for lipid abnormality; and (4) triglycerides (TG) ≥1.70 mmol/L or specific treatment for lipid abnormality.12

2.1 | Anthropometric assessment

The height and weight of the study participants were measured to the nearest 0.1 cm and 0.1 kilogram without bulky clothes and shoes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m²). Waist circumference was measured at the midway between the lowest rib and the top of the iliac crest. Neck circumference (NC) was measured in the midpoint of the neck between mid-cervical spine and mid-anterior neck to 0.5 cm just below the laryngeal prominence.

2.2 | Pulmonary function testing

Every participant got pulmonary function testing according to the European Respiratory Society guidelines with the use of standard spirometry (spirometer: Masterscreen Pneumo, Viasys Healthcare, Germany).13 The forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and FEV1/FVC ratio were obtained. The diagnosis of COPD was made by a post-bronchodilator FEV1/FVC ratio <0.70 in accordance with current GOLD guidelines.13 COPD patients were stratified by disease severity as “mild” (GOLD stage I), “moderate” (GOLD stage II), “severe” (GOLD stage III) or “very-severe” (GOLD stage IV).

2.3 | Blood pressure measurements

Blood pressure was measured by a sphygmomanometer (Omron MX3 Plus, Omron, Japan) on the right arm of the seated participant and was recorded as a mean of three readings taken at 15 minutes interval.

2.4 | Polysomnography

For a diagnosis of OSA, full-night PSG (EEG- 9200 Neurofax®; Nihon Koden, Tokyo, Japan), which consisted of continuous recordings from four electroencephalographic (EEG) leads, two electrooculography (EOG) leads and three electromyographic (EMG) leads (one submental and bilateral anterior tibialis); nasal airflow measurements; thoraco-abdominal movements; pulse oximetry and ECG, was done in all patients diagnosed with COPD. Apnea was defined as a cessation of airflow for 10s or longer and hypopnea as 50% reduction in airflow lasting 10s or longer accompanied by ≥4% desaturation. The apnea-hypopnea index (AHI) was defined as the average number of apnea plus hypopnea episodes per hour during sleep recording time. The participants were diagnosed with OSA with an AHI ≥5 events/h. Entire analysis was done according to the American Academy of Sleep Medicine (AASM) guidelines.14 Mild OSA was defined if AHI was between 5 and 15 h⁻¹, moderate if it is between 15 and 30 h⁻¹, and severe if AHI is >30 h⁻¹, respectively.

2.5 | Laboratory measurements

Venous blood samples were collected after an overnight (≥10 h) fast. Fasting glucose level was measured by glucose oxidase-peroxidase reagents using a Beckman Glucose Analyzer (Beckman Instruments, Irvine, CA, USA), so was glycated hemoglobin (HgbA1C) on Variant analyzer (Variant II Analyzer (Beckman Instruments, Irvine, CA, USA), so was glycated hemoglobin (HgbA1C) on Variant analyzer (Variant II TURBO, Bio-Rad, Hercules, CA, USA). Immunoradiometric assays specific for insulin (Linco, St. Louis, Mo., USA) was used for the measurement of fasting insulin based on an antisem with <1% cross-reactivity for pro-insulin. Triglycerides and total cholesterol were determined by enzymatic methods on the analyzer Beckman Coulter (USA). In order to evaluate the CRP level, the immunoturbidimetric method was applied (analyzer Beckman Coulter, USA). Plasma renin concentration was measured using an immunochemilumino metric assay (Nichols Advantage Direct Renin Assay, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA, USA). Angiotensin concentration was determined through the immuno-fluorescence assay as described in the instruction manual (Fluorescent EIA Kit, phoenix pharmaceuticals). Serum aldosterone was measured by a sensitive radioimmunoassay (Quest Diagnostics, Cambridge, MA). Enzyme-linked
immunosorbent assay (ELISA) were performed with responding kits (Invitrogen Inc, USA) for IL-6, TNF-α, leptin, resistin, adiponectin as manufacturer’s instructions.

