Burden of CKD-Associated Pruritus and Adverse Clinical Outcomes in Patients Receiving Dialysis: The Stockholm Creatinine Measurements (SCREAM) Project

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Rationale & Objective: Pruritus is a common but not well-characterized complaint of patients receiving maintenance dialysis. This study sought to quantify the burden of pruritus and its associated adverse health outcomes in this population.

Study Design: Observational study.

Setting & Participants: All patients receiving maintenance dialysis in Stockholm, Sweden, during 2005-2021.

Exposure: Clinically recognized pruritus defined using *International Classification of Diseases, Tenth Revision* codes or a prescription for antipruritus treatments (including UV therapy).

Outcomes: All-cause mortality, severe infection–related hospitalizations (composite of endocarditis, peritoneal dialysis–related peritonitis, hemodialysis/peritoneal dialysis–related catheter infection, sepsis due to *Staphylococcus* spp., or skin infection) and incident diagnoses of anxiety/depression and sleep disorders.

Analytical Approach: Multivariable logistic regression and cause-specific hazards models to analyze factors associated with prevalent and new-onset pruritus, respectively. Multivariable cause-specific hazards models with time-varying exposure were used to explore the association of prevalent and new-onset pruritus with adverse health outcomes.

Results: Among 3,281 dialysis recipients (median age, 64 years; 66% men; 69% receiving hemodialysis, 77% with incident dialysis), 456 (14%) had pruritus at enrollment. During a median follow-up of 3.3 (IQR, 1.3-9.2) years, 539 (19%) additional patients experienced pruritus. Older age, female sex, a lower serum albumin level, and higher C-reactive protein, serum calcium, and phosphorus levels were independently associated with pruritus. Compared with patients without pruritus, patients with pruritus were at a higher risk of sleep disorders (adjusted HR, 1.96; 95% CI, 1.60-2.39), developing anxiety/depression (adjusted HR, 1.56; 95% CI, 1.23-1.98), and being hospitalized for severe infections (adjusted HR, 1.36; 95% CI, 1.18-1.57), the latter attributed to higher risk of sepsis and peritoneal dialysis–related peritonitis. There was no detectable association between the development of pruritus and all-cause mortality.

Limitations: Potential misclassification bias if pruritus is not clinically recognized, lack of information on pruritus intensity/severity, use of diagnostic codes for exposure and outcome diagnoses.

Conclusions: At least one third of patients experience pruritus during their first years undergoing dialysis, and pruritus was consistently associated with adverse health outcomes.

Visual Abstract online

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Pruritus, a strong sensation of itching, is one of the most burdensome uremic symptoms experienced by patients with advanced chronic kidney disease (CKD)[1,2] and is considered an important research priority for patients who are undergoing dialysis or will be soon.[3] Self-reported pruritus has been described in approximately 25% of patients with non–dialysis-dependent CKD stages 3-5[4] and approximately 40% of patients undergoing maintenance dialysis.[5,6] The unremitting and refractory nature of this condition may persist over a period of years,[7,8] and the condition causes distress that ranges from sporadic discomfort to complete restlessness.

There is a need to better characterize the burden of this condition and identify populations at risk of developing pruritus who might benefit from screening or diagnosis and subsequent initiation of treatment or who might be potential research participants.[3] Patients underrecognize and underreport their pruritus, probably because they are unaware of its link with CKD, and may interpret it as a symptom they must live with.[6,9,10] Further, nephrologists and other health care providers underestimate its prevalence and severity, prioritizing other health issues over pruritus.[6,9,11] Data from previous observational studies showed that pruritus was associated with poor quality of life, restless sleep, depression, infections, and mortality.[4-6,12-17] However, most of the previous work comes from cross-sectional studies conducted in patients undergoing hemodialysis (HD) with self-reported symptoms of pruritus, which may lead to possible recall or misclassification bias. Studies involving patients undergoing peritoneal dialysis (PD) are scarce,[16-22] often from single centers and with small sample sizes. More dynamic evaluations that included

PLAIN-LANGUAGE SUMMARY

Pruritus is a common but not well-characterized symptom of patients receiving dialysis. We analyzed data from 3,281 patients receiving maintenance hemodialysis or peritoneal dialysis in the region of Stockholm, Sweden. At baseline, 14% of patients had pruritus, and pruritus developed in an additional 19% of patients during their time receiving dialysis. We identified conditions associated with the development of pruritus (eg, older age, female sex, lower serum albumin level, and higher C-reactive protein, serum calcium, and phosphorus levels) and observed that the presence of pruritus was associated with higher risks of sleep disorders, developing anxiety and depression, and being hospitalized for severe infections. No association between pruritus and all-cause mortality was identified.

incident cases would allow for a better quantification of the burden of this condition and potential risk factors.

Using a large contemporary health care extraction of patients receiving maintenance dialysis in Stockholm, Sweden, we quantified the population affected by clinically recognized pruritus, their clinical determinants, and the associated adverse health outcomes.

