HEALTHCARE RESOURCE USE RELATING TO CHRONIC KIDNEY DISEASE-ASSOCAITED PRURITUS INFROMED BY UK REAL WORLD AND CLINICAL TRIAL DATASETS

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Declarations

Ethics approval and consent to participate

Trained, delegated research nurses gained written informed consent to participate from prevalent HD patients established on centre-based haemodialysis. The SHAREHD study adhered to the

declaration of Helsinki, ethical approval was obtained from West London & GTAC Research Ethics Committee (IRAS project ID 212395) and the trial was registered (ISRCTN Number 93999549). The mapping dataset obtained ethical approval from the North West - Haydock Research Ethics Committee (IRAS project ID 285714).

Consent for Publication

Not applicable.

Availability of data and materials

A minimal dataset required to reach the conclusions drawn from this manuscript required the linkage of identifiable patient information collected during the trial to Hospital Episode Statistics data, which at the time of writing is provided by the NHS Digital Data Access Request Service (NHS DARS, https://digital.nhs.uk/services/data-access-request-service-dars), and then appropriate processing. An application to NHS DARS can be submitted detailing lawful processing of the combined dataset and the period which HES data is required for. NHS DARS would verify appropriate permissions were in place as a result of this process. A data sharing agreement between the relevant parties would allow data to be transferred from the University of Sheffield to NHS DARS and on to those wishing to perform the enclosed analyses. Please contact ctru@sheffield.ac.uk for further information about the unlinked dataset which has the personal information required for linkage.

Conflict of interest statement

PH, MHA and JF received an unconditional research grant by Vifor Pharma Intl. TS and MS are CSL Vifor employees. MG is an academic clinical fellow funded by the NIHR. MEW has received speakers' honoraria from Baxter and Fresenius, as well as a research grant from Baxter.

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Authors' contributions

Study design: PH, MHA, MS, TS, RP, MEW, JF, MEW, Analytical Plan: PH, MHA, JF, Study Management: PH, LD, MEW, JF, Site Setup: LD, Data Collection: MG, RP, JF, Data Analysis: PH, JF, Manuscript Writing: All.

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Abstract

Background: Chronic kidney disease-associated pruritus (CKD-aP) is very common affecting 40% of patients with end-stage kidney disease and associated with a reduction in health-related quality of life and patient survival. However, little is known about healthcare resource utilisation in patients with CKD-aP. This study examined the healthcare resource use and costs associated with varying degree of CKD-aP severity to support the economic argument for improving CKD-aP in haemodialysis patients.

Methods: In order to quantify health care resource use with varying CKD-aP severity, two existing datasets from the UK : a questionnaire-based mapping dataset of CKD-aP in haemodialysis patients designed to generate the mapping between measures of CKD-aP and EQ-5D HRQoL, and the SHAREHD stepped wedge trial designed to assess the effectiveness and economic impact to support patient involvement in centre-based haemodialysis were analysed. Proportions of medication utilization, medication use in relation to location of pruritus, haemodialysis frequency and duration, and the associated costs were descriptively assessed, stratified by varying degree of CKD-aP severity, using the verbal rating scale categories: none, slightly, moderately and severely.

Results: 204/486 (42.1%) and 203/532 (38.2%) of participants reported moderate to severe degree of CKD-aP in the mapping dataset and SHAREHD respectively. Proportion of antipruritic medication use and associated costs were highest in the severe CKD-aP group (56.0%). Anti-pruritus medication use was the highest in those reporting pruritus in their upper limbs (38.8%). Use of hospital transport was similar across all CKD-aP categories although an association between severe pruritus with reduced physical functioning and energy level was observed. Compared to none CKD-aP, severe CKD-aP patients were more likely to be dialysed >3 times a week, (2.1% vs 2.7%, and 2.4% vs 3.5% for the mapping dataset and the SHAREHD respectively), resulting in an increased 28-day HD session cost of £20-30. Duration of HD session did not vary with severity of CKD-aP.

Conclusion: Severe CKD-aP was commonly reported despite half of the patients with severe CKD-aP receiving antipruritic medication, justifying the demand for new intervention to treat this. . This study

provides the contemporary insight into the economic impact of CKD-aP to healthcare providers, and comparableness of clinical trial and questionnaire data for economic evaluations.

Keywords

CKD-associated pruritus, symptoms, haemodialysis, resource use, pruritus distribution, health care resource, health related quality of life.

Background

Chronic kidney disease-associated pruritus (CKD-aP), previously known as uraemic pruritus, affects approximately 80% of patients with end-stage kidney disease (ESKD), with 37% reporting moderate to severe degree of pruritus (1) and is associated with poor health related quality of life (HRQoL), impaired sleep, depression, and increased mortality (2). The pathogenesis of pruritus in ESKD patients receiving haemodialysis (HD) is multifactorial with multiple theories underlying the cause of pruritus including metabolic disequilibrium, endocrine disorders, iron deficiency anaemia and inadequate dialysis (3). Studies have also shown that relative to those with less severe CKD-aP, patients with moderate to severe CKD-aP have substantial healthcare resource use through a range of other mechanisms including their medications (4). Unfortunately, CKD-aP is a chronic condition where individuals continue to have this symptom for months, even years in some (5). Although the cost and service delivery implications of the direct management of CKD and ESKD are well characterised (6), little is known about healthcare resource utilisation in line with varying degree of CKD-aP severity.

While studies have shown that increasing pruritus severity in haemodialysis patients contributed to missing HD sessions (4) with associated increased hospitalisation and mortality (7), an augmented dialysis regimen can be offered to patients to address symptoms, in addition to those who are unable to achieve adequacy targets or fluid control on a standard thrice weekly 4-hourly schedule (8). Haemodialysis recovery time is longer in patients with more severe CKD-aP, as shown by data from the Dialysis Outcomes and Practice Patterns Study (DOPPS), even after adjustment for sleep quality

(1). These longer recovery times affect physical function and energy level in addition to high symptom burden that HD patients have already experienced and may increase the likelihood of a patient requiring hospital transportation for dialysis: Hospital transport for haemodialysis is part of non-emergency patient transport (NEPT) and the estimated cost is at least £150 million a year in England. Moreover, the average costs for a haemodialysis patient using NEPT may be around £3,750/year in addition to HD cost (9), further adding to the cost of CKD-aP.

