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Research article

Cluster of symptoms in kidney failure: A systematic review

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ABSTRACT

Background: Chronic kidney disease is a global problem characterized by a progressive decrease in kidney function with associated symptoms. A better understanding of these symptoms could lead to the development of personalized strategies.
Objective: This systematic review aims to describe the clusters of symptoms in kidney failure and categorize them according to their time of onset and how disabling they are for patients.
Design: A systematic review was carried out.
Methods: This systematic review was conducted according to the PRISMA declaration standards. The search engines used were initially limited to WOS, Embase, and PubMed, and they were employed between November 2022 and January 2023. In addition, the bibliographic search was supplemented with databases of the grey literature, such as OpenGrey, in May 2023. The following inclusion criteria were established: cross-sectional studies, studies on adult populations, and studies dealing with clusters of symptoms associated with kidney failure. Before an article was definitively selected, the checklist of the STROBE initiative, with a maximum of 22 points, was applied, assessing the quality of cross-sectional articles. Articles were selected independently and blinded by two researchers, and a third researcher was involved in case of disagreement.
Results: After carrying out the bibliographic search, we found that eight articles, out of the 46 articles that were evaluated, fully met the inclusion criteria. Two tables were made, which include important information, such as the participants' profiles or the way the authors extracted a cluster of symptoms.
Limitations: The main area for improvement is that it was not possible to perform a meta-analysis due to the methodology used in the articles analysed. Constraining the selection of articles to those written in Spanish or English could be a limitation as not all articles dealing with symptom clusters in kidney failure were considered.
Conclusions: Common symptoms in clusters of symptoms in kidney failure were nausea or vomiting (gastrointestinal problems), fatigue or muscle weakness (neuromuscular symptoms/problems), low interest in sex or difficulty feeling sexually excited (sexual symptoms), dry skin or skin itching (skin problems), lack of appetite, feeling squeezed, feeling weak or dizzy and difficulty breathing (uraemic), fatigue or muscle weakness (energy/vitality), and chest pain (cardiac-related problems). Providing treatment based on clusters of symptoms would benefit the patient more than providing treatment based on isolated symptoms. The identification of symptom clusters in kidney failure has clinical relevance, and this research could facilitate the development

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of adequate intervention strategies, simplifying the treatment offered to patients and even reducing the side effects of treatments.

1. Background

Chronic kidney disease (CKD) is a global problem characterized by a progressive decrease in kidney function with associated symptoms [1,2]. The KDIGO guidelines define CKD as "abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1-G5), and Albuminuria category (A1-A3), abbreviated as CGA" [3]. The estimated glomerular filtration rate may vary, with values > 90 ml/min considered normal, 89–60 ml/min classified as mildly decreased, 59–45 ml/min as mildly to moderately decreased, 44–30 ml/min as moderately to severely decreased, 29–15 ml/min as severely decreased, and <15 ml/min indicating kidney failure (KF). The categories of albuminuria range from normal to mildly increased (<30 mg/g), moderately increased (30–300 mg/g), and severely increased (>300 mg/g) [3]. The aetiology of CKD needs to be clearly defined. However, we found that risk factors include family inheritance, ageing, low birth weight, hypertension, drug administration, diabetes mellitus, and systemic or urinary infections, among others [3–6], with hypertension and diabetes being the most common causes of CKD [3].

The profile of KF patients includes an age of around 75 years, fragility, and pluripathology [2,7,8]. According to the National Kidney Foundation, about 10 % of the world's population is affected by this condition [1]. KF is the highest grade in CKD and can be treated through kidney transplantation, dialysis (haemodialysis or peritoneal dialysis), or supportive care [9–11]. Symptoms of CKD include fatigue, anorexia, anxiety, sleep problems, itching, dry mouth, muscle weakness, constipation, depression, and nausea or vomiting [10–12].

Patients on haemodialysis treatment experience a high burden of physical and emotional symptoms [9–11]. Another treatment modality in KF is supportive care [13,14]. Patients who do not require kidney replacement therapy also suffer from a significant burden of symptoms [15]. A few studies have tried to group the symptoms associated with CKD, realizing that CKD symptoms occur in clusters rather than in isolation [16–18]. We can define clusters of symptoms as the concurrent appearance of several symptoms that have synergies with each other but that do not necessarily share their aetiology [19]. Symptoms may decrease KF patients' quality of life [20–22], and control of the burden of symptoms is often deficient [7,23]. Some studies compare the burden of symptoms in KF with symptoms experienced in cancer [1,2,16]. Treatment of isolated symptoms versus cluster treatment is perceived as less effective [19].

