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ORIGINAL ARTICLE

A retrospective analysis of 4000 patients with obstructive sleep apnea in Okinawa, Japan

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Abstract

The causes and risks of death, and role of severity of obstructive sleep apnea (OSA), obesity, and pulmonary function (PF) in OSA patients treated with or without continuous positive airway pressure (CPAP) have been questioned. Using the Okinawa Nakamura Sleep (ONSLEEP) registry, we studied 4000 patients with an obstructive apnea-hypopnea index (AHI) of >5 events/h. Kaplan–Meier analysis determined survival rates based on use of CPAP therapy and OSA severity. Multivariate Cox proportional hazard analysis determined effects of AHI, body mass index (BMI), PF, and use of CPAP. A total of 135 deaths (3.4%) were registered at the end of follow-up period (62.0 ± 43.4 months, mortality rate 8 per 1000 patient-years). Main causes of death were cardiovascular diseases. Multivariate predictors of mortality were male sex, age, BMI, and PF. Although both AHI and use of CPAP tended to affect prognosis, both effects were insignificant. Mortality rate was ~9-fold higher in non-CPAP users with pulmonary impairment (PI) than non-CPAP users with normal lung function. The mortality rate of non-obese (BMI < 25 kg/m^2) OSA patients with PI was ~10-fold higher than that of non-obese patients with normal PF. In patients with OSA, body weight and PI, but not AHI, independently predict mortality. CPAP therapy reduced the risk of death in OSA. The risk of mortality was lowest, as 3 per 1000 patient-year, with normal PF and non-CPAP treatment.

Key words: body weight, cause of death, continuous positive airway pressure, mortality, obstructive sleep apnea (OSA), pulmonary impairment.

INTRODUCTION

Obstructive sleep apnea (OSA) affects 4% of middle-aged men and 2% of middle-aged women,[1] and is associated with high morbidity and mortality, mostly due to cardiovascular diseases (CVD).[2,3] The incidence of OSA correlates with obesity, especially in patients with a body mass index (BMI) of ≥30 kg/m^2.[4,5] However, the relationship between severity of obesity and mortality is not clear at present. Several studies have investigated the paradoxical effects of high BMI on survival in chronic conditions.[6–8]

Since the advent of continuous positive airway pressure (CPAP),[9] several trials have shown a substantial improvement in OSA patients using this therapy.[10–12] However, survey of the causes of death and analysis of the outcome of the historical cohort of OSA patients on long-term CPAP therapy have been unclear, especially in Japan.

The survival rate of OSA patients with chronic obstructive pulmonary disease (COPD), also termed as the overlap syndrome, is significantly lower than in OSA

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patients without COPD.[13] Factors related to nutritional status and obesity independently influence mortality of COPD.[14,15] The present retrospective study was designed to determine the effect of CPAP, severity of OSA, body weight, and pulmonary function (PF) on OSA mortality. For this purpose, we stratified patients according to obesity, PF, and CPAP therapy.

METHODS

Onsleep study population

In December 2000, all staff, medical equipment, and patients transferred to the Nakamura Clinic, with the full support of the Urasoe General Hospital (UGH). The present study included patients who were first seen at UGH and later cared for by the Nakamura Clinic.

The Okinawa Nakamura Sleep (ONSLEEP) registry database was compiled in January 2004 and comprised polysomnography (PSG) findings with information on anthropometric features, blood gases, and PF tests examined since September 1990. The diagnosis of OSA was based on a full standard PSG consisting of electroencephalogram, electrooculogram, submental and tibial electromyograms, oronasal airflow, thoraco-abdominal movement, and arterial oxygen saturation. Each record was scored manually by experienced scorers. Apnea was defined as complete cessation of airflow for >10 s and was classified as obstructive or central based on the presence or absence of respiratory efforts, respectively. Hypopnea was defined as a reduction of ≥50% in oronasal flow for >10 s accompanied by a decrease of >3% in SaO_2. Apnea-hypopnea index (AHI) was calculated as the sum of apneas and hypopneas per hour of sleep. OSA was defined as AHI ≥5/h and obstructive in type when obstructive apneas + mixed apneas + hypopneas constituted ≥50% of total apnea-hypopnea events.

