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Relationship between slow-wave sleep and serum γ-glutamine transaminase in non-obese men with obstructive sleep apnea–hypopnea syndrome

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Abstract

Background Obstructive sleep apnea–hypopnea syndrome (OSAHS) is a disease characterized with intermittent hypoxia and sleep fragmentation. Obesity and gender are major risk factors for the onset of OSAHS. Previous studies on obese men with OSAHS have been performed, while few studies on non-obese men with OSAHS have been carried out. The purpose of this study was to explore the clinical characteristics of polysomnography and blood biochemical indexes in non-obese men with OSAHS and to identify the possible influencing factors.

Methods This retrospective study included patients with OSAHS who underwent polysomnography in our hospital. General clinical data such as overnight polysomnography and biochemical indicators were recorded. The patients were divided into two groups according to the apnea–hypopnea index (AHI): mild to moderate OSAHS and severe OSAHS. The differences in biochemical parameters such as the levels of γ-glutamine transaminase (GGT), triglyceride (TG), glucose (GLU), and sleep structure parameters such as N1, N2, slow-wave sleep (SWS), and rapid eye movement (REM) sleep were compared and analyzed. Spearman correlation analysis and logistic regression were used to identify the risk factors of non-obese men with OSAHS. ROC curves were used to evaluate the predictive ability of SWS and GGT on disease severity.

Results Of 94 non-obese men with OSAHS, 49 had mild to moderate OSAHS and 45 had severe OSAHS. Our data suggested that the levels of low oxygen saturation (L-SaO_2), mean oxygen saturation (M-SaO_2), SWS, and GGT were significantly changed in the mild to moderate OSAHS group compared with the severe group ($p < 0.05$). For patients with OSAHS, the proportion of SWS in the group with severe OSAHS was higher than that in the mild to moderate group ($p < 0.05$), and the serum GGT enzyme levels were significantly elevated in the severe group compared to the mild to moderate group ($p < 0.05$). Using logistic regression analyses, our data revealed that both SWS and GGT enzyme levels were independent risk factors for AHI ($p < 0.05$). In addition, the results of correlation analysis indicated that SWS was related to triglyceride (TG), total cholesterol (TC), apolipoprotein E (APOE), and triglyceride glucose (TyG) index ($p < 0.05$); GGT was related to TG, TC, APOE, and TyG index ($p < 0.05$). Furthermore, SWS was independently associated with GGT ($p < 0.05$). The area under the ROC curve plotted with the combined coefficient of SWS and serum GGT was 0.728, which was predictive of the disease severity.

Conclusions These results suggest that SWS and GGT are independent associated factors of the severity of the disease. However, TyG index was not an independent associated factor of the severity of disease in non-obese men with OSAHS. In addition, SWS and GGT were negatively correlated. SWS combined with serum GGT may be predictive of the severity of the disease. This study may have added to our understanding of the pathogenesis of OSAHS in non-obese men.

Keywords Obstructive sleep apnea–hypopnea syndrome · γ-glutamyl transferase · Slow-wave sleep · Triglyceride-glucose index

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive collapses (apnoeas) or near collapses (hypopnoeas) of the upper airway during sleep, resulting in intermittent

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hypoxemia and increased sympathetic arousal. With symptoms of daytime dysfunction and other neurological impairments caused by the apneas and hypopneas in sleep, the disorder is also known as obstructive sleep apnea-hypopnea syndrome (OSAHS) [1]. Patients with untreated sleep-disordered breathing exhibit an increased risk of hypertension, stroke, heart failure, diabetes, car accidents, depression, and impairment of cognition [2–8]. Epidemiological studies have indicated that OSAHS is considered to be a gender-related disease, with male:female ratio ranging from 3:1 to 5:1 in the general population and from 8:1 to 10:1 in selected clinical populations [9]. Obesity is a major risk factor for OSAHS [10]. Previous studies have shown that the prevalence of OSAHS ranges from 55 to 90% in the severely obese [11], and only approximately 20% of adults with OSA are non-obese [12]. However, most previous studies on OSAHS have focused on obese subjects, but few studies have been performed on non-obese patients with OSAHS, which may affect the diagnosis and treatment. Therefore, the comorbidity burden is high in non-obese patients with OSA [13, 14].

