Age-adjusted Charlson Comorbidity Index as a predictor of all-cause mortality risk in older adult patients with obstructive sleep apnea: a prospective cohort analysis

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Abstract

Background: To explore the prognostic and therapeutic value of the age-adjusted Charlson Comorbidity Index (ACCI) for patients with obstructive sleep apnea (OSA) aged 60 years and older.

Methods: Between January 2015 and October 2017, this multicenter, prospective, observational cohort study continuously enrolled 1183 older patients (age ≥60 years) with clinician-diagnosed OSA (sleep-laboratory-based overnight polysomnography) from sleep centers of six hospitals. Baseline demographics, clinical characteristics, sleep parameters, and medical history were obtained from electronic patient records, the ACCI was calculated, and participants were followed up prospectively to determine the primary outcome of all-cause mortality. Based on an ACCI cutoff of 4.5, participants were classified into the low-ACCI and high-ACCI groups and the receiver operating characteristic (ROC) curves were plotted. Kaplan–Meier survival analysis with log-rank test and Cox proportional hazards regression modeling was performed.

Results: During a median 43-month follow-up, 63 (5.3%) patients died. ROC curves revealed an optimal ACCI cutoff of 4.5, and the area under the curve (AUC) of 0.70 [95% confidence interval (CI): 0.63–0.77] reached statistical significance (P<0.001). Kaplan–Meier survival analysis revealed 6-year survival rate of 56.04% and 92.17% for the high-ACCI and low-ACCI (ACCI ≥5 and <5; n=336 and n=847) groups, respectively. Regardless of sex or OSA severity, the ACCI was associated with the all-cause mortality risk of older OSA patients (log-rank, both P<0.001). After controlling for confounding variables, the mortality risk was 3.32 times (95% CI: 1.91–5.77) higher in the high-ACCI group than in the low-ACCI group. Multivariate Cox stepwise regression analyses indicated that total sleep time (TST), Mean Corpuscular Volume (MCV), and ACCI (aHR [95% CI]=1.258 [1.053–1.503], 1.047 [1.007–1.087], and 1.583 [1.384–1.815]; P=0.011, 0.019, and 0.000, respectively) were significant independent predictors of all-cause mortality.

Conclusion: The ACCI is a predictor of all-cause mortality in older OSA patients (age≥60 years), with a higher ACCI indicating a higher mortality risk. The ACCI can guide clinical treatment selection for older OSA patients.

1 Background

Obstructive sleep apnea (OSA; apnea–hypopnea index [AHI] cutoff ≥ 5 events/h) is a potentially fatal disease that has an estimated prevalence of 14% and 5% in male and female populations, respectively, as well as a higher prevalence in the older adult population[1]. OSA is characterized by a history of habitual snoring as well as hypopneic and apneic events during sleep that increase the risk of hypertension[2], metabolic syndrome (MS)[3], cardiovascular and cerebrovascular diseases[4], and motor vehicle accidents[5]. Based on a 10-year follow-up study, Marin et al.[4] reported a significantly higher incidence of non-fatal cardiovascular events and cardiovascular mortality in patients with untreated severe OSA than in healthy individuals (2.13 vs. 0.45 and 1.06 vs. 0.3 per 100 person-years, P< 0.0001 and P= 0.0012, respectively). During a mean follow-up duration of 13.4 years, patients with moderate–severe OSA had a 6.24-fold higher all-cause mortality risk than individuals without OSA[6]. Furthermore, sleep apnea was an independent risk factor for a composite endpoint of all-cause mortality or incident stroke (hazard ratio [HR] = 1.97, 95% confidence interval [CI]: 1.12–3.48) when compared to a population without sleep apnea[7]. OSA is a leading health concern because of its growing prevalence and strong association with all-cause mortality.

The Charlson Comorbidity Index (CCI), including 19 common comorbidities, is a scoring system that facilitates a rapid evaluation of the clinical disease severity and prediction of the mortality risk of patients with chronic diseases or cancer[8]. The Age-adjusted Charlson Comorbidity Index (ACCI), which quantifies age and comorbidity, has better predictive value for evaluating the risk of postoperative complications[9] and the prognosis of patients with cancer[10], heart failure (HF)[11], and chronic obstructive pulmonary disease[12]. Yang et al.[10] reported that, for 3-year overall survival of lung cancer patients, the ACCI provided a better comprehensive comorbidity risk adjustment with a lower AIC (18 753.089) and higher C-statistic (0.7236) than the CCI. A large-cohort long follow-up study showed that survival rates in HF patients decreased with increasing quintiles of the ACCI, which was a significant incremental predictor of mortality and the combined endpoint of death or cardiovascular hospitalizations (HR = 1.37, 95% CI:1.34–1.40, $P < 0.0001$)[11].

Although the ACCI is a strong predictor of disease outcome, few studies have used the ACCI to evaluate the prognosis of OSA, and there is limited research on the ACCI as a predictive indicator of all-cause mortality risk in older adult OSA patients. This study aimed to investigate the usefulness of the ACCI as a predictive indicator of the long-term outcome of older adult OSA patients. The primary objective was to evaluate the predictors of all-cause mortality in older adult OSA patients.

2 Methods

2.1 Study population and design

In this prospective, observational, multicenter cohort study, we continuously screened and enrolled 1290 older adult OSA patients (age ≥ 60 years) from sleep centers of the People's Liberation Army General Hospital (PLA; n = 313), Peking University International Hospital (n = 242), Peking University People's Hospital (n = 242), Beijing Chaoyang Hospital (n = 337), 960th Hospital of PLA (n = 48), and the Affiliated Hospital of Gansu University of Chinese Medicine (n = 112) between January 2015 and October 2017. All participants underwent full-night polysomnography, supervised by sleep technicians, in a temperature-controlled and noise-free room at the hospital sleep centers. The inclusion criteria were: 1) age ≥ 60 years and 2) a diagnosis of OSA confirmed by a clinician based on the findings of nocturnal polysomnography. Patients were excluded if they had: 1) incomplete clinical data (clinical data, hematologic examination, or medical history, etc.); 2) fever, urinary tract infection, acute diabetes-related complications, or malignant hypertension; or 3) a mental disorder. Furthermore, participants were excluded from the final analysis for the following reasons: 1) lost-to-follow-up (n = 20); 2) receiving continuous positive airway pressure (n = 71); and 3) undergoing ear, nose and throat surgery (n = 17). The statistical analysis included 1183 participants (Fig. 1). This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines and the principles evinced in the Declaration of Helsinki. The ethics committee of the PLA General Hospital approved the study protocol (S2019-352-01). Written informed consent was available from all participants.

2.2 Polysomnography Examination

Polysomnography is the gold standard investigation for OSA diagnosis. After clinical stabilization during hospitalization, all participants underwent in-laboratory overnight polysomnography (from 21:00 to 07:00 the

next day) and OSA was diagnosed by a clinician based on the polysomnography reports. The polysomnography scores were assigned in accordance with the American College of Physicians 2014[13] or the American Academy of Sleep Medicine 2017[1] guideline by polysomnography technologists who were blinded to the demographics and clinical characteristics of the participants and registered with the American Academy of Sleep Medicine. A laboratory-based polysomnography instrument (Compumedics, Melbourne, Australia) was used to measure sleep parameters, including electroencephalography (EEG), electrooculography (EOG), electrocardiography (ECG), airflow measured by nasal pressure and oronasal thermistor, monitoring of respiratory effort with a chest and abdominal band, continuous pulsoximetry, body position and snoring, the AHI (defined as the number of apnea and hypopnea events per hour during sleep), the oxygen desaturation index (ODI; number of oxygen desaturation events per hour), total sleep duration, sleep duration with oxygen saturation less than 90% (CT90), the mean apnea–hypopnea time(MAT), the mean peripheral oxygen saturation ($MSpO_2$), the lowest peripheral oxygen saturation ($LSpO_2$), and heart rate [14]. Apnea was defined as the continuous cessation of airflow for more than 10 s, whereas hypopnea was defined as a 30% or greater drop in flow for 10 s or longer that was associated with a 4% or greater oxygen desaturation (OSA, if respiratory efforts were present). OSA severity was determined as follows using an AHI cutoff of $\geq$ 5/h for the presence of OSA; AHI $\geq$ 5 to < 15, $\geq$15 to < 30, and $\geq$ 30 indicated mild, moderate, and severe OSA, respectively[1, 13, 14].