Acknowledging the potential mechanisms through which a person with increasing severity of CKD-aP on haemodialysis may consume more healthcare resources, a better understanding of the costs associated with medications, transport and dialysis duration and frequency is important alongside the existing knowledge on the negative impact on health-related quality of life (10) which more generally informs the health economics of CKD-aP.

A better understanding of resource use in these areas may stimulate further research and improvements in clinical practice. We present secondary analyses of a total of five in-centre haemodialysis centres in England, participating in a cohort study (mapping dataset) and the twelve centre SHAREHD trial (11), with the aims of quantifying both the resource use and associated costs with increasing severity of CKD-aP in this group.

Methods

This study aims to quantify the healthcare resource use and associated cost of medications for CKD-aP, prescribed haemodialysis regimen and associated transportation to and from the dialysis unit with varying CKD-aP severity in people receiving haemodialysis for kidney failure. Two existing datasets were used to estimate healthcare resource use according to CKD-aP severity by prevalent patients receiving haemodialysis for ESKD: first, a questionnaire-based study collecting measures of CKD-aP severity and the EQ-5Dfor the purpose of mapping, and second, a stepped wedge cluster randomised

trial evaluating an intervention to increase patient participation in the in-centre haemodialysis process, SHAREHD (11).

Primary data collection for the mapping of CKD-aP severity to EQ-5D

This was a cross-sectional study collecting established patient reported outcome measures for pruritus across five UK centres between November 2020 and July 2021 (12). The primary aim of this study was to generate the first published mapping (a conversion algorithm) between measures of CKD-aP and EQ-5D HRQoL. The study collected EQ-5D-5L data which was converted to EQ-5D-3L using for the purpose of mapping (13)(14)(15)(16). In addition to EQ-5D-5L and the four pruritus-related endpoints (Verbal rating scale, the Worst Itching Intensity Numerical Rating Scale (17), SKINDEX-10 (3), 5-D Itch Scale (18)), demographic data on patients including their comorbidities, dialysis frequency and duration, and medications use attributable to management of pruritus were also collected. Inclusion criteria included individuals established on in-centre haemodialysis for ESKD for more than three months, over the age of 18 years. Exclusion criteria included individuals who were unable to give consent or understand written English. Those who agreed to participate were consented to the study by trained members of the research team and then given questionnaires to complete either during their initial encounter or to be taken home for completion in their own time. The verbal rating scale (VRS) pruritus measure was used to inform this analysis. In this study, we refer to this dataset as the mapping dataset.

The case report form for the study asked for the use (including dose and frequency) of the following medications which have been used in management of CKD-aP (19)(20)(21) and its associated symptoms such as depression and impaired sleep (2).

- Anti-histamines (Chlorphenamine, Cetirizine, Loratadine, Fexofenadine, Hydroxyzine)
- Gabapentin / Pregabalin
- Montelukast
- Topical corticosteroids

- Oral corticosteroids (prednisolone, dexamethasone, fludrocortisone, hydrocortisone)
- Antidepressants/antipsychotics (Amitriptyline, Citalopram, Sertraline, Duloxetine, Fluoxetine, Dosulepin, Mirtazapine, Paroxetine, Nortrptyline, Olanzapine, Quetiapine, Venlafaxine, Trazodone)
- Anxiolytics/Sedatives (Clonazepam, Diazepam, Haloperidol, Nitrazepam, Prochlorperazine, Zopiclone).

The SHAREHD Stepped Wedge Cluster Randomised Trial

SHAREHD was an 18-month closed cohort stepped wedge cluster randomised trial (SWCRT) (11) conducted in 12 renal centres (units of cluster randomisation) in England to evaluate the impact of a quality improvement collaborative intervention to improve patient participation on haemodialysis related tasks. Between October 2016 and February 2017, prevalent HD patients treated at these centres were approached by trained members of the research team, and written informed consent was obtained to participate in a questionnaire-based study. 586 patients were recruited and followed up for 18 months. Patient-level inclusion criteria included patients established on centre-based HD with capacity to give written informed consent. Exclusion criteria included the clinical team perception that the patient was too unwell to engage in the study or unable to understand written and verbal communication in English. Patient questionnaires included the POS-S Renal (17 symptoms which include pruritus severity measured using verbal rating scale (VRS)) and the EQ-5D-5L, every 6 months across four timepoints. In addition, the questionnaires collected information on dialysis access, frequency, and dialysis transportation (nature of the dialysis transport). For the purpose of this analysis, we used the data and instruments collected at baseline. In this study, we referred to this SHAREHD SWCRT as SHAREHD.

Sample size and power calculation

Mapping Dataset: In order to perform a successful mapping between pruritus measures and the EQ5D-5L, it is important that the entire range of responses for all measures are observed in the dataset.

In order to ensure a sample of 500 prevalent patients would be sufficient to capture this range of responses, SHAREHD existing data on in-centre haemodialysis patients in whom pruritus was measured using an ordinal scale from none to overwhelming, along with EQ5D-5L was examined (22). The group first ensured that all the relevant permutations of the EQ5D-5L were observed within this sample, and that a measure of pruritus was successfully collected simultaneously. The mapping technique which involves fitting a mixture of several distributions simultaneously to the data was undertaken. *'Models involving two and three component distributions were successfully fitted with no convergence issues. The included variables were significant at standard significance levels and had the expected signs. Graphical methods suggested that a model with three component distributions was sufficient to capture the characteristics of the data, suggesting a mapping using a sample size of 500 patients would be sufficient* (23).*'*

The SHAREHD SWCRT : The informing SWCRT sample size was determined using a recommended ICC value of 0.05 (15), to have a 90% power to detect an increase in the proportion undertaking five or more haemodialysis-related tasks from 15% to 30% with statistically significance at the 5% two-sided level: 12 clusters of 25 patients, with six clusters randomised at each step of SWCRT was arrived at. In recognition of the background mortality and renal transplantation rate and to mitigate the risk of incomplete data collection, the target recruitment per participating site was doubled to 50 (11).