Methods

Population Source and Study Population

The Stockholm Creatinine Measurement (SCREAM) study is a health care use cohort of the complete population of the Stockholm region of Sweden.[23] Via each citizen's unique personal identification number, SCREAM links various national and regional government-run registries that collect information on health care access and health processes. For this study, we included all patients initiating or undergoing maintenance dialysis (HD or PD) during the period of 2005-2021. Information for these patients was obtained primarily from the interlinked Swedish Renal Registry, a nationwide quality registry that annually randomly records clinical and laboratory data of patients receiving maintenance dialysis at any nephrology clinic. Therefore, in this study, incident dialysis recipients are those with less than 1 year of dialysis therapy. These data were enriched with administratively coded clinical diagnoses and procedures (via linkage with the regional health care use database), medications dispensed at any Swedish pharmacies (via linkage with the Drug Prescription Registry), and vital status (via linkage with the Death Registry). The date of the first registered annual visit recorded in the Swedish Renal Registry constituted the index date (ie, baseline) and the start of follow-up (Fig S1). The study was approved by the Swedish Ethical Review Authority. Individual-level informed consent was not required by the National Review Ethics Board for this type of study.

Exposure and Outcomes

This study encompasses 2 complementary analyses. In the first analysis, the study outcome was clinically recognized pruritus, and we assessed its prevalence, incidence, and main baseline determinants. In the second analysis, pruritus was considered as a time-varying exposure, and we analyzed the association between prevalent/new-onset pruritus and a range of adverse health outcomes.

Clinically recognized pruritus was defined by the presence of a clinical diagnosis (*International Classification of Diseases, Tenth Revision* codes L298, L299, and F458) in the patient medical records, the chronic use of pruritus medications (at least 2 consecutive dispensations), and/or the use of UV therapy (in the absence of a diagnosis of psoriasis; Table S1). At the time of data collection, treatments used by nephrologists in Sweden for the management of CKD-associated pruritus included hydroxyzine, clemastine, gabapentin, pregabalin (the latter 2 being assumed to be prescribed for pruritus treatment in the absence of a clinical diagnosis of diabetes, peripheral neuropathy, or epilepsy), and an extemporaneously compounded topical preparation with levomenthol, camphor, chloral-hydrate (specific for pruritus treatment and classically known as *klådsalva* in Swedish, meaning "ointment for itching"). Prevalent pruritus was defined by the presence of a clinical diagnosis of pruritus at baseline or a recent (12 months before enrollment) prescription for a pruritus treatment. New-onset pruritus was defined by a de novo clinical diagnosis or an initial prescription for a chronic treatment for pruritus during follow-up.

Adverse health outcomes included all-cause mortality, severe infection–related hospitalizations, de novo anxiety/depression, and sleep disorders. Severe infection–related hospitalizations considered the composite of endocarditis, PD-related peritonitis, HD-/PD-related catheter infection, sepsis due to *Staphylococcus* spp. or unspecified *Staphylococcus*, or skin infection (erysipelas, infective dermatitis, impetigo, abscess, cellulitis, and other skin infections). De novo anxiety/depression or sleep disorders were ascertained in patients free from these conditions at baseline by incident clinical diagnoses or the initiation of related treatments. Detailed definitions of study outcomes are presented in Table S1. For each outcome, patients were followed until the first occurrence of an event, kidney transplant, death, or the end of follow-up (December 31, 2021).

Covariates

Covariates were derived at the index date and were updated at the time of new pruritus onset during the follow-up period. They included age, sex, comorbidities, clinical and laboratory data, information on dialysis therapy, as well as ongoing medications (detailed definitions

in Table S1). Comorbidities considered included hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, myocardial infarction, cerebrovascular disease, peripheral artery disease, heart failure, arrhythmia, anxiety/depression, restless legs syndrome, peripheral neuropathy, and skin infection. Clinical assessment data included systolic and diastolic blood pressure, body mass index, hemoglobin, C-reactive protein (CRP), serum albumin, total calcium, phosphate, and parathyroid hormone. Information on dialysis therapy included dialysis modality and vintage, Kt/V, and type of vascular access. Ongoing medications considered, besides treatments for pruritus, included the use of phosphate binders, calcimimetic agents, iron supplements, erythropoiesis-stimulating agents, and opioids dispensed in the 6 months before the index date.

Statistical Analyses

Values are expressed as means and standard deviations for continuous variables with normal distribution, medians with IQRs for variables with nonnormal distribution, and numbers with percentages of the total for categorical variables.

We evaluated baseline clinical determinants of prevalent pruritus by multivariable logistic regression and of new-onset pruritus with a multivariable cause-specific hazards model overall and by dialysis modality. Determinants were selected a priori on the basis of current knowledge on the pathophysiology of pruritus[7] and included age, sex, diabetes, systolic blood pressure, body mass index, cardiovascular disease, peripheral neuropathy, restless legs syndrome, dialysis modality, dialysis vintage, Kt/V, hemoglobin, CRP, serum calcium, serum phosphate, parathyroid hormone, and serum albumin levels. Continuous variables were standardized as per 1–standard deviation increase. Kt/V for patients undergoing PD was standardized referent to all patients undergoing PD, and HD was treated similarly. When converted to standard deviations, the 2 metrics were combined.

Next, we analyzed the association between pruritus and adverse health outcomes with time-varying cause-specific hazards models. Pruritus was considered a time-varying exposure, thus patients developing new-onset pruritus developed contributed to the nonexposed group from enrollment until the occurrence of pruritus, and contributed to the exposed group thereafter (Fig S2). For the evaluation of risks of de novo anxiety/depression and sleep disorders, we excluded patients with a history of these conditions at baseline. The proportional hazard assumption was checked using log(–log[S]) plots and Schoenfeld residuals against time.