2.3 Covariates

Demographics and clinical data of all OSA patients were collected by investigators from the electronic patient records. Demographic data included sex, age, height, weight, and body mass index (BMI was defined as weight in kilograms divided by height in meters squared and was expressed in units of kg/m^2); the self-reported history of smoking ascertained whether the participant smoked consecutively or cumulatively for a duration exceeding 6 months; and alcohol consumption was defined as drinking at least once a week for more than a year, currently drinking, or as having quit drinking for less than 3 years. The hematological (red cell distribution width [RDW], mean corpuscular volume [MCV], red blood cell, mean platelet volume [MPV], platelet distribution width, platelets, white blood cell, the absolute values of eosinophils, and hemoglobin) and biochemical (total bilirubin, direct bilirubin, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum creatinine [SCr], serum urea, blood glucose, and serum cystatin C) indicators in serum samples were routinely measured in this study. The medical and systematic history, including hypertension, myocardial infarction (MI), congestive heart failure (CHD), cerebrovascular disease, peripheral vascular disease (PVD), dementia, chronic obstructive pulmonary disease(COPD), connective tissue diseases, peptic ulcers, mild liver disease, diabetes mellitus (DM), hemiplegia, moderate and severe kidney disease, DM with end-stage organ damage, any tumor, leukemia, lymphoma, moderate and severe liver disease, metastases, and acquired immune deficiency syndrome (AIDS), of the participants were recorded.

2.4 ACCI

Age and comorbidities were quantified by the ACCI based on the age of the patient and the number and severity of diseases. The ACCI incorporates 19 different medical categories, with each weighted according to its potential impact on mortality[15]. Information on preexisting comorbidities before a diagnosis of OSA was available from the medical records available from the sleep centers of six hospitals. The ACCI was scored according to the following guideline for OSA patients: in participants with MI, CHD, cerebrovascular disease,

PVD, dementia, COPD, connective tissue diseases, peptic ulcers, mild liver disease, or DM, 1 point was assigned for each disease; in participants with hemiplegia, moderate and severe kidney disease, DM with end-stage organ damage, any tumor, leukemia, or lymphoma, 2 points were assigned for each disease; in participants with moderate or severe liver disease, 3 points were assigned; in participants with metastases or AIDS, 6 points were assigned for either of these conditions; and 1 point was added for each decade over 40 years of age, up to a total of 4 points. A higher cumulative score (the ACCI) indicated greater severity of the comorbidity (Table 1)[8]. The receiver operating characteristics (ROC) curve of the participants was drawn and divided the study cohort into the high ACCI and low ACCI groups based on the critical value of the ACCI.

Table 1
Comorbidity distribution of participants

Score	comorbidity	n = 1183,n(%)
Assign weights by disease		
1	Myocardial Infarction	20(1.7)
	Congestive heart failure	30(2.5)
	Cerebrovascular disease	**188(15.9)**
	Peripheral vascular disease	57(4.8)
	Dementia	5(0.4)
	Chronic obstructive pulmonary disease.	**84(7.1)**
	Connective tissue diseases	11(0.9)
	Peptic ulcers	20(1.7)
	Mild liver disease	**64(5.4)**
	Diabetes mellitus	**241(20.4)**
2	Hemiplegia	23(1.9)
	Moderate and severe kidney disease	9(0.8)
	Diabetes with end-stage organ damage	**34(2.9)**
	Any tumor	33(2.8)
	Leukemia	0(0)
	Lymphoma	0(0)
3	Moderate and severe liver disease	3(0.3)
6	Metastases	0(0)
	Acquired immune deficiency syndrome.	1(0.1)
Assign weights by age		
1	41–49 years	0(0)
2	50–59 years	0(0)
3	60–69 years	804(68.0)
4	≥ 70 years	379(32.0)

2.5 Follow-up and outcome assessment

All patients diagnosed with OSA were scheduled to be discharged from the hospital after the clinician had developed a detailed treatment plan. After discharge, patients were prospectively followed-up telephonically

by researchers at 1, 3, 6, and 12 months, and every 6 months thereafter. The follow-up duration was defined as the time from the date of OSA diagnosis to the date of death or until the last date of follow-up (December 2020).

The primary outcome was the all-cause mortality at a median follow-up duration of 43 months. The cause of death was ascertained from hospital discharge letters or the death certificates provided by the patients' family members, and we also verified against a national registry.

2.6 Statistical Analysis

Normally distributed variables were expressed as means ± standard deviations, and the t-test was used for comparisons between groups. while non-normally distributed variables were expressed as medians and interquartile ranges, and the Mann-Whitney U test was used for comparisons between groups. Count data were expressed as percentage (%), and chi-square tests were used for comparisons between groups. ROC analysis was performed to assess the sensitivity and specificity of ACCI for predicting all-cause mortality in elderly OSA patients. The optimal specific cut-off values of ACCI were determined at the point to maximize Youden s J statistic. We evaluated the association between ACCI and all-cause mortality of subjects using a Kaplan–Meier method comparing groups, and the log-rank test was used to determine differences in the survival distribution between the low-ACCI group and the high-ACCI group. The independent prognostic factors affecting all-cause mortality of subjects were identified by univariate and multivariate Cox regression analyses. All data were analyzed using SPSS version 20.0 (SPSS Inc, Chicago, IL, USA), the difference was considered statistically significant when $P < 0.05$.

3 Results

3.1 Distribution of comorbidities

In this study with a follow-up duration of 1–72 months (median 43 months), we enrolled 1183 older adult patients with OSA (Table 1), among whom 241 (20.4%) were diagnosed with DM, which was the commonest comorbidity. In the subgroup analysis of 1-point comorbidities, cerebrovascular disease, COPD, and mild liver disease followed DM as the most prevalent comorbidities (15.9%, 7.1%, and 5.4%, respectively). In the subgroup analysis of comorbidities that scored 2 points, diabetes with end-stage organ damage was observed in 34 patients (2.9%), whereas the analysis of comorbidities accounted for more than 2 points revealed that 3 (0.3%) participants had moderate/severe liver disease and 1 (0.1%) participant had AIDS. The ACCI of the participants ranged from 3 to13 points (median 4 points), and 71.6% of the participants had an ACCI of 3–4 points (Fig. 2).

3.2 Participant characteristics

ROC curves were plotted to determine the best ACCI cutoff values, and the area under the curve (AUC) in this study of 0.70 (95% CI: 0.63–0.77) reached statistical significance ($P = 0.000$). The maximum value of the Youden Index (0.32 [J = 0.587–0.267]) was used to select the optimal cutoff ACCI value of 4.5. In the absence of decimal values of the ACCI, an ACCI cutoff of 5 was used to assign participants to the low-ACCI (n = 847) and high-ACCI (n = 336) groups (Fig. 3).

Of the 1183 participants included in the final analyses, 61.8% were male, the median age was 66 years, and the median follow-up period was 43 months. Based on OSA severity, participants were divided into three groups as follows: 275 (23.2%), 366 (30.9%), and 542 (45.8%) in the mild, moderate, and severe OSA. Compared with the low-ACCI group, participants in the high-ACCI group were older (71 years vs. 65 years, $P < 0.001$), had a higher BMI (26.86 kg/m^2 vs. 26.45 kg/m^2, $P = 0.037$), and comprised a higher proportion of smoking (27.7% vs, 20.4%, $P = 0.007$), drinking (28.3% vs. 16.5%, $P < 0.001$), hypertension (71.4% vs. 62.9%, $P = 0.006$), and all-cause mortality (11.0% vs. 3.1%, $P < 0.001$). Sleep parameters, including $MSpO_2$ and $LSpO_2$, were lower, whereas the MAT was longer, in the high-ACCI group than in the low-ACCI group ($P < 0.05$). The MPV, SCr, serum urea, and cystatin C levels differed significantly between the two study groups ($P < 0.05$; Table 2).