Data collection instruments

In the mapping dataset, pruritus severity was assessed using verbal rating scale, the Worst Itching Intensity Numerical Rating Scale (WI-NRS), 5-D Itch Scale and in the SHAREHD, pruritus severity was measured in VRS. The numeric rating scale (NRS) and the verbal rating scale (VRS) are widely used

instruments to assess pruritus severity in clinical practice and randomised trials, and are closely correlated (17) (24) (25). For the purpose of this analysis, CKD-aP was assessed using the 5-level ordinal VRS in both cohorts. VRS asks the patient to report over the last week how much their itching bothers them: None, slightly, moderately, severely and overwhelmingly. VRS ordinal scale "severe" correlates with a NRS of ≥ 7– <9 and "overwhelming" correlates with NRS ≥9 (25) but are not well separated based on the clinically meaningful difference of ≥3 points. With consultation with stakeholders and in line with the original publication, severe and overwhelming responses were merged (17).

5-D Itch Scale measures the five dimensions of pruritus: degree, duration, direction, disability and distribution over a two-week recall period. All items of the first four domains were measured on a five-point scale. The distribution domain includes 16 potential locations of itch, comprising 15 body part items (Head, face, chest, abdomen, back, upper arms, forearms, hands/fingers, palms, groin, buttocks, thighs, lower legs, top feet and soles) and one point of contact with clothing. 5-D Itch scores can potentially range between 5 (least affected) and 25 (most affected) (18).

Resource use and associated cost estimations

We obtained the cost of each medication from the British National Formulary between September to October 2021 and calculated the cost for 28 days treatment. We used the mean cost across multiple drugs within the same group (e.g., antihistamines group) if the cost for the drugs were similar. For different dosage regimens within a medication, we weighted the cost by proportions of patient with each different dose regimen. Haemodialysis session cost was obtained from National Cost Collection reference cost data publication 2019/2020. (26)

Statistical methods

Descriptive statistics were used to summarize the frequency and distribution of the CKD-aP and other baseline characteristics in both study cohorts. Patient baseline characteristics (demographics, comorbidities) were compared across CKD associated pruritus category using chi-square tests of trend for proportions and ANOVA for mean differences for all continuous outcomes. Descriptive statistics

were used to report the proportions of medication utilization and costs, dialysis transport, haemodialysis frequency and duration with results stratified by CKD-aP severity. To test the hypothesis that some patients in the none CKD-aP group were on these medication for indications other than CKD-aP, additional sensitivity analyses were carried out for medication analyses excluding those who had no pruritus in other pruritus measures (patients who responded as zero for the WI-NRS, none in 5-D Itch "Degree" and score of 5 in 5-D Itch measures of pruritus). In addition to primary analysis, descriptive analyses were performed for proportions of dialysis hospital transport use stratified by age and use of medication in relation to the "Distribution" of CKD-aP from the 5-D Itch reported by the respondents. This study also used additional variables from the SHAREHD dataset POS-S renal questionnaires (weakness, poor mobility and lack of sleep, all of which have VRS levels of none to overwhelming) to assess the relationship between the longer recovery time and use of hospital transport. All analyses were carried out in Stata version 17.

Results

Patient's baseline characteristics and demography

Out of 487 patients recruited in the mapping dataset, 486 patients completed CKD-aP questionnaires and of the 586 in-centre haemodialysis patients recruited to the SHAREHD, 532 patients provided CKD-aP data during the baseline phase (Figure 1), with 42.1% and 38.2% of patients reporting moderate to severe degree of CKD-aP in the mapping dataset and SHAREHD respectively. Baseline characteristics of the participants in the mapping dataset and SHAREHD stratified by CKD-aP VRS are summarized in Table 1 and Table 2. Although there is a trend that the patients who reported severe CKD-aP were approximately four years younger than other severity groups in the mapping dataset, it was not statistically significant CKD-aP severity did not vary with years on haemodialysis in both datasets.

In both cohorts, the majority of patients were white, male, one to five years on haemodialysis and Arterio-venous Fistula (AVF) was the most commonly used HD access. Use of tunnelled haemodialysis

286 catheters was higher in none and mild CKD-aP compared to moderate and severe in both cohorts. The

287 prevalence of diabetes was high in both cohorts across all CKD-aP severity groups.

288 **Table 1: Baseline demography of patients in the Mapping study stratified by CKD-aP severity**

		None	Mild	Moderate	Severe	Total	P value for the trend
Proportions/Number of patients		33.7%(n=164)	24.2%(n=117)	25.4%(n=123)	16.7%(n=81)	100% (n=486)	
Age (years), mean (SD)		66.7(SD14)	64.6(SD 15.8)	65.2(SD 14)	62.4 (SD17.8)	65.1 (SD 15)	P 0.06
Sex- Male		68.1% (111)	74.1% (86)	66.4% (81)	56.3% (45)	67.2(324)	P 0.13
White		76.2% (125)	81.2% (95)	76.4% (94)	79.0% (64)	78.0% (379)	P 0.4
Years on HD*	<1yr	21.3% (35)	25.6% (30)	18.7% (23)	21% (17)	21.6% (105)	P 0.16
	1-5yr	49.4% (81)	41.9% (49)	56.9% (70)	48.2% (39)	49.4% (240)	
	>5yr	29.3% (48)	32.5% (38)	24.4% (30)	30.9% (25)	29.0% (141)	
HD* access	AVF**	59.8% (98)	52.1% (61)	54.5% (67)	56.8% (46)	56.0% (272)	P 0.15
	AVG**	4.3% (7)	2.6% (3)	4.1% (5)	9.9% (8)	4.7% (23)	
	Tunnelled line	25.6% (41)	34.2% (40)	26.0% (32)	25.9% (21)	28.0% (136)	
Coronary artery disease		11.0% (18)	7.7% (9)	14.6% (18)	8.6% (7)	10.7% (52)	P 0.30
Heart failure		1.2% (2)	0.9% (1)	3.3% (4)	2.5% (2)	1.9% (9)	P 0.50
Diabetes		39.0% (64)	26.5% (31)	40.7% (50)	37% (30)	36.0% (175)	P 0.09
Cancer		7.3% (12)	8.6% (10)	9.7% (12)	6.2% (5)	8.0% (39)	P 0.79
Lung disease		7.3% (12)	2.6% (3)	9.8% (12)	9.9% (8)	7.2% (35)	P 0.08

