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Original Article

Electromyography activity level in rapid eye movement sleep predicts neurodegenerative diseases in idiopathic rapid eye movement sleep behavior disorder: a 5-year longitudinal study

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ABSTRACT

Objectives: To investigate whether baseline electromyography (EMG) activity during rapid eye movement (REM) sleep predicts the development of neurodegenerative diseases over time in patients with idiopathic REM sleep behavior disorder (iRBD).

Methods: A total of 216 patients with polysomnography-confirmed iRBD were recruited from September 1997 to December 2016 with a mean follow-up duration of 5.0 ± 3.7 years (median: 4.0, range: 0.5–19.0). Neurodegenerative diseases were ascertained according to standard diagnostic criteria during follow-up. Time-dependent receiver operating characteristic (ROC) curves were employed to evaluate the dynamic predictive performance of EMG activity over time. Both tonic and phasic EMG activity were dichotomized into 'mild' and 'severe' categories by the ROC curves estimated optimal cut-offs.

Results: A total of 58 patients (26.9%) developed neurodegenerative diseases. The predictive performance of tonic EMG activity was stable (area under the curve of approximately 0.68) over time, while the performance of phasic EMG activity was significantly superior to chance only after five years of follow-up. The optimal cut-off for prediction at five years was 15.4% (sensitivity, 0.69; specificity, 0.57) and 7.8% (sensitivity, 0.79; specificity, 0.47) for tonic and phasic EMG activity, respectively. Cox proportional hazards regression analyses further revealed that severe tonic (adjusted HR: 2.76, 95% CI: 1.35–5.62) and phasic EMG activity (adjusted HR: 3.10, 95% CI: 1.10–8.71) were associated with early development of Parkinson's disease (PD) and dementia with Lewy bodies (DLB), respectively.

Conclusions: Tonic but not phasic EMG activity may serve as a stable biomarkers for predicting the progression of neurodegeneration in iRBD.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by dream enactment behaviors during REM sleep and REM sleep without atonia (RSWA), including both increased phasic and tonic electromyographic (EMG) activity [1]. Accumulating evidence has confirmed that idiopathic RBD (iRBD) in adults >50 years old is a highly specific marker for neurodegenerative diseases, predominantly α-synucleinopathies, such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [2–4]. The conversion rate from iRBD to evident α-synucleinopathies is approximately 80–90% at a mean interval of approximately 14 years after the diagnosis of RBD [5,6].

As the time interval from iRBD to neurodegenerative disease varies from one year to over a decade in different patients [5–7],

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identifying biomarkers for predicting the conversion rate of neurodegeneration in iRBD is of utmost importance in terms of monitoring disease progression and identifying ultra-high-risk individuals for enrollment in potential neuroprotective trials. RSWA, a core feature of RBD on polysomnographic (PSG) recording, has been suggested as a potential marker for predicting the progression of neurodegeneration in patients with iRBD. Postuma et al., previously reported that tonic but not phasic EMG activity during REM sleep was significantly higher in iRBD patients who converted neurodegenerative diseases, especially PD, compared with unconverted patients [8]. Another recent study from the same research group further reported that RBD patients with tonic EMG activity >50% had a higher risk of conversion [9]. Both studies strongly suggest that tonic EMG activity, but not phasic EMG activity, is a biomarker for neurodegenerative diseases in patients with iRBD. However, another study suggested a trend of higher phasic rather than tonic EMG activity in converted iRBD patients compared with unconverted iRBD patients ($p = 0.086$) [10]. These contradictory findings warrant further longitudinal studies with larger sample sizes to determine the association of the level of EMG activity with the conversion of neurodegenerative diseases in iRBD. Furthermore, the varied time period of the follow-up duration should be taken into account when investigating the predictive value of RSWA because the rate of conversion to neurodegenerative diseases is time-dependent [11,12]. Therefore, we aimed to investigate RSWA, including both chin tonic and phasic EMG activity, in predicting the development of neurodegenerative diseases in a longitudinal study of iRBD patients.

2. Methods

2.1. Patient recruitment

Patients with video-PSG-confirmed iRBD between September 1997 and December 2016 were consecutively recruited for participation in this study [13]. This study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee. All recruited patients provided informed consent for the use of their clinical information for research purposes. Clinical information including age at RBD symptom onset and prescription of medications at baseline were collected according to patients' medical record.