2.6 | Statistical analysis

Statistical analysis was performed using the SPSS 20 (SPSS Inc., Chicago, IL) software package. All values were reported as mean ± standard deviation (SD), and categorical variables as counts and percentage. Continuous variables that did not show a normal distribution are expressed as the median value (25-75th percentile range). To compare the difference between groups we used the Student t test or Mann-Whitney test for continuous variables, while the Chi-square test or Fisher exact test were expressed for categorical variables. Linear relationships between key variables were determined using Pearson’s correlation coefficient. A multiple logistic regression analysis was conducted to evaluate clinical variables that were significantly associated with Mets in patients with COPD overlapped OSA, after variables with non-normal distribution were transformed logarithmically. P < 0.05 was considered statistically significant.

3 | RESULTS

The clinical and biochemical features of the subjects stratified by gender are shown in Table 1. The average age was 58.26 years (50-66years). Neck circumference and waist circumference were much higher in males than in females.

Cardiovascular risk factors and inflammatory markers in two groups with COPD and overlap are shown in Table 2. Compared to COPD group, subjects with overlap group had high levels of fasting glucose, fasting insulin and HgbA1C (all P < 0.001). The levels of TC, LDL-C and TG were significantly higher in the overlap group than in the COPD group, while HDL-C was significantly lower in overlap group (P < 0.05). The inflammatory profile in overlap group differed from that in COPD group. We evaluated TNF-α, IL-6, leptin, resistin and adiponectin. As shown in Table 2, levels of TNF-α, IL-6 were significantly higher in the overlap group than in the COPD group (P < 0.05), the same as leptin, resistin and adiponectin (P < 0.05).

Table 3 shows the detection rates of MS and its components in the two groups. There was a higher incidence of MS in overlap group than that in COPD group (51.7% versus 9.0%). Compared with COPD group, there were higher detection rates of abdominal obesity, high BP, high TG, low HDL-C and high glucose levels in overlap group with 79.3%, 55.2%, 37.9%, 24.1% and 58.6%, respectively.

Independent associations between cardiovascular risk factors and inflammatory markers and OSA in COPD according to logistic analysis are shown in Table 4. After multiple factors adjustment, BMI, recumbent angiotens and recumbent aldosterone are the independent factors of OSA, with BMI OR 2.552 (95% CI, 1.286-5.064), and Recumbent angiotens OR 1.293 (95% CI, 1.124-1.287), and Recumbent aldosterone OR 1.502 (1.076-2.098). For an additional 1 kg/m² each in BMI, the occurrence risk of OSA in COPD increased 2.552-fold, the occurrence risk of OSA in COPD increased 1.166-fold, for additional 1 mmol/L each in recumbent angiotens, the occurrence risk of OSA in COPD increased 1.293-fold.

4 | DISCUSSION

In the present study, the estimated prevalence of OSA in COPD patients was 19.2%, which was similar to the prevalence reported in early studies. Moreover, the prevalence rates of general obesity in overlap subjects were high up to 79.3%, suggesting that general obesity were strongly associated with OSA on the basis of COPD. Moreover, we observed that blood pressure, metabolic profiles and inflammatory biomarkers was significantly abnormal in overlap group compared to COPD alone. In the end, we demonstrated that BMI was a potential predictor of OSA independent of NC or WC, thus BMI might be a powerful physical sign prone to OSA in COPD patients. Such an independent relationship of OSA and COPD is reported for the first time.

In the present study, subjects in overlap syndrome had higher prevalence of MetS (51.7%), suggesting that overlap may contribute to the development of MetS. Vujic

| Variable         | Total (N = 151) | Female (N = 35) | Male (N = 116) | P   |
|------------------|----------------|----------------|---------------|-----|
| Gender #         |                | 23.2%          | 76.8%         |     |
| Age, years #     | 58.26 ± 8.319  | 56.06 ± 7.673  | 58.88 ± 8.462 | 0.08|
| NC (cm) #        | 38.250 ± 3.359 | 34.94 ± 3.412  | 39.29 ± 3.661 | 0.001|
| WC (cm) #        | 93.227 ± 10.550| 88.31 ± 10.414 | 95.33 ± 10.193| 0.001|
| BMI(kg/m²) #     | 25.587 ± 3.529 | 26.00 ± 3.597  | 26.80 ± 3.542 | 0.244|

Abbreviations: COPD, chronic obstructive pulmonary disease; NC, neck circumference; WC, waist circumference; BMI, body mass index. A values expressed as n (%) or mean ± SD; SD, Standard deviation.