Polysomnography (PSG) is an essential method to diagnose and evaluate this disease, and PSG provides detailed information about sleep architecture, duration, and quality. SWS is a category of non-rapid eye movement (NREM) sleep and clinical studies have shown that increased depth of NREM sleep may improve OSA [15]. Energy conservation [16], immune regulation [17], memory consolidation [18], and other neuroendocrine changes also occur during SWS, and include increased growth hormone release, insulin sensitivity, and decreased adrenocorticotropic hormone, [19] as well as sympathetic nervous system activity [20].

Previous studies have also found that serum biochemical indicators were also related to the severity of OSAHS, such as the levels of glucose, triglyceride(TG), andγ-glutamine transamina(GGT) enzyme. TyG index is calculated as Ln (fasting triglycerides (mg/dl) × fasting blood glucose (mg/dl)/2). Previous studies have revealed that the TyG index is a reliable marker of insulin resistance (IR) [21–24]. Kang et al. [25] have indicated that the TyG index was an independent predictor of increased OSA risk. And previous studies have suggested that intermittent hypoxia, oxidative stress, sympathetic activation, elevated serum GGT, and GGT are related to the severity of this disease [26].

As OSAHS seems to occur more commonly in men, previous studies on obese men with OSAHS have been carried out, but few studies have been performed on non-obese men. Therefore, this study included non-obese men with OSAHS as the study population, and the clinical characteristics of polysomnography and blood biochemical indexes in these patients were examined, and possible influencing factors were explored.

Methods

Population sampling

This observational study included adults who underwent polysomnography (PSG) at the Second Hospital of Chongqing Medical University from February 2013 to June 2022. The study was approved by the ethics committee of our hospital (2022 Colum Review No. (144)). Inclusion criteria were as follows: participants with a body mass index (BMI) < 28 kg/m^2, BMI was calculated as weight in kilograms divided by height by in meters squared. Exclusion criteria were: (1) Under the age of 18; (2) History of upper airway surgery, oral appliances, or continuous positive airway pressure therapy; (3) Active infection within the last 4 weeks; (4) Other sleep disorders (severe insomnia, restless legs syndrome or narcolepsy); (5) Alcohol abuse or use of drugs that can cause liver damage;(6) Acute ischemic stroke. OSAHS [27] was classified as mild to moderate (5 times/h ≤ AHI < 30 times/h) and severe (AHI ≥ 30 times/h) according to the diagnostic criteria.

Polysomnography

Sleep recording was performed in all individuals using ambulatory polysomnography (Philips, Alice 5 and NicoletOne), during which synchronized eye movements, oral and nasal airflow, chest and abdominal activity, oxygen saturation, electroencephalogram, and electrocardiogram were evaluated. The monitoring results were automatically analyzed by Alice software and then interpreted by a specialist. Sleep apnea was defined as the absence or significant reduction of oronasal airflow during sleep, with a reduction of 90% or more compared to baseline time and a duration of 10 s or longer. Hypopnea [28] was defined as follows: (1) 30% or greater reduction in oronasal airflow from baseline level during sleep. This is accompanied by a decrease in oxygen saturation of 4% or more for 10 s or longer. Or (2) 50% or greater reduction in oronasal airflow from baseline level accompanied by 3% or greater decrease in oxygen saturation for 10 s or longer. AHI, minimum saturated carbon saturation (L-SaO_2), and mean oxygen saturation (M-SaO_2) were recorded. TST was recorded as the total number of minutes of any form of sleep. Sleep efficiency was determined by calculating the ratio of TST to time spent in bed. N1, N2, SWS (stage N3), and duration of rapid eye movement (REM) sleep were also recorded.

Biochemical measurements

Fasting venous blood was collected from all participants at 7 am, then the levels of serum GGT enzyme levels and serum total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (APOA1), apolipoprotein B (APOB), and

apolipoprotein E (APOE) were measured using the autoanalyzer (H-7600, Hitachi, Tokyo, Japan).