As patients with iRBD were recruited during different periods of time, the diagnosis of iRBD was based on the International Classification of Sleep Disorder (ICSD) and ICSD-2 criteria (for those recruited before 2014) or based on the ICSD-3 criteria (for those recruited during or after 2014). In summary, the iRBD patients included in this study all: (1) had a history of repetitive or video-PSG-captured dream enactment behavior, and (2) showed excessive EMG activity during REM sleep according to the PSG assessment. The exclusion criteria included: (1) RBD comorbid with narcolepsy; (2) RBD symptoms secondary/related to previously diagnosed neurodegenerative diseases; (3) and RBD symptoms caused by severe obstructive sleep apnea (Pseudo-RBD) [14]. We noted that some iRBD patients showed mild RSWA which did not meet the EMG cut-offs that reported by other studies groups [15,16]. These patients with mild RSWA were also recruited in this study because they were clinically diagnosed and further follow-up confirmed that the mild RSWA deteriorated over time (data has been presented on 12th IRBDSG conference on 14 September 2018 in Germany).

2.2. PSG recording and EMG scoring at baseline

All patients underwent one or two consecutive nights of video-PSG monitoring at baseline to confirm their diagnosis of RBD, to evaluate the presence of comorbid sleep disorders, and to rule out potential conditions that might mimic apparent RBD features, such as “pseudo-RBD” induced by severe obstructive sleep apnea [14]. REM sleep was scored according to the American Academy of Sleep Medicine 2012 criteria with modification of the criteria on increased EMG activity during REM sleep [17].

Only chin EMG activity during REM sleep was used to determine the severity of RSWA, as chin EMG has been found to possess the highest rate of excessive activity during REM sleep in patients with RBD [18]. The artifacts of EMG activity associated with arousal or respiratory events were excluded when scoring the EMG activity during REM sleep. The scoring was based on a 30-second epoch of PSG tracing. Phasic EMG activity was defined as any burst of EMG activity lasting 0.1–5 s with an amplitude exceeding four times the background EMG activity [19]. The level of phasic EMG activity was calculated as the percentage of time of overall 3-second mini epochs presenting with phasic EMG activity in total REM sleep time. Tonic EMG activity was defined as EMG activity lasting longer than 5 s with an amplitude exceeding two times the baseline EMG activity. The 30-second epoch was scored as a tonic epoch if it presented with overall tonic EMG activity lasting more than 15 s (>50% of the 30-second epoch). The severity of tonic EMG activity was calculated as the percentage of time of tonic epochs during the total REM sleep period [20]. There were favorable inter-rater reliability (for scoring phasic EMG activity: intra-class correlation coefficient (ICC) = 0.984, 95% confidence interval (CI) = 0.955–0.995; for tonic EMG activity: ICC = 0.990, 95% CI = 0.971–0.996) and intra-rater reliability in our sleep center (for scoring phasic EMG activity: ICC = 0.929, 95% CI = 0.768–0.978; for tonic EMG activity: ICC = 0.988, 95% CI = 0.962–0.996).

2.3. Neurodegenerative diseases ascertainment during follow-up

All iRBD patients included in this study were followed in our sleep clinic or other general clinics within the public health care system in Hong Kong. During the follow-up period, the presence of parkinsonism and cognitive function impairment were identified by specialists (eg, neurologists, psychiatrists, or geriatricians) and would be referred to neurologists specialized in neurodegenerative diseases by for further confirmation of the diagnoses [7,13]. In brief, parkinsonism and dementia syndromes were diagnosed with reference to the standard diagnostic criteria of PD [21], MSA [22], and DLB [23].

2.4. Statistical analysis

The statistical analyses were performed using SPSS version 22.0 (Armonk, NY: IBM Corp.) and R project (version 3.4.1 with packages ‘*timeROC*’ and ‘*survivalROC*’). Continuous variables between groups were compared by the nonparametric Mann–Whitney *U* test or independent samples T test. Categorical variables between groups were compared using the Chi-square or Fisher exact test where appropriate. The follow-up duration was calculated from the date of PSG-confirmed diagnosis of RBD to the date of last visit (before June 30, 2017), or to the date of diagnosis of a neurodegenerative disease, or to the date of death (censored data).

