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Original Article

Restless legs syndrome does not affect 3-year mortality in hemodialysis patients

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Highlights of the study

We evaluated the relationship of RLS and mortality in chronic hemodialysis patients

For the diagnosis of RLS we implemented standard methodology, i.e. the essential clinical criteria of the International RLS Study Group.

This is the first time this issue is investigated in an epidemiological survey in Greece.

In contrast to previous reports the diagnosis of RLS does not influence the 3-year mortality in HD patients.

ABSTRACT

Objective: In chronic hemodialysis (HD) patients, the prevalence of restless legs syndrome (RLS) is significantly higher than in the general population. Uremic RLS has been related to an enhanced mortality of HD patients. In the general population, however, studies of this association have yielded inconsistent results. The aim of the present study was to re-evaluate the relationship of RLS and mortality in HD patients. *Methods:* We recorded the 3-year mortality rate in a population of 579 HD patients after assessment for RLS symptoms. In addition we analyzed the 5-year mortality rate after end-stage renal disease onset (i.e., commencement of HD). This HD patient population has been previously included in a cross-sectional survey of RLS prevalence in which RLS diagnosis was based on the essential clinical criteria of the International RLS Study Group. Mortality data were acquired from the national end-stage renal disease registry. Survival probability was calculated by means of the Kaplan–Meier method and analyzed by the log-rank (Mantel–Cox) test. For multivariate survival analysis, we implemented a proportional hazards regression (Cox regression) model.

Results: During the 3-year follow-up period, we documented 118 deaths and an overall 3-year mortality of 20.6%. Mortality was 15.6% in patients with RLS and 22.3% in patients without RLS ($p = 0.079$). According to the Cox regression analysis, there was no significant association between RLS and 3-year mortality, either in an age- and gender-adjusted model (hazard ratio [HR] = 0.772, 95% confidence interval [CI] = 0.488–1.219, $p = 0.267$) or in a multivariate adjusted model (HR = 0.667, 95% CI = 0.417–1.069, $p = 0.092$). Similarly, there was no association between RLS and 5-year mortality after end-stage onset based on our univariate (HR = 0.653, 95% CI = 0.417–1.022, $p = 0.063$) and multivariate (HR = 0.644, 95% CI = 0.399–1.0380, $p = 0.071$) analyses.

Conclusion: Diagnosis of RLS according to the essential clinical criteria of the International RLS Study Group does not seem to influence the 3-year mortality in HD patients. Our findings are in contrast to those in some previous reports, and reinforce the need for further studies of RLS and mortality in HD patients.

1. Introduction

Restless legs syndrome (RLS), or Willis–Ekbom disease, is a neurological, sensorimotor disorder that frequently leads to sleep disturbances. It is characterized by an urgent, uncontrolled need to move the limbs that is accompanied or caused by peculiar, unpleasant sensations (paresthesiae). Symptoms appear or worsen at rest, are temporarily relieved by movement of the affected extremities, and are more severe in the evening or at night [1–3].

RLS is typically an idiopathic disorder (i.e., primary RLS); however, secondary forms are not infrequent. In this context, results from several cross-sectional studies suggest an association of RLS with chronic kidney disease and cardiovascular diseases [4–7]. Secondary RLS in chronic kidney disease is frequently called “uremic RLS” [7]. In a recent epidemiological survey, in agreement with previous studies [5,8 –10], we found a high prevalence of RLS in patients on chronic hemodialysis (HD) [11].

Uremic RLS has been frequently associated with increased morbidity and enhanced mortality in patients with end-stage renal disease [12–15]. In the general population, however, studies of this association have reported inconsistent results. A prospective cohort study of the Health Professionals Follow-up Study, which included 18,425 U.S. men free of diabetes, arthritis, and renal failure, suggested that men with RLS had a higher overall mortality independently of known risk factors [16]. Notably, when duration of symptoms was taken into account, previously healthy women with RLS for ≥3 years showed a higher risk of coronary heart disease than women with a shorter duration of symptoms [17]. In contrast, according to results from four large, prospective cohort surveys from Germany and the United States, RLS did not increase all-cause mortality [18].

In the present study, our aim was to evaluate the association between RLS status and 3-year all-cause mortality, after assessment of RLS, in a cohort of HD patients who were recently surveyed by our group. An additional aim was to investigate possible modifiers of this association, that is, parameters related to uremia, quality of dialysis, renal anemia, iron status, cachexia–inflammation, and bone metabolism, all presumed predictors of all-cause and cardiovascular mortality in HD patients.