Between 1 September 1990 and 31 December 2003, 4463 patients were diagnosed with sleep apnea. We excluded patients with central sleep apnea (n = 56), non-Japanese (n = 241); and those who failed to answer follow-up phone calls or letters (n = 166). A total of 4000 (89.6%) patients with OSA at the first PSG evaluation were the subjects for this study.

Pulmonary function (PF) tests, forced expiratory volume in one second ($FEV_{1.0}$%; $FEV_{1.0}$/FEV), and percent vital capacity (%VC; VC/predicted VC), were performed just before or after baseline PSG prior to CPAP therapy in 2888 patients. Subjects were considered normal (%VC ≥ 80% and $FEV_{1.0}$% ≥ 70%), or to have obstructive impairment (%VC ≥ 80% and FEV1.0% < 70%), restrictive impairment (%VC < 80% and $FEV_{1.0}$% ≥ 70%), or mixed impairment (%VC < 80% and $FEV_{1.0}$% < 70%).[16] With regard to OSA, patients were stratified into those with mild-moderate OSA (AHI < 30/h) and with severe OSA (AHI ≥ 30/h).[17] Patients were also divided into non-obese (BMI <25 kg/m^2), overweight, (25 ≤ BMI < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). Although obesity has been defined as BMI ≥25 kg/m^2 in Japan,[18] the obesity classification in this study in Okinawa was based on the World Health Organization report *Obesity: Preventing and Managing the Global Epidemic*.[19]

Continuous positive airway pressure (CPAP)

Japanese national insurance provided full coverage of CPAP treatment in April 1998.[20] Prior to such coverage (September 1990 to March 1998), patients with AHI ≥5/h and daytime clinical signs and symptoms of OSA were provided with CPAP on a fee-for-service basis ($US90 per month). Implementation of national insurance for CPAP stipulated an AHI ≥20/h for medical insurance cover ($US44 for ≤age 70 years; $20 for >age 70 years per month). Some qualified and eligible patients refused CPAP for personal reasons, and were assigned as CPAP non-users. Users of CPAP in this study were those who agreed to the treatment and actually borrowed the apparatus.

The CPAP level was adjusted within 3 months following the initiation of therapy and was repeated every 2 years when necessary according to subjective complaints and changes in clinical condition.

Follow-up

Patients were followed up in the UGH and consecutively in this clinic on a monthly basis. The follow-up ended in December 2003. The cause of death and survival rate at this point were surveyed by using a questionnaire completed through check-up visits, hospital records, mail, telephone calls, and death certificates issued by the UGH and other hospitals between April to November 2004.

Patients who used CPAP for ≥1 day for the first time, irrespective of previous treatments, e.g. oral appliances or surgical intervention, were defined as CPAP users. Subjective compliance was used because built-in time counters in CPAP devices were not available until the late 1990s, but the monthly follow-up visits required by

national insurance would enhance compliance. In patients who discontinued CPAP therapy for a period of time and restarted using it, the duration of CPAP therapy was calculated as the total sum of each period of CPAP treatment.

The survival time of patients who were not followed up until the endpoint was censored at the date of the last visit, or the last contact was included in the statistical analysis. The total duration of follow-up was calculated from the time of the PSG study until death or last follow-up and expressed as patient-years.

The study protocol was approved by the Human Ethics Review Committee of UGH and a signed consent form was obtained from each subject.

