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ORIGINAL ARTICLE

Moderate-to-severe pruritus in untreated or non-responsive hemodialysis patients: results of the French prospective multicenter observational study Pruripreva

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ABSTRACT

Background. Chronic kidney disease-associated pruritus (CKD-aP) is a common condition in patients treated with hemodialysis, and has a negative impact on quality of life (QoL). Due to the lack of standardized diagnostic tools and frequent underreporting, pruritus prevalence remains poorly documented.

Methods. Pruripreva was a prospective multicenter observational study that aimed to evaluate the prevalence of moderate to severe pruritus in a cohort of French hemodialysis patients. The primary endpoint was the rate of patients with mean Worst Itch Numerical Rating Scale (WI-NRS) score ≥ 4 calculated over 7 days (moderate pruritus, 4–6; severe, 7–8; very severe, 9–10). Impact of CKD-aP on QoL was analyzed according to its severity (WI-NRS), using 5-D Itch scale, EQ-5D and Short Form (SF)-12.

Results. Mean WI-NRS was ≥ 4 in 306 patients (mean age, 66.6 years; male, 57.6%) out of 1304 and prevalence of moderate to very severe pruritus was 23.5% (95% confidence interval 21.2–25.9). Pruritus was unknown prior to the systematic screening in 37.6% of patients, and 56.4% of those affected were treated for this condition. The more severe the pruritus, the poorer the QoL according to the 5-D Itch scale, EQ-5D and SF-12.

Conclusion. Moderate to very severe pruritus was reported in 23.5% of hemodialysis patients. CKD-aP was underrated although it is associated with a negative impact on QoL. These data confirm that pruritus in this setting is an

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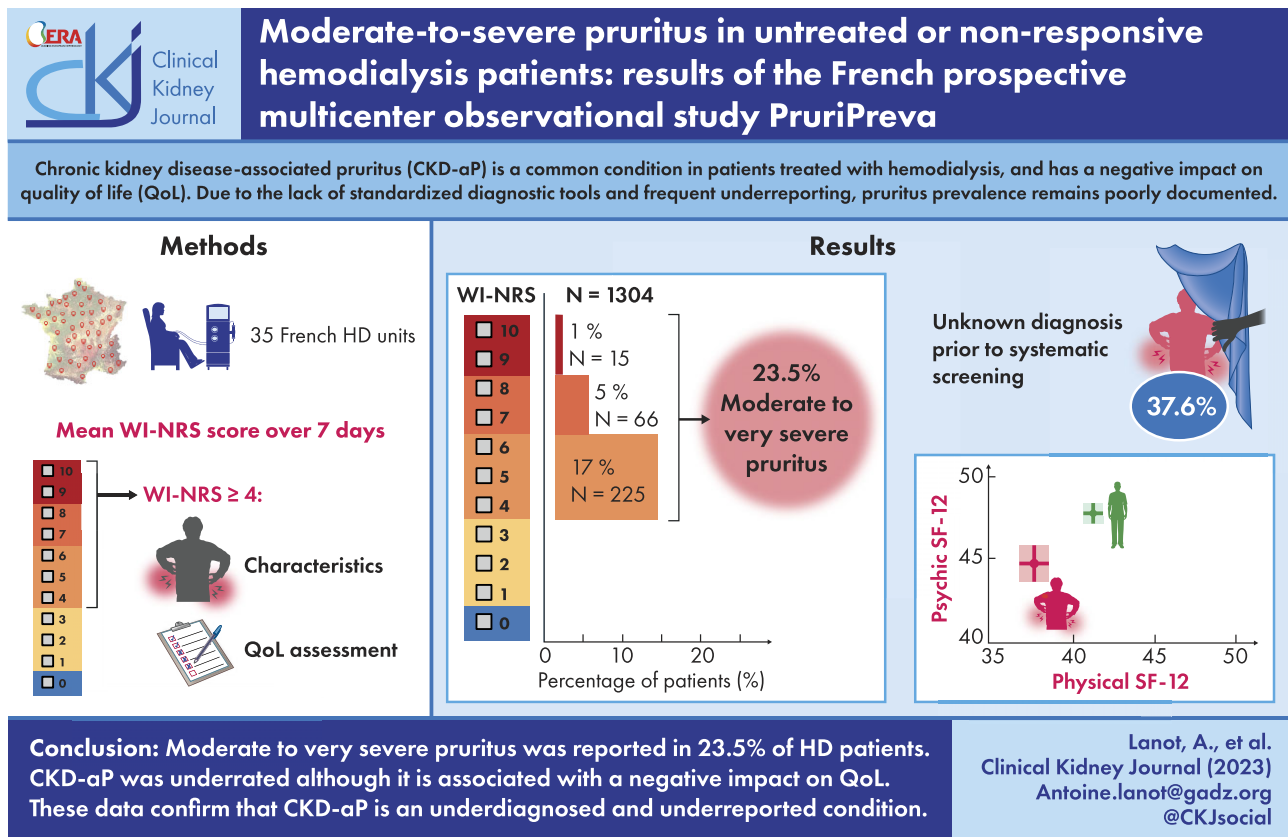
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underdiagnosed and underreported condition. There is an urgent demand for new therapies to treat chronic pruritus associated with CKD in hemodialysis patients.

LAY SUMMARY

Pruritus is a common complaint in patients undergoing hemodialysis and it affects their quality of life. Estimates of the prevalence of pruritus vary among studies. Using the Worst Itch Numerical Rating Scale (WI-NRS), we found that 23.5% of hemodialysis patients had moderate to severe pruritus, including 37.6% in which this condition was not known prior to the study. We showed with different scales of quality of life that the more severe the pruritus, the worse the quality of life. In particular, sleep and mood disorders were increased with pruritus severity. Our results confirm the urgent demand for new therapies of pruritus in patients treated with hemodialysis.