2. Methods

We conducted an observational, prospective cohort investigation in a population of 579 HD patients. This population consisted of all patients with end-stage renal disease who were receiving chronic HD treatment (≥2 times per week for at least 3 months), in six renal units in Greece between January and September 2010. In a previous cross-sectional survey of our group [11], conducted by means of standard methodology [19–21], we assessed the prevalence and severity of RLS in this population. Briefly, the local version of the four essential clinical criteria of the International Restless Legs Syndrome Study Group (IRLSSG) rating scale, which has been validated in previous studies, was implemented as a screening tool for RLS diagnosis [11,20]. In cases that fulfilled all four criteria, diagnosis was confirmed, and RLS severity was evaluated according to the IRLSSG rating scale (Greek version) during a personal interview conducted by an RLS expert (G.M.H.) [11,19,20]. According to the IRLSSG rating scale, severity was classified as mild (<11 on the IRLSSG rating scale), moderate (11–20), severe (21–30), and very severe (31–40) [21]. The

prevalence of RLS found in that study was 26.6% (154/579). The study presented here was approved by the Ethics Review Board of the University Hospital of Larissa.

The main outcome (primary endpoint) of the study was mortality during a 3-year observation period (2011–2013) after the assessment for RLS at baseline. Overall survival time was defined as the time interval from the enrollment until the date of death (event) or until 36 months after enrollment. The observation time of 3 years was held in all cases. An additional outcome was mortality assessed during a 5-year period after the initiation of HD. In this case, survival time was defined as the time interval from commencement of the HD treatment until the date of death (event) or until 60 months after commencement of HD. Mortality data were acquired from the national end-stage renal disease registry [22]. Clinical and laboratory data relevant for mortality that had been recorded at baseline from the medical records are shown in Tables 1 and 2. During the 3-year follow up period, no additional data from patients or patients' records were acquired except if necessary to confirm or to clarify registry mortality data. To calculate the probability of error for comparison of these baseline characteristics among survivors and nonsurvivors, we used the χ^2 test for categorical variables and the Student *t* test for continuous variables (alternatively the Mann–Whitney *U* test where applicable). Kaplan–Meier survival curves were generated for survival probability and analyzed by the log-rank (Mantel–Cox) test. Hazard ratios (HR) and respective 95% confidence intervals (95% CI) were estimated by a stratified proportional hazards regression (Cox regression) analysis. RLS existence at study baseline (yes/no), RLS existence before the onset of dialysis (yes/no), and RLS severity (mild, moderate, severe, very severe) served as stratifying variables. The proportional hazards assumption was tested graphically by means of log minus log survival curves.

For multivariate survival analysis, we applied the proportional hazards regression (Cox regression). In the first analysis, all variables that were different between RLS positive and negative cases (potential determinants of RLS diagnosis) according to the findings of the primary cross-sectional study (Tables 1 and 2) were included as covariates in the Cox regression models. In the second analysis, every potential determinant of mortality in HD patients, among the clinical and laboratory data recorded at baseline (Tables 1 and 2), was included as a covariate. Outcomes were 3-year survival after the assessment for RLS symptoms (i.e., initiation of study) and 5-year survival after end-stage onset (i.e., initiation of HD). Consequently, we implemented the proportional hazards regression (Cox regression) in four separate models. The existence of RLS (yes/no) at baseline served as a categorical (stratifying) variable in all four models. Only cases with full data sets were used for these analyses.

In the first model, in which the outcome was 3-year mortality after RLS assessment, the following covariates were included (Tables 1 and 2): age (years), β_2-microglobulin (mg/L), ferritin (ng/mL), phosphorus (P; mg/dL), and intact parathyroid hormone (iPTH) (pg/mL). In the second model (3-year mortality after RLS assessment), the following covariates were included: age (years), sex (male/female), diabetic nephropathy (yes/no), duration of dialysis (months), dialysis mode (HD or hemodiafiltration), body mass index (kg/m^2), serum urea before HD (mg/dL), urea reduction ratio (URR; %), Kt/V, β_2-microglobulin (mg/L), C-reactive protein (mg/L), albumin (g/dL), hemoglobin (g/dL), serum iron (µg/dL), ferritin (ng/mL), transferrin (mg/dL), transferrin saturation (TSAT; %), calcium (Ca; mg/dL), phosphorus (P; mg/dL), CaxP product (mg^2/dL^2), and iPTH (pg/mL).

Comment [KVS2]: AUTHOR: Please verify that "iPTH" is correct as expanded.

Comment [KVS3]: AUTHOR: Please expand "Kt/V" at first mention in text and in table footnotes.

In the additional two models, in which the outcome was the 5-year survival after initiation of HD, the above two sets of covariates were used, principally unchanged. Exceptions were the duration of dialysis (months), which being zero per definition was not taken into account, and the age at RLS assessment (i.e. age at study initiation), which was substituted with the age at end-stage onset (i.e. age at initiation of HD). Covariates, even if they do not have a statistical significant influence on the outcome, may have a considerable influence on the estimation of model parameters for the other covariates, especially if they are associated with each other. Therefore, based on the above primary multivariate analyses we calculated certain reduced forms of all the models, first, by omitting the covariates which were significantly correlating with each other and, second, by including only the covariates which were significantly contributing to outcome on primary analysis.

