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Risk factors for restless legs syndrome in hemodialysis patients in Taiwan

A case–control study

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Abstract

Restless legs syndrome (RLS) increases the risks of cardiovascular disease and death in hemodialysis (HD) patients. Previous studies of risk factors for RLS in HD patients have yielded varying results. We attempted to identify risk factors for RLS in HD patients in Taiwan.

This case–control study recruited 59 HD patients with RLS and 353 HD patients without RLS from the largest HD center in Taiwan during the period from April 1, 2015 through August 31, 2015. Demographic and disease characteristics, information from the International Restless Legs Syndrome Study Group (IRLSSG) diagnostic questionnaire, and IRLSSG Severity Scale scores were collected by interview. Clinical laboratory data were abstracted from medical records and then analyzed with logistic regression and Pearson correlation analysis. A P value of less than .05 was considered to indicate statistical significance.

A dialysis duration of longer than 5 years (odds ratio [OR] = 2.32; 95% CI = 1.23–4.39; $P = .002$) and a low high-density lipoprotein cholesterol level (<40 mg/dL in men; <50 mg/dL in women) (OR = 2.73; 95% CI = 1.44–5.15; $P = .009$) were associated with increased risk of RLS. Among the 59 patients with RLS, 48 (81.3%) had moderate or severe symptoms (IRLSSG Severity Scale >10), and RLS severity was significantly correlated with dialysis duration ($r = .26$; $P = .043$).

Among HD patients, RLS was more common among those receiving dialysis for longer than 5 years and those with a low serum high-density lipoprotein cholesterol (HDL-C) level.

Abbreviations: BMI = body mass index, Fe = iron, HDL-C = high-density lipoprotein cholesterol, iPTH = intact parathyroid hormone, LDL-C = low-density lipoprotein cholesterol, RLS = restless legs syndrome, TIBC = total iron-binding capacity, TSAT = percent transferrin saturation.

Keywords: hemodialysis, high-density lipoproteins (HDL), restless legs syndrome (RLS)

1. Introduction

Restless legs syndrome (RLS), also known as Will–Ekbom disease, is a neurological sensorimotor disorder associated with pathological changes – particularly iron deficiency – in motor and sensory brain areas. Other biological systems, including the dopaminergic, oxygen-sensing, opioid, glutamatergic, and serotonergic systems, have been implicated.[1,2] RLS patients experience discomfort in their legs or other body parts. Symptoms include numbness, swelling, tightness, soreness, itching, burning, pain, wormian sensation, and other unusual feelings, which cause affected persons to move their limbs to lessen the discomfort. Patients usually experience from discomfort when resting, immobile, or sleeping.[1,3] RLS can be classified as primary or secondary, depending on the cause. Primary RLS is strongly related to genetic background: about 60% of patients have a family history of RLS. Secondary RLS is more common among persons with end-stage renal disease (ESRD), iron deficiency, pregnancy, and Parkinson disease.[4,5]

Secondary RLS is most strongly associated with ESRD. Hemodialysis (HD) is the most common treatment for ESRD patients, and the prevalence of RLS is 19.4% to 57.3% in HD patients.[4,6–10] RLS is associated with worse cardiovascular disease outcomes and increases the risks of new cardiovascular events and death in HD patients.[8,11,12] Identifying risk factors for RLS in HD patients is therefore important in providing

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optimal care. However, the underlying cause for the increased prevalence of RLS in HD patients is unclear. Previous studies investigated associations of RLS with HD patient sex, age, dialysis duration, HD timing, history of type 2 diabetes, history of cardiovascular disease, body mass index (BMI), serum hemoglobin level, serum iron level, serum ferritin level, serum transferrin saturation (TSAT) level, and intact parathyroid hormone (iPTH) level.[4,6–10,13,14] Unfortunately, the results of these studies were inconsistent or conflicting. Dyslipidemia is more common in persons with chronic kidney disease (CKD), and hypertriglyceridemia is present in about 50% of CKD patients. Although concentrations of serum total cholesterol and low-density lipoprotein cholesterol (LDL-C) were normal or high in this subgroup, high-density lipoprotein cholesterol (HDL-C) levels were low.[15] Lipid profile (triglyceride [TG], total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], and HDL-C) was reported to be a risk factor for RLS in the general population[16,17]; however, because few studies have investigated the relation between lipid profile and RLS in HD patients, this association deserves further investigation. In Taiwan, hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection are endemic (prevalence rates, 15–20% and 2–3%, respectively) in the general adult population.[18] The role of hepatitis virus in RLS among HD patients thus warrants further study.

