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ORIGINAL ARTICLE

# The relationship between chronic kidney disease–associated pruritus and health-related quality of life: a systematic review

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## ABSTRACT

**Background.** Chronic kidney disease–associated pruritus (CKD-aP) is a common and burdensome condition for end-stage kidney disease (ESKD) patients, especially those receiving haemodialysis. High-quality evidence of the relationship between CKD-aP and health-related quality of life (HRQoL) can therefore inform clinicians and policymakers about treatment choice and reimbursement decisions.

**Methods.** A systematic literature review and narrative synthesis stratified by study design and HRQoL instrument was conducted to evaluate in adult ESKD patients receiving in-centre haemodialysis the relationship between CKD-aP and HRQoL assessed using multi dimensional generic or condition-specific preference- or non-preference-based measures. MEDLINE, Embase, Web of Science, BIOSIS Citation Index, Cochrane Library and PsycINFO from inception to March 2020 were searched, with two reviewers extracting data independently.

**Results.** Searches identified 2684 unique records, of which 20 papers relating to 18 unique studies [5 randomised controlled trials (RCTs) and 13 observational studies] were included. HRQoL was assessed using four generic and eight disease-specific measures. The impact of CKD-aP was assessed by comparison of means, linear regression and correlation. Observational studies employing comprehensively adjusted multivariable linear regression largely found associations between CKD-aP severities and HRQoL. Analyses suggest this relationship is partially mediated by the sleep disturbance caused by CKD-aP. RCTs showing improvements in CKD-aP severity were associated with clinically meaningful improvements in HRQoL. Compared with generic measures, disease-specific HRQoL instruments reported greater changes with reduced CKD-aP. Heterogeneity in study design and reporting precluded meta-analysis.

**Conclusions.** CKD-aP severity was found to be associated with a worsening of HRQoL in the majority of observational and RCT studies. Parallel improvements in CKD-aP and HRQoL with interventions may support their use (PROSPERO registration 175035).

**Keywords:** haemodialysis, itch, pruritus, quality of life, systematic review

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## INTRODUCTION

Uraemic or chronic kidney disease–associated pruritus (CKD-aP) is a common, burdensome and undertreated condition in end-stage kidney disease (ESKD) patients, particularly in those receiving haemodialysis (HD) [1]. There is increasing recognition that urea, other uraemic toxins and phosphate do not have a mechanistic role in the development of pruritus in this patient group, leading to the revised term CKD-aP. Existing evidence suggests that the severity of the pruritus has been associated with depression, poor sleep quality, increased mortality and reduced health-related quality of life (HRQoL) [2]. This was identified as an outer tier condition in stakeholder exercises by the Standardising Outcomes in Nephrology initiative [3]. A range of interventions have demonstrated varying success as therapies for CKD-aP [4].

Combining the improvements in HRQoL with any cost savings for pharmaco- and non-pharmacotherapy for CKD-aP allows for estimation of the health economic benefits of improving CKD-aP in ESKD patients, more specifically the estimation of the cost per quality-adjusted life year (QALY) [5]. Decision-makers use QALY cost thresholds to make reimbursement decisions [e.g. the UK's National Institute for Health and Care Excellence (NICE)], to set value-based pricing (the US Institute for Clinical and Economic Review) or to inform prioritization of research questions [6].

Current and best available evidence relating to the impact of CKD-aP on HRQoL is needed to support future research for optimal therapy and inform cost-effectiveness analysis. To support this, we conducted and report here a systematic review of the relationship between CKD-aP in HD patients and HRQoL.

## MATERIALS AND METHODS

We conducted a systematic literature review to understand the relationship between CKD-aP and HRQoL in patients receiving HD for ESKD, following good practice and reporting guidelines recommended by the Centre for Reviews and Dissemination [7] and the NICE Decision Support Unit [8]. The protocol is registered on PROSPERO (175 035).

### Literature searching

We conducted electronic literature searches in March 2020 to retrieve studies characterizing the impact of CKD-aP on HRQoL of patients on HD. We searched the following databases from the date of inception: MEDLINE, Embase, Web of Science: Science Citation Index Expanded and Conference Proceedings Citation Index, BIOSIS Citation Index, Cochrane Database of Systematic Reviews and Central Register of Controlled Trials and PsycINFO. A multidisciplinary team including an information specialist and a kidney clinical expert developed a search strategy (Supplementary data, File 1). We also searched several grey literature sources (ClinicalTrials.gov, National Institute for Health Research Journals Library, Kidney Care Research UK, Kidney Care UK, Open Grey and World Health Organization Global Index Medicus) and reference lists of included studies. All retrieved records were collected and transferred into a reference management database (Clarivate 2013, EndNote X9 Philadelphia, PA, USA).

### Selection criteria for studies

Using pre-specified criteria, two reviewers independently examined the title, then the abstract and finally the full text of all retrieved records. Where there were disagreements on study selection, a third reviewer or clinical expert was consulted. Randomized controlled trials (RCTs), non-RCTs and observational studies were eligible for inclusion in the review if the studies reported the association between pruritus and HRQoL in a well-defined population or sub-group of people with ESKD who were undergoing in-centre HD; measured a patient's exposure to pruritus by symptom scores, visual analogue scale (VAS), itch intensity scores or any other investigator or patient-reported pruritus measure and included patient-reported HRQoL using multidimensional, generic, condition-specific or study-specific measures. To allow a robust investigation of the association between pruritus and HRQoL, we excluded studies only conducted in patients with coexisting comorbidities or conditions that may influence HRQoL, studies with <30 patients and conference abstracts.

### Data extraction, methodological assessment and analytical approach

We extracted data using a pre-piloted data extraction form (Supplementary data, File 2). All data extractions were completed by one reviewer and checked by a second reviewer. As quality assessment of studies reporting HRQoL is not standardized, a bespoke assessment tool (Supplementary data, File 3) was developed following relevant recommendations [7, 8].

A meta-analysis with relevant subgroup analyses to assess the association between CKD-aP and HRQoL was planned but was not possible due to the considerable heterogeneity of the available literature. Therefore we summarized data and presented narrative syntheses, grouping studies according to study type (interventional or observational) and analysis performed (e.g. multivariable, comparison of means or correlation).

## RESULTS

Following removal of duplicates, we screened 2684 unique records. Of these, 20 full-text papers relating to 18 unique studies (studies with experimental design, $n = 5$ [9–13]; studies with non-experimental design, $n = 13$ [2, 14–29]) were included in the review (Figure 1).