Statistical analysis

All statistical analyses were performed using SPSS software (version: 22.0, IBM Corp., Armonk, USA), and a two-sided p-value < 0.05 was considered significant. The data conforming to the normal distribution shall be averaged; the data were presented as mean ± standard deviation. If they did not conform to the normal distribution, the data were presented as the median (interquartile interval). The data has been inspected by Shapiro Wilk according to the inspection level $\alpha = 0.05$, $p > 0.05$, and it was considered that the data conform to the normal distribution. For the comparison of two groups, two independent t-test was used for data that conform to a normal distribution, and Mann Whitney U test was used for data that do not conform to the normal distribution, and Kruskal Wallis H (K) test was used for continuous variables with non-normal distribution. Chi-square tests or Fisher exact tests were used for variable classification. Correlation between two variables: Pearson correlation analysis was used for continuous variables with normal distribution, otherwise Spearman correlation analysis was used. Independent risk factors for disease severity in non-obese men with OSAHS were analyzed by logistic regression. The ROC curve was used to evaluate the predictive ability of SWS and GGT on disease severity.

Results

Overall baseline characteristics

Of 94 patients with OSAHS 49 had mild to moderate disease and 45 had severe disease. The average age was 46.6 ± 11.0 years. There were 27 cases with hypertension, 8 cases with diabetes, 4 cases with coronary heart disease, 4 cases with arrhythmia, and 36 cases with hyperlipidemia. The baseline characteristics of the cohort are summarized in Table 1.

Table 1 Baseline characteristics of the study population ($n = 94$ patients)

Parameters	Value
Age (years)	46.6 ± 11.0
BMI (kg/m^2)	25.4 (23.6–26.6)
Drinking *n* (%)	48 (51)
Smoking *n* (%)	47 (50)
Comorbidities	
Cardiac arrhythmias *n* (%)	4 (4)
Coronary heart disease *n* (%)	4 (4)
Diabetes *n* (%)	8 (9)
Hyperlipidaemia *n* (%)	36 (38)
Hypertension *n* (%)	27 (29)
Biochemical variables	
APOA1 (mg/dl)	143 ± 23
APOB (mg/dl)	111 ± 32
APOE (mg/dl)	3.64 (2.84–4.57)
GGT (u/l)	31.00 (22.00–44.25)
GLU (mg/dl)	92.7 (82.44–102.42)
HDL-C (mg/dl)	19.8 (16.92–22.50)
LDL-C (mg/dl)	51.66 ± 16.20
TC (mg/dl)	85.14 (73.44–99.90)
TG (mg/dl)	32.04 (23.4–46.08)
TyG index	7.30 (6.93–7.77)
Polysomnography	
AHI (times/h)	27.8 (16.3–51.0)
L-SaO_2 (%)	77.0 (70.8–83.0)
M-SaO_2 (%)	92.7 (88.9–94.2)
TST (min)	465.6 (385.3–524.0)
SE (%)	88.9 (77.2–96.1)
Sleep stage 1 (%), N1	35.8 (11.0–63.0)
Sleep stage 2 (%), N2	44.1 ± 20.8
SWS (%)	7.0 (0.0–18.1)
REM (%)	0.5 (0.0–9.5)

OSAHS, obstructive sleep apnea–hypopnea syndrome; *BMI*, body mass index; *GGT*, gamma-glutamyl transpeptidase; *GLU*, glucose; *TG*, triglycerides; *TC*, total cholesterol; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *APOA1*, apolipoprotein A1; *APOB*, apolipoprotein B; *APOE* apolipoprotein E; *TyG*, triglyceride-glucose index; *TST*, total sleep time; *SE*, sleep efficiency; *AHI*, apnea–hypopnea index; *L-SaO_2*, low oxygen saturation; *M-SaO_2*, mean oxygen saturation; Sleep stage 1 (%), N1, Phase N1 as a percentage of total sleep time; Sleep stage 2 (%), N2, Phase N2 as a percentage of total sleep time; Sleep stage 3 (%), N3, Phase SWS as a percentage of total sleep time; REM (%), Phase REM as a percentage of total sleep time

Differences of clinical characteristics in non-obese men with OSAHS with various disease severity

Our data suggested that there were significant differences in L-SaO_2, M-SaO_2, SWS, and GGT between the mild to moderate and severe OSAHS group ($p < 0.05$). The proportion of SWS in the severe OSAHS group was significantly reduced compared to the mild to moderate group ($p < 0.05$). The biochemical index revealed that for patients with OSAHS, the serum GGT levels were remarkably increased as the severity of OSAHS enhanced, and the differences were statistically significant ($p < 0.05$). The results were presented in Table 2.