Study covariates had no missing values or were missing in <5% of patients (Table S2) except for parathyroid hormone, serum calcium, and CRP, which were missing in 19%, 26%, and 27% of participants, respectively. Because these laboratory tests are part of the routine monitoring of patients receiving dialysis, we assumed them to be missing at random and attributed this to a lack of reporting to the registry. We performed single imputations, replacing missing data by the next laboratory test carried backward or the median value of the cohort if no other laboratory measurement was reported to the registry.

We performed subgroup analyses to assess the consistency of our results by stratum of age, sex, presence/absence of cardiovascular disease, diabetes, and dialysis modality. As a sensitivity analysis, we repeated our outcome analysis as follows: (1) excluding patients with pruritus at baseline and evaluating adverse health outcomes after new-onset pruritus (n = 2,825), (2) in patients receiving incident dialysis (n = 2,510), and splitting the pruritus definition into (3) the presence of a clinical diagnosis and (4) prescription of specific treatments (chronic use of hydroxyzine or clemastine or use of the pruritus-specific extemporaneously compounded topical preparation *klådsalva*), ie, those that do not depend on an assumption regarding the indications for prescription.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology statement for the reporting of observational studies.[24] All statistical analyses were conducted using R software (version 3.6.3; R Foundation for Statistical Computing).

Results

Baseline Characteristics and Identification of Pruritus Cases

We identified 3,281 patients receiving maintenance dialysis (77% of whom had been receiving dialysis for less than 1 year at baseline) in Stockholm during 2005-2021. Their median age was 64 years, 66% were men, 69% were receiving HD, and their mean dialysis vintage was 2.2 years (Table 1). At baseline, 456 (13.9%) patients (14.8% of patients receiving HD and 12.0% of patients receiving PD) had clinically recognized pruritus. Overall, 36% of pruritus cases were identified through *International Classification of Diseases* codes and 64% solely through initiation of a pruritus treatment. Compared with patients who were free from pruritus, patients with prevalent pruritus were older; more often women; had higher prevalences of cardiovascular disease, anxiety/depression, sleep disorders, and skin infections; and were more often receiving HD.

During a median follow-up of 3.3 (IQR, 1.3-9.2) years, an additional 539 patients (19.1%) who were pruritus-free at baseline (21.2% of patients receiving HD and 14.4% of patients receiving PD) experienced pruritus, with a total period prevalence of 33%. Overall, 19.3% of incident cases were identified through *International Classification of Diseases* codes and the remaining solely through initiation of a pruritus treatment. This period prevalence was higher in HD than in PD (36.0% of patients receiving HD and 26.4% of patients receiving PD had pruritus; $P < 0.01$).

Table 1. Characteristics of Patients Receiving Maintenance Dialysis at Enrollment (Baseline) and at the Time of New Pruritus Occurrence After Enrollment

Characteristic	Pruritus at Enrollment		*P* Value	New-Onset Pruritus After Enrollment (n = 539)
	No (n = 2,825)	Yes (n = 456)		
Demographic and clinical data				
Median age, y	64 [51-73]	66 [55-75]	0.003	67 [56-75]
Female sex	944 (33%)	183 (40%)	0.006	200 (37%)
Systolic BP, mm Hg	140 ± 23	139 ± 24	0.5	140 ± 24
Diastolic BP, mm Hg	78 ± 14	75 ± 15	0.002	77 ± 15
BMI, kg/m^2	25.3 ± 5.4	25.6 ± 5.3	0.2	25.6 ± 5.3
Comorbidities				
Hypertension	2,777 (98%)	456 (100%)	0.009	539 (100%)
Diabetes mellitus	1,049 (37%)	214 (47%)	<0.001	203 (38%)
Dyslipidemia	1,313 (47%)	227 (50%)	0.2	238 (44%)
Ischemic heart disease	651 (23%)	150 (33%)	<0.001	156 (29%)
Myocardial infarction	443 (16%)	103 (23%)	<0.001	107 (20%)
Cerebrovascular disease	431 (15%)	75 (16%)	0.6	104 (19%)
Peripheral arterial disease	313 (11%)	73 (16%)	0.003	88 (16%)
Heart failure	776 (26%)	158 (35%)	0.002	178 (33%)
Arrhythmia	559 (20%)	110 (24%)	0.04	127 (24%)
Peripheral neuropathy	43 (2%)	13 (3%)	0.07	14 (3%)
Restless legs syndrome	90 (3%)	23 (5%)	0.06	14 (3%)
Depression/anxiety	478 (17%)	129 (28%)	<0.001	132 (25%)
Sleep disorders	965 (34%)	243 (53%)	<0.001	266 (49%)
Skin infection	458 (16.2%)	97 (21%)	0.009	127 (24%)
Biological data				
Hemoglobin, g/dL	11.4 ± 1.5	11.4 ± 1.5	0.4	11.5 ± 1.5
C-reactive protein, mg/L	11.9 ± 24.4	16.7 ± 32.4	0.002	13.1 ± 22.6
Serum albumin, g/L	31.8 ± 5.2	31.1 ± 5.8	0.005	31.9 ± 4.7
Serum calcium, mmol/L	2.3 ± 0.2	2.3 ± 0.2	0.1	2.3 ± 0.2
Serum phosphate, mmol/L	1.7 ± 0.5	1.7 ± 0.5	0.6	1.8 ± 0.6
PTH, pmol/L	33.5 ± 45.2	34.2 ± 41.8	0.8	40.4 ± 64.3
Dialysis modality				
Dialysis duration, y	2.2 ± 5.2	2.5 ± 5.4	0.3	3.8 (5.4)
Dialysis modality, PD	907 (32%)	124 (27%)	0.04	128 (24%)
Access			0.1	
HD catheter	863 (30%)	134 (29%)		160 (30%)
Arteriovenous fistula	780 (28%)	144 (32%)		184 (34%)
Arteriovenous graft	256 (9%)	51 (11%)		62 (12%)
Other access	19 (0.7%)	3 (0.7%)		5 (0.9%)
PD catheter	907 (32%)	124 (27%)		128 (24%)
Kt/V per week				
Kt/V, HD	2.1 ± 0.5	2.1 ± 0.5	0.3	2.3 ± 0.4
Kt/V, PD	2.3 ± 0.6	2.2 ± 0.6	0.3	2.3 ± 0.7
Ongoing medications				
Hydroxyzine	79 (3%)	158 (35%)	<0.001	193 (36%)
Clemastine	118 (4%)	177 (39%)	<0.001	247 (46%)
Pregabalin	25 (0.9%)	14 (3%)	<0.001	25 (5%)
Gabapentin	46 (2%)	27 (6%)	<0.001	41 (8%)
Compounded topical preparation for pruritus (*klådsalva*)	0	27 (6%)	<0.001	33 (6%)
Erythropoiesis-stimulating agents	2,224 (79%)	357 (78%)	0.9	398 (74%)
Any iron	1,385 (49%)	247 (54%)	0.05	282 (52.3)
Calcimimetics	295 (10%)	48 (11%)	1.0	83 (15%)
Phosphate binders	1,728 (61%)	304 (67%)	0.03	365 (68%)
Opioids	309 (11%)	99 (22%)	<0.001	92 (17%)