### Included studies

The study characteristics of included experimental and observational studies are presented in Table 1 and Table 2, respectively. Five studies with experimental study designs [9–13] included two international multicentre studies [9, 13], two single-country multicentre studies in Iran [10] and Turkey [12] and a single-centre study conducted in Brazil [11]. Three RCTs had only active comparator arms, with 30–128 patients per arm, and compared doxepin versus pregabalin [10], gabapentin versus dexchlorpheniramine [11] and nalbuphine 120 mg versus 60 mg [13]. Three studies compared an inactive treatment arm with an active control arm (35–189 patients per arm) and compared baby oil [12], difelikefalin [9] and nalbuphine (two different doses) [13] with an inactive control. Eligibility criteria (Table 1) varied according to the frequency and severity of pruritus.

Thirteen unique observational studies reported in 16 papers and a parallel publication [2, 14–29] were included in the review (Table 2). Eligible studies included five cohort studies: the Dialysis Outcomes and Practice Patterns Study (DOPPS) (an international multicentre study) [2, 17], the German Epidemiological Haemodialysis Itch Study (GEHIS) [20, 28], the ITCH National Registry Study [19] and two studies conducted in Iran and Italy [25,

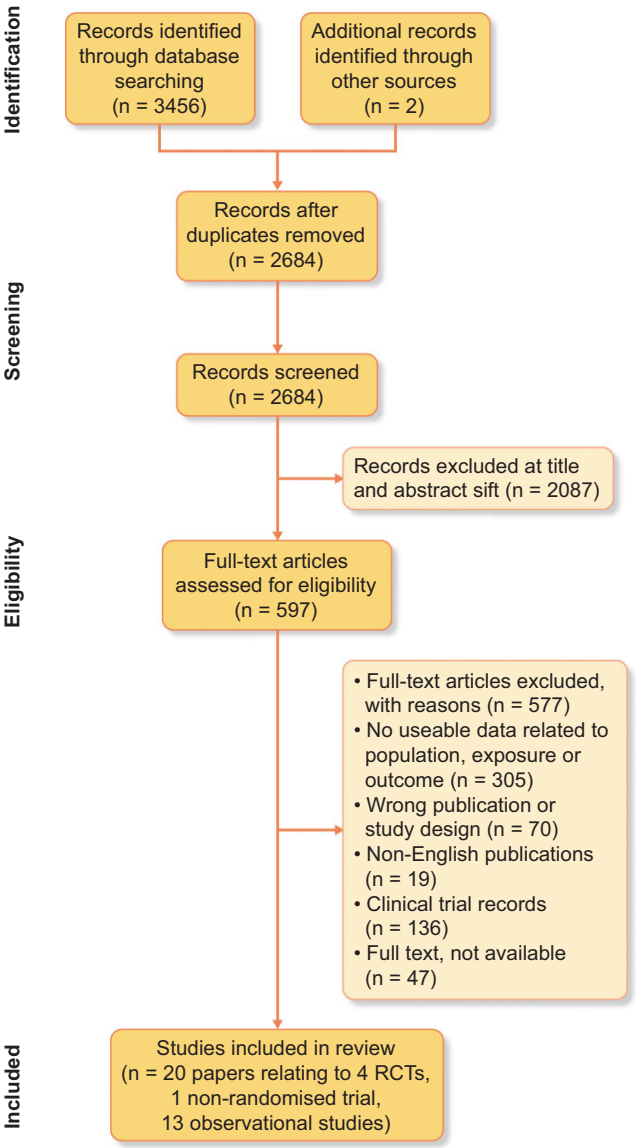


**FIGURE 1:** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram of study selection.

26]; and eight cross-sectional studies from the USA [14], Egypt [16], Pakistan [21, 23], Malaysia [22], Poland [24], Brazil [18, 27, 28] and Turkey [29]. Evaluation of the impact of pruritus on HRQoL in HD patients was reported as one of several study outcomes in 12 observational papers [2, 14, 16–24, 26, 28]; however, it was the primary aim of only 3 papers [14, 26, 28] to estimate the impact of pruritus on HRQoL.

## Methodological quality of included studies

Based on the bespoke assessment tool developed following accepted recommendations [7, 8], all studies fell into the 'good' or 'fair' category, although none scored well across all items (Table 3). Issues for both study types included representativeness of the sampled patients and lack of sample size calculations relating to the assessment of the association between CKD-aP and HRQoL. Methods for handling missing data were not often presented. Few RCT studies defined and measured confounders and observational studies did not always adjust for all important potential confounders relating to patient characteristics, comorbidities and biochemical variables. The severity of pruritus for patients to be included was not always well specified, while HRQoL was more consistently well-defined across studies.

## Measurements of pruritus and HRQoL

There was extensive clinical and methodological heterogeneity in assessment and reporting of the impact of CKD-aP on HRQoL in experimental and observational studies (Table 1 and Table 2). Pruritus instruments included study-specific tools, generic scales assessing intensity of itchiness [VAS and Worst Itch Numeric Rating Scale (WI-NRS)] and condition-specific measures comprising items assessing duration, degree, distribution and disability related to itchiness (e.g. 5-D itch scale). HRQoL instruments also varied across studies. These included four generic and eight disease-specific measures, which are listed with the domains assessed in Table 4. Follow-up periods varied from 1 to 12 weeks in experimental studies, while the majority of epidemiological studies [2, 17, 20, 27, 28] were cross-sectional analyses.

In interventional studies, pruritus was assessed using the VAS [10–12], WI-NRS, [9, 13], Itch Severity Scale (ISS) [12] and 5-D itch scale [10]. Four observational studies utilised the VAS [20, 24, 26, 29], four used ordinal severity (none to extreme, five levels) [17, 2, 16, 18], three observational studies used the multi dimensional 5-D itch scale [21–23] and one study asked about the presence or absence of pruritus [20].

## Association between pruritus and HRQoL

Eligible outcomes were reported as mean for the entire study population or different pruritus categories at baseline or specified time points using different scales, instruments, recall periods and time points (Supplementary data, File 4 and Supplementary data, File 5). Overall, studies reporting condition-specific and itch-specific HRQoL outcomes [e.g. Brief Itch Inventory, Dermatology Life Quality Index (DLQI) questionnaire, ItchyQoL, Skindex-10 and Skindex-29] showed a more consistent relationship between worsening pruritus and worse perceived HRQoL compared with generic tools such as the 12- and 36-item Short Form Health Surveys (SF-12 and SF-36).

## Non-experimental studies

Two studies [2, 17] reported SF-36 or SF12 scores using DOPPS data ($n = 9659$ patients) [2] and a subgroup from Japan [Japanese DOPPS (JDOPPS), $n = 3755$ patients] [17]. The prevalence of moderate to extreme pruritus over a 4-week recall period ranged between 36% and 50%. Following adjustment for patient and dialysis characteristics, comorbidities and laboratory variables, relative to no itching, there was a linear reduction in SF-12 mental component summary (MCS) and physical component summary (PCS) scores of between 1.5 and 8.6 points as pruritus worsened from 'bothered somewhat' to 'extremely bothered' in both studies [2, 17]. Following the inclusion of sleep disturbance in the regression, the effect size of the association was reduced to between 0.4 for 'somewhat bothered' to 4.4 points for 'extremely bothered', suggesting that some of the impact on HRQoL by CKD-aP is mediated by sleep quality [17].