Statistical analysis

All data were expressed as mean ± SD. Differences in continuous variables between groups were examined for statistical significance using the Student's *t*-test and χ^2-test, and in categorical variables by ANOVA. Survival rates for OSA severity and CPAP therapy were calculated using the Kaplan–Meier method, and compared with the log-rank test. Cox proportional hazard analysis was used to identify independent predictors of death. In multivariate analysis, BMI, AHI, and age were treated as either categorical or continuous variables. Results were expressed as hazard ratio (HR) with 95% confidence intervals (CI). A *P*-value of less than 0.05 denoted the presence of a statistically significant difference. The above statistical analyses were conducted using SAS software version 8.2 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

A total of 4000 OSA patients consisted of 80.3% males and 19.7% females, with a mean age of 51.2 ± 13.2 years, AHI 39.8 ± 32.8 events/hr, and BMI 27.9 ± 4.7 kg/m^2 (Table 1). Analysis of PF tests of 2888 (72.2%) patients showed normal results in 2347 (81.3%), an obstructive pattern in 131 (4.5%), a restrictive pattern in 314 (10.9%), and mixed PI in 96 (3.3%) patients.

Of 4000 patients, 2263 (56.6%) were treated with CPAP. The number of CPAP users was 725 (32%) during the period of no insurance coverage (prior to April 1998), and 1538 (68%) with insurance coverage (after April 1998). With regard to the use of CPAP, 460 (43.9%) of 1046 non-obese OSA patients, 1065 (57.9%) of 1840 overweight, and 732 (67.1%) of 1091 obese patients used CPAP. Furthermore, 643 (31.8%) of 2017 patients with AHI <30/h, and 1621 (81.8%) of 1982 patients with AHI ≥30/h used CPAP.

During the follow-up period, 135 deaths were confirmed (Table 1). Among them, analysis of PF tests of 92 (8.1%) patients showed normal results in 40 (43.5%), an obstructive pattern in eight (8.7%), a restrictive pattern in 24 (26.1%), and mixed PI in 20 (21.7%) patients at baseline. CVDs (myocardial infarction, sudden death, and stroke) caused 45 (33.3%) of 135 total deaths. COPD and lung cancer were the major death-related pulmonary disease and malignancy, respectively. The mean age at death was 63.3 years for males and 71.3 years for females. The total duration of follow-up was 62.0 ± 43.4 months (range, 0.6 to 160.3 months), with a total of 16 917 patient-years. The mortality rate was 8 per 1000 patient-years.

Kaplan–Meier survival rate

Kaplan–Meier survival analysis based on the use of CPAP therapy showed a better survival rate for CPAP users (n = 2263) compared with CPAP non-users (n = 1737) (log-rank test, $P < 0.003$, Fig. 1). For patients with severe OSA (AHI ≥ 30/h), the same analysis showed that the use of CPAP (n = 1621) significantly improved survival rate, relative to non-users of CPAP (n = 362). Interestingly, the survival rate of CPAP-treated patients with severe OSA was similar to that of CPAP-untreated patients with mild-to-moderate OSA (n = 1375) and CPAP-treated patients with mild-to-moderate OSA (n = 642) (log-rank test, $P < 0.001$, Fig. 2).

Univariate and multivariate analyses

Table 2 shows that the univariate variables correlated with total deaths in this cohort were age, BMI, AHI, and PI. The variables that showed statistical significance were being male (HR, 2.009; 95% CI, 1.096–3.684; $P = 0.0241$), age in both continuous (HR, 1.083; 95% CI, 1.061–1.106; $P < 0.0001$) and every categorical variables, BMI in continuous variables (HR, 0.926; 95% CI, 0.873–0.979; $P = 0.0068$), and only in the BMI ≥ 30/h group (HR, 0.485; 95% CI, 0.241–0.947; $P = 0.034$) in categorical variables, AHI in continuous variables (HR, 1.014; 95% CI, 1.007–1.021; $P = 0.001$), and PI in categorical variables (HR, 3.109; 95% CI, 1.956–4.941; $P = 0.0001$).