Taiwan has the highest incidence and prevalence of ESRD in the world[4] (493 and 3392 persons per million, respectively, in 2016). In 2016, there were 79,848 ESRD patients, and 71,623 (89.7%) were receiving HD treatment.[19] Lin et al investigated risk factors for RLS in HD patients in Taiwan[4] but did not investigate the effects of BMI, serum lipid profile, HBV, HCV, or liver disease on RLS incidence. The present study therefore investigated risk factors for RLS in HD patients in the largest HD center in Taiwan. The findings should prove useful in the medical care of this population.

2. Methods

2.1. Setting and sample

Patients at least 20 years of age who received HD for longer than 3 months were invited to participate at the HD center of X Hospital, Northern Taiwan, from April 1, 2015 through August 31, 2015. Those who consented to participate underwent face-to-face interviews to collect information on demographic characteristics, disease history, dialysis information (duration), BMI, and RLS syndrome. Clinical laboratory data were abstracted from their most recent medical records.

2.2. Ethical considerations

The Institutional Review Board of the study hospital approved this study (103-7670B). All participants signed a consent form after the purpose of the study was explained to them.

2.3. Measurements

2.3.1. RLS status. The diagnostic criteria developed by the International Restless Legs Syndrome Study Group (IRLSSG) in 2003 were used for RLS diagnosis. During the face-to-face interviews, every participant was asked the following four questions:

(1) "During the past month, have you had any uncomfortable sensations or an urge to move your legs at rest?";
(2) "During the past month, did the uncomfortable sensations or urge to move your legs occur or worsen when you were sitting or lying down?";
(3) "During the past month, were the uncomfortable sensations or urge to move your legs relieved by movement – by walking around, for example?";
(4) "During the past month, did the uncomfortable sensations or urge to move your legs worsen during the evening or night, when compared with the daytime?".

RLS was diagnosed when a patient answered affirmatively to all 4 questions.[1] Patients who answered negatively to all 4 questions were classified as non-RLS patients. Those who answered affirmatively to any of the 4 questions underwent further assessment of RLS severity. The severity of RLS questionnaire consists of 10 items with a scale of 0 (no impact) to 4 (very severe impact) for each item. RLS severity was defined as mild (0–10 points), moderate (11–20 points), severe (21–30 points), or very severe (31–40 points) RLS.[20]

2.3.2. Demographics and disease characteristics. During face-to-face interviews, information was collected on demographic characteristics (sex, age, employment status, marriage, number of children, and educational status), disease characteristics (including dialysis duration, HD shift [morning, afternoon, and night]), and comorbidities (diabetes, hypertension, heart diseases, liver disease, and hepatitis B/C).

2.3.3. BMI and clinical laboratory data. BMI was calculated as body weight (kg)/[body height (m)]^2 and categorized as normal (18.5–24 kg/m^2) and abnormal (<18.5 or >24 kg/m^2). All HD patients at the study center underwent clinical laboratory testing every 3 months, and the most recent laboratory test results were abstracted from medical records, including TC, TG, LDL-C, HDL-C, hemoglobin, iron (Fe), ferritin, total iron-binding capacity (TIBC), TSAT, and iPTH.

2.4. Study design

A case–control study design was used. RLS cases were those who answered affirmatively to all 4 questions on the IRLSSG. The controls (non-RLS patients) were those who answered negatively to all 4 questions on the IRLSSG.

