scientific reports

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Quality of life and clinical data in hemodialysis patients with different degrees of pruritus

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Chronic kidney disease-associated pruritus (CKD-aP), a persistent itching sensation, is prevalent among hemodialysis patients. This study aims to understand its prevalence, its possible association with selected solutes, and impact on quality of life (QoL) in hemodialysis patients. Involving 434 hemodialysis patients in Spain, this observational study employed a survey based on validated pruritus assessment tools, alongside demographic, clinical, and biochemical data collection. The study used statistical analyses to examine the correlation between CKD-aP and various QoL dimensions. CKD-aP affected 46,4% (202) of the participants, with no significant variation across gender and age ($p = 0.222$ and $p = 0.379$, respectively). There were no significant associations between CKD-aP and biochemical markers like calcium, phosphate, and C-reactive protein ($p > 0.05$, in all cases). Each reporting period (morning, midday, evening, and night) revealed distinct patterns in pruritus prevalence and severity ($p < 0.05$). The nighttime report exhibited the most significant differences, as more than half of the patients with moderate to severe pruritus reported constant and frequent itching (23.0% and 27.9%, respectively). Concerning other variables and symptoms associated with QoL, pruritus group exhibited higher rates of anxiety, depression, decreased sexual desire and sexual function, and sometimes to most of the time reported sleep onset problems, sleeping pill use, and drowsiness on waking ($p < 0.001$ in all cases). When stratifying by pruritus intensity differences persisted across anxiety ($p < 0.001$) and sleep onset problems ($p = 0.018$). The findings underscore the high prevalence and severe impact of CKD-aP in QoL among hemodialysis patients, indicating a need for standardized screening and treatment approaches in clinical practice. The lack of correlation with common biochemical markers suggests an intricate pathophysiology, warranting further investigation. These insights emphasize the necessity of holistic management strategies and more research to understand CKD-aP complex nature for better patient outcomes.

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Keywords Biochemical markers, Chronic kidney disease, CKD-aP, Sexuality, Psychosocial disorders

Chronic pruritus, commonly called itching, is a skin sensation leading to an urge to scratch, persisting for six weeks or more. This symptom, varying in intensity and location across the body, arises from a multitude of factors in patients with advanced chronic kidney disease (CKD), encompassing systemic, neurological, mental, dermatological, and also uremic pruritus. The designation CKD-associated pruritus (CKD-aP) is increasingly used, acknowledging the unclear direct cause-effect link with uremia[1–5].

As chronic kidney disease (CKD) advances, pruritus becomes increasingly common, affecting nearly half of patients. Depending on the study, it is reported in 40–90% of those undergoing hemodialysis (HD)[6–8], with its prevalence rising significantly in the later stages of CKD. Approximately 19% of patients present with predialysis pruritus[9]. Despite the significant impact of pruritus on quality of life (QoL), including severe sleep disturbances, mood disorders, and an overall decrease in life satisfaction, its prevalence is often underestimated[10,11]. This underestimation is partly due to a tendency among HD patients to underreport the condition to healthcare professionals, with around with around 18% failing to mention their symptoms[11]. Furthermore, the lack of standardized screening and assessment protocols in routine clinical practice means that pruritus prevalence remains poorly documented, and healthcare professionals often underdiagnose the condition[10,11].

The correlation between pruritus and increased mortality rates in CKD patients signifies the symptom severity, suggesting it may be an indicator of more severe underlying health issues[12,13]. The mortality rate is 17% higher in HD patients with pruritus versus non pruritus[14]. Nevertheless, its pathophysiology is complex, and it is considered to be the result of the accumulation of uremic toxins. Moreover, pruritus involves a range of factors such as skin dryness (xerosis), immune system abnormalities, inflammatory conditions intrinsic to CKD, neurological issues like uremic neuropathy, and metabolic imbalances[15,16]. Nonetheless, several studies indicate that no specific solutes are associated with pruritus in HD patients, suggesting the complexity of its etiology and the necessity for more targeted research[17–19].

The debilitating nature of pruritus extends beyond the physical discomfort, encompassing a wide range of psychosocial challenges. Patients often suffer from disrupted sleep patterns leading to insomnia and reduced sleep quality[20], which can exacerbate mental health conditions such as increased anxiety and depression[14,21–23]. The persistent itch-scratch cycle is a complex process in which the sensation of itch triggers an automatic scratching response, reinforcing the cycle. This ongoing cycle can impair a patient's ability to engage in normal work and social activities, potentially leading to social withdrawal and a decrease in self-esteem.