Frequently experienced symptoms and their association with SF-36 MCS and PCS scores were examined in 307 HD patients randomly selected from 14 dialysis centres in the USA, in

**Table 1. Included studies with an experimental design: study characteristics**

| First author, year, study design, country | Comparisons | Inclusion criteria (brief description) | Exclusion criteria (brief description) | Patient demographics (age, gender, comorbidities | Pruritus measurement tool(s) and details | HRQoL instrument(s) and timing |
|---|---|---|---|---|---|---|
| Gobo-Oliveira 2018 [11]<br>Randomized double-blind, controlled, parallel<br>Brazil (1 dialysis unit, Clinical Hospital of the Botucatu Medical School) | Gabapentin, $n = 30$<br>versus<br>Dexchlorpheniramine, $n = 30$ | Age >18 years, HD for at least 3 months, pruritus at least thrice a week and lasting ≥30 days)<br>Only patients who completed phase 1 (T0 to T15, i.e. 15 days of cold cream) and still complained of pruritus were randomized. | Chronic skin disease (allergic, parasitic, or infectious), internal malignancy<br>Use of opioids or corticosteroids | Age mean 59 ± 12 years<br>Male 19 (63%) | VAS scale:<br>Cut-offs, not specified<br>Characterized period or duration of pruritus as: episodic during or shortly after HD (score of 1), day or night (score of 2), or all the time (score of 3) | DLQI questionnaire |
| Foroutan 2017 [10]<br>Single blind RCT<br>Iran (6 dialysis centres of the Kerman University of Medical Sciences) | Doxepin, $n = 44$<br>versus<br>Pregabalin, $n = 46$ | Patients on haemodialysis aged 16 to 80 years experiencing pruritus | Patients with: major systemic conditions and other conditions associated with pruritus | Age mean<br>59.7 ± 15.8 years<br>Male 54 (75%) | VAS scale:<br>0 points, no itching<br>0.1 to 3.9 points, mild<br>4 to 6.9 points, moderate<br>7 to 8.9 points, severe<br>9 to 10 points, very severe | DLQI questionnaire |
| Karadag 2014 [12]<br>Non-randomized controlled trial—pretest–post-test model with control groups<br>Turkey (1 state hospital in 2 provinces) | Baby oil, $n = 36$<br>versus<br>No baby oil, $n = 35$ | Intermittent pruritus for 6 months plus three episodes of VAS ≥ 5 within last 2 weeks | Oedema; open wound, cellulitis, infection, DVT, epilepsy, haemorrhage, paraplegia or pacemaker; Pruritus treatment<br>Thrombocytosis, | Age mean<br>54.0 ± 16.0 years<br>Male 41 (54.7%) | VAS scale:<br>0–2 cm, no itching;<br>3–4 cm, mild itching;<br>5–6 cm, moderate itching;<br>7–8 cm, severe itching;<br>9–10 cm, unbearable itching<br>itching severity scale (ISS) (4-item scale) | SF-36 Quality of Life Scale |
| Fishbane 2020 [9]<br>KALM-1 (NCT03422653)<br>RCT<br>USA | Difelikefalin, $n = 189$<br>Placebo, $n = 189$ | Age >18 years, moderate-to-severe pruritus on HD at least three times weekly for at least 3 months | Pruritus due to other non-ESKD causes; scheduled kidney transplant; allergic to opiates | Difelikefalin: Age mean<br>58.2 ± 11.2 years<br>Male 112 (59.3%)<br>Placebo:<br>Age mean<br>56.8 ± 13.9 years<br>Male 118 (62.8%) | WI-NRS, 0–10 points<br>Higher scores indicate worse itch | 5-D itch scale<br>Skindex-10 |
| Mathur 2017 [13]<br>RCT<br>USA, Romania, Poland | Group 1: Nalbuphine 120 mg, $n = 120$<br>Group 2: Nalbuphine 60 mg, $n = 128$<br>Group 3: placebo, $n = 123$ | HD for ≥ 3 months,<br>Patient Assessed Disease Severity category of 'B' or 'C, mean WI-NRS score = 6 during the week prior to randomization | Pruritus due to cholestasis, atopic dermatitis, lymphoma or any condition unrelated to end-stage renal disease | | WI-NRS, 0–10 points (no itching to worst possible itching)<br>Baseline: Daytime and night-time WI-NRS score before three dialysis visits<br>Follow-up: Daytime and night-time WI-NRS score weekly for 10 weeks | Skindex-10 |

ER, extended release.

**Table 2. Included studies with an observational design: study aims and population characteristics**

| First author, reported study design country study/trial name Relevant comparisons | Primary aims/objectives of the study | Inclusion and exclusion criteria (brief description) | Patient demographics (age, gender) | Pruritus measurement | HRQoL measurement | Timing/frequency of assessments (pruritus; HRQoL) |
|---|---|---|---|---|---|---|
| Afsar 2012 [29]<br>Cross-sectional study<br>Turkey<br>*Diabetics and non-diabetics with CKD-aP* | To assess relationship between pruritus and HbA1c | Inclusion: HD patients receiving no systemic treatment for pruritus and neuropathy, including antihistamines and gabapentin; no concomitant dermatological, liver or metabolic diseases-associated with pruritus<br>Exclusion: Not reported | Age 51.9 ± 13.5 years<br>Males 41 (54.7%) | VAS<br>10 cm horizontal line: 0 (indicating no itch) to 10 (indicating worst possible imaginable itch) | SF-36 | Baseline, only (cross-sectional study) |
| Curtin 2002 [14]<br>Cross-sectional study<br>USA | To examine the relationship between symptoms in HD patients and SF-36 PCS and MCS outcomes | Inclusion: Age, ≥18 years<br>Able to read and write in English<br>Exclusion: Not reported | Age<br>58.2 ± 15.10 years<br>Males 147 (47.9%) | Likert, frequency (5 categories)<br>Patients reported frequency of experiencing pruritus and 46 additional listed symptoms in the last 4 weeks, prior to the study.<br>Responses<br>0 = never<br>1 = a little of the time<br>2 = some of the time<br>3 = most of the time<br>4 = all of the time | SF-36 | Baseline, only (cross-sectional study) |
| Tayebeh 2017 [25]<br>Observational cohort study<br>Iran | To examine predictors of pruritus and insomnia, the impact of pruritus on quality of health, sleeping problems, hospitalization and mortality in HD patient | Age ≥18 years<br>Maintenance HD patients; receiving HD ≥ 2 weeks<br>Exclusion: Not reported | Age 57.2 ± 15.4 years<br>Males 235 (56.5%) | NR<br>Self-reporting of severity of itching on a 5-point Likert scale | SF-36 | NR followed-up for 28 months |
| Ibrahim 2016 [16]<br>Cross-sectional case-control study<br>Egypt<br>HD patients with UP and those without UP | To assess the influence of UP on QOL by comparing HD patients with UP to those without UP | Age ≥18 years<br>Undergoing regular HD<br>Exclusion: Other possible causes of pruritus, such as: skin diseases or haematological diseases | Age 49.5 ± 11.5<br>Males 37/100 (37%) | NRS, limited details about how comparator groups were identified | WHOQoL-BREF[a] | Baseline, only (cross-sectional study) |

