Restless legs syndrome enhances cardiovascular risk and mortality in patients with end-stage kidney disease undergoing long-term haemodialysis treatment

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Abstract

Background. Restless legs syndrome (RLS) is a sensori-motor neurological disorder characterized by paraesthesia, dyseaesthesia and the irresistible urge to move the legs especially at night. Its prevalence is much higher among dialysis patients at 12 to 62% compared to 3 to 9% in the general population. Here, we investigated the association between RLS and cardiovascular events risk and laboratory parameters in end-stage kidney disease (ESKD) patients on dialysis.

Methods. One hundred ESKD patients undergoing haemodialysis were enrolled in an 18-month prospective observational study. The main outcomes were the associations of RLS with new cardiovascular events and laboratory parameters in end-stage kidney disease patients at 12 to 62% compared to 3 to 9% in the general population. Here, we investigated the association between RLS and cardiovascular events risk and laboratory parameters in end-stage kidney disease (ESKD) patients on dialysis.

Results. RLS affected 31% of the study population. It was associated with female gender, gradual reduction in residual diuresis, lower albumin (P = 0.039) and inflammation, but not the dialysis parameters Kt/V and URR. During observation, 47% of patients experienced new cardiovascular events (64.5% with and 39.1% without RLS; P = 0.019). New cardiovascular events increased with severity of RLS [intermittent (I-RLS) vs continuous (C-RLS)]. Mortality was 20.0% in all patients, 32.3% in those with and 14.5% in patients without RLS (P = 0.04). In patients with I-RLS, mortality was 23.8% compared to 55.6% in patients with C-RLS (P = 0.014). Multivariate analysis confirmed the relationship between RLS and mortality.

Conclusions. This study confirmed the high prevalence of RLS among dialysis patients and the associations between the severity of RLS and the risk of new cardiovascular events and higher short-term mortality.

Keywords: cardiovascular outcome; haemodialysis; mortality; restless legs syndrome

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Introduction

Restless legs syndrome (RLS) is a neurological disorder characterized by sensorimotor symptoms such as paraesthesia and restlessness that mainly affect the lower limbs, occurring during rest in the evenings or overnight and are at least partially relieved by movement [1]. RLS can be primary or can occur as a secondary disorder in association with medical conditions, including iron deficiency or other neurological disorders, or with physiological situations such as pregnancy, that may precipitate symptoms [2]. From epidemiological studies carried out in Northern Europe, the prevalence of RLS is 5 to 10% in adults with a high occurrence of familial patterns. RLS may occur at any age and its clinical course is linked to the age at onset: early-onset RLS (before the age of 45 years) shows an intermittent course (I-RLS) that generally worsens to daily occurrence of symptoms later in life, whereas late-onset RLS frequently begins with or rapidly progresses to a continuous course (C-RLS) [2].

Studies in patients with end-stage kidney disease (ESKD) showed a prevalence of RLS ranging from 12 to 62%, which is significantly higher compared to the general population [3–15]. The aetiology of RLS in uraemia is still not well defined, but the role of renal insufficiency is confirmed by the resolution or improvement of RLS symptoms after kidney transplantation and by their recurrence after graft failure [16,17]. Additional evidence of the association between RLS and declining renal function in transplanted patients further suggests a link with the severity of chronic kidney insufficiency [17].

RLS negatively impacts outcomes in patients with ESKD undergoing long-term haemodialysis, with prominent effects on sleep quality [10,12], quality of life [9,10], precocious dialysis discontinuation (‘off-signs’) [4] and a notable higher mortality at 2.5 years of follow-up [4,9,17]. Recently, an association between RLS and cardiovascular disease (CVD) or cardiovascular risk factors was established in the general population [18–23]. CVD represents the main cause of morbidity and mortality in patients with ESKD undergoing haemodialysis with a CVD-related mortality 10–20 times higher than the general population [24,25]. The increased cardiovascular events are not completely attributable to well-known cardiovascular risk factors such as arterial hypertension, diabetes, smoking, obesity and physical inactivity. An additional risk may be ascribed to risk factors specific to ESKD conditions such as uraemia, mineral metabolism disorders, inflammation, oxidative stress and malnutrition [26]. Moreover, chronic inflammation affects 30 to 50% of haemodialysis patients, and high C-reactive protein (CRP) levels are strongly associated with a 3 to 5-fold increased rate of coronary events and of cardiovascular or all-causes mortality in the general population as well as in ESKD patients undergoing haemodialysis [27]. Finally, systemic inflammation has been linked to poor sleep quality in haemodialysis patients [28] and in the general population [29], but evidence connecting RLS directly to inflammation is still lacking.