2.5. Data analysis

Frequency, percentage, mean, and standard deviation were used to describe the demographic and disease characteristics of patients and their laboratory results, BMI, and RLS severity. The independent *t* test, chi-square test, and chi-square test for trend were used to compare data between RLS and non-RLS patients, where appropriate. Variables with a *P* value of less than .1 in univariate analysis were entered into multiple logistic regression. Forward selection was then used to identify significant risk factors for RLS. Odds ratios (ORs) with 95% CIs were calculated to indicate RLS risk. Pearson correlation and multiple linear regression were used to quantify the linear magnitude of RLS severity with respect to dialysis duration and HDL-C level. A *P* value of less than .05 was considered to indicate statistical significance.

3. Results

From April 1 through August 31, 2015, a total of 823 patients received HD in the study hospital; 330 refused to participate in

Table 1

Demographic and disease characteristics between cases (RLS) and controls (non-RLS) of hemodialysis patients.

Variables	Total (n = 412)	RLS (n = 59)	Non-RLS (n = 353)	P
Gender				.41†
Male	223 (54.1%)	29 (49.1%)	194 (54.9%)	
Female	189 (45.8%)	30 (50.8%)	159 (45.0%)	
Age (years)	58.67 ± 12.23	56.59 ± 11.83	59.02 ± 12.27	.16‡
<40	38 (9.2%)	7 (11.8%)	31 (8.7%)	.09§
41–64	260 (63.1%)	41 (69.4%)	219 (62.0%)	
≥65	114 (27.6%)	11 (18.6%)	103 (29.1%)	
Education				.68§
Illiterate and Elementary	158 (38.3%)	20 (33.9%)	138 (39.0%)	
Junior and senior high	174 (42.2%)	28 (47.4%)	146 (41.3%)	
College or above	80 (19.4%)	11 (18.6%)	69 (19.5%)	
Employed				.34†
No	300 (72.8%)	46 (77.9%)	254 (71.9%)	
Yes	112 (27.1%)	13 (22.0%)	99 (28.0%)	
Marital status				.03†,*
Single	47 (11.4%)	10 (16.9%)	37 (10.4%)	
Married	358 (86.8%)	46 (77.9%)	312 (88.3%)	
Divorced, widowed, separated	7 (1.7%)	3 (5.0%)	4 (1.1%)	
Children				.13§
0	68 (16.5%)	12 (20.3%)	86 (15.8%)	
1–3	258 (62.6%)	39 (66.1%)	219 (62.0%)	
≥4	86 (20.8%)	8 (13.5%)	78 (22.1%)	
Dialysis duration (years)	8.30 ± 7.26	9.83 ± 7.56	8.04 ± 7.19	.08‡
<5	162 (39.3%)	16 (27.1%)	146 (41.3%)	.04†,*
≥5	250 (60.6%)	43 (72.8%)	207 (58.6%)	
Shift of dialysis				.26†
Morning	125 (30.3%)	19 (32.3%)	106 (30.0%)	
Afternoon	138 (33.5%)	24 (40.6%)	114 (32.2%)	
Evening	149 (36.1%)	16 (27.1%)	133 (37.6%)	
Diabetes				.59†
No	278 (67.4%)	38 (64.4%)	240 (67.9%)	
Yes	134 (32.5%)	21 (35.5%)	113 (32.0%)	
Hypertension				.58†
No	160 (38.8%)	21 (35.5%)	139 (39.3%)	
Yes	252 (61.1%)	38 (64.4%)	214 (60.6%)	
Heart disease				.12†
No	319 (77.4%)	41 (69.4%)	278 (78.7%)	
Yes	93 (22.5%)	18 (30.5%)	75 (21.2%)	
Liver disease				.99†
No	370 (89.8%)	53 (89.8%)	317 (89.8%)	
Yes	42 (10.1%)	6 (10.1%)	36 (10.2%)	
Hepatitis B				.99†
No	355 (86.3%)	51 (86.4%)	304 (86.3%)	
Yes	56 (13.6%)	8 (13.5%)	48 (13.6%)	
Hepatitis C				.73†
No	375 (91.0%)	53 (83.8%)	322 (91.2%)	
Yes	37 (8.9%)	6 (10.1%)	31 (8.7%)	
Comorbid disease				.19§
0	71 (17.2%)	5 (8.5%)	66 (18.7%)	
1	155 (37.6%)	26 (44.1%)	129 (36.5%)	
2	113 (27.4%)	15 (25.4%)	98 (27.7%)	
≥3	73 (17.7%)	13 (22.0%)	60 (17.0%)	