For the purposes of the present repos, the study power calculation method suitable for survival analysis by the log-rank test was used prospectively [23;24]. The minimum number of subjects required to detect a ratio of median survival times (experimental group/control group) with a certain power and a two sided type I error probability of 5% was estimated [23,24]. A study power of 80% corresponds to a mean survival times ratio of 0.70 for the above given sample size of patients (154 with RLS) and controls (425 without RLS).

Data for continuous variables are given as a mean value and standard deviation (SD). Categorical variables are presented as number of cases (*n*) or percentage (%). *p* Values ≤ 0.05 (two-sided) were regarded as statistically significant. Statistical analyses were carried out using the Statistical Package for Social Sciences 13.0 (SPSS 13.0) for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

Overall, the epidemiological survey included 579 patients (236 females; mean age 65 ± 13 years) with end-stage renal disease treated with chronic HD. Among the HD patients who were informed about the study, none denied participation, but 24 patients were not included for reasons irrelevant to the study protocol (Fig. 1). For all patients included in the study (N = 579), there was a full dataset. No false-positive cases were assessed during the interview conducted by the RLS expert (G.M.H.); that is, RLS was confirmed in all patients who fulfilled all four criteria.

During the 3-year period (2011–2013), we documented 118 deaths among 579 HD patients, that is, a 3-year all-cause mortality of 20.6% overall. Specifically, 94 patients without RLS (94/425; 3-year mortality 22.3%) and 24 patients with RLS (24/154; 3-year mortality 15.6%) died. Clinical profiles and laboratory findings at initial assessment of patients on chronic HD are shown on Tables 1 and 2. Between survivors and nonsurvivors with RLS, there were no significant differences in clinical profiles, especially concerning the existence of RLS before the onset of HD (p = 0.229) or the severity of RLS (p = 0.430) at initial assessment (Table 1). In contrast, there were significant differences regarding patient age (60 ± 13 vs 67 ± 10 years, p = 0.041), TSAT (18.5% ± 11.7% vs 13.6% ± 7.4%, p = 0.044), serum levels of transferrin (186 ± 40 vs 213 ± 51 mg/dL, p = 0.013), and serum levels of C-reactive protein (1.0 ± 2.3 vs 2.8 ± 5.8 mg/L, p = 0.036). However, between survivors and nonsurvivors, there were no significant differences regarding Kt/V (1.1 ± 0.2 vs 1.1 ± 0.3, p = 0.647), URR (64.5% ± 5.0% vs 64.5% ± 8.5%, p = 0.632), or serum levels of β_2-microglobulin (3.5 ± 1.2 vs 5.4 ± 5.8 mg/L, p = 0.068) (Table 2).

Comment [KVS4]: AUTHOR: Please note that "microgrobulin" has been changed to "microglobulin" throughout.

The Kaplan–Meier survival curves and the log-rank (Mantel–Cox) test values ($p = 0.079$) for the 3-year survival after assessment of RLS are shown in Fig. 2. The proportional hazards assumption holds. The respective univariate Cox regression analysis showed no significant association of mortality with the diagnosis of RLS (HR = 0.671, 95% CI = 0.429–1.051, $p = 0.081$), the existence of RLS before the onset of HD (HR = 0.800, 95% CI = 0.564–1.135, $p = 0.211$), or the severity of RLS (HR = 0.899, 95% CI = 0.720–1.120, $p = 0.346$). In the same analysis, diabetic nephropathy as the primary disease ($p = 0.039$), aging ($p < 0.001$), and enhanced serum β_2-microglobulin ($p < 0.001$), C-reactive protein ($p < 0.001$), and calcium ($p < 0.001$) all favored mortality in HD patients, whereas increased hemoglobin ($p = 0.037$), serum iron ($p = 0.004$), and TSAT ($p = 0.005$) did not (Table 3).

In a primary multivariate proportional hazards regression (Cox regression) analysis, there was no significant association between RLS and 3-year all-cause mortality even in the age- and sex-adjusted model (HR = 0.772, 95% CI = 0.488–1.219, $p = 0.267$). After adjustment for potential determinants of RLS there was no significant effect of the diagnosis RLS on survival of HD patients (HR = 0.669, 95% CI = 0.413–1.084, $p = 0.102$). In this first model, only age ($p = 0.001$) and β_2-microglobulin ($p < 0.001$) were independent survival predictors. The reduced final model, calculated on the basis of the above findings, is shown in Table 4. Similarly, after adjustment for all potential determinants of mortality, there was no significant effect of RLS on survival (HR = 0.676, 95% CI = 0.412–1.110, $p = 0.122$). In this second model, diabetic nephropathy as primary disease ($p = 0.013$), age ($p = 0.027$), β_2-microglobulin ($p = 0.002$), and C-reactive protein ($p < 0.001$) were the only independent survival predictors. The final results of the respective reduced model are shown in Table 3.

