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Association between Restless Legs Syndrome and Sleep Disturbance and 3-Year Mortality in Hemodialysis Patients

Lanbo Teng[a] Huanan Li[b] Yingying Han[a] Tao Yuan[c] Chuhan Xu[d] Tao Tan[b] Wenxiu Chang[a]

[a]Department of Nephrology, Tianjin First Center Hospital, Tianjin, China; [b]Department of Tuina, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, China; [c]Tianjin Medical University, Tianjin, China; [d]Tianjin University of Traditional Chinese Medicine, Tianjin, China

Keywords
Restless legs syndrome · Sleep disturbance · Mortality · Hemodialysis

Abstract
Introduction: Whether restless legs syndrome (RLS) and sleep disturbance (SD) in hemodialysis (HD) patients influence all-cause and cardiovascular mortality remains controversial. The aim of this study was to evaluate the association between RLS or SD and 3-year mortality in HD patients. ***Methods:*** A total of 301 patients who underwent HD were examined in April 2021 and were followed up for 3 years. The median follow-up time was 36.0 [33.3, 36.0] months. Fifty-four patients fulfilled the diagnosis of RLS (17.9%), 126 patients complained of SD (41.9%). Demographic parameters, clinical features, laboratory indices, and two questionnaires to assess the diagnosis of RLS and sleep status were collected. All-cause mortality and cardiovascular mortality in this population were evaluated. Cox regression analyses and Kaplan-Meier curves were performed to determine the effect of RLS or SD on 3-year mortality. ***Results:*** The RLS group reported that 29 patients (53.8%) exhibited concurrent symptoms of SD. The presence of RLS or SD alone did not significantly elevate the risk of all-cause mortality ($p = 0.053$ and $p = 0.193$). However, the coexistence of RLS and SD was identified as an independent risk factor for all-cause mortality ($p = 0.011$). Furthermore, the various combinations associated with RLS or SD were found to be independently correlated with the risk of cardiovascular death ($p < 0.05$). ***Conclusion:*** The combination of RLS and SD in HD patients is associated with an increased risk of cardiovascular and all-cause mortality, underscoring the clinical significance of this association.

Introduction

Restless legs syndrome (RLS) is a sleep-related sensory-motor disorder characterized by intolerable discomforts including sensations of insect crawling, pins and needles, and itching in the deep part of the calf between the knee and ankle joints [1]. The typical manifestation is an unpleasant urge to move the body, particularly during periods of rest, to alleviate the discomfort. The disorder follows a circadian rhythm, with

karger@karger.com
www.karger.com/kdd

Correspondence to:
Tao Tan, 13072240977@163.com
Wenxiu Chang, changwx@sina.com

maximal intensity occurring in the evening. Moving the limb can temporarily relieve the symptoms [2]. It is noteworthy that patients undergoing hemodialysis (HD) represent a group with an elevated risk of developing secondary RLS [3, 4].

The pathophysiology of RLS remains poorly understood. However, evidence suggests that aberrant dopamine pathways within the nervous system play a pivotal role in the development of this syndrome [5]. Furthermore, it has been suggested that certain factors, including anemia, iron deficiency, uremic retention products, oxidative stress, and inflammation, may increase the likelihood of ESRD patients developing RLS. Abnormalities of the central nervous system and peripheral neuropathy, secondary to uremia or the underlying cause of ESRD (such as diabetes), may also contribute to this phenomenon [6].

Indeed, RLS is linked to an elevated risk of a range of adverse conditions, including sleep disturbances (SD), severe anxiety, depression, and fatigue [7]. The symptoms of RLS are exacerbated at night, resulting in patients being roused from sleep. This can lead to SD, which may further exacerbate the emotional changes, particularly in RLS patients with HD [8]. SD is a recognized morbidity in patients with RLS. It has been documented that over 90% of individuals diagnosed with RLS report experiencing difficulties with sleep [9]. The combined impact of RLS and SD on the quality of life of CKD patients is significantly detrimental, with a marked effect on prognosis and an elevated risk of cardiovascular events and mortality [10].

The present study employed a cross-sectional survey methodology to examine the state of RLS and SD among patients undergoing regular maintenance HD treatment at Tianjin First Central Hospital between February 2021 and April 2021. A subsequent 3-year follow-up period was then conducted to record any deaths that may have occurred. The objective was to evaluate the association between RLS or SD status, as well as their coexistence, and 3-year cardiovascular and all-cause mortality.