RLS = restless leg syndrome.

* $P < .05$.

† Chi-square test.

‡ Independent *t* test.

§ Chi-square test for trend.

this study, 22 could not communicate well, and 4 did not complete the interview. Among the remaining 467 patients, 59 answered affirmatively to all 4 questions on the IRLSSG, 55 answered affirmatively to 1 to 3 questions, and 353 answered negatively to all 4 questions. Hence, data from 59 RLS and 353 non-RLS patients were analyzed. There were slightly more men (54.1%), and mean age was 58.67 (±12.23) years (range, 21–93). About 42% had a junior/senior high school education, and 19% had graduated from college or above. Most participants were unemployed (72.8%) and married (86.8%); 62.6% had 1 to 3 children. Marital status was the only demographic characteristic that significantly differed between RLS and non-RLS patients (Table 1).

Among disease characteristics, mean duration of dialysis was 8.30 (±7.26) years, and 60.6% of patients had received HD for longer than 5 years. The numbers of patients undergoing dialysis in the morning, afternoon, and evening were roughly equal. Analysis of comorbidities showed that 32.5% of patients

Table 2

Body mass index and clinical laboratory data between cases (RLS) and controls (non-RLS) of hemodialysis patients.

Variables	Total (n = 412)	RLS (n = 59)	Non-RLS (n = 353)	*P*
BMI (kg/m^2)	22.52 ± 3.39	22.99 ± 3.11	22.44 ± 3.43	.27[†]
Normal (≥18.5 to ≤24)	237 (60.1%)	35 (58.1%)	205 (60.4%)	.75[‡]
Abnormal (<18.5 or >24)	157 (39.8%)	23 (41.8%)	134 (39.5%)	
Total cholesterol (TC) (mg/dL)	169.87 ± 38.53	165.7 ± 38.17	170.6 ± 38.60	.38[†]
Normal (≤200)	325 (80.6%)	49 (89.9%)	276 (79.7%)	.27[‡]
Abnormal (>200)	78 (19.3%)	8 (14.0%)	70 (20.2%)	
Triglyceride (TG) (mg/dL)	158.68 ± 140.82	174.6 ± 213.9	156.0 ± 124.4	.52[†]
Normal (≤200)	297 (75.9%)	47 (82.4%)	250 (74.8%)	.21[‡]
Abnormal (>200)	94 (24.0%)	10 (17.5%)	84 (25.1%)	
LDL-C (mg/dL)	95.71 ± 31.93	92.48 ± 26.92	96.26 ± 35.69	.41[†]
Normal (≤130)	347 (85.8%)	53 (91.3%)	294 (84.9%)	.19[‡]
Abnormal (>130)	57 (14.1%)	5 (8.6%)	52 (15.0%)	
HDL-C (mg/dL)	43.92 ± 14.46	39.38 ± 11.73	44.68 ± 14.75	.003[†,**]
Normal (male: ≥40, female: ≥50)	173 (42.8%)	15 (25.8%)	158 (45.6%)	.005[‡,**]
Abnormal (male: <40, female: <50)	231 (57.1%)	43 (74.1%)	188 (54.3%)	
Hemoglobin (g/dL)	10.42 ± 1.18	10.43 ± 1.52	10.41 ± 1.12	.94[†]
Normal (≥11)	120 (29.7%)	17 (29.3%)	103 (29.7%)	.94[‡]
Abnormal (<11)	284 (70.3%)	41 (70.6%)	243 (70.2%)	
Fe (mg/dL)	65.83 ± 26.11	61.77 ± 24.23	66.03 ± 26.46	.74[†]
Normal (≥65)	156 (42.9%)	23 (42.5%)	133 (43.0%)	.95[‡]
Abnormal (<65)	207 (57.0%)	31 (57.4%)	176 (56.9%)	
Ferritin (mg/dL)	340.64 ± 329.90	328.2 ± 299.6	342.8 ± 335.4	.76[†]
Normal (≥200)	163 (43.8%)	24 (42.8%)	139 (43.9%)	.88[‡]
Abnormal (<200)	209 (56.1%)	32 (57.1%)	177 (56.0%)	
TIBC (mg/dL)	253.15 ± 50.42	254.6 ± 54.19	252.9 ± 49.80	.82[†]
Normal (≥200 to ≤400)	329 (89.1%)	48 (85.7%)	281 (89.7%)	.37[‡]
Abnormal (<200 or >400)	40 (10.8%)	8 (14.2%)	32 (10.2%)	
TSAT (%)	26.59 ± 10.42	26.09 ± 10.12	26.68 ± 10.48	.70[†]
Normal (≥20%)	266 (72.0%)	38 (67.8%)	228 (72.8%)	.44[‡]
Abnormal (<20%)	103 (27.9%)	18 (32.1%)	85 (27.1%)	
iPTH (pg/mL)	355.78 ± 357.67	422.1 ± 529.2	344.6 ± 317.6	.28[†]
Normal (≤300)	218 (54.2%)	30 (51.7%)	188 (54.6%)	.68[‡]
Abnormal (>300)	184 (45.7%)	28 (48.2%)	156 (45.3%)	