Table 2
participants characteristic

	Total (n = 1183)	Low-ACCI group (n = 847)	High-ACCI group (n = 336)	*P* value
Demographics				
Male, n(%)	731(61.8)	523(61.7)	208(61.9)	0.960
Age (y)	66.00(62.00,71.00)	65.00(62.00,68.50)	71.00(65.00,76.00)	**<0.001**
Height (cm)	167.00(160.00,172.00)	167.00(160.00,172.00)	165.00(160.00,170.00)	0.119
Weight (kg)	73.00(65.00,81.25)	73.00(65.00,81.00)	73.00(65.00,82.00)	0.826
BMI(kg/m^2)	26.56(24.17,29.33)	26.45(24.10,28.92)	26.86(24.21,29.88)	**0.037**
Smoking, n(%)	266(22.5)	173(20.4)	93(27.7)	**0.007**
Drinking, n(%)	221(18.7)	140(16.5)	95(28.3)	**<0.001**
Sleep parameters				
AHI(events/h)	27.60(15.50,45.60)	27.80(15.15,45.75)	27.40(16.30,45.15)	0.982
ODI (events/h)	22.60(11.20,41.00)	22.70(11.10,40.00)	22.20(11.75,42.10)	0.823
TST(h)	7.10(6.17,7.64)	7.10(6.10,7.60)	7.10(6.48,7.70)	0.216
TSA90(min)	14.45(2.50,59.16)	14.70(2.69,55.00)	13.96(1.74,73.51)	0.869
MAT (s)	22.10(19.46,25.01)	22.00(19.35,24.79)	22.62(19.68,26.00)	**0.049**
MSpO2(%)	93.20(91.95,95.00)	93.70(92.00,95.00)	93.00(91.00,95.00)	**0.002**
LSpO2(%)	80.00(72.00,85.00)	81.00(73.00,85.00)	78.00(68.00,85.00)	**<0.001**
Heart rate	63.00(57.60,68.00)	64.00(58.00,68.85)	62.65(57.00,67.75)	0.222
serum biochemical				
TB(μmol/L)	10.50(8.00,14.10)	10.50(8.00,14.25)	10.30(7.90,13.60)	0.273
DB (μmol/L)	3.54(2.90,4.80)	3.50(2.90,4.85)	3.60(2.99,4.75)	0.721
TC(mmol/L)	4.21(3.56,4.94)	4.24(3.59,4.95)	4.19(3.43,4.87)	0.194

ACCI: age-adjusted charlson comorbidity index; BMI: body mass index; AHI: the apnea-hypopnea index; ODI: the oxygen desaturation index; TST: total sleep time; TSA90: the duration of time with SaO_2 < 90%; MAT: the mean apnea time; $MSpO_2$: the mean pulse oxygen saturation; $LSpO_2$: the lowest pulse oxygen saturation; TB: total bilirubin; DB: direct bilirubin; TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SCr: serum creatinine; GLU: Blood glucose; RDW: red cell distribution width; MCV: Mean Corpuscular Volume; PLTs: platelets; MPV: Mean Platelet Volume; PDW: platelet distribution width; RBC: red blood cell; WBC: white blood cell; Hb: hemoglobin; OSA : obstructive sleep apnea

	Total (n = 1183)	Low-ACCI group (n = 847)	High-ACCI group (n = 336)	*P* value
TG (mmol/l)	1.40(1.01,1.92)	1.40(1.01,1.90)	1.40(0.96,1.93)	0.618
LDL-C (mmol/L)	2.42(1.89,2.98)	2.44(1.88,2.99)	2.42(1.93,2.96)	0.888
HDL-C (mmol/L)	1.10(0.90,1.35)	1.10(0.90,1.36)	1.10(0.89,1.33)	0.519
SCr(μmol/L)	72.33(61.73,84.00)	71.70(61.58,81.57)	75.00(62.55,90.05)	**0.002**
serum urea(mmol/L)	6.20(5.00,8.90)	6.30(5.00,9.00)	6.07(4.90,8.00)	**0.014**
GLU(mmol/L)	5.67(5.06,6.50)	5.69(5.10,6.43)	5.60(5.00,6.70)	0.361
cystatin C	0.98(0.80,1.13)	0.93(0.80,1.09)	0.99(0.83,1.19)	**0.003**
Routine blood				
RDW,%	12.90(12.50,13.20)	12.90(12.50,13.20)	12.90(12.50,13.20)	0.876
MCV, fl	90.90(88.15,94.10)	90.80(88.10,94.10)	91.40(88.35,94.40)	0.170
RBC(10^12/L)	4.49(4.19,4.82)	4.48(4.21,4.80)	4.53(4.13,4.84)	0.641
WBC(10^9/L)	6.23(5.27,7.19)	6.23(5.31,7.19)	6.24(5.16(7.17))	0.473
PLTs(10^9/L)	10.40(9.70,11.10)	207.00(172.24,239.00)	198.50(167.50,237.00)	0.097
PDW,%	12.70(11.00,13.80)	12.70(11.00,13.80)	12.80(11.25,13.90)	0.064
MPV, fl	10.40(9.70,11.10)	10.30(9.60,11.10)	10.60(9.90,11.50)	**0.001**
Absolute eosinophil value(10^9/L)	0.02(0.01,0.05)	0.02(0.015,0.049)	0.023(0.013,0.046)	0.051
Hb (g/L)	138.14(129.00,147.00)	138.38(129.00,146.50)	138.00(128.00,148.00)	0.754
Medical history				
Hypertension, n(%)	773(65.3)	533(62.9)	240(71.4)	**0.006**
OSA, n(%)				0.275

ACCI: age-adjusted charlson comorbidity index; BMI: body mass index; AHI: the apnea-hypopnea index; ODI: the oxygen desaturation index; TST: total sleep time; TSA90: the duration of time with SaO_2 < 90%; MAT: the mean apnea time; $MSpO_2$: the mean pulse oxygen saturation; $LSpO_2$: the lowest pulse oxygen saturation; TB: total bilirubin; DB: direct bilirubin; TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SCr: serum creatinine; GLU: Blood glucose; RDW: red cell distribution width; MCV: Mean Corpuscular Volume; PLTs: platelets; MPV: Mean Platelet Volume; PDW: platelet distribution width; RBC: red blood cell; WBC: white blood cell; Hb: hemoglobin; OSA : obstructive sleep apnea

	Total (n = 1183)	Low-ACCI group (n = 847)	High-ACCI group (n = 336)	*P* value
mild	275(23.2)	207(24.4)	68(20.2)	
moderate	366(30.9)	255(30.1)	111(33.0)	
severe	542(45.8)	385(45.5)	157(46.7)	
All-cause mortality, n(%)	63(5.3)	26(3.1)	37(11.0)	**0.001**

ACCI: age-adjusted charlson comorbidity index; BMI: body mass index; AHI: the apnea-hypopnea index; ODI: the oxygen desaturation index; TST: total sleep time; TSA90: the duration of time with SaO_2 < 90%; MAT: the mean apnea time; $MSpO_2$: the mean pulse oxygen saturation; $LSpO_2$: the lowest pulse oxygen saturation; TB: total bilirubin; DB: direct bilirubin; TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SCr: serum creatinine; GLU: Blood glucose; RDW: red cell distribution width; MCV: Mean Corpuscular Volume; PLTs: platelets; MPV: Mean Platelet Volume; PDW: platelet distribution width; RBC: red blood cell; WBC: white blood cell; Hb: hemoglobin; OSA : obstructive sleep apnea

3.3 Associations of ACCI with all-cause mortality

During the follow-up period, 63 patients (5.3%) died. The Kaplan–Meier survival curve showed that the 3-, 5-, and 6-year survival rates of 94.29%, 74.20%, and 56.04% for the high-ACCI group and 98.93%, 92.17%, and 92.17% for the low-ACCI group, respectively. The cumulative survival rate in the low-ACCI group was significantly higher than that in the high-ACCI group among all the elderly patients with OSA (Log-rank P< 0.000 1; Fig. 4). As patients with severe OSA showed a trend for worse prognosis in previous studies, the Kaplan–Meier analysis was stratified according to the severity of OSA, based on the AHI. The 6-year survival rates were 51.80% and 58.28% for the high-ACCI and 95.84% and 88.30% for the low-ACCI group in older patients with mild-moderate ($5 \leq AHI < 30$) and severe OSA ($AHI \geq 30$), respectively. Regardless of which OSA severity, the cumulative survival rate in the low-ACCI group was significantly higher than that in the high-ACCI group (log-rank P< 0.0001 and P= 0.0002, respectively; Figs. 5 and 6). Survival curves stratified by sex showed that a higher ACCI was associated with a higher mortality risk in all participants (women and men, log-rank P< 0.0001 and P= 0.0002, respectively; Figure S-1, S-2).