Material and Methods

Study Population

This present study was conducted at Tianjin First Central Hospital and data were collected from February 2021 to April 2021. Informed consent from participants was obtained from participants before a face-to-face interview. After data collection was completed, we designed a 3-year prospective surveillance to record deaths and causes of death during the follow-up period to April 2024.

Inclusion criteria were age 18 years or older, taking HD for at least 3 months, with 2–3 times per week for 4 h each time. Exclusion criteria were as follows: patients with (1) Parkinson's disease or psychosis; (2) impaired cognition unable to answer the questionnaires; (3) peripheral neuropathy; (4) secondary RLS such as pregnancy, narcolepsy; (5) diagnosis of RLS before starting HD; (6) unstable conditions such as severe infections; (7) missing or incomplete information; (8) lost to follow-up during the study period. After applying the criteria, 301 participants were included in the final analysis.

Data Collection

We collected patients' demographic and clinical data from electronic medical records, including sex, age, original disease, height, body weight, systolic blood pressure (SBP), comorbid conditions such as hypertension and diabetes mellitus and residual renal function. SBP was measured at the dialysis center before the dialysis session. Biochemical data included hemoglobin (Hb), blood urea nitrogen, creatinine (Cr), β_2-microglobulin, serum calcium (Ca), inorganic phosphorus (P), serum ferritin (SF), hypersensitive C-reactive protein, and intact parathyroid hormone (iPTH). All blood samples were analyzed using commercially available kits and an automated analyzer (Cobas 8000 or e411 for iPTH, Roche Diagnostics Ltd. for others, Germany).

HD information included the total HD duration and dialysis adequacy (single pool total urea clearance index). All patients used dialyzers with a surface area of 1.3/1.5/1.6 m^2. Information on comorbidity such as previous illnesses and hyperparathyroidism was obtained from medical records. Corresponding drug treatments were recorded including antihypertensive agents, erythropoietin et al. This study allowed the use of iron agents, phosphorus binders, gabapentin, pregabalin, and benzodiazepines agents.

Questionnaire Survey

We used a questionnaire survey to assess patients' diagnosis of RLS and sleep status. Patient interviews and assessments were conducted by a designated physician to minimize inter-investigator variability. All interviews were performed on site within the dialysis facilities.

The 2003 International Legs Syndrome Study Group (IRLSSG) diagnostic criteria was used to diagnose RLS in participants [11]. The following four essential criteria must be met to diagnose RLS: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and

unpleasant sensations in the legs; (2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting; (3) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues, and (4) the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

In addition, the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality in the past month. Patients with a score greater than 10 were classified as SD group and those with a score less than or equal to 10 were classified as un-SD group.

Primary Endpoint

The primary outcomes of the study were all-cause mortality and cardiovascular mortality during 3-year of follow-up. All-cause mortality is defined as death from any cause by 30 April 2024. CVD mortality is defined as death from cardiovascular causes and not from non-cardiovascular or unspecified causes.

Statistical Analysis

Normally distributed continuous variables were presented as mean ± standard deviation (SD), non-normally distributed continuous variables as medians and interquartile ranges, and categorical variables as frequencies and percentages. Comparisons of continuous variables were analyzed by independent *t* test or Mann-Whitney U test. Chi-squared test was used for the categorical variables.

All patients were divided into RLS and un-RLS groups based on the presence or absence of RLS symptoms. Similarly, based on the PSQI sleep score, the participants were divided into SD and un-SD groups. Furthermore, according to the combination of RLS, un-RLS, SD, and un-SD, the patients were divided into the following four groups: RLS+SD (n = 29), RLS+un-SD (n = 25), un-RLS+SD (n = 97), un-RLS+un-SD (n = 150).

Univariate and multivariate Cox regression analyses were performed to determine the adjusted hazard ratio (aHR) and 95% confidence interval (CI) between categorical groups and all-cause and cardiovascular mortality. We performed survival analysis using standardized Kaplan-Meier curves with the log-rank test to compare the cumulative probability risk of all-cause and cardiovascular mortality between categorical groups. All statistical analyses were performed using SPSS version 22 (IBM, Japan) and STATA version 14 (Stata Corp LP, College Station, TX, USA). A p value of less than 0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics of RLS and Un-RLS Patients

Table 1 shows the general characteristics and scale scores of the enrolled patients with and without RLS. The study included 301 patients, of which 54 patients were diagnosed with RLS (17.9%) and 126 patients with SD (41.9%). The RLS group reported 29 (53.8%) patients with concurrent SD symptoms, and the un-RLS group reported 97(39.3%) patients. This suggests that the RLS group is more prone to SD.