GRAPHICAL ABSTRACT



Keywords: chronic kidney disease, end-stage renal disease, hemodialysis, pruritus, quality of life

INTRODUCTION

Pruritus associated with chronic kidney disease (CKD-aP) is considered a common condition in hemodialysis patients [1, 2]. Pruritus mainly affects the face, chest and limbs, and can be generalized in up to 50% of patients. Moderate to severe pruritus has been reported in 20%–40% of hemodialysis and peritoneal dialysis patients, and in 40%–84% of end-stage renal disease (ESRD) patients [3–5]. However, the prevalence of CKD-aP remains highly variable because it is often underreported by patients or not assessed by healthcare providers, in part because of uncertainty about its pathogenesis and treatment [5]. Rayner et al. reported that 69% of department heads underestimated

the prevalence of pruritus in their ward. In addition, approximately 17% of patients with moderate pruritus did not report itching to healthcare staff and 18% did not use any treatment for pruritus [3]. CKD-aP has been shown to be associated with a deterioration of quality of life (QoL) and with sleep and mood disorders [6–9].

Several mechanisms are involved in the pathophysiology of CKD-aP: toxins accumulation, peripheral neuropathy, immune system dysregulation and imbalance of peripheral opioid receptors [10–13]. Several medications are often used off-label to manage pruritus, and until recently there was no approved treatment for pruritus in dialysis patients [14].

The data in the literature concerning pruritus in dialysis patients in France deserve to be consolidated. The objective of this study was therefore to evaluate the prevalence of moderate to severe pruritus in a cohort of French hemodialysis patients, and to evaluate the impact of this pruritus on QoL.

MATERIALS AND METHODS

Study design and patients

The Pruripreva study was a French prospective multicenter observational study performed in hemodialysis patients.

The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. It was approved by a local independent Ethics Committee prior to its implementation ["Comité Protection des Personnes (CPP) Ile de France VII"].

Patients were included if they met the following criteria: 18 years of age or older with CKD requiring dialysis at least three times a week for at least 3 months. Patients were excluded if they were under guardianship, curatorship or other legal protection, or deprived of liberty by judicial or administrative decision.

After having received oral and written information about the study, each patient orally indicated to the investigator both his/her non-objection to participation in the study and agreement to the processing of personal data. This agreement was recorded in the patient's file in accordance with European regulations (General Data Protection Regulation). The patient was free at any time to terminate participation in the study without affecting the relationship with the healthcare providers.

Data collected

During Visit 1, the physician verified the eligibility criteria and provided the patient with the Worst Itch Numerical Rating Scale (WI-NRS).

Visit 2 was performed 7 days after Visit 1 and included calculation of the mean WI-NRS from the self-completed score over the past 7 days. The following data were collected in patients with WI-NRS ≥ 4 : socio-demographic data, history of CKD and dialysis, dry body weight, height, body mass index, type of vascular access (arteriovenous fistula, central venous catheter), dialysis technique (hemodiafiltration, hemodialysis), type of center, membrane, type of concentrate (hydrochloric acid, acetate, citrate), use of intravenous antihistamines, last available Kt/V, comorbidities and modified Charlson's score, last available biological workup within the last 3 months, pruritus treatments and pruritus-inducing treatments (e.g. statins, angiotensin II receptor blockers, opioids). In all patients included in the study the following questionnaires were completed: Short Form (SF)-12 questionnaire and EQ-5D questionnaire. For patients with a mean WI-NRS score ≥ 4 , the 5-D Itch questionnaire was also completed. Characteristics from the nationwide French ESRD registry REIN were listed in order to compare with characteristics of the patients with moderate to severe pruritus included in the study [15].

Pruritus assessment

The WI-NRS is a single-item patient-reported outcome measure. Patients report the intensity of the worst itching they experienced over the past 24 h, from 0 ("no itch") to 10 ("worst itch imaginable"). It has been validated, with a good reproducibility and internal consistency in French and other languages [16, 17]. The mean score allows rating pruritus severity as: no pruritus, 0;

mild pruritus, 1–3; moderate, 4–6; severe, 7–8; very severe, 9–10 [16].

Questionnaires

The 5-D Itch scale is a devoted questionnaire of five domains (Duration, Degree, Direction, Disability and Distribution) scoring from 5 (no pruritus) to 25 (most severe pruritus) which assesses pruritus within the last 2 weeks [18] (Supplementary data, Fig. S1).

The EQ-5D questionnaire is a generalist scale of QoL [19]. The first part corresponds to a visual analog scale (VAS) graduated from 0 to 100 to auto-evaluate the current state of health. The second part includes questions corresponding to five dimensions: Mobility, Self-care, Daily activities, Pain/discomfort and Anxiety/depression (Supplementary data, Fig. S2).

The SF-12 questionnaire is a generalist 12-item patient-reported survey of patient health [20]. It is composed of 12 questions on physical activity, life and relationships with others, physical pain, perceived general health, vitality, limitations due to psychological state, limitations due to physical condition and psychological health. The eight dimensions combine synthetic information to calculate Physical Component Summary (PCS) score and Mental Component Summary (MCS) score. The higher the score, the greater the patient's ability (Supplementary data, Fig. S3).

Statistical analysis

The primary endpoint was the rate of patients with a mean WI-NRS ≥ 4 calculated over 7 days. The 95% confidence interval (CI) of prevalence rate was calculated using the Clopper–Pearson exact method formula.

Mean values, standard deviations (SD), medians and ranges were calculated for continuous variables whereas counts and percentages were calculated for categorical variables. Missing data were not replaced. For quantitative variables, subgroup comparisons were made using analysis of variance, Student's *t*-test or non-parametric tests (Wilcoxon or Kruskal–Wallis), depending on the distribution of the variables. The Chi² test or Fisher's exact test were used for categorical variables.

The sample size was calculated on the basis of the Dialysis Outcomes and Practice Patterns Study (DOPPS), which reported that about 40% of patients treated with dialysis experienced pruritus [21]. Therefore, a total of 1500 patients with CKD requiring dialysis were to be included in this study; 600 patients with moderate to severe pruritus were expected. In order to include 1500 patients, it was necessary to select 30–50 dialysis centers with at least 50 patients on dialysis.

The statistical analysis was performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Patient disposition

A total of 1368 patients were screened in 34 dialysis units from 17 January 2022 to 20 May 2022, of whom 1304 were analyzed (95.3%). A total of 15 patients were excluded from the analysis (withdrawal of consent, *n* = 1; inclusion/exclusion criteria not met, *n* = 10; missing consent dates, *n* = 5; patients recorded as "not included," *n* = 9; duplicates, *n* = 2) and WI-NRS was missing or could not be calculated in 49 patients (Fig. 1).