The goal of this study was to evaluate the potential association of RLS with inflammation, the occurrence of new cardiovascular events and mortality at 18-month follow-up in a population of 100 ESKD patients undergoing long-term haemodialysis treatment.

Materials and methods

Study subjects

All patients receiving long-term haemodialysis at the Dialysis Centre of the S. Orsola University Hospital were evaluated for inclusion in this study. The protocol was approved by the institution ethics committee of the S. Orsola University Hospital, and a written informed consent was obtained from all subjects to participate in a study with non-invasive tests (Protocol SLEEP 09-01, approved on 10 February 2009). Among the 126 patients, 8 did not give consent, 18 were not enrolled based on exclusion criteria and 100 were eligible for the study. Patients were included if they had chronic kidney disease and were on dialysis three times a week. Exclusion criteria were beginning dialysis treatment <3 months before the study entry or presence of malignancies including myeloma and lymphoproliferative disorders, cachexia or severe infection.

Study design

This was a prospective observational study of 100 prevalent dialysis patients with an 18-month follow-up, which carefully assessed neurological symptoms of RLS in all patients at baseline with subsequent observation of major clinical and laboratory parameters.

RLS assessment

Neurological evaluation was conducted through direct interview by a neurologist trained in Sleep Medicine who assessed the presence of the four diagnostic criteria established by the International RLS Study Group [1]. The RLS severity was also investigated by means of the international RLS rating scale (IRLSS) [31]. RLS diagnosis required positive answers to the four diagnostic criteria, an IRLSS score ≥ 4 and the occurrence of symptoms at least twice per week. Additionally, RLS was classified as intermittent (I-RLS) or continuous (C-RLS) on the basis of the reported clinical course from the start of RLS symptoms to the time of neurological assessment.

Data collection

The main clinical outcomes were all-cause mortality and occurrence of a cardiovascular event (myocardial infarction, cerebral stroke or peripheral artery occlusion). The causes of kidney failure (glomerular, interstitial, diabetic, vascular, polycystic or ESKD) were systematically recorded.

As Table 1A shows, diabetic patients and patients with renal transplants were not excluded from the study, representing 29 and 18% of the total population, respectively. Table 1A also reports the clinical characteristics of the population [age, gender, body mass index (BMI)], including the evaluation of comorbidities using the Charlson index and the ESRD comorbidity index [30] and the dialysis characteristics, namely dialysis technique, dialysis vintage (months from the start of haemodialysis), dialysis schedule, dialysis efficacy by means of urea reduction rate (URR) and single pool Kt/V (spKt/V) and residual diuresis.

Laboratory determinations

As depicted in Table 1B, the laboratory analyses, performed within 4 weeks from clinical assessment, included white blood cell count, haemoglobin, haematocrit, iron status (iron; ferritin; transferring; TIBC, total iron binding capacity), inflammation markers (ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; and fibrinogen), standard biochemical indices, electrolytes and intact parathyroid hormone (i-PTH).

Statistical analysis

All data were explored with descriptive statistics (mean and standard deviation or median and interquartile range for continuous variables and frequency for categorical data) for the whole population and for the subpopulations with or without RLS. Box plot representation was used
to describe dialysis vintage in patients without RLS and in patients with I-RLS or C-RLS.

Patients with RLS were compared to those without RLS using the chi-square test, Fisher's exact test or Wilcoxon test as appropriate and differences were considered significant if the P-value was <0.05. Kaplan–Meier curves for patients with or without RLS were constructed for all-cause mortality and compared by log-rank test. Each factor significantly associated with clinical outcome in the univariate analysis was included in two Cox regression models with occurrence of new cardiovascular events and mortality as the dependent variable. Interactions between RLS and clinical or laboratory variables were also tested by the Cochran–Mantel–Haenszel test. Two models were fit for each outcome, one including RLS classified as absent or present and a second including RLS classified as absent, intermittent and continuous.