A better understanding of KF symptoms could lead to the development of personalized strategies for managing KF [2,15,16]. In this context, this systematic review aims to describe and categorize the clusters of symptoms in KF according to their time of onset and how disabling they are for patients.

2. Methods

2.1. Design

A systematic review was performed. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), with registration number CRD42023388061. This systematic review was carried out according to the PRISMA declaration standards [24].

2.2. Search methods

All three authors selected the potentially eligible articles and discussed their eligibility. The article search was initially limited to updated databases such as WOS, Embase, and PubMed, with eight different searches between November 2022 and January 2023. In addition, we used databases of the grey literature, such as OpenGrey, in May 2023. The search terms used were end-stage kidney disease, kidney failure, symptom, cross-sectional studies, symptom cluster, dialyses, quality of life, and chronic kidney disease (see Annex 1).

2.3. Inclusion and exclusion criteria

The following inclusion criteria were established: cross-sectional studies, studies on adult populations, and studies dealing with clusters of symptoms associated with KF. The only exclusion criterion was an article language different from Spanish or English.

2.4. Search variables

In the extraction of data from the articles, the primary variable was defined as KF symptom clusters suffered by patients.

2.5. Quality appraisal

Before the selection of an article, the STROBE checklist was applied. This checklist measures the quality of cross-sectional articles,

which is determined by a 22-point list [25]. It was the responsibility of all the authors to assess the pre-selected articles according to the checklist and discuss the scores awarded to establish a final score (Table 1).

2.6. Data extraction

Once the bibliographic searches were carried out, the articles were selected through the following process: reading the titles, reading the abstracts, and reading the articles thoroughly. After applying the search engines, we found 1309 articles, of which 32

Table 1
Strobe Checklist.

AUTHOR'S	Almutary H., 2016	Amro A., 2014	Curtin R., 2002	Gutiérrez-Sánchez D., 2019	Jablonski A., 2007	Thong M., 2009	You A., 2022	Yu I., 2012
TITLE/ABSTRACT								
1 a	●	●	●	▬	▬	▬	●	●
1 b	●	●	●	●	●	●	●	●
INTRODUCTION								
2	●	●	●	●	●	●	●	●
3	●	●	●	●	●	●	●	●
METHODS								
4	●	●	▬	●	●	●	●	●
5	●	●	●	●	●	●	●	●
6	●	●	●	●	●	●	●	●
7	●	●	●	●	●	●	●	●
8	●	●	●	●	●	●	●	●
9	▬	▬	▬	▬	▬	▬	▬	▬
10	●	●	●	●	●	▬	▬	▬
11	●	●	●	●	●	●	●	●
12 a	●	●	●	●	●	●	●	●
12 b	●	●	●	●	●	▬	●	●
12 c	▬	▬	▬	▬	▬	▬	▬	▬
12 d	▬	▬	▬	▬	▬	▬	▬	▬
12 e	●	●	●	●	●	●	●	●
RESULTS								
13 a	▬	●	●	▬	▬	▬	▬	●
13 b	▬	●	●	●	▬	▬	▬	●
13 c	▬	●	▬	▬	▬	▬	▬	▬
14 a	●	●	●	●	●	●	●	●
14 b	▬	▬	●	▬	▬	●	▬	●
15	●	●	●	●	●	●	●	●
16 a	●	●	●	●	●	●	●	●
16 b	●	●	▬	●	●	●	●	▬
16 c	▬	▬	▬	▬	▬	▬	▬	▬
17	●	●	●	●	●	●	●	●
DISCUSSION								
18	●	●	●	●	●	●	●	●
19	●	●	●	●	●	●	●	▬
20	●	●	●	●	●	●	●	●
21	●	●	▬	●	●	▬	●	▬
OTHER INFORMATION								
22	●	●	●	●	▬	●	●	▬

▬ Not mentioned in the article ● Mentioned in the article

occurred more than once, 882 were discarded after reading the title, and 455 articles were screened after reading the abstract. Finally, 46 articles were read completely, with 38 articles excluded for different reasons (Fig. 1). Two of the three authors (DPC and JGR) were blinded and selected the articles independently. If there were doubts about the inclusion of an article, the third researcher (DGS) decided whether to include the article.