In light of these challenges, this study aims to provide a comprehensive examination of the prevalence, pathophysiology, and impact associated with pruritus among CKD patients undergoing HD. It focuses on the multifaceted effects of pruritus on the QoL and underscores the necessity for enhanced recognition, evaluation, and management strategies.

Methods

Study design and participants

This retrospective observational study aimed to estimate the prevalence of HD-associated pruritus (CKD-aP), identify the association of selected solutes, and its impact on various QoL dimensions in the HD patients.

The study cohort included 435 patients with advanced CKD undergoing HD, belonging to 4 dialysis centers of the Fundación Renal (Renal Foundation). All patients over 18 years of age who had been on hemodialysis in these centers during the study period were included in the analysis. Patients who declined to complete the questionnaires or were unable to do so due to language barriers or physical or psychological conditions were excluded from the study.

The patients who participated were stratified into non-pruritus and pruritus group. Patients with pruritus were stratified into two categories based on the intensity of the itching: 1) mild and 2) moderate and severe (see survey instruments and data collection).

Ethics

The collection of information from patients was carried out as standard clinical practice in all patients on dialysis in the units from September 27 to October 30, 2021, and the analytical data were recorded in the usual clinical history. Prior to the analysis of the data for the study, authorization was requested from the ethics committee. The study received approval by the Ethics Committee of Principado de Asturias (Principality of Asturias, Spain); approval number 2023/532). Patients provided informed consent to participate in the study which was conducted following the principles of the Declaration of Helsinki.

Survey instrument and data collection

A short survey, comprising seven questions derived from validated pruritus assessment tools, was used for this study. Questions included:

1) Item 20 from the KDQOL ™ survey[24], assesses the extent to which patients were bothered by itchy skin over the past four weeks ("During the past 4 weeks, to what extent were you bothered by itchy skin?").
2) To measure the severity of pruritus, the following tools were used:

a) The Worst Itch Numeric Rating Scale (WI-NRS)[25], evaluating the severity of itch experienced in the last 24 h in which 0 means no itch and 10 the worst itch imaginable.
b) Self-Assessed Disease Severity (SADS)[26,27], assessing the impact of pruritus on health-related quality of life (HRQL). On this scale, patients select the degree of severity of their pruritus by comparing it to one of three reference cases: A (mild), B (moderate), or C (severe).

Patients who scored a mean score ≥ 4 points on the WI-NRS and categories B or C on the SADS were categorized as patients with moderate-severe pruritus.

- Four items from the Itch Severity Scale (ISS)[28]: ISS-1 addressed the frequency of itching throughout the day; ISS-5 addressed the impact of itching on patients mood, specifically whether it caused feelings of depression or anxiety; ISS-6 addressed the effect of itching on sexual activity and desire; while ISS-7 focused on its impact on sleep quality.

The questionnaire, distributed according to guidelines from the Spanish Society of Nephrology to its members, was subsequently administered to their patients with advanced CKD[29] and self-completed.

Demographic and clinical data

Patient data collected included sex and age, the presence and intensity of CKD-aP, and dialysis quality standards (hours per session in HD, conventional HD vs. online hemodiafiltration, type vascular access and parameter Kt).

Biochemical variables

The biochemical variables that may be associated with the appearance of pruritus were analyzed. That is serum levels of calcium (Ca), phosphorus (P), intact PTH (PTH-i), albumin, hemoglobin, erythrocyte sedimentation rate (ESR). The sample was obtained by fasting venous blood samples from participants during one of their regular HD sessions (in the middle of the week). The sample was collected at the beginning of the session.

Calcium and phosphate were determined by an enzymatic method (Integra® 400 analyzer, Roche Diagnostics, Mannheim, Germany). Albumin, hemoglobin, and erythrocyte sedimentation rates were performed using standard methods (ADVIA 2400 Clinical Chemistry System, Siemens, Germany). Intact PTH (PTH-i) was analyzed by a second-generation automated chemiluminescence method (Elecsys® 2010 platform, Roche Diagnostics, Mannheim, Germany). The normal ranges in the laboratory were: calcium 8.5–10.2 mg/dL, phosphate 2.5–4.5 mg/dl, albumin 3.4–5.4 g/dl, hemoglobin 12–16 g/dl, and erythrocyte sedimentation rates < 20 mm and PTH 15–65 pg/ml.

Quality of life (QoL) questionnaires and symptoms

The assessment of the QoL was done by comprehensive questionnaires provided in which patients reported how pruritus affects them throughout the day, classified into four intervals: morning, midday, evening, and night. In addition, variables and symptoms related to QoL were evaluated, such as anxiety, depression, sexual desire and function, sleep onset problems, sleeping pill use, and drowsiness on waking.