Results

Of the dialysis patients enrolled, 31% had RLS, with continuous and intermittent course in 30 and 70%, respectively. The demographic, clinical and biochemical characteristics of the whole study population and of the patients with and without RLS are shown in Table 1.
The laboratory features of the groups are summarized in Table 1B. There were no significant differences between dialysis patients with and without RLS in terms of haemoglobin, proteins, uric acid levels, phosphorus and i-PTH. Likewise, iron status was similar in the two groups.

Compared to those without RLS, the patients with RLS presented significantly higher levels of white blood cell count, ESR and fibrinogen and decreased levels of albumin.

With regard to cardiovascular outcome, we observed that the patients who experienced new cardiovascular events had significantly higher values of CRP and fibrinogen (P = 0.008 and P = 0.021, respectively; Table 2). However, the effect of CRP could not be considered an independent risk factor for the outcome because its association with new cardiovascular events was not statistically significant in multivariate analysis (Table 3).

**RLS and outcomes**

In the whole study population, 47% of patients experienced a new cardiovascular event during the observation period following neurological evaluation, and the mortality at 18 months was 20%. The incidence of new cardiovascular events in patients with RLS was 64.5% compared to 39.1% in patients without RLS (chi-square = 5.53, P = 0.019; Figure 1A). Table 3 shows that the association between RLS and new cardiovascular events was unchanged in multivariate analysis.

Comparing the subsets of patients with intermittent (I-RLS) and continuous (C-RLS) RLS, there were increased new cardiovascular events in patients with more severe RLS characterized by persistent symptoms (57.1 and 88.9% in I-RLS and C-RLS patients, respectively; Figure 1B). In the multivariate model, patients with C-RLS had a higher risk (more than 2-fold) of incurring a new cardiovascular event compared to patients without RLS (HR = 2.36, 95% CI = 0.83–6.71), while patients with I-RLS had an 80% increase in the risk of new cardiovascular events (HR = 1.83, 95% CI = 0.77–4.36), although these findings did not meet statistical significance.

The presence of RLS was also significantly associated with mortality at 18 months. Figure 2 shows the Kaplan-Meier curves which highlighted a higher survival rate in patients without than in patients with RLS (log-rank test P = 0.057). Mortality in patients with RLS was 32.3% compared to 14.5% in patients without RLS (chi-square = 4.21, P = 0.04; Figure 3A). Mortality was also increased in patients with C-RLS (55.6%) compared to patients with I-RLS (23.8%; chi-square = 8.54, P = 0.014; Figure 3B). The association between RLS and mortality was confirmed by multivariate analysis, taking into account the confounding effects of other clinical or demographic factors, and patients with RLS had a significantly higher mortality with hazard ratio of 3.28 (95% CI = 1.08–9.93).

