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Serum Transferrin Level Is Associated with the Severity of Obstructive Sleep Apnea Independently of Obesity: A Propensity Score-Match Observational Study

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Keywords
Transferrin · Iron metabolism · OSA · Obesity · Bariatric surgery

Abstract

Introduction: Dysregulation of iron metabolism is closely associated with the development of obesity and obstructive sleep apnea (OSA), but little is known about the relationship between serum transferrin (TF) level and OSA severity. We aimed to verify this relationship and fit into account for obesity-related confounders among bariatric candidates. ***Methods:*** We compared data retrospectively collected in 270 bariatric candidates. A propensity score-matched (PSM) analysis was used to determine the impact of iron metabolism on OSA severity independently of obesity. Univariate analysis was used to evaluate the relationship between serum TF level and the severity of OSA reflected by hypoxia and night awakenings parameters. Serum TF level to predict the severity of OSA was assessed by using univariate and multiple logistic regression model. ***Results:*** The preliminary analysis showed that serum ferritin (113 ng/mL [50–203] vs. 79 ng/mL [40–130], $p = 0.009$) and TF (2.72 g/L [2.46–3.09] vs. 2.65 g/L [2.34–2.93], $p = 0.039$) level was significantly higher in the moderate/severe OSA group than the no/mild OSA group. After PSM analysis, there were 75 patients in each group and only serum TF level remained significant ($p = 0.014$). The proportion of patients with combined T2D and hyperlipidemia also remained higher in moderate/severe OSA groups. Univariate analysis showed that the group with higher degree of hypoxia had higher serum TF levels no matter the severity of OSA was grouped by oxygen desaturation index (ODI; 2.79 g/L [2.56–3.06] vs. 2.55 g/L [2.22–2.84], $p < 0.001$) or minimum oxygen saturation (SpO_2nadir; 2.75 g/L [2.50–3.03] vs. 2.56 g/L [2.24–2.92], $p = 0.009$). Univariate and multiple logistic regression analysis further showed that serum TF level emerged as a significant and independent factor associated with OSA severity especially grouped by ODI (odds ratio: 2.91, 95% CI: 1.36–6.23, $p = 0.006$). ***Conclusion:*** The existence of OSA exacerbates obesity comorbidities, particularly type 2 diabetes and hyperlipidemia. Serum TF level is associated with the severity of OSA independently of obesity and might be a potential identification and therapeutic targets.

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Introduction

Obstructive sleep apnea (OSA), characterized by chronic intermittent hypoxia and sleep fragmentation, is a common disorder affecting about 14% of men and 5% of women, and prevalence is rapidly rising due to the strong association with obesity [1]. The incidence of OSA in the obese population is nearly twice that of a normal-weight person [2]. The concurrence of obesity and OSA had a complicated and far more serious impact on the cardiovascular and metabolic sequelae than either of these conditions on their own [3]. Hence, it is crucial to identify and treat OSA among candidates for metabolic surgery, which may contribute to perioperative safety and ultimate weight loss outcomes.

Obesity, an excessive accumulation and/or abnormal distribution of adipose tissue that may have adverse effects on health, has been closely linked to iron metabolism perturbations [4]. Interestingly, some studies have shown iron deficiency (ID) in the context of anemia of chronic inflammation disease among children, pregnant, and the morbidly obese population [5–7] while other studies reported the presence of excess iron or dysmetabolic iron overload syndrome (DIOS) associated with obesity, as in patients with nonalcoholic fatty liver disease [8]. Similar results of iron overload were seen in overweight or obese women with polycystic ovary syndrome and patients with metabolic syndrome [9, 10]. Some studies have even reported seemingly contradictory results that there is the co-existence of elevated levels of hepcidin and DIOS (iron overload) in the obese population [11]. It is evident that iron metabolism in the obese population is complex, and whether it is ID or DIOS may depend on the consequence of multiple factors (such as age, sex, body mass index [BMI], and comorbidities) working together.

Similar to obesity, the important perturbations of iron metabolism may be linked to the progression of OSA. There are many studies on iron metabolism and OSA [12–15], but only limited studies focus on body iron transport as reflected by serum TF levels and the results are controversial. Baik et al. [16] indicated that OSA cases showed lower serum TF saturation levels than those without OSA no matter with male-pattern baldness or not. Shalitin et al. [17] showed that no differences between OSA and non-OSA obese children and adolescents were found regarding body iron regulator levels. Le Tallec-Esteve et al. [18] showed that transferrin saturation was higher in moderate/severe OSA compared to absent/mild OSA patients and independently associated with the severity of OSA, but the sample size was relatively small and there was a confounding effect of obesity. In this study, we hypothesized that iron metabolism parameters especially serum TF level has a close relationship with OSA severity independently of obesity, and the existence of OSA plays an important role in the relationship between iron metabolism and obesity-related comorbidity. To address those questions and fit into account for confounders, we conducted a propensity score-matched analysis, using data from our bariatric and metabolic disease surgery center.