3. Results

3.1. Characteristics of the studies

After applying the search engines following the PRISMA standards, we found that eight articles published between December 2002 and April 2022 fully met the inclusion criteria [16–18,26–30]. These articles were submitted to the STROBE checklist, as shown in Table 1, obtaining different scores for its 22 sections [31].

Of the eight articles that conformed to the criteria of this systematic review, one included patients with KF and grade IV CKD [16], and the rest included KF patients exclusively [17,18,26–30]. With respect to treatment, two articles included patients in supportive care or patients on dialysis (peritoneal dialysis and haemodialysis) [16,18], and the remaining articles included patients on dialysis treatment [17,28] or haemodialysis treatment [26,27,29,30]. Regarding the sociodemographic characteristics, we found that all the articles included the age and gender of the participants (1767 men vs. 1322 women), while six articles also added marital status (1603 married vs. 846 divorced, widowed, single, or otherwise) [16,18,27–30], four articles included educational level [16,27–29], and four articles included ethnicity or race [18,26,27,30]. All articles evaluated the symptoms through different scales, but three articles did not include a comorbidity index in their analysis [26,27,29] (Table 2).

Furthermore, Table 3 summarizes the methods used by the studies to extract symptom clusters in patients with KF, the instruments used to extract the prevalence of symptoms, the names given to the symptom clusters, and the symptoms included in each symptom cluster.

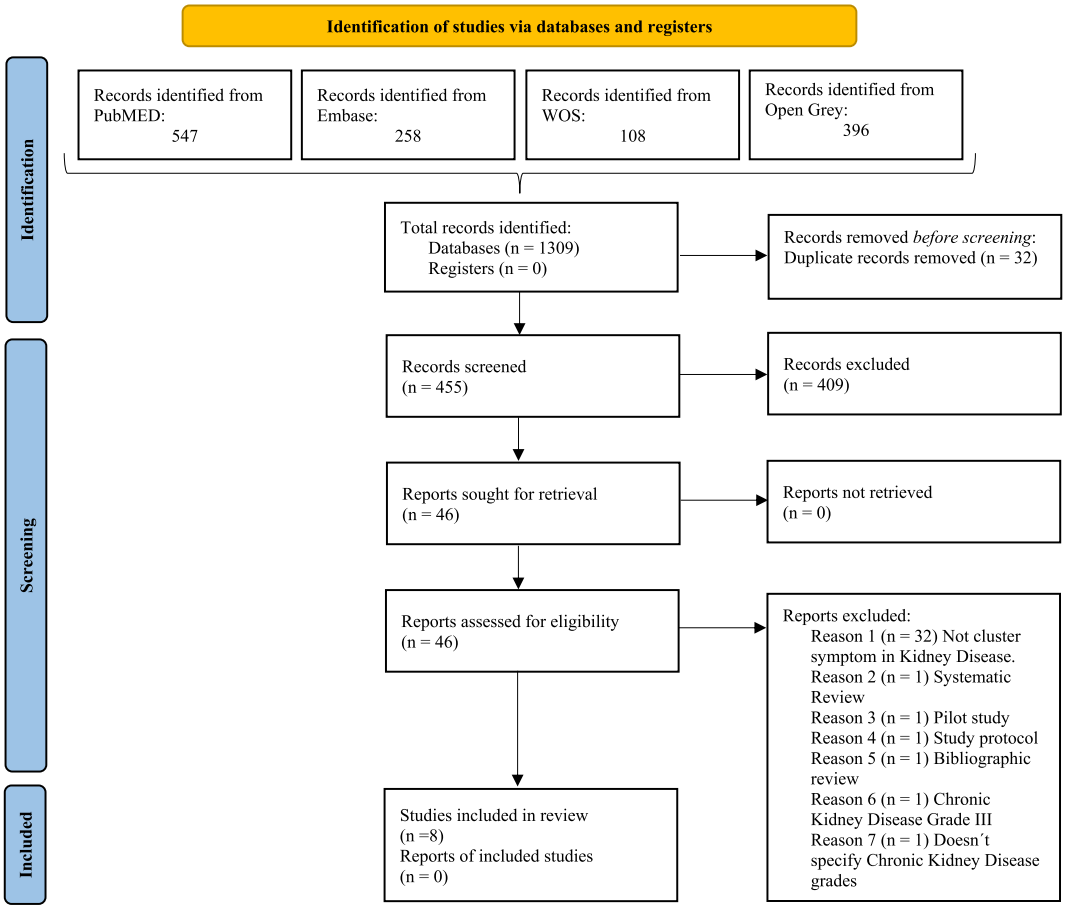

Fig. 1. Flow diagram of the study.