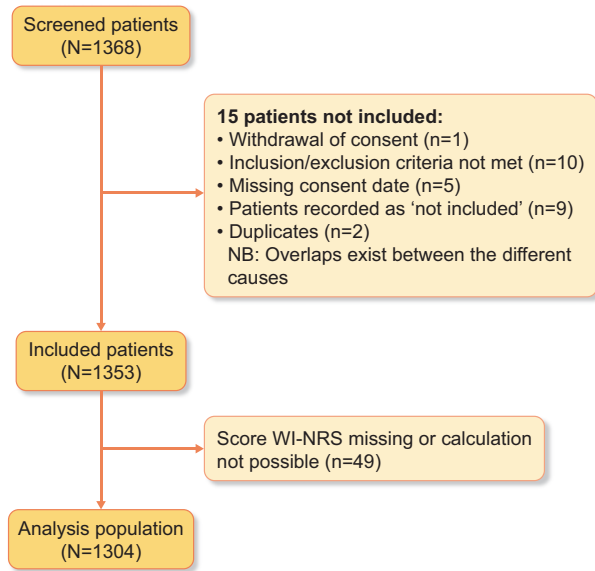


Figure 1: Flow chart.

Prevalence of moderate to severe pruritus

The prevalence of moderate to severe/very severe pruritus (mean WI-NRS ≥ 4) was 23.5% (95% CI 21.2–25.9) (Fig. 2). Pruritus was moderate in 17.3%, severe in 5.1% and very severe in 1.2%.

Characteristics of CKD patients with moderate to severe pruritus

The mean (SD) age of patients with a mean WI-NRS ≥ 4 was 66.6 (14.1) years and 65.2% were older than 65 years. The sex ratio (male/female) was 1.4 (Table 1). Almost all patients (98.0%) had at least one comorbidity. The most frequent were hypertension (80.5%), diabetes (45.2%) and peripheral vascular disease (31.7%). The mean (SD) Charlson's score was 6.1 (3.0). The nephropathy was diabetes in 22.4% of patients, glomerulonephritis in 19.1% and hypertension in 10.6% (Table 2). A total of 14.2% of patients had an history of kidney transplantation. The median (interquartile range) time to first dialysis was 43.0 (18.0–93.0) months.

Characteristics of dialysis

The patients were followed in dialysis centers for 70.0%, in satellite in-center dialysis units for 19.8% and in self-dialysis units for

10.2% (Table 3). Satellite in-center hemodialysis units are units with no requirement for continuous medical presence during the session, but where the medical team must be able to intervene during the session. In such units, the nephrologist visit is carried out at least once a week [22]. Arteriovenous fistula was used for dialysis in 71.9% of patients and central venous catheter in 28.7%. The most frequent type of dialysis membrane was poly(ether) sulfone (72.3%). The type of concentrate used was acetate in 49.5% of patients, citrate in 36.0% and chloride in 14.5%. Hemodiafiltration was used in 47.5% of patients compared with conventional hemodialysis in 52.5% of patients. Hemodiafiltration was not associated with a lower rate of severe pruritus.

Treatment of pruritus

Among the patients with WI-NRS ≥ 4 , 114 (37.6%) had no known diagnosis of CKD-aP prior to study inclusion. One hundred and seventy-one patients (56.4%) were taking pruritus-related treatments: emollient or moisturizing creams 39.9%; antihistamines 21.1% (including hydroxyzine 9.2% and loratadine 5.9%), corticosteroids 6.6% and gabapentinoids 5.3%. Intravenous antihistamines were more frequently used in patients with severe/very severe vs moderate pruritus (23.8% vs 11.2%, respectively; $P = .0063$) (Table 3).

There was more use of poly(ether)sulfone membrane in the group of patients with known pruritus prior to the study inclusion compared with those with no pruritus known prior to the study inclusion (respectively 75.1% vs 67.5%), but no difference in the use of PMMA membranes (respectively 12.7% vs 12.3%) (Supplementary data, Table S1).

Treatments potentially inducing pruritus were taken by 48.2% (146/303) of patients and were mainly statins (64.4%; 94/146).

Biological parameters

Compared with moderate pruritus, severe/very severe pruritus was more frequently associated with higher mean eosinophil count (0.3 vs $0.2 \times 10^9/L$; $P = .0414$) (Table 4). The other biological parameters were comparable according to the severity of pruritus.

Quality of life

5-D Itch scale

The mean (SD) total score of the 5-D Itch scale increased significantly with the severity of the pruritus: 13.7 (3.1) in moderate, 15.6 (2.5) in severe and 18.8 (3.4) in very severe ($P < .0001$) pruritus. Itching duration per day ($P = .0053$), degree of

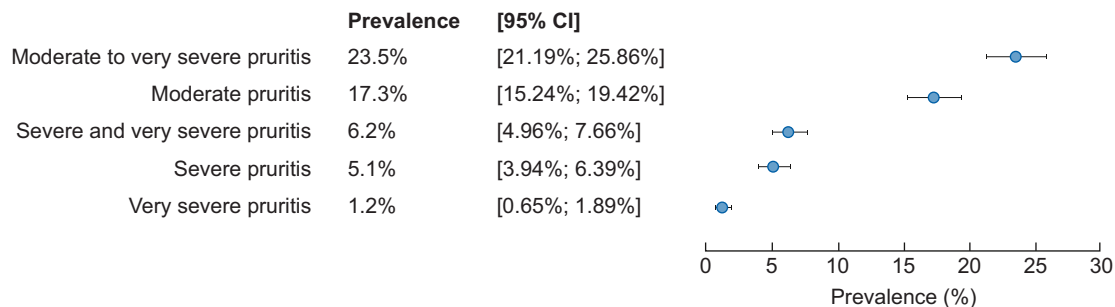


Figure 2: Prevalence of pruritus.

Table 1: Characteristics of patients with moderate to very severe pruritus.