Kaplan–Meier survival curves and log-rank (Mantel Cox) test values (p = 0.052) for the 5-year survival after initiation of HD are shown in Fig. 3. The proportional hazards assumption holds. The univariate Cox regression analysis of the 5-year survival showed no significant association of mortality either with the diagnosis of RLS (HR = 0.653, 95% CI = 0.417–1.022, p = 0.063) or with the severity of RLS (HR = 0.881, 95% CI = 0.707–1.098, p = 0.260). In the same analysis, age at dialysis onset (p < 0.001), diabetic nephropathy as the primary disease (p = 0.001), HDF as dialysis modus (p = 0.023), and enhanced serum levels of β_2-microglobulin (p < 0.001), C-reactive protein (p < 0.001), or calcium (p = 0.001) all favored mortality in HD patients, whereas increased levels of hemoglobin (p = 0.002), serum iron (p = 0.007), and TSAT (p = 0.005) favored survival (Table 5).

In the primary multivariate proportional hazards regression (Cox regression) analysis there was no significant effect of the diagnosis of RLS on the 5-year survival of HD patients after adjustment for potential determinants of RLS (HR = 0.691, 95% CI = 0.427–1.117, p = 0.131). The reduced model, calculated on the basis of this analysis, is shown in Table 4. Similarly, after adjustment for potential determinants of mortality, we found no significant effect of RLS on survival (HR = 0.694, 95% CI = 0.419–1.151, p = 0.157). In this model, the age at HD onset (p = 0.003), diabetic nephropathy as the primary disease (p = 0.005), and enhanced serum levels of β_2-microglobulin (p = 0.022) or C-reactive protein (p = 0.003) were found to be independent survival predictors in HD patients. Findings from the reduced final model, calculated on the basis of the above results, are shown in Table 5.

4. Discussion

The data from the current study did not confirm the hypothesis of a positive association between RLS and increased mortality in the HD population. Similarly, in contrast to previous surveys [13], in our study there was no observed association between mortality of HD patients and severity of RLS.

Large epidemiological studies have revealed a positive association between RLS and mortality in the general population [16,17]. This outcome has been explained mainly by the detrimental effect of idiopathic RLS on metabolic, biochemical, and immunological factors, all known to directly or indirectly increase the risk for overall and/or cardiovascular mortality [6,16,25]. However, other recent studies strongly argue against the link between RLS and high overall mortality or cardiovascular morbidity and mortality [18,26].

Similarly with the case of idiopathic RLS, the issue of mortality and uremic RLS is still controversial. Only a few studies have reported an association between the presence and/or severity of uremic RLS and high mortality rates [12–15]. In particular, increased severity of uremic RLS has been associated with an increased incidence of cardiovascular events as well as with a higher mortality rate in patients treated with HD [15] or with a kidney transplant [14]. The study by Unruh et al. (2004) also reported an association of severe RLS with mortality [13]. The number of patients analyzed was quite limited in these reports [12,15], and lack of power might be a plausible explanation for the conflicting findings between the present and previous reports of mortality in uremic RLS. Publication bias may be another reason for this contradiction. Survival studies, all positive, seem to be very scarce [12,13,15] among epidemiological surveys on RLS in HD patients [11,14,27–36].

According to further recent publications, various factors may be involved in the potentially increased mortality risk for the uremic RLS patients. It seems that the

common denominator of those factors is the detrimental effect of RLS on sleep, which in turn affects a number of physiological and psychological parameters that may be associated with increased mortality. Briefly, uremic RLS has been reported to be associated with diabetes mellitus [13], chronic inflammation, as indicated by the increased C-reactive protein levels [15], and sleep impairment [33,37], a factor that is well known to be associated with a cascade of pathological conditions that affect health and mortality [38].

In our current study, the probability of survival in patients with RLS somehow exceeded that of HD patients free of RLS, an unexpected trend that did not reach statistical significance. Survivor bias induced by the cross-sectional design might be another causative factor for this trend. In this context, a second survival analysis taking into account the time from the onset of HD treatment yields mostly identical findings. Furthermore, confounders, namely, RLS-predisposing variables according to the primary cross-sectional study, were checked in a separate multivariate (adjusted) analysis. In this model, only aging and increased β_2-microglobulin levels were significantly predictive of mortality. Both of these confounding factors might influence results, especially taking into account that, in the present study, the RLS-positive group was approximately 5 years younger that the RLS-negative group.