Categorical variables are reported as frequencies (percentages), and continuous variables are reported as means ± standard deviations or medians [first and third interquartile values]. Abbreviations: BMI, body mass index; BP, blood pressure; HD, hemodialysis; PD, peritoneal dialysis; PTH, parathyroid hormone.

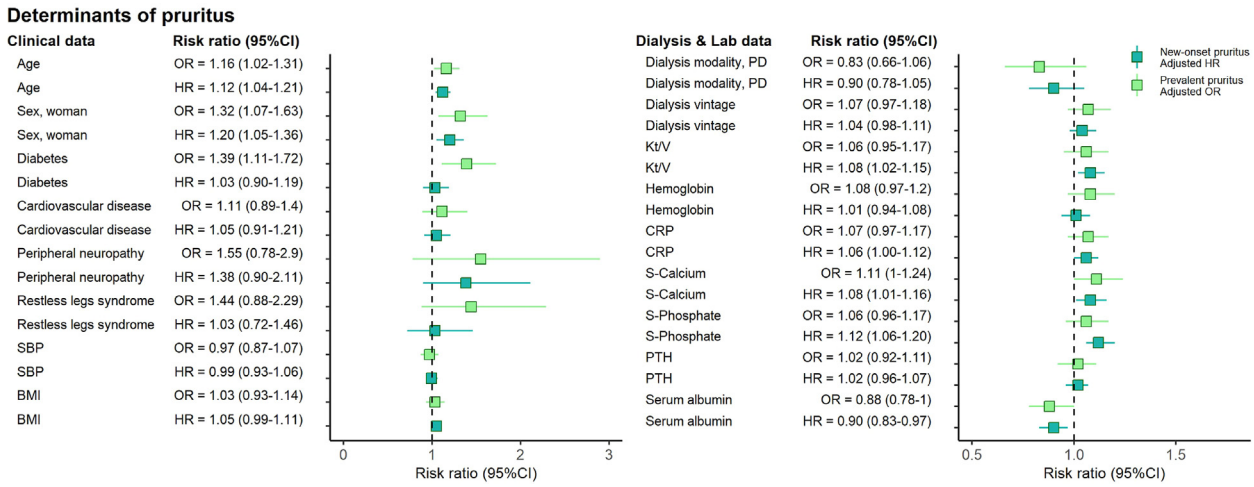

Figure 1. Determinants of prevalent (odds ratios) and new-onset (hazard ratios) pruritus were estimated using a multivariable logistic regression model and a cause-specific hazards regression model, respectively. All covariates were included in the same model, but the figure has been divided into 2 panels for easier presentation. The risk associated with continuous variables (ie, age, systolic blood pressure, body mass index, dialysis vintage, Kt/V, and all biological data) is expressed per each 1–standard deviation increase. Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; OR, odds ratio; PD, peritoneal dialysis; PTH, parathyroid hormone; S-calcium, total serum calcium; S-phosphate, serum phosphate; SBP, systolic blood pressure.

Determinants of Prevalent and New-Onset Pruritus

The clinical determinants of prevalent or new-onset pruritus were consistent in general and included older age, female sex (vs male), higher levels of CRP, serum calcium, and phosphate, and a lower level of serum albumin (Fig 1; Table S3). Diabetes was associated with prevalent but not with new-onset pruritus. PD (vs HD) tended to be inversely associated with pruritus, but the confidence intervals were broad (Fig 1; Table S3). Determinants of pruritus were consistent in general across dialysis modalities (HD vs PD; Figs S3 and S4) and dialysis vintage (incident vs prevalent; Figs S5 and S6), although the smaller sample sizes across subgroups yielded broad confidence intervals.