**Table 2. Continued**

| First author, reported study design country study/trial name Relevant comparisons | Primary aims/objectives of the study | Inclusion and exclusion criteria (brief description) | Patient demographics (age, gender) | Pruritus measurement | HRQoL measurement | Timing/frequency of assessments (pruritus; HRQoL) |
|---|---|---|---|---|---|---|
| Rehman 2019 [21]<br>Cross-sectional study<br>Pakistan | To examine the relationship between CKD-aP and QOL in HD patients | Age ≥18 years both genders, undergoing HD; proficient in the Urdu language and willing to participate<br>Exclusion: Not reported | Age median 42.0 (range NR, IQR 35.0–51.0)<br>Male 176 (67.2%) | Urdu 5-D itch scale<br>5 domains (duration, degree, direction, disability, distribution)<br>Overall score—sum of scores for all 5 domains. A score <5 indicates no pruritus, a score of 25 indicates severe pruritus | Urdu FANLTC scale[b] | Baseline, only (cross-sectional study) |
| Rehman 2020 [22]<br>Cross-sectional study<br>Malaysia | To examine the association between CKD-aP and QOL in HD patients | Age ≥18 years both genders, undergoing HD; Proficient in the Malay language<br>Exclusion: None | Age: median 58.00 (IQR 47.00–67.00)<br>Male 81 (40.7%) | Malay 5-D itch scale<br>4 domains: duration, degree, direction, overall score—sum of scores for all 5 domains. A score <5 indicates no pruritus; a score of 25 indicates severe pruritus | Malay FANLTC scale | Baseline, only (cross-sectional study) |
| Satti 2019 [23]<br>Cross-sectional study<br>Pakistan | To report the prevalence of UP and identify a subset of patients at high risk for UP.<br>To investigate the impact of UP on QOL in HD patient | Male patients with ESKD on HD ≥3 months<br>Exclusion: Mini-mental state examination score <9<br>Other causes of pruritus, (psoriasis, eczema or dermatitis) | Age not reported for subgroup of $n = 85$ (with pruritus) who were analysed<br>Male 173 (100%) | 5-D itch | DLQI[c] | Baseline, only (cross-sectional study) |
| Susel 2014 [24]<br>Cross-sectional study<br>Poland | To examine the effect of UP on depressive symptoms and QOL in patients with ESKD | Adults with ESKD undergoing regular HD<br>Exclusion: Other causes or pruritus | Age mean 59.05 years (range 22–88)<br>male 124 (62%) | VAS<br>0–10 scale<br>4-item Itch questionnaire | SF-36 PCS and MCS<br>DLQI | Baseline, only (cross-sectional study) |
| Tessari 2009 [26]<br>Cohort study<br>Italy | To examine the impact of pruritus on QOL in patients receiving chronic dialysis | Consecutive patients treated with HD and PD with pruritus occurring regularly for 6 months or at least thrice in the 2 weeks or less of study entry.<br>UP was accepted if pruritus was experienced after dialysis in the absence of an active condition-associated pruritus<br>Exclusion: Other causes or pruritus | HD + PD:<br>Age 62.2 ± 13.7 years, (range 22.7–79.4)<br>Male 111 (66%)[d] | VAS | SF-36<br>Skindex 29 | Baseline, only (cross-sectional study) |

**Table 2. Continued**

| First author, reported study design country study/trial name Relevant comparisons | Primary aims/objectives of the study | Inclusion and exclusion criteria (brief description) | Patient demographics (age, gender) | Pruritus measurement | HRQoL measurement | Timing/frequency of assessments (pruritus; HRQoL) |
|---|---|---|---|---|---|---|
| Lopes 2012 [18]<br>Cross Sectional<br>Brazil—(four dialysis units)<br>Prospective Study of the Prognosis of Chronic Hemodialysis Patients (PROHEMO) | To investigate the impact of depressive symptoms, poor sleep and dry skin bother on the association between pruritus and kidney disease in HD patients. | Adult HD patients—no further information<br>Exclusion: Not reported | No pruritus,<br>Age 47.60 ± 14.3 years<br>Male 323 (58.6%)<br>Mild pruritus,<br>Age 49.59 ± 14.14 years<br>Male 150 (62.8%)<br>Severe pruritus,<br>Age 51.21 ± 13.52 years<br>Male 112 (58.9%) | Kidney Disease Quality of Life Short Form (KDQOL-SF)—pruritus subscale<br>Patients indicated the extent to which they were bothered by itchy skin (pruritus) and dry skin for the last 4 weeks, prior to data collection | Kidney Disease Quality of Life Short Form (KDQOL-SF)[e]—disease burden subscale | Baseline, only (cross-sectional study) |
| Kimata 2014 [17]<br>Observational study<br>Japan<br>DOPPS | To estimate the prevalence of pruritus, and examine its relationship to QOL, sleep quality, medication use, and mortality in HD patient | See Pisoni 2006 [2] for general DOPPS inclusion and exclusion criteria. | Moderate. to extreme bother by itch, JDOPPS 1 + 3<br>Age 61.7 ± 12.6 years<br>Male 1923 (67%)<br>No bother to somewhat bother by itch, JDOPPS 1 + 3<br>Age 59.38 ± 12.5 years<br>Male 2093 (58%) | Study-specific assessment<br>Patients indicated the extent to which they were bothered by itchy skin during a 4-week period prior to data collection<br>Responses were not at all bothered or somewhat, moderately, very much or extremely bothered | SF-36 or SF-12 | Baseline, only (cross-sectional study) |
| Mathur 2010 [19]<br>Cohort study<br>USA<br>ITCH National Registry Study | To study the natural history of UP; to compare rating scales of itching intensity and investigate the assess utility of HRQOL instruments for CKD-aP | Age ≥18 years, had been receiving chronic HD ≥3 times a week. Pruritus (defined as a score of 10 mm on a 100-mm VAS). Able to understand and complete the patient questionnaires<br>Exclusion: Other causes or pruritus. Recent change in HD regime | Patient Type A<br>Age 63 ± 11.7 years<br>Male 20 (57%)<br>Patient Type B<br>Age 54 ± 15.3 years<br>Male 21 (49%)<br>Patient Type C<br>Age 53 ± 3.2 years<br>Male 13 (50%) | Study-specific UP intensity scales, adapted from the 100-mm VAS and the 11-point NRS<br>Assessment of worse itching over the preceding 24 hours, with separate measurements for worst daytime and worst night-time itching | Skindex-10<br>Brief Itching Inventory | Scheduled intervals (not specified) over 3.5 months |