3.4 Predictors of all-cause mortality risk

ACCI scores ranged from 3 to 13, and participants were classified into the low-ACCI group (ACCI 3–4) or high-ACCI group (ACCI 5–13). After controlling for confounding variables, including age, sex, BMI, history of smoking, history of drinking, hypertension, AHI, TST, MAT, SpO_2, and heart rate, we found that patients in the high-ACCI group had a 3.32 times (95% CI: 1.91–5.77) higher mortality risk than patients in the low-ACCI group (Table 3).

Table 3
Association between ACCI and all-cause mortality

	Unadjusted analysis		**Adjusted analysis**	
	HR (95% *CI*)	*P*-Value	*aHR* (95% *CI*)	*P*-Value
ACCI-1		0.000		0.000
Low-ACCI	Reference		Reference	
High-ACCI	3.86(2.33,6.40)		3.32 (1.91, 5.77)	
ACCI-2		0.000		0.000
3–4 points	Reference		Reference	
5–6 points	3.32 (1.92,5.74)		2.93 (1.62, 5.30)	
7–8 points	4.78 (2.15, 10.60)		3.44 (1.46, 8.10)	
9–10 points	23.61 (3.17, 175.443)		25.03 (3.11, 201.44)	
≥ 11 points	87.97(20.24, 382.41)		65.04(13.68,309.28)	

a: after adjusting for possible confounding factors: age, sex, BMI, history of drinking, smoking, AHI, TST, TSA90, MAT, SpO_2, HR, and hypertension; ACCI-1: participants were divided in 2 groups according to ACCI = 5; ACCI-2: participants were divided in 5 groups according to ACCI scoring

Univariate Cox regression analysis (HR [95% CI]) showed that age (1.044 [1.009–1.080], *P* = 0.013), TST (1.292 [1.093–1.528], *P* = 0.003), heart rate (0.964 [0.933–0.995], *P* = 0.024), MCV (1.056 [1.016–1.097], *P* = 0.005), and ACCI (1.625 [1.422–1.858], *P* = 0.000) were associated with all-cause mortality of older OSA patients(Table 4). The all-cause mortality-related factors identified by univariate Cox regression analyses were subsequently analyzed using multivariate Cox stepwise regression (presented as HR [95% CI]), which showed that TST (1.258 [1.053–1.503], *P* = 0.011), MCV (1.047 [1.007–1.087], *P* = 0.019), and ACCI (1.583 [1.384–1.815], *P* = 0.000) were significant independent predictors of all-cause mortality (Table 4).

Table 4
Predictors of all-cause mortality as determined via univariate and multivariate Cox proportional hazards regression analyses.

Index	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-Value	*HR (95% CI)*	*P*-Value
Sex	0.829(0.494,1.393)	0.480	——	
Age	1.044(1.009,1.080)	0.013	unselected	
BMI	1.015(0.957,1.076)	0.621	——	
Smoking	0.827(0.466,1.469)	0.518	——	
Drinking	1.384(0.826,2.384)	0.217	——	
AHI	1.005(0.993,1.016)	0.440	——	
TST	1.292(1.093,1.528)	0.003	1.258(1.053,1.503)	0.011
TSA90	1.002(1.000,1.005)	0.101	——	
MAT	1.000(0.967,1.034)	0.986	——	
$MSpO_2$	0.962(0.901,1.028)	0.255	——	
Heart rate	0.964(0.933,0.995)	0.024	unselected	
TB	0.992(0.946,1.040)	0.729	——	
TC	0.869(0.698,1.080)	0.206	——	
TG	1.009(0.763,1.334)	0.949	——	
LDL-C	1.076(0.823,1.408)	0.593	——	
HDL-C	0.939(0.483,1.827)	0.854	——	
SCr	1.001(0.995,1.007)	0.835	——	
serum urea	1.014(0.955,1.076)	0.649	——	
GLU	1.034(0.895,1.196)	0.649	——	
cystatin C	0.998(0.970,1.027)	0.903	——	
RDW	0.970(0.816,1.154)	0.731	——	
MCV	1.056(1.016,1.097)	0.005	1.047(1.007,1.087)	0.019

ACCI: age-adjusted charlson comorbidity index; BMI: body mass index; AHI: the apnea-hypopnea index; ODI: the oxygen desaturation index; TST: total sleep time; TSA90: the duration of time with $SaO_2 < 90\%$; MAT: the mean apnea time; $MSpO_2$: the mean pulse oxygen saturation; $LSpO_2$: the lowest pulse oxygen saturation; TB: total bilirubin; DB: direct bilirubin; TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SCr: serum creatinine; GLU: Blood glucose; RDW: red cell distribution width; MCV: Mean Corpuscular Volume; PLTs: platelets; MPV: Mean Platelet Volume; PDW: platelet distribution width; RBC: red blood cell; WBC: white blood cell; Hb: hemoglobin; OSA : obstructive sleep apnea

Index	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-Value	*HR (95% CI)*	*P*-Value
RBC	0.932(0.593,1.464)	0.759	——	
WBC	0.937(0.807,1.088)	0.393	——	
PLTs	1.000(0.995,1.004)	0.847	——	
PDW	1.019(0.900,1.153)	0.770	——	
MPV	1.010(0.944,1.018)	0.773	——	
Hb	0.996(0.982,1.010)	0.529	——	
Hypertension	1.500(0.859,2.619)	0.154	——	
Mild OSA	reference		——	
Moderate OSA	0.598(0.296,1.208)	0.152	——	
Severe OSA	0.709(0.398,1.262)	0.242	——	
ACCI	1.625(1.422,1.858)	0.000	1.585(1.384,1.815)	0.000

ACCI: age-adjusted charlson comorbidity index; BMI: body mass index; AHI: the apnea-hypopnea index; ODI: the oxygen desaturation index; TST: total sleep time; TSA90: the duration of time with SaO_2 < 90%; MAT: the mean apnea time; $MSpO_2$: the mean pulse oxygen saturation; $LSpO_2$: the lowest pulse oxygen saturation; TB: total bilirubin; DB: direct bilirubin; TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SCr: serum creatinine; GLU: Blood glucose; RDW: red cell distribution width; MCV: Mean Corpuscular Volume; PLTs: platelets; MPV: Mean Platelet Volume; PDW: platelet distribution width; RBC: red blood cell; WBC: white blood cell; Hb: hemoglobin; OSA : obstructive sleep apnea

Discussion

In this study, we found that the ACCI was a significant independent predictor of all-cause mortality in older OSA patients. An ACCI cutoff of 5, identified using ROC curve analysis, could better discriminate the mortality risk of older OSA patients. The Kaplan–Meier survival curve showed the cumulative survival rate of all participants in the low-ACCI group was significantly higher than those in the high-ACCI group. Regardless of sex or OSA severity, a higher ACCI was associated with a higher mortality risk in older OSA patients. Therefore, personalized multidisciplinary treatment, based on comorbidities, may improve the prognosis of older OSA patients.

The ACCI, a comorbidity scoring system, includes age as a factor to the CCI, and can more comprehensively assess the overall condition of the patient and predict the clinical outcome[15]. Especially in older patients, comorbidity can influence the patient's selection of treatment options. Unfortunately, the ACCI is not widely utilized in clinical practice. Levine et al.[16]reported that the CCI significantly correlated with the physical function subscale of the Short Form−36(r_s = − 0.39, P< 0.001) and is a good predictor of the SF-36 physical function score in patients with sleep apnea. Kravitz et al.[17] showed that the CCI is a significant risk factor for coronavirus disease-related hospitalization of patients with sleep apnea (aOR = 1.45, 95% CI 1.19–1.81, P = 0.0006). Tang et al.[18] indicated that, during the 1-year follow-up, the all-cause mortality of OSA patients

(age 60.6 ± 9.6 years) was 10.1%, and the CCI (aHR = 1.273, 95% CI 1.050–1.543, *P* = 0.014) was identified as an independent predictor of all-cause mortality. Thus, these results further confirmed that the long-term prognosis of the patients with sleep apnea in the low-CCI group was better than that of patients in the high-CCI group. The ACCI seems to be a more appropriate prognostic indicator and has been confirmed to have better predictive value in the prognosis of patients with cancer[19], infection[20], and postoperative complications[21]. Therefore, we comprehensively analyzed and validated the effects of the ACCI in the prediction of the prognosis of older OSA patients and found that a 1-point increase in the ACCI score would result in a 58.5% increase in the risk of all-cause mortality in the participants.