Impact of Pruritus on Adverse Clinical Outcomes

During follow-up, 1,532 deaths, 949 infection-related hospitalizations, 328 new cases of anxiety/depression, and 485 new cases of sleep disorders occurred. Compared with pruritus-free periods, pruritus was associated with higher risks of de novo anxiety/depression (adjusted hazard ratio, 1.56; 95% confidence interval, 1.23-1.98) and sleep disorders (adjusted hazard ratio, 1.96; 95% confidence interval, 1.60-2.39). The presence of pruritus was also associated with the risk of subsequent severe infections (adjusted hazard ratio, 1.36; 95% confidence interval, 1.18-1.57), mainly attributed to a higher risk of sepsis and PD-related peritonitis (Fig 2; Tables S4 and S5). Pruritus was not associated with the risk of all-cause mortality.

Results were consistent across subgroups of age, sex, diabetes, cardiovascular disease, and dialysis modality (Fig 3). Excluding patients with prevalent pruritus at enrollment (Table S6) or restricting the study population to patients receiving incident dialysis (Table S7) yielded similar associations with adverse health outcomes. Similar trends were also observed when pruritus was defined only by *International Classification of Diseases* codes (Table S8) or by the use of treatment (Table S8).

Discussion

We observed that at least one third of patients (33%) experience pruritus during their first years receiving maintenance dialysis. We also identified subpopulations that are consistently at higher risk of having pruritus, including older patients, women, and those with higher levels of serum calcium, phosphate, CRP, or lower levels of serum albumin. Finally, our findings showed that patients with pruritus were at high risk of adverse health outcomes including de novo anxiety/depression, sleep disorders, and infection-related hospitalizations.

Pruritus is common in patients undergoing dialysis. Although data from older studies and clinical experience suggest that the prevalence of pruritus was substantially higher in the early years of dialysis,[25] it still remains high, affecting at least one third of the patients receiving maintenance dialysis in our study. Our observed period prevalence is consistent with other previous contemporary reports,[12,18,20] showing, for instance, that approximately 37% of patients self-reported being moderately to extremely bothered by pruritus in DOPPS (the Dialysis Outcomes and Practices Pattern Study) during 2009-2018.[12] Whereas preceding evidence comes from cross-sectional studies that were mainly restricted to patients

