# Restless legs syndrome in hemodialysis patients: Prevalence and association to daytime functioning

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**ORIGINAL ARTICLE**

# Restless legs syndrome in hemodialysis patients: Prevalence and association to daytime functioning

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**Abstract**

The prevalence of restless legs syndrome and its impact on daytime function were explored in a hemodialysis population, particularly addressing the response consistency of restless legs syndrome symptoms. A two-point internet-based questionnaire survey with a one week interval was administered to 645 subjects of a hemodialysis population. Five hundred and four candidates (332 men and 172 women with mean [SD] age of 59.1 [12.8] years) with hemodialysis who completed the two surveys were selected for analysis. Questionnaire items included personal data, four criteria items for diagnosis of restless legs syndrome, Athens Insomnia Scale, Center for Epidemiologic Studies Depression Scale, Short Form 8-items for health survey, and items of the International Restless Legs Syndrome Severity Scale. Factors associated with deteriorated mental component summary and physical component summary on Short Form 8-items for health survey and depression were assessed. Prevalence of restless legs syndrome was the rate of those meeting the four diagnostic criteria items for this disorder in both surveys: 12.9%. Restless legs syndrome category defined by response consistency to the restless legs syndrome criteria items was significantly associated with the physical component summary score deterioration. This two-point survey indicated reliable prevalence of restless legs syndrome in a hemodialysis population, and revealed that stability of restless legs syndrome symptoms might contribute to the presence of certain daytime dysfunctions in this population.

**Key words:** depression, dialysis, prevalence, quality of life, restless legs syndrome.

## INTRODUCTION

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by unpleasant leg sensations and irresistible urges to move the lower extremities, mainly at night.[1] Population-based epidemiological studies have estimated that the prevalence rate of RLS in the general population is 2–12% in Western countries[2–8] and 1–8% in Asian countries.[9–11] This disorder is also frequently comorbid with end-stage renal disease (ESRD), especially in patients receiving hemodialysis, with higher but variable prevalence rate of 4–32% in Western countries[12,13] and 14–25% in Asian countries.[14–16] Fluctuation of RLS symptoms in these populations possibly contributes this wide variation. In Japan, however, no reported study has explored this issue to date.

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The major consequences of RLS are daytime impairments such as decreased vitality or energy and nighttime sleep difficulties. Difficulty in initiating sleep or maintaining sleep, waking up too early, and non-restorative sleep were emphasized in the Second edition of International Classification of Sleep disorders (ICSD-2).[17] Specifically regarding daytime functions, several previous studies have emphasized that deteriorated quality of life (QOL)[4,7] and depression[7] are frequently observed, especially in ESRD populations having RLS symptoms. Nevertheless, few reports in the relevant literature have described a systematic study elucidating the association between these daytime disturbances and RLS symptoms or dialysis-related variables in numerous ESRD patients. Moreover, little is known about RLS symptom fluctuation, which can cause a difference in positivity/negativity of RLS in a questionnaire-based survey, or the relation between RLS symptom fluctuation and the daytime dysfunctions.

To resolve these issues, we administered a two-point web-based questionnaire survey to an ESRD population. The aims of this study were: (i) to investigate the prevalence rate of RLS among numerous hemodialysis patients in a two-point survey so that we can assess factors contributing to the variety of prevalence rate of the disorder described above; and (ii) to clarify the relation of response consistency to RLS criteria items and hemodialysis-related variables to presence/absence of coronary heart diseases or daytime dysfunctions such as deteriorated QOL or depression.

## METHODS

### Participants and procedures

During 5–23 March 2012, this two-point web-based questionnaire survey was administered throughout Japan to participants with ESRD receiving dialysis treatment. In all, 645 participants aged 20–70 years were recruited with stratified random sampling from a list provided by a marketing research company that maintains a panel of dialysis patients for marketing and survey purposes. The Ethical Committee of the Neuropsychiatric Research Institute approved this study. Informed consent was obtained from all participants.