**Table 2. Continued**

| First author, reported study design country study/trial name Relevant comparisons | Primary aims/objectives of the study | Inclusion and exclusion criteria (brief description) | Patient demographics (age, gender) | Pruritus measurement | HRQoL measurement | Timing/frequency of assessments (pruritus; HRQoL) |
|---|---|---|---|---|---|---|
| Pisoni 2006 [2]<br>Prospective, longitudinal, observational study<br>Multiple countries<br>DOPPS | To estimate the prevalence of pruritus and examine its relationship to QoL, sleep quality, medication use and mortality in HD patient | A dialysis unit treating ≥25 HD patients within the unit to be eligible for study participation (participating facility eligibility criteria)<br>Age ≥17 years (patient eligibility criterion)<br>Exclusion: Other dialysis modalities or locations | Moderate to extreme itch<br>Age 60.7 ± 14.49 years<br>Male 3459 (60.3%)<br>Mild itch<br>Age 60.3 ± 14.64 years<br>Male 4266 (56.4%) | Study-specific assessment<br>Patients indicated the extent to which they were bothered by itchy skin during a 4-week period prior to data collection | SF-36 or SF-12 | Baseline, only (cross-sectional study) |
| Plewig 2019 [20]<br>Cohort study<br>Germany<br>GEHIS | To examine the impact chronic itch in HD patients over time and its association with HRQoL, comorbidities and laboratory values. | All patients who had participated in GEHIS study in 2013 and had agreed to be contacted again<br>Exclusion: Not reported | All patients, age mean 60.8 ± 13.3 years (range 29.0–89.2)<br>Male 57 (54.8%)[f]<br>Patients with no current but previous chronic itch<br>Age 58.9 ± 12.9 years<br>Male 33 (63.5%)<br>Patients with persistent chronic itch<br>Age 62.7 ± 13.6 years<br>Male 24 (46.2%) | VAS, 0 (no itch) to 10 (worst imaginable itch)<br>IFSI classification based on dermatological examination | ItchyQoL[g] | 2017 (4-year follow-up data of 2013 GEHIS study) |
| Weiss 2016 [27, 28]<br>Cross-sectional study<br>Germany<br>GEHIS | To examine the prevalence and impact of chronic itch on QOL in patients with ESKD | Age ≥18 years<br>Diagnosis of ESKD and on HD treatment<br>Proficient in German language<br>No current cognitive impairment<br>Exclusion: Not reported | All participants<br>Age 68.2 ± 13.9 years<br>Male 492 (57.2%)<br>Patients with current chronic itch<br>Age 64.3 ± 13.8 years<br>Patients with no chronic itch<br>Age 68.2 ± 13.2 years | VAS, 0 (no itch) to 10 (worst imaginable itch) | ItchyQoL SF-12 | Baseline, only (cross-sectional study) |

[a]WHOQoL-BREF: 26 items; four domains: physical health (four items), psychological health (six items), social relationships (three items) and environmental health (eight items); it also contains QOL and general health items.
[b]FANLTC: 26- item scale with 4 subscales (physical well-being, social/family well-being, emotional well-being and functional well-being). In each subscale, each item is scored from 0 ('not at all') to 4 ('very much'). The scoring of positively stated items is 4, 3, 2, 1 and 0, while the negatively stated items are reverse scored. Subscale scores equal the sum of item scores multiplied by the number of items in each subscale and divided by the number of items answered. Overall FANLTC score equals the sum of the 4 subscale scores (range 0–104, with a higher score indicating better quality of life.
[c]Score of 0–1 = no effect of pruritus, 2–5 = small effect, 6–10 = moderate, 11–20 = large effect and 21–30 = very large and severe limiting effects on the patient's life.
[d]Data for HD and PD patients.
[e]Assessment of perceived disease burden related to impact of patient's life (including time commitment for care) emotions, specifically frustration and family life. Responses (five options) ranging from definitely true to definitely false.
[f]Gender data relate to 2013 data.
[g]22 items regarding symptoms, functions, emotions and self-perception.
BII, Brief Itch Inventory; FANLTC, Functional Assessment for Non-Life-Threatening Conditions; PROHEMO, Prospective Study of the Prognosis of Chronic Haemodialysis Patients.

**Table 3. Summary of risk of bias of included studies**

| | Patient selection and allocation | | Outcome reporting | | | | | Analysis | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author, date | Representative sample | Groups balanced at baseline | Pruritus definition and assessment | Pruritus measured same way in all | HRQoL definition and assessment | HRQoL measured in same way in all | Follow up period | Sample size | Groups comparable at analysis | Complete outcome data for all patients | Reported loss to follow up with reasons | Accounted for missing data | Confounders defined and measured | Appropriate accounting for confounding was undertaken | Overall rating |
| **Experimental studies** | | | | | | | | | | | | | | | |
| Fishbane 2020 [9] | N | Y | Y | Y | Y | Y | CT | CT | Y | N | Y | Y | N | P | Good |
| Foroutan 2017 [10] | N | Y | P | Y | Y | Y | CT | CT | Y | N | Y | N | N | P | Good |
| Gobo-Oliveira 2018 [11] | N | Y | Y | Y | P | Y | CT | CT | P | N | Y | Y | P | P | Good |
| Karadag 2014 [12] | N | CT | P | Y | Y | Y | CT | CT | Y | N | Y | CT | N | N | Fair |
| Mathur 2017 [13] | N | Y | P | Y | Y | Y | CT | CT | P | N | P | Y | N | P | Good |
| **Observational studies** | | | | | | | | | | | | | | | |
| Afsar 2012 [29] | CT | NA | Y | Y | Y | Y | NA | CT | CT | CT | CT | CT | P | N | Fair |
| Curtin 2002 [14] | Y | NA | Y | Y | Y | Y | NA | CT | CT | N | N | N | P | P | Good |
| Ibrahim 2016 [16] | CT | NA | N | Y | Y | Y | NA | Y | N | Y | Y | Y | N | N | Good |
| Kimata 2014 [17] | Y | NA | P | Y | Y | N | NA | P | N | N | N | N | P | P | Good |
| Lopes 2012 [18] | CT | NA | Y | Y | Y | Y | NA | CT | P | CT | CT | Y | P | P | Good |
| Mathur 2010 [19] | CT | NA | P | Y | Y | Y | CT | CT | N | CT | CT | CT | P | N | Fair |
| Pisoni 2006 [2] | Y | NA | Y | Y | P | N | NA | P | N | N | N | N | P | P | Good |
| Plewig 2019 [20] | CT | NA | CT | Y | Y | Y | Y | CT | P | N | N | N | N | N | Fair |
| Rehman 2019 [21] | CT | NA | Y | Y | Y | Y | NA | Y | N | Y | Y | NA | P | P | Good |
| Rehman 2020 [22] | CT | NA | Y | Y | Y | Y | NA | Y | N | Y | Y | NA | P | P | Good |
| Satti 2019 [23] | P | NA | Y | Y | Y | Y | NA | Y | N | Y | Y | NA | N | N | Good |
| Susel 2014 [24] | CT | NA | Y | Y | Y | Y | NA | Y | CT | N | P | N | N | N | Fair |
| Tayebeh 2017 [25] | CT | NA | Y | Y | Y | Y | NA | CT | N | CT | CT | CT | P | P | Fair |
| Tessari 2009 [26] | Y | NA | Y | Y | Y | Y | NA | CT | P | N | N | CT | P | P | Good |
| Weiss 2016 [28] | P | NA | CT | Y | Y | Y | NA | CT | CT | N | N | N | P | P | Fair |

N, no; Y, yes; CT, can't tell; P, partial; NA, not applicable.