Statistical analysis

Prevalence rates of CKD-aP were calculated and stratified by treatment modality. The association between CKD-aP and various QoL dimensions (mood changes, sexual activity, sleep quality) was evaluated, considering the severity of pruritus. Descriptive statistics, mean and standard deviation for quantitative variables, and percentages for qualitative variables are presented. Non-parametric data were analyzed using the Kruskal–Wallis and Mann–Whitney-Wilcoxon tests. Pearsons chi-squared test was employed for analyzing qualitative data, while the t-test was utilized for quantitative data. Statistical significance was set at $p < 0.05$. Analyses were performed using IBM SPSS Statistics 29.0 and R software (v4.0.2) in R Studio (v1.4), with libraries such as *ggplot2*, *jmv*, *finalfit*, and *gtsummary*.

Results

Prevalence and demographic characteristics

The study included 435 individuals, of whom 62.3% were male and 37.7% female. Two hundred and two (46.4%) patients presented CKD-aP. Among them, 80 (39.6%; 18.4% of the total population) had mild manifestation, and 122 (60.4%; 28.0% of the total population) experienced moderate to severe. No statistically significant differences in sex distribution were observed between individuals with or without pruritus ($p = 0.222$) or between groups with different intensities of pruritus ($p = 0.699$). The mean age was 66.67 (SD = 14.17) years, with no significant age differences between individuals with or without pruritus ($p = 0.379$), nor compared to different pruritus groups ($p = 0.409$). One hundred twenty-seven patients (29.2%) had diabetes comorbidity; however, no significant differences were found between the non-pruritus and pruritus groups ($p = 0.837$), nor among the various degrees of pruritus ($p = 0.207$) (Table 1).

Dialysis quality standards

There were no significant differences in hours per session between individuals without pruritus or in the pruritus intensity groups ($p = 0.388$, and $p = 0.079$, respectively). They were not observed in the other parameters either: conventional type of HD vs. online hemodiafiltration ($p = 0.256$, and $p = 0.354$, respectively), type vascular access ($p = 0.806$, and $p = 0.334$, respectively) and Kt ($p = 0.844$, and $p = 0.240$, respectively) (Table 1).

Biochemical variables

None of the biochemical variables showed significant variations in any of the comparisons made nor pruritus vs. non-pruritus, nor pruritus intensity levels (Table 1).

QoL questionnaires and symptoms

The assessment of QoL through comprehensive questionnaires provided a nuanced understanding of how pruritus affects patients throughout the day. Each reporting period (morning, midday, evening, and night) revealed distinct patterns in pruritus prevalence. Significant differences were observed across all time periods throughout the day when comparing patients without pruritus to those experiencing pruritus ($p < 0.001$

CHARACTERISTIC (N = 435)	Non-Pruritus n = 233 (53.6%)	Pruritus n = 202 (46.4%)	p-value	Mild pruritus n = 80 (39.6%)	Moderate & Severe Pruritus n = 122 (60.4%)	p-value
DEMOGRAPHIC CHARACTERISTICS						
Sex (n = 435)			0.222			0.699
Male	139 (59.7%)	132 (65.3%)		51 (63.7%)	81 (66.4%)	
Female	94 (40.3%)	70 (34.7%)		29 (36.3%)	41 (33.6%)	
Age (yr) (n = 432)	66.48 (14.48)	66.90 (13.83)	0.379	66.62 (13.71)	67.08 (13.97)	0.409
COMORBIDITIES						
Diabetes mellitus (n = 435)			0.837			0.207
No	164 (70.4%)	144 (71.3%)		61 (76.2%)	83 (68.0%)	
Yes	69 (29.6%)	58 (28.7%)		19 (23.8%)	39 (32.0%)	
DIALYSIS QUALITY STANDARDS						
Hours per session (n = 432)	3.68 (0.38)	3.69 (0.37)	0.388	3.65 (0.37)	3.72 (0.36)	0.079
HD (n = 370)			0.256			0.354
Conventional	71 (35.0%)	68 (40.7%)		24 (36.4%)	44 (43.6%)	
HDF	132 (65.0%)	99 (59.3%)		42 (63.6%)	57 (56.4%)	
Vascular access (n = 432)			0.806			0.334
Catheter	90 (39.0%)	76 (37.8%)		27 (33.8%)	49 (40.5%)	
Others	141 (61.0%)	125 (62.2%)		53 (66.2%)	72 (59.5%)	
Kt (n = 430)			0.844			0.240
< 45	42 (18.3%)	38 (19.0%)		18 (23.1%)	20 (16.4%)	
> 45	188 (81.7%)	162 (81.0%)		60 (76.9%)	102 (83.6%)	
BIOCHEMICAL VARIABLES						
Calcium (mg/dL) (n = 433)	8.97 (0.62)	8.97 (0.58)	0.473	8.91 (0.59)	9.00 (0.57)	0.147
Phosphorus (mg/dL) (n = 432)	4.67 (1.36)	4.90 (1.49)	0.054	4.91 (1.40)	4.88 (1.55)	0.447
PTH-i (pg/mL) (n = 380)	359.00 (355.48)	368.56 (334.43)	0.394	369.85 (355.29)	367.65 (320.68)	0.483
Albumin (g/dL) (n = 407)	3.97 (0.35)	3.96 (0.34)	0.399	3.94 (0.36)	3.97 (0.32)	0.274
Hemoglobin (g/dL) (n = 433)	11.66 (1.55)	11.78 (1.67)	0.239	11.82 (1.50)	11.75 (1.79)	0.380
ESR (mm/h) (n = 427)	29.64 (10.76)	30.67 (13.71)	0.196	28.75 (10.97)	31.94 (15.16)	0.054