Logistic regression models for disease severity in non-obese men with OSAHS

In logistic regression analyses, increased GGT enzyme and SWS were independent risk factors for disease severity after adjusting for other confounding parameters (OR = 1.014,

$p = 0.007$; OR = 1.071, $p = 0.002$). The results were presented in Table 3.

The association between other variables and SWS, GGT, and AHI

Our data indicated that SWS was negatively correlated with TC, TG, APOE, and TyG index ($r = -0.211$, $p = 0.041$; $r = -0.263$, $p = 0.010$; $r = -0.239$, $p = 0.020$; $r = -0.218$, $p = 0.035$), respectively; GGT was positively correlated with TC, TG, APOE, and TyG index ($r = 0.229$, $p = 0.027$; $r = 0.345$, $p = 0.001$; $r = 0.299$, $p = 0.003$; $r = 0.376$, $p = 0.000$). The result was presented in Table 4.

Table 3 Logistic regression models for the AHI

Logistic regression of AHI	Coefficient (95% CI)	*p*
GGT	1.014 (1.004–1.024)	**0.007**
L-SaO_2	0.957 (0.904–1.012)	0.124
M-SaO_2	0.865 (0.735–1.018)	0.081
SWS	1.071 (1.026–1.118)	**0.002**

Correlation between SWS and serum GGT in non-obese men with OSAHS

SWS was correlated with the serum GGT levels. After the age was adjusted, smoking, alcohol consumption, BMI, comorbidities, and SWS were negatively correlated with serum GGT ($r = 0.420$, $p < 0.001$). The results are presented in Fig. 1.

Table 2 Differences of clinical characteristics in non-obese men with OSAHS with various disease severity

Characteristic	Mild-to-moderate ($n = 49$)	Severe ($n = 45$)	*p*-value
Demographics			
Age (years)	47.0 ± 10.1	46.3 ± 11.9	0.755
BMI (kg/m^2)	25.3 (23.3–26.9)	25.6 (24.1–26.1)	0.964
Drinking *n* (%)	24 (49)	24 (53)	0.673
Smoking *n* (%)	24 (49)	23 (51)	0.836
Comorbidities			
Cardiac arrhythmias *n* (%)	2 (4)	2 (4)	0.931
Coronary heart disease *n* (%)	3 (6)	1 (2)	0.349
Diabetes *n* (%)	3 (6)	5 (11)	0.387
Hyperlipidaemia *n* (%)	23 (47)	13 (29)	0.072
Hypertension *n* (%)	11 (22)	16 (36)	0.161
Biochemical variables			
APOA1 (mg/dl)	139 (100–163)	144 ± 26	0.904
APOB (mg/dl)	100 (90–120)	115 ± 30	0.165
APOE (mg/dl)	3.64 (2.84–4.57)	3.47 (2.93–4.24)	0.661
GGT (u/l)	30.00 (19.00–38.50)	35.00 (25.50–54.00)	**0.007**
GLU (mg/dl)	92.34 (83.7–101.52)	92.7 (81.36–108.18)	0.768
HDL-C (mg/dl)	19.80 (17.28–22.32)	19.62 (16.56–23.04)	0.880
LDL-C (mg/dl)	50.94 ± 16.74	52.56 ± 15.66	0.640
TC (mg/dl)	87.30 ± 19.44	84.60 (72.00–101.70)	0.655
TG (mg/dl)	30.24 (20.16–50.04)	33.84 (24.12–44.28)	0.350
TyG index	7.27 ± 0.61	7.31 (7.00–7.77)	0.305
Polysomnography			
AHI (times/h)	16.5 (10.5–21.5)	54.1 (37.6–67.6)	**0.001**
L-SaO_2 (%)	79.0 (72.5–85.0)	74.0 (66.0–79.0)	**0.004**
M-SaO_2 (%)	93.5 (89.7–94.9)	91.3 (87.8–93.1)	**0.002**
TST (min)	462.5 (364.0–525.5)	467.1 (396.8–522.3)	0.970
SE (%)	90.2 (72.7–95.2)	89.9 (78.5–96.1)	0.586
Sleep stage 1 (%), N1	40.5 (12.2–64.6)	31.4 (9.7–55.8)	0.416
Sleep stage 2 (%), N2	47.1 ± 23.8	40.7 ± 16.5	0.135
SWS (%)	5.0 (0.0–14.4)	9.7 (0.4–25.0)	**0.012**
REM (%)	0.4 (0.0–6.9)	0.5 (0.0–11.0)	0.432