289 * HD=Haemodialysis

290 ** AVF = arteriovenous fistula, AVG = arteriovenous graft

Numbers reported in brackets are sample sizes apart from age where they refer to standard deviations.

Table 2: Baseline demography of patients in SHAREHD stratified by CKD-aP severity

		None	Mild	Moderate	Severe	Total	
Proportions (Number of patients)		34.4%(n=183)	27.4%(n=146)	21.1%(n=112)	17.1%(n=91)	100%(n=532)	
Age		62.8 (SD 15)	62.9 (SD 15.8)	62.3(SD 14.8)	63.2 (SD 14.4)	62.8(SD 15.5)	P 0.8
Sex- Male		61.1% (110)	61.8% (84)	57.1% (60)	64.4% (58)	61.1% (312)	P 0.55
White		83.1% (148)	79.1% (106)	82.1% (87)	81.8% (72)	81.6% (413)	P 0.49
Years on HD*	Mean years (SD)	2.24 (SD 0.43)	2.33 (SD 0.47)	2.27 (SD 0.44)	2.31 (SD 0.46)	2.29 (SD 0.46)	P 0.49
	<1yr	20.3% (32)	22.8% (26)	27.3% (24)	27.3% (21)	23.6% (103)	P 0.57
	1-5yr	44.3% (70)	46.5% (53)	54.5% (48)	50.6% (39)	48.1% (210)	
	>5yr	35.4% (56)	30.7% (35)	18.2% (16)	22.1% (17)	28.4% (124)	
HD* access	AVF**	72.8% (123)	68.5% (87)	78.6% (77)	77.9% (67)	73.8% (354)	P 0.32
	AVG**	8.3% (14)	5.5% (7)	1.0% (1)	0.0% (0)	4.6% (22)	
	Tunnelled line	17.2% (29)	22.8% (29)	16.3% (16)	17.4% (15)	18.5% (89)	
	Temporary line	1.8% (3)	3.1% (4)	4.1% (4)	4.7% (4)	3.1% (15)	
Coronary artery disease		19.5% (31)	17.6% (24)	24.2% (24)	17.2% (15)	19.5% (94)	P 0.16
Heart failure		13.2% (21)	19.1% (26)	27.3% (27)	21.8% (19)	19.3% (93)	P 0.82
Diabetes		39.0% (62)	36.8% (50)	47.5% (47)	39.1% (34)	40.1% (193)	P 0.78
Cancer		5.0% (8)	8.1% (11)	12.1% (12)	11.5% (10)	8.5% (41)	P 0.12
Lung disease		14.5% (23)	21.3% (29)	23.2% (23)	27.6% (24)	20.6% (99)	P 0.96

*** HD=Haemodialysis**

**** AVF = arteriovenous fistula, AVG = arteriovenous graft**

Numbers reported in brackets are sample sizes apart from age where they refer to standard deviations.

Medication use

Proportions of medication use in relation to CKD-aP severity (Mapping Dataset)

The mapping dataset showed that approximately 42.0% of haemodialysis patients in this cohort are using one or more antipruritic medications. Antipruritic medication use was highest in the severe group where 56% of patients with severe CKD-aP used one or more antipruritic medication (Table 3).

Within each medication group, the medication use was highest in the severe CKD-aP group except for Montelukast (Table 3). We also noted that proportions of some medication use were also high in the none CKD-aP group compared to mild and moderate. Additional analyses excluding those who reported no pruritus in other CKD-aP measures with different recall periods (patients who responded as zero for the Worst Itching Intensity Numerical Rating Scale (recall period – the last day), none in 5-D Itch degree and score of 5 in 5-D Itch measures of pruritus (recall periods – two weeks)) result in reduction in antidepressants/antipsychotics use (from 16.5% to 12.5%) in none CKD-aP group but there were no significant differences in the proportions of other medication use in this group (Additional file 1).

Proportion cost of each medication use per CKD-aP severity (Mapping Dataset)

The cost per 28 days for each medication use are described in Table 3. This cost was calculated based on medication cost in patients in the cohorts who were prescribed with anti-pruritus medications. The 28-days cost for each medication multiplied by the proportion of patients in each CKD-aP severity group were summarised in Table 3, and this reflects the 28-day cost for all patients within each CKD-aP severity group. Although cost differences were not large, cost across all patients in severe CKD-aP was higher than in the other CKD-aP groups in all studied medications except Montelukast.