Therefore, two major methods, namely, time-dependent ROC curve analysis and Cox proportional hazards regression model, were employed to determine the performance of tonic and phasic EMG activity for predicting the development of neurodegenerative diseases. The ‘*timeROC*’ package was employed to draw the figure depicting the dynamic performance of RSWA for predicting neurodegenerative diseases. The ‘*survivalROC*’ package was used to determine the optimal cut-off points of tonic and phasic EMG activity. Then, patients with iRBD were dichotomized into two groups

named 'mild' and 'severe'. As '*timeROC*' analysis revealed that both tonic and phasic EMG activity achieved stable prediction performance at five years, this time point was selected for the '*survivalROC*' analysis to determine the optimal cut-offs for grouping based on tonic and phasic EMG activity, respectively.

To quantify the risk for developing neurodegenerative diseases based on the EMG activity, Cox proportional hazards regression model, a classical statistical method estimating the proportional hazards, was further used to calculate the hazard ratio (HR) and the 95% confidence interval (CI) for developing PD (after excluding patients developed DLB and MSA) and DLB (after excluding patients developed PD and MSA) in iRBD patients by dichotomizing tonic and phasic EMG activity into mild and severe categories after adjustment for age, sex, and baseline clonazepam use. Kaplan–Meier curves were also used to depict the progressive development of overall neurodegenerative diseases, PD and DLB between iRBD patients with mild and severe tonic/phasic EMG activity. A p value < 0.05 was considered statistically significant for the group comparison.

3. Results

3.1. Demographic, clinical, and polysomnographic characteristics of patients

A total of 216 patients (male, 77.3%) meeting the criteria were recruited. Table 1 shows the demographic, clinical, and polysomnographic characteristics of the patients. The mean age at RBD onset and PSG-confirmed RBD diagnosis were 62.4 ± 8.3 and 67.5 ± 7.8 years, respectively. The mean follow-up duration was 5.0 ± 3.7 (median, 4.0; range, 0.5–14.9) years. During the follow-up period, 17 patients (10.1%) died without any diagnosis of neurodegenerative disease (censored data), and 58 patients (26.9%) developed a neurodegenerative disease (34 patients developed PD, 23 DLB, and 1 MSA).

Based on EMG cut-offs revealed by '*survivalROC*', patients with iRBD were further classified into different groups. Compared with patients with mild EMG activity, patients with severe tonic and phasic EMG activity had a shorter follow-up duration (tonic EMG activity: 4.1 ± 3.3 vs. 5.7 ± 3.9 years, p = 0.001; phasic EMG activity: 4.1 ± 3.1 vs. 7.3 ± 4.1 years, p < 0.001), which may be due to earlier development in patients with severe tonic and phasic EMG activity. Compared with patients with mild tonic EMG activity, patients with severe tonic EMG activity had a higher rate of clonazepam use before PSG assessment (41.0% vs. 19.8%, p = 0.001). No statistically significant differences were found in age, sex, education level, Epworth Sleepiness Scale (ESS) score, other medication use, and other polysomnographic parameters between patients with mild and severe tonic/phasic EMG activity.

3.2. The prediction performance of increased EMG activity

Fig. 1 shows the results of the time-dependent ROC curve analyses which demonstrating the dynamic performances of both tonic and phasic EMG activity levels in predicting neurodegenerative diseases with time. The red solid line represents the dynamic AUC for tonic EMG activity, while the blue solid line represents the AUC for phasic EMG activity between the 25th percentile and the 75th percentile of the follow-up period. The dotted lines represent the lower and upper limits of the 95% CI of the AUC for both tonic and

Table 1
The demographic, clinical, and polysomnographic characteristics of overall patients and patients in groups.