Besides the ACCI, all-cause mortality was associated with other factors, including TST and MCV in our study, which differed from the results of other studies. Marshall et al.[6] found that the all-cause mortality rate was 33.3% in participants with moderate–severe OSA (6/18) after follow-up for up to 14 years. Moderate–severe OSA was independently associated with a higher mortality risk (aHR = 7.35, 95% CI: 2.40–22.49, *P* < 0.05). A prospective longitudinal study with an average follow-up duration of 10.5 ± 4.1 years found that age (HR = 1.07, 95% CI 1.06–1.08, *P* < 0.001), male sex (HR = 1.68, 95% CI 1.24–2.28, *P* = 0.001), high AHI (HR = 1.01, 95% CI 1.01–1.02, *P* < 0.001), high periodic limb movement index (HR = 1.014, 95% CI 1.01–1.02, *P* = 0.002), and low sleep efficiency (HR = 0.949, 95% CI 0.916–0.984, *P* = 0.004) were significantly associated with increased all-cause mortality[22]. A study in Denmark that included 22,135 OSA patients showed that male sex, age > 40 years, DM, hypertension, and CHD were associated with greater mortality risk[23]. The reasons for the differences in the results of our study with those of earlier studies are as follows: compared to the median follow-up of more than 10 years in other studies, the duration of follow-up in our study was relatively short as the median age in our study population was 66 years, which is not considered advanced age. Mostly, individuals aged about 65 years rarely have comorbidities and are in a good physical health state due to improved living standards. Moreover, we found that 10.7% (126/1183) of participants undertook exercise training to reduce body weight, and 12.6% (149/1183) took TCM products over the last 43 months of follow-up, both of which may have influenced all-cause mortality in our study population. Furthermore, we focused on routine hematological and biochemical indicators during hospitalization as important covariates and found that MCV is an important predictor of all-cause mortality in older OSA patients, which conferred a 4.7% increased risk of mortality for every 1 unit increase in the MCV; this indicator could improve the prognosis of OSA patients by guiding treatment selection.

MCV is a routine parameter in complete blood count examination and is closely associated with the RDW; the RDW-coefficient of variation (CV) is derived from the Eq. (1 standard deviation unit of erythrocyte volumes divided by MCV) × 100%)[24]. The RDW is an independent risk factor for not only cardiovascular mortality but also all-cause mortality. A study of a community-dwelling cohort of non-anemic individuals in Taiwan showed that participants with high RDW had an increased all-cause mortality risk (HR = 1.46, 95% CI: 1.17–1.81, *P* < 0.001) than participants with low RDW during a median follow-up period of 15.9 years[25]. Arbel et al.[26] conducted a community-based cohort study of 225,006 eligible patients aged 40 years or more and found that 21,939 incident cases of a major cardiovascular event and 4,287 deaths were documented during the 6-year follow-up. Compared with patients with an RDW level < 13%, the HR of total mortality gradually increased to 4.57 (95% CI: 3.35–6.24, *P* < 0.001) and 3.26 (95% CI: 2.49–4.28, *P* < 0.001) among male and female patients with an RDW of 17% or higher. However, most studies have focused on the RDW rather than the MCV

so far. Wu et al.,[27] in a large population-based study with a median 6.21-year follow-up duration, found that an elevated MCV significantly increased the cerebrovascular and cardiovascular mortality risk (aHR = 1.42; 95% CI: 1.15–1.76, $P < 0.05$), and the results of our study match their results as the MCV was associated with an increased risk of all-cause mortality in older OSA patients. In general, OSA is associated with increased all-cause and cardiovascular mortality risks. We preliminarily confirmed that the MVC is associated with all-cause mortality although we could not identify the exact mechanism involving MCV in OSA pathogenesis.

In our study, there was a 25.8% increased risk of all-cause mortality in older OSA patients for every 1 h increase in the TST. Persistent short or long sleep duration in late adulthood was associated with an increased risk of all-cause mortality, and especially of cardiovascular mortality. Soh et al.[28] study showed that, compared with participants with a sleep duration of 7 h, individuals with persistently long sleep duration had an increased risk of all-cause (HR = 1.47, 95% CI: 1.24–1.73, $P < 0.05$) and cardiovascular mortality (HR = 1.40, 95% CI: 1.04–1.89, $P < 0.05$). The proportion of long-sleepers increased with age (6–23.7%). A study about sleep duration and chronic diseases among US adults aged 45 and older indicated that short and long sleep durations were significantly associated with the risk of CHD, stroke, and DM after controlling for sex, age, race, and education. The sleep duration had a U-shaped relationship with the leading chronic diseases[29]. Notably, our study population is older (≥ 60 years), with TST maintained at 5.5–7.0 hours (median 7.1 hours). Longer sleep duration and decreased vitality of brain cells can decrease memory in older adults. Moreover, decreased metabolism and age-related changes in blood vessels were noted in older individuals. Prolonged sleep durations could result in increased blood viscosity and an increased risk of stroke in older adults. Moreover, increased sleep durations could further decrease the basal metabolic rate, which will affect the body's metabolism of carbohydrates and increase the risk of DM. CHD, stroke, and DM are the main mortality-associated risk factors among older adults. The OSA patients in this study not only slept for long durations, but also experienced sleep fragmentation and disrupted sleep architecture that reduced the efficacy of restorative processes during sleep and was probably associated with the unfavorable prognosis of OSA patients.

This study was a multicenter, large-sample, prospective, observational cohort study, and we have attempted to comprehensively analyze whether the ACCI plays a crucial role in predicting the all-cause mortality risk of older OSA patients. However, a few limitations need to be mentioned: 1) this cohort study, with a median follow-up of just 43 months, had a relatively short follow-up period compared to other studies; 2) the study population consisted only Asian participants, and the relative homogeneity of the population limits the generalizability of the results; therefore, the findings of this study should be evaluated in other ethnically diverse populations; 3) the all-cause mortality risk of OSA is mediated by a complex process that correlates with multiple factors. We adjusted our analysis for as many related factors as possible; however, there may be other unmeasured confounders; and 4) our study showed that the ACCI has a predictive effect on all-cause mortality from OSA in older adults. Further research into the association between the ACCI or specific comorbidities and other outcomes of OSA is needed.

Conclusions

In our Asian population-based multicenter cohort study, the ACCI was an effective predictor of all-cause mortality, which independently increased the risk of all-cause mortality in older OSA patients (age ≥ 60 years).

Kaplan–Meier survival curves showed that 6-year survival rates of 56.04% and 92.17% for the high-ACCI and low-ACCI group (ACCI ≥ 5 and < 5, respectively). Regardless of sex or OSA severity, a higher ACCI was associated with a higher mortality risk in older OSA patients. Further investigations to apply this prediction tool are needed in order to reduce the all-cause mortality and poor outcomes of OSA patients.

Abbreviations

ACCI Age-Adjusted Charlson Comorbidity Index

BMI Body Mass Index

AHI The Apnea-Hypopnea Index

ODI The Oxygen Desaturation Index

TST Total Sleep Time

TSA90 The Duration Of Time With Sao2<90%

MAT The Mean Apnea Time

MSpO2 The Mean Pulse Oxygen Saturation

$LSpO_2$ The Lowest Pulse Oxygen Saturation

TB Total Bilirubin

DB Direct Bilirubin

TC Total Cholesterol

TG Triglyceride

HDL-C High Density Lipoprotein Cholesterol

LDL-C Low Density Lipoprotein Cholesterol

SCr Serum Creatinine

GLU Blood Glucose

RDW Red Cell Distribution Width

MCV Mean Corpuscular Volume

PLTs Platelets

MPV Mean Platelet Volume

PDW Platelet Distribution Width

RBC Red Blood Cell; Wbc: White Blood Cell

Hb Hemoglobin

OSA Obstructive Sleep Apnea

Declarations

Ethics approval and consent to participate

The Ethics Committee of Chinese PLA General Hospital (S2019-352-01) approved the study. Written informed consent was obtained from all participants.