Materials and Methods

Study Design and Population

This was a retrospective study of a longitudinally collected dataset of 270 obese patients who planned to undergo metabolic surgery in the Bariatric and Metabolic Disease Surgery Center, Zhongnan Hospital of Wuhan University, Wuhan, China, from June 2020 to February 2021. Inclusion criteria were patients aged 18–65 years with BMI ≥32.5 kg/m^2 or BMI ≥27.5 kg/m^2 with inadequately controlled type 2 diabetes (T2D) or metabolic syndrome according to Chinese Surgical Guidelines for Obesity and Type 2 Diabetes (2019 edition) [19]. The exclusion criteria were alcohol or drug abuse, severe eating disorder, depression or other severe disease contraindicating metabolic bariatric surgery, previous diagnosis of OSA, iron metabolism dysregulation-related diseases (genetic hemochromatosis), and taking iron supplementation medications. The procedures were performed by the same bariatric surgeon (Li Zhen) in a comprehensive, multidisciplinary program setting. Written informed consent was obtained from all participants, and this study was approved by the Institutional Ethics Board of Zhongnan Hospital of Wuhan University.

Data Collection

Clinical data and biochemical data were collected from the patients' medical records by two independent researchers during preoperative multidisciplinary evaluation for metabolic bariatric surgery. Clinical data collection included age, sex, weight, height, waist circumference, hip circumference, hypertension, T2D, hyperlipemia, hyperuricemia, and fatty liver disease. BMI was calculated as weight (kg) per height squared (m^2) and categorized as Class I Obesity (BMI ≥27.5–32.4 kg/m^2), Class II Obesity (BMI ≥32.5–37.4 kg/m^2), Class III Obesity (BMI ≥37.5–50.0 kg/m^2), and Class IV Obesity (BMI ≥50.0 kg/m^2) according to the World Health Organization's recommendation for Asian populations [20]. Waist/hip ratio was calculated as the waist circumference divided by the hip circumference. Hypertension was defined as systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or ongoing antihypertensive medication(s). T2D was defined as fasting glycemia ≥7.0 mmol/L or the need for treatment. Hyperlipemia was defined as plasma total cholesterol (TC) >5.2 mmol/L, low-density lipoprotein (LDL) >3.4 mmol/L, triglycerides (TGs) >3.4 mmol/L, or high-density lipoprotein (HDL) <1.0 mmol/L. Hyperuricemia was defined as plasma uric acid (UA) >420 (male) or 360 (female) μmmol/L. Fatty liver disease was diagnosed by abdominal ultrasonography.

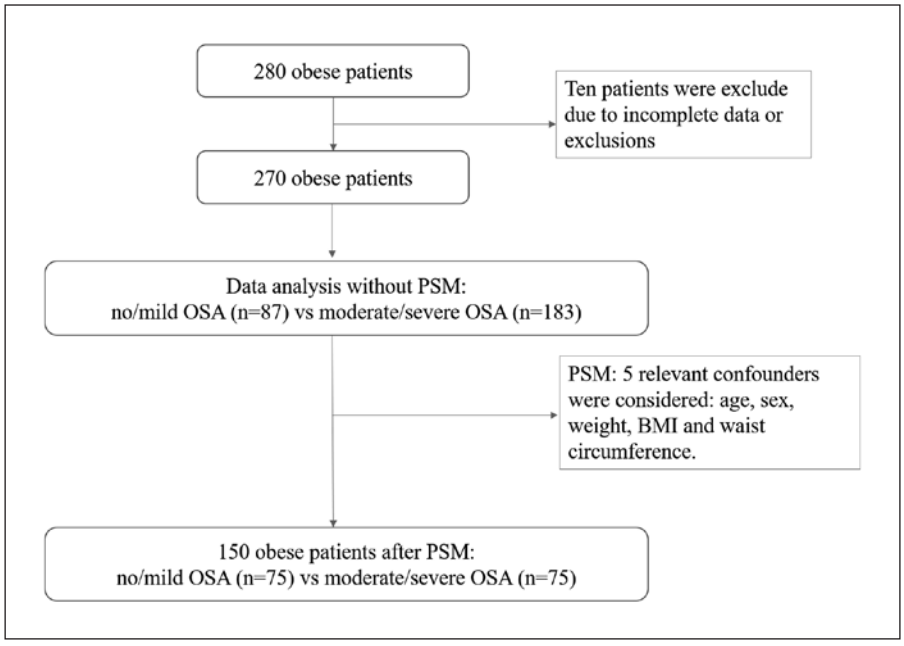

Fig. 1. Study flow chart. OSA, obstructive sleep apnea; PSM, propensity score match; BMI, body mass index.

Biochemical data for blood cell counts (i.e., white blood cell counts [WBC], red blood cell counts [RBC], platelet counts [PLT], and hemoglobin [HGB]), coagulation indexes (i.e., prothrombin time [PT] and activated partial thromboplastin time [APTT]), liver function indexes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT], and albumin [ALB]), kidney function indexes (creatinine [Cr], cystatin C [CYSC], and uric acid [UA] levels), blood lipid profiles (total cholesterol [TC], triglyceride [TG], high-density lipoprotein [HDL], and low-density lipoprotein [LDL]), serum iron parameters (serum iron [SI], transferrin [TF], serum ferritin [SF], total iron-binding capacity [TIBC], and unsaturated iron-binding capacity[UIBC]), as well as fasting blood glucose (FBG) and insulin (FBI) levels were collected. Insulin resistance was estimated by the homeostasis model assessment (HOMA-IR) = insulin (μUI/mL) × fasting blood glucose (mmol/L)/22.5 [21].

