SLEEP AND NEUROLOGICAL DISORDERS

Mortality and Its Risk Factors in Patients with Rapid Eye Movement Sleep Behavior Disorder

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Study Objectives: To determine the mortality and its risk factors in patients with rapid eye movement (REM) sleep behavior disorder (RBD).
Methods: A total of 205 consecutive patients with video-polysomnography confirmed RBD (mean age = 66.4 ± 10.0 y, 78.5% males) were recruited. Medical records and death status were systematically reviewed in the computerized records of the health care system. Standardized mortality ratio (SMR) was used to calculate the risk ratio of mortality in RBD with reference to the general population.
Results: Forty-three patients (21.0%) died over a mean follow-up period of 7.1 ± 4.5 y. The SMR was not increased in the overall sample, SMR (95% confidence interval [CI]) = 1.00 (0.73–1.33). However, SMR (95% CI) increased to 1.80 (1.21–2.58) and 1.75 (1.11–2.63) for RBD patients in whom neurodegenerative diseases and dementia, respectively, eventually developed. In the Cox regression model, mortality risk was significantly associated with age (hazard ratio [HR] = 1.05; 95% CI, 1.01–1.10), living alone (HR = 2.04; 95% CI, 1.39–2.99), chronic obstructive pulmonary disease (HR = 3.38; 95% CI, 1.21–9.46), cancer (HR = 10.09; 95% CI, 2.65–38.42), periodic limb movements during sleep (HR = 3.06; 95% CI, 1.50–6.24), and development of neurodegenerative diseases (HR = 2.84; 95% CI, 1.47–5.45) and dementia (HR = 2.66; 95% CI, 1.39–5.08).
Conclusions: Patients with RBD have a higher mortality rate than the general population only if neurodegenerative diseases develop. Several risk factors on clinical and sleep aspects are associated with mortality in RBD patients. Our findings underscore the necessity of timely neuroprotective interventions in the early phase of RBD before the development of neurodegenerative diseases.
Keywords: mortality, neurodegenerative disease, REM sleep behavior disorder, SMR
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Significance
This is the first study to determine the mortality risk and its correlated factors in patients with RBD. The current study clearly demonstrated that RBD per se will not increase mortality risk, but the mortality risk will only increase upon the conversion of RBD into neurodegenerative diseases. In addition, several novel correlates, such as PLMS, were associated with the mortality risk. The findings of the study could help further understanding of the disease burden and pathological process of RBD. Furthermore, it underscores the timely need of neuroprotective intervention at the stage of idiopathic RBD.

INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by dream-enacting behaviors associated with a loss of the normal muscle atonia during REM sleep.[1] A number of prospective studies have consistently suggested that idiopathic RBD is a prodromal marker for neurodegenerative diseases, especially for α-synucleinopathy related diseases, such as Parkinson disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA).[2,3] According to a recent study with a mean follow-up period of 14 y, the risk of developing neurodegenerative disease is over 80% in patients with RBD.[2]

Mortality is one of the most robust and definitive endpoints in the assessment of outcome of a disease condition, which is considered as a gold standard of clinical performance.[4] In past decades, some studies have investigated whether neurodegenerative diseases would lead to increased mortality. For example, a recent meta-analysis has demonstrated a 2.2-fold increased risk of mortality in PD.[5] In addition, previous studies found that the increased risk of mortality in patients with neurodegenerative diseases is contributed by several risk factors, including age, male sex, disease severity, and dementia.[6] Although neurodegenerative diseases will eventually develop in the majority of patients with RBD,[2] it remains unclear (1) whether RBD *per se* leads to the increased mortality, especially in view of its associated frequent and severe sleep-related injuries; (2) whether neurodegenerative diseases plays a role in the mortality risk in RBD; and (3) whether there is any risk factor predicting mortality in RBD.

Therefore, we conducted an observational cohort study with a considerable sample size in patients with RBD to: (1) determine the mortality risk of RBD patients by comparing to that of the general population with the use of standardized mortality ratio (SMR); (2) investigate the potential risk predictors of mortality in RBD; and (3) examine the potential role of neurodegenerative diseases in the mortality risk of RBD.