Table 1. Demographic, clinical, and biochemical results comparing non-pruritus vs. pruritus patients, and different severity degrees of pruritus (mild vs. moderate-severe). HD = hemodialysis; HDF = hemodiafiltration; PTH-i = intact PTH; ESR = erythrocyte sedimentation rate.

morning to night comparison). Additionally, comparisons between patients with mild pruritus and those with moderate to severe pruritus showed significant differences in pruritus severity at different times of the day: morning ($p = 0.001$), midday ($p = 0.016$), evening ($p = 0.008$), and night ($p < 0.001$) (Table 2). The nighttime report exhibited the most significant differences, as more than half of the patients with moderate to severe pruritus reported constant and frequent itching (23.0% and 27.9%, respectively), compared to 2.5% and 10.0%, respectively, of those who suffered mild pruritus.

Concerning other variables and symptoms associated with QoL, the comparison between individuals with non-pruritus and those with pruritus yielded statistically significant differences in the presence of anxiety, depression, sexual desire and function, sleep onset problems and pill use, and drowsiness on waking ($p < 0.001$ in all cases). The pruritus group exhibited higher rates of anxiety (41.6% vs. 3.9% in non-pruritus patients), depression (10.9% vs. 0.9%), decreased sexual desire (12.4% vs. 1.3%) and sexual function (9.9% vs. 1.7%), and sometimes to most of the time reported sleep onset problems (47.6% vs. 5.2%), sleeping pill use (29.2% vs. 15.4%), and drowsiness on waking (38.6% vs. 4.3%) (Table 2; Fig. 1A-B).

Stratifying by pruritus intensity, no significant differences were noted in depression ($p = 0.715$), sexual desire ($p = 0.425$) and function ($p = 0.657$), and sleeping pill use ($p = 0.225$). Nevertheless, the differences persisted across the anxiety and sleep parameters. Patients with moderate-severe pruritus reported higher anxiety (55.7%) compared to those who suffered from mild pruritus (10.0%; $p < 0.001$). They also showed higher sleep onset problems (47.7% reported having difficulty falling asleep sometimes or most of the time, vs. 36.2%; $p = 0.018$) and drowsiness on waking (45% sometimes or most of the time vs. 28.7%; $p = 0.005$) (Table 2).

It is worth mentioning among unanswered questions, those concerning sexual desire and function were the most frequently left blank (around 17% to 25% marked as DK/NO, "don't know" or "no opinion"), both among patients with pruritus and those without (Table 2; Fig. 1A). On the contrary, questions concerning the other factors (anxiety, depression, sleep quality) obtained almost 99.5–100% of answers.

Discussion

The findings of this study offer a comprehensive insight into the multifaceted nature of CKD-aP, particularly its prevalence, solutes not associated, impact on QoL, and the complexity in its management among the