The predictive value of SWS and serum GGT on disease severity

ROC curve revealed the area under SWS (AUC = 0.647; $p < 0.05$) and GGT curve (AUC = 0.661; $p < 0.01$). The area under SWS combined GGT curve was also presented (AUC = 0.728; $p < 0.05$). The predictive efficacy of SWS + GGT was better than SWS/GGT alone. The results were presented in Fig. 2.

Discussion

Previous studies have suggested that BMI is an independent predictor of enhanced OSA risk [10]. However, no significant difference was observed in the TyG index between severe and mild to moderate OSAHS in this study. The reason could be most of the previous studies focus on obese men with OSAHS, but little was known about non-obese

Table 4 The association between other variables and SWS, GGT, and AHI

	SWS		GGT		AHI	
	r	*p* value	*r*	*p* value	*r*	*p* value
APOA1	−0.180	0.083	0.110	0.293	0.102	0.327
APOB	−0.127	0.222	0.213	**0.039**	0.236	**0.022**
APOE	−0.239	**0.020**	0.299	**0.003**	0.017	0.871
GGT	−0.293	**0.004**	-	-	0.415	**0.000**
GLU	−0.104	0.316	0.340	**0.001**	0.076	0.464
HDL-C	−0.034	0.748	−0.005	0.965	0.009	0.928
LDL-C	−0.109	0.298	0.142	0.172	0.085	0.417
TC	−0.211	**0.041**	0.229	**0.027**	0.048	0.644
TG	−0.263	**0.010**	0.345	**0.001**	0.180	0.083
TyG index	−0.218	**0.035**	0.376	**0.000**	0.187	0.071
AHI	0.171	0.100	0.415	**0.000**	-	-
L-SaO_2	−0.072	0.492	−0.213	**0.040**	-	-
SWS	-	-	−0.264	**0.010**	0.143	0.168