The questionnaires of the first survey requested personal data, clinical information of dialysis (type, vintage, and weekly frequency), presence of comorbidity, and presence and severity of RLS, quality of life (QOL) and status of nocturnal sleep together with depression as follows: (i) the four criteria items for diagnosis of RLS;[18] (ii) the Japanese version of International Restless Legs Syndrome Severity Scale (IRLS)[19] for evaluating severity of the disorder; (iii) the Japanese version Short Form-8 (SF-8)[20,21] for assessing QOL; (iv) the Japanese version of the Athens Insomnia Scale (AIS)[22,23] for assessing the level of insomnia; (v) the 12-item version of the Center for Epidemiological Studies Depression Scale (CES-D)[24,25] for estimating depressive status; and (vi) comorbid conditions of the participants as follows: hypertension, hyperlipidemia, diabetes mellitus, anemia, pain, pruritus, cerebrovascular diseases (including cerebral infarction and hemorrhage), coronary heart diseases (including angina and myocardial infarction) and other conditions.

The four diagnostic criteria items for RLS, proposed by the RLS Diagnosis And Epidemiology Workshop at the National Institutes of Health (NIH) in collaboration with members of the International RLS Study Group (IRLSSG),[18] were used to estimate the presence/absence of RLS, similarly to our previous epidemiological studies.[11,26] These criteria comprise the following four items: (i) an urge to move the legs usually accompanied or caused by an uncomfortable sensation in the legs; (ii) beginning or worsening of symptoms during periods of rest or inactivity; (iii) partial or total relief of symptoms by movement; and (iv) symptoms worsening in the evening or at night, or occurring only in the evening or at night. Regarding the evaluation of RLS severity, the IRLS was used to self-rate the severity of participants' RLS symptoms.[19] This scale comprises 10 items related to nighttime and daytime symptoms of RLS during the prior 2 weeks.

The SF-8 consists of two domains: physical QOL (physical component summary, PCS) estimating general health, physical function, role physical and bodily pain, and mental QOL (mental component summary, MCS) manifesting vitality, social function, mental health, and role emotional. Scores of these domains were calculated according to standard methods.[20] Based on general population averages for the scores, a participant with a score of less than 50 in each domain was inferred to have deteriorated QOL.[20,21] In the present study, however, cut-off values to define deteriorated QOL were set at median values for each domain (PCS, 44.7; MCS, 48.6) because most participants receiving hemodialysis showed deteriorated QOL when adopting the general cut-off values.

The AIS was developed to assess the severity of insomnia during a recent one-month period according to the International Classification of Diseases (ICD)-10. The questionnaire consists of eight items: the first five