	Moderate pruritus (N = 225)	Severe pruritus (N = 66)	Very severe pruritus (N = 15)	All (N = 306)	P-value ^a	REIN data
Age, n	224	65	15	304		50 501
Mean (SD)	66.8 (14.4)	66.2 (13.1)	64.2 (13.0)	66.6 (14.1)	.58	69 (15.1)
Age classes, n (%)	224	65	15	304		
20–44 years	24 (10.7)	4 (6.2)	2 (13.3)	30 (9.9)	.17	3802 (7.5)
50–64 years	50 (22.3)	21 (32.3)	5 (33.3)	76 (25)		12 890 (25.5)
[65–74 years	81 (36.2)	24 (36.9)	4 (26.7)	109 (35.9)		23 763 (25.9)
≥75 years	69 (30.8)	16 (24.6)	4 (26.7)	89 (29.3)		23 362 (25.4)
Gender, n (%)	224	65	15	304		50 501
Male	127 (56.7)	40 (61.5)	8 (53.3)	175 (57.6)	.61	30 995 (61.2)
Female	97 (43.3)	25 (38.5)	7 (46.7)	129 (42.4)		19 506 (38.6)
Body mass index, kg/m ² , n	223	65	15	303		Unknown
Mean (SD)	27.2 (6.9)	28.1 (7.8)	29.2 (10.4)	27.5 (7.3)	.27	
Median (IQR)	25.6 (22.3; 30.7)	27.9 (22.4; 32.1)	27.2 (21.5; 36.9)	26.0 (22.3; 30.9)		
Number of comorbidities	223	65	15	303		Unknown
Mean (SD)	3.2 (1.8)	3.3 (1.6)	3.3 (1.5)	3.2 (1.8)	.61	
≥1, n (%)	219 (98.2)	63 (96.9)	15 (100)	297 (98.0)	.66	
Modified Charlson's score	133	39	9	181		Unknown
Mean (SD)	6.0 (2.9)	6.4 (3.4)	6.0 (2.8)	6.1 (3.0)	.51	
Median (IQR)	6.0 (4.0; 8.0)	7.0 (4.0; 9.0)	5.0 (4.0; 8.0)	6.0 (4.0; 8.0)		
Professional status, n (%)	224	65	15	304		Unknown
Retired	150 (67.0)	41 (63.1)	8 (53.3)	199 (65.5)	.53	
Not working	27 (12.1)	8 (12.3)	2 (13.3)	37 (12.2)		
Invalid	27 (12.1)	6 (9.2)	3 (20.0)	36 (11.8)		
Professionally active	19 (8.5)	10 (15.4)	2 (13.3)	31 (10.2)		
Student	1 (0.4)	0	0	1 (0.3)		

^aModerate vs severe/very severe pruritus.

IQR, interquartile range.

Table 2: Characteristics of CKD.

	Moderate pruritus (N = 225)	Severe pruritus (N = 66)	Very severe pruritus (N = 15)	All (N = 306)	REIN data
Cause of CKD, n (%)	223	65	15	303	50 501
Diabetes	64 (28.7)	26 (40)	4 (26.7)	94 (31)	11 422 (22.6)
Glomerulonephritis	47 (21.1)	10 (15.4)	1 (6.7)	58 (19.1)	6658 (13.2)
Hypertension	21 (9.4)	9 (13.8)	2 (13.3)	32 (10.6)	11 563 (22.9)
Polycystic kidney disease	15 (6.7)	5 (7.7)	3 (20)	32 (10.6)	2929 (5.8)
Uropathy	18 (8.1)	2 (3.1)	0	20 (6.6)	2538 (5)
Vascular kidney disease	6 (2.7)	4 (6.2)	0	10 (3.3)	289 (0.6)
Undetermined	26 (11.7)	6 (9.1)	3 (20.0)	35 (11.6)	7851 (15.5)
Other	28 (12.6)	4 (6.2)	3 (20)	35 (11.6)	9789 (19.4)
Transplant patient, n (%)	223	65	15	303	Unknown
Yes	38 (17.0)	3 (4.6)	2 (13.3)	43 (14.2)	
Time from 1st dialysis (months), n	222	65	15	302	50 501
Mean (SD)	81.0 (100)	59.5 (65.1)	80.0 (83.4)	76.3 (93.0)	
Median (IQR)	45.0 (18.0; 102.0)	33.0 (16.0; 82.0)	50.0 (32.0; 82.0)	43.0 (18.0; 93.0)	38.4 (16.8; 84)
Time from 1st dialysis (month) after last transplant, n	38	3	2	43	Unknown
Mean (SD)	71.0 (65.4)	46.0 (39.4)	85.5 (112.4)	70.0 (64.8)	
Median (IQR)	60.0 (26.0; 103.0)	34.0 (14.0; 90.0)	85.5 (6.0; 165.0)	57.0 (24.0; 103.0)	
Mean (SD) number of usual dialysis sessions per week in the last 3 months, n (%)	223	64	15	302	43 149
3	211 (94.6)	60 (93.8)	15 (100)	286 (94.7)	40 111 (93)
4	5 (2.2)	2 (3.1)	0	7 (2.3)	532 (1.2)
5	5 (2.2)	0	0	5 (1.7)	249 (0.6)
6	2 (0.9)	2 (3.1)	0	4 (1.3)	510 (1.2)

IQR, interquartile range.

Table 3: Characteristics of dialysis.