Table 2
Articles interventions and outcomes.

AUTHOR(S)	STUDY DESIGN	PARTICIPANTS PROFILE	COUNTRY OF ORIGIN	NUMBER OF PARTICIPANTS	TREATMENT MODALITY	POPULATION MEAN AGE ± SD	OUTCOMES (Measurement)
Almutary H., 2016	CSS	Adults with CKD grade IV or KF (SC, HD or PD)	Saudi Arabia	N = 436	n1 (G 4): 69 n2 (G 5 SC): 38 n3 (G 5 HD): 287 n4 (G 5 PD): 42	48.29 ± 14.86	• Demographic characteristics (age, gender, marital status, educational status or employment status) • Disease Characteristics (Davies comorbidity index 2002) • CKD symptoms (CKD symptom burden index) • Symptom correlation (KMO and Bartlett's test of Sphericity)
Amro A., 2014	CSS	Adults with KF (HD or PD)	Norway	N = 301	n1 (G 5 HD): 243 n2 (G 5 PD): 58	59.8 ± 16.2	• Sociodemographic data (age, gender, dialysis modality, time in dialysis, smokers (%), BMI, systolic blood presure, diastolic blood presure, haemoglobin, ferritin, blood urea nitrogen, albumin, creatine, among others) • Co-morbidity (CCI) • Depressive symptoms (Beck depression inventory [BDI]) • Health related QoL (Kidney disease quality of life short form- 36) • Physical symptoms (Using a 5 point Likert scale on the 12 symptoms of the Kidney disease quality of life short form – 36) • Symptoms correlation (KMO and Bartlett's test of Sphericity) • Relationships between symptom clusters and demographic and clinic characteristics and BDI and Health related QoL scores (Multivariate linear regresión analyses) • Effect of demographic, clinic characteristics and symtom clusters on BDI and QoL (Multivariate linear regresión analyses)
Curtin R., 2002	CSS	Adults with KF (HD)	Denver Colorado (USA)	N = 307	N (G 5 HD): 307	58.2 ± 15.10	• Demographic characteristics (age,

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Table 2 (*continued*)

AUTHOR(S)	STUDY DESIGN	PARTICIPANTS PROFILE	COUNTRY OF ORIGIN	NUMBER OF PARTICIPANTS	TREATMENT MODALITY	POPULATION MEAN AGE ± SD	OUTCOMES (Measurement)
							gender, race, cause of KF and diabetic status) • Symptom burden (List of 47 symptoms of literature review and transcripts of interviews, evaluated with a Likert scale) • Functioning and well-being (Medical outcomes study short form-36) • Physical function (Physical component summary [PCS]) • Mental function (Mental component summary [MCS]) • Symptoms correlation (Pearson correlation coefficients) • Relationships between symptom clusters, miscellaneous symtoms and PCS or MCS
Gutiérrez-Sánchez D., 2019	CSS	Adults with Kidney Failure (HD, PD or SC)	Málaga (Spain)	N = 123	n1 (G 5 SC): 63 n2 (G 5 HD): 47 n3 (G 5 PD): 16	*Total:* 63.3 ± 14.7 *S5 Dialysis:* 58.9 ± 15.5 *S5 CM:* 67.4 ± 12.6	• Sociodemographic and clinical characteristics (age, gender, ethnicity, marital status, disease severity in estimated glomelural filtration rate, months in SC and causes of CKD) • Symptoms (Spanish modified versión of Palliative Care Outcome Scale-Symptoms) • Estimated glomelural filtration rate (equation of CKD-epidemiology collaboration 2010 CKD-EPI) • Comorbidity (CCI) • Symptom correlation (Factor análisis with the KMO and Bartlett's test of Sphericity) • Association between disease severity and symptoms • Association between comorbidities and symptoms
Jablonski A., 2007	CSS	Adults over 21 years old with KF (HD)	United States	N = 130	N (G 5 HD): 130	60.22 ± 15.62	• Demographic data (age, gender, race, marital status, employment status,