QUALITY OF LIFE QUESTIONNAIRES (N = 435)	Non-Pruritus n = 233 (53.6%)	Pruritus n = 202 (46.4%)	p-value	Mild pruritus n = 80 (39.6%)	Moderate & Severe Pruritus n = 122 (60.4%)	p-value
DAILY REPORT						
Morning			**< 0.001**			**0.001**
Constant itching	0 (0%)	9 (4.4%)		0 (0%)	9 (7.4%)	
Frequent itching	0 (0%)	21 (10.4%)		2 (2.5%)	19 (15.6%)	
Occasional itching	9 (3.9%)	85 (42.1%)		36 (45.0%)	49 (40.1%)	
No itching	224 (96.1%)	86 (42.6%)		42 (52.5%)	44 (36.1%)	
DK/NO	0 (0%)	1 (0.5%)		0 (0%)	1 (0.8%)	
Midday			**< 0.001**			**0.016**
Constant itching	0 (0%)	6 (3.0%)		0 (0%)	6 (4.9%)	
Frequent itching	0 (0%)	20 (9.9%)		3 (3.7%)	17 (14.0%)	
Occasional itching	12 (5.2%)	78 (38.6%)		31 (38.8%)	47 (38.5%)	
No itching	221 (94.8%)	97 (48.0%)		46 (57.5%)	51 (41.8%)	
DK/NO	0 (0%)	1 (0.5%)		0 (0%)	1 (0.8%)	
Evening			**< 0.001**			**0.008**
Constant itching	1 (0.4%)	7 (3.5%)		0 (0%)	7 (5.7%)	
Frequent itching	2 (0.9%)	38 (18.8%)		9 (11.2%)	29 (23.8%)	
Occasional itching	13 (5.6%)	89 (44.0%)		36 (45.0%)	53 (43.5%)	
No itching	217 (93.1%)	67 (33.2%)		35 (43.8%)	32 (26.2%)	
DK/NO	0 (0%)	1 (0.5%)		0 (0%)	1 (0.8%)	
Night			**< 0.001**			**< 0.001**
Constant itching	1 (0.4%)	30 (14.8%)		2 (2.5%)	28 (23.0%)	
Frequent itching	4 (1.7%)	42 (20.8%)		8 (10.0%)	34 (27.9%)	
Occasional itching	22 (9.5%)	90 (44.6%)		49 (61.3%)	41 (33.6%)	
No itching	206 (88.4%)	39 (19.3%)		21 (26.2%)	18 (14.7%)	
DK/NO	0 (0%)	1 (0.5%)		0 (0%)	1 (0.8%)	
SYMPTOMS						
Anxiety			**< 0.001**			**< 0.001**
No	224 (96.1%)	117 (57.9%)		64 (80.0%)	53 (43.4%)	
Yes	9 (3.9%)	84 (41.6%)		16 (20.0%)	68 (55.8%)	
DK/NO	0 (0%)	1 (0.5%)		0 (0%)	1 (0.8%)	
Depression			**< 0.001**			0.715
No	231 (99.1%)	179 (88.6%)		71 (88.8%)	108 (88.5%)	
Yes	2 (0.9%)	22 (10.9%)		9 (11.2%)	13 (10.7%)	
DK/NO	0 (0%)	1 (0.5%)		0 (0%)	1 (0.8%)	
Sexual desire			**< 0.001**			
No change	174 (74.7%)	141 (69.8%)		59 (73.8%)	82 (67.2%)	0.425
Decrease	3 (1.3%)	25 (12.4%)		7 (8.7%)	18 (14.8%)	
DK/NO	56 (24.0%)	36 (17.8%)		14 (17.5%)	22 (18.0%)	
Sexual function						
No change	171 (73.4%)	139 (68.8%)	**< 0.001**	58 (72.5%)	81 (66.4%)	0.657
Decrease	4 (1.7%)	20 (9.9%)		7 (8.7%)	13 (10.7%)	
DK/NO	58 (24.9%)	43 (21.3%)		15 (18.8%)	28 (22.9%)	
Sleep onset problems			**< 0.001**			**0.018**
Never	221 (94.8%)	106 (52.5%)		51 (63.8%)	55 (45.1%)	
Sometimes	10 (4.3%)	68 (33.6%)		23 (28.7%)	45 (36.9%)	
Most of the time	2 (0.9%)	28 (13.9%)		6 (7.5%)	22 (18.0%)	
DK/NO	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Sleeping pill use			**< 0.001**			0.225
Never	197 (84.6%)	143 (70.8%)		61 (76.3%)	82 (67.2%)	
Sometimes	15 (6.4%)	18 (8.9%)		4 (5.0%)	14 (11.5%)	
Most of the time	21 (9.0%)	41 (20.3%)		15 (18.7%)	26 (21.3%)	
DK/NO	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Drowsiness on waking			**< 0.001**			**0.005**
Never	223 (95.7%)	124 (61.4%)		57 (71.3%)	67 (54.9%)	
Sometimes	8 (3.4%)	66 (32.7%)		23 (28.7%)	43 (35.3%)	

Continued

QUALITY OF LIFE QUESTIONNAIRES (N = 435)	Non-Pruritus	Pruritus	p-value	Mild pruritus	Moderate & Severe Pruritus	p-value
	n = 233 (53.6%)	n = 202 (46.4%)		n = 80 (39.6%)	n = 122 (60.4%)	
Most of the time	2 (0.9%)	12 (5.9%)		0 (0%)	12 (9.8%)	
DK/NO	0 (0%)	0 (0%)		0 (0%)	0 (0%)	

Table 2. Quality of life results about daily report and symptoms, comparing non-pruritus vs. pruritus patients, and different severity degrees of pruritus (mild vs. moderate-severe). DK/NO = Do not know / No opinion.