Consent to 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

The authors declare no conflict of interest, financial or otherwise.

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Authors’ contributions

Yinghui Gao, Huanhuan Wang, Yazhuo HU, JianHua Li, Weihao Xu, LiBo Zhao, Xiaofeng Su collected the data. Yinghui Gao, Huanhuan Wang and Yazhuo HU analyzed the data and wrote the manuscript draft.

Tianzhi Li, Xiangqun Fang, and Lin Liu designed this study. All the authors contributed to the paper review.

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Figures

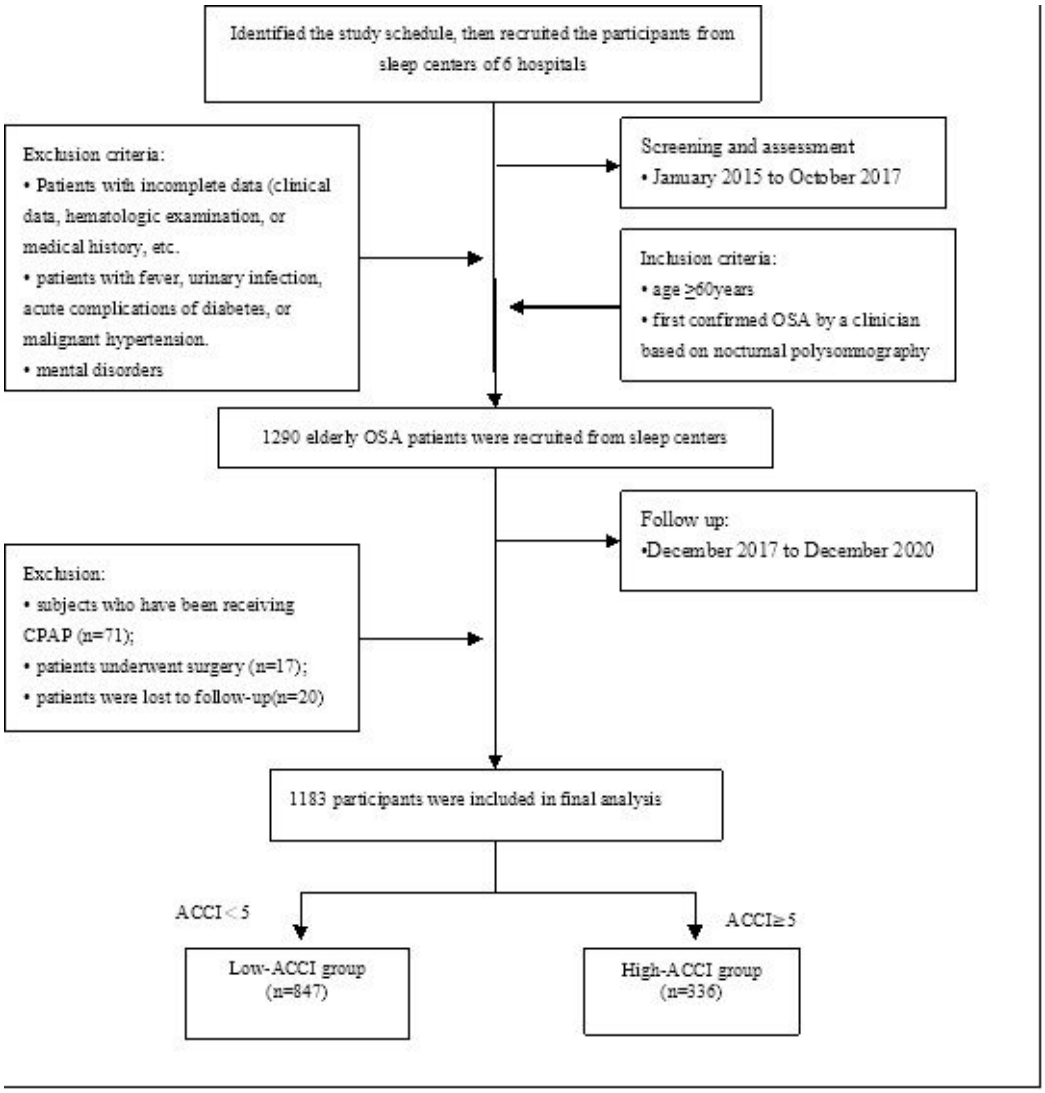

Figure 1

Study flowchart. OSA: obstructive sleep apnea; CPAP: continuous positive airway pressure; ACCI: the age-adjusted charlson comorbidity index.

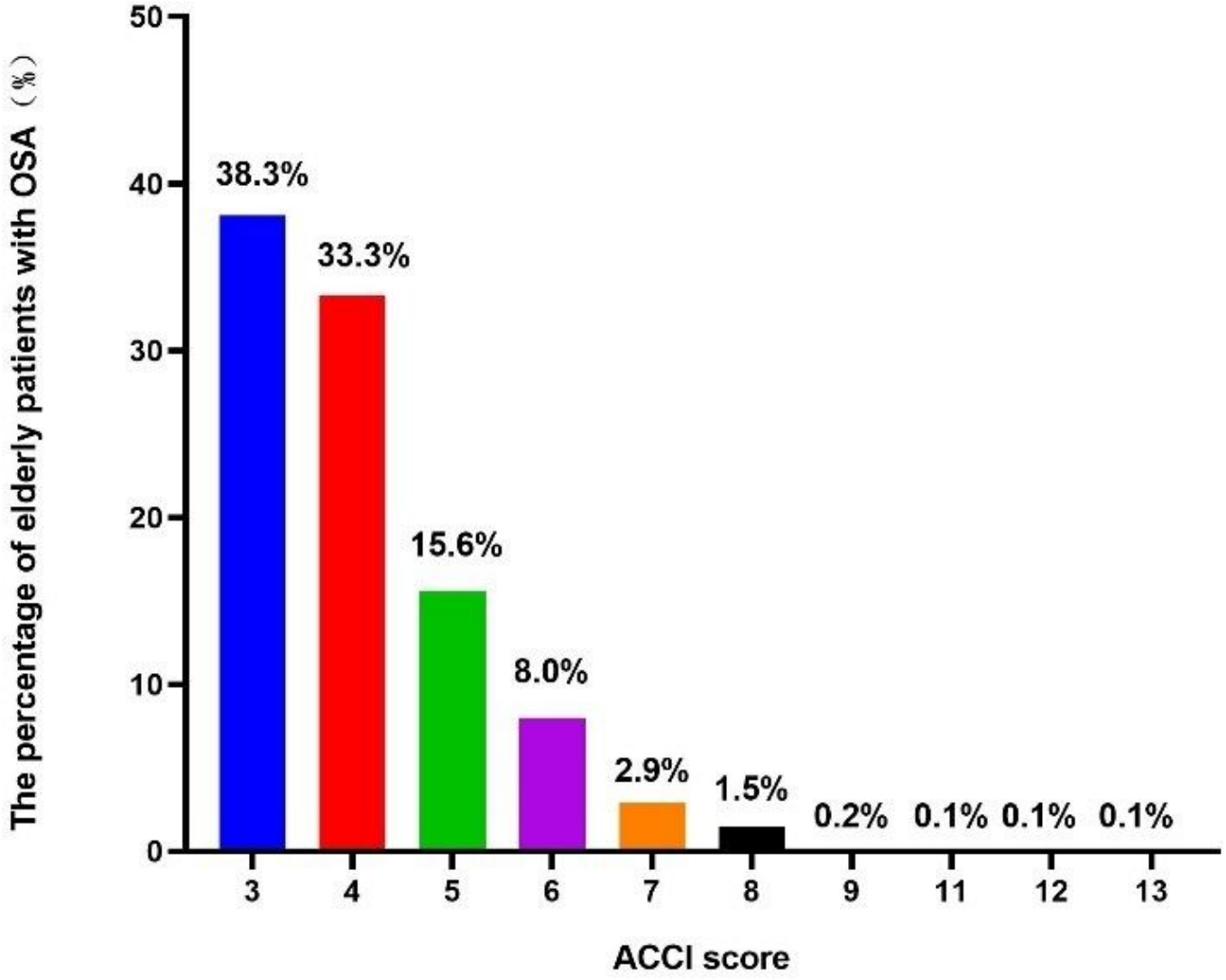

Figure 2

Distribution of ACCI score in participants. OSA: obstructive sleep apnea; ACCI: the age-adjusted charlson comorbidity index.