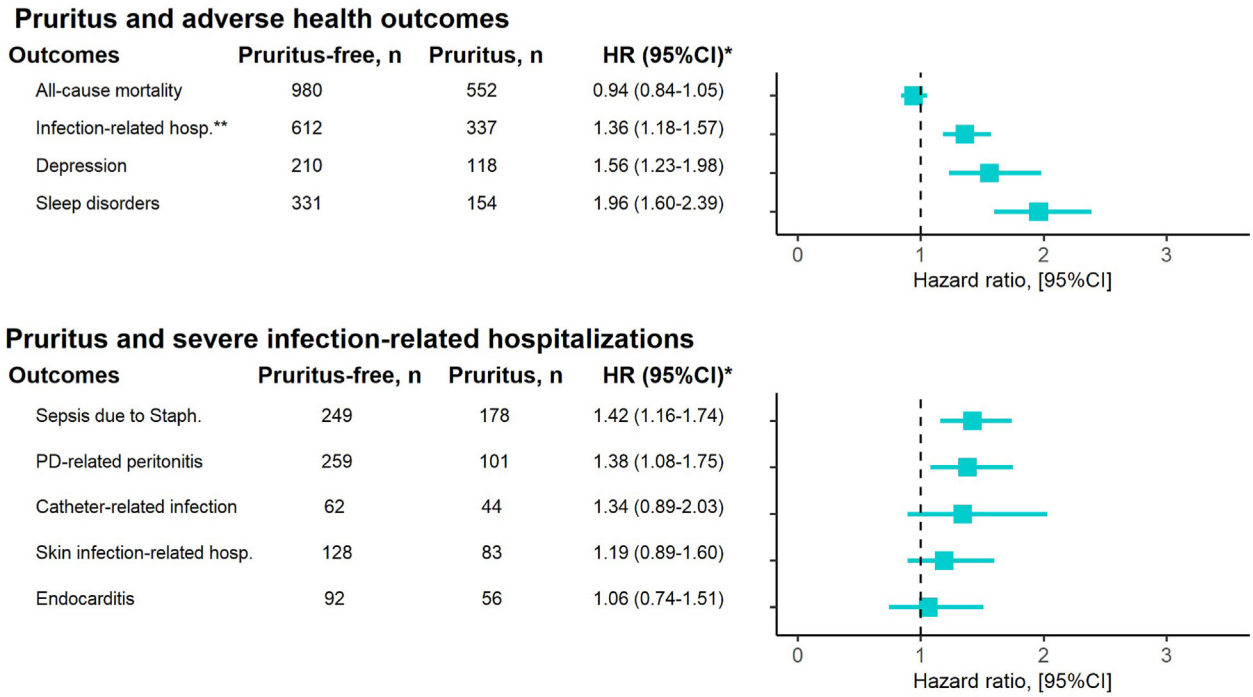

Figure 2. Adjusted hazard ratios for the association between pruritus and adverse health outcomes. The figure represents the number of events in each time period (pruritus-free and pruritus periods) and adjusted hazard ratios for the association between pruritus, adverse health outcomes, and severe infection-related hospitalizations. Single asterisk: cause-specific hazards models were fitted using pruritus as a time-varying exposure and were adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, heart failure, arrythmia, peripheral artery disease, cerebrovascular disease, peripheral neuropathy, restless legs syndrome, systolic blood pressure, body mass index, hemoglobin, C-reactive protein, serum albumin, serum calcium, parathyroid hormone, dialysis modality, dialysis vintage, Kt/V, iron, erythropoiesis-stimulating agents, calcimimetics, and phosphate binders. For de novo anxiety/depression and sleep disorders, analyses were performed in patients free from these conditions at baseline. Double asterisks: severe infection-related hospitalization, a composite of hospitalizations for sepsis due to *Staphylococcus* spp. or unspecified *Staphylococcus*, catheter-related infection, peritoneal dialysis–related peritonitis, skin infection (erysipelas, infective dermatitis, impetigo, abscess, cellulitis, and other skin infections), or endocarditis. Abbreviations: CI, confidence interval; HR, hazard ratio; PD, peritoneal dialysis.

receiving HD, we included patients receiving HD and PD and also evaluated new cases during follow-up to better capture the total pruritus burden of this population. However, because pruritus is widely underreported by patients[6,9] and underrecognized or underestimated by health care professionals,[6,11] the real burden is possibly higher and could explain, at least in part, the poor outcomes in this population. Moreover, patient-reported symptom burden may differ from the clinically recognized symptoms we report. A recent study conducted in incident dialysis recipients from the European QUALity (EQUAL) cohort described a self-reported pruritus prevalence of approximately 60%, of which 25% of the patients were bothered at least "quite a bit."[26] In this study, pruritus was one of few symptoms that increased in burden during the first year of dialysis.

An important finding of the present study is the consistent association between pruritus and a range of adverse health outcomes. The observational nature of our study cannot demonstrate the causality of this finding and may simply highlight a population with multiple complications. The higher rate of infection in patients with pruritus can be explained by immune system dysregulation—that results in new-onset pruritus and higher risks of infection—and the presence of a central venous catheter.[27] However, it may also be a direct consequence of scratching and excoriation, especially skin infections and sepsis due to *Staphylococcus* spp. Other studies have also linked pruritus with infection-related hospitalizations,[12,13,16] skin-related infections,[12] catheter-associated infections,[13] and intravenous antibiotic agent use.[16]

The distress caused by persistent pruritus has been reported to impact patients' quality of life,[5,12,14,16,28] and we observed higher subsequent risks of developing sleep disorders. Pruritus may be worse during the night,[8] and other reports have related pruritus intensity with poor quality of sleep[5,8,12,14,15,17,29]; restless sleep[6]; feeling tired, "washed out," or "drained"[12,14]; daily somnolence or difficulty sleeping at night[5]; and longer recovery time from HD sessions.[12] This persistent distress may