Spanish CKD population undergoing HD. The results highlight the nuanced relationship between pruritus and various psychosocial aspects, underscoring the importance of considering both its presence and severity in understanding its multidimensional impact. Furthermore, there is no influence of the accumulation of specific solutes or their combination, traditionally associated with CKD-aP, on the presence or absence of pruritus. It suggests that its etiology is more complex than previously believed.

Prevalence and demographic characteristics

This study demonstrates a significant prevalence of CKD-aP among HD patients, consistent with prior research indicating high rates of pruritus in this demographic[8–11]. Depending on the study, real-world observational data indicate a prevalence of 40% to 80%[30,31]. Particularly, the 46.4% diagnosis rate of pruritus in the current study closely mirrors the 50.5% recently reported in the Spanish population[6].

Data on the intensity of pruritus are highly variable depending on the study, but most of them show that mild and moderate manifestations are the most[7,19,30]. Even so, the international study DOPPS (Dialysis Outcomes and Practice Patterns Study), carried out in 23,264 patients across 21 countries (phases 4 to 6 from spanning 2009 to 2018), mild pruritus in 44.8% of patients with pruritus (representing 30% of the total population), and moderate to severe pruritus in 55.2% of those with pruritus (representing 37% of the total population)[7]. While the percentages from our study are slightly lower for both the total and Spanish populations compared to the cited work, they still closely align with our findings: mild pruritus in 39.6% with pruritus (18.4% of the total population) had mild manifestation, and moderate to severe in 60.4% (28.0% of the total population).

About demographic characteristics, some studies have found a correlation between pruritus and age[20,31], and sex[14,32]. Nevertheless, data from the present work coincide with others in which no correlation was found between the prevalence of pruritus and neither age nor sex[19,33]. No significant differences in the prevalence of pruritus across sex and age groups suggest that CKD-aP is a broadly experienced complication, underlining the need for universal screening approaches in clinical practice.

Dialysis quality standards

Previous studies also failed to identify an association between KT and pruritus[17,31,34–37], or yielded conflicting results[14]. In this study, no correlation was observed among either pruritus/non-pruritus patients or the different levels of pruritus intensity. Considering that the KT index measures the HD dose, the implication of this data in treatment management should be analyzed in future works to assess dialysis adequacy. In this sense, some authors consider that, even when dialysis is appropriately optimized, pruritus is inevitable[36], which would mean that its etiology is multifactorial.

Biochemical variables

Prevailing hypotheses about the etiology of CKD-aP suggested a correlation between pruritus presence and biochemical markers values, as calcium[14,31,34], phosphorus[14,31,34], PTH[17], albumin[7,14,34], CRP[7], and hemoglobin[7,14]. The explanations for those associations lie in various suppositions as the accumulation of uremic solutes in the skin, imbalance in the immune system or bone metabolism, poor adherence to the diet, the presence of neuropathies, or the influence of inflammation[17,18,31,37,38]. The pruritus often resolves after a transplant, supporting those hypotheses[18].

Many of those works, however, present conflicting results depending on the biomarker analyzed, and recent studies directly show no association between a specific solute or a combination of several and the development of CKD-Ap[18,19]. Previous data indicate that biomarkers such as calcium, phosphorus, PTH, albumin, CRP, and hemoglobin do not correlate with the prevalence or severity of itch, consistent with the findings of this investigation. This suggests that the pathogenesis and pathophysiology of pruritus remain unclear, warranting further research.

QoL and symptomatology

Biomarkers seem not to be correlated with pruritus, but there does seem to be a correlation with QoL and psychosocial parameters. This is consistent with previous studies that have shown a link between CKD-aP and worsening QoL in HD patients, particularly regarding factors such as mood disorders, day-to-day activities, depression, and sleep[7,10,39].