Table 3: Proportion of medication use and associated cost per 28 days (cost*proportions) stratified by CKD-aP severity

Current medication and gross cost per tablet for 28 days in GBP		None (n=164)	Mild (n=117)	Moderate (n=123)	Severe (n=81)	Total (n=486)
Proportions of patients on any meds	Proportions (number)	40.2% (65)	38.5% (45)	36.6% (45)	55.6% (46))	41.6% (201)
Antihistamines £2.47	Proportions (number)	4.9% (8)	7.7% (9)	13.8% (17)	24.7% (20)	11.1% (54)
	Proportion Cost per 28 days in GBP	0.12	0.19	0.34	0.61	0.27
Gabapentin/ Pregabalin £2.47	Proportions (number)	11% (18)	7.7% (9)	6.5% (8)	17.3% (14)	10.1% (49)
	Proportion Cost per 28 days in GBP	0.27	0.19	0.16	0.43	0.25
Montelukast £2.33	Proportions (number)	1.8% (3)	2.6% (3)	0.8% (1)	1.2% (1)	1.6% (8)
	Proportion Cost per 28 days in GBP	0.04	0.06	0.02	0.03	0.04
Oral Corticosteroids £2.39	Proportions (number)	15.2% (25)	9.4% (11)	8.1% (10)	16% (13)	12% (59)
	Proportion Cost per 28 days in GBP	0.36	0.22	0.19	0.38	0.29
Topical corticosteroids £11.32	Proportions (number)	2.4% (4)	3.4% (4)	1.6% (2)	7.4% (6)	3.3% (16)
	Proportion Cost per 28 days in GBP	0.27	0.39	0.19	0.84	0.37
Antidepressants/ antipsychotics	Proportions (number)	16.5% (27)	17.9% (21)	16.3% (20)	21% (17)	17.5% (85)
	Proportion Cost per 28 days in GBP	0.69	0.75	0.68	0.87	0.73
Anxiolytics/sedatives	Proportions (number)	4.3% (7)	4.3% (5)	1.6% (2)	4.9% (4)	3.7% (18)
	Proportion Cost per 28 days in GBP	0.27	0.27	0.10	0.31	0.23

Numbers reported in brackets are sample sizes.

Mapping dataset was used to inform this analysis.

Medication use in relation to Distribution of CKD-aP (Mapping Dataset)

In addition to severity, the 5-D Itch from the mapping dataset assesses distribution of CKD-aP. Among the patients who reported the presence of CKD-aP in any degree (mild, moderate and severe), groin (21.9%), upper arms (21.1%) and forearms (11.1%) were reported as the areas most affected (Figure 2). Among the patients with mild to severe CKD-aP, medication use was the highest in those reporting pruritus in their upper limbs (38.8%), followed by groin (21.0%) and lower legs (14.5%) (Figure 3). Although patients reported the presence of pruritus in different body parts, more than 50% of these patients were not on any anti-pruritus medications (Additional file 5).

Relationship between haemodialysis transport and CKD-aP severity (SHAREHD)

The SHAREHD found that patients with a severe degree of pruritus have reduced levels of physical function and energy as evidenced by increasing weakness, poor mobility and lack of sleep as pruritus severity increases (Additional file 2). To explore if this influences the method a patient is transported to haemodialysis, 512 patients who provided data for mode of transport in the SHAREHD study were analysed. The proportion of hospital transport used was similar across all CKD-aP severity groups (Additional file 2). In the analysis of transport use stratified by age (less than or more than 60 years), although younger patients tend to use less hospital transport, its proportion in relation to CKD-aP severity was similar across all levels (Additional file 3).

Dialysis frequency, duration and HD access use associated with CKD-aP severity

Proportions of HD frequency in relation to CKD-aP

In the mapping dataset, there were 425 patients with data on HD sessions per week with the majority of patients on three times a week haemodialysis schedules (Table 4). Fewer people were on haemodialysis schedules less than three times per week in patients with moderate and severe degree of CKD-aP. Higher proportions of patients with moderate to severe degree of pruritus dialysed more than three times per week, compared to those who did not have any pruritus. Although patients who

reported the presence of any degree of CKD-aP dialysed longer than those who had no pruritus, HD duration did not go up with increasing severity of CKD-aP (Table 4).

A similar trend was also seen in SHAREHD where those who reported moderate to severe degree of pruritus were more likely to dialyse more than three times a week (Table 4).

Table 4: Proportions of Dialysis frequency and duration of HD associated with CKD-aP severity

Study	HD session per week	None	Mild	Moderate	Severe	Total
Mapping study	2 (n=16)	4.9% (7)	4.0% (4)	3.9% (4)	1.4% (1)	3.8% (16)
	3 (n=398)	93.1% (134)	93.1% (95)	93.2% (97)	96.0% (71)	93.7% (398)
	>3 (n=11)	2.1% (3)	2.9% (3)	2.9% (3)	2.7% (2)	2.6% (11)
SHAREHD study	1 (n=2)	1.2% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.4% (2)
	2 (n=9)	0.6% (1)	2.3% (3)	3.0% (3)	2.3% (2)	1.9% (9)
	3 (n=457)	96.0% (157)	97.0% (125)	93.1% (94)	94.2% (81)	65.2% (457)
	>3 (n=12)	2.4% (4)	0.8% (1)	4.0% (4)	3.5% (3)	2.5% (12)
HD duration in mapping study	2.5 hrs (n=2)	0.0% (0)	1.0% (1)	1.0% (1)	0.0% (0)	0.5% (2)
	3hr (n=28)	7.6% (11)	6.7% (7)	3.9% (4)	6.8% (5)	6.6% (28)
	3.5hr (n=193)	50.7% (73)	35.3% (36)	46.2% (48)	48.7% (36)	45.4% (193)
	4 hr (n=186)	39.6% (57)	51.0% (52)	45.2% (47)	40.5% (30)	43.8% (186)
	>4hrs (n=16)	1.4% (3)	5.9% (6)	3.9% (4)	2.7% (3)	3.3% (16)
HD session cost per 28 days in GBP	Mapping data	1954.29	1987.29	1961.64	1976.86	1968.07
	SHAREHD	1964.00	1958.03	1974.50	1983.42	1968.13

Numbers reported in brackets are sample sizes.