METHODS

Participants

A consecutive series of patients in whom RBD was diagnosed during the period from July 1996 to October 2014 were recruited into this study. The diagnostic criteria of RBD as based on the International Classification of Sleep Disorders, Second Edition,[1] included: (1) clinical RBD symptoms that are potentially harmful to self or sleep partner or result in sleep-related injuries, or abnormal behaviors during REM sleep as documented during polysomnographic (PSG) monitoring; (2) PSG

features of a loss of REM-related muscle atonia; (3) an absence of electroencephalographic epileptic form activity during REM sleep; (4) the features are not better explained by other disorders. In particular, RBD mimicking symptoms produced by obstructive sleep apnea (OSA) episodes were carefully excluded. As there has been increasing recognition of early-onset RBD variants related to narcolepsy, psychiatric disorders, or medications,[7,8] and their relationship with neurodegenerative diseases remains unclear, patients with these early-onset RBD variants were excluded from the current study. Thus, only those patients with typical RBD were recruited into this study.

The medical records of all the recruited patients from the date of RBD diagnosis to the censoring date (January 28, 2015) were systematically reviewed in the computerized Clinical Management System (CMS) of the public health care sectors in Hong Kong. The CMS is an open-source clinical management system, in which the Electronic Patient Record provides an integrated, longitudinal, lifelong view of a patient's clinical history.[9] This system is operated within the public hospitals under the Hospital Authority of Hong Kong, which covers over 95% of the healthcare provision in Hong Kong. Ethical approval was obtained from the Joint Chinese University of Hong Kong-New Territories East Cluster clinical research ethics committee.

Demography and Clinical Records

Demographic characteristics, including age of onset, age of diagnosis, sex, years of education, living and sleeping environment, were collected at baseline. Comorbid medical conditions, including diabetes mellitus, chronic obstructive pulmonary disease (COPD), cardiovascular diseases (including hypertension and heart diseases), cerebrovascular diseases, cancers, neurodegenerative diseases, dementia, and psychiatric disorders were reviewed in the CMS. Neurodegenerative diseases included PD, MSA, DLB, and Alzheimer disease (AD). Dementia included different types, such as Parkinson disease dementia (PDD), DLB, AD, and vascular dementia (VD).

During the follow-up period, diagnoses of the parkinsonian and dementia syndromes were ascertained by the specialists (e.g., neurologists, psychiatrists, geriatricians) with reference to the standard diagnostic criteria of PD,[10] MSA,[11] DLB,[12] AD,[13] VD,[14] and PDD.[15] In addition, information on the new diagnoses of medical comorbidity during follow-up was collected from the CMS until the censoring date.

Questionnaires

A set of lifestyle factors was assessed by a structured questionnaire at baseline. Smoking status, coffee consumption, and alcohol intake were assessed by the questionnaire, with the response options including "never," "former," and "current." Insomnia was defined according to the presence of self-reported insomnia symptoms at least three times per week. Depressive symptoms and excessive daytime sleepiness were measured by the Chinese version of Beck Depression Inventory[16] and Epworth Sleepiness Scale,[17] respectively.

Polysomnography

All patients underwent at least one overnight video-polysomnography (v-PSG) assessment to ascertain RBD diagnosis. The v-PSG recording included standard electroencephalogram (EEG) (C4-A1, O2-A1, C3-A2, with added F4-M1 since 2007), electrooculogram (EOG) (LE-A2, RE-A1), and electrocardiogram (ECG). Electromyogram (EMG) included submental and bilateral anterior tibialis EMG. Other measurements included nasal-oral flow, thoracic and abdominal respiratory efforts, oxygen saturation, and body position. Sleep stages and associated events were manually scored in 30-sec epochs according to Rechtschaffen and Kales criteria with the modifications to allow for the persistence of EMG tone during epochs that are otherwise clearly REM sleep.[18] OSA was defined as apnea-hypopnea index greater than 15 events per hour. All the patients with OSA were treated with continuous positive airway pressure on the second night and possible mimic RBD were excluded. Periodic limb movements during sleep (PLMS) was defined as periodic limb movement index (PLMI) > 15 events per hour. Video was recorded simultaneously with the PSG to document any REM sleep-related motor activity.