We compared the clinical characteristics between the different groups. There were no differences between the RLS and un-RLS groups in age, sex, HD duration, original disease and the proportion of diabetes/hypertension, SBP, and body mass index (BMI). Similarly, no differences were found in Hb, blood urea nitrogen, Cr, β_2-microglobulin, Ca, P, SF, and iPTH. In items of scale scores, the PSQI score was higher in the RLS group than in the un-RLS group (11.0 [8.0, 14.0] vs. 8.0 [7.0, 12.0], p = 0.002), which meant that the RLS group had poorer sleep quality. However, there were still 46.2% of patients without SD (RLS+un-SD, or the RLS-only group), so the PSQI score of these patients were lower than 10 points, which was the cut-off value for the diagnosis of SD. This meant that not all RLS patients developed SD symptoms.

Associations between Various Comorbidities of RLS or SD and All-Cause Mortality

During the 3-year follow-up period, the median follow-up time was 36.0 [33.3, 36.0] months. A total of 52 deaths occurred in this study, including 24 cardiovascular deaths. There were 13 deaths in the RLS group, of which 9 died from cardiovascular disease. There were 39 deaths in the un-RLS group, of which 15 were due to cardiovascular disease. In our study, 3-year all-cause mortality was 17.3%, cardiovascular mortality was 8.0%.

We performed univariate and multivariate Cox regression analysis on the risk factors for all-cause mortality. Sex, age, original disease, SBP, BMI, HD duration, Hb, ALB, Scr, β_2-microglobulin SF, Ca, P, iPTH, hypersensitive C-reactive protein, single pool total urea clearance index, residual renal function, use of phosphorus binders, and use of iron supplements were adjusted in the multivariate model, which finally showed that patients with only RLS or only SD did not increase the risk of all-cause mortality. However, when RLS and SD coexisted, patients with this comorbidity state (RLS+SD) had a higher risk of all-cause mortality than those without RLS and SD, with an aHR (95% CI) of 3.18

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Table 1. Clinical characteristics and score of the scales among RLS groups (n = 301)