**Table 3. Results from multivariate Cox analysis for new cardiovascular events**

<table>
<thead>
<tr>
<th>Model 1</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04 (1.01–1.07)</td>
<td>0.014</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.15 (0.57–2.30)</td>
<td>0.705</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>1.08 (0.90–1.30)</td>
<td>0.418</td>
</tr>
<tr>
<td>Proteinemia</td>
<td>0.70 (0.30–1.65)</td>
<td>0.417</td>
</tr>
<tr>
<td>Residual diuresis (&gt;0 vs 0)</td>
<td>0.66 (0.28–1.58)</td>
<td>0.349</td>
</tr>
<tr>
<td>CRP</td>
<td>1.16 (0.75–1.80)</td>
<td>0.504</td>
</tr>
<tr>
<td>Albumin</td>
<td>1.20 (0.37–3.91)</td>
<td>0.768</td>
</tr>
<tr>
<td>Dialysis vintage</td>
<td>1.00 (0.99–1.01)</td>
<td>0.451</td>
</tr>
<tr>
<td>Dialysis hours/session</td>
<td>1.21 (0.05–30.34)</td>
<td>0.908</td>
</tr>
<tr>
<td>RLS vs No RLS</td>
<td>2.01 (0.98–4.12)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 2</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04 (1.00–1.07)</td>
<td>0.025</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.13 (0.56–2.28)</td>
<td>0.732</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>1.09 (0.90–1.31)</td>
<td>0.386</td>
</tr>
<tr>
<td>Proteinemia</td>
<td>0.65 (0.26–1.64)</td>
<td>0.363</td>
</tr>
<tr>
<td>Residual diuresis (&gt;0 vs 0)</td>
<td>0.66 (0.27–1.58)</td>
<td>0.349</td>
</tr>
<tr>
<td>CRP</td>
<td>1.19 (0.76–1.86)</td>
<td>0.457</td>
</tr>
<tr>
<td>Albumin</td>
<td>1.22 (0.37–4.01)</td>
<td>0.743</td>
</tr>
<tr>
<td>Dialysis vintage</td>
<td>1.00 (0.99–1.01)</td>
<td>0.405</td>
</tr>
<tr>
<td>Dialysis hours/session</td>
<td>1.10 (0.04–27.99)</td>
<td>0.956</td>
</tr>
<tr>
<td>I-RLS vs No RLS</td>
<td>1.83 (0.77–4.36)</td>
<td>0.173</td>
</tr>
<tr>
<td>C-RLS vs No RLS</td>
<td>2.36 (0.83–6.71)</td>
<td>0.108</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein.
aSignificant P-values are indicated in bold.
bModel 1 includes age, gender, Charlson comorbidity index, proteinemia, residual diuresis, CRP and RLS classified as present (RLS) or absent (No RLS).
cModel 2 includes age, gender, Charlson comorbidity index, proteinemia, residual diuresis, CRP and RLS classified as absent (No RLS), intermittent (I-RLS) and continuous (C-RLS).
compared to patients without RLS. This risk was doubled in a dose–response fashion when considering only patients with C-RLS (HR = 6.29, 95% CI = 1.74–22.79) (Table 4).

**RLS and dialysis patients**

Table 1 describes the association between RLS and some of the main parameters of the dialysis population studied. Patient age, Charlson comorbidity index and ESKD comorbidity index were not correlated with RLS. However, increasing patient age by 1 year resulted in a rise for the risk of new cardiovascular events of 7% (HR = 1.07, CI = 1.02–1.13, P = 0.025; Table 3), and increasing Charlson score was associated with a rise in mortality risk of 33% (HR = 1.33, CI = 1.11–1.61, P = 0.003; Table 4).

Among laboratory parameters, there was no correlation of RLS with serum iron, ferritin, transferrin, haemoglobin levels or phosphorus concentration.

Likewise, Kt/V was not associated with RLS. Table 1 shows that URR, dialysis technique, dialysis vintage and dialysis schedule were not correlated with RLS, while the residual diuresis, as assessed by categories >500 mL, 0–500 mL and 0 mL, was associated with RLS (P = 0.001). As illustrated in Figure 4, RLS in general was not related to the dialysis vintage, but when we considered the subclasses, patient with C-RLS had lower dialysis vin-

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**Table 4. Results from multivariate Cox analysis for all-cause mortality**

<table>
<thead>
<tr>
<th>Model 3 ( ^b )</th>
<th>HR (95% CI)</th>
<th>P-value ( ^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (0.99–1.08)</td>
<td>0.185</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.79 (0.55–5.87)</td>
<td>0.337</td>
</tr>
<tr>
<td>BMI</td>
<td>0.80 (0.66–0.97)</td>
<td><strong>0.024</strong></td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>1.33 (1.11–1.61)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Albumin</td>
<td>0.40 (0.11–1.43)</td>
<td>0.157</td>
</tr>
<tr>
<td>Residual diuresis (&gt;0 vs 0)</td>
<td>0.53 (0.06–4.78)</td>
<td>0.574</td>
</tr>
<tr>
<td>RLS vs No RLS</td>
<td>3.28 (1.08–9.93)</td>
<td><strong>0.035</strong></td>
</tr>
</tbody>
</table>

**Model 4 \( ^c \)**

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P-value ( ^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02 (0.98–1.07)</td>
</tr>
<tr>
<td>Gender male</td>
<td>1.45 (0.43–4.82)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.8 (0.66–0.97)</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>1.35 (1.13–1.63)</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.29 (0.07–1.15)</td>
</tr>
<tr>
<td>Residual diuresis (&gt;0 vs 0)</td>
<td>0.55 (0.06–5.03)</td>
</tr>
<tr>
<td>I-RLS vs No RLS</td>
<td>1.87 (0.47–7.40)</td>
</tr>
<tr>
<td>C-RLS vs No RLS</td>
<td>6.29 (1.74–22.79)</td>
</tr>
</tbody>
</table>

BMI, body mass index.