Overnight PSG Parameters

As part of the systematic preoperative assessment, all patients underwent overnight polysomnography (PSG) via in-laboratory study at our Sleep Medicine Center. The PSG variables were recorded by Embletta Gold software (Embla Systems, Inc., Broomfield, CO, USA). All graphs obtained during sleeping time were analyzed by two experienced PSG technologists based on the updated 2012 American Academy of Sleep Medicine (AASM) criteria [22]. The presence and the severity of OSA were estimated by the number of apnea and hypopnea events per hour (AHI). Briefly, AHI < 5 was defined as no OSA, AHI ≥ 5 as mild, AHI ≥ 15 as moderate, AHI ≥ 30 as severe OSA, respectively. The oxygen desaturation index (ODI) was defined as the number of times per hour of sleep that the blood oxygen level dropped by ≥4% from baseline. The microarousal index (MAI) was defined as the number of arousals per hour of sleep. The mean and lowest pulse oxygen saturation were the mean and the lowest oxygen saturation value recorded during sleep (SpO_2mean and SpO_2nadir). The time and percentage of total sleep time spent with SaO_2 <90% were also recorded during sleep (ST90_min and ST90_%). The sleep efficiency (SE) was measured by obtaining percentage of total time in bed actually spent in sleeping.

Statistical Analysis

Because of the unbalanced numbers of patients between the no, mild, moderate, and severe OSA groups, no and mild cases were combined in one group while moderate and severe were combined in another group for analysis. A propensity score method (PSM) was used to account for confounders. Briefly, a logistic regression model was used to compute the propensity score between no/mild OSA and moderate/severe OSA groups. The PSM was rigorously constructed and implemented according to expert statistician guidelines [23]. In order to generate the PSM, five obese-associated confounders were considered: age, sex, weight, BMI, and waist circumference. The PSM was performed to match each patient in the no/mild OSA group with a patient of the moderate/severe group based on the closest propensity score by using a nearest-neighbor matching algorithm. The caliper was set at 0.05. Unpaired cases were discarded from analysis.

Statistical analyses were performed by SPSS version 25 (IBM corporation, Armonk, NY, USA). Our continuous data were not normally distributed according to the Kolmogorov-Smirnov test. Hence, details of basic characteristics were given using number and percentage for qualitative variables and median and 25th–75th interquartile range for quantitative variables. Comparisons between two groups (no/mild OSA vs. moderate/severe OSA) were performed using a χ^2 or Fisher exact test for qualitative variables and a nonparametric Mann-Whitney U test for quantitative variables. The value of $p < 0.05$ was considered statistically significant.

Table 1. Clinical and demographic characteristics of obese patients with OSA before and after PSM

Variables	Median (25th–75th IQR), *N* (%)	
	before matching (*n* = 270)	after matching (*n* = 150)
Age	31 (27–36)	31 (27–35)
18–30 years	108 (40)	62 (41)
30–40 years	125 (46)	70 (47)
40–50 years	29 (11)	13 (9)
50–65 years	8 (3)	5 (3)
Female sex	212 (78)	141 (94)
Weight, kg	96 (85–112)	90 (82–100)
BMI, kg/m^2	35 (32.2–39.1)	36.2 (33.6–39.1)
27.5–32.5	71 (26)	55 (37)
32.5–37.5	111 (41)	71 (47)
37.5–50	79 (29)	24 (16)
≥50	9 (4)	0 (0)
Waist circumference, cm	110 (103–119)	107 (101–116)
Waist/hip ratio	0.96 (0.92–1.01)	0.96 (0.91–1.00)
Comorbidities		
T2D	57 (21)	29 (19)
Arterial hypertension	29 (11)	11 (7)
Hyperlipidemia	146 (54)	73 (49)
Hyperuricemia	193 (71)	106 (71)
Fatty liver disease	261 (97)	146 (97)
Level of sleep disordered breathing		
No OSA (AHI < 5)	18 (7)	13 (9)
Mild OSA (AHI 5–15)	69 (26)	62 (41)
Moderate OSA (AHI 15–30)	64 (24)	36 (24)
Severe OSA (AHI < 30)	119 (44)	39 (26)
Sleep parameters		
AHI	24.6 (13.2–51.6)	15 (10–27.5)
ODI	20 (8–50)	13 (6.7–24.3)
MAI	21.2 (14.0–36.8)	18.25 (11.13–25.55)
SpO_2mean	93.7 (92–95)	94.2 (93.1–95.3)
SpO_2nadir	81 (73–87)	84 (78–88)
ST90_min	10 (0.9–42.2)	3.2 (0.3–19.0)
ST90_%	3.2 (0.3–14.2)	1.1 (0.1–5.2)
SE	81.26 (69.07–88.43)	82.16 (69.00–90.00)
N1	10.6 (7.7–15.7)	9.80 (6.48–13.23)
N2	66.4 (60.8–72.3)	67.85 (61.28–73.50)
N3	0 (0–4.4)	0 (0–5.33)
R	18.3 (14.0–21.9)	19.0 (14.9–22.4)