Although AHI ≥30/h correlated negatively with survival in categorical variables (HR, 1.666; 95% CI,

Table 1 Demographics of subjects and causes of death in patients with obstructive sleep apnea diagnosed at Nakamura Sleep Respiratory Clinic, Okinawa, Japan

	Total	Male	Female
Number of patients	4000	3210	790
Age, years†	51.2 (13.3), 20 to 88	49.9 (13.2)	56.7 (12.2)
BMI, kg/m^{2}†	27.9 (4.7), 14.2 to 55.8	27.9 (4.4)	27.8 (5.8)
AHI, events/h†	39.8 (32.8), 5 to 312.9	42.9 (33.2)	27.2 (27.8)
Number of deaths	135	112	23
Causes of death			
Myocardial infarction	22 (16.3%)	19	3
Pulmonary diseases	20 (14.8%)	13	7
COPD	15	10	5
Old tuberculosis	2	2	0
Pulmonary fibrosis	2	0	2
Others	1	1	0
Malignancy	19 (14.1%)	17	2
Lung cancer	7	6	1
Liver (hepatoma)	5	4	1
Leukemia	2	2	0
Others	5	5	0
Infection	15 (11.1%)	11	4
Sudden death	12 (8.9%)	11	1
Stroke	11 (8.1%)	8	3
Traffic accident	1 (0.7%)	1	0
Others	5 (3.7%)	5	0
Unknown	30 (22.2%)	27	3
Time between PSG and death, days†	1753 (1214), 18 to 4487		

†Data are mean (SD). Polysomnography (PSG) was performed between September 1990 and December 2003. AHI, apnea-hypopnea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

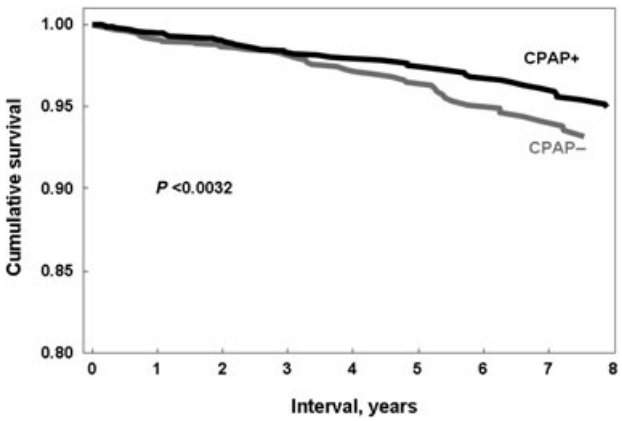

Figure 1 Kaplan–Meier survival rates according to use of continuous positive airway pressure (CPAP) therapy (n = 4000 patients).

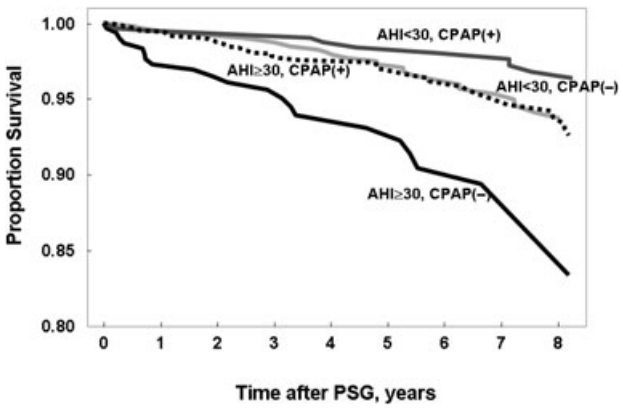

Figure 2 Survival rates according to continuous positive airway pressure (CPAP) use and severity of obstructive sleep apnea (OSA) (represented by the apnea-hypopnea index [AHI]). PSG, polysomnography.

0.997–2.793; NS), and CPAP use tended to improve survival in categorical variables (HR, 0.617; 95% CI, 0.377–1.011; NS), neither of correlations were statistically significant. AHI in CPAP-treated patients (52.5 [33.1]/h) was significantly higher than that of CPAP-untreated patients (23.2 [23.8]/h) ($P < 0.0001$). Also, BMI in CPAP-treated patients (28.6 [4.7] kg/m^2) was significantly higher than that of CPAP-untreated patients (27.1 [4.6] kg/m^2) ($P < 00001$).