Characteristic	RLS group (n = 54)				un-RLS group (n = 247)				p value#
	all	RLS+SD (n = 29)	RLS +un-SD (n = 25)	p value*	all	un-RLS+SD (n = 97)	un-RLS+un-SD (n = 150)	p value*	
Age, years	53.0±13.2	54.3±13.6	51.5±12.8	0.437	53.2±12.7	54.0±13.0	52.7±12.4	0.436	0.914
HD duration (m)	60.0 [24.8, 99.0]	60.0 [25.0, 102.0]	66.0 [24.0, 96.0]	0.715	72.0 [36.0, 108.0]	72.0 [40.0, 104.0]	72.0 [32.3, 120.0]	0.713	0.313
Gender, male, n (%)	33 (61.1)	17 (58.6)	16 (64.0)	0.783	171 (69.2)	64 (66.0)	107 (71.3)	0.399	0.263
Original disease, n (%)				0.063				0.835	0.498
Glomerulonephritis	27 (50.0)	15 (51.7)	12 (48.0)		147 (59.5)	56 (57.7)	91 (60.7)		
Diabetic nephropathy	8 (14.8)	1 (3.4)	7 (28.0)		40 (16.2)	18 (18.6)	25 (16.7)		
Hypertensive nephropathy	12 (22.2)	8 (27.6)	4 (16.0)		43 (17.4)	18 (18.6)	22 (14.7)		
Polycystic kidney	4 (7.4)	2 (6.9)	2 (8.0)		10 (4.0)	3 (3.1)	7 (4.7)		
Others	7 (2.8)	3 (10.3)	0 (0.0)		3 (5.6)	2 (2.1)	5 (3.3)		
DM, n (%)	11 (20.4)	2 (6.9)	9 (36.0)	0.015	61 (24.7)	27 (27.8)	34 (22.7)	0.369	0.599
Hypertension, n (%)	47 (87.0)	25 (86.2)	22 (88.0)	1.000	232 (93.9)	89 (91.8)	143 (95.3)	0.282	0.087
SBP, mm Hg	144.5±20.4	143.0±19.9	146.3±21.3	0.569	148.4±20.7	148.9±22.3	148.1±19.8	0.789	0.224
BMI, kg/m^2	22.5±3.9	22.5±4.2	22.5±3.5	0.988	22.7±4.3	23.1±5.0	22.4±3.8	0.256	0.736
spKT/V	1.3 [1.2–1.5]	1.3 [1.2, 1.4]	1.3 [1.2–1.5]	0.541	1.3 [1.2, 1.4]	1.2 [1.2, 1.3]	1.3 [1.2, 1.5]	0.001	0.960
RRF, mL/min	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.653	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.880	0.800
Blood parameters									
Hb, g/dL	111.7±13.4	113.1±14.1	110.0±12.6	0.402	113.3±13.5	112.5±13.2	113.8±13.8	0.488	0.430
Alb, g/dL	40.2±3.0	40.4±3.6	39.9±2.2	0.627	40.8±3.4	40.9±3.7	40.7±3.2	0.655	0.211
BUN, mmol/L	24.4±7.0	23.7±7.8	25.2±6.0	0.434	25.2±5.6	25.5±6.0	25.0±5.4	0.500	0.364
Cr, μmol/L	920.1±259.3	894.3±261.1	949.9±259.3	0.437	920.5±22–0.1	907.5±208.5	928.8±232.2	0.465	0.991
Ca, mg/dL	2.3±0.2	2.3±0.2	2.3±0.3	0.940	2.2±0.2	2.3±0.2	2.2±0.2	0.127	0.577
P, mg/dL	2.1±0.7	2.1±0.8	2.0±0.6	0.368	2.0±0.6	2.0±0.6	2.0±0.6	0.857	0.654
β_2-MG, mg/L	44.5 [34.7, 50.3]	44.0 [33.7, 48.7]	45.0 [36.3, 52.8]	0.633	45.6 [37.4, 52.4]	45.9 [37.8, 51.3]	45.4 [37.0, 52.8]	0.817	0.339
iPTH, pg/mL	323.3 [195.7, 618.3]	359.5 [203.0, 673.2]	318.3 [162.7, 602.7]	0.420	315.6 [162.9, 511.8]	351.9 [188.6, 630.6]	285.7 [154.0, 473.0]	0.051	0.325
SF, ng/mL	152.5 [54.6, 304.3]	149.0 [43.9, 237.0]	163.0 [86.5, 313.5]	0.143	176.0 [71.8, 298.0]	170.0 [75.2, 291.0]	183.5 [67.8, 310.5]	0.686	0.399
hsCRP	4.8 [1.5–11.4]	5.0 [1.6, 9.6]	4.2 [1.2, 13.0]	0.748	3.0 [1.2, 7.6]	3.8 [1.6, 8.2]	2.6 [1.2, 7.5]	0.246	0.204
PSQI score	11.0 [8.0, 14.0]	14.0 [12.0, 16.0]	8.0 [6.0, 9.0]	< 0.001	8.0 [7.0, 12.0]	12.0 [11.0, 14.0]	7.0 [6.0, 8.0]	<0.001	0.002
Treatment, n (%)									
Use of phosphorus binders	54 (100)	29 (100)	25 (100)	–	247 (100)	97 (100)	150 (100)	–	–
Use of iron supplements	46 (85.2)	24 (82.8)	22 (88.0)	0.547	213 (86.2)	84 (86.6)	129 (86.0)	0.436	0.192

RLS, restless legs syndrome; SD, sleep disturbance; HD, hemodialysis; DM, diabetes mellitus; SBP, systolic blood pressure; BMI, body mass index; spKT/V, single pool total urea clearance index; RRF, residual renal function; Hb, hemoglobin; Alb, albumin; BUN, blood urea nitrogen; Cr, creatinine; Ca, calcium; P, phosphorus; β_2-MG, β_2-microglobulin; iPTH, intact parathyroid hormone; SF, serum ferritin; hsCRP, hypersensitive C-reactive protein; PSQI, Pittsburgh Sleep Quality Index. *Independent sample t test, Mann-Whitney U test, χ^2 test or Fisher's exact test as appropriate between patients with or without sleep disorders. #Independent sample t test, Mann-Whitney U test, χ^2 test or Fisher's exact test as appropriate between RLS group and un-RLS group.