	All patients (n = 216)	Mild tonic EMG activity (n = 111)	Severe tonic EMG activity (n = 105)	P value	Mild phasic EMG activity (n = 60)	Severe phasic EMG activity (n = 156)	P value
Age at PSG, year	67.5 ± 7.8	67.9 ± 8.4	67.1 ± 7.3	0.48	67.4 ± 8.2	67.5 ± 7.7	0.93
Sex, Male (%)	167 (77.3)	86 (77.5)	81 (77.1)	0.97	50 (83.3)	117 (75.0)	0.19
Age at onset of iRBD,[a] year	62.4 ± 8.3	62.3 ± 9.7	62.5 ± 6.6	0.95	62.9 ± 8.5	62.2 ± 8.2	0.59
Disease course at baseline,[a] year	4.9 ± 4.7	5.3 ± 5.6	4.5 ± 3.4	0.23	4.7 ± 3.8	5.0 ± 5.0	0.75
Follow-up duration from RBD diagnosed, year	5.0 ± 3.7	5.7 ± 3.9	4.1 ± 3.3	0.001	7.3 ± 4.1	4.1 ± 3.1	<0.001
Education level (<6 years), n (%)	72 (33.3)	39 (35.1)	33 (31.4)	0.56	16 (26.7)	56 (35.9)	0.20
Epworth Sleepiness Scale score	7.6 ± 5.4	7.7 ± 5.5	7.5 ± 5.3	0.74	7.7 ± 5.9	7.6 ± 5.2	0.86
Medication use at PSG confirmation							
Clonazepam, n (%)	65 (20.4)	22 (19.8)	43 (41.0)	0.001	17 (28.3)	48 (30.8)	0.73
Melatonin, n (%)	2 (0.9)	2 (1.8)	2 (1.9)	0.96	0 (0)	4 (2.6)	0.58
Antidepressants, n (%)	28 (13.0)	12 (10.8)	16 (15.2)	0.33	8 (13.3)	20 (12.8)	0.92
Total sleep time, min	333.8 ± 77.2	340.5 ± 78.7	326.5 ± 75.3	0.18	341.0 ± 80.5	330.9 ± 76.0	0.39
Sleep efficiency, %	69.7 ± 13.8	71.4 ± 13.5	67.9 ± 14.0	0.07	70.9 ± 14.8	69.2 ± 13.4	0.42
Sleep latency, min	23.5 ± 22.4	23.3 ± 26.7	23.6 ± 16.7	0.92	20.4 ± 15.1	24.7 ± 24.6	0.21
REM sleep latency, min	125.9 ± 80.1	119.7 ± 81.0	132.5 ± 77.9	0.24	128.8 ± 78.8	124.7 ± 80.7	0.74
WASO, min	120.8 ± 61.1	114.3 ± 59.9	128.1 ± 62.0	0.10	116.2 ± 61.1	122.6 ± 61.2	0.50
Arousal index,/h	18.3 ± 13.3	19.9 ± 15.9	19.7 ± 11.1	0.99	18.6 ± 15.2	18.2 ± 12.7	0.83
Stage 1, %	17.3 ± 9.1	17.0 ± 8.4	17.6 ± 9.8	0.66	17.0 ± 9.7	17.4 ± 8.9	0.77
Stage 2, %	60.5 ± 11.3	60.2 ± 10.9	60.8 ± 11.7	0.70	61.0 ± 11.8	60.2 ± 11.1	0.63
Stage 3, %	2.6 ± 4.8	2.4 ± 4.4	2.8 ± 5.3	0.58	1.8 ± 3.4	2.9 ± 5.3	0.06
Stage REM, %	19.4 ± 7.8	19.4 ± 7.1	19.4 ± 8.6	0.99	19.2 ± 7.6	19.3 ± 7.9	0.87
AHI,/h[b]	17.6 ± 19.9	18.3 ± 20.1	17.0 ± 19.8	0.71	21.4 ± 24.2	16.3 ± 17.9	0.45
AHI in NREM, h[b]	17.6 ± 20.6	17.7 ± 20.3	17.4 ± 21.0	0.84	21.6 ± 24.4	16.0 ± 18.7	0.37
AHI in REM, h[b]	18.1 ± 21.0	18.5 ± 20.7	17.7 ± 21.3	0.82	20.4 ± 24.4	17.3 ± 19.5	0.50
PLMI,/h[b]	19.7 ± 28.3	18.6 ± 23.4	20.9 ± 32.9	0.55	25.5 ± 32.1	17.5 ± 26.4	0.08
PLMI in NREM,/h[b]	20.9 ± 31.7	18.7 ± 25.5	23.2 ± 37.2	0.84	27.9 ± 36.3	18.1 ± 29.4	0.11
PLMI in REM,/h[b]	5.4 ± 19.1	3.3 ± 13.3	7.7 ± 23.7	0.20	8.5 ± 28.9	4.3 ± 13.5	0.89
Phasic EMG activity level	14.2 ± 9.3	12.7 ± 8.2	15.8 ± 10.1	0.01	4.6 ± 2.3	17.9 ± 8.3	<0.001
Tonic EMG activity level	22.6 ± 24.7	4.3 ± 4.0	42.0 ± 22.5	<0.001	22.3 ± 29.6	22.8 ± 22.7	0.90