Multivariate analysis on interaction among categories

Table 3 demonstrates that using severity of BMI as a categorical variable, the HRs were significantly higher for both non-obese (HR, 6.785; 95% CI, 3.085–14.929; $P < 0.0001$) and overweight (HR, 2.883; 95% CI, 1.278–6.503; $P < 0.0107$) with impaired PF, compared with BMI <25 kg/m^2 with normal PF. The mortality rate of non-obese patients with PI was ~10-fold that of OSA patients with normal PF (Fig. 3). Thus, the mortality rate (deaths/1000 patients-year) of patients with PI tended to decrease with increase in BMI. For interaction between obesity and severity of OSA, BMI of ≥30 kg/m^2 and mortality hazard rate for patients with AHI of 5–29/h was statistically lower than that of the reference group (HR, 0.209; 95% CI, 0.047–0.921; $P = 0.0386$). Effect of BMI on survival was significant only in the CPAP non-treatment group (adjusted HR, 0.911; 95% CI, 0.840–0.988; $P < 0.0001$) (Table 4). Regardless of the CPAP treatment, the higher the AHI, the greater the risk of death.

With regard to comparison of the HRs between obesity and CPAP therapy to a reference group (non-obese patients who did not use CPAP), the mortality rate was significantly lower in every category of obesity. The

Table 2 Results of Cox proportional hazard analysis on the risk of death in patients with obstructive sleep apnea

	Univariate			Multivariate		
	HR	95% CI	*P*-values	HR	95% CI	*P*-values
Sex						
Women (*n* = 790)	1.000, reference			1.000, reference		
Men (*n* = 3210)	1.206	0.764–1.901	NS	2.009	1.096–3.684	0.0241
Age, years						
Continuous (*n* = 4000)	1.089	1.073–1.106	<0.0001	1.083	1.061–1.106	<0.0001
20– (*n* = 828)	1.000, reference			1.000, reference		
40– (*n* = 980)	3.697	1.050–13.02	0.0416	12.97	1.658–101.4	0.0146
50– (*n* = 1063)	6.352	1.906–21.19	0.0026	14.91	1.908–116.5	0.0100
60– (*n* = 775)	17.35	5.37–56.04	<0.0001	33.98	4.480–257.8	0.0006
70– (*n* = 354)	44.18	13.67–142.1	<0.0001	82.54	10.71–636.3	<0.0001
BMI, kg/m^2						
Continuous (*n* = 3977)	0.903	0.864–0.944	<0.0001	0.924	0.873–0.979	0.0068
<25 (*n* = 1046)	1.000, reference			1.000, reference		
25–29 (*n* = 1840)	0.447	0.302–0.661	<0.0001	0.608	0.367–1.005	NS
≥30 (*n* = 1091)	0.416	0.260–0.666	0.0003	0.485	0.241–0.947	0.0344
AHI, per hour						
Continuous (*n* = 4000)	1.009	1.004–1.014	0.0001	1.014	1.007–1.021	0.0001
<30 (*n* = 2017)	1.000, reference			1.000, reference		
≥30 (*n* = 1983)	1.133	0.804–1.598	NS	1.669	0.997–2.795	NS
CPAP treatment						
No (*n* = 1737)	1.000, reference			1.000, reference		
Yes (*n* = 2263)	0.772	0.548–1.089	NS	0.617	0.377–1.011	NS
Pulmonary function						
Normal (*n* = 2347)	1.000, reference			1.000, reference		
Impaired (*n* = 541)	6.133	4.015–9.368	<0.0001	3.109	1.956–4.941	<0.0001

CPAP was available for general use from April 1998. Pulmonary function was evaluated after polysomnography in 2888 patients (72.2%). Normal pulmonary function was defined as %VC ≥80% and FEV1.0% ≥70%. Multivariate analysis was performed after adjusting for other confounding variables listed in this table. AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; CPAP, patients prescribed continuous positive airway pressure; HR, hazard ratio; NS, not significant.