Confirmation of Mortality

Date and cause of death were obtained from the Electronic Patient Record of the CMS of the public health care system. Over 90% of medical services in Hong Kong are currently provided by public health care services and most of our RBD patients (96.5%) were followed up at the public health care system. In Hong Kong, all the individuals who died in a public hospital were recorded in the CMS. Death outside of a hospital is usually uncommon and will usually certified by the public hospital (e.g., at the accident and emergency department). The information recorded in the system included the time and cause of death. The main cause of death was coded according to the International Classification of Diseases, Tenth Revision (ICD-10). The SMRs of the RBD patients, as compared to that of the general population in Hong Kong, were determined by calculating the ratio of observed deaths to expected deaths within the same period of time.[19] The SMR and its asymptotic 95% confidence interval (CI) were calculated as follows:

$$\mathrm{SMR} = \frac{O}{E}$$

whereas:

$$95\%\ \mathrm{CI} = \left(\mathrm{SMR} - 1.96 \times \frac{\sqrt{O}}{E},\ \mathrm{SMR} + 1.96 \times \frac{\sqrt{O}}{E}\right)$$

where O is the observed number of deaths in the study population and E is the expected number of deaths. The age- and sex-specific mortality rates in the general population were obtained from the Census and Statistics Department of the Hong Kong Government which utilized the population census data over the period from 1981 to 2013.[20] SMR was calculated for the overall sample and several subsets of patients, including male, female, and patients with idiopathic RBD, neurodegenerative diseases, dementia, and PLMS until the censoring date, respectively.

Statistical Analysis

Differences in the clinical characteristics and PSG variables between survived and deceased patients were compared using

chi-square test, Fisher exact test, *t*-tests, or Mann-Whitney *U* test, where appropriate. The potential predictors of mortality were evaluated by means of Cox proportional hazards regression model after adjusting for baseline age and sex. The time variable was set as years from the date of confirmed diagnosis of RBD to the censoring date (January 28, 2015) for survived patients or to the date of death for deceased patients. As age and sex are two major demographic factors influencing longevity, they were forced into the model by the "Enter" method in the first step. In the second step, variables with a trend of differences ($P < 0.1$) in the crude analyses between survived and deceased groups were selected and included in the Cox proportional hazards regression model by using forward stepwise procedure. By this criterion, variables including education, baseline lifestyle factors (living alone, sleeping alone, coffee drinking, and smoking), and baseline medical comorbidities (neurodegenerative diseases, dementia, COPD, cancers, and PLMS) were selected as covariates in the Cox regression model. Predictors of mortality risk were explored among baseline factors, and the time-dependent neurodegenerative diseases and dementia models (neurodegenerative diseases and dementia as time-dependent covariate, by incorporating new-onset neurodegenerative diseases and dementia during follow-up).

Kaplan-Meier survival curves were also performed for those comorbid conditions showing significant associations with mortality in the Cox regression model, which included baseline COPD, cancer, and PLMS, as well as time-dependent neurodegenerative diseases. As only a few cases had a follow-up period over 13 y (less than 10%), we used 13 y as a cutoff period for estimating the Kaplan-Meier curves. As neurodegenerative diseases are considered as a disease progression of RBD, this variable was treated as time-dependent one. The time for patients in whom neurodegenerative diseases developed was set from the date of confirmed diagnosis of neurodegenerative diseases to the censoring date or to the date of death. The IBM SPSS Statistics 20.0 for Windows (SPSS Inc, Chicago, IL) was used for all tests. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