*Significant P-values are indicated in bold.

\( ^a \)Model 3 includes age, gender, Charlson comorbidity index, BMI, albumin, residual diuresis and RLS classified as present (RLS) and absent (No RLS).

\( ^b \)Model 4 includes age, gender, Charlson comorbidity index, BMI, albumin, residual diuresis and RLS classified as absent (No RLS), intermittent (I-RLS) or continuous (C-RLS).
RLS enhances cardiovascular risk and mortality in patients with ESKD and showed significantly higher mortality and higher incidence of cardiovascular events compared to patients with I-RLS or unaffected individuals (respectively, 14 (1–24), 46 (22–110) and 21 (10–75); P = 0.022).

Discussion

Secondary RLS is a frequently occurring disorder with primary forms being a minority of all RLS cases. The pathophysiology of RLS is largely unknown, but it has been associated with several diseases such as neurological disorders affecting the central or peripheral nervous system [32], as well as with medical disorders characterized by a prominent vascular component such as chronic venous disorders or pulmonary hypertension [33,34]. Within the latter conditions, we can consider patients with chronic renal failure with [35] or without [36] requirement for dialysis treatment. Similar to previous studies [3–7,11,12,14], the prevalence of RLS was 31% in our study population of patients with ESKD undergoing haemodialysis. In other vascular conditions, the prevalence of RLS may be higher than that found in dialysis patients [34], although comparisons among different studies may be difficult due to different, frequently unreliable study approaches (e.g. questionnaires versus clinical interview) used to assess RLS [7].

The association between chronic renal failure and cardiovascular comorbidities has been extensively documented in the scientific literature [37–40]. In our haemodialysis population, the occurrence of new cardiovascular events at 18 month follow-up was ~65 and 40% in patients with and without coexistent RLS, respectively, showing an adjusted risk of cardiovascular events that was three times greater, albeit not statistically significant, in RLS versus non-RLS patients. The probability of a new cardiovascular event further rose among RLS patients with a continuous clinical course reaching a significant adjusted risk two times greater compared to dialysis patients without RLS.

Evidence from previous studies and from our population points to a strong correlation between specific phenotypes (i.e. continuous or intermittent course) of RLS and dysfunction of the cardiovascular system comparable to the correlation between the frequency of RLS symptoms and CVD in the general population [18–21]. There are well-established connections among RLS, periodic limb movement during sleep (PLMS), transient rises of heart rate [41–43] and arterial blood pressure [44,45] probably mediated by sympathetic overactivity. Based on this and the strong detrimental effect of nocturnal hypertension on the cardiovascular system, some authors recently hypothesized that nocturnal hypertension may contribute to increased cardiovascular risk in dialysis patients with RLS [46]. RLS may directly cause nocturnal hypertension by PLMS with subsequent development of daytime hypertension. To our knowledge, the presence of a non-dipping status has been proven only in a single study of children with PLMS [47], whereas in patients suffering from daytime hypertension, an association with higher prevalence of PLMS was reported [48,49], suggesting a potential role for hypertension itself in the development of RLS/PLMS. Given the lack of association between RLS and hypertension in some studies [20,21], other mechanisms such as increased atherosclerotic plaque formation and rupture or confounding comorbidities have been postulated to link RLS to CVD [23]. In uraemic patients with low plasma levels of tyrosine (amino acid precursor to dopamine) [50], we speculate that overall reduced dopaminergic activity may underlie the pathogenesis of both RLS and hypertension through different levels of the nervous and renal systems [51].

Conversely, a top-down link between nocturnal changes of blood flow dynamics in the legs and RLS has also been proposed [52]. It is therefore possible that conditions leading to an acceleration or alteration of peripheral venous blood flow may play a role in the pathogenesis of some RLS phenotypes, and accordingly, patients undergoing surgery for chronic venous disorders experience amelioration of RLS symptoms [53]. It is worth emphasizing that in our population, the spKt/V was not associated with RLS, new cardiovascular events or mortality. This may reflect the good clearance achieved by haemodialysis techniques as reflected by the limited spKt/V range (median of 1.28, range of 0.34–2.33). This also downplays the potential role of inadequate depuration and of the mean molecules in the pathogenesis of uraemic RLS. The relationship with other parameters also contributes to weakening this hypothesis. Age of dialysis, dialysis technique, dialysis duration and URR had a ‘paradoxical’ behaviour and were not correlated with RLS. The only parameter that had significant univariate correlation was the lower prevalence of RLS in patients with maintained urine output.