Several known mortality risk factors in CKD (i.e., albumin, Kt/V, CaxP product) were not significantly associated with shorter survival of HD patients with RLS in our study. Confounding bias might be a reason for these conterintuitive findings. Nevertheless, in our study, there were significant differences between survivors and nonsurvivors regarding other clinical and biochemical characteristics, which have already been reported to be associated with increased mortality. In particular, serum levels of C-reactive protein were found to be significantly greater in

the nonsurvivor group of patients. In the multivariate model, increased serum levels of C-reactive protein are significant predictors of mortality. Interestingly, according to previous studies, uremic RLS may be associated with elevated C-reactive protein levels [15]. Other study results, however, contradict the above findings [13].

We recently reported that increased serum levels of β_2-microglobulin may be associated with an increased prevalence of uremic RLS in HD patients [11]. In the present study, β_2-microglobulin levels appeared to be significantly increased in nonsurvivors. In multivariate models, increased β_2-microglobulin levels were significantly predictive of mortality.

Diabetes mellitus, a major cause of mortality among HD patients [39], has been also reported to be associated with severe RLS symptoms [13]. In the current study, the frequency of diabetic nephropathy was higher in RLS HD patients who did not survive in comparison to those who did survive. Although this difference was not statistically significant, in the multivariate model, diabetic nephropathy as a primary renal disease was a significant predictor against survival. This is in contrast with outcomes of previous studies in which diabetes mellitus was not associated with survival in HD patients with RLS [12].

Various comorbidities and, in particular, cardiovascular risk factors are reported to be significant independent predictors of idiopathic RLS [40]. However, idiopathic RLS itself has not been shown to be a risk factor for cardiovascular morbidity [40,41] unless perhaps when duration of RLS symptoms is taken into account [17]. It is well known that patients with RLS (either secondary or idiopathic) also experience increased leg movement activity during the night, known as periodic limb movements in sleep (PLMS), which is reportedly present in 80% of cases [42,43]. PLMS severity was reported to be associated with high mortality in patients

with end-stage renal disease [44]. In addition, our group has reported that HD patients with severe PLMS were found to exhibit significant alternations in cardiac structure [45], which has been also confirmed in patients with idiopathic RLS [46]. Interestingly, in this previous study [45], the severity of RLS, in contrast to the severity of PLMS, was not related to structural cardiac abnormalities. In addition, it has been shown that RLS patients with severe PLMS present with significantly enhanced C-reactive protein levels in comparison to those with fewer PLMS [47]. In the current study, we did not assess PLMS, which is common in studies of uremic RLS, as it is difficult to persuade HD patients to undergo a full polysomnography for the purposes of an epidemiological study. Moreover, in the current study, the severity of RLS, assessed by the IRLSSG rating scale, was not associated with all-cause mortality in HD patients.

The main strengths of this study are the large number of patients (one of the highest in the literature) and the validated measures used for the initial RLS diagnosis (including personal interview and confirmation by an expert neurologist) [11]. Limitations of the current study are all those of a survival analysis with a cross-sectional and retrospective design. Cross-sectional investigations of survival with prevalent case assessment may be associated with a significant survivor bias. In addition, the time-point of RLS onset was not assessed, although duration of RLS symptoms might significantly influence mortality [17]. Patient data were drawn from medical records kept in the different dialysis units, and mortality data were acquired from the national end-stage renal disease registry [22] and confirmed or clarified when necessary from the above medical records. No time-dependent variables were assessed. In the 3-year follow-up, no information was assessed about treatment of RLS in our patients. It is important to recognize this as another study limitation,

especially because participation in the primary cross-sectional study has probably enhanced awareness and also the treatment rate of RLS, which in turn might have significantly influenced survival. In this context, data about kidney transplantation during the 3-year follow-up time were not assessed. Taking into account these limitations, any conclusions about mortality based on this study must be drawn with great caution [48,49]. A further weakness is that we did not assess PLMS, which has been associated with increased cardiovascular risk in HD patients [45] and could prove to be a significant factor in explaining literature discrepancies regarding mortality or cardiovascular risk in HD patients.

In conclusion, the existence of an RLS diagnosis according to the essential clinical criteria of the IRLSSG did not influence the 3-year mortality rate in HD patients. Likewise, there was no association between RLS and 5-year mortality after HD onset. Our findings are in contrast to those of some previous studies, and reinforce the need for further investigations regarding RLS and mortality in HD patients.

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Fig. 1. Flowchart of participants in the epidemiological survey on the RLS in hemodialysis (HD) patients in Greece. There were 24 patients who were unable to participate due to inability to communicate (n = 2) or due to absence from the dialysis unit because of hospitalization (n = 18) or vacation (n = 6). These reasons for exclusion were irrelevant to the study protocol. In total, 579 HD patients gave informed consent and were analyzed in the epidemiological study.