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Table 2 (*continued*)

AUTHOR(S)	STUDY DESIGN	PARTICIPANTS PROFILE	COUNTRY OF ORIGIN	NUMBER OF PARTICIPANTS	TREATMENT MODALITY	POPULATION MEAN AGE ± SD	OUTCOMES (Measurement)
							level of education and time on dialysis) • Symptoms (Symptom list created by the authors and added to the health questionnaire developed by Parfrey and colleages, rating symptom experienced as intensity, frequency, distress and duration by a 5 point Likert scale) • QoL (Ferrans and Powers QoL index) • Symptom correlation [Factor análisis with the Kaiser-Mayer-Olkin (KMO) and Bartlett's test of Sphericity]
Thong M., 2009	CSS	Adults with KF (HD or PD)	Netherlands	N = 1553	n1 (G 5 HD):1010 n2 (G 5 PD): 543	*S 5 HD:* 63.2 ± 13.8 *S 5 PD:* 53.3 ± 14.6	• Demographic data (Gender, age, marital status and education level) • Clinical data (comorbidity with 3 point Davies score, cause of KF, renal function, erythropoietin administrated, laboratory level, BMI, functional or nutritional status) • Symptoms (Kidney disease QoL short form) • QoL (Short form 36 health survey) • Symptoms correlation (Chi-square test and Varimax rotation)
You A., 2022	CSS	Adults with KF (HD receiving KRT at least 4 consecutive weeks)	California (United States)	N = 122	N (G 5 HD): 122	*60* ± 13	• Sociodemographic data (Gender, age, race, marital status, insurance, BMI and weight) • Comorbidities • Dialysis treatment characteristics (Vascular access type)

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Table 2 (*continued*)

AUTHOR(S)	STUDY DESIGN	PARTICIPANTS PROFILE	COUNTRY OF ORIGIN	NUMBER OF PARTICIPANTS	TREATMENT MODALITY	POPULATION MEAN AGE ± SD	OUTCOMES (Measurement)
Yu I., 2012	CSS	Adults with KF (HD with 2 or 3 sessions per week and receiving KRT at least 3 months ago)	Taiwan	N = 117	N (G 5 HD): 117	52.27 ± 12.13	• Symptoms (Dialysis Symptom Index) • Demographic data (gender, age, marital status, education, occupation, incomes and religion) • Clinical data (Chronic disease, urine output, dialysis treatment duration in years, and laboratory results as hemoglobin, creatine or red blood counted among others • Symptoms (Somatic symptoms disturbance index) • Depression (Taiwanese depression scale) • Symptom correlation (Factor análisis with the KMO and Bartlett's test of Sphericity) • Correlation of demographic and clinic characteristics and symptom clusters

BDI: Beck depression inventory. **BMI:** Body mass index. **BPI:** Brief pain inventory. **CCI:** Charlson comorbidity index. **CKD:** Chronic kidney disease. **CSS:** Cross-sectional study. **ESAS:** Edmonton symptom assessment system. **G:** Grade. **HD:** Haemodialysis. **IADL:** Instrumental activities od daily life. **IPOS:** Integrated palliative care outcome scale. **KF:** Kidney Failure. **KMO:** Kaiser-Mayer-Olkin. **KRT:** Kidney Replacement Therapy. **MCS:** Mental component summary. **PCS:** Physical component summary. **PD:** Peritoneal dialysis. **PHQ-9:** Patient health questionnaire 9. **QoL:** Quality of life. **SC:** Supportive care. **VAS:** Visual analogue scale. **WHOQOL:** World health organization quality of life.

3.2. Cluster analysis and extraction method

The most used methodologies for identifying clusters of symptoms were principal component analysis [17,27–29], followed by exploratory factor analysis [16,18] and Pearson's correlation, alone [26] or in conjunction with Spearman's correlation [30]. To evaluate the symptoms experienced in patients with KF, with the goal of summarizing the symptom clusters, the studies used different scales, whether validated or not.