**Table 4. Summary of domains assessed by identified QoL instruments**

| Instruments | High-level QoL[a] | Pain | Energy | Appearance | Mobility | Sleep | Anxiety/ depression | Intrusion/ achievement | Social | Work | Itch severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Generic measures** | | | | | | | | | | | |
| SF-12 (PCS and MCS) | Y | Y | Y | N | Y | N | Y | Y | Y | Y | N |
| SF-36 total score and domain scores | Y | Y | Y | N | Y | N | Y | Y | Y | Y | N |
| WHOQOL-BREF | Y | Y | Y | Y | Y | Y | Y | N | Y | N | N |
| FANLTC | N | Y | Y | N | N | Y | Y | N | Y | Y | N |
| **Disease-specific measures** | | | | | | | | | | | |
| Brief Itching Inventory | N | N | N | N | N | Y | Y | Y | Y | Y | |
| DLQI | N | N | N | N | N | N | N | Y | Y | Y | Y |
| KDQOL-SF36 | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y |
| Skindex-10 | N | N | N | Y | N | N | Y | N | Y | Y | Y |
| Skindex-29 | N | Y | Y | N | N | Y | Y | Y | Y | Y | Y |
| ItchyQoL | N | Y | N | Y | N | Y | N | N | N | Y | N |

Y: yes, the domain is assessed by instrument; N: no, the domain is not assessed by instrument
[a]The patient is asked 'What is your quality of life today?'
FANLTC, Functional Assessment for Non-Life-Threatening Conditions.

whom 73.2% experienced pruritus at least a little of the time [14]. In a multiple linear regression model including age, gender, race, diabetes, difficulty with sleep, mobility, sexual concerns and the symptoms of dry mouth, restless legs and lack of appetite, increasing pruritus severity (e.g. from some to most of the time) was associated with a 1.43-point reduction in the SF-36 PCS [95% confidence interval (CI) −0.69 to −2.17], but no reduction in MCS [0.25 points (95% CI −0.61–1.11)] [14].

Moderate to extreme pruritus was experienced by 38% of the 532 HD patients sampled from nine facilities to identify predictors of pruritus and insomnia and the impact of pruritus on HRQoL, sleep, hospitalization and mortality [25]. A significant inverse correlation between SF-36 PCS but not MCS scores and pruritus severity was reported alongside progressive reductions in total and component scores from 56 to 59 in the 'no pruritus' group to between 35 and 39 for the 'extreme pruritus' group. The authors reported that using multivariate linear regression '20% variation of SF36 score was respectively explained by insomnia and pruritus'; however, the adjusted effect sizes for this model were not reported [25].

The impact of pruritus (VAS) on HRQoL (SF-36 and Skindex-29) was assessed in 139 HD and 30 peritoneal dialysis (PD) patients [26]. The prevalence of pruritus in HD and PD patients was similar (52%), with one-third of these patients reporting pruritus as continuous. The dialysis modality (HD or PD) was a covariate in a multiple linear regression on all 168 dialysis patients. The regression did not find a significant relationship between a unit change in pruritus VAS score and SF-36 PCS and MCS scores (PCS: 0.07, P = 0.535; MCS: 0.01, P = 0.483). However, an association between pruritus scores and the Skindex-29 subscales of symptoms (0.34, P = 0.012), social functioning (0.29, P = 0.01) and emotions (0.22, P = 0.039) were noted [26].

Three publications [20, 27, 28] based on the GEHIS ($n$ = 860 patients) reported SF-12 and ItchyQoL outcomes. Comparing patients with and without pruritus, the prevalence of pruritus (not considering severity) at the time of questioning was 25.2%, with 35.2% reporting having chronic pruritus previously. Statistically significantly worse SF-12 PCS (34.6 versus 37.1) and MCS (52.0 versus 54.3) scores were reported in those with pruritus [27, 28]. A multivariable linear regression adjusting for various patient characteristics including pain, sleep impairment, anxiety and depression reported a significant correlation between mean chronic itch severity and ItchyQoL total score (ß = 0.40), with higher ItchyQoL scores indicative of the greatest impairments in the emotions and self-efficacy subscales (0.46 and 0.34, respectively; P < 0.001) [28]. These effect sizes were greater when evaluating the worst severity of chronic itch in the last 6 weeks compared with severity at the time the instruments were being completed. There was no significant relationship between ItchyQoL scores and sleep quality, although pruritus severity was not specifically evaluated. In a separate univariate analysis comparing patients with persistent chronic itch from study entry to the GEHIS ($n$ = 52) and those whose itching at baseline had resolved between 2013 and 2017 ($n$ = 52) [13], those with resolved chronic itch had statistically better ItchyQoL scores (1.7 versus 2.1; P < 0.05). However, no significant difference in SF-12 MCS and PCS scores were observed for the relevant subgroups.

One study used the Brazilian version of the Kidney Disease Quality of Life Short Form (KDQOL-SF) to assess the extent of bother due to pruritus and dry skin (i.e. perceived disease burden) over the previous 4-week period in 980 patients recruited from four dialysis units in Brazil [18]. Mild pruritus or worse was experienced by 43.8% of patients. The five-level 36-item KDQOL-SF pruritus category was recoded into three categories in a multivariable logistic regression analysis predicting the KDQOL-SF disease burden (total score) with sequential adjustment for sociodemographic, HD and laboratory variables and comorbidities. Although severity of pruritus had a negative impact on the perceived burden of disease in univariate analyses (−5.11 and −11.2 for mild and severe categories, respectively, compared to none), no statistically significant relationship was observed following adjustment for depression, sleep and bother with dry skin.