$p < 0.05$ was considered statistically significant

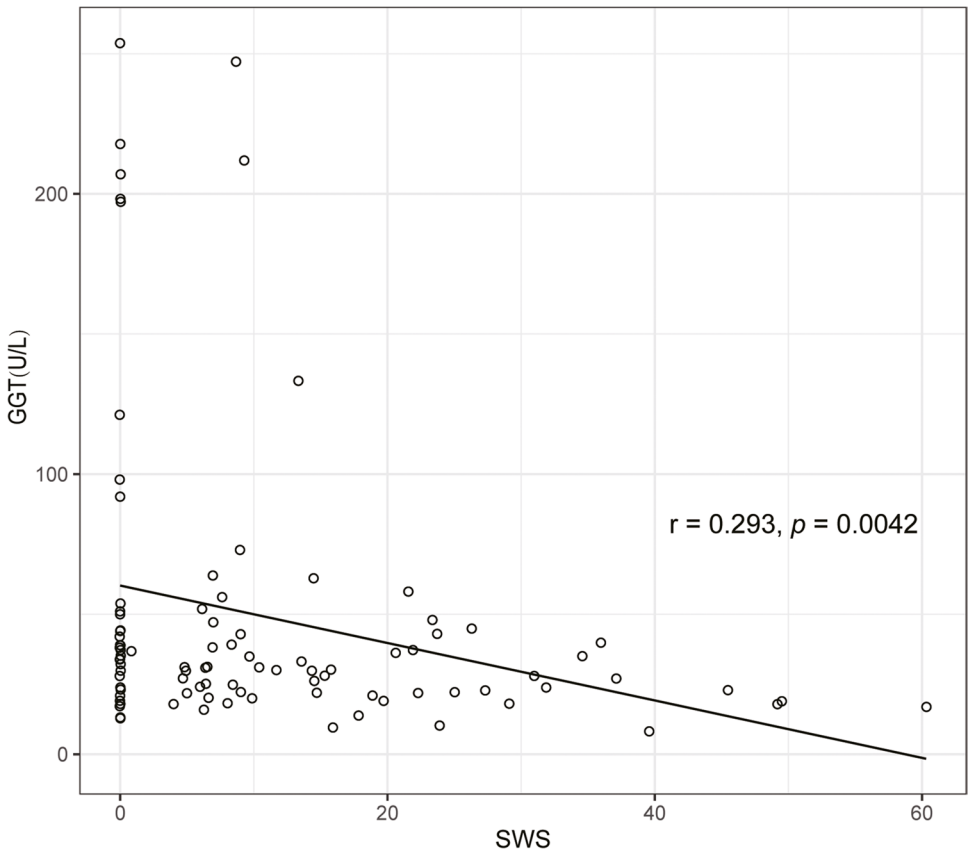

Fig. 1 Correlation between SWS and serum GGT in non-obese men with OSAHS

men. Secretion of free fatty acids (FFA) is increased in obesity, and adipocytokines secreted by adipose tissue may damage the insulin signaling [29, 30]. A recent study has indicated that OSA combined with SWS exhibits greater effects on insulin resistance (IR) [31]. However, the roles of SWS and IR in OSAHS remain unclear.

Previous studies have suggested that the proportion of SWS was reduced as the severity of OSAHS increases. However, our results indicated that the proportion of SWS in the severe OSAHS group was higher than that in the mild to moderate OSAHS group. The reason could be that as the disease progresses, other SWS-associated factors lead to the increase of AHI. Consistent with the findings of Sánchez-Armengol A et al. [26], our data revealed that the serum GGT enzyme levels were increased as the severity of OSAHS increased. Furthermore, logistic regression analyses indicated that SWS and GGT enzyme levels were independently associated factors of AHI. Thus, SWS might be associated with GGT levels in non-obese men with OSAHS.

In addition, previous study has suggested that IR was related to GGT in non-obese men with OSAHS, which may be caused by increased TG synthesis [32]. Consistent with these findings, this study revealed that the TyG index was associated with GGT. In addition, Huang et al. [31] have indicated that SWS is involved in insulin resistance. Feng et al. [33] have suggested that the proportion of SWS is negatively correlated with glucose and triglyceride (TG) levels. Xu et al. [34] have revealed that the apnea–hypopnea index (AHI) during NREM sleep (AHI_{NREM}) is closely correlated with blood lipid composition such as TC, TG, and APOB. Moreover, Bikov et al. [35] suggested that AHI_{NREM} is related to TG levels. Consistent with previous results, this study further indicated that SWS was related to TG, TC, TyG index, and APOE. In addition, previous studies have revealed that GGT is related to IR and TG in non-obese patients with OSAHS. In this study, our results suggested that GGT was also related to TG, TC, TyG index, and APOE. As GGT and SWS exhibit similar physiological functions, both of them can reflect the severity of OSAHS [15, 26] and are involved in the regulation of lipid metabolism [31–35]. Therefore, we hypothesized that SWS could be related to GGT through lipid metabolism and IR. However, further investigations are required to confirm this.