Proportions of HD access use in relation to CKD-aP

In the UK, the haemodialysis tariff cost is different depending on haemodialysis access use. The majority of patients were dialysed using an AVF in both cohorts and haemodialysis via a tunnelled line

was higher in the mapping dataset compared to SHAREHD (29% versus 19%) (Table 1 and Table 2). We found that use of a tunnelled catheter for haemodialysis did not increase with increasing severity of CKD-aP in both cohorts. (Additional file 4)

Total Cost of HD frequency weighed by HD access in relation to CKD-aP

The mean cost for each HD session was £164 based on National Cost Collection reference cost data publication 2019/2020. In the mapping dataset, the twenty-eight-day HD session cost was higher in severe CKD-aP group compared to none CKD-aP group (1954.29£ vs 1976.86£) (Table 4). Higher cost in mild group in the mapping dataset was primarily driven by a small number of patients (n=2) dialysed 6 times per week. In SHAREHD, 28 days HD session cost was highest in severe CKD-aP by approximately £20-30 compared to none and mild CKD-aP.

Discussion

In this study evaluating health care resource use in in-centre HD patients with CKD-aP, we established that broadly speaking patient baseline characteristics and co-morbidities did not vary across CKD-aP severity. We observed that 42% of the patients were prescribed medications to manage CKD-aP and its associated symptoms: the largest usage was observed in the severe CKD-aP group, however, use of gabapentin/pregabalin, oral steroids and anxiolytics/sedatives were also high in patients with no CKD-aP, consistent with the fact that the approved indications for these medications are others than CKD-aP. Increasing severity of CKD-aP was associated with increasing haemodialysis intensity: patients with moderate and severe CKD-aP were more likely to dialyse more than three times per week and milder CKD-aP patients dialysed less frequently.

Approximately 40% of people receiving HD reported moderate or worse CKD-aP severity in this study and this is comparable to other CKD-aP prevalence studies (2). The patient baseline characteristics in both cohorts are comparable to national registry data describing prevalent haemodialysis patients (27) and KALM1 randomised control trial describing prevalent HD patients with moderate or worse

CKD associated pruritus (28). The prevalence of CKD associated pruritus in varying degree was also similar to other studies describing epidemiology of CKDaP (29). Prescribing practice for CKDaP in the mapping dataset was comparable to other studies (21)(19). No variation in co-morbidities and central venous catheter access use were observed in patients with most severe degree of CKD-aP in contrast to another study observing greater comorbidity and higher central venous catheter use in patients most bothered by CKD-aP (1). An increase in the proportion of people on HD using any antipruritic medication was observed with increasing CKD-aP severity and these medication use were higher than the 20-25% use of antipruritic medication described in other studies (4). Although we observed a clear association between severe pruritus with reduced physical functioning and energy level which could result in longer recovery time comparable with other studies (1), hospital transport use was not influenced. It is possible that the cross-sectional nature of this study did not capture the patients who no longer reported symptoms as they have resolved even if there had been an issue previously. Medication use is high in those who reported the upper arm and forearm as the most affected area. This could be related to their haemodialysis access arm where healthcare professionals reviewed more often on dialysis compared to other parts of the body, although this study did not show significant variation in use of AVF or Arteriovenous Graft (AVG) in relation to severity of CKD-aP. Although the groin area was the most commonly affected area, more than 50% of patients affected in this area were not on antipruritic medications. It is likely that patients may not alert healthcare professionals to this symptom unless they are asked directly.

The main strengths of this study are that it provides a contemporary insight into the economic burden of patients with CKD-aP to healthcare providers, contributes further evidence on direct and indirect healthcare costs of patients such as transport use with varying degree of CKD-aP and is the first to describe the body part distribution of CKD-aP. However, there are limitations to this analysis: while this study offers additional insight into the association of higher antipruritic medication use in patients with CKD-aP, we could not specify if these medications are prescribed for other conditions rather than treating for CKD-aP, since there was no medication indicated for management of CKD-aP at the time

of the data collection. The severity of pruritus in the mapping dataset was collected using an instrument that asked the patient to reflect on the past week and therefore recall bias may affect the evaluations. However, the validity and reliability of this instrument in assessing chronic pruritus has been shown in several studies (30) (31). Studies have shown that the single itch-related question for pruritus is comparable to the more elaborate Skindex-10 questionnaire (32). The systematic review examining the effect of a one-day versus seven-day recall duration on PROM and HRQoL instrument scores in adults with a range of clinical conditions reported that symptoms tended to be reported as more severe when assessed with a weekly recall than with a one-day recall however, this difference was not statistically significant (33). Over the counter topical therapies were not assessed due to the range of sources patients may obtain these from. The cross-sectional nature of the study means those who had no pruritus may have had pruritus in the past which resolved in response to the medications prescribed and reported in these analyses. This may explain the high use of medications in the none CKD-aP group, as would use of these medications for other indications. Medication use in the none CKD-aP group does not reflect a population who never had CKD-aP. Health Economic analyses employing the proportion of medication usage in the mild group for the none group may be justified for these reasons. Alternately, participants may have just started on their treatment and not have enough time to see the affect**.** We avoided using significance testing in line with STROBE guidelines reporting observational studies (34). Health care resource cost in this study was limited the medication use and dialysis cost. The health care utilisation cost associated with inpatient admissions and other outpatient attendance were not taken into account.

In this study, more than half the people reporting severe CKD-aP severity despite being on current standard of care to manage CKD-aP and its associated symptoms justify the demand for new intervention to treat this condition. This study has provided evidence for the generalization of trial results to the real-world broader patient population. Future studies exploring longitudinal changes in CKD-aP severity in response to standard care may help understand high medication use in those with

no CKD-aP. In addition, we recommend exploring medication use for other indications beyond CKD-aP given the high presence of comorbidities.