A total of 205 RBD patients (78.5% males, mean age = 66.4 ± 10.0 y) were recruited into this study. At baseline, 182 were idiopathic RBD and 23 were symptomatic RBD with comorbid neurodegenerative diseases (15 PD, 2 MSA, 1 DLB, and 5 probable AD). Of 205 recruited patients, 198 (96.5%) were followed up at sleep clinic or other clinical departments of the public health care system within 1 y from the last visit to the censoring date. Only seven patients were lost to follow-up in any public health sector but they have not been confirmed dead as according to their status in the CMS. Forty-three patients (21.0%) died over a mean follow-up period of 7.1 y (standard deviation = 4.5 y, range 0.3–18.8 y). Comparisons of the clinical and demographic data between survived and deceased patients are shown in Table 1. The deceased RBD were older, less educated, more likely to sleep alone, and had a higher rate of dementia when compared with survived patients at baseline ($P < 0.05$). In addition, there was a marginal significance in that deceased patients were more likely to have been a smoker, lived alone, and had a diagnosis of neurodegenerative disease, and were less likely to have been a coffee drinker ($P < 0.10$). There were no differences in age at onset, sex, follow-up duration, and duration of RBD between groups ($P > 0.10$). Similarly, there were no differences in the occurrence of major chronic physical diseases between the patients who survived and died, except for a higher prevalence of baseline COPD and cancer in the deceased patients.

During the follow-up, neurodegenerative diseases developed in 50 patients (27.5%) with idiopathic RBD at baseline (31 survived, 19 died). Neurodegenerative diseases developed in nearly two-thirds of the deceased RBD patients (n = 27, 62.8%) and dementia developed in almost half of them (n = 21, 48.8%) (Table 1).

Sleep Variables

Table 2 shows the comparisons of baseline PSG variables between survived and deceased patients with RBD. The deceased RBD patients spent longer time in bed ($P = 0.006$) and had lower sleep efficiency ($P = 0.02$) and more wake after sleep onset ($P = 0.004$). In particular, deceased patients had a higher PLMI ($P = 0.009$) and a higher rate of PLMS ($P = 0.01$) than survived patients. There were no significant differences in total sleep time, sleep latency, percent of sleep stages (N1–3 and REM sleep), and apnea-hypopnea index.

Standardized Mortality Ratio

Table 3 shows the results of SMR analyses. SMR was 1.00 (95% CI, 0.73–1.33, $P = 1.00$) for the overall RBD patients, 0.92 (95% CI, 0.64–1.27; $P = 0.62$) for males, and 1.43 (95% CI, 0.73–2.55, $P = 0.26$) for females. In the idiopathic RBD, the SMR was 0.80 (95% CI, 0.47–1.27; $P = 0.37$) with no significant difference when compared to the general population. However, SMRs increased substantially in RBD patients in whom neurodegenerative diseases and dementia developed, with a SMR of 1.80 (95% CI, 1.21–2.58; $P = 0.002$) and 1.75 (95% CI, 1.11–2.63; $P = 0.009$), respectively. Similarly, RBD patients with PLMS had an increased SMR of 1.62 (95% CI, 1.03–2.43; $P = 0.027$).

Predictors of Mortality

Table 4 shows the results of the Cox regression models including neurodegenerative diseases at baseline (model 1), neurodegenerative diseases and dementia as time-dependent covariates, separately (model 2 and model 3). In model 1, baseline age (hazard ratio [HR] = 1.05; 95% CI, 1.01–1.10), living alone (HR = 2.04; 95% CI, 1.39–2.99), and medical comorbidities including COPD (HR = 3.38; 95% CI, 1.21–9.46), cancer (HR = 10.09; 95% CI, 2.65–38.42), and PLMS (HR = 3.06; 95% CI, 1.50–6.24) were the independent predictors of mortality in patients with RBD. However, the baseline neurodegenerative diseases were not significantly associated with mortality and therefore were not included with this model, which may be due to limited sample size in patients with baseline neurodegenerative diseases.

In model 2, when new-onset neurodegenerative diseases were taken into account as a time-dependent covariate,

Table 1—Demographic and clinical characteristics at baseline and follow-up.