Data are presented as mean ± standard deviation or n (%).
PSG, polysomnography; EMG, Electromyography; iRBD, idiopathic REM sleep behavior disorder; WASO, wake after sleep onset; AHI, apnea hypopnea index; PLMI, periodic limb movement index.
[a] n = 198 due to missing or unknown data.
[b] Nonparametric Mann–Whitney *U* test were performed.

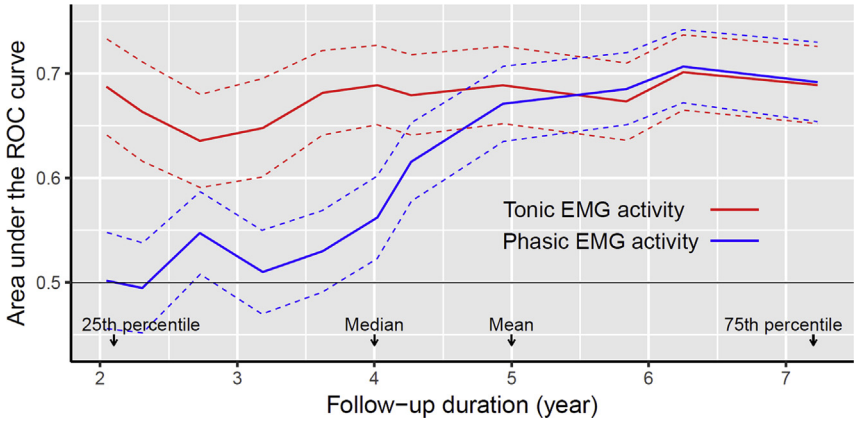

Fig. 1. Time-dependent area under the receiver operating characteristic curve. Dotted lines show the 95% confidence interval of area under the receiver operating characteristic curve. The lower limit of 95% confidence interval of phasic EMG activity (dotted blue line) is under 0.5 level when follow-up duration less than four years, indicating no significant predicting value. ROC, receiver operating characteristic; EMG, Electromyography.

phasic EMG activity. Tonic EMG activity reliably predicted the development of a neurodegenerative disease within 2.1 years (25th percentile) to 7.2 years (75th percentile), as the AUC was significantly different from chance, with an overall AUC of approximately 0.68. However, phasic EMG activity had poor performance in predicting the development of a neurodegenerative disease within the first four years of the follow-up period, which is indicated by the overlap between its 95% CI and the chance line. Nevertheless, phasic EMG activity reliably predicted the development of a neurodegenerative disease five years after RBD diagnosis. The results of '*survivalROC*' revealed that the optimal cut-off at five years was 15.4% for tonic EMG activity (sensitivity, 0.69; specificity, 0.57) and 7.8% for phasic EMG activity (sensitivity, 0.79; specificity, 0.47).

Fig. 2 presents the Kaplan–Meier survival curves of the risk of developing PD and DLB in patients with RBD with mild and severe tonic and phasic EMG activity. In general, severe tonic EMG activity was associated with a higher risk of PD than mild tonic EMG activity (log-rank test, $p = 0.006$), while severe phasic EMG activity was associated with a higher risk of DLB than mild phasic EMG activity (log-rank test, $p = 0.03$).