(1.31–7.73) (Table 2). This study confirmed that the coexistence of RLS and SD was an independent risk factor for all-cause mortality.

Associations between Various Comorbidities of RLS or SD and Cardiovascular Mortality

Using the same statistical methods, we investigated the effect of different comorbidity states of RLS and SD on cardiovascular death in HD patients. Table 3 summarized the following statistical results. RLS and SD were two independent risk factors for cardiovascular mortality with an aHR (95% CI) of 4.20 (1.61–10.93) and 2.74 (1.15–6.47), respectively. The coexistence of RLS and SD (RLS+SD) also increased the risk of cardiovascular death compared to those without RLS and SD, with an aHR (95% CI) of 8.94 (2.09–38.27). In conclusion, the different comorbidity states of RLS and SD were independently correlated with the risk of cardiovascular death.

Comparison of All-Cause and Cardiovascular Survival among Different Groups

Kaplan-Meier curves were used to compare the cumulative probability of all-cause and cardiovascular survival during the follow-up period in all patients. As shown in the Kaplan-Meier survival curves (Fig. 1), the coexistence of RLS and SD (RLS+SD) significantly decreased all-cause survival in HD patients compared to un-RLS+un-SD ($p = 0.010$). However, RLS+un-SD and un-RLS+SD, in other words, RLS alone and SD alone had no effect on all-cause survival.

In contrast to overall survival, we found significant statistical differences in the likelihood of cardiovascular survival between the different groups. Compared to un-RLS patients, RLS patients had a lower probability of cardiovascular survival (log rank $p = 0.0073$). SD and un-SD showed similar results (log rank $p = 0.0293$). In other words, the presence of RLS or SD alone increased the risk of cardiovascular death in HD patients. In addition, compared to the un-RLS+un-SD group, the other three groups increased the likelihood of cardiovascular death in patients in the RLS+un-SD group, or un-RLS+SD group and RLS+SD group, respectively (log rank $p = 0.007$, 0.025, and 0.001, respectively). Notably, patients with coexisting RLS and SD (RLS+SD) had the lowest cardiovascular survival.

Discussion

The current study showed that RLS and SD were common in HD patients, and more than half of RLS patients coexisted with SD, resulting in poorer sleep. The coexistence of RLS and SD was confirmed as an independent risk factor for all-cause and cardiovascular mortality.

In recent years, the epidemiology of RLS has been reported more frequently, and the prevalence has varied considerably. Giannaki et al. [12] reported a prevalence of RLS ranging from 20% to 73% in HD patients. In comparison, Matar et al. [13] reported a prevalence of 30% in global databases. The recent meta-analysis showed that the global prevalence of RLS in HD patients was 27.2%, which was remarkably higher compared to the general adult population (3%) [14, 15]. Our results showed a lower RLS prevalence (17.9%) than recent global data. The differences may be due to differences in sample size, method of data collection, gender, race, diagnostic criteria, and geographical region.

Sleep, as a health-related behavior, is thought to play an important role in regulating complex physiological processes that are essential for maintaining metabolic homeostasis. HD patients have been shown to have varying degrees and types of sleep disturbance. The main manifestations are difficulty falling asleep (84.5%), insomnia and excessive daytime sleepiness. In one survey, 65% of HD patients reported SD [16]. RLS is also a risk factor for poor sleep quality in patients with CKD. Patients with ESRD and RLS had significantly higher PSQI scores than those without RLS [17]. Therefore, RLS is an important cause of SD in ESRD patients, which affects mental health and is associated with increased cardiovascular risk. Conversely, SD may influence the presence or clinical severity of RLS. It can be assumed that RLS and SD interact and exacerbate each other. In this study, the overall prevalence of SD among all patients was 41.9%, which is lower than the 65% mentioned above. However, 53.8% of patients in the RLS group reported SD, exceeding the un-RLS group (39.3%), which supported a significant association between RLS and SD.

The risk of death in dialysis patients is high but varies greatly from patient to patient. Length of follow-up also affects mortality. A study in the UK showed that the 3-year all-cause mortality in dialysis patients (HD and peritoneal dialysis) was 29.7% [18]. The data from the study of Dimitrijevic et al. [19] was 23.9%. He also reported a cardiovascular mortality of 17.4% [19]. In our study, the 3-year all-cause mortality was 17.3% and the cardiovascular mortality was 8.0% in all HD patients.