Characteristic	All Patients (n = 205)	Survived (n = 162)	Deceased (n = 43)	P
Age at diagnosis, y	66.4 ± 10.0	65.3 ± 10.1	70.9 ± 8.5	0.001
Sex, male, n (%)	161 (78.5)	128 (79.0)	33 (76.7)	0.75
Age at onset, y	61.2 ± 12.9	60.6 ± 11.6	62.5 ± 15.8	0.10
Age at death, y	NA	NA	77.7 ± 8.7	NA
Follow-up period, y	7.1 ± 4.5	7.1 ± 4.8	7.1 ± 3.3	0.53
Duration of RBD before baseline, y	4.6 ± 4.3	4.4 ± 4.2	5.0 ± 4.7	0.59
≤ Primary education, n (%) [a]	91 (49.5)	67 (45.3)	24 (66.7)	0.02
BMI	24.4 ± 4.9	24.5 ± 4.4	24.3 ± 6.5	0.18
Obesity (BMI ≥ 26), n (%)	65 (31.9)	53 (32.9)	12 (27.9)	0.53
Living alone, n (%) [a]	15 (8.4)	10 (6.7)	5 (17.2)	0.06
Sleeping alone, n (%) [a]	83 (46.6)	64 (43.0)	19 (65.5)	0.03
Coffee drinking, n (%) [a]	80 (44.7)	72 (48.0)	8 (27.6)	0.04
Smoking, n (%) [a]	66 (36.9)	51 (34.0)	15 (51.7)	0.07
Alcohol, n (%) [a]	89 (49.7)	75 (50.0)	14 (48.3)	0.87
Depression (BDI > 14), n (%)	16 (7.9)	13 (8.1)	3 (7.0)	1.00
EDS (ESS ≥ 14), n (%)	51 (25.5)	39 (24.5)	12 (29.3)	0.54
Insomnia, n (%) [a]	27 (15.1)	23 (15.3)	4 (13.8)	1.00
Medical comorbidities (at baseline)				
Neurodegenerative diseases, n (%)	23 (11.2)	15 (9.3)	8 (18.6)	0.08
Dementia, n (%)	14 (6.8)	8 (4.9)	6 (14.0)	0.03
Hypertension, n (%)	73 (35.6)	54 (33.3)	19 (44.2)	0.19
Diabetes mellitus, n (%)	24 (11.7)	16 (9.9)	8 (18.6)	0.11
COPD, n (%)	10 (4.9)	5 (3.1)	5 (11.6)	0.02
Cerebrovascular disease, n (%)	8 (3.9)	5 (3.1)	3 (7.0)	0.37
Heart disease, n (%)	25 (12.2)	19 (11.7)	6 (14.0)	0.69
Cancer, n (%)	4 (1.5)	1 (0.6)	3 (7.0)	0.03
Mental disorder, n (%)	57 (27.8)	44 (27.2)	13 (30.2)	0.69
Conversion to neurodegenerative diseases during follow-up				
Newly neurodegenerative diseases, n (%) [b]	50 (27.5)	31 (21.1)	19 (54.3)	< 0.001
Newly dementia, n (%) [b]	29 (15.9)	14 (9.5)	15 (42.9)	< 0.001

[a] n < 205 because of missing data. [b] n = 182 (idiopathic RBD at baseline). BDI, Beck Depression Inventory; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; NA, not applicable; RBD, rapid eye movement sleep behavior disorder.

neurodegenerative diseases were associated with an increased risk of mortality (HR 2.84; 95% CI, 1.47–5.45, P = 0.002). Similarly, in model 3, dementia was associated with the mortality risk as a time-dependent covariate (HR = 2.66; 95% CI, 1.39–5.08). In keeping with findings from model 1, baseline age, living alone, and other comorbidities including COPD, cancer, and PLMS were associated with mortality in RBD patients. Sex was not a significant predictor in both Cox regression models. Kaplan-Meier survival curves with regard to the presence of COPD, cancer, PLMS at baseline, and neurodegenerative diseases as the time-dependent covariate are shown in Figure S1 in the supplemental material.

Causes of Death

The most common cause of death in our cohort was infection (n = 18 [41.9%], including 27.9% pneumonia, 4.7% pressure ulcer, and 9.3% sepsis), which was possibly related to the immobility at the later stage of the neurodegenerative diseases. The second leading cause of death was cancer (n = 10, 23.3%), among which, lung cancer (n = 4, 40.0%) was commonly seen. Altogether, the exact causes of death were unknown for six cases (Table 5).