AHI, apnea-hypopnea index; ODI, oxygen desaturation index; MAI, microarousal index; SpO_2mean, mean oxygen saturation; SpO_2nadir, minimum oxygen saturation; ST90_min, total sleep time spent with SaO_2 <90%; ST90_%, the ratio of total sleep time spent with SaO_2 <90%; SE, sleep efficiency; N1, nonrapid-eye-movement 1 stage; N2, nonrapid-eye-movement 2 stage; N3, nonrapid-eye-movement 3 stage; R, rapid-eye-movement stage.

Results

Baseline Characteristics of Patients before PSM

The flow diagram is illustrated in Figure 1. The baseline characteristics of the 270 patients before PSM are presented in Tables 1 and 2. About 190 (70%) patients belong to Class II Obesity and Class III Obesity. The majority (78%) were female and the age distribution was concentrated between 20 and 40 years old, accounting for 233 (86%) patients. Up to 252 obese patients (93%) had some degree of sleep disordered breathing (AHI ≥ 5.0) and 183 (68%) had moderate/severe OSA (AHI ≥ 15.0).

Table 2. Univariate analysis of factors associated with OSA severity before PSM (*n* = 270)

Variables	Median (25th–75th IQR), *N* (%)		*p* value
	absent/mild OSA (*n* = 87)	moderate/severe OSA (*n* = 183)	
Age	30 (26–35)	32 (27–37)	0.099
18–30 years	40 (46)	68 (37)	
30–40 years	37 (43)	89 (49)	
40–50 years	7 (8)	21 (11)	
50–65 years	3 (3)	5 (3)	
Female sex	82	130	<0.001
Weight, kg	89 (80–98)	101 (90–120)	<0.001
BMI, kg/m^2	32.7 (30.5–35.9)	36.5 (33.6–41.2)	<0.001
27.5–32.5	43 (49)	28 (15)	
32.5–37.5	33 (38)	78 (43)	
37.5–50	11 (13)	69 (38)	
≥50	0 (0)	8 (4)	
Waist circumference, cm	105 (98–114)	113 (105–121)	<0.001
Waist/hip ratio	0.95 (0.91–0.99)	0.97 (0.92–1.02)	**0.041**
Comorbidities, *n* (%)			
T2D	9 (10)	48 (26)	**0.003**
Arterial hypertension	4 (5)	25 (14)	**0.025**
Hyperlipidemia	31 (36)	115 (63)	<0.001
Hyperuricemia	57 (66)	136 (74)	0.134
Fatty liver disease	81 (93)	180 (98)	**0.025**
Blood parameters			
SI, μmol/L	17 (13.5–22.4)	18.60 (14.20–23.5)	0.131
SF, ng/mL	79.38 (39.58–129.71)	112.61 (49.62–203.14)	**0.009**
TF, g/L	2.65 (2.34–2.93)	2.72 (2.46–3.09)	**0.039**
IUBC, μmol/L	43.6 (36.10–51.00)	43.3 (37.50–51)	0.490
TIBC, μmol/L	62.0 (55.4–68.0)	63.7 (58.2–70.1)	0.088
WBC, 10^9/L	7.3 (5.8–8.4)	7.6 (6.5–9.0)	**0.025**
RBC, 10^{12}/L	4.5 (4.3–4.7)	4.7 (4.5–5.1)	<0.001
PLT, 10^9/L	274.0 (234.5–316.5)	281.0 (243.5–315.5)	0.877
HGB, g/L	131.7 (126.4–138.8)	139.0 (129.4–148.9)	<0.001
PT, s	11.9 (11.3–12.4)	11.7 (11.3–12.1)	0.468
APTT, s	30.4 (27.9–32.1)	30.8 (28.9–33.4)	0.174
ALT, U/L	23.0 (14.5–42.5)	37.0 (24.0–62.8)	<0.001
AST, U/L	18.0 (16.0–27.5)	27.0 (20.0–40.0)	<0.001
GGT, U/L	23.0 (17.0–33.5)	37 (28–55.8)	<0.001
ALB, g/L	42.0 (40.4–44.3)	42.6 (40.2–45.2)	0.585
CREA, μmol/L	55.0 (50.8–60.1)	54.9 (47.8–63.7)	0.782
CYSC, mg/L	0.8 (0.7–0.9)	0.8 (0.7–1.0)	0.198
UA, μmol/L	402.2 (332.0–459.3)	454.0 (383.9–533.5)	**0.001**
TC, mmol/L	4.7 (4.2–5.3)	5.1 (4.5–5.7)	**0.006**
TG, mmol/L	1.4 (0.9–1.9)	1.7 (1.3–2.4)	<0.001
LDL, mmol/L	3.1 (2.7–3.6)	3.4 (2.8–3.8)	0.057
HDL, mmol/L	1.2 (1.0–1.3)	1.1 (0.9–1.3)	**0.024**
FBG, mmol/L	5.23 (4.86–5.62)	5.41 (4.96–6.67)	**0.011**
FBI, μU/L	17.8 (13.9–24.0)	24.2 (18.0–34.4)	<0.001
HOMA-IR	4.3 (3.1–6.1)	6.0 (4.2–9.6)	<0.001