Several studies have reported a possible association between RLS and all-cause and cardiovascular mortality in HD patients, but the results are inconsistent

Table 2. The correlations of RLS and SD with all-cause mortality in HD patients (n = 301)

Parameter	Model 1			Model 2			Model 3		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
RLS	1.61	0.86–3.01	0.139	1.62	0.86–3.06	0.139	1.98	0.93–4.09	0.053
SD	1.69	0.98–2.92	0.058	1.80	1.04–3.12	0.036	1.53	0.81–2.92	0.193
Four groups									
RLS+SD	2.53	1.15–5.56	0.021	2.75	1.20–6.27	0.016	3.18	1.31–7.73	0.011
RLS+un-SD	1.26	0.43–3.70	0.669	1.26	0.42–3.76	0.674	1.20	0.32–4.57	0.785
un-RLS+SD	1.53	0.82–2.87	0.183	1.63	0.87–3.08	1.634	1.22	0.57–2.61	0.617
un-RLS+un-SD	Reference			Reference			Reference		

Model 1: univariate. Model 2: adjusted for sex, age, original disease, DM, hypertension, SBP, BMI, HD duration. Model 3: adjusted for sex, age, original disease, DM, hypertension, SBP, BMI, HD duration, Hb, ALB, Scr, β_2-MG, Ca, P, iPTH, SF, hsCRP, spKT/V, RRF, use of phosphorus binders, and use of iron supplements. RLS, restless legs syndrome; SD, sleep disturbance.

Table 3. The correlations of RLS and SD with cardiovascular mortality in HD patients (n = 301)

Parameter	Model 1			Model 2			Model 3		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
RLS	2.87	1.26–6.56	0.012	3.20	1.37–7.44	0.007	4.20	1.61–10.93	0.003
SD	2.41	1.05–5.50	0.037	2.58	1.12–5.92	0.026	2.74	1.15–6.47	0.044
Four groups									
RLS+SD	5.59	1.62–19.31	0.007	6.49	1.78–23.65	0.005	8.94	2.09–38.27	0.003
RLS+un-SD	4.98	1.34–18.55	0.017	5.72	1.48–22.16	0.012	6.92	1.33–26.15	0.022
un-RLS+SD	3.20	1.10–9.37	0.034	3.46	1.18–10.16	0.024	4.12	1.12–11.45	0.045
un-RLS+un-SD	Reference			Reference			Reference		

Model 1: univariate. Model 2: adjusted for sex, age, original disease, DM, hypertension, SBP, BMI, HD duration. Model 3: adjusted for sex, age, original disease, DM, hypertension, SBP, BMI, HD duration, Hb, ALB, Scr, β_2-MG, Ca, P, iPTH, SF, hsCRP, spKT/V, RRF, use of phosphorus binders, and use of iron supplements. RLS, restless legs syndrome; SD, sleep disturbance.

and do not allow convincing conclusions. La Manna et al. [20] suggested that RLS was associated with worse cardiovascular outcomes and increased the risk of new cardiovascular events and death [21]. AUS queue study showed that RLS was associated with increased all-cause mortality in ESRD patients, but not with cardiovascular mortality [22]. In contrast, Stefanidis et al. [23] and Santos et al. [24] reported that RSL did not influence the 3-year mortality rate in HD patients. Furthermore, a 15-year follow-up study showed that mortality in HD patients was not influenced by concomitant RLS [25].

According to the literature, SD has been associated with increased cardiovascular risk and may contribute to mortality in people with ESRD and those on dialysis [7, 26]. In HD patients, poor sleep quality has also been shown to be an important predictor of all-cause mortality [27]. RLS is characterized by insufficient and disturbed sleep, which in turn affects a variety of physiological and psychological parameters that may be associated with increased mortality. In addition, comorbidities, such as diabetes, hypertension, iron deficiency and anemia may increase the risk of mortality and CV events in HD patients with RLS. Furthermore, RLS plays an important role in sympathetic hyperactivity, which leads to non-dipping nocturnal blood pressure and atherosclerotic plaque rupture, resulting in cardiac disease [28]. Theoretically, the combination of RLS and SD should have adverse effects on the cardiovascular outcomes and long-term prognosis of HD patients.