DISCUSSION

To the best of our knowledge, this is the first study to determine the mortality and its potential risk factors of RBD patients. The SMR analyses in the current study demonstrated that, when compared with the general population, RBD *per se* was not associated with increased mortality until neurodegenerative diseases were developed. We also identified several other risk factors in predicting the mortality in RBD patients, including baseline age, living alone, COPD, cancer, and PLMS.

The finding of SMR in our RBD cohort with neurodegenerative diseases is rather similar to those previously reported

Table 2—Comparison of polysomnographic variables at baseline between survived and deceased patients with rapid eye movement sleep behavior disorder.

	All Patients (n = 205)	Survived (n = 162)	Deceased (n = 43)	P
Time in bed, min	485.3 ± 53.7	480.6 ± 50.6	502.9 ± 61.6	0.006
Total sleep time, min	337.9 ± 79.9	340.5 ± 76.9	328.2 ± 90.5	0.19
Sleep efficiency, min	69.9 ± 14.5	71.1 ± 14.0	65.3 ± 15.6	0.02
Sleep latency, min	25.4 ± 27.0	24.6 ± 26.8	28.3 ± 27.7	0.29
REM sleep latency, min	131.9 ± 80.1	126.7 ± 77.5	150.9 ± 87.6	0.08
Wake after sleep onset, min	117.5 ± 63.4	110.9 ± 60.3	142.6 ± 69.1	0.004
N1, %	16.4 ± 8.9	16.3 ± 9.3	16.9 ± 7.3	0.17
N2, %	62.8 ± 14.5	62.8 ± 15.0	62.9 ± 12.5	0.60
N3, %	2.4 ± 5.9	2.6 ± 6.4	1.9 ± 3.7	0.56
REM, %	18.3 ± 8.8	18.8 ± 8.8	16.6 ± 8.5	0.14
Arousal index, events/h	18.8 ± 20.1	17.9 ± 13.8	23.1 ± 38.1	0.84
AHI, events/h	19.2 ± 20.6	19.2 ± 20.9	19.0 ± 19.3	0.80
OSA (AHI > 15 events/h), n (%)	78 (38.2)	60 (37.3)	18 (41.9)	0.58
PLMI, events/h	18.2 ± 31.7	13.7 ± 22.7	35.0 ± 50.4	0.009
PLMI in NREM, events/h	19.2 ± 32.6	15.2 ± 25.4	35.7 ± 50.4	0.04
PLMI in REM, events/h	7.4 ± 23.7	5.5 ± 18.2	15.4 ± 38.5	0.11
PLMS (PLMI > 15 events/h), n (%)	68 (33.2)	47 (29.0)	21 (48.8)	0.01
PLMS in NREM, n (%)	65 (33.2)	45 (28.5)	20 (52.6)	0.005
PLMS in REM, n (%)	24 (12.2)	17 (10.8)	7 (18.4)	0.19

AHI, apnea-hypopnea index; NREM, nonrapid eye movement; OSA, obstructive sleep apnea; PLMI, periodic limb movement index; PLMS, periodic limb movements during sleep; REM, rapid eye movement.

Table 3—Mortality ratio between observed and expected deaths in rapid eye movement sleep behavior disorder.

	Deaths				
	Observed	Expected	SMR	95% CI	P
RBD [a]	43	43	1.00	0.73–1.33	1.00
Sex [a]					
Male	33	36	0.92	0.64–1.27	0.62
Female	10	7	1.43	0.73–2.55	0.26
Idiopathic RBD [a]	16	20	0.80	0.47–1.27	0.37
Neurodegenerative diseases [b]	27	15	1.80	1.21–2.58	0.002
Dementia [c]	21	12	1.75	1.11–2.63	0.009
PLMS [d]	21	13	1.62	1.03–2.43	0.027

[a] RBD patients who remained idiopathic throughout the follow-up period. [b] RBD patients with a diagnosis of neurodegenerative disease. [c] RBD patients with a diagnosis of dementia. [d] RBD patients with a diagnosis of PLMS. CI, confidence interval; PLMS, periodic limb movements during sleep; RBD, rapid eye movement sleep behavior disorder; SMR, standardized mortality ratio.

in the patients with PD[5,6,21] and dementia.[22] Findings from the Cox regression analysis showed that neurodegenerative diseases as a time-dependent covariate were associated with increased mortality risk (HR = 2.84). However, RBD patients in whom neurodegenerative diseases did not develop did not have a higher SMR. Interestingly, probable RBD symptoms in patients with PD was not associated with an increase in mortality.[23] Nonetheless, the determination of RBD in this study was only measured by a single-item question rather than v-PSG. Taken together, the existing findings suggested that the conversion to neurodegenerative diseases is predictive of an increased risk of worse outcomes in patients with RBD.