BMI, body mass index; WBC, white blood cell; RBC, red blood cell; PLT, platelet; HGB, hemoglobin; PT, prothrombin time; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALB, albumin; CREA, creatinine; CYSC, cystatin C; UA, uric acid; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SI, serum iron; SF, serum ferritin; TF, transferrin; UIBC, unsaturated iron-binding capacity; TIBC, total iron-binding capacity; FBG, fasting blood glucose; FBI, fasting blood insulin; HOMA-IR, homeostasis model assessment insulin resistant.

Table 3. Univariate analysis of factors associated with OSA severity after PSM (n = 150)

Variables	Median (25th–75th IQR), *N* (%)		*p* value*
	absent/mild OSA (n = 75)	moderate/severe OSA (n = 75)	
Age	31 (27–37)	31 (27–36)	0.964
18–30 years	31 (41)	31 (41)	
30–40 years	34 (45)	36 (48)	
40–50 years	7 (9)	6 (8)	
50–65 years	3 (5)	2 (3)	
Female sex	70 (93)	71 (95)	0.754
Weight, kg	88 (80–98)	93 (84–102)	0.265
BMI, kg/m^2	33.5 (30.8–36.2)	33.7 (31.9–36.4)	0.221
27.5–32.5	32	23	
32.5–37.5	32	39	
37.5–50	11	13	
≥50	0	0	
Waist circumference, cm	106 (98–117)	108 (103–115)	0.907
Waist/hip ratio	0.95 (0.91–1.00)	1.00 (0.96–1.05)	0.856
Comorbidities, *n* (%)			
T2D	8 (11)	21 (28)	**0.007**
Arterial hypertension	4 (5)	7 (9)	0.347
Hyperlipidemia	28 (37)	45 (60)	**0.005**
Hyperuricemia	47 (63)	59 (79)	0.368
Fatty liver disease	71 (95)	75 (100)	0.120
Blood parameters			
SI, μmol/L	16.80 (13.10–22.36)	18.80 (13.30–23.90)	0.296
SF, ng/mL	73.11 (39.43–120.58)	77.57 (33.86–165.46)	0.556
TF, g/L	2.61 (2.28–2.91)	2.79 (2.49–3.07)	**0.014**
IUBC, μmol/L	42.90 (36.16–51.10)	43.60 (38.30–51.60)	0.427
TIBC, μmol/L	61.90 (54.65–67.35)	63.60 (56.85–70.05)	0.115
WBC, 10^9/L	7.30 (5.95–8.36)	7.16 (6.35–8.70)	0.318
RBC, 10^{12}/L	4.52 (4.34–4.73)	4.68 (4.42–4.94)	0.414
PLT, 10^9/L	280.0 (240.5–317.5)	283.0 (245.5–314.5)	0.978
HGB, g/L	132 (127.9–138.9)	135 (129.6–142.2)	0.458
PT, s	11.9 (11.3–12.4)	11.8 (11.4–12.1)	0.714
APTT, s	30.0 (27.7–31.7)	30.3 (28.4–32.7)	0.556
ALT, U/L	24.00 (16.00–45.50)	29.00 (19.00–50.50)	**0.009**
AST, U/L	19.00 (16.00–29.00)	22 (17–37.5)	**0.005**
GGT, U/L	23 (18–36)	35 (23.5–45.5)	<0.001
ALB, g/L	42.0 (40.3–44.1)	42.2 (39.1–45.5)	0.876
CREA, μmol/L	55.0 (50.6–60.7)	53.5 (46.3–60.0)	0.101
CYSC, mg/L	0.79 (0.71–0.91)	0.81 (0.69–0.90)	0.807
UA, μmol/L	404.2 (332.0–462.6)	426.4 (375.3–496.7)	0.129
TC, mmol/L	4.95 (4.35–5.42)	5.05 (4.42–5.60)	0.252
TG, mmol/L	1.40 (0.97–2.24)	1.69 (1.24–2.24)	**0.022**
LDL, mmol/L	3.18 (2.71–3.84)	3.27 (2.67–3.74)	0.708
HDL, mmol/L	1.21 (1.01–1.35)	1.10 (0.96–1.24)	**0.016**
Fasting glucose, mmol/L	5.26 (4.98–5.64)	5.21 (4.77–6.29)	0.398
Fasting insulin, μU/L	17.8 (14.1–23.4)	20.7 (14.8–28.2)	**0.033**
HOMA-IR	4.29 (3.25–6.22)	5.36 (3.82–9.13)	**0.024**

BMI, body mass index; WBC, white blood cell; RBC, red blood cell; PLT, platelet; HGB, hemoglobin; PT, prothrombin time; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALB, albumin; CREA, creatinine; CYSC, cystatin C; UA, uric acid; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SI, serum iron; SF, serum ferritin; TF, transferrin; UIBC, unsaturated iron-binding capacity; TIBC, total iron-binding capacity; FBG, fasting blood glucose; FBI, fasting blood insulin; HOMA-IR, homeostasis model assessment insulin resistant. * p value by nonparametric Mann-Whitney U test for non-normal data; χ^2 test for categorical data.