3.3. Measurement instruments

Among the scales employed in the articles included in this systematic review, KDQoL-SF36 was the most used [17,28]. KDQoL-SF36 is a widely used instrument in studying kidney disease, which, through 36 self-reported questions, tries to measure a patient's quality of life. KDQoL-SF36 is currently considered the gold standard [32]. It is important to highlight that KDQoL-SF36 has been validated in patients with KF; nevertheless, it is not currently validated in patients with grade IV CKD [2]. The remaining articles used scales developed by their authors themselves, such as the Somatic Symptoms Disturbance Index, 23 physical symptoms [19], or other surveys that measured between 11 and 47 symptoms [26,27]. The remaining articles used previously created scales, such as the Chronic Kidney Disease Symptom Burden Index, 32 symptoms [16], the Palliative Care Outcome Scale – Symptoms (Spanish version), 18 symptoms in patients with KF [18], or the Dialysis Symptom Index, which is a validated scale in patients with CKD symptoms [30].

3.4. Clusters

The studies included in this systematic review identified a minimum of two symptom clusters [18] and a maximum of eight symptom clusters [30], with the cluster of symptoms called "gastrointestinal problems" being the most frequent one [17,18,27,29,30]. One article unified the gastrointestinal cluster with cardiac and pulmonary symptoms [29]. Another article did not name this symptom cluster, but "cluster 2" of this article had similarities with the "gastrointestinal problems" clusters, so we were able to analyse these clusters of symptoms together [18]. Symptoms common to the "gastrointestinal problems" cluster were nausea and vomiting.

Symptom clusters called "neuromuscular symptoms/issues" or "mobility index" were equally mentioned in the studies [16,17,26,

Table 3
Symptom clusters.

AUTHOR(S)	METHODS USED TO IDENTIFY SYMPTOM CLUSTERS	INSTRUMENT USED TO MEASURE SYMPTOMS	SYMPTOM CLUSTERS	
			CLUSTER NAMES	SYMPTOMS INTO THE CLUSTER
Almutary H., 2016	Exploratoy factor analysis	**Chronic Kidney Disease Symptom Burden Index-** This scale check the severity, distress and occurrence of 32 chronic kidney disease symptoms	1 Uraemic 2 Neuromuscular 3 Skin	1 Naussea, dizziness/faintness, poor appetite, shortness of breath, chest pain and feeling "squeezed out" 2 Sore muscle, cramps and numbness in extremities 3 Dry skin and itching
Amro A., 2014	Principal component analysis determined by Eigenvalues >1, scree plot and factor loading >0.4	**Kidney Disease Quality of Life Short Form-36-** This scale measures 36 items, which are divided into eight subscales: role limitations due to emotional problems, role limitations due to physicall problems, physical function, pain, vitality, health condition, social function and mental health. The scores range from 0 to 100. High scores means better quality of life	1 Fluid volumen Symptoms 2 Neuromuscular symptoms 3 Sexual symptoms 4 Psycological symptoms 5 Gastrointestinal symptoms	1 Cough, chest pain, shortness of breath, difficulty concentrating and light headedness or dizziness 2 Muscle sorenness and numbness or tingling in feet 3 Difficulty become sexual aroused and low interest in sex 4 Worrying, sadness, depression, feeling anxious and nervous 5 Nausea and vomiting
Curtin R., 2002	Pearson correlation coefficients to assess the association between symptoms and clusters created through the values of the individual symptom included in each cluster	**List of 47 symptoms made by authors** and evaluated with a Likert scale- This list was made by common symptoms in recent surveys and the analysis of more than 100 interviews with dialysis patients. Symptoms posted at this survey were suffered by the patients during one month as mínimum.	1 Fatigue/Sleep index 2 Sexual concerns index 3 Mobility index 4 Miscellaneous symptoms	1 Feeling tired, lack of energy, trouble falling asleep, trouble trying to be awake, not getting enough sleep and waking up along the nigth 2 Inability to enjoy sex, difficulty becoming aroused, and lack of interest in sex 3 Muscle soreness, muscle weakness, joint/bone pain and numbness in extremities 4 Itchy skin, dry mouth and restless legs
Gutiérrez-Sánchez D., 2019	Exploratoy factor analysis	**Palliative Care Outcome Scale – Symptoms (Spanish versión)-** This scale measures 18 tipical symptoms in chronic kidney disease	1 Cluster 2 Cluster	1 Weakness, poor mobility, mouth problems, feeling anxious or depressed and trouble to sleep 2 Diarrhea, naussea and vomiting
Jablonski A., 2007	Principal component analysis using varimax rotation (Kaiser-Guttman rule; scree plot; and theoretical soundness) Eigenvalues >1	**List of symtoms created by authors** and added to the health questionnaire developed by Parfrey and colleages- This tool include 11 physical symptoms and was designed to measure the severity, frequency and distress of symptoms experienced by kidney disease patients. This tool measures symptom experienced with a Likert scale, being 0 points the symptoms aussence and 4 to 20 the puntuation to the bad symptom experiences.	1 Energy/Vitality 2 Cardiac related problems 3 Pain/Confort 4 Gastrointestinal problems	1 Tiredness, muscle weakness and sleeping problems 2 Shortness of breath and chest pain 3 Headache, joint pain and itching 4 Nausea, cramps, vomiting and abdominal pain
Thong M., 2009	Principal component analysis using varimax rotation (Eigenvalues >1)	**Kidney Disease Quality of Life Short Form-** This scale measures 36 items were are divided into eight subscales: role limitations due to emotional problems, role limitations due to physicall problems, physical function, pain, vitality, health condition, social function and mental health. The scores ranging from 0 to 100. High scores means better quality of life	1 Uraemic syndrome 2 Neuromuscular problems 3 Skin problems	1 Feeling dizzy/faint, naussea, feeling "squeezed out", lack of appetite and shortness of breath 2 Numbness in hands or feet, sore muscles and chest pain 3 Dry skin and itchy skin
You A., 2022	Pearson correlation and Spearman correlation to examine correlations of individual symptoms from the Dialysis Symptom Index	**Dialysis symptom Index-** This scale works as a validated instrument to measure the unpleasant symptoms in patients with Kidney Failure. This scale its formed by 30 specific symptoms whose will be evaluated with a Lickert scale from 0 to 4 (where 0 indicates ausence and 4	1Gastrointestinal System 2 Cardiopulmonar System 3 Dermatologic System 4 Psychiatric System 5 Sleep System 6 Pain System	1 Nausea, constipation, vomiting, decreased appetite and diarrhea 2 Swelling in legs, shortness of breath and cough 3 Dry mouth, dry skin and itching 4 Feeling nervous, worrying, feeling anxious, feeling sad and feeling irritable