BMI = body mass index, Fe = iron, HDL-C = high-density lipoprotein cholesterol, iPTH = intact parathyroid hormone, LDL-C = low-density lipoprotein cholesterol, RLS = restless leg syndrome, TIBC = total iron-binding capacity, TSAT = percent transferrin saturation.

[**] $P < .01$.

[†] Independent *t* test.

[‡] Chi-square test.

had diabetes, 61.1% had hypertension, 22.5% had heart disease, 10.1% had liver disease, 13.6% had hepatitis B, and 8.9% had hepatitis C. Only 17.2% of patients had no comorbidities other than kidney disease; 37.6% had 1 comorbidity, 27.4% had 2 comorbidities, and 17.7% had 3 or more comorbidities. The only significant difference between RLS and non-RLS patients was duration of dialysis ($P = .08$, when analyzed as a continuous variable; $P = .04$, when analyzed as a binary variable; Table 1).

About 40% of the patients had an abnormal BMI (a BMI of <18.5 kg/m^2 in 10.2% and >24 kg/m^2 in 29.7%). Many patients had abnormal clinical laboratory results, the most common of which was hemoglobin concentration (70.3%), followed by HDL-C (57.1%), Fe (57.0%), ferritin (56.1%), iPTH (45.7%), TSAT (27.9%), TG (24.0%), TC (19.3%), LDL-C (14.1%), and TIBC (10.8%) values. Among these variables, only HDL-C significantly differed between RLS and non-RLS patients ($P = .003$, when analyzed as a continuous variable; $P = .005$, when analyzed as a binary variable); HDL-C was lower in the RLS group than in the non-RLS group (Table 2).

Multiple logistic regression with forward selection showed that dialysis duration and HDL-C were important risk factors for RLS. Patients with a low HDL-C level (<40 mg/dL in men; <50 mg/dL in women) were 2.73 times as likely to have RLS as those with a normal HDL-C level (≥40 mg/dL in men; ≥50 mg/dL in women) (95% CI = 1.44–5.15, $P = .009$) (Table 3). Patients with a dialysis duration of longer than 5 years were 2.32 times as likely to have RLS as those with a dialysis duration less than 5 years (95% CI = 1.23–4.39, $P = .002$). Figure 1 illustrates the association between dialysis duration and HDL-C level by group (RLS and non-RLS). Multiple linear regression with HDL-C level as the outcome variable and dialysis duration and study group as independent variables showed no interaction between dialysis year and group ($P = .433$), which suggests that these two factors are independently associated with RLS. The RLS group had an HDL-C level that was consistently 5.81 mg/dL lower than that of the non-RLS group, regardless of duration of dialysis.