Table 3 Results of Cox proportional hazard analysis on the risk of death in patients with obstructive sleep apnea

		Multivariate analysis		
		HR	95% CI	*P*-values
BMI, kg/m^2	PF			
<25	Normal	1.000, reference		
25–29	Normal	1.021	0.460–2.266	NS
≥30	Normal	1.317	0.528–3.287	NS
<25	Impaired	6.785	3.085–14.92	<0.0001
25–29	Impaired	2.883	1.278–6.503	0.0107
≥30	Impaired	1.094	0.345–3.466	NS
BMI, kg/m^2	AHI, per hour			
<25	5–29	1.000, reference		
25–29	5–29	0.541	0.270–1.085	NS
≥30	5–29	0.209	0.047–0.921	0.0386
<25	≥30	1.148	0.527–2.503	NS
25–29	≥30	0.945	0.469–1.904	NS
≥30	≥30	1.193	0.547–2.600	NS
BMI, kg/m^2	CPAP therapy			
<25	No	1.000, reference		
25–29	No	0.487	0.238–0.999	0.0497
≥30	No	0.144	0.032–0.648	0.0115
<25	Yes	0.389	0.183–0.827	0.0141
25–29	Yes	0.319	0.162–0.627	0.0009
≥30	Yes	0.327	0.141–0.761	0.0095
AHI, per hour	PF			
5–29	Normal	1.000, reference		
≥30	Normal	2.850	1.357–5.985	0.0056
5–29	Impaired	5.606	2.724–11.539	<0.0001
≥30	Impaired	6.770	3.108–14.746	<0.0001
AHI, per hour	CPAP therapy			
5–29	No	1.000, reference		
≥30	No	2.575	1.288–5.357	0.0114
5–29	Yes	0.935	0.471–1.855	NS
≥30	Yes	1.238	0.715–2.144	NS
CPAP treatment	PF			
No	Normal	1.000, reference		
Yes	Normal	0.999	0.477–2.089	NS
No	Impaired	5.588	2.630–11.87	<0.0001
Yes	Impaired	2.168	0.967–4.862	NS

Pulmonary function was evaluated after polysomnography in 2888 patients (72.2%). Normal pulmonary function was defined as %VC ≥80% and FEV1.0% ≥70%. Multivariate analysis was performed after adjusting for other confounding variables listed in this table. AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; CPAP, patients prescribed continuous positive airway pressure; HR, hazard ratio; NS, not significant; PF, pulmonary function.

highest mortality rate was noted in the reference group; the lowest mortality rate was in obese patients who did not use CPAP (HR, 0.144; 95% CI, 0.032–0.648; $P = 0.0115$).

Comparing the HRs between OSA severity and PI to a reference group (non-obese patients with normal PF), the mortality rates increased in every category of obesity, and the highest rate (HR, 6.770; 95% CI, 3.108–14.746; $P < 0.0001$) was noted in patients with severe OSA and impaired PF. We further analyzed the effect of PI with two categories such as obstructive and restrictive impairment (Table 4). In the CPAP-treated group, restrictive pulmonary impairment remained as an independent predictor of death.

For interaction between severity of OSA and CPAP therapy, the HR was highest for patients with severe

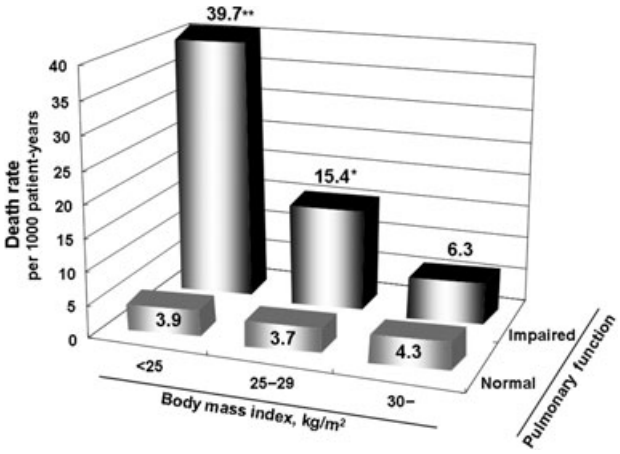

Figure 3 Mortality rate according to body mass index and presence or absence of pulmonary impairment.