The results of the Cox proportional hazards regression models (Table 2) are consistent with the findings from the Kaplan–Meier survival curves. Compared with patients with mild tonic EMG activity, patients with severe tonic EMG activity were at a higher risk of overall neurodegenerative diseases (HR: 2.25; 95% CI, 1.32–3.84, $p = 0.003$) and PD (HR, 2.76; 95% CI, 1.35–5.52, $p = 0.005$) but not DLB (HR: 2.06; 95% CI, 0.87–4.88, $p = 0.10$), even when adjusted for age, sex, and clonazepam use. Compared with patients with mild phasic EMG activity, patients with severe phasic EMG activity were at a higher risk of overall neurodegenerative diseases (HR: 1.89; 95% CI, 1.05–3.38, $p = 0.03$) and DLB (HR: 3.10; 95% CI, 1.10–8.71, $p = 0.03$) but not PD (HR: 1.71; 95% CI, 0.80–3.63, $p = 0.17$), even when adjusted for age and sex (Table 2). In addition, after exclusion of those patients who were taking antidepressants at baseline ($n = 28$), the HR values were similar to those in original analyses.

4. Discussion

This study found that baseline tonic EMG activity possessed stable and favorable performance in predicting the development of PD over time, while baseline phasic EMG activity appeared to predict DLB in an unstable manner (only for patients with relatively longer follow-up durations). Findings from the Cox regression analysis, which revealed that patients with severe tonic and phasic EMG activity were over two times more likely to develop neurodegenerative diseases than patients with mild tonic and phasic EMG activity, further corroborated findings in the ROC curve analyses. This study provided consistent evidence that the levels of RSWA, especially tonic EMG activity, is potential biomarkers in predicting the conversion of neurodegenerative diseases in patients with iRBD.

Previous studies have reported inconsistent findings regarding the values of tonic and phasic EMG activity levels for predicting the development of neurodegenerative diseases among patients with iRBD [8–10]. We speculated that these inconsistent findings may be derived from different study designs (case–control study vs. cohort study), relatively small sample sizes [8,24], and different statistical approaches for data analysis [9]. A recent study with larger sample size found that among those patients who have developed neurodegenerative diseases or symptoms (PD, DLB, and mild cognitive impairment), the baseline tonic EMG activity level was significantly higher among patients who developed PD when compared with patients who developed DLB and mild cognitive impairment, which strongly suggested that the tonic EMG activity level is tightly associated with PD [25].

It is unclear why severely increased tonic EMG activity predicts the early development of neurodegenerative diseases. One explanation may be that the increased EMG activity may represent longer disease duration, as it has been found that the level of EMG activity increases over time [26]. However, a previous study demonstrated that even by comparing patients who were matched for disease duration, patients who converted to PD were still found to have a higher level of baseline tonic EMG activity [8]. In the current study, the disease courses at baseline were similar between groups. Thus, increased EMG activity may represent an advanced stage of Lewy body pathology in the locus subcoerluleus or its analogous neuro-structure in the brainstem and reflect more pervasive damage in this area, which is independent of disease duration [27–29]. It has been found that the emergence of tonic EMG activity during REM sleep is related to dysfunction of the locus subcoerluleus nucleus or its analogous neuro-structure in the brainstem, which inhibits spinal motoneurons [27]. As the locus subcoerluleus nucleus is on the pathway of Lewy body pathology spreading and ahead of the substantia nigra, the key nuclei responsible for the etiology of PD [30], its dysfunction as presented by the severity of tonic EMG activity may reflect the degree of degeneration of these nuclei and further suggest a stronger Lewy body pathology to substantia nigra. Thus, stronger prediction by tonic EMG activity may reflect the closer link of the locus subcoerluleus nucleus with future risk of PD [8].