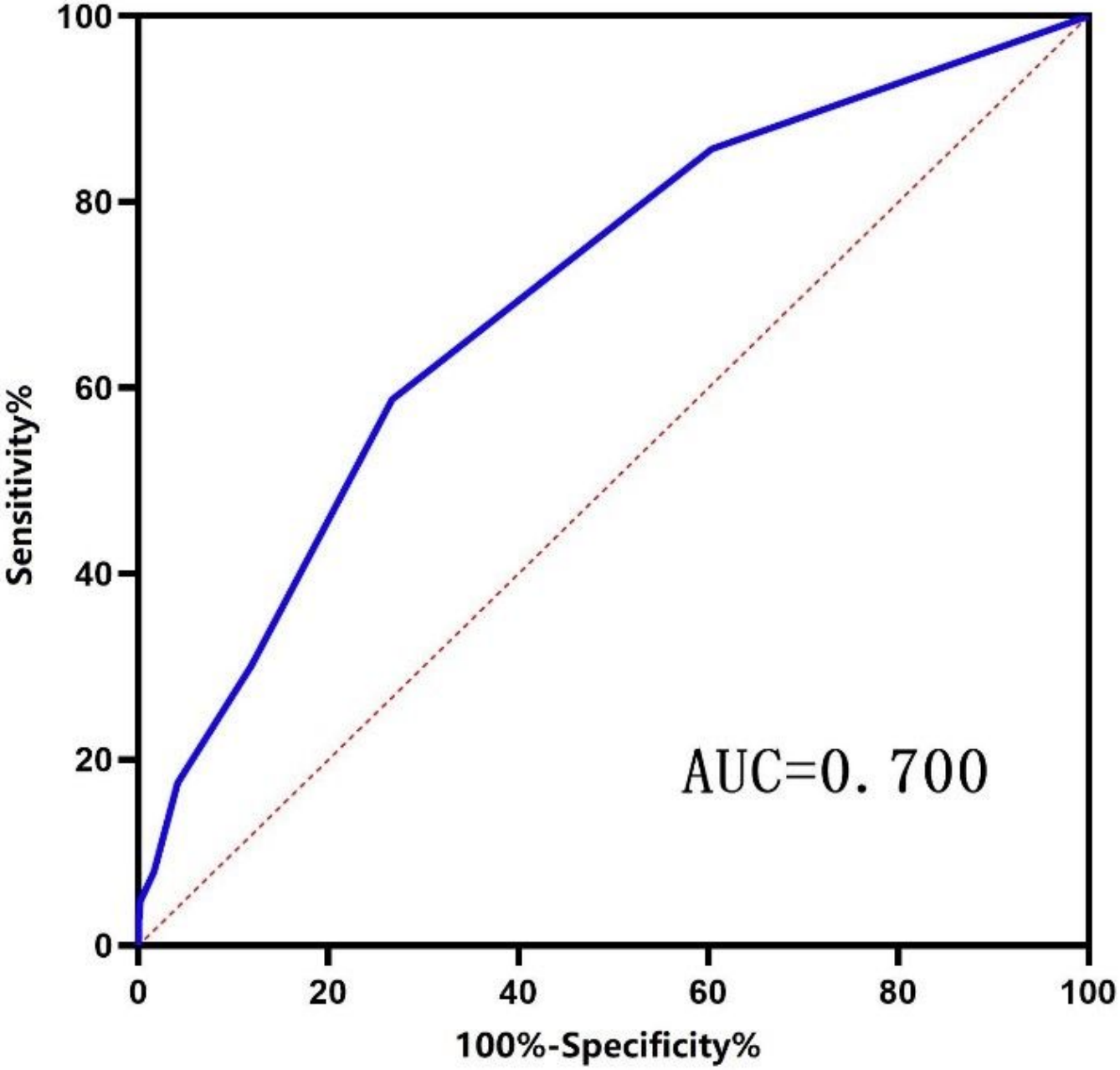

Figure 3

ROC curve of ACCI. AUC=0.70, *P*=0.00; AUC: Area under the curve

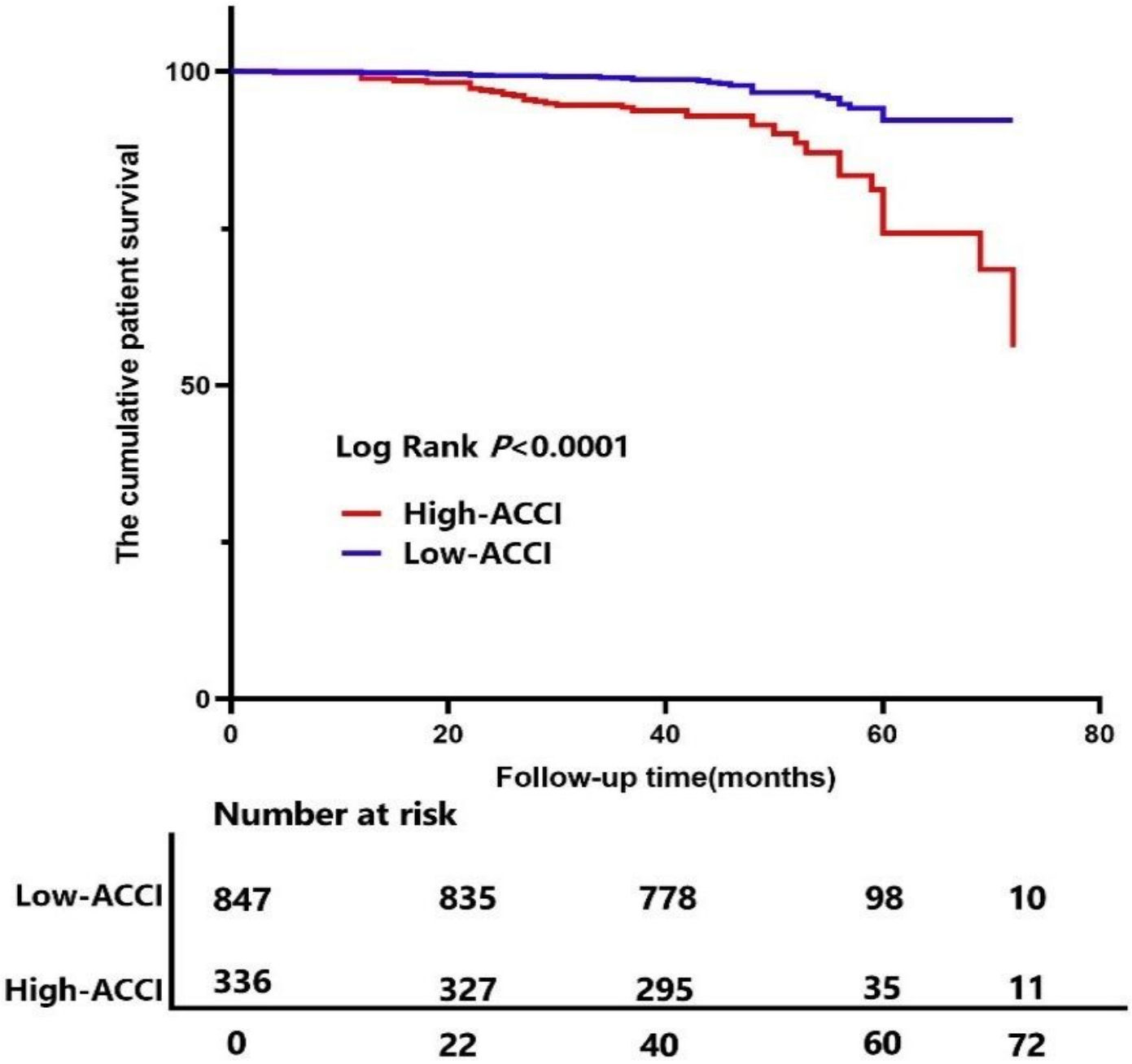

Figure 4

Kaplan–Meier survival curves by high-ACCI and low-ACCI groups in all participants (all-cause mortality). Log-rank test: *P* 0.000 1. ACCI: the age-adjusted charlson comorbidity index.