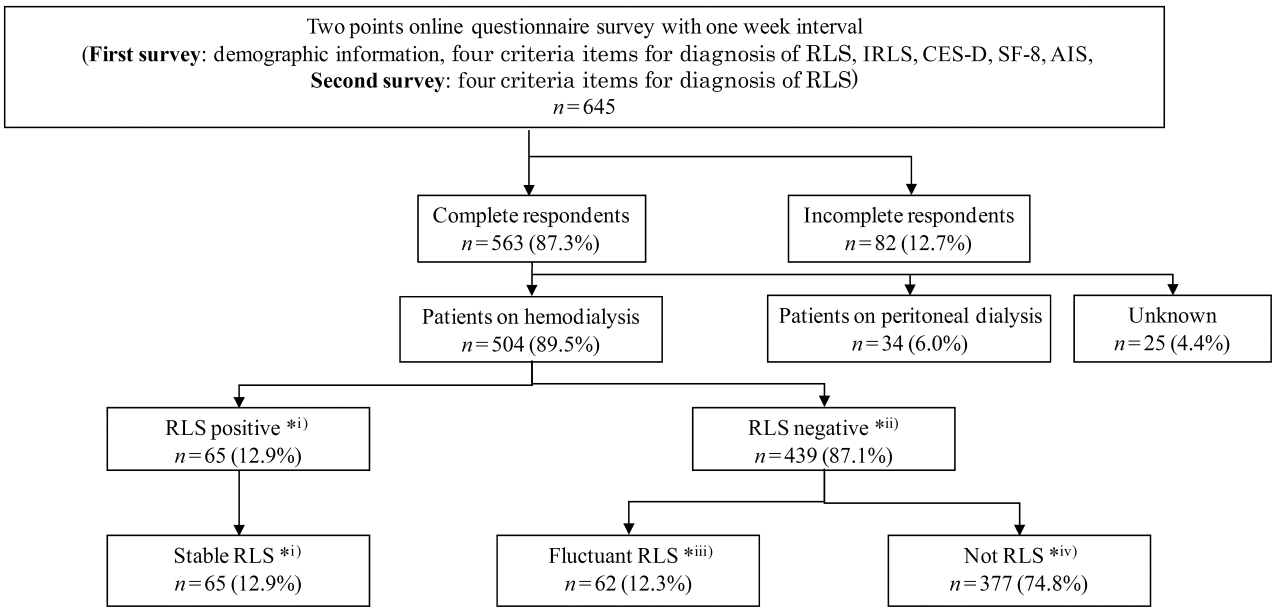


**Figure 1** Patient flow. *Patients who met four criteria items for diagnosis of restless legs syndrome (RLS); (i) in both of the two surveys, (ii) in one time or less in the two surveys, (iii) in one of two surveys, and (iv) neither of the two surveys. AIS, Athens Insomnia Scale; CES-D, Center for Epidemiologic Studies Depression Scale; IRLS, International Restless Legs Syndrome Severity Scale; SF-8, Short-Form 36-Item Health Survey.

items correspond to sleep conditions identical to nocturnal insomnia symptoms; the last three items cover the next-day consequence of insomnia. Each item of AIS is rated 0–3: 0, no problem at all; 3, very severe problem. The cut-off value for the presence of sleep disturbance is set as 6 points.[22,23]

The CES-D, which is a commonly used self-rating scale of depressive symptom in epidemiological surveys, provided an index of cognitive, affective, and behavioral features of depression and the frequency of symptoms. It had four response options for each question: "never or rarely," "sometimes," "often," and "always," coded as 0–3. A score of 16 points or higher indicates depressive symptomatology.[24,25]

One week after the first survey, we conducted the second survey requesting questionnaires only for the four criteria items for diagnosis of RLS. Based on the results of the two surveys, participants were classified into two groups. Participants who met the four criteria items in both surveys were defined as "RLS positive (stable RLS)" and in one time or less in the two surveys as "RLS negative". Among the RLS-negative participants, those who met the four criteria in one of the two surveys were defined as "fluctuant RLS" and neither in the two surveys as "not RLS" (Fig. 1).

## Statistical analyses

$\chi^2$ tests were used to compare the concordance rates of the four criteria items for diagnosis of RLS between the two surveys in participants with fluctuant RLS, and to compare the rates of the participants having each comorbidity among the three groups of stable RLS, fluctuant RLS and not RLS. Kruskal–Wallis tests followed by Bonferroni post-hoc analysis was used to compare age, hemodialysis vintage, scores of IRLS, AIS, CES-D, PCS, and MCS among the three groups of stable RLS, fluctuant RLS, and not RLS. Mann–Whitney's *U*-test was used to compare the duration of RLS morbidity between the groups with stable RLS and fluctuant RLS.

Factors associated with depression and deterioration of MCS and PCS scores were examined using a series of logistic regression analyses with the following explanatory variables: age, sex, frequency of hemodialysis, hemodialysis vintage and severity of RLS, insomnia (AIS cut off score ≥6) or depression (CES-D score ≥16). All variables were examined initially in univariate models followed by multivariate logistic regression analyses. These statistical analyses were conducted using software (Statistical Package for the Social Sciences [SPSS], ver.

11.5J, SPSS, Tokyo, Japan) with the significance level set at a two-tailed $\alpha$ level of 5%.