Table 4. Univariate analysis of serum iron parameters with OSA severity measured in multiple sleep parameters after PSM (n = 150)

	Patient, n	TF, g/L	SF, ng/mL	SI, μmol/L	IUBC, μmol/L	TIBC, μmol/L
AHI						
<15	75	2.61 (2.28–2.91)	73.11 (39.43.23–120.58)	16.80 (13.10–22.36)	42.90 (36.16–51.10)	61.90 (54.65–67.35)
≥15	75	2.79 (2.49–3.07)	77.57 (33.86–165.46)	18.80 (13.30–23.90)	43.60 (38.30–51.60)	63.60 (56.85–70.05)
p value	–	**0.014**	0.556	0.296	0.427	0.115
ODI						
< median	69	2.55 (2.22–2.84)	79.74 (42.26–133.76)	16.50 (12.80–22.40)	43.20 (36.10–50.30)	59.70 (55.20–66.00)
≥ median	81	2.79 (2.56–3.06)	77.57 (35.02–164.69)	18.40 (14.30–22.90)	43.60 (38.70–52.20)	63.60 (56.80–70.80)
p value	–	**<0.001**	0.959	0.107	0.23	**0.023**
SpO_2nadir						
≥85	64	2.56 (2.24–2.92)	79.38 (40.95–120.58)	17.70 (13.30–22.90)	41.00 (34.25–50.40)	61.50 (55.20–67.45)
<85	86	2.75 (2.50–3.03)	76.97 (35.47–167.59)	16.30 (13.25–21.53)	44.75 (38.85–50.93)	63.21 (56.40–69.20)
p value	–	**0.009**	0.567	0.353	0.088	0.334
MAI						
< median	75	2.67 (2.37–2.96)	74.00 (38.52–127.39)	16.30 (13.10–22.40)	44.00 (37.17–50.40)	61.50 (55.70–66.60)
≥ median	75	2.68 (2.45–3.02)	79.32 (38.44–162.72)	19.15 (13.47–22.92)	43.60 (38.05–52.20)	62.95 (56.40–70.90)
p value	–	0.285	0.509	0.189	0.604	0.101

AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SpO_2nadir, minimum oxygen saturation; MAI, microarousal index; TF, transferrin; SF, serum ferritin; SI, serum iron; UIBC, unsaturated iron-binding capacity; TIBC, total iron-binding capacity. p value by nonparametric Mann-Whitney U test for non-normal data.

The median AHI was 24.6 (13.2–51.6). Table 2 shows the comparison of groups at univariate analysis. We observed that moderate/severe OSA patients exhibited more overweight and a higher BMI. As expected, the moderate/severe OSA groups had a higher proportion of patients with combined T2D, hypertension, hyperlipidemia, and fatty liver disease.

Baseline Characteristics of Patients after PSM

After PSM, there were 75 subjects in each group, no/mild OSA and moderate/severe OSA, with matched baseline characteristics and univariate analysis as summarized in Tables 1 and 3. Still 137 obese patients (91%) had some degree of sleep disordered breathing (AHI ≥5.0) and 75 (50.0%) had moderate/severe OSA (AHI ≥15.0). The median AHI was 15.0 (10.0–27.5). In this matched population, no difference between the two groups were observed regarding age, sex, weight, BMI, waist circumstance, and waist/hip ratio. However, the proportion of patients with combined T2D and hyperlipidemia remained higher in moderate/sever OSA groups.

Relationships between Iron Parameters and OSA Severity

Bio-clinical data according to OSA severity before and after PSM were presented in Tables 2 and 3. SF and TF levels (113 ng/mL [50–203] vs. 79 ng/mL [40–130], p = 0.009, 2.72 g/L [2.46–3.09] vs. 2.65 g/L [2.34–2.93], p = 0.039, respectively) were significantly higher in the moderate/severe OSA group than those in the no/mild OSA group before PSM, while only the difference regarding TF level (2.79 g/L [2.49–3.07] vs. 2.61 g/L [2.28–2.91], p = 0.014) remained statistically significant after PSM. Other iron parameters such as SI, IUBC, and TIBC were not statistically significantly before and after PSM. Moreover, we grouped OSA severity in multiple sleep parameters such as hypoxia and night awakenings and compared with iron metabolism indicators again. The results also showed that the group with higher degree of hypoxia had higher serum TF levels (Table 4).