Among the 59 patients with RLS, 2 (3.3%), 9 (15.2%), 37 (62.7%), and 11 (18.6%) had very severe, severe, moderate, and mild RLS, respectively. The correlation between RLS severity and dialysis duration was significant ($r = .26$, $P = .042$; Fig. 2). There was no significant correlation between RLS severity and HDL-C level ($r = .04$, $P = .714$).

Table 3

Multiple logistic regression of RLS in hemodialysis patients.

Factors	Adjusted odds ratio	95% confidence interval	*P*
HDL-C (mg/dL)			.009**
Normal (male: ≥40 mg/dL, female: ≥50 mg/dL)	Reference		
Abnormal (male: <40 mg/dL; female: <50 mg/dL)	2.73	1.44–5.15	
Duration of dialysis (years)			.002**
<5	Reference		
≥5	2.32	1.23–4.39	

HDL-C = high-density lipoprotein cholesterol, RLS = restless leg syndrome.
** $P < .01$.

4. Discussion

In this study, a dialysis duration of longer than 5 years and a low HDL-C level were identified as risk factors for RLS among HD patients; however, dialysis year and HDL-C level were uncorrelated. Among the 59 patients with RLS, 81.4% had moderate or severe symptoms, and RLS severity was significantly correlated with dialysis duration.

Dialysis duration was significantly associated with RLS, which was consistent with the findings of Lin et al in Taiwan[4] and Higuchi et al in Japan[21] but contrary to findings in other countries. Some previous studies reported that dialysis duration was not significantly correlated with RLS prevalence.[6,9,10] This discrepancy may be attributable to a difference in HD duration. In the present study, mean dialysis duration was 9.83 ± 7.56 years for patients with RLS and 8.04 ± 7.19 years for patients without RLS. In contrast, Giannaki et al reported a mean dialysis duration of 3.7 ± 3.5 for patients with RLS and 2.5 ± 1.6 years for patients without RLS,[6] and other studies reported durations of 4.5 ± 2.4 and 4.1 ± 2.6 years[9] and 6.0 ± 5.3 and 6.9 ± 6.3 years,[10] respectively.

Oxidative stress is common in patients with CKD and progresses in persons undergoing long-term HD. It is caused by an imbalance between pro-oxidant production and antioxidant defense mechanisms.[22] Several studies reported increased oxidative stress and decreased antioxidant enzymes in ESRD patients undergoing dialysis.[22–26] Oxidative stress is associated with cardiovascular disease, cachexia, anemia, and many other complications in patients with CKD and might explain in part the increased RLS risk among patients undergoing long-term HD. Higuchi et al hypothesized that longer HD duration and oxidative stress increase RLS incidence and that oxidative stress is associated with RLS severity.[21] We did not examine oxidative stress in this study, so a comparison with previous results was not feasible. We hope to investigate oxidative stress in future research.

Few studies have evaluated the association between lipid profile and RLS in HD patients. In the present analysis of the association between lipid profile and RLS, TG, TC, and LDL-C levels were not associated with RLS. This result was consistent with those of other studies.[8,21] However, patients with low HDL-C levels were 2.73 times as likely as those with normal HDL-C levels to have RLS. This result was inconsistent with those of previous studies, which reported that HDL-C levels were not correlated with RLS,[8,21] perhaps because of the small