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Table 3 (*continued*)

AUTHOR(S)	METHODS USED TO IDENTIFY SYMPTOM CLUSTERS	INSTRUMENT USED TO MEASURE SYMPTOMS	SYMPTOM CLUSTERS	
			CLUSTER NAMES	SYMPTOMS INTO THE CLUSTER
		indicates very uncomfortable symptoms)	7 Neurologic System 8 Endocrine System	5 Trouble falling asleep, restless legs, feeling tired/lack of energy and trouble staying asleep 6 Bone/joint pain, muscle cramps, muscle soreness and chest pain 7 Numbness or tingling in feet, lightheadeness/dizziness, difficulty concentration and headache 8 Decreased interest in sex and difficulty becoming sexually aroused
Yu I., 2012	Principal component analysis using varimax rotation (Eigenvalues >1; scree plot; and factor loading >0.3)	**Somatic Symptoms Disturbance Index-** This scale was developed by authors of this study and was based upon the Physical Symptom Distress Scale developed by Chiou at 1998 and the Dialysis Symptom Index developed by Weisbord at 2005. This index contains 23 items bases on physical symptoms. Measurement of symptoms were made by a Likert scale.	1 Energy and sensory disconfort 2 Gastrointestinal and cardiac-pulmonary symptoms 3 Cardiovascular symptoms 4 Electrolyte imbalance	1 Tiredness, muscle weakness, poor vitality and dry mouth 2 Naussea, vomiting, chest pain and tightness 3 Vertigo, dyspnea, headache, shortness of breath 4 Arrhythmia, numbness, restless legs and joint pain

28], including muscle pain or limb numbness as symptoms common to these clusters. Regarding the "sexual symptoms/concerns" clusters, three articles presented a shared symptomatology [17,26,30], although one study called it the "endocrine system" cluster [30]; common symptoms in this cluster were low interest in sex and difficulty becoming sexually aroused. Three articles also distinguished a "skin problems" or "dermatologic system" cluster [16,28,30], with symptoms such as dryness or itching of the skin. The following symptom clusters occurred in equal measure: "uraemic" [16,28], "energy/vitality or sensory discomfort" [27,29], and "