	Moderate pruritus (N = 225)	Severe pruritus (N = 66)	Very severe pruritus (N = 15)	All (N = 306)	P-value ^a	REIN data
Dialysis site, n (%)	223	65	15	303	.88	43 149
Dialysis centers	155 (69.5)	47 (72.3)	10 (66.7)	212 (70.0)		24 442 (56.6)
Satellite in-center dialysis units	44 (19.7)	12 (18.5)	4 (26.7)	60 (19.8)		11 391 (26.4)
Self-dialysis units	24 (10.8)	6 (9.2)	1 (6.7)	31 (10.2)		6515 (15.1)
Arteriovenous fistula, n (%)	160 (71.7)	50 (76.9)	8 (53.3)	218 (71.9)	.90	33 358 (79.2)
Central venous catheter, n (%)	64 (28.7)	16 (24.6)	7 (46.7)	87 (28.7)	.99	8599 (20)
Type of dialysis, n (%)	223	65	15	303		43 135
Hemodialysis	115 (51.6)	38 (58.5)	6 (40)	159 (52.5)	.60	27 477 (63.7)
Hemodiafiltration	108 (48.4)	27 (41.5)	9 (60)	144 (47.5)		15 226 (35.3)
Type of dialysis membrane, n (%)	223	65	15	303	.08	Unknown
Poly(ether)sulfone	167 (74.9)	39 (60.0)	13 (86.7)	219 (72.3)		
PMMA	25 (11.2)	11 (16.9)	2 (13.3)	38 (12.5)		
Polyacrylonitrile	10 (4.5)	3 (4.6)	0	13 (4.3)		
Vitamin E-coated dialysis membrane	2 (0.9)	5 (7.7)	0	7 (2.3)		
Medium cut-off	6 (2.7)	1 (1.5)	0	7 (2.3)		
Cellulosic	4 (1.8)	1 (1.5)	0	5 (1.7)		
Other	7 (3.1)	2 (3.1)	0	9 (3.0)		
Unknown	2 (0.9)	3 (4.6)	0	5 (1.7)		
Type of concentrate, n (%)	223	65	15	303	.17	Unknown
Acetate	105 (47.1)	34 (52.3)	11 (73.3)	150 (49.5)		
Citrate	81 (36.3)	24 (36.9)	4 (26.7)	109 (36.0)		
Chloride	37 (16.6)	7 (10.8)	0	44 (14.5)		
Use of intravenous antihistamines, n (%)	223	65	15	303		Unknown
Yes	25 (11.2)	16 (24.6)	3 (20.0)	44 (14.5)	.01	
Last Kt/V, n	216	63	15	294		7570
Mean (SD)	1.5 (0.4)	1.4 (0.4)	1.6 (0.7)	1.5 (0.4)	.21	1.5 (-)
<1.2, n (%)	39 (18.1)	20 (31.7)	4 (26.7)	63 (21.4)	.04	1424 (18.8)
1.2–1.4, n (%)	56 (25.9)	13 (20.6)	0	69 (23.5)		1718 (22.7)
≥1.4, n (%)	121 (56.0)	30 (47.6)	11 (73.3)	162 (55.1)		4428 (58.5)

^aModerate vs severe/very severe pruritus.

itching ($P < .0001$) and impact on sleep ($P < .0001$), leisure/social relationships ($P < .0001$), housework/errands ($P = .0004$) and work/school ($P = .0004$) increased significantly with pruritus severity (Supplementary data, Table S2). Thus, the mean (SD) duration of itching per day was 1.7 (1.1) h in patients with moderate pruritus and increased to 2.0 (1.3) h and 3.7 (1.7) h ($P = .0019$) in patients with severe or very severe itching, respectively (Fig. 3). The mean degree of itching increased from 3.2 (0.8) in patients with moderate pruritus to 3.6 (0.8) and 4.3 (0.9) ($P < .0001$) in patients with severe or very severe itching, respectively.

Body parts most affected by itching were back (59.3%), arms (58.6%), head (52.9%), thighs (45.8%), forearms (40.1%), body extremities (36.7%) and chest (36.0%) (Fig. 4).

EQ-5D

All domains (Mobility, Self-care, Daily activities, Pain/discomfort and Anxiety/depression) of the EQ-5D showed a significant association between decreased QoL and pruritus severity ($P < .0001$ for each domain, except for Self-care, $P = .0065$) (Supplementary data, Table S3).

The mean (SD) EQ-5D index was 0.58 (0.33) for patients with a WI-NRS score <4 , 0.47 (0.31) for those with moderate pruritus and 0.37 (0.37) for those with severe or very severe pruritus ($P < .0001$). The mean (SD) VAS was 58.6 (21.0) for patients with a WI-NRS score <4 , 51.7 (19.9) for those with moderate pruri-

tus and 50.3 (22.3) for those with severe or very severe pruritus ($P < .0001$) (Fig. 5).

SF-12

All SF-12 domains showed a significant association between decreased QoL and pruritus severity ($P < .0001$ for all domains except Vitality, $P = 0.0016$) (Supplementary data, Table S4).

The mean SF-12 MCS score was 47.8 for patients with WI-NRS <4 , 45.2 for those with moderate pruritus and 43.6 for those with severe or very severe pruritus ($P < .0001$) (Fig. 5). The mean SF-12 PCS score was 41.2 for patients with WI-NRS <4 , 37.3 for those with moderate pruritus and 38.4 for those with severe or very severe pruritus ($P < .0001$).

DISCUSSION

The prevalence of moderate to very severe pruritus was 23.5% (95% CI 21.2–25.9) in our cohort of 1304 CKD patients treated with hemodialysis. In the entire population, we found a correlation between the WI-NRS score and the QoL evaluated either by the EQ-5D index or the PCS and MCS of the SF-12 questionnaire. The rate of pruritus and its severity are poorly documented in the French setting and these results are the first to our knowledge on a large cohort of hemodialysis patients in France. The use of the WI-NRS allowed consistent quantification of pruritus among the 34 centers. No significant differences in sociodemographic or clinical characteristics were observed between

Table 4: Biological parameters (within the last 3 months).