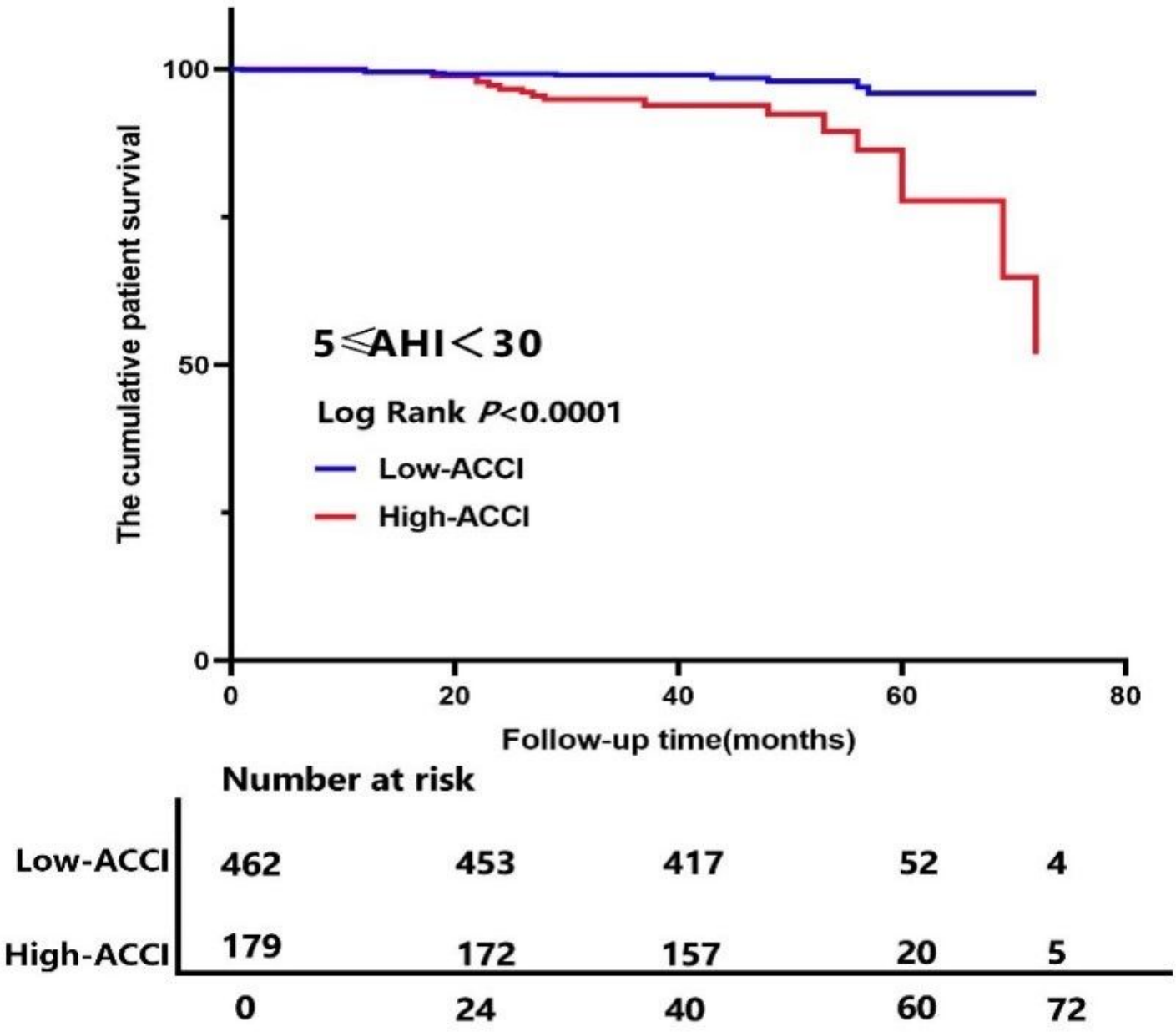

Figure 5

Kaplan–Meier survival curves by high-ACCI and low-ACCI groups in mild-moderate OSA patients (all-cause mortality). Log-rank test: *P*□0.000 1. ACCI: the age-adjusted charlson comorbidity index.

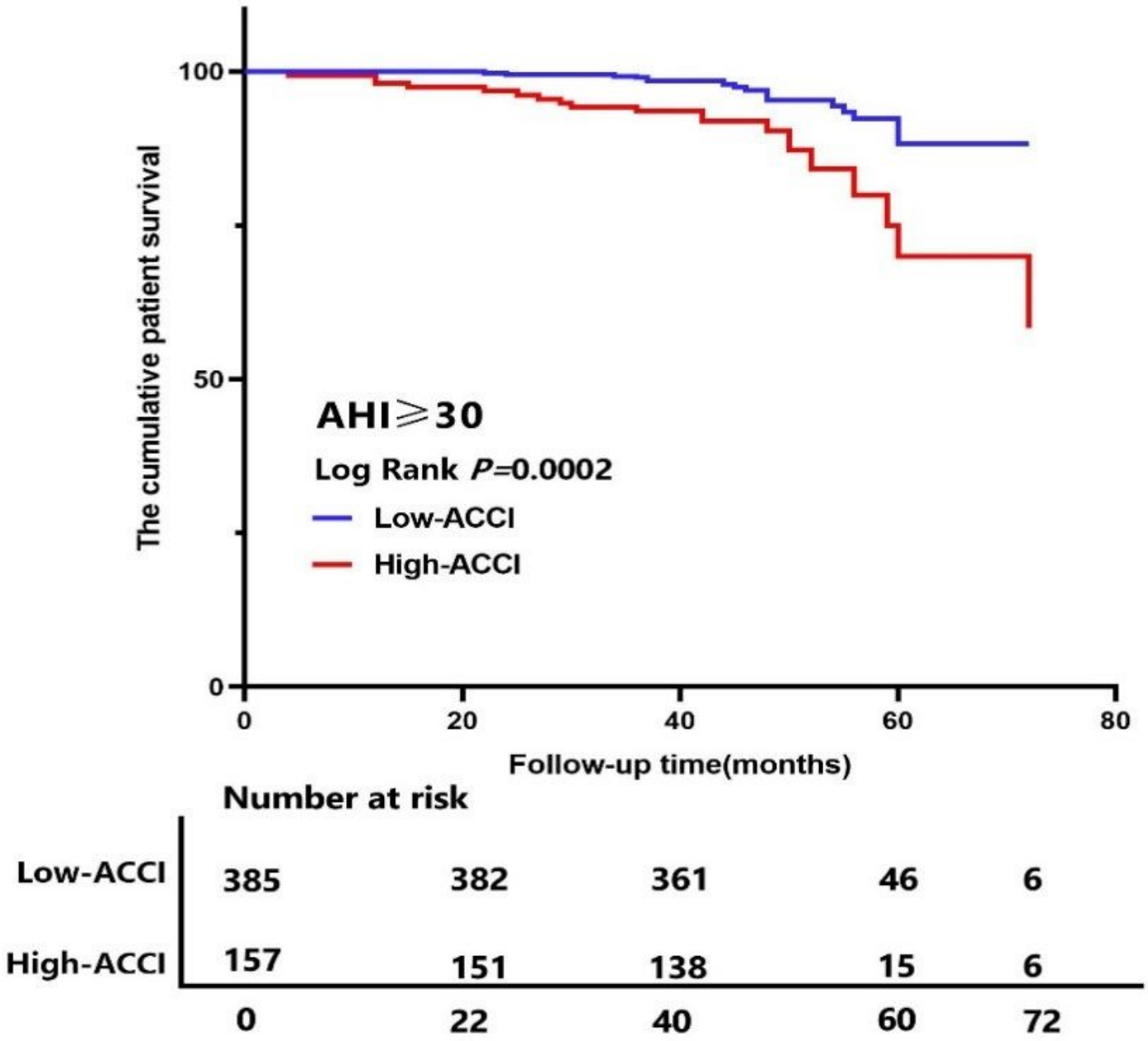

Figure 6

Kaplan–Meier survival curves by high-ACCI and low-ACCI groups in severe OSA patients (all-cause mortality). Log-rank test: *P*=0.000 2. ACCI: the age-adjusted charlson comorbidity index.

Supplementary Files

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- S1.jpg
- S2.jpg