OSA who did not use CPAP therapy compared with the reference group (patients with mild-to-moderately severe OSA who did not use CPAP) (HR, 2.573; 95% CI, 1.288–5.357; $P < 0.0114$). No significant differences were observed in other categorical groups between AHI and CPAP therapy.

Excess mortality rate was identified in only those patients who did not use CPAP who had impaired PF (HR, 5.558; 95% CI, 2.630–11.87; $P < 0.0001$). The mortality rate in patients with PI who did not use CPAP was ~9-fold that of patients who had normal PF and did not use CPAP (Fig. 4).

DISCUSSION

We confirmed that the main cause of death in patients with OSA was CVD irrespective of CPAP treatment or not.[21,22] The other most common causes of death were pulmonary disease, mainly COPD. The main reasons for high death rate due to pulmonary disease in our OSA patients could be the high mortality rates associated with COPD in Okinawa in the general population,[23] or institutional bias since this clinic provides care for patients with pulmonary and sleep disorders.

Our results support the notion that CPAP is an effective treatment modality for OSA. Although Kaplan–Meier analysis showed that CPAP treatment was effective in reducing mortality (Fig. 1), multivariate analysis showed a weak improvement. This suggests the role of other confounding factors and/or the strict definition of CPAP users may have undervalued the effectiveness of therapy. For example, in patients with severe heart failure, CPAP did not affect survival[24] In our cohort, patients with heart failure were not excluded.

Our findings, as in another study,[25] showed that mortality rates increased linearly with age from 20 to 70 years. On the other hand, other studies have shown an excess mortality rate only for males aged <50 years.[26,27] The discrepancy in regards to the trend of age between Lavie[26] and our study is probably due to differences in ages of the two groups at diagnosis (48 ± 12.3 *vs* 63.3 ± 11.7 years, for males).

Moreover, severity of OSA was a contributing factor to mortality, but was not a risk factor for mortality in adequately treated OSA patients (Fig. 2). Some found that increased severity of OSA was associated with a moderate increase in all-cause mortality hazards,[26] whereas others did not find any association after adjustment for confounders, such as medical condition at diagnosis.[27]

Our study showed that OSA patients with high BMI (obese) were at reduced risk for death compared with those with a BMI <25 kg/m^2 (Fig. 3), and the mortality rates of untreated and/or patients with PI were higher than that of CPAP-treated patients without PI (Fig. 4). Moreover, body weight, PI, and CPAP therapy correlated independently with all-cause mortality of OSA. Possible explanations for the paradoxical effect of obesity on survival are, first, inclusion of a large number of patients with pulmonary disorders as a comorbid condition. A total of 19% of patients who underwent PF testing had lung disorders, especially COPD. Veale[28] and Chaouat[29] reported that PF (FEV_1 percent predicted) and lung disease were independent significant predictors of death in patients with OSA. A combination of lung disease and OSA increases the risk of death compared with each condition alone.[20] Among patients with COPD on long-term oxygen therapy, body weight (BMI <25 kg/m^2) and associated comorbid conditions (e.g. congestive heart failure, diabetes) are highly relevant factors in both all-cause and respiratory mortalities.[30] Second, fewer non-obese OSA patients received CPAP therapy (43.9% of non-obese, compared with 57.9% of overweight and 67.1% of obese patients). CPAP therapy might have been recommended more selectively for obese patients because the severity of OSA seemed to be closely associated with obesity.