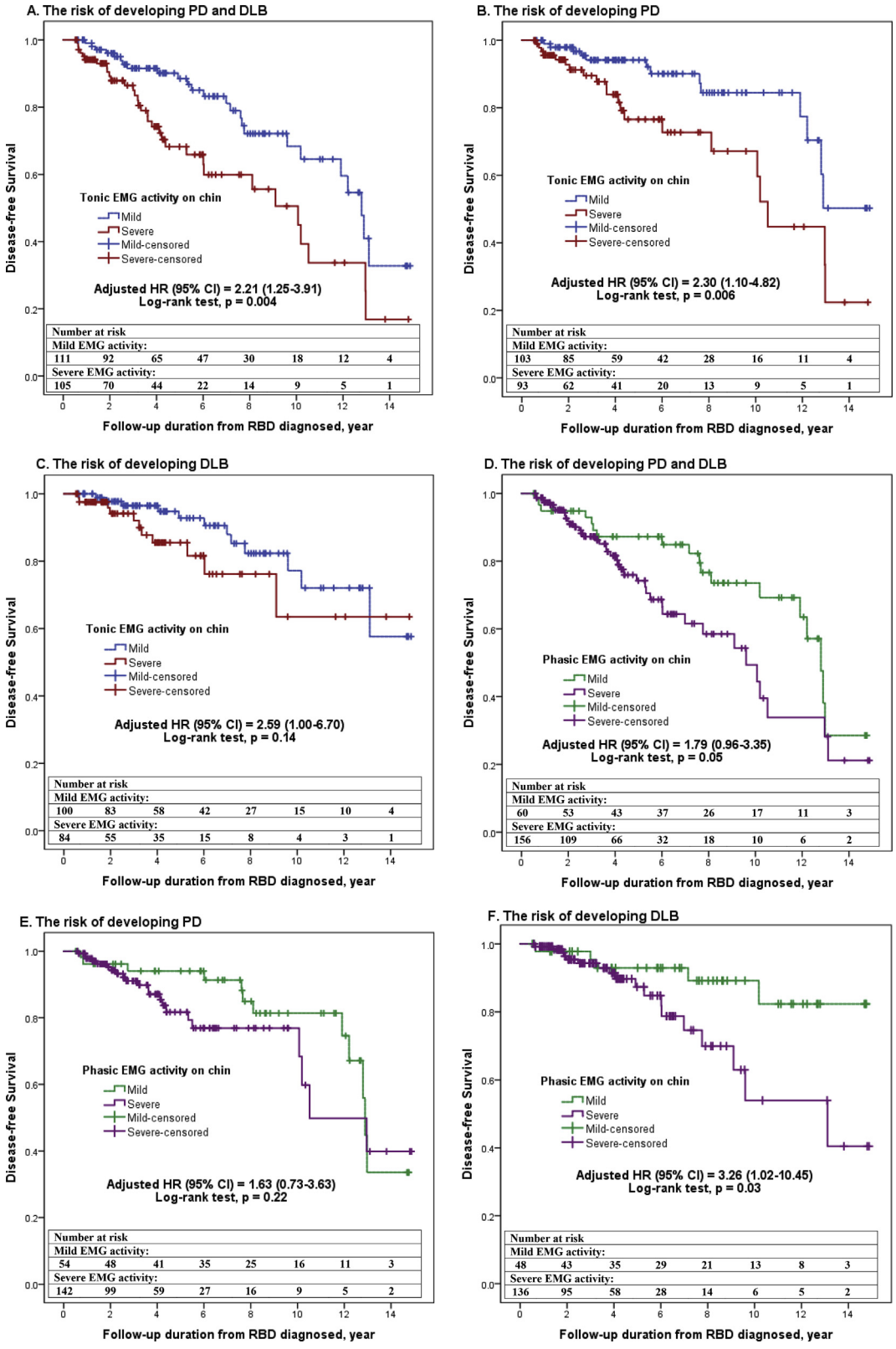

Fig. 2. Kaplan–Meier survival curves of risk developing PD and dementia in patients with RBD with mild and severe EMG activity. Hazard ratio in Figures A, B, C adjusted for age and sex. Hazard ratio in Figure C, D, E adjusted for age, sex, and clonazepam use.

It is intriguing that phasic EMG activity could predict DLB in those patients with longer follow-up duration which is inconsistent with findings of several previous studies [8,9,25]. The finding in current study was probably due to the random variation related to a somewhat artificial split of EMG activity as we found phasic EMG failed to stably predict neurodegenerative diseases during follow-up. Alternately, we noted that in this study with relatively large sample size, severely increased phasic EMG activity level still

Table 2
The risk of neurodegenerative diseases in iRBD patients with severe tonic and severe phasic EMG activity, respectively.