It is widely acknowledged that demographic variables, especially age and sex, may potentially influence the risk and clinical course of RBD.[24] In the current study, we found that deceased patients were older than the patients who survived, and the association of age and mortality was significant in the Cox regression model after controlling for other baseline factors. Although there is a significant male predominance in the occurrence of RBD,[25] it seemed that male patients do not have a higher risk of development of neurodegenerative diseases[24,25]

Table 4—Predictors of mortality risk in patients with rapid eye movement sleep behavior disorder in the Cox regression models.

Model 1 [a]		
Age	1.05 (1.01, 1.10)	0.02
Sex	0.92 (0.41, 2.08)	0.84
Living alone	2.04 (1.39, 2.99)	< 0.001
COPD	3.38 (1.21, 9.46)	0.02
Cancer	10.09 (2.65, 38.42)	0.001
PLMS	3.06 (1.50, 6.24)	0.002
Model 2 [b]		
Age	1.04 (1.00, 1.08)	0.09
Sex	0.93 (0.42, 2.06)	0.86
Living alone	1.99 (1.35, 2.92)	< 0.001
COPD	4.06 (1.42, 11.59)	0.009
Cancer	7.25 (1.90, 27.59)	0.004
PLMS	3.37 (1.64, 6.93)	0.001
Neurodegenerative diseases	2.84 (1.47, 5.45)	0.002
Model 3 [c]		
Age	1.03 (1.00, 1.07)	0.17
Sex	0.97 (0.44, 2.15)	0.93
Living alone	2.06 (1.39, 3.03)	< 0.001
COPD	3.83 (1.35, 10.90)	0.01
Cancer	8.06 (2.08, 31.32)	0.003
PLMS	3.38 (1.63, 7.01)	0.001
Dementia	2.66 (1.39, 5.08)	0.003

[a] Baseline neurodegenerative diseases and other factors were tested in the model. [b] Neurodegenerative diseases were treated as time-dependent covariate in the model. [c]Dementia was treated as time-dependent covariate in the model. CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PLMS, periodic limb movements in sleep.

Table 5—Causes of death according to International Classification of Diseases, Tenth Revision classification.

Causes of Death	n (%)
Infectious disease (sepsis)	4 (9.3)
Neoplasm	10 (23.3)
Ischemic heart disease and heart failure	3 (7.0)
Cerebrovascular disease	1 (2.3)
Disease of veins (DVT)	1 (2.3)
Pneumonia	12 (27.9)
COPD	2 (4.7)
Disease of the skin and subcutaneous tissue (Pressure ulcers)	2 (4.7)
Uremia	1 (2.3)
Poisoning	1 (2.3)
Unknown	6 (14.0)
Total	43 (100)

COPD, chronic obstructive pulmonary diseases; DVT, deep vein thrombosis.

or an increased mortality risk (as found in the current study). Interestingly, we found that living alone was associated with an increased risk of mortality in patients with RBD. This result was consistent with studies in both general population and clinical patients, which indicated that living alone was an independent and significant predictor of all-cause mortality in elderly people.[26,27] The exact reason is unclear but living alone in elderly patients is related to adverse health outcomes, probably related to psychosocial distress or/and increased risk of physical disease such as cardiovascular diseases.