## RESULTS

### Participant population and prevalence of RLS

Figure 1 demonstrates the participant flow. Two-point online questionnaire surveys with a one-week interval were performed in 645 candidates regularly receiving dialysis therapy. Among these candidates, 563 (87.3%) completed the second survey. After excluding candidates receiving peritoneal dialysis or unknown type of dialysis for maintaining the homogeneity of the candidates, 504 (89.5%) who were regularly receiving hemodialysis were selected for the current analysis. They were 332 men and 172 women with mean [SD] age of 59.1 [12.8] years (range: 24–79 years). The range of age of the current subjects was slightly younger than that of them.[27] Based on the results of the questionnaires of four diagnostic criteria items of RLS in the two-point surveys, the 504 participants were classified into two groups: RLS positive ($n$ = 65, 12.9%) and RLS negative ($n$ = 439, 87.1%). Thereafter, the 439 RLS negative participants were classified into two groups: fluctuant RLS ($n$ = 62, 12.3%) and not RLS ($n$ = 377, 74.8%). The prevalence of stable RLS in participants receiving hemodialysis was estimated as 12.9% (65/504) (Fig. 1).

### Comparison of the concordance/discordance rate for the four diagnostic criteria items of RLS between the two surveys in participants with fluctuant RLS

Table 1 presents a comparison of the concordance/discordance rate between the two surveys for the four diagnostic criteria items of RLS: "urge to move," "worsening at rest," "relief by movement," and "worsening at night" in participants with fluctuant RLS. No significant differences in the concordance rates were found among the items ($\chi^2$ = 6.392, $P$ = 0.092). However, the concordance rate was higher in "worsening at rest" (67.7%) and "urge to move" (62.9%) than in "relief by movement" (48.4%) and "worsening at night" (51.6%), as judged from percent contributions (adjusted residual: 1.9 for "worsening at rest," 1.0 for "urge to move," –1.7 for "relief by movement," and –1.1 for "worsening at night").

**Table 1** Comparison of the rates for concordance/discordance between surveys for four diagnostic criteria items for restless legs syndrome (RLS) in patients with fluctuant RLS

| | Concordant | Discordant |
|---|---|---|
| Urge to move | 39 (62.9) | 23 (37.1) |
| Worsening at rest | 42 (67.7) | 20 (32.3) |
| Relief by movement | 30 (48.4) | 32 (51.6) |
| Worsening at night | 32 (51.6) | 30 (48.4) |

$\chi^2$ = 6.392 ($df$ = 3), $P$ = 0.092.
Values are expressed as number (rate) of patients.

### Comparison of descriptive variables and rate of participants having comorbidity among the RLS category groups

Table 2 presents a comparison of descriptive variables and rates of participants having comorbidity among the three groups: stable RLS, fluctuant RLS, and not RLS. Significant differences were found in the scores of the IRLS ($\chi^2$ = 154.60, $df$ = 2, $P$ < 0.01), AIS ($\chi^2$ = 41.72, $df$ = 2, $P$ < 0.01), CES-D ($\chi^2$ = 20.06, $df$ = 2, $P$ < 0.01), PCS ($\chi^2$ = 18.92, $df$ = 2, $P$ < 0.01), and MCS ($\chi^2$ = 12.14, $df$ = 2, $P$ < 0.01). Post hoc analysis revealed that participants with stable RLS and fluctuant RLS showed significantly higher scores of IRLS, AIS and CES-D, and lower scores of PCS and MCS than in the not RLS group (all $P$ < 0.01). Regarding the IRLS score, the stable RLS group showed a significantly higher score than the fluctuant RLS group did ($P$ < 0.01).

As for comorbidity, the rates of participants having hypertension were significantly lower in the "not RLS" group than in the "stable RLS" or "fluctuant RLS" group ($\chi^2$ = 6.08, $P$ < 0.05). The comorbidity rate of hyperlipidemia, pain, pruritus, and coronary heart disease were significantly higher in the "stable RLS" group than in the "not RLS" group ($\chi^2$ = 13.78, $P$ < 0.01; $\chi^2$ = 10.71, $P$ < 0.01; $\chi^2$ = 20.43, $P$ < 0.01; $\chi^2$= 8.54, $P$ < 0.05) (Table 2).