Furthermore, linear analyses indicated that SWS was correlated with serum GGT. The potential underlying mechanisms may involve the synthesis of TC, TG, APOE, and TyG index. First, chronic intermittent hypoxia and activation of the pituitary-adrenocortical (HPA) axis lead to elevated levels of adrenocorticotropic hormone and cortisol, further inducing lipolysis [36]. Second, a lack of SWS could cause a reduction of growth hormone at night, and the deficiency of growth hormone may lead to lipid metabolism disorders,

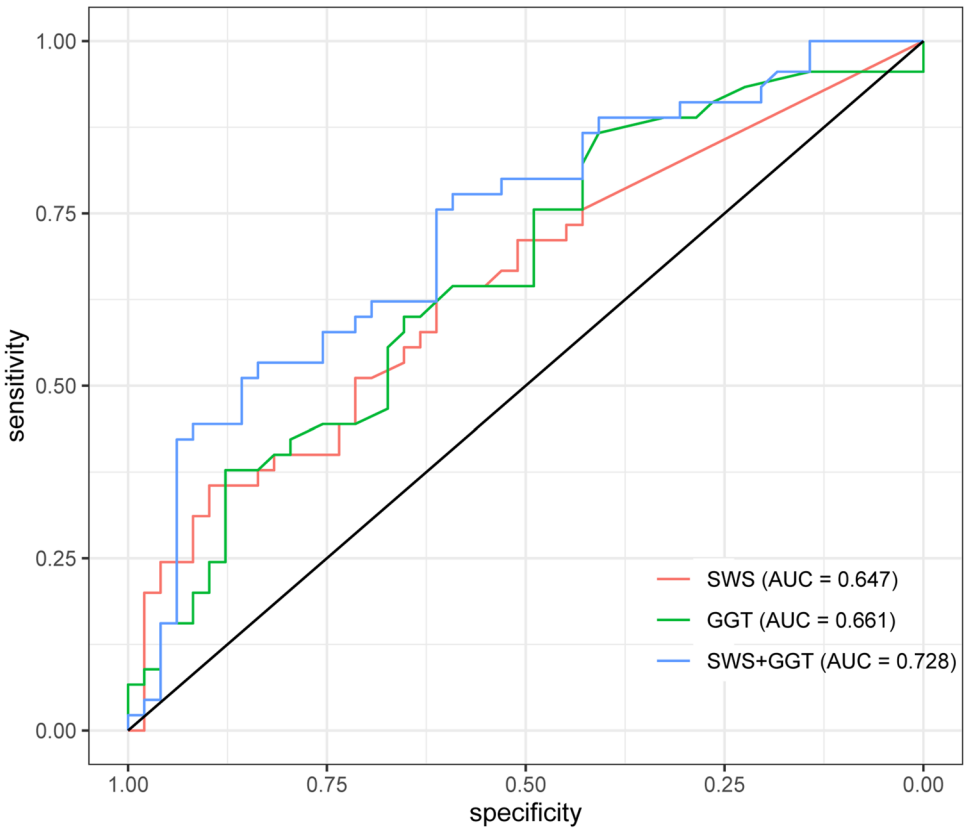

Fig. 2 The predictive value of SWS and serum GGT on disease severity

further resulting in insulin resistance [37, 38]. In addition, intermittent hypoxia and sleep fragmentation could lead to systemic inflammation, resulting in the disruption of lipid homeostasis [39]. Defects in the ApoE gene may also lead to the retention of chylomicrons, resulting in the increase of TG [40]. Third, triglyceride deposition decreasing fluidity and increasing permeability of hepatocyte membrane may lead to elevated serum GGT. Due to the relationship between SWS and GGT, SWS combined diagnosis may be helpful to predict the progress of this disease. Furthermore, ROC curve analyses indicated that SWS combined with GGT enzyme exhibit a higher predictive value for severe non-obese men with OSAHS.

There are several limitations in the current study. First, the sample size is relatively small, which may cause selection bias. Second, this study is single-centered potentially limiting the ability to generalize the results.

Conclusions

A higher percentage of SWS and serum GGT enzyme levels were found in non-obese men with severe OSAHS, and SWS and GGT enzyme levels were independent associated factors of disease severity. However, the TyG index was not an independent associated factor. In addition, SWS was correlated with serum GGT enzyme levels. A reduced percentage of SWS combined with increased GGT enzyme levels may exhibit a stronger association with increased disease severity in non-obese men with OSAHS.

Data availability Data will be made available on reasonable request.

Declarations

Ethical approval This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (2022 Colum Review No. (144)).

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

Conflict of interest The authors declare no competing interests.

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