Logistic Regression Analysis of the Association between Serum TF Level and OSA Severity

Serum TF levels were significantly higher in the moderate/severe OSA group than in the no/mild OSA group before and after PSM at univariate analysis (Fig. 2). As expected, other variables such as ALT, AST, GGT, TG, HDL, FBI, and HOMA-IR also showed significant difference according to OSA severity (Table 3). Then logistic regression analysis was employed to examine whether serum TF level was independently and significantly associated with OSA severity (Table 5). Model 1, which included serum TF level and not adjusted for obesity- related confounders before PSM, showed that serum TF level was associated with the severity of OSA reflected by AHI (odds ratio [OR]: 1.69,

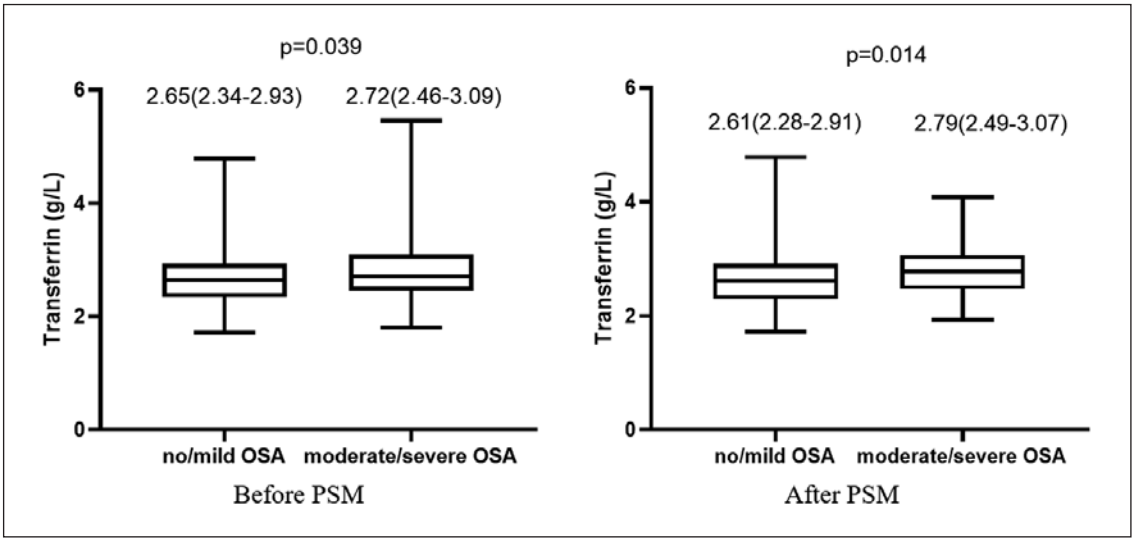

Fig. 2. Associations between serum TF level and OSA severity before and after PSM. OSA, obstructive sleep apnea; PSM, propensity score match; TF, transferrin.

Table 5. Univariate and multiple logistic regression analysis of serum TF level associated with OSA severity

	Patients, *n*	Model 1			Model 2			Model 3		
		OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
AHI										
<15	75	Reference			Reference			Reference		
≥15	75	1.69	1.01–2.83	**0.045**	2.09	1.06–4.12	**0.033**	2.09	1.02–4.25	**0.043**
ODI										
< median	69	Reference			Reference			Reference		
≥ median	81	1.60	1.01–2.53	**0.043**	2.97	1.42–6.18	**0.004**	2.91	1.36–6.23	**0.006**
SpO_2nadir										
≥85	64	Reference			Reference			Reference		
<85	86	1.56	0.94–2.57	0.085	1.95	0.98–3.88	0.058	1.73	0.86–3.49	0.126

Model 1: before PSM. Model 2: after PSM. Model 3: model 2 and adjusted for ALT, TG, HDL, and FBI. OR, odds ratio; CI, confidence interval; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SpO_2nadir, minimum oxygen saturation; PSM, propensity score match; TF, transferrin; ALT, alanine aminotransferase; TG, triglyceride; HDL, high-density lipoprotein; FBI, fasting blood insulin.

95% confidence interval [CI]: 1.01–2.83, $p = 0.045$) and ODI (OR: 1.60, 95% CI: 1.01–2.53, $p = 0.043$). Model 2, which included serum TF level and adjusted for obesity after PSM, showed that serum TF level was independently associated with the severity of OSA reflected by AHI (OR: 2.09, 95% CI: 1.06–4.12, $p = 0.033$) and ODI (OR: 2.97, 95% CI: 1.42–6.18, $p = 0.004$). Model 3, which included serum TF level and adjusted for obesity, ALT, TG, HDL, and FBI, showed that serum TF level was a reliable factor independently associated with the severity of OSA reflected by AHI (OR: 2.09, 95% CI: 1.02–4.25, $p = 0.043$) and ODI (OR: 2.91, 95% CI: 1.36–6.23, $p = 0.006$).

Discussion

Obesity was the largest confounding factor in the study of OSA-related comorbidities, which had yet a close connection with OSA severity. Before PSM, our results, which

were consistent with other studies [24, 25], showed that moderate/severe OSA patients had higher weight, BMI, waist circumference, and a higher prevalence of T2D, hypertension, hyperlipidemia, and fatty liver disease. After accounting for obesity-related confounders by PSM, moderate/severe OSA patients still had a higher risk of developing T2D and hyperlipidemia than those with no/mild OSA. It was important to note that serum SF and TF levels were higher in moderate/severe OSA obese patients before PSM, but only serum TF levels showed a significant difference after PSM. This suggested that the elevated levels of SF in moderate/severe OSA patients may be attributable to the effects of obesity. In contrast, increased serum TF level was more relevant to OSA per se, especially to intermittent hypoxia.