One case–control study [16] assessed pruritus using the numerical rating scale (NRS) and HRQoL with the 26-item World Health Organization Quality of Life Brief (WHOQoL-BREF) instrument, which assesses the following: physical health, social relationships, psychological health and environmental health. Overall, a significant difference in HRQOL in all four domains was

**Table 5. Summary of findings: impact of pruritus on HRQoL**

| Author, year | Analysed, *n* | HRQoL measure | Pruritus measure | Study design | Analysis[a] | Statistical relationship summary | Overall assessment of relationship |
|---|---|---|---|---|---|---|---|
| BII | | | | | | | |
| Mathur 2010 [19] | 103 | BII | VAS/NRS adaptation | Observational | Linear regression | $P < 0.001$, effect size not reported | √ |
| DLQI | | | | | | | |
| Foroutan 2017 [10] | 72 | DLQI | VAS (0–5) | RCT | Mean at different time points | Statistical significance NR, data largely consistent with P-HRQoL inverse relationship | √ |
| Gobo-Oliveira 2018 [11] | 60 | DLQI | VAS (0–10) | RCT | Spearman's rank correlation | $r = 0.76$, $P < 0.01$ | √ |
| Susel 2014 [24] | 76 | DLQI | VAS (0–10) | Observational | Spearman's rank-order correlation | $r = 0.56$, $P < 0.0001$ | √ |
| Satti 2019 [23] | 173 | DLQI | 5-D Itch | Observational | Spearman's rank-order correlation | $r = 0.78$, $P < 0.000$ | √ |
| Susel 2014 [24] | 76 | DLQI | 4-Item Itch | Observational | Spearman's rank-order correlation | $r = 0.48$, $P < 0.0001$ | √ |
| FANLTC | | | | | | | |
| Rehman 2019 [21] | 262 | FANLTC | 5-D itch (Urdu) | Observational | Multivariate linear regression | Statistically significant association between pruritus severity and HRQoL [ß = −0.949 (95% CI −1.450 to −0.449)] | √ |
| Rehman 2020 [22] | 205 | FANLTC | 5-D itch (Malay) | Observational | Bivariate analysis with Pearson's correlation coefficient | $r = -0.282$, $P \leq 0.001$ | √ |
| ItchyQoL | | | | | | | |
| Plewig 2019 [20] | 83 [20] | ItchyQoL | VAS (0–10) | Observational | Mean HRQoL in different pruritus categories, *t*-test/ANOVA | Statistically significantly worse HRQoL by pruritus severity for most subscales and total score | √ |
| Weiss 2016 [28] (GEHIS cohort) | 189 [28] | *ItchyQoL* | VAS (0–10) | *Observational* | *Multivariable linear regression* | *Mean severity, worst severity in past 6 weeks and at-the-time severity statistically significant Beta (range 0.23–0.46) for total score, and symptom, functional and emotion domains for most analyses*[b] | |

**Table 5. Continued**

| Author, year | *n* analysed | HRQoL measure | Pruritus measure | Study design | Analysis[a] | Statistical relationship summary | Overall assessment of relationship |
|---|---|---|---|---|---|---|---|
| KDQOL-SF | | | | | | | |
| *Lopes 2012* [18] | 980 | *KDQOL-SF* | *KDQOL-SF* | *Observational* | *Linear regression (various adjustments)* | *No statistically significant association after adjustment for depression, sleep and bother with dry skin* | ✗ |
| SF-36 | | | | | | | |
| Karadag 2014 [12] | 70 | SF-36 | VAS (0–10) | RCT | Mean at different time points | Statistical significance NR, data largely consistent with P-HRQoL inverse relationship | √ |
| Afsar 2012 [29] | 75 | SF-36 | VAS (0–10) | Observational | Linear regression analysis | Not statistically significant | ✗ |
| Susel 2014 [24] | 76 | SF-36 | VAS (0–10) | Observational | Spearman's rank-order correlation | $r = -0.35$, $P = 0.002$ | √ |
| *Tessari 2009* [26] | 169[c] | *SF-36* | *VAS (0–10)* | *Observational* | *Multiple linear regression* | *PCS: 0.07, P = 0.535*[c] *MCS: 0.01, P = 0.483*[c] | ✗ |
| Karadag 2014 [12] | 70 | SF-36 | ISS | RCT | Mean at different time points | Statistical significance NR, data largely consistent with P-HRQoL inverse relationship | √ |
| *Curtin 2002* [14] | 306 | *SF-36* | *Likert, frequency (5 categories)* | *Observational* | *Linear multiple regression (adjusted)* | *PCS: $\beta = -1.43$, $P < 0.000$* *MCS: $\beta = -0.25$, $P = 0.564$* | *PCS:* √ *MCS:* ✗ |
| Susel 2014 [24] | 76 | SF-36 | 4-Item Itch | Observational | Spearman's rank-order correlation | $r = -0.43$, $P \leq 0.001$ | √ |
| Tayebeh 2017 [25] | 532 | *SF-36* | *Likert intensity (5 categories)* | Observational | *Multivariate regression analysis* | *20% of variation SF-36 score explained by pruritus (statistical significance NR)* | √ |
| SF-12 | | | | | | | |
| Plewig 2019 [20] | 87 [20] | SF-12 | VAS (0–10) | Observational | Mean HRQoL in different pruritus categories, t-test/ANOVA | No statistically significant association | ✗ |
| SF-36 or SF-12 | | | | | | | |
| *Kimata 2014* [17] *(JDOPPS)* Pisoni 2006 [2] (DOPPS) | 3755 | *SF-36 or SF-12* | *Likert intensity (5 categories)* | *Observational* | *Mean HRQoL in different pruritus categories (adjusted)* | *MCS and PCS in pruritus patients, 2.3–6.7 points lower ($P < 0.0001$)* | √ |
| | 9659 | SF-36 or SF-12 | Likert intensity (5 categories) | Observational | Mean HRQoL in different pruritus categories | MCS and PCS 3.1–8.6 points lower ($P < 0.0001$) | |

**Table 5. Continued**

| Author, year | *n* analysed | HRQoL measure | Pruritus measure | Study design | Analysis[a] | Statistical relationship summary | Overall assessment of relationship |
|---|---|---|---|---|---|---|---|
| Skindex-10 | | | | | | | |
| Fishbane 2020 [9] | 189 | Skindex-10 | WI-NRS (0–10), 5D-itch | RCT | Mean change over time | Statistical significance NR, data largely consistent with P-HRQoL inverse relationship | √ |
| Mathur 2017 [13] | 128 | Skindex-10 | WI-NRS (0–10) | RCT | Mean at different time points | Statistical significance NR, Some evidence of correlation from *post-hoc* analysis of most severe pruritus patients | ?/✗ |
| Mathur 2010 [19] | 103 | Skindex-10 | VAS/NRS adaptation | Observational | Linear regression | $P < 0.001$ | √ |
| Skindex-29 | | | | | | | |
| *Tessari 2009* [26] | *169*[c] | *Skindex-29* | *VAS (0–10)* | *Observational* | *Multiple linear regression* | *Symptoms score:* $\beta = 0.34$, $P = 0.012$[c]<br>*Social functioning:* $\beta = 0.29$, $P = 0.01$[c]<br>*Emotions:* $\beta = 0.22$, $P = 0.039$[c] | √ |
| WHOQoL-BREF | | | | | | | |
| Ibrahim 2016 [16] | 100 | WHOQoL-BREF | NRS (no details) | Observational | Mean in pruritus cases versus controls, Chi-squared. | Statistically significantly worse HRQoL in pruritus cases versus controls for most physical, social, psychological and environmental aspects of WHOQoL-BREF | √ |

*Note*: Italics indicate adjusted analyses

√: presence of a significant relationship between pruritus and HRQoL; ?: absence of a significant relationship between pruritus and HRQoL; χ: data inconclusive.