Abbreviations

CKD-aP: chronic kidney disease associated Pruritus

DOPPS: Dialysis Outcomes and Practice Patterns Study

EQ-5D-5L: European quality of life (QoL) 5-dimension 5 level score

HD: Haemodialysis

HRQoL: Health related quality of life

ICC: Intraclass correlation coefficient

NEPT: Non-emergency patient transport

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Figures

Figure 1: Patient recruitment flow diagram

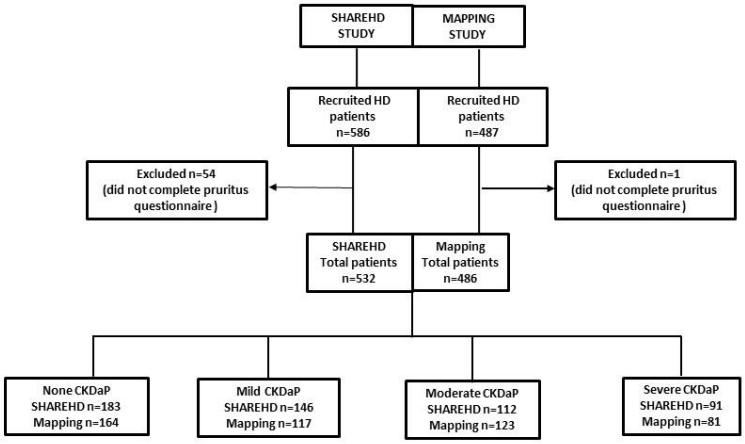


Figure 2: Prevalence of Itch distribution in different body parts (numbers in boxes are sample sizes / number of patients)

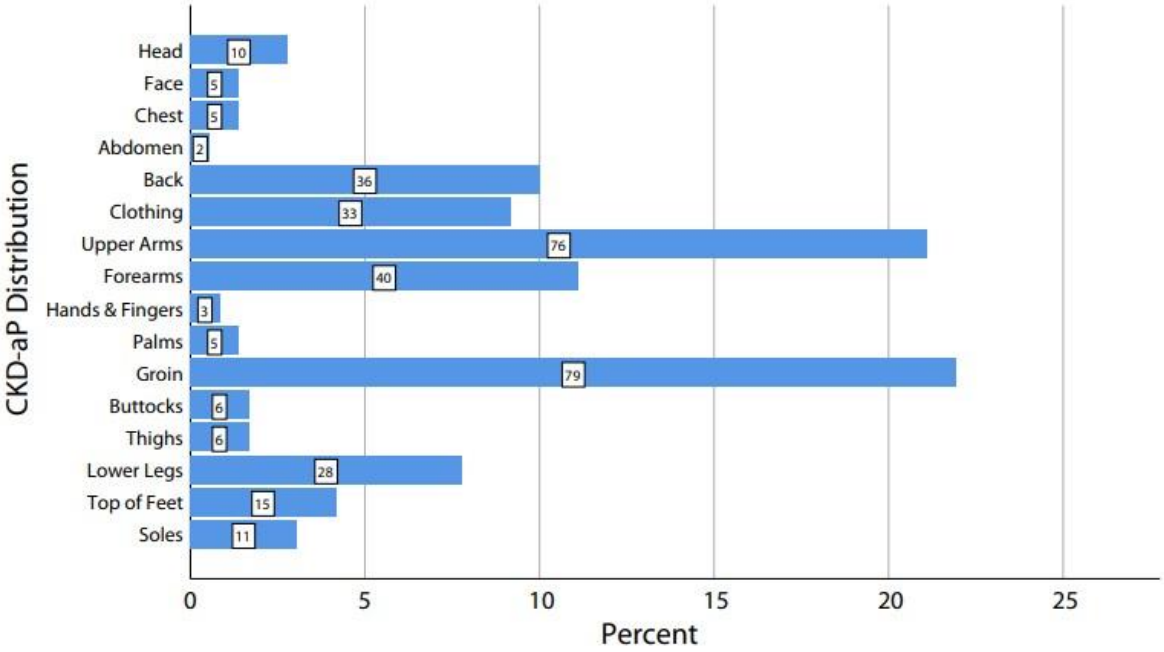
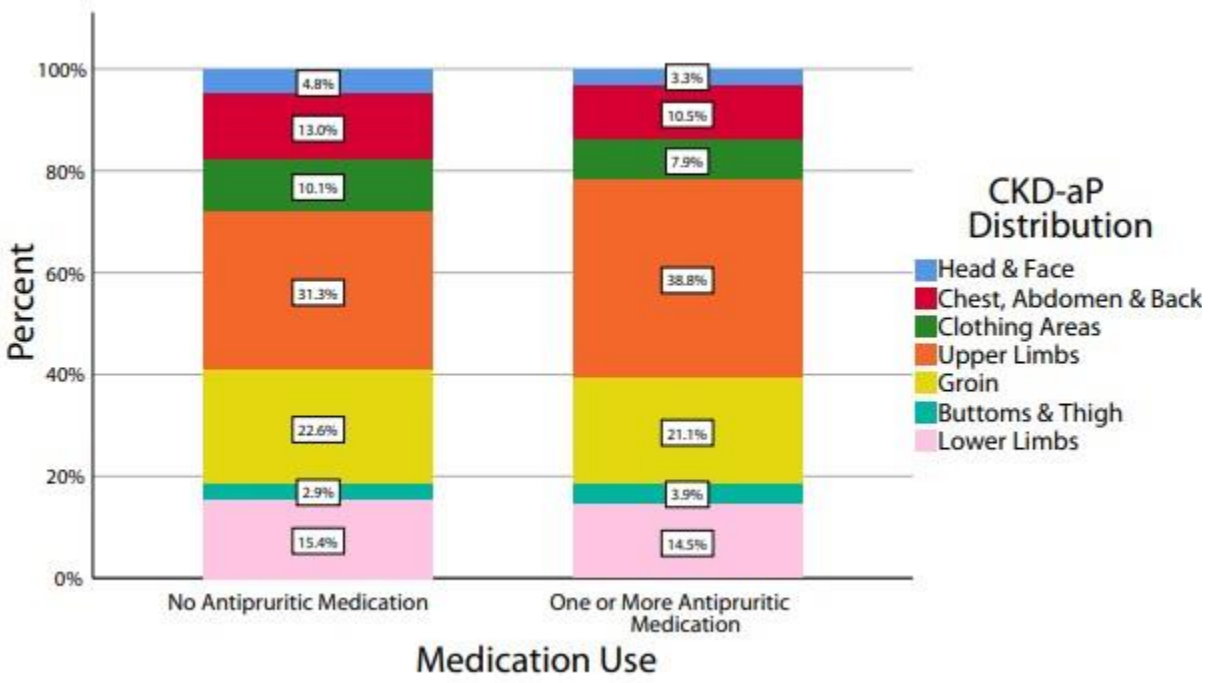


Figure 3: Proportion of CKD-aP body distribution in relation to antipruritic medication use (numbers in white boxes are the percentages of participants)

Upper limbs include upper arms, forearms, hands/fingers and palms.