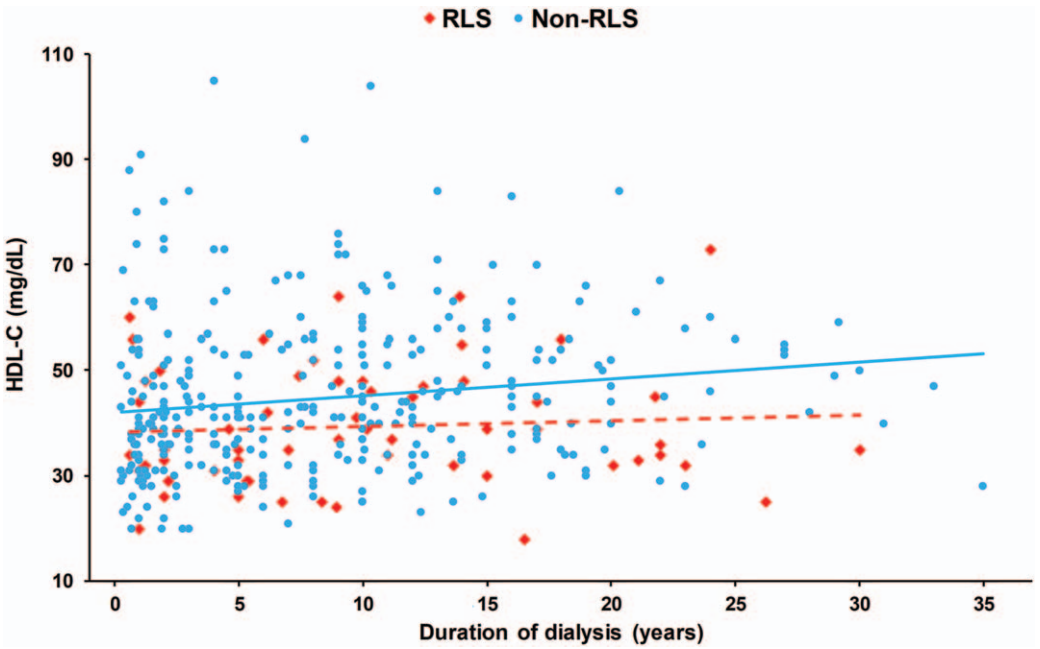

Figure 1. Correlation of HDL-C level and dialysis duration, by group (n = 412).