RLS was not associated with dialysis vintage, but when we considered the population with C-RLS, this condition assumed statistical significance: as Figure 4 shows, the patients with more severe RLS (C-RLS), characterized by higher mortality and higher incidence of cardiovascular events, had low dialysis vintage and median value lower than those with I-RLS or unaffected by RLS (respectively, 14 (1–24), 46 (22–110) and 21 (10–75); P = 0.022). These findings may suggest some daring ideas such as the existence of a ‘specific’ subpopulation with a lower dialytic age that is predisposed to more severe, persistent forms of RLS with a high incidence of cardiovascular events and greater mortality. However, it is possible that these patients die earlier, and over time, the dialysis population less prone to develop RLS survives.

From a molecular standpoint, inflammation may play a more significant role, since dialysis patients frequently have a chronic inflammatory condition. Inflammation in the context of the malnutrition inflammation and atherosclerosis syndrome (MIA) [54,55] was initially correlated to dialysis dose and efficacy, and this complex interplay was suggested as a stronger trigger for RLS occurrence than spKt/V itself. In this view, the association between low levels of albumin and RLS is of interest because a reduced concentration of albumin may represent a state of malnutrition.

This study showed that the presence of RLS and new cardiovascular events was associated with increased inflammatory markers, CRP and fibrinogen. This aspect is reported for the first time in our study [56]. We can hypothesize that the CVD may be in correlation with haemodynamic alterations and impairment of the periph-
erical microcirculation, favouring an increased blood flow and thus triggering some phenotypes of secondary RLS.

Although we failed to find a statistically significant association of CRP with new cardiovascular events in multivariate analysis, it is known that inflammation has a well-documented clinical correlation with molecules that are in themselves well-known independent cardiovascular risk factors [57,58] and are associated with increased cardiovascular mortality [59,60]. However, this point deserves better elucidation in future studies, since in our patients we found other parameters linked to inflammation, such as the BMI (protective) and the Charlson score (worsening), to be significantly associated with mortality. In our dialysis population, RLS patients had an increased risk of new cardiovascular events and mortality, the latter finding having been previously reported in two studies of ESKD patients undergoing haemodialysis [4,9]. A mortality of 32.3 and 14.5% was documented in patients with and without RLS, respectively, with further rise to 53.6% among patients with a continuous RLS course, comparable to the risk of new cardiovascular events. A significant finding is that, in patients with the persistent form of C-RLS, CRP was significantly lower than both patients with intermittent RLS in patients with the persistent form of C-RLS, CRP was significantly associated with mortality. In our dialysis population, RLS patients had an increased risk of new cardiovascular events and mortality, the latter finding having been previously reported in two studies of ESKD patients undergoing haemodialysis [4,9]. A mortality of 32.3 and 14.5% was documented in patients with and without RLS, respectively, with further rise to 53.6% among patients with a continuous RLS course, comparable to the risk of new cardiovascular events. A significant finding is that, in patients with the persistent form of C-RLS, CRP was significantly lower than both patients with intermittent RLS and individuals without RLS. This population was also characterized by a much lower dialysis vintage than the other subgroups. These findings are difficult to interpret, but suggest that RLS symptoms could be a grouping of similar clinical states or diseases resulting from different pathological mechanisms.

Conclusion

Our study confirms the high prevalence of RLS in ESKD patients undergoing long-term haemodialysis but emphasizes the need to carefully phenotype RLS with an intermittent or a continuous clinical course that may well represent different disease severities. Moreover, severe RLS (with continuous clinical course) is independently associated with the risk of new cardiovascular events and with higher mortality. Finally, RLS is also associated with some atherosclerosis-related parameters, suggesting that microcirculatory alterations may play a role in RLS pathogenesis in ESKD patients undergoing haemodialysis, representing an epiphenomenon common to different pathological processes.

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Conflict of interest statement. None declared.

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