Lower limbs include lower legs, top feet and soles.



Additional Files

1. **Additional File 1 Docx**

Title: Proportion of medication use stratified by CKD-aP severity excluding those who had no pruritus* (Mapping data)

Current medication (Number of patients)	None (n=96)	Mild (n=117)	Moderate (n=123)	Severe (n=81)	Total (n=418)
Proportions of patients on any meds	40.6%	38.5%	36.6%	55.6%	41.9%
Antihistamine	5.2%	7.7%	13.8%	24.7%	11.7%
Gabapentin/Pregabalin	12.0%	7.7%	6.5%	17.3%	10.3%
Montelukast	1.0%	2.6%	0.8%	1.2%	1.4%
Oral Corticosteroids	1.5%	9.4%	8.1%	16.0%	1.15%
Topical Corticosteroids	2.1%	3.4%	1.6%	7.4%	3.4%
Antidepressant/Antipsychotics	12.5%	17.9%	16.3%	21.0%	17.0%
Anxiolytic/sedatives	4.2%	4.3%	1.6%	4.9%	3.6%

68 patients were excluded in this analysis.

Patients who reported no pruritus in other CKD-aP measures with different recall periods (patients who responded as zero for the Worst Itching Intensity Numerical Rating Scale, none in 5-D Itch degree and score of 5 in 5-D Itch measures of pruritus).

605 **2. Additional File 2 Docx**

606 **Title: Proportions of physical functioning, energy level and mode of transport used in**

607 **relation to CKD-aP (SHAREHD)**

Physical functioning and energy level and mode of transport used		**None**	**Mild**	**Moderate**	**Severe**	**total**
Weakness or lack of energy	None	30%	8.3%	9.9%	12.4%	16.9%
	Mild	27.3%	35.2%	11.7%	17.9%	24.6%
	Moderate	25.1%	32.4%	45.0%	29.2%	32.0%
	Severe	17.5%	24.1%	33.0%	40.5%	26.5%
Poor mobility	None	45.6%	30.8%	17.9%	15.6%	30.6%
	Mild	15.4%	24.7%	26.8%	16.7%	20.6%
	Moderate	22.5%	25.3%	23.2%	33.0%	25.3%
	Severe	16.5%	19.2%	32.1%	34.4%	23.6%
Difficult sleeping	None	48.1%	33.1%	23.2%	17.6%	33.5%
	Mild	20.2%	24.1%	24.1%	18.7%	21.9%
	Moderate	20.8%	22.8%	28.6%	25.3%	23.7%
	Severe	10.9%	20.0%	24.1%	38.5%	20.9%
Mode of transport used	Hospital transport	42.7%	42.3%	43.1%	44.5%	43.0%
	Car	41.5%	40.6%	37.6%	43.3%	41.0%
	Bus	4.1%	3.5%	3.7%	0.0%	3.0%
	Taxi	8.8%	12.7%	13.8%	10.0%	11.0%

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3. Additional File 3 Docx

Title: Proportions of different mode of transport used stratified by age (SHAREHD)

Mode of transport		None	Mild	Moderate	Severe	Total
<60yrs	Hospital transport	35.5%	40.4%	35.6%	40.0%	37.7%
	Non hospital transport	64.5%	40.4%	64.4%	60.0%	62.3%
>60yrs	Hospital transport	46.8%	43.5%	48.4%	47.3%	46.3%
	Non hospital transport	53.1%	56.5%	51.6%	52.7%	53.7%

4. Additional File 4 Docx

Title: Proportions of HD access use in relation to CKD-aP

	HD access	None (n=147)	Mild (n=104)	Moderate (n=106)	Severe (n=75)	Total (n=432)
Mapping dataset	AVF*	66.7% (98)	58.7% (61)	63.2% (67)	61.3% (46)	63.0% (272)
	AVG*	4.8% (7)	2.9% (3)	4.7% (5)	10.7% (8)	5.3% (23)
	Tunnelled line	28.6% (42)	38.5% (40)	30.2% (32)	28.0% (21)	31.3% (135)
	Temporary line	0.0% (0)	0.0% (0)	1.9% (2)	0.0% (0)	0.5% (2)
SHAREHD	HD access	None (n=169)	Mild (n=127)	Moderate (n=106)	Severe (n=98)	Total (n=480)
	AVF*	73.0% (123)	69.0% (87)	79.0% (77)	78.0% (67)	74.0% (354)

	AVG*	8.0% (14)	6.0% (7)	1.0% (1)	0.0% (0)	5.0% (22)
	Tunnelled line	17.0% (29)	23.0% (29)	16.0% (16)	17.0% (15)	19.0% (89)
	Temporary line	2.0% (3)	3.0% (4)	4.0% (4)	5.0% (4)	3.0% (15)

Numbers reported in brackets are sample sizes.

AVF = arteriovenous fistula, AVG = arteriovenous graft

5. Additional File 5 docx

Title: Use of anti-pruritus medication in relation to itch distribution.

Numbers in column are patient numbers (sample size)

Upper limbs include upper arms, forearms, hands/fingers and palms

Lower limbs include lower legs, top feet and soles