Fig. 2. Kaplan–Meier analysis of 3-year survival probability after initialization of the study. On comparison, performed by log-rank (Mantel–Cox) test, there was no significant difference (p = 0.079) of survival between hemodialysis (HD) patients with restless legs syndrome (RLS; n = 154) and HD patients without RLS (n = 425).

Fig. 3. Kaplan–Meier analysis of 5-year survival probability after commencement of hemodialysis (HD) treatment. On comparison, performed by log-rank (Mantel–Cox) test, there was no significant difference ($p = 0.052$) of survival between HD patients with restless legs syndrome (RLS; $n = 154$) and HD patients without RLS ($n = 425$).

Table 1

Clinical profiles of patients with end-stage renal disease on hemodialysis (HD) treatment (N = 579).

	HD patients						
	Total	RLS^{-}	RLS^{+}	p *	RLS^{+} survived	RLS^{+} died	p *
	n (%) [a]	n (%) [b]	n (%) [b]		N (%) [b]	n (%) [b]	
Primary kidney disease							
Diabetic nephropathy	135 (23.3)	105 (77.8)	30 (22.2)		23 (76.7)	7 (23.3)	
Vascular kidney disease	135 (23.3)	93 (68.9)	42 (31.1)		36 (85.7)	6 (14.3)	
Glomerulonephritis	102 (17.6)	71 (69.6)	31 (30.4)		28 (90.3)	3 (9.7)	
Polycystic kidney disease	37 (6.4)	26 (70.3)	11 (29.7)		8 (72.7)	3 (27.3)	
Chronic interstitial nephritis	51 (8.8)	40 (78.4)	11 (21.6)		9 (81.8)	2 (18.2)	
Systemic disease	27 (4.7)	19 (70.4)	8 (29.6)		7 (87.5)	1 (12.5)	
Other causes	76 (13.1)	58 (76.3)	18 (23.7)		16 (88.9)	2 (11.1)	
Unknown etiology	16 (2.8)	13 (81.2)	3 (18.8)	0.624	3 (100)	0 (0)	0.741

Sum	579 (100)	425 (73.4)	154 (26.6)	N/A	130 (84.4)	24 (15.6)	N/A
Profile of HD patients with RLS	*n* (%) [a]	*n* (%) [a]	*n* (%) [a]		*n* (%) [a]	*n* (%) [a]	
RLS family history[§]	6 (1.04)	1 (0.24)	5 (3.25)	0.006	5 (3.8)	0 (0)	0.329
RLS beginning before HD	31 (5.35)	N/A	31 (20.1)	N/A	24 (18.5)	7 (29.2)	0.229
Peripheral neuropathy	86 (14.8)	52 (12.2)	34 (22.1)	0.005	27 (20.8)	7 (29.2)	0.362
Severity (IRLSSG rating scale)	*n* (%) [a]	*n* (%) [a]	*n* (%) [a]		*N* (%) [a]	*n* (%) [a]	
Mild RLS (<11)	66 (11.4)	N/A	66 (42.9)		59 (45.4)	7 (29.2)	
Moderate RLS (11–20)	63 (10.9)	N/A	63 (40.9)		52 (40.0)	11 (45.8)	
Severe RLS (21–30)	21 (3.6)	N/A	21 (13.6)		16 (12.3)	5 (20.8)	
Very severe RLS (31–40)	4 (0.7)	N/A	4 (2.6)	N/A	3 (4.2)	1 (4.2)	0.430

Comparison between HD patients with RLS (*n* = 154) or without RLS (*n* = 425) in an initial assessment and comparison between survivors (n = 130) or nonsurvivors (*n* = 24) with RLS in a 3-year survival analysis. *p* Values were calculated by the Mann–Whitney *U* test for continuous variables or the χ^2 test for categorical variables. IRLSSG, International Restless Legs Syndrome Study Group; N/A, ; RLS, restless legs syndrome; RLS family history, RLS diagnosis in at least one first-degree relative (free of nephropathy) of the patient.

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[a] Percentage of column total number (*n*).

[b] Percentage of row total number (*n*).

Table 2

Clinical and laboratory parameters in patients with end-stage renal disease on hemodialysis (HD) treatment (*N* = 579).