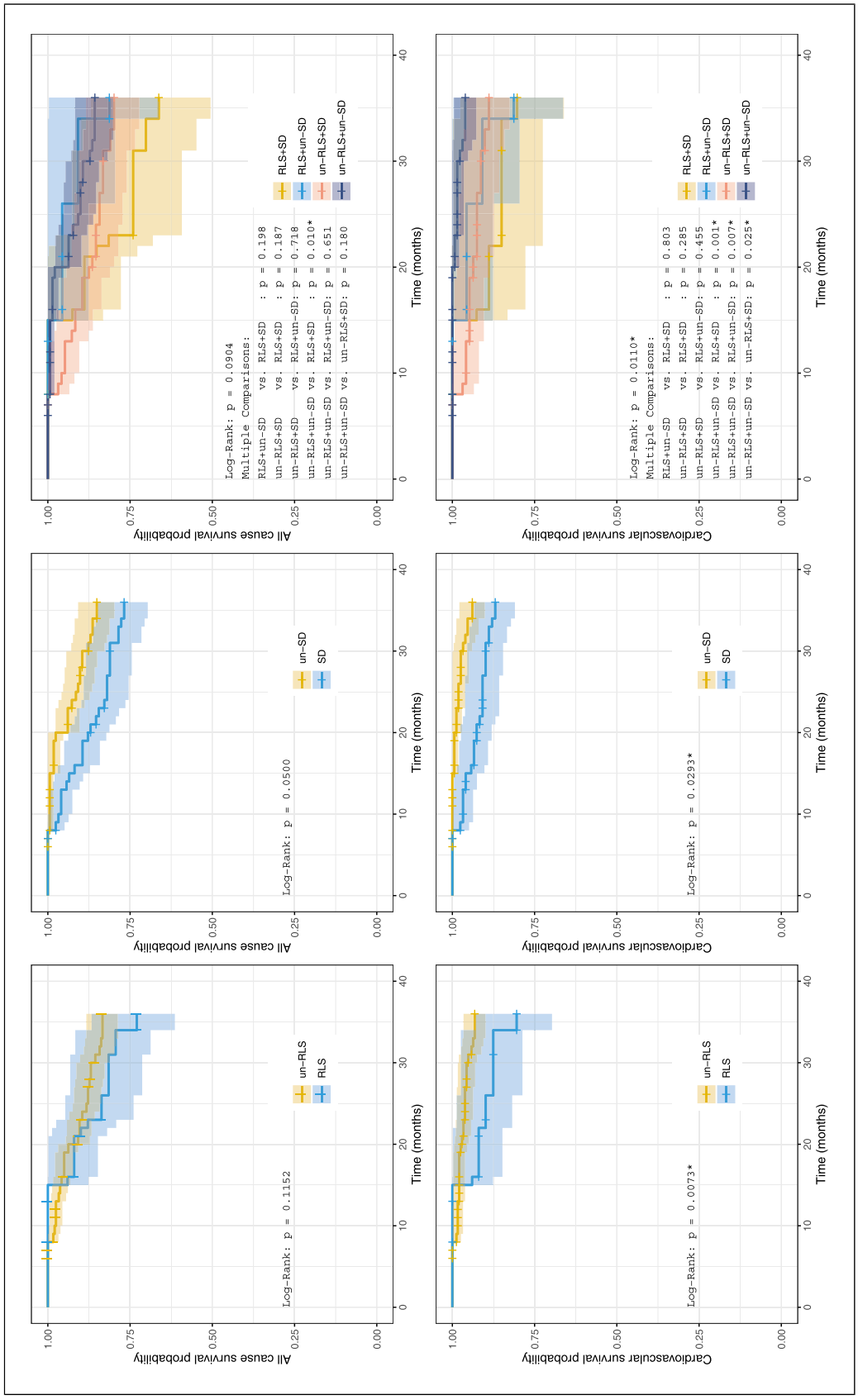

Fig. 1. Kaplan-Meier estimates of cardiovascular and all-cause mortality at 3 years for patients with and without RLS, SD or coexistence. The subgroups are RLS and un-RLS groups, SD and un-SD groups, as well as different combination states of RLS and SD (RLS+SD, RLS+un-SD, un-RLS+SD, and un-RLS+un-SD), respectively. The first row shows the comparison for all-cause survival, the second row for cardiovascular survival. The first and second columns show that the presence of RLS or SD alone can reduce the likelihood of cardiovascular survival, but not for all-cause survival in HD patients. The third column shows the *p* values for pairwise comparisons. When RLS and SD coexisted (RLS+SD), patients had the lowest all-cause and cardiovascular survival in the following life. RLS, restless legs syndrome; SD, sleep disturbance.