# Chi-square test.

TABLE 1 General characteristics of study population (N = 151), by group
investigated 98 consecutive stable COPD patients, the prevalence of MetS in COPD patients was 37.8%. And there was a 1.58-fold increase in the risk of MetS in OSA patients with high CRP level compared with non-OSA participants with low CRP level. Overlap syndrome increases the risk of metabolic diseases and cardiovascular diseases, therefore a cost-effective way to appropriately screen for OSA is urgent. COPD may frequently be complicated by OSA with a prominent risk factor of edema in the pharyngeal soft tissues associated with elevated pulmonary pressures, right ventricular dysfunction and right heart failure.

Overlap syndrome may have greater degree of inflammatory cell activation and hypoxia and consequently contribute to several adverse outcomes including metabolic dysfunction. The relationship between obesity and inflammation has been further confirmed by Xu et al which showed that obesity is associated with infiltration of macrophages into white adipose tissue. Similarly, our results showed that TNF-α and IL-6 levels were significantly higher in overlap group.

Table 2: Comparisons of cardiovascular risk factors and inflammatory markers between the two groups of COPD and Overlap (N = 151)

| Variable                  | COPD (N = 123) | Overlap (N = 28) |
|---------------------------|----------------|------------------|
| Current smoker, n(%)      | 51 (41.46)     | 17 (60.71)       |
| BP                        |                |                  |
| Systolic BP               | 117.260 ± 13.481* | 135.610 ± 18.291* |
| Diastolic BP              | 75.240 ± 8.345* | 86.860 ± 11.540*  |
| RAAS                      |                |                  |
| Recumbent renin           | 0.758 ± 0.1705* | 1.045 ± 0.2294*  |
| Recumbent angiotensin     | 50.064 ± 9.7739* | 73.696 ± 10.3558* |
| Recumbent aldosterone     | 16.520 ± 3.8225* | 24.761 ± 4.3942* |
| Fasting glucose (mmol/L)  | 4.978 ± 0.6072* | 5.829 ± 0.5530*  |
| HgbA1C (%)                | 5.268 ± 0.5620* | 6.304 ± 0.5506*  |
| Fasting insulin (mIU/L)   | 8.7559 ± 0.50747* | 12.9125 ± 1.28308* |
| Lipid profile             |                |                  |
| Serum Triglycerides (mg/dL)| 1.5843 ± 0.30544* | 1.9079 ± 0.34409* |
| HDL-C (mmol/L)            | 1.4737 ± 0.30392* | 1.2611 ± 0.24289* |
| Total cholesterol (mmol/L)| 4.7436 ± 0.64156* | 5.5993 ± 0.58681* |
| Sleep parameters          |                |                  |
| AHI, events/h             | 1.9837 ± 1.31811* | 47.2143 ± 24.14517* |
| Minimum O2 %              | 90.6422 ± 2.150601* | 67.6071 ± 11.8676* |
| %<90% O2 Sat              | 0.2584 ± 0.936301* | 31.1725 ± 29.57122* |
| Inflammatory markers      |                |                  |
| TNF-α (ng/L)              | 423.51 ± 184.883* | 1504.46 ± 203.033* |
| IL-6 (ng/L)               | 24.1062 ± 11.72166* | 91.5607 ± 12.22028* |
| Leptin (ng/L)             | 862.66 ± 159.913* | 1294.46 ± 173.177* |
| Resistin (ng/L)           | 2752.295 ± 471.2200* | 4300.310 ± 657.1664* |
| Adiponectin (ng/L)        | 8.063 ± 0.8578* | 3.293 ± 1.8570*  |

Abbreviations: BP, blood pressure; COPD, chronic obstructive pulmonary disease; Overlap, chronic obstructive pulmonary disease combined with obstructive sleep apnea; HgbA1C, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol (HDL-C); IL-6: interleukin-6; RAAS, renin-angiotensin-aldosterone system; TNF-α, tumor necrosis factor-α.