		Moderate pruritus (N = 225)		Severe pruritus (N = 66)		Very severe pruritus (N = 15)		All (N = 306)	P-value ^a
Creatinine, µmol/L	223	1212 (2793)	64	1620 (4760)	13	1743 (2619)	300	1322 (3298)	.4307
Calcium, mmol/L	219	2.2 (0.2)	63	2.2 (0.2)	15	2.2 (0.2)	297	2.2 (0.2)	.0537
Total bilirubin, µmol/L	79	5.2 (3.6)	29	6.3 (6.5)	8	5.2 (2.1)	116	5.5 (4.4)	.4382
Hemoglobin, g/dL	223	11.27 (1.27)	65	11.14 (1.38)	15	11.13 (1.44)	303	11.24 (1.3)	.4377
White blood cells, ×10 ⁹ /L	223	7.1 (2.7)	65	6.5 (1.8)	15	6.7 (2.3)	303	7.0 (2.5)	.0627
Monocytes, ×10 ⁹ /L	218	0.7 (0.3)	65	0.7 (0.2)	15	0.6 (0.2)	298	0.7 (0.2)	.0781
Eosinophils, ×10 ⁹ /L	218	0.2 (0.2)	65	0.3 (0.3)	15	0.3 (0.2)	298	0.3 (0.2)	.0414
Lymphocytes, ×10 ⁹ /L	218	1.3 (0.8)	65	1.3 (0.6)	15	1.1 (0.4)	298	1.3 (0.8)	.3133
Phosphorus, mmol/L	218	1.7 (0.6)	62	1.7 (0.6)	15	1.3 (0.6)	295	1.7 (0.6)	.3686
ASAT, U/L	185	18.0 (10.0)	53	19.1 (12.8)	13	23.9 (17.5)	251	18.5 (11.1)	.2853
ALAT, U/L	185	15.9 (11.3)	52	16.4 (15.8)	13	17.8 (10.4)	250	16.1 (12.3)	.6801
Gamma-glutamyl transferase, U/L	179	60.3 (92.1)	50	45.6 (53.0)	13	41.2 (34.4)	242	56.3 (83.3)	.0936
Albumin, g/L	201	37.7 (4.6)	54	36.9 (4.9)	14	35.8 (5.9)	269	37.5 (4.7)	.1222
C-reactive protein, mg/L	205	15.2 (28.1)	59	15.1 (31.3)	15	9.2 (9.8)	279	14.9 (28.1)	.7204
Parathyroid hormone, pmol/L	174	38.7 (36.7)	44	41.3 (35.2)	12	39.8 (30.7)	230	39.2 (36.0)	.6819
Vitamin D (25-OH), nmol/L	131	81.4 (36.4)	34	87.5 (49.3)	9	85.2 (25.2)	174	82.7 (38.7)	.4069
β2 microglobulin, mg/L	102	27.0 (8.1)	30	28.0 (6.9)	9	27.3 (6.4)	141	27.2 (7.7)	.5809

Results are given as mean (SD).

^aModerate vs severe/very severe pruritus.

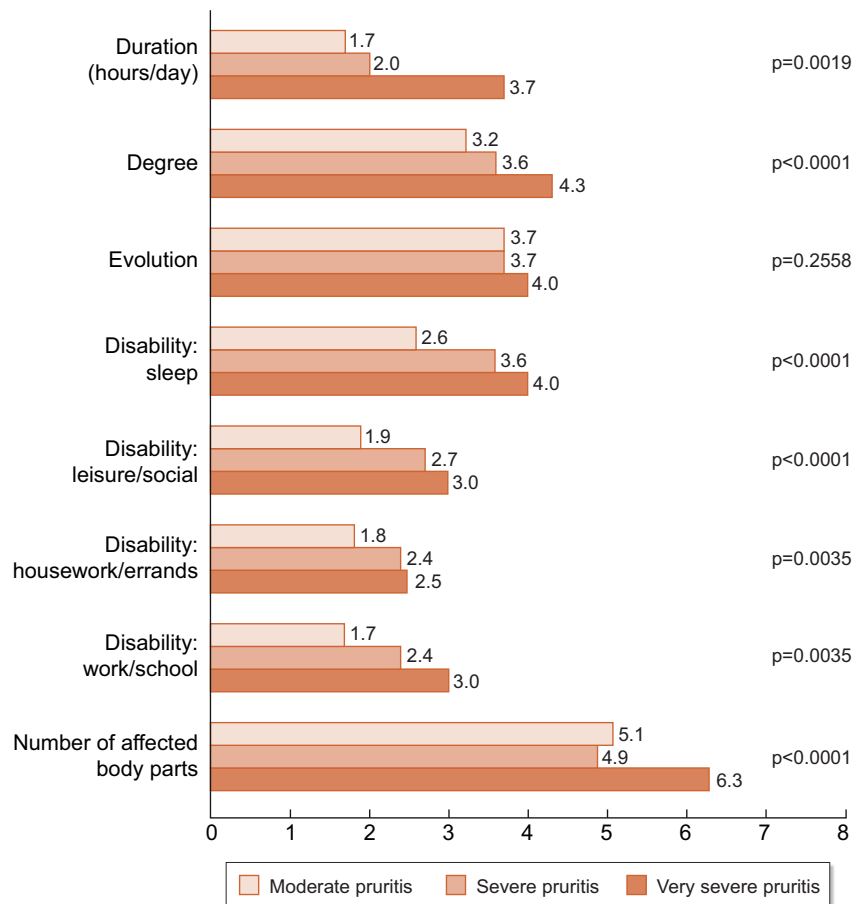


Figure 3: Mean values of dimensions of 5-D Itch scale in patients with pruritus moderate to very severe (N = 306) during the last 2 weeks.