The association of pruritus with anxiety and depression, suggests a specific psychological impact of these conditions, as previously described[20,33,38,40,41], with patients with severe degrees of pruritus being more affected by anxiety disorder (according to our results, one out of every two patients with moderate-severe). Around 5–30% of patients with CKD-aP experience depression and depressive symptoms, being more prevalent in female patients[33]. Similar to previous studies[14,33], The present study demonstrates a significant increase in the presence of anxiety and depression among patients with pruritus, which escalates significantly in the case of

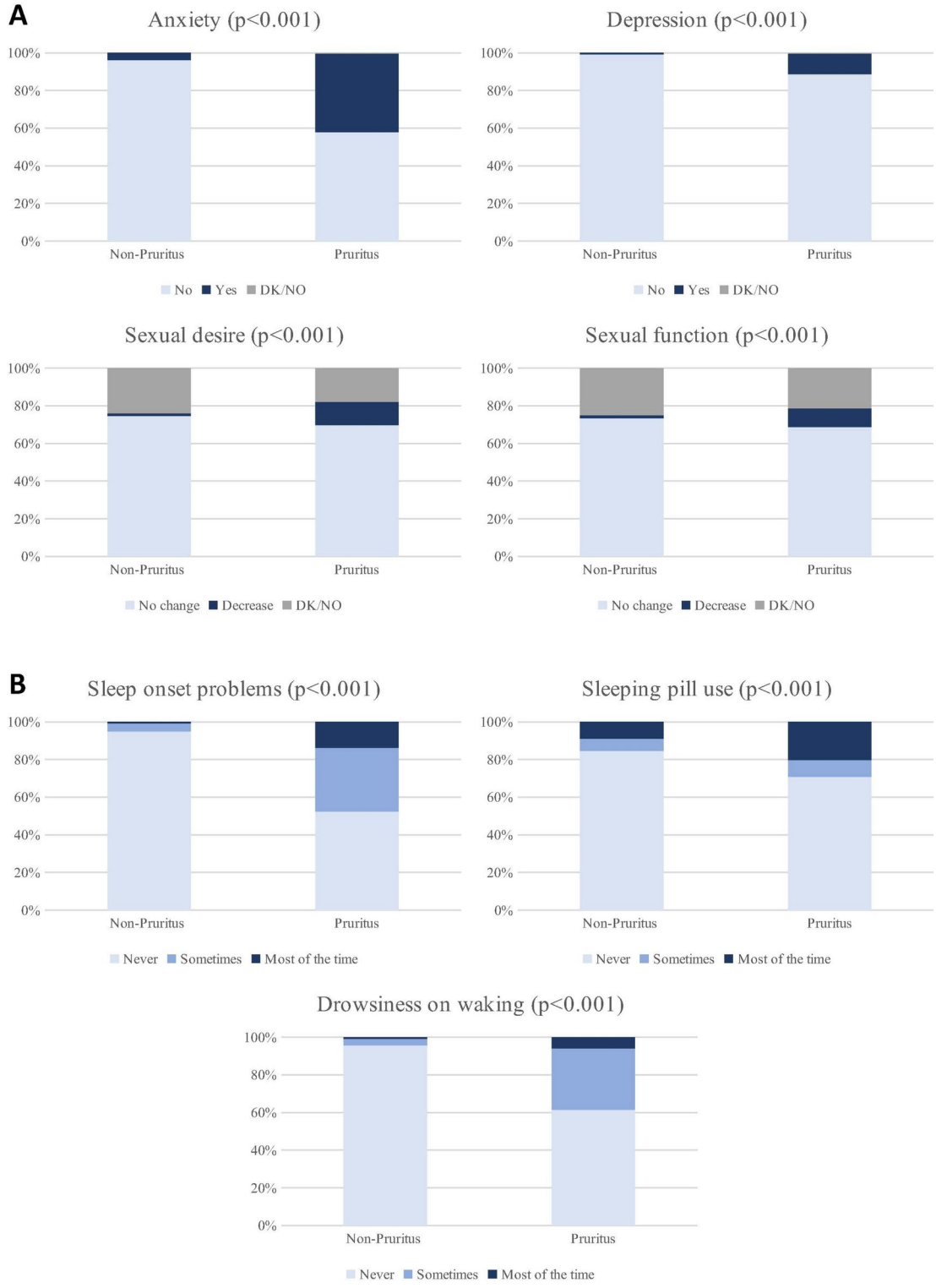

Fig. 1. Main symptoms related with emotional sphere and sexuality (**A**), and sleep quality (**B**) in patients with pruritus vs. non-pruritus.

anxiety with its severity ($p < 0.001$). However, more research would be needed in this regard, since depression is associated with poor treatment and diet adherence, higher mortality, and worse QoL[40].