	HD patients						
Parameter	Total HD	RLS$^-$	RLS$^+$	*p**	RLS$^+$ survived	RLS$^+$ died	*p*[1]
No. of patients (*n*)	579	425	154	N/A	130	24	N/A
Sex (male/female)	343/236	260/165	83/71	0.126	71/59	12/12	0.824
Age (y)	65 ± 13	66 ± 13	61 ± 13	**<0.001**	60 ± 13	67 ± 10	**0.041**
Time on HD (mo)	42.9 ± 44.7	41.3 ± 45.0	47.4 ± 43.6	0.071	48.6 ± 44.2	40.6 ± 40.1	0.311
Body mass index (kg/m^2)	25.3 ± 4.1	25.3 ± 4.0	25.4 ± 4.2	0.925	25.2 ± 3.9	26.5 ± 5.2	0.388
Mode of treatment (HDF/HD)	134/445	93/332	41/113	0.265	36/94	5/19	0.618
Diabetic nephropathy (yes/no)	135/444	105/320	30/124	0.118	23/107	7/17	0.192
Serum urea before HD (mg/dL)	152 ± 35	150 ± 36	155 ± 33	0.197	155 ± 34	156 ± 38	0.749
Urea reduction ratio (%)	65.1 ± 6.2	65.3 ± 6.4	64.5 ± 5.6	0.144	64.5 ± 5.0	64.5 ± 8.5	0.632
Kt/V	1.1 ± 10.2	1.1 ± 0.2	1.1 ± 0.2	0.343	1.1 ± 0.2	1.1 ± 0.3	0.647

β_2-Microglobulin (mg/L)	3.4 ± 1.8	3.3 ± 1.3	3.8 ± 2.6	**0.011**	3.5 ± 1.2	5.4 ± 5.8	0.068
C-reactive protein (mg/L)	1.2 ± 2.7	1.2 ± 2.5	1.3 ± 3.2	0.890	1.0 ± 2.3	2.8 ± 5.8	**0.036**
Albumin (g/dL)	4.09 ± 0.36	4.07 ± 0.37	4.13 ± 0.32	0.100	4.15 ± 0.32	4.05 ± 0.32	0.254
Hemoglobin (g/dL)	11.3 ± 1.2	11.3 ± 1.2	11.2 ± 1.3	0.632	11.2 ± 1.3	11.2 ± 1.1	0.594
Serum iron (μg/dL)	48.3 ± 27.4	49.4 ± 28.0	45.2 ± 25.5	0.067	46.4 ± 26.5	38.6 ± 18.1	0.408
Ferritin (ng/mL)	270 ± 259	275 ± 249	254 ± 286	**0.035**	221 ± 289	217 ± 274	0.733
Transferrin (mg/dL)	191 ± 44	191 ± 44	190 ± 43	0.582	186 ± 40	213 ± 51	**0.013**
Transferrin saturation (%)	18.9 ± 11.6	19.3 ± 11.7	17.8 ± 11.3	0.109	18.5 ± 11.7	13.6 ± 7.4	**0.044**
Calcium (mg/dL)	8.8 ± 0.8	8.8 ± 0.8	8.8 ± 0.8	0.390	8.7 ± 0.8	9.1 ± 1.0	0.153
Phosphorus (mg/dL)	5.5 ± 1.7	5.4 ± 1.6	5.8 ± 1.7	**0.037**	5.8 ± 1.8	5.8 ± 1.2	0.585
CaxP product (mg^2/dL^2)	48.8 ± 15.9	47.9 ± 15.3	51.2 ± 17.1	0.072	50.9 ± 17.6	52.9 ± 14.7	0.420
Alkaline phosphatase (U/L)	97 ± 52	96 ± 52	98 ± 50	0.757	100 ± 52	84 ± 36	0.350

Intact parathormone (pg/mL)	294 ± 259	272 ± 240	356 ± 298	**0.001**	341 ± 298	434 ± 293	0.108

Comparison between HD patients with restless legs syndrome (RLS) (*n* = 154) and without RLS (*n* = 425) at initial assessment and between survivors (*n* = 130) and nonsurvivors with RLS (*n* = 24) in a 3-year survival analysis. Continuous variables are expressed as mean and standard deviation (mean ± SD), categorical values are expressed as frequency (*n*). *p* Values were calculated by the Mann–Whitney *U* test for continuous variables or the χ^2 test for categorical variables. HDF, hemodiafiltration.

Table 3

Multivariate survival analysis by proportional hazards regression (Cox regression) model.

	Proportional hazards (Cox) regression analysis for 3-year mortality			
Predictor variable	Crude HR (95% CI)	*p*	Adjusted HR (95% CI)	*p*
RLS	0.671 (0.429–1.051)	0.079	0.667 (0.417–1.069)	0.092
Age (y)	1.030 (1.014–1.047)	<0.001	1.024 (1.007–1.041)	**0.005**
Diabetic nephropathy	1.511 (1.021–2.236)	0.039	1.316 (1.008–1.956)	**0.017**
C-reactive protein (mg/L)	1.106 (1.065–1.148)	<0.001	1.102 (1.059–1.146)	**<0.001**
β_2-Microglobulin (mg/L)	1.102 (1.048–1.158)	<0.001	1.107 (1.049–1.167)	**<0.001**