	Unadjusted model		Adjusted model[a]	
	HR	95% CI	Adjusted HR	95% CI
Severe tonic EMG activity				
Overall neurodegenerative diseases	2.14	1.27–3.62**	2.25	1.32–3.84**
PD	2.56	1.27–5.13**	2.76	1.35–5.62**
DLB	1.87	0.81–4.30	2.06	0.87–4.88
Severe phasic EMG activity				
Overall neurodegenerative diseases	1.78	1.00–3.15*	1.89	1.05–3.38*
PD	1.57	0.77–3.28	1.71	0.80–3.63
DLB	2.91	1.05–8.06*	3.10	1.10–8.71*

*P < 0.05; **P < 0.01.
EMG, Electromyography; HR, hazard ratio; CI, confidence interval; PD, Parkinson's disease; DLB, dementia with Lewy bodies.
[a] Model for phasic EMG activity adjusted for age, sex. Model for tonic EMG activity adjusted for age, sex, and baseline clonazepam use.

yielded a HR = 1.9 in predicting neurodegenerative diseases when compared with mildly increased phasic EMG activity. This finding suggested that severity of phasic EMG may also reflect the severity of neurodegeneration somehow.

Some other aspects in the current study need to be addressed. One concern is that clonazepam is a confounding factor underlying the association between tonic EMG activity and the development of neurodegenerative diseases, as patients with severe tonic EMG activity had a higher rate of clonazepam use at the time of video-PSG confirmation. However, it has been found that clonazepam may suppress phasic EMG activity rather than alter tonic EMG activity [31]. While our previous study found that clonazepam did not change the level of phasic EMG activity after a follow-up duration of 29 months [32]. Therefore, we believe that clonazepam use is unlikely to be a confounding factor. Another concern is whether antidepressants use at baseline had an influence of the finding. It has been found that antidepressant, especially selective serotonin reuptake inhibitors are associated with increasing of EMG activity [33,34]. Thus, inclusion of these patients may not be inappropriate as these patients may serve as false subjects with 'pseudo-increased' EMG activity. However, antidepressants using in this study seemed not to confound the results as the results of subgroup analysis after excluding patients who were taking antidepressants did not change.

One may argue that some patients in our present study who showed a relatively lower level of EMG activity than that of a previous report might be not 'true' iRBD patients [8,15]. However, the follow-up video-PSG data confirmed they were 'true' RBD patients. In addition, we should note that some clinical patients with extremely low chin phasic EMG activity, however, they showed substantially EMG activity on limbs channels. We should also note that there were different criteria in scoring amplitude of phasic EMG activity between the study of Frauscher et al., which was employed by ICSD-3 (twice the background) and most of other and our studies (four times the background) [16]. Moreover, a recent study found that there were substantial differences in visual analysis of EMG activity even among expert raters [35]. This may partially explain the great inter-center variability. However, we found the inter-rater reliability was favorable in our sleep center.

We have previous reported that severe daytime sleepiness is associated with a faster conversion of neurodegenerative disease in this RBD cohort [13]. Yet, this study did not find a difference in the mean ESS score between patients with mild and severe RSWA, which suggests a different mechanisms might underlie the sleepiness and RSWA.

Several limitations should be noted when interpreting the findings in the current study. First, although this was one of the largest iRBD cohorts in a single center, the number of patients who developed neurodegenerative diseases was still relatively small, especially in the subgroup analysis regarding the subtypes of neurodegenerative diseases. Second, all neurodegenerative diseases were clinically diagnosed, and the underlying Lewy body pathology was not pathologically confirmed. Nevertheless, standardized clinical diagnosis of neurodegenerative diseases is considered reliable and acceptable according to previous studies [5–8]. Finally, the cut-off employed in the current study for cox regression analysis were derived from the time-dependent ROC curve analysis, which may be also arbitrary.

5. Conclusions and clinical implications

The present study confirmed that increased EMG activity during REM sleep is a reliable biomarker for predicting neurodegenerative diseases, selecting high-risk subjects for further neuroprotective trials, and understanding the subtype of neurodegenerative diseases as related to tonic and phasic EMG activity levels.

Author contributions

Dr YP Liu conceptualized and conducted the data analyses, drafted the initial manuscript, reviewed and revised the manuscript. Drs JH Zhang and YK Wing conceptualized and designed the study, supervised all the aspects of the research project and critically reviewed the manuscript. Ms MWM Yu scored the electromyographic activity of the patients and collected the data of this study. Drs SX Li, NY Chan, SP Lam, JY Zhou, J Wang, and HL Feng managed the data, conducted the data analyses and critically reviewed the manuscript. Drs A Chan and V Mok conceptualized and designed the study and confirmed the diagnoses of neurodegenerative diseases. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Conflict of interest

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