Our study has several limitations. First, this is a retrospective cohort study and not a random population sample. Second, preexisting chronic illness and smoking are possible potential biases, because both conditions tend to reduce BMI and increase risk of death.[3,31,32] Usually, cardiovascular morbidity and

Table 4 Results of multivariate Cox proportional hazard analysis on the risk of death in patients with obstructive sleep apnea performed after adjusting for other confounding variables listed in this table

	CPAP treatment – yes			CPAP treatment – no		
	HR	95% CI	*P*-values	HR	95% CI	*P*-values
Sex	1.752	0.735–4.177	NS	1.556	0.692–3.497	NS
Age, years	1.088	1.060–1.117	<0.0001	1.075	1.041–1.109	<0.0001
BMI, kg/m^2	1.004	0.935–1.078	NS	0.911	0.840–0.988	<0.0001
AHI, per hour	1.017	1.008–1.026	0.0001	1.032	1.020–1.043	<0.0001
Obstructive pulmonary dysfunction	1.718	0.926–3.189	NS	4.023	1.937–8.353	0.0002
Restrictive pulmonary dysfunction	4.435	1.047–18.783	0.0431	2.912	1.278–6.632	0.0109

Pulmonary dysfunction was divided into obstructive or restrictive dysfunction. CPAP was available for general use from April 1998. Pulmonary function was evaluated after polysomnography in 2888 patients (72.2%). Normal pulmonary function was defined as %VC ≥80% and FEV1.0% ≥70%. Multivariate analysis was performed after adjusting for other confounding variables listed in this table. AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; CPAP, patients prescribed continuous positive airway pressure; HR, hazard ratio; NS, not significant.

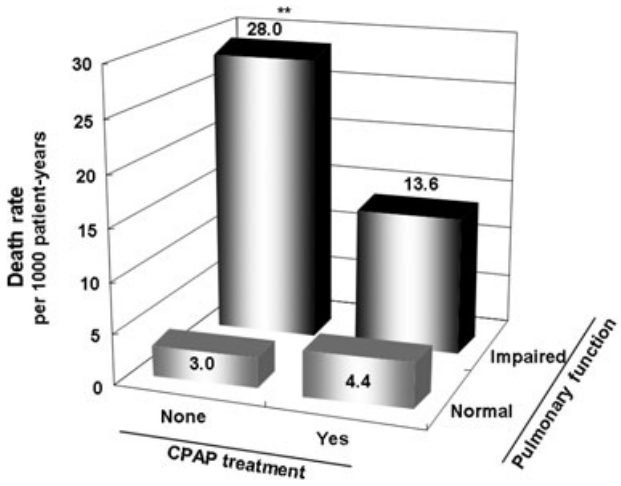

Figure 4 Mortality rate according to continuous positive airway pressure (CPAP) use and presence or absence of pulmonary impairment.

mortality are high in obese people,[33] but we did not analyze the effects of OSA on blood pressure, diabetes, smoking, and other cardiovascular risk factors.[34] Third, although compliance is important in the prognosis of OSA,[35] objective data relevant not only to the duration but also to frequency of use of CPAP could determine the effectiveness of such therapy. We defined users of CPAP according to self-reported compliance records and only the duration.[36] Fourth, as the criteria for the selection of patients for CPAP therapy was changed before and after insurance coverage, the rates of CPAP users increased (32% *vs* 68%). Fifth, we did not take into consideration the influence of other additional treatments of OSA (i.e. surgical intervention and oral appliances).

In conclusion, we demonstrated the long-term prognosis of patients with OSA. Body weight and PI were independent predictors of mortality in patients with OSA. The prognosis was poor in patients with low BMI. Our results also emphasized the paradoxical effect of obesity and OSA associated with PI. However, the mechanism underlying the paradox is not clear, and further studies are needed to understand the effects of obesity. We confirmed the effectiveness of CPAP on survival; however, further analysis is required to carefully examine other confounding variables related to the selection of CPAP therapy. In this regard, a prospective cohort study is needed. Non-obese OSA patients with PI may need to be followed carefully. Until April 2004, our clinic was the only institution that provided full PSG in Okinawa. We believe that our database is one of the largest registries of sleep breathing disorders in Japan, with the longest duration in assessing and observing OSA patients. Thus, our study reflects the actual daily medical practice concerning the effectiveness of OSA treatment.

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