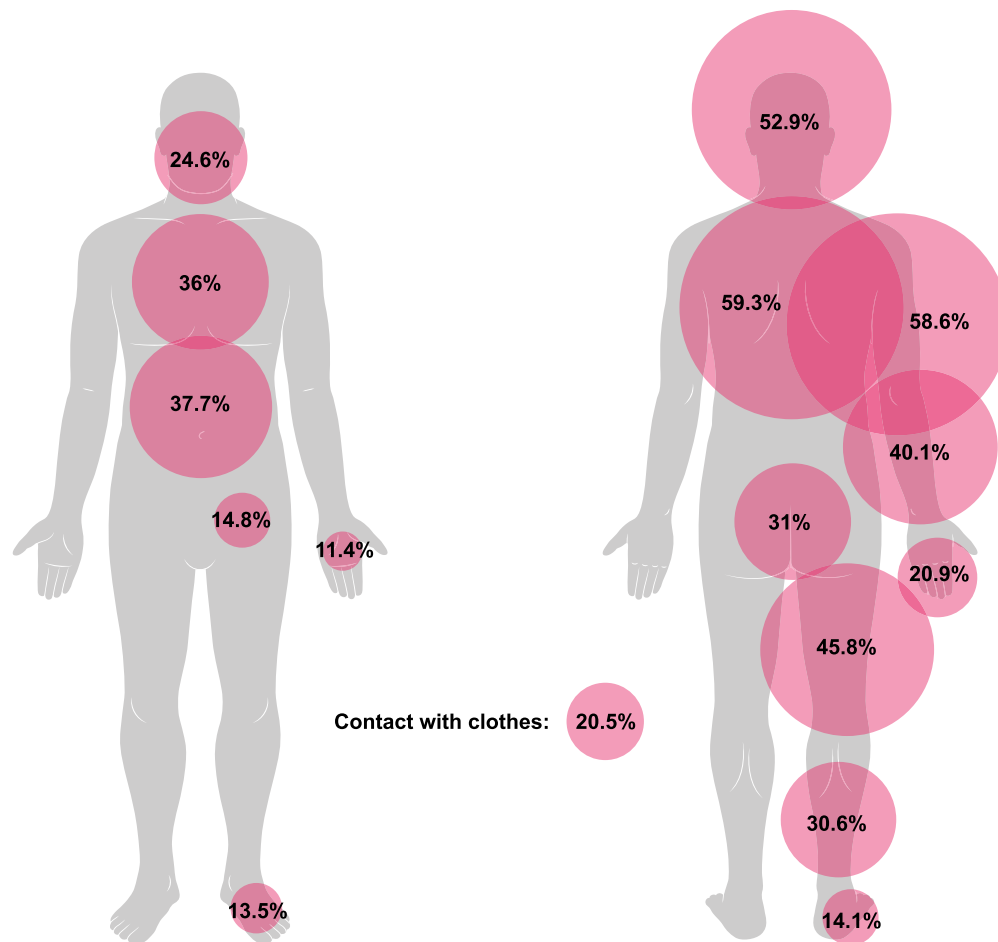


Figure 4: Localizations of pruritus according to 5-D Itch scale in patients with WI-NRS ≥ 4 . Diameter of each circle is proportional to the frequency of pruritus in that localization. Localizations on the limbs are symmetrical.

patients with moderate vs severe/very severe pruritus. The prevalence rate of CKD-aP reported in our study is in lower range of the values reported in the literature.

The most comprehensive database on CKD pruritus comes from the DOPPS [23]. This large-scale observational study in hemodialysis patients was conducted in 12 countries (Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, UK and USA) in 2002–03. The rate of patients with moderate to extreme pruritus was 41.7%. More recent DOPPS analyzes corresponding to the phases 4–6 (2009–18) in 23 264 hemodialysis patients from 21 countries reported that the rate of patients at least moderately bothered by pruritus was 37%; this prevalence was 39% for French patients [21]. The meta-analysis of Hu *et al.* evaluated 42 cross-sectional studies (11 800 adult patients) reporting the prevalence of CKD-aP [24]. The overall prevalence of pruritus in hemodialysis patients was 55% (95% CI 49–61). However, large variations are observed between studies. The prevalence rate was only 25.2% in the German Epidemiology HD Itch Study (GEHIS) performed in 2015 in 860 patients on hemodialysis, with findings close to those of our study [25]. It is noteworthy that in the DOPPS study, the prevalence of pruritus was not measured using WI-NRS, but via a self-reported question: “during the past 4 weeks, how much were you bothered by itchy skin?” This could explain part of the difference in prevalence between the results from DOPPS and Pruripreva.

To minimize this variability, similar definitions and comparable tools for evaluating the severity of CKD-aP are needed. Indeed, several patient-reported outcomes scales are available for the measurement of pruritus severity (e.g. visual analog scales, numeric rating scale, verbal rating scale) [26]. Variability may also be a consequence of inconsistent reporting and physician awareness, leading to an underestimation of the true prevalence of CKD-aP [27]. Rayner *et al.* observed that up to 17% of patients with severe pruritus did not report it to a healthcare professional [3]. The same authors also noted that 65% of medical directors largely underestimated the rate of severe pruritus in their own dialysis unit [3].

Data are conflicting concerning the factors associated with CKD-aP. In DOPPS 1–5 (35 452 patients), older age, higher C-reactive protein and lower serum albumin level were associated with a greater risk of CKD-aP, whereas no association was found for serum phosphorus, calcium, calcium–phosphorus product, parathyroid hormone, Kt/V and hemodiafiltration [3]. In DOPPS 4–6 (23 264 patients), Sukul *et al.* found a trend toward older age, higher serum phosphorus levels and lower hemoglobin and serum albumin levels in patients more bothered by pruritus [21]. The effects of dialysis parameters on CKD-aP are not consistent, with absent or conflicting results concerning Kt/V, dialysis modality (hemodialysis, hemodiafiltration, extended hemodialysis, frequency), or type of membrane and dialysate [3, 6, 21, 23].