Table 3: Components of MS in COPD and overlap patients

| Variable                  | COPD (N = 123) | Overlap (N = 28) | P     |
|---------------------------|----------------|------------------|-------|
| Abdominal                 |                |                  |       |
| Obesity, n %              | 69 (56.0)      | 23 (82.1)        | <0.005|
| High BP, n %              | 24 (19.5)      | 16 (57.1)        | <0.005|
| High TG, n %              | 14 (11.3)      | 11 (39.2)        | <0.005|
| Low HDL-C, n %            | 21 (17.0)      | 7 (25.0)         | <0.005|
| High glucose, n %         | 29 (23.5)      | 17 (60.7)        | <0.005|
| MS, n %                   | 11 (8.9)       | 15 (53.5)        | <0.005|

Abbreviations: BP, blood pressure; COPD, chronic obstructive pulmonary disease; Overlap, chronic obstructive pulmonary disease combined with obstructive sleep apnea; HDL-C, high density lipoprotein cholesterol (HDL-C); TG, triglyceride.

and his colleagues found that TNF-α and IL-6 levels are not only increased in OSA, but also significantly associated with insulin resistance, MS and obesity. The research indicated...
that serum IL-6 level was statistically significant correlated with MetS in COPD patients.\(^\text{19}\) Leptin and Adiponectin are important biomarkers produced by adipocytes that play a key role in regulating metabolic processes, including glucose regulation and fatty acid oxidation. The level of leptin is proportional to the degree of IR. The level of adiponectin correlates positively with insulin sensitivity and is of anti-inflammatory or protective effects for vasculature system under the exposure to hypoxia. A significant reduction in insulin sensitivity has been described in patients with OSA, which was correlated with severity of OSA\(^\text{20}\) as well as COPD.\(^\text{21}\) This may be explained by the fact that long standing hypoxia mediated increase in hypoxia-inducible factor-1α (HIF-1α) may detrimentally induce adipose tissue fibrosis and resistance to insulin and hyperglycemia. Subsequently, patients with overlap syndrome experience higher incidence of cardiovascular disease and arterial hypertension,\(^\text{22}\) but its relationship with Non-alcoholic fatty liver disease (NAFLD) is poorly studied. It is in debate whether OSA or COPD accelerates liver injury independently of coexisting comorbidities, including insulin resistance and MetS. In this study, we found that mean levels of TC, LDL-C, TG and level of AST and ALT in overlap was significantly higher than that in COPD alone, while HDL-C was lower. Studies suggest that OSA appears to have an impact on lipid metabolism with functional abnormalities in HDL and elevations in TC, LDL and TG levels.\(^\text{23}\) Another study reported that COPD is one of the elements promoting the evolution of MetS including abnormal lipid metabolism.\(^\text{24}\) Our early study showed that there was synergistic effect between hepatic inflammation and coagulability and a more significant liver-derivative inflammatory and prothrombotic status in rat exposure to emphysema combined with sleep hypoxia.\(^\text{25}\) For the mechanism, animal studies suggested that a higher degree of systemic inflammation plays an important role in the development of fatty liver in obesity, resulting in decreased lipoprotein clearance, increased lipolysis and enhanced hepatic lipid output.

There were several limitations of our study. First, the sample size is small and the study was performed in a single center, which makes it difficult to describe causal relationships of detected associations. Second, prospective studies are needed for further understanding of MetS in patients with COPD, such as the effect of CPAP on MetS components and systemic inflammatory profile with overlap syndrome.

## CONCLUSION

In summary, this study demonstrates that MetS is frequent in patients with overlap syndrome and is associated with higher levels of systemic inflammatory. Thus, overlap syndrome indicates a higher cardiometabolic risk that could manifest as metabolic complications. Finally, the important clinical implications of these findings highlight the importance of early identification and accurate management of all patients with OSA and COPD.

## CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

### AUTHOR CONTRIBUTIONS

**Literature search:** Wei Zhou, Cai-li Li; **Data collection:** Wei Zhou, Cai-li Li; **Study design:** Cai-li Li, Jing Feng; **Analysis of data:** Wei Zhou, Cai-li Li, Jing Feng; **Manuscript preparation:** Wei Zhou, Cai-li Li, Jie Cao; **Review of manuscript:** Jie Cao, Jing Feng.

### ETHICS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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