### Factors associated with depression, and deterioration of PCS and MCS of SF8

With regard to depression, the mean [SD] score of CES-D was 16.7 [11.1] in the total sample. In the logistic regression analyses, we categorized participants whose scores were higher than the cut-off value (16 point) as positivity for depression. Results showed that the mean [SD] score was 25.0 [9.5] in the group with

**Table 2** Comparison of descriptive variables among the three restless legs syndrome (RLS) category groups

| | Stable RLS ($n$ = 65) | Fluctuant RLS ($n$ = 62) | Not RLS ($n$ = 377) | $P$ |
|---|---|---|---|---|
| Age | 57.0 [29–79] | 57.0 [34–79] | 61.0 [25–79] | |
| Duration of RLS (months) | 36.0 [6–360] | 36.0 [2–240] | – | |
| Hemodialysis vintage (months) | 72.0 [9–504] | 48.0 [1–420] | 72.0 [2–480] | |
| IRLS | 18.0 [3–40]*[a,b] | 15.0 [0–33]*[b] | 5.0 [0–30] | |
| AIS | 8.0 [0–24]*[b] | 8.0 [0–20]*[b] | 5.0 [0–24] | |
| CES-D | 20.0 [3–53]*[b] | 17.5 [3–51]*[b] | 13.0 [0–50] | |
| PCS | 40.7 [18.6–57.0]*[b] | 43.0 [20.8–56.3]*[b] | 45.6 [15.3–60.0] | |
| MCS | 46.3 [24.8–65.8]*[b] | 45.0 [21.1–57.3]*[c] | 49.2 [21.2–65.4] | |
| Comorbid disease | | | | |
| Hypertension | 39 (60.0) | 38 (61.3) | 181 (48.0)*[e] | <0.05 |
| Hyperlipidemia | 15 (23.1)*[d] | 5 (8.1) | 31 (8.2) | <0.01 |
| Diabetes mellitus | 27 (41.5) | 19 (30.6) | 118 (31.3) | *n.s.* |
| Anemia | 17 (26.2) | 21 (33.9) | 86 (22.8) | *n.s.* |
| Pain | 11 (16.9)*[d] | 6 (9.7) | 21 (5.6) | <0.01 |
| Pruritus | 21 (32.3)*[d] | 22 (35.5)*[d] | 58 (15.4) | <0.01 |
| Cerebrovascular disease | 7 (10.8) | 6 (9.7) | 21 (5.6) | *n.s.* |
| Coronary heart disease | 16 (24.6)*[e] | 10 (16.1) | 43 (11.4) | <0.05 |

AIS, Athens Insomnia Scale; CES-D, Center for Epidemiologic Studies Depression Scale; IRLS, International Restless Legs Syndrome Rating Scale; MCS, mental component summary; PCS, physical component summary.
Figures are expressed as median value [range] and number of patients (rate) for comorbid diseases.
Stable RLS met four criteria items for diagnosis of RLS in both of the two surveys.
Fluctuant RLS met four criteria items for diagnosis of RLS in one survey.
Not RLS met four criteria items for diagnosis of RLS neither of the two surveys.
*[a]$P < 0.01$ compared to "fluctuant RLS" group.
*[b]$P < 0.01$ compared to "not RLS" group.
*[c]$P < 0.05$ compared to "not RLS" group.
*[d]$P < 0.01$ defined by adjusted rest errors.
*[e]$P < 0.05$ defined by adjusted rest errors.

depression, although the value was 8.1 [3.7] in the group without depression. Multivariate logistic regression analysis following univariate logistic regression analysis, revealed only the presence of insomnia was significantly associated with depression (OR = 6.271, 95%CI: 4.257–9.237) (Table 3).