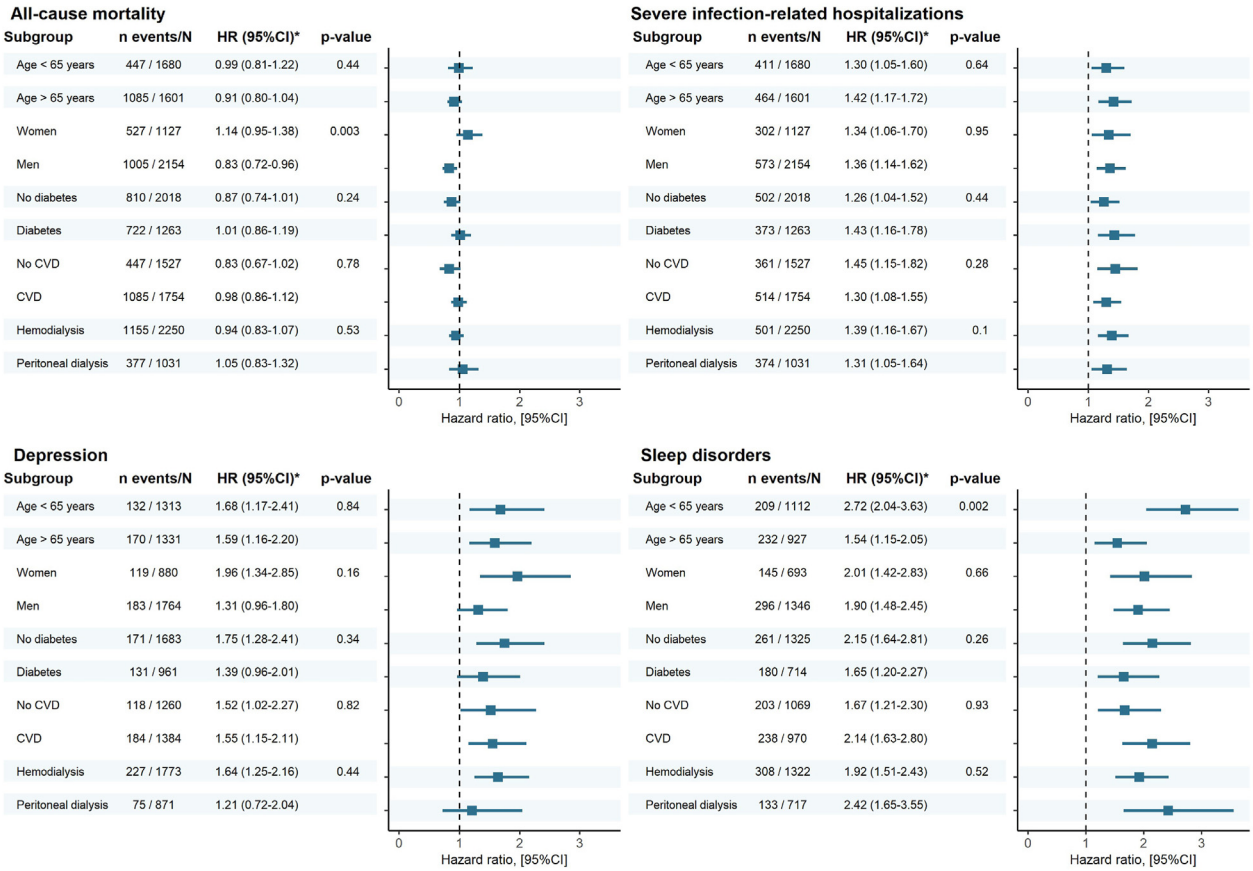

Figure 3. Hazard ratios for the association between pruritus and adverse outcomes according to baseline subgroup. Asterisk: cause-specific hazards models were fitted using pruritus as a time-varying exposure and were adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, heart failure, arrythmia, peripheral artery disease, cerebrovascular disease, peripheral neuropathy, restless legs syndrome, systolic blood pressure, body mass index, hemoglobin, C-reactive protein, serum albumin, serum calcium, parathyroid hormone, dialysis modality, dialysis vintage, Kt/V, iron, erythropoiesis-stimulating agents, calcimimetics, and phosphate binders. For de novo anxiety/depression and sleep disorders, analyses were performed in patients free from these conditions at baseline. The association between pruritus and the risk of death was stronger in women ($P = 0.003$ for interaction). The association between pruritus and the risk of sleep disorders was stronger in patients younger than 65 years ($P = 0.002$ for interaction). The other tested interactions were not significant. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

psychologically impact the patient with a higher risk of anxiety/depression, as observed in our study and expanding on previous works.[5,12,17] Finally, we did not observe any association between pruritus and all-cause mortality, which contrasts with reports from DOPPS[5,12,14] and may be explained by differences in study power or pruritus ascertainment (self-reported symptoms vs clinically recognized diagnoses).

The pathophysiology of CKD-associated pruritus is not fully understood and is thought to occur in the setting of a complex metabolic environment that may involve uremic toxin deposition, inflammation and/or immune system dysregulation, peripheral neuropathy, and opioid imbalance.[7] Our multivariable risk analyses of prevalent and new-onset pruritus based on the aforementioned pathophysiological mechanisms is broadly consistent with prior findings. Characteristics and findings of the main epidemiological studies in this regard are summarized in Table S9. In general, the consistency of some clinical predictors is conflicting, possibly impacted by the evaluation of small single-center cohorts of low-powered, cross-sectional analyses and self-reports.

In the present study, pruritus was independently associated with older age and female sex. This agrees with some,[6,8,13,14,16,28,30] but not all,[5,8,14,16,22,28,29] preceding studies. Although itch-related mechanisms may differ between sexes,[31] it is possible that these differences may also be explained by gender differences in the perception and experience of pruritus: men and women may experience and react differently to pruritus and may choose to express it differently; men more often perceive themselves as better able to cope with the physical aspects of their disease or are less prone to tell others about their pruritus,[32] and health care professionals may therefore believe pruritus to

be more burdensome and more often require treatment among women.

Pruritus might be related to skin deposition of pruritogens such as calcium, phosphorus, protein-bound uremic toxins, and middle molecules that are less effectively removed by the current dialysis modalities. Our study agrees with this hypothesis, as patients at risk of pruritus had higher calcium and phosphate levels, which is consistent with some,[5,14,16,21,29,33] but not all,[6] prior studies. However, in agreement with a recent study from DOPPS,[6] we did not find an association between pruritus and parathyroid hormone levels. Also in line with previous studies, our observed association of pruritus with high levels of CRP[6,34,35] and low levels of albumin[5,6,14,16,19,30,36] is consistent with the hypothesis that pruritus is a consequence of local microinflammation, systemic inflammatory syndrome, and immune system dysregulation.[7,35] Neuropathy and dysautonomia may also be involved in the pathophysiology of pruritus,[7] but, even though the prevalences of restless legs syndrome and peripheral neuropathy tended to be higher in our patients with pruritus, we found no statistically significant association in our study. We acknowledge that these associations may be confounded by the inclusion of gabapentinoids, which are also used in the treatment of restless legs syndrome, in our definition of pruritus. Nevertheless, these conditions are not always well captured by clinical diagnoses. Finally, we did not find an association between hemoglobin level and pruritus. Discrepancies exist in the literature in regard to the impact of anemia and iron-related parameters on pruritus.[5,6,8,16]

Dialysis vintage tended to be longer (although the 95% confidence intervals overlapped) in patients with pruritus than in those without, which was consistent with previous studies[14-17,34] However, our study population's short dialysis vintage (most patients had less than 1 year of dialysis therapy) compared with previous reports may have contributed to this lack of association. In addition, in line with recent literature,[6,14,16,17,29,33] we did not observe any association between pruritus and dialysis dose (ie, Kt/V). The direction of the association was the opposite of our expectation, which may be the result of reverse causation bias: a higher prescribed dialysis dose may be the consequence of itching, and there is a natural delay between the reporting of symptoms and the diagnosis and initiation of treatments. A higher prescribed Kt/V may also be related to lower residual kidney function, which induces a decrease in tubular secretion of protein-bound organic anions and uremic toxins, contributing to pruritus.[18] Other hypotheses are that Kt/V does not accurately quantify the removal of the medium- and large-sized molecules involved in the pathophysiology of pruritus or that the range of Kt/V values in our study is narrow and close to the recommended target.