The relationship between iron metabolism, metabolic syndrome, obesity, and insulin resistance is well known. After PSM, our results showed that moderate/severe OSA patients still had significant differences in liver function parameters (ALT, AST, and GGT) and glucolipid metabolism profiles (FBI, HOMA-IR, TG, and HDL) except for serum TF level. To further explore the relationship between serum TF level and OSA severity, logistic regression analysis was employed to adjust for potential confounders, and the result showed that serum TF level was a reliable factor independently associated with the severity of OSA. This suggested that increased serum TF level to predict the severity of OSA in the moderate/severe group was twice that of the no/mild OSA group. In addition, although AHI was a reliable indicator of OSA severity, it did not represent the entire status of OSA. Therefore, we grouped OSA severity in multiple sleep parameters such as hypoxia and night awakenings and compared with iron metabolism indicators again. The results showed that the group with higher degree of hypoxia had higher serum TF level. We also found that serum TF level was not linked with MAI. To this point, our study revealed that the elevated serum TF level in moderate/severe obese OSA patients may be related to the extent of intermittent hypoxia but not to sleep fragmentation.

So far, the role of TF in the pathogenesis and progression of OSA is not yet clear. TF, an iron-carrier protein, is a 76-kDa glycoprotein that is mainly produced in the liver and has a half-life of approximately 8 days in the serum [26]. Serum TF is a powerful chelator which can bind iron tightly but reversible and has been known for years as a central player in iron metabolism, designated to circulate iron in a soluble nontoxic form and deliver it to red blood cells and other tissues [26]. Under hypoxia conditions, the body bone marrow hematopoiesis was active, increased the rate of erythropoiesis, leading to a significant increase in peripheral red blood cells and HGB, and aging red blood cells [27]. At the same time, the average lifespan of red blood cells became shorter owing to the increased fragility of its membrane, which sped up the destruction of red blood cells and increased the release of iron from them, which then were phagocytized by macrophages. Macrophages degrade HGB and catabolize heme in a reaction catalyzed by heme oxygenases (HO-1 or HO-2) that liberates inorganic ferrous iron (Fe^{2+}) and generates CO and biliverdin [28]. Macrophages export Fe^{2+} through the transmembrane transporter ferroportin (FPN1), in a process coupled by re-oxidation of Fe^{2+} to Fe^{3+} by ceruloplasmin and followed by loading of Fe^{3+} to TF [29]. Recycled iron can then be stored in ferritin or released back to serum TF at a rate that correlated with the iron needs for erythropoiesis [30]. After this series of processes, the rate of iron metabolism increased, including SI, SF, and TF level, as we see in obese patients with OSA. Furthermore, TF serves as an upstream regulator of hepcidin, a liver-derived peptide hormone that controls iron homeostasis, by triggering hepcidin transcriptional activation via hemochromatosis-associated proteins (HFE and TfR2) [31].

The current study also had some limitations. First, as it was a retrospective study design, it did not prove a causal relationship between serum TF level and OSA severity, further longitudinal or interventional studies were required to confirm. Second, even though there is statistically significant relationship between serum TF level and OSA severity, serum TF level remained within the normal value. However, as found in candidates for metabolic surgery, ID was commonly identified in the absence of anemia [32], the slight elevation of serum TF level may be an indicator of the compensatory phase of anemia, and the progression of OSA might break this compensation state. Finally, females constituted the majority of studying subjects. This gender bias may limit the population to which our findings could be applied. We will continue to expand the sample size to prevent gender bias in future studies.

Our study suggested that serum TF level was correlated with OSA severity, especially the degree of intermittent hypoxia, but not linked with sleep fragmentation among candidates for metabolic surgery. This presented evidence to suggest that iron metabolism was involved in the progression of OSA. Furthermore, intermittent hypoxia secondary to OSA might have a crucial role in the relationship between iron metabolism and obesity. Further exploration of the mechanism of the association may enhance our understanding of the pathogenesis of obese OSA and identify specific therapeutic targets for future development.

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Statement of Ethics

Written informed consent was obtained from all participants. All procedures performed in this study were in accordance with the ethical standards of the National Research Committee, and the study was approved by the Institutional Ethics Board of Zhongnan Hospital of Wuhan University (ethics number 2019021).

Conflict of Interest Statement

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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Author Contributions

Design: Xiaoping Ming, Xiuping Yang, Minlan Yang, Yufeng Yuan, and Xiong Chen. Conduct/data collection: Xiaoping Ming, Zhen Li, Weisong Cai, Gaoya Wang, and Dingyu Pan. Analysis: Xiaoping Ming, Xiuping Yang, Zhen Li, Yufeng Yuan, and Xiong Chen. Writing manuscript: All authors contributed to the writing and revision of this manuscript and approved the final submitted draft.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (X.C.) upon request.

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