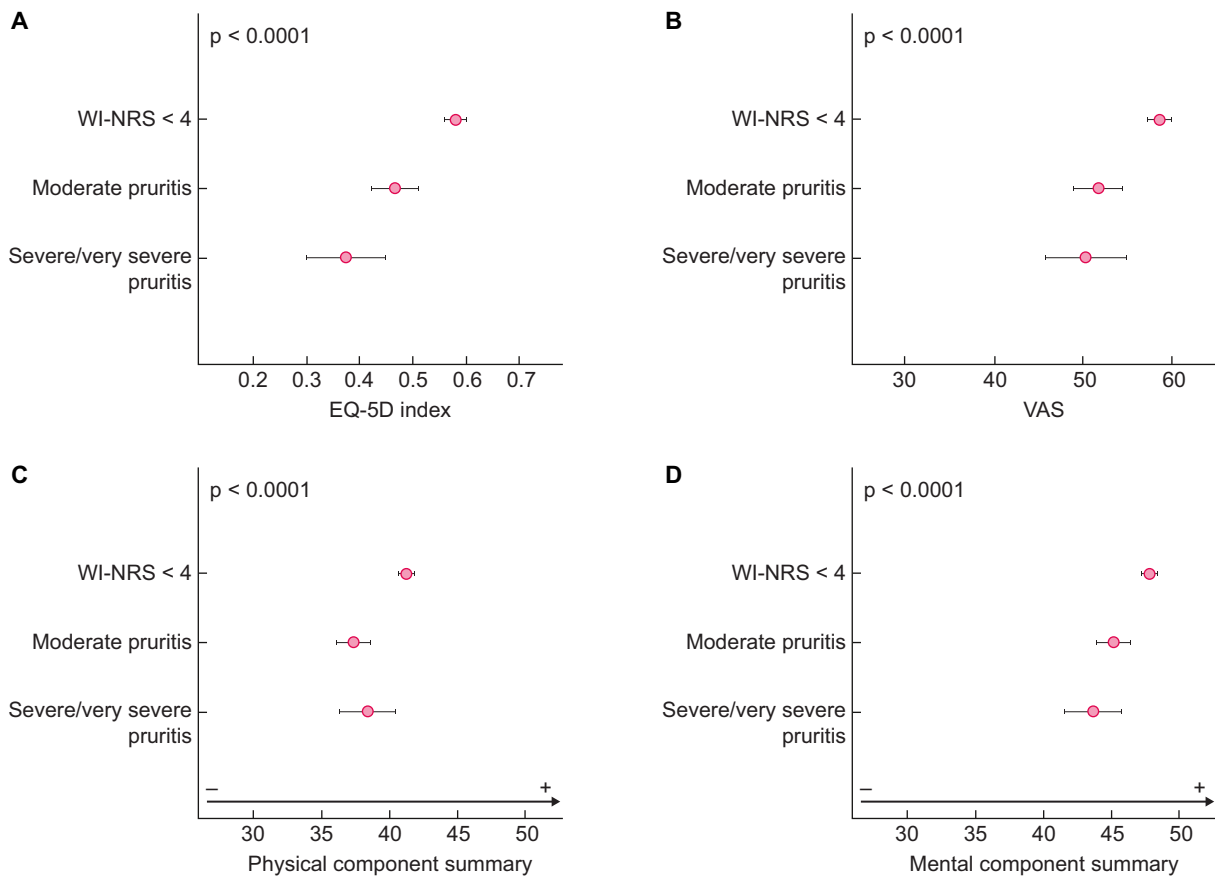


Figure 5: Quality of life according to pruritus intensity. Mean (95% CI) (A) EQ-5D index score and (B) EQ-5D VAS according to pruritus severity, and (C) SF-12 PCS and (D) SF-12 MCS.

We presented the data from the REIN registry encompassing all the French hemodialysis patients (Tables 1–3). Compared with these data from these national data, patient with moderate to severe pruritus did not seem to present different characteristics, with close age (mean 67 vs 69), sex ratio (1.4 vs 1.6) or causal nephropathy. In contrast, patients with pruritus were more likely to have longer dialysis vintage (median 43 vs 38.4 months). Frequent dialysis (more than three sessions per week) did not seem to be associated with lower rate of CKD-aP. Hemodiafiltration was more frequent in patients with WI-NRS ≥ 4 , but this could be due to more comorbidities in patients treated in dialysis centers, which is the only place where hemodiafiltration is allowed in France. Dialysis centers were over represented in our population. Here again, studies evaluating risk factors of CKD-aP are needed.

Hemodialysis patients are also at risk for depressive disorders and low mood. The prospective study of Khan et al. in 220 hemodialysis patients reported a high rate of depression (more than 70%) using the Hospital Anxiety and Depression Scale (HADS) questionnaire [28]. It could be hypothesized that itchy skin could accentuate depressive symptoms. Thus, the study of Lopes et al. in hemodialysis patients showed strong dose-response associations of pruritus with higher depression symptoms, poorer sleep and dry skin problems [29]. In our study, the scores of the anxiety/depressive domain of the EQ-5D scale were significantly increased in moderate and severe/very severe pruritus. The MCS score of the SF-12 scale was also significantly de-

creased in patients with moderate to severe pruritus. Increased depressive symptoms in the CKD population have been associated with poor adherence to dialysis, prescribed treatments, dietary restrictions, poor QoL and increased mortality [30]. Among the many factors potentially responsible for depressive disorders, pruritus itself may promote depressive symptoms by affecting QoL, making social relationships difficult and disturbing sleep by continuous itchiness. Depression symptoms may in turn aggravate itchiness [9].

The main limitation of our study is the absence of comparisons with the group of patients without pruritus or with mild pruritus since patients' characteristics were reported per protocol only for those with WI-NRS ≥ 4 . The dialysis centers that participated in the study were voluntary and may not be representative of all centers, therefore some selection bias may be present. We have reported data from the exhaustive French ESRD registry REIN to assess the comparability of the patients included in Pruripreva with the general population of French hemodialysis patients. In addition, the generalizability of the data to other countries is uncertain. No data were obtained about pruritus prior to the study, so some patients could have been classified as not suffering from CKD-aP whereas they were, but had been successfully treated. This could have lowered the estimated prevalence of CKD-aP.

In conclusion, moderate to very severe pruritus was reported in 23% of hemodialysis adults in France, and in 38% of these patients, CKD-aP was unknown to the caregivers prior to the

systematic screening due to the study. These data confirm that pruritus in this setting is an underdiagnosed and underreported medical need. Finally, CKD-aP and its intensity were associated with poor QoL regarding its different components. There is an urgent demand for new therapies to treat CKD-aP in hemodialysis patients.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj](#) online.

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AUTHORS' CONTRIBUTIONS

All authors participated in the design of the study, were investigators, and participated in the analysis and interpretation of the results. All authors reviewed the manuscript and approved the final version for publication.

CONFLICT OF INTEREST STATEMENT

A.L. is on an advisory board for CSL Vifor and has received speaker honoraria and/or travel sponsorship from AstraZeneca and Bayer Health and CSL Vifor. G.R. reports consultancy fees from Astellas (board on roxadustat, 2019–2021), GlaxoSmithKline (board on daprodustat, 2022) and Vifor (board on difelikefalin, 2021–2022); reports research funding for scientific presentations from Amgen, Astellas, Baxter, Hemotech, Gambro Hospital, Nipro, Physidia and Theradial; reports honoraria from

Amgen, Astellas, GlaxoSmithKline, Roche, Sanofi and Vifor; and is on the speakers' bureau for Astellas and Baxter. P.B. reports consultancy fees from Astellas (board on roxadustat, 2019–21), GlaxoSmithKline (board on daprodustat) 2022, Vifor (board on avacopan and difelikefalin, 2021–22), AstraZeneca (speaker honoraria for dapagliflozin) and Gilead (speaker honoraria), and travel sponsorship from Sanofi. P.C. is a member of advisory board for CSL Vifor and has received speaker honoraria and/or travel sponsorship from Fresenius Kabi and Theradial. M.T. reports conflicts of interest with Vifor Pharma and Astellas. L.M. reports conflicts of interest with Vifor Pharma and Trevi. S.B. reports no conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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