Although coffee drinking and smoking have been considered to be the most consistent protective factors for PD in various epidemiological studies,[28,29] several studies have found that coffee drinking and smoking are not protective factors for the occurrence of RBD[30] and conversion of RBD into PD.[24] In line with these findings,[24,30] we further showed that coffee drinking and smoking are neither protective nor risk factors for mortality in RBD patients. Cigarette smoking increased the mortality among men without PD, but it seemed to impose little additional risk on patients with PD.[31–33] Nonetheless, we found a trend of higher smoking rate among deceased patients with RBD when compared to those patients who survived. This result may further explain our finding that COPD was a risk factor for mortality in RBD. Similarly, a multicenter study has reported that COPD was likely related to the higher prevalence of smoking in RBD patients.[34]

PLMS is a prevalent comorbid condition in RBD.[35] The current study also found that PLMS is a common comorbid condition (33.2%) by using International Classification of Sleep Disorders, Second Edition criteria of PLMI > 15 events/h. Although the clinical implications of PLMS in patients with RBD are largely unknown, our study demonstrated that PLMS is a risk factor for mortality in RBD patients. Interestingly, the presence of PLMS in patients with renal failure and amyotrophic lateral sclerosis is also associated with increased risk of mortality in these clinical populations.[36,37] We speculate that several pathways may underlie the close association of PLMS with mortality. First, PLMS is postulated as a potential biological marker of dopaminergic mechanisms involved in the pathophysiology of PD, which has some support from imaging studies demonstrating an association of PLMI with the severity of striatonigral dopaminergic degeneration in patients with PD.[38] Indeed, PLMS in RBD patients was postulated as a biomarker of disease severity.[39] Second, PLMS is associated with some unfavorable cardiovascular and cerebrovascular outcomes.[40] Nonetheless, our study did not show any significant associations of cardiovascular and cerebrovascular diseases with mortality in the final Cox regression model. Third, PLMS-related sleep disturbances or poor sleep may also account for the association, albeit we did not find any associations of insomnia and PSG-measured sleep quality with mortality.

In addition, two medical comorbid conditions, COPD and cancer, were responsible for the mortality risk in patients with RBD. Furthermore, the analyses on the causes of death revealed that infection-related diseases and cancers were two major causes of death. These findings are in concordance with the majority of studies that pneumonia was the most common

cause of death in patients with neurodegenerative diseases.[5,41,42] Similarly, cancer has been reported as a common cause of death in PD.[21,43] Growing evidence suggests the expression of the PD-linked genes in various cancers, which suggests some shared biological pathways between these two divergent diseases.[44] Nonetheless, other studies found a decrease in cancer-related mortality risk in patients with PD, regardless of smoking or nonsmoking-related cancers.[32,42,45]

Strengths of the current study include a considerable cohort size with sufficient follow-up duration, v-PSG confirmation, low attrition rate and inclusion of both clinical and PSG variables. However, some limitations should be noted when interpreting the findings. First, although the sample size was large enough to identify the risk factors with moderate effect size, there was still a lack of power for subgroup analyses (such as sex differences). Second, the diagnosis of neurodegenerative disease was based on the case note reviews from the CMS and the medical conditions may be underdiagnosed if the conditions never came to medical attention. Finally, there were no autopsy studies for the deceased patients and therefore the ultimate neuropathology and causes of death could not be verified.

CONCLUSIONS

In summary, patients with RBD have a higher mortality risk than the general population only if neurodegenerative diseases develop. Several risk factors are associated with mortality in RBD that have clinical implications for identifying at-risk individuals and for understanding the disease progression. Our findings further underscore the necessity of timely neuroprotective intervention in the early phase of RBD before the development of neurodegenerative diseases.[46]

ABBREVIATIONS

AD, Alzheimer disease
AHI, apnea-hypopnea index
CI, 95% confidence interval
CMS, Clinical Management System
COPD, chronic obstructive pulmonary disease
DLB, dementia with Lewy bodies
ECG, electrocardiogram
EEG, electroencephalogram
EMG, electromyogram
HR, hazard ratio
MSA, multiple system atrophy
OSA, obstructive sleep apnea
PD, Parkinson disease
PDD, Parkinson disease dementia
PLMI, periodic limb movement index
PLMS, period limb movements during sleep
PSG, polysomnography
RBD, rapid eye movement sleep behavior disorder
REM, rapid eye movement
SMR, standardized mortality ratio
VD, vascular dementia
WASO, wake after sleep onset

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