Covariates included in the model are as follows: age (i.e., age in years at study initiation), sex (male/female), diabetic nephropathy (yes/no), duration of dialysis (months), dialysis mode (hemodiafiltration or hemodialysis), body mass index (kg/m^2), serum urea before HD (mg/dL), urea reduction ratio (%), Kt/V, β_2-microglobulin (mg/L), C-reactive protein (mg/L), albumin (g/dL), hemoglobin (g/dL), serum iron (μg/dL), ferritin (ng/mL), transferrin (mg/dL), transferrin saturation (%), calcium (mg/dL), phosphorus (mg/dL), CaxP product (mg^2/dL^2), and intact parathyroid hormone (pg/mL). Outcome in model was 3-year survival of hemodialysis patients after assessment of RLS (i.e., initiation of cross-sectional study). Existence of RLS served as a categorical variable, and potential determinants of mortality recorded in hemodialysis patients were independent variables (covariates) in the model. Only covariates that were significant determinants of survival in the primary multivariate analysis were included in reduced model shown. CI, confidence interval; HR, hazard ratio; RLS, restless legs syndrome.

Table 4

Multivariate survival analysis by two proportional hazards regression (Cox regression) models.

	Proportional hazards (Cox) regression analysis			
	Model for 3-year mortality [a]		Model for 5-year mortality [b]	
Predictor variable	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*p*
RLS	0.709 (0.443–1.135)	0.152	0.762 (0.476–1.220)	0.258
Age (y) [c]	1.028 (1.011–1.045)	**0.001**	1.037 (1.020–1.054)	**<0.001**
β_2-Microglobulin (mg/L)	1.113 (1.058–1.171)	**<0.001**	1.115 (1.054–1.181)	**<0.001**

Only the covariates that were significant determinants of survival in the primary multivariate analysis were included in the finally applied reduced models shown. Outcome in the first model was the 3-year survival of hemodialysis patients after assessment for RLS symptoms (i.e., initiation of the primary cross-sectional study); outcome in the second model 5-year survival after end-stage onset (i.e., initiation of hemodialysis). Existence of RLS served as a categorical variable and potential determinants of the diagnosis RLS recorded in hemodialysis patients were the independent variables (covariates) in the model. CI, confidence interval; HR, hazard ratio; RLS, restless legs syndrome.

[a] Covariates in first model (for 3-year mortality): age (i.e., age in years at study initiation), β_2-microglobulin (mg/L), ferritin (ng/mL), phosphorus (mg/dL), and intact parathyroid hormone (pg/mL).

[b] Covariates in second model (for 5-year mortality): age at end-stage onset (i.e., age in years at initiation of hemodialysis), β_2-microglobulin (mg/L), ferritin (ng/mL), phosphorus (mg/dL), and intact parathyroid hormone (pg/mL).

[c] Age (y) represents the age at RLS assessment (i.e., age in years at study initiation) in the first model (for 3-year mortality) and the age at end-stage onset (i.e., age in years at initiation of hemodialysis) in the second model (for 3-year mortality), respectively.

Table 5

Multivariate survival analysis by a proportional hazards regression (Cox regression) model.

	Proportional hazards (Cox) regression analysis for 5-year mortality			
Predictor variable	Crude HR (95% CI)	*p*	Adjusted HR (95% CI)	*p*
RLS	0.653 (0.417–1.022)	0.063	0.644 (0.399–1.0380)	0.071
Age (y)	1.039 (1.022–1.055)	<0.001	1.021 (1.005–1.038)	**0.012**
Diabetic nephropathy	1.938 (1.306–2.875)	0.001	1.693 (1.131–2.535)	**0.010**
C-reactive protein (mg/L)	1.080 (1.041–1.121)	<0.001	1.080 (1.037–1.125)	**<0.001**
β_2-Microglobulin (mg/L)	1.109 (1.048–1.173)	<0.001	1.106 (1.042–1.174)	**0.001**

Only the covariates that were significant determinants of survival in the primary multivariate analysis were included in the reduced model shown. Covariates included in the model were as follows: age (in years, at initiation of hemodialysis), sex (male/female), diabetic nephropathy (yes/no), dialysis mode (hemodiafiltration or hemodialysis), body mass index (kg/m^2), serum urea before hemodialysis (mg/dL), urea reduction ratio (%), Kt/V, β_2-microglobulin (mg/L), C-reactive protein (mg/L), albumin (g/dL), hemoglobin (g/dL), serum iron (μg/dL), ferritin (ng/mL), transferrin (mg/dL), transferrin saturation (%), calcium (mg/dL), phosphorus (mg/dL), CaxP product (mg^2/dL^2), and intact parathyroid hormone (pg/mL). Outcome in the model was the 5-year survival of hemodialysis patients after disease onset (i.e., initiation of hemodialysis). Existence of RLS served as a categorical variable and potential determinants of mortality recorded in hemodialysis patients were the independent variables (covariates) in the model. CI, confidence interval; HR, hazard ratio; RLS, restless legs syndrome.