As for PCS, the mean [SD] score of PCS was 43.4 [9.0] in the total sample. We designated participants whose scores were lower than the median value of the total sample (44.9 point) as poor PCS. Results showed that the mean [SD] score was 36.1 [7.1] in the group with poor PCS; whereas the value was 50.4 [3.5] in the group with good PCS. Multivariate logistic regression analysis following univariate logistic regression analysis, revealed a deteriorated PCS score was significantly associated with higher age (OR = 1.314, 95%CI: 1.121–1.540), longer hemodialysis vintage (OR = 1.003, 95%CI: 1.001–1.005), RLS category, and presence of insomnia (OR = 2.654, 95%CI: 1.736–4.057) as well as depression (OR = 3.056, 95%CI: 2.015–4.634). With respect to RLS category, participants with stable RLS but not those with fluctuant RLS showed a significant association with deteriorated PCS score (OR = 1.969, 95%CI: 1.046–3.704) (Table 3).

With regard to MCS, the mean [SD] score was 47.8 [7.2] in the total sample. We determined participants whose scores were lower than the median value of the total sample (48.6 point) as poor MCS. Results show that the mean [SD] score was 41.9 [5.4] in the group with poor MCS; the value was 53.4 [3.1] in the group with good MCS. Multivariate logistic regression analysis following univariate logistic regression analysis, revealed deteriorated MCS score was significantly associated with presence of insomnia (OR = 1.948, 95%CI: 1.275–2.974) and depression (OR = 6.559, 95%CI: 4.289–10.030) (Table 3).

## DISCUSSION

The current study investigated the difference in the prevalence rate of RLS between two point surveys with the term interval, the factors associated with the response consistency to RLS criteria between the two surveys, and the impact of stable RLS on daytime

**Table 3** Factors associated with deteriorated score of physical component summary (PCS) or mental component summary (MCS), depression

| Predictor | Multivariate Relative Risk[1] (95%*CI*) | | |
|---|---|---|---|
| | Depression[2] | PCS deterioration[3] | MCS deterioration[3] |
| Age | *n.s.* | 1.314 (1.121–1.540)** | *n.s.* |
| Sex | *n.s.* | *n.s.* | *n.s.* |
| Frequency of hemodialysis(/w) | *n.s.* | *n.s.* | *n.s.* |
| Hemodialysis vintage | *n.s.* | 1.003 (1.001–1.005)** | *n.s.* |
| RLS category[4] | | | |
| Not RLS | Ref | Ref | Ref |
| Fluctuant RLS[i)] | *n.s.* | *n.s.* | *n.s.* |
| Stable RLS[ii)] | *n.s.* | 1.969 (1.046–3.704)* | *n.s.* |
| Insomnia | | | |
| AIS <6 | | | |
| AIS ≥6 | 6.271 (4.257–9.237)** | 2.654 (1.736–4.057)** | 1.948 (1.275–2.974)** |
| Depression | | | |
| CES-D <16 | | | |
| CES-D ≥16 | – | 3.056 (2.015–4.634)** | 6.559 (4.289–10.030)** |

AIS, The Athens Insomnia Scale; CES-D, Center for Eidemilogic Studies Depression Scale; RLS, restless legs syndrome; Ref, reference. *$P < 0.05$; **$P < 0.01$; *CI*; confidence interval, *n.s.*; not significant.
[1]Relative risks approximated to odds ratios, [2]CES-D ≥16, [3]Deterioration was defined as lower score than the median values; 48.6 for MCS and 44.9 for PCS, [4]Defined by response consistency to four criteria items for diagnosis of RLS: i) in one or fewer, ii) in both surveys.
Not RLS group is set as a reference category.

dysfunction in patients' cohort of end stage renal disease receiving chronic hemodialysis using web-based questionnaires.