[a]Where adjusted and unadjusted analyses reported, only the adjusted analysis was included in this table.

[b]Except between ItchyQoL symptoms domain and VAS pruritus severity at the time of investigation ($\beta = 0.16$, $P = 0.05$); ItchyQoL functional domain and VAS worst severity in the past 6 weeks ($\beta = 0.19$, $P = 0.02$) and ItchyQoL pruritus functional domain and severity at the time ($\beta = 0.19$, $P = 0.02$). Significance level at $P < 0.01$.

[c]The adjusted analysis included both HD and PD patients, but type of HD was a covariate in the multiple linear regression.

ANOVA, analysis of variance; BII, Brief Itch Inventory; FANLTC, Functional Assessment for Non-Life-Threatening Conditions; IFSI, International Forum for the Study of Itch; NR, not reported.

noted between patients with CKD-aP compared with patients without pruritus (Table 5).

### Experimental studies

Five RCTs evaluated treatments with itching severity instruments (WI-NRS, VAS) alongside changes in the SF-36 and disease-specific HRQoL measures. HD patients ($n = 378$) with a WI-NRS of >4 points were randomized to difelikefalin or placebo in a US study. [9] After 12 weeks, 51.9% patients experienced a ≥3-point improvement in the WI-NRS, compared to 30.9% in the placebo group, while the least squares mean change in the 5-D itch and Skindex-10 was −5.0 and −17.2 in the difelikefalin arm compared with −3.7 and −12.0 in the control arm (all endpoints <0.001). A single-blind study conducted in Iran randomized 72 HD patients to pregabalin or doxepin [10]. Although the level of pruritus severity at baseline was not reported, after 4 weeks of treatment the VAS improved from 7.5 to 2.1 in the pregabalin group compared with an improvement from 7.1 to 4.2 in the doxepine group. In parallel, greater improvements in the 5-D itch (19.2 to 8.5 versus 17.0 to 12.7) and the DLQI score (3.8 to 1.2 versus 3.6 to 2.2) were observed in the pregabalin group.

One study showed that gabapentin was comparable to dexchlorpheniramine after 21 days in 60 HD patients experiencing pruritus at least three times a week for a minimum of 30 days [11]. Patients were randomized following a 15-day run-in period with cold cream. Overall, median VAS scores significantly improved from 8 to 5 in the run-in period and 5 to 1 in the intervention period, while the median DLQI improved from 4 to 2 and from 2 to 1 during the respective periods [11].

Extended release nalbuphine at doses of 120 or 60 mg or placebo for 8 weeks were randomly assigned to 373 HD patients who during the preceding week had a mean NRS score ≥4.5, with two scores >5 [13]. From an overall mean of 6.9, the NRS improved by 3.5, 3.1 and 2.8, while the Skindex-10 improved by 17.0, 13.8 and 15.0 in the respective groups. Seventy Turkish HD patients with three episodes of itching lasting 5 minutes or longer during the preceding 2 weeks were randomized to cooled baby oil three times a week for 1 month or no intervention [12]. The VAS significantly improved by 2.51 in the baby oil group compared with 0.05 in the control, while the SF-36 PCS improved by 9.87 and 0.28 and the MCS improved by 8.45 and 0.82, respectively. Both of these studies reported improvements in sleep disruption where pruritus severity improved.

## DISCUSSION

This systematic review examined the impact of CKD-aP on HRQoL in HD patients. Inclusion criteria, assessment methods, duration of follow-up and statistical techniques varied across included studies, precluding a meta-analysis. A number of studies reported the presence of a relationship between increased reductions in HRQoL as pruritus severity worsened. Persistent pruritus resulted in worsening HRQoL over time. Overall, condition-specific pruritus tools were more sensitive to changes in HRQoL. Improvements in sleep disruption were observed with improvement in pruritus severity as a result of interventions [12, 13]. Multivariable regressions on observational data suggested that sleep disruption partially mediates the relationship between pruritus and HRQoL [17].

This review highlighted the challenges in the conduct of research in this area. Swarna *et al.* [30] conducted a review of CKD-aP but did not focus on HRQoL. The authors also stated that 'most studies are not comparable given their small group samples, study designs, and lack of standardized study measures' [30]. However, this review has yielded new insights: the available longitudinal data on the condition of CKD-aP informs the natural history and placebo effect in this condition. Although the experimental studies [9–13] were unlikely to be adequately powered to assess these questions, a placebo effect for both pruritus and HRQoL was observed in blinded [11, 13] but not unblinded [12] randomized studies. This could also represent regression to the mean, as these studies included a severity threshold for inclusion; however, no studies reported data that could be used to assess for the presence of this phenomena.

The strengths of this systematic review include adherence to recommended standards and searches conducted on a broad selection of databases. Limitations include that 50% of included studies were not primarily designed to characterize the impact of pruritus on HRQoL and planned subgroup analyses were not feasible due to a lack of available evidence.

The available data could be used to consider if meaningful gains in HRQoL would be obtained through treatment of pruritus. The associated improvements in HRQoL exceeded 0.5 SD of the baseline value where reported, generally recognized as a clinically meaningful difference [31]. The placebo effect combined with the observation around the impact of persistent pruritus on HRQoL might argue for the serial measurement of pruritus in clinical practice. Generally, serial measurement of symptoms and responses to them are the subject of ongoing trials in nephrology, having shown promising results in other chronic diseases such as cancer [32, 33]. Further research could include assessing the appropriateness of generic HRQoL instruments [34] (e.g. European Quality of Life 5-Dimensions questionnaire) that are used to evaluate health technologies in Europe or to generate value-based prices in the USA. As HD patients prioritize fatigue as a core outcome measure in clinical trials [35] and sleep disruption tends to modify the relationship between HRQoL and pruritus, instruments that capture energy or fatigue should be prioritized.

In conclusion, this systematic review has demonstrated that CKD-aP severity was associated with HRQoL in the majority of observational and RCT studies. Parallel improvements in CKD-aP and HRQoL with interventions may support the clinical and health-economic argument for their use in clinical practice.

## SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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## DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

## CONFLICT OF INTEREST STATEMENT

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