Regarding sexual desire and function, this study represents, to our knowledge, the first to describe pruritus in CKD patients as a risk factor for sexual dysfunction. Only one study suggested that the presence of atrophic vaginitis is associated with pruritus, vaginal dryness, and dyspareunia[42]. Despite this, the association between sexual dysfunction and kidney disease is well documented in predialysis and dialysis patients, and has an

important implication for patient self-perception of their QoL[42,43]. This condition is underdiagnosed and undertreated since kidney health professionals and patients do not often discuss these issues openly, which makes it difficult to establish treatment[42–44]. This is reflected in our study by the high percentage of patients who left the questions about sexual desire and function unanswered (17% to 25%). Understanding the reasons behind this disparity could be crucial for exploring aspects of CKD patients sexuality in future research. Sexual dysfunction requires a preventive approach and individualized therapy because it has different mechanisms in men and women[43,44], and it implies other psychosocial factors such as depression or poor self-esteem[42].

Furthermore, in terms of sleep quality, night reports indicated a significantly higher prevalence and severity of pruritus (significantly associated with pruritus intensity) aligning with the disruptive nature of CKD-aP on sleep patterns[20]. For this reason, a significant difference is also observed in other sleep-related parameters as drowsiness on waking and sleeping pill use (regardless of intensity). These data are in line with the results of other studies in which poor sleep quality and disturbances, and fatigue are correlated with pruritus[7,20,38,39,41,45].

Prevalence of sleep disturbances has been reported in 9–76% of HD patients with CKD-aP[20]. The effect of this condition on sleep is related to its nocturnal exacerbation, which could be due to several factors, for example an increase in body temperature. The concern arises from its potential devastating effects, as it encompasses cardiovascular, endocrine, metabolic, and inflammatory implications[45]. Furthermore, it impacts patients social and work lives due to the associated lack of rest.

According to a recent study by Weiner et al. (2024)[46], the intensity of pruritus is not only associated with worse sleep quality parameters but also with improvements when treated. Thus, relief from itching can help address a significant clinical burden and improve the daily lives of patients on hemodialysis by enhancing sleep quality.

For many reasons, all the above psychosocial parameters should be considered to improve patients care. Many debilitating symptoms, such as sleep disturbances, depression, pain, or drained legs, often occur in combination, comprising what are called "symptom clusters" associated with CKD-aP[38]. Also, these variables related to lifestyle and mental health are important, since often they show the patient own perception of their health.

Treatment and management implications

CKD-aP has a high prevalence and significant impact on QoL, which necessitates a more standardized approach. Screening and treatment need to be asserted and the psychosocial situation of HD patients cannot be underestimated. The introduction of new specific treatments for this indication opens a new horizon for the improvement of quality of life of these patients[46–48].

Limitations and future research

This study highlights the importance of finding therapeutic targets in patients with pruritus. It constitutes the first study in Spain that correlates demographic, clinical, and QoL parameters in patients with pruritus. However, the research faced limitations. On the one hand, the observational nature of the study limits the ability to establish causality. Longitudinal studies could provide more insight into the temporal relationships between CKD-aP and its impacts on QoL. On the other hand, the relationship between pruritus, anxiety and depression is bidirectional, making it difficult to establish the cause-effect relationship between pruritus and depression[7]. On the other hand, a limitation of the present study is the absence of information on whether patients received any treatment for their pruritus and whether this had any impact on patient-reported outcomes.

In future interventions, the influence of receiving treatment for pruritus should be studied, as well as the relationship between pruritus-related events on dialysis and non-dialysis days. Additionally, the total duration of a patient time on dialysis should be analyzed as an influential parameter in the onset of pruritus, considering that the relationship between the onset and severity of pruritus with time on dialysis has not yet been conclusive among studies[17,18,31,40]. Also in some studies, it has been proposed that seasonal changes in the specific geographic region and local temperatures may affect pruritus[18,31,37], which should be assessed in future works.

Conclusions

In conclusion, this study underscores the significant burden of CKD-aP in HD patients, highlighting its pervasive impact on various aspects of QoL, as anxiety, depression, sexuality and sleep parameters. The findings emphasize the need for a holistic approach to managing CKD-aP, encompassing both physical and psychological aspects, and advocate for enhanced efforts in research to unravel its complex pathophysiology for better patient outcomes.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Received: 9 July 2024; Accepted: 17 December 2024
Published online: 20 February 2025

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Acknowledgements

We sincerely thank the reviewers for their thorough and insightful feedback, which has significantly contributed to improving the quality and clarity of this manuscript. The authors would also like to thank the patients that participated in this study and all the healthcare professionals of Fundación Renal. Especially to those who collaborated in distributing the questionnaires. We would like to express our sincere gratitude to the Prurito Working Group and the Fundación Renal Working Group for their valuable collaboration on this project.

Author contributions

MDA conceptualized the work; SMF, PM, JAG, and MDA analyzed data, wrote the main manuscript and prepared de Tables and Figures. All authors substantively reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

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