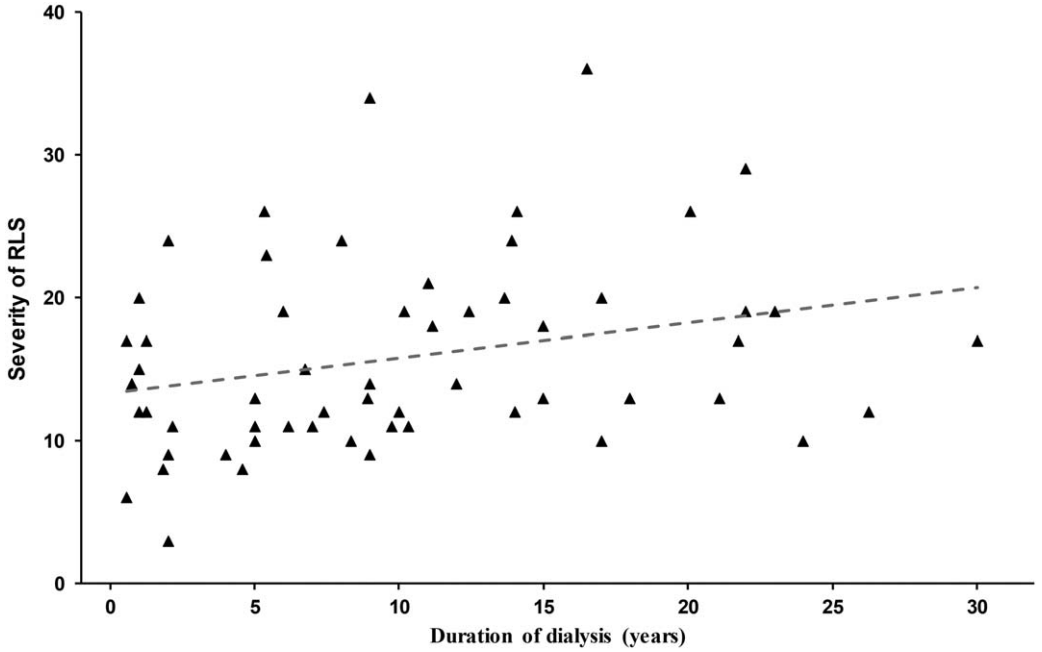

Figure 2. Correlation of RLS severity and dialysis duration (n = 59, $r = .26$, $P = .043$).

sample sizes of previous studies (31 patients with RLS and 69 patients without RLS[8] and 33 patients with RLS and 124 patients without RLS[21]).

Persons with RLS in the general population are more likely to have hypercholesterolemia.[17] Moreover, serum HDL-C level and HDL/LDL cholesterol ratio were significantly lower in those with RLS than in those without RLS in the general population.[16] However, Dredla et al reported that serum cholesterol level was not correlated with RLS in a general population.[27] The pathological mechanisms by which serum HDL-C level and serum cholesterol level are related to RLS were not described in studies by Schlesinger et al[16] and De Vito et al.[17] HD patients typically have low HDL-C levels. HDL protects against plaque formation and progression via reverse cholesterol transport and prevention or reversal of LDL oxidation. In addition, HDL is a potent antioxidant, anti-inflammatory, and antithrombotic factor.[28] However, studies have not yet clarified whether RLS risk is elevated in HD patients when HDL-C levels are low. Therefore, the effects of lipid profile, oxidative stress, and inflammation on RLS in HD patients warrant further investigation in large-scale studies.

The present HD patients with and without RLS did not significantly differ in relation to sex, age, dialysis shift, comorbidities (diabetes, hypertension, heart disease, liver disease, HBV, HCV), BMI, hemoglobin level, Fe level, ferritin level, TIBC, TSAT, or iPTH. These results are consistent with those of previous studies. Several studies reported that RLS was not associated with hemoglobin, ferritin, or Fe levels.[6,9,10] Lin et al found that RLS was not significantly associated with iPTH.[4] Giannaki et al found no significant difference in BMI[6] or age[4,6,7,9] between HD patients with and without RLS. In addition, Lin et al and Salman reported no significant association between RLS and sex.[4,9]

Among the 59 present patients with RLS, 81.4% had moderate or severe symptoms. RLS severity was significantly correlated with dialysis duration but was not associated with HDL level. A study of 139 RLS patients in Iran reported that 99 (71.2%) had moderate/severe RLS; however, neither diabetes, hypertension, heart disease, HBV, or HCV were significantly associated among HD patients with RLS.[30] In a study of 286 patients with RLS in Taiwan, 171 (59.8%) had moderate/severe RLS, and dialysis duration was associated with moderate/severe RLS (OR = 1.01; 95% CI = 1.01–1.02; $P < .001$).[4]

This study had several limitations. First, the case–control study design does not permit inferences regarding the causal relationship between reduced HDL-C level and RLS. Indeed, there was no significant correlation between RLS severity and HDL-C level. The HDL-C level was consistently 5.81 mg/dL lower in the RLS group than in the non-RLS group, regardless of dialysis year (Fig. 1), which suggests that lower HDL-C level is not necessarily a risk factor or cause of RLS. Second, data on RLS onset and treatment were not collected. As 81.4% of the present patients had moderate or severe RLS, data on the effectiveness and adverse effects of treatments for severe RLS, including non-pharmaceutical measures, should be collected and analyzed in future studies. Third, participants were recruited from a large HD center and may not be representative of all HD patients in Taiwan. Fourth, because of the small sample size of this study, larger multicenter trials are necessary.

5. Conclusion

RLS is common among HD patients in Taiwan, particularly among those receiving dialysis for longer than 5 years and those with low serum HDL-C levels (<40 mg/dL in men; <50 mg/dL in women).

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