We found that pruritus tended to be less common in patients undergoing PD versus HD, but it was similarly associated with adverse health outcomes. We believe this is important to emphasize because new treatments for pruritus are not yet available for patients undergoing PD. More preserved residual kidney function and less inflammation may explain the lower incidence of pruritus observed in PD. Previous literature has been mixed in this regard: although an equal number of studies report a higher prevalence of pruritus in patients receiving HD[20,21] or PD,[19,22] others found a similar prevalence between the 2 dialysis modalities.[18]

Strengths of our study include a large sample size of well-phenotyped patients with a relatively high proportion of patients receiving PD, long follow-up, careful study design with evaluation of new cases during follow-up to better capture the pruritus burden in this population, and the setting involving patients from a country with universal tax-funded health care, which minimizes selection bias from disparate access to health care. Limitations include the observational nature of the study, which is prone to residual time-varying confounding; potential misclassification bias if pruritus is not reported or recognized by patients and/or health care professionals or because medications for pruritus are nonspecific, which obliged us to make some considerations and assumptions when ascertaining that medications were used for the management of pruritus and not for other indications; and the lack of assessment of pruritus intensity/severity—the pruritus status having been extracted from medical records—and the relationship between pruritus and the type of vascular access (central venous catheter vs fistula) as a result of the small number of patients in each subgroup. We also recognize the absence of validation of our approach to identify pruritus. However, the fact that pruritus, by our definition, is predicted by many of the variables we would hypothesize to be predictive, and is associated with the expected adverse outcomes provides construct validity to our definition.

In conclusion, our study illustrates the commonness of clinically recognized pruritus in patients receiving dialysis, identifies populations at risk of having/developing pruritus, and shows that patients with pruritus are at high risk of adverse health outcomes. Our findings may inform clinical decisions for periodic pruritus screening, especially in high-risk populations. Individualized clinical management to prevent and treat this burdensome uremic symptom might significantly improve patients' quality of life and potentially health outcomes. Approaches to pruritus management include optimization of dialysis, treatment of CKD-associated mineral and bone disease, extemporaneous compounded topical preparations, systemic pharmacological treatments, UV therapy,[37] and, in HD, difelikefalin, a recently introduced selective agonist of κ-opioid receptors.[38]

Supplementary Material

Supplementary File (PDF)

Figure S1: Study design.

Figure S2: Pruritus as a time-varying exposure.

Figure S3: Associations of baseline variables with prevalent (odds ratios) and new-onset (hazard ratios) pruritus in patients undergoing maintenance hemodialysis.

Figure S4: Associations of baseline variables with prevalent (odds ratios) and new-onset (hazard ratios) pruritus in patients undergoing maintenance peritoneal dialysis.

Figure S5: Associations of baseline variables with prevalent (odds ratios) and new-onset (hazard ratios) pruritus in incident dialysis recipients.

Figure S6: Associations of baseline variables with prevalent (odds ratios) and new-onset (hazard ratios) pruritus in prevalent dialysis recipients.

Table S1: Definitions of comorbidities, medications, and outcomes.

Table S2: Number of missing values at baseline and at the time of new-onset pruritus by time period.

Table S3: Crude and multivariable regression models of baseline determinants of prevalent (odds ratios with 95% CIs) and new-onset (hazard ratios with 95% CIs) pruritus.

Table S4: Incidence rates and hazard ratios for the association between pruritus and adverse clinical outcomes.

Table S5: Incidence rates and hazard ratios for the association between pruritus and severe infection–related hospitalizations.

Table S6: Hazard ratios for the association between pruritus and adverse clinical outcomes in patients free from pruritus at baseline.

Table S7: Hazard ratios for the association between pruritus and adverse clinical outcomes in incident dialysis recipients.

Table S8: Hazard ratios for the association between pruritus and severe infection–related hospitalizations using different pruritus definitions.

Table S9: Comparison of the main epidemiological studies on pruritus conducted in patients undergoing maintenance dialysis.

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CKD-Associated Pruritus and Adverse Clinical Outcomes in Patients Receiving Dialysis

Setting & Participants

Observational study

SCREAM Project
Stockholm, Sweden
(2005-2021)

N = 3,281 patients
- Median age: 64 years
- 66% men
- 69% on hemodialysis
- 77% incident dialysis patients

Occurrence and Determinants

At enrollment:
N = 456 (14%) had pruritus

Median follow-up of 3 years:
N = 539 (19%) additional patients developed pruritus

Pruritus was more common with:
- Older age
- Female sex
- Lower serum albumin level
- Higher C-reactive protein
- Higher serum calcium & phosphorus levels

Associated Adverse Outcomes

Compared to patients without pruritus

	Adjusted HR (95% CI)
Sleep Disorders	1.96 (1.60-2.39)
Anxiety/Depression	1.56 (1.23-1.98)
Infection-related Hospitalization	1.36 (1.18-1.57)

No association between pruritus and all-cause mortality

CONCLUSION: At least one third of patients on maintenance dialysis experience pruritus, and pruritus was consistently associated with adverse health outcomes.

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