In this study, the rate of participants with stable RLS among the studied population through two-point questionnaire surveys was estimated as 12.9%, which is clearly higher than the rate in the general Japanese population (1–4%).[10,11] Meanwhile, the rate was also within the range of reported rates in hemodialysis population of any race (5–32%),[12,13] but lower than those reported from Asian countries (14–23%).[14–16] However, the rate found in this study confirmed through two-point questionnaire surveys was inferred to be more reliable. This study revealed that the rate of total participants with "fluctuant RLS" or "stable RLS" was 25.2% of the studied population. Of note, the rate of the participants with "fluctuant RLS", who had a discordance in positivity/negativity of RLS between the two point surveys, was almost similar to that with "stable RLS." Thus, the rate of participants with stable RLS symptoms in hemodialysis population was unexpectedly low.

This report is the first of a study investigating the change in RLS positivity/negativity between the two surveys. It is particularly interesting that the "fluctuant RLS" group had significantly lower IRLS score than the "stable RLS" group had. This finding suggests that milder RLS symptoms are more likely to fluctuate than severer ones, leading to the discordance of RLS positivity/negativity between the two point surveys in this population. Another possible reason for the discordance could be fluctuation of motivation for answering the questionnaire items. Further study is needed to clarify the confounding factors for the discordance of RLS positivity/negativity in multiple surveys.

As for the concordance/discordance rates between the two surveys among the four diagnostic criteria items for RLS, considerable but not significant differences were found. The rates of discordance in responses were higher for the two items, "relief by movement" and "worsening at night," than for the other two items in participants with "fluctuant RLS." The reason for the discordance in those two items remains unclear, but worsening of RLS symptom under daytime rest condition, especially while undergoing hemodialysis, possibly engenders a negative response to the item "worsening at night".[13]

In the present study, the stable RLS group was revealed to have higher comorbidity rate of hyperlipidemia, pain, pruritus and coronary heart diseases than the not RLS group. The higher comorbidity rate of coronary heart diseases in subjects with stable RLS symptoms was consistent with a previous study result showing that patients with continuous RLS symptoms had higher prevalence of cardiovascular events.[28] However, in order to clarify the

causal relationship between RLS/PLMS and cardiovascular disease in hemodialysis population, additional longitudinal studies would be necessary.

It is widely accepted that patients with RLS are likely to have depression[7,29] or deteriorated QOL.[4,7] Many previous studies have addressed this issue in an RLS-affected ESRD population,[12,14,30] but few reports have described the association between RLS and the above daytime disturbances controlling for dialysis condition, insomnia or comorbid diseases with consideration of stability of RLS symptoms. The current study showed that stable RLS through the two surveys was not associated with deterioration of MCS or depression after controlling for insomnia and hemodialysis conditions, possibly because the presence of RLS can cause depression or deterioration of MCS through the formation of insomnia.[31,32]

This study has several limitations. First, in this study, positivity/negativity of RLS was determined solely on the basis of a self-rated questionnaire administered via the internet without a face-to-face interview. Second, potential responder bias should be considered. In web-based questionnaire survey of this kind, younger persons having leg discomfort or sleep disturbances are assumed to be more likely to respond. In fact, the mean age of the current study participants was younger than these in the previously described age of ESRD patients in Japan[27] (59.1 years *vs* 66.5 years). Possibly depending on this age difference, either the comorbidity rate of hypertention or the rate of diabetes mellitus of the current study was lower than those in the ESRD patients reported in Japan.[27,33] Considering these, the prevalence rate of RLS as well as comorbid diseases in the ESRD patients could be underestimated in the present study. Third, the interval of one week between the two surveys might be relatively short to evaluate the stability of RLS symptoms. However, the present study first addressed response consistency of RLS symptoms in ESRD patients in multiple surveys. In future study, multiple point survey on this issue with longer interval period would be desirable.

This study specifically addressed the response consistency to RLS criteria items through a two-point web-based survey administered to a population regularly receiving hemodialysis. The prevalence of RLS in the studied population was 12.9% after neglecting participants with fluctuant RLS positivity. Considering the negative impact of RLS including the risk of deterioration of physical QOL suggested in this study, proper diagnosis and early therapeutic intervention of RLS are desirable in this population.

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