With this in mind, we examined the effect of the clinical status of RLS and SD on all-cause mortality using multivariate Cox regression analyses. Patients with only RLS or only SD did not have an increased risk of all-cause mortality which is consistent with some previous research [23–25]. However, compared with patients without RLS and SD, patients with the coexistence of RLS and SD showed an independent association with the risk of all-cause mortality after 3 years of follow-up. Furthermore, the Kaplan-Meier analysis showed a lower survival probability in patients with RLS and SD concurrent compared with patients without RLS and SD, with a symmetric trend of mortality in both the groups at any time point. Therefore, we proposed that RLS has an impact on all-cause mortality only when coexisting with SD in HD patients. All-cause mortality in HD patients is not influenced by the presence of RLS alone, nor by the presence of SD.

Using the same statistical methods, we demonstrated a significant association between the different co-morbidity states of RLS or SD and cardiovascular mortality. The presence of RLS or SD alone was an independent risk factor for cardiovascular death, and the coexistence dramatically increased the impact weight on cardiovascular death. HD patients with RLS, SD, or RLS+SD would have a lower likelihood of survival. This was consistent with most previous research [10]. Therefore, either RLS or SD on the long-term prognosis of patients should not be underestimated or ignored. Particularly, coexistence should be given more attention and active intervention. This is one of the clinical implications of this study.

As mentioned above, the effect of RLS on survival is controversial in the literature, as is SD. In this study, we found that the presence of RLS or SD alone was only an independent risk factor for cardiovascular mortality, but not for all-cause mortality. The coexistence is a common independent risk factor for both cardiovascular mortality and all-cause mortality. The reasons are considered as follows. There are many influencing factors for all-cause mortality, the existence of RLS or SD alone has a relatively small impact on all-cause mortality, so a positive result cannot be obtained. The combination of the two strengthens the weight of the effect on all-cause mortality, which in turn produces a synergistic effect and obtains a positive result. Cardiovascular mortality is limited to direct death caused by cardiovascular disease, the influencing factors are much less than that of all-cause death, the weight of the RLS or SD alone on cardiovascular mortality appears to be larger. So, a positive result was obtained. This effect is amplified by the combination of the RLS and SD; therefore, the result is still positive.

Our study had several limitations. First, the questionnaire survey is mainly subjective in nature and may result in interobserver variability in scoring. Second, we did not differentiate the effect of RLS severity on mortality. Third, the study population was homogenous; all patients were Chinese. Therefore, extrapolation of the results to other populations may be biased. Fourth, the generalization of the results obtained may be biased due to the single-center design. The present results should be confirmed in prospective multicenter studies.

Conclusion

In this 3-year survival follow-up study of HD patients, we confirmed that RLS or SD alone was associated with only cardiovascular mortality but not with all-cause mortality. However, the coexistence of RLS and SD was a common and serious risk factor for both cardiovascular mortality and all-cause mortality. Clinicians need to pay more attention to RLS and SD. Proper and timely management of RLS or SD, especially their coexistence, can not only improve patients' quality of life, but also greatly improve their long-term prognosis. This is a work of significant importance. With the guidance of a doctor, appropriate supplementation of iron, taking dopamine receptor agonists, forming and maintaining good sleep habits, and moderate aerobic exercise are all beneficial for ameliorating RLS or SD.

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Statement of Ethics

Verbal consent was obtained from participants before a face-to-face interview. This protocol in the study was approved by the Institutional Review Board of Tianjin First Center Hospital (IRB; ethics approval document No. 2023DZX52) and the Ethics Committee approved the method of verbal consent. The protocol was conducted in accordance with the principles of the Helsinki Declaration.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.T. and H.L. drafted the manuscript. W.C. and T.T. critically reviewed the manuscript. H.L., C.X., and T.Y. collected the data. L.T. and Y.H. critically reviewed data and management. T.T. performed English editing. W.C. performed statistical analysis. T.T. critically reviewed the statistical data. All authors read and approved the final manuscript.

Data Availability Statement

This paper contains all of the data generated or analyzed during the study. Any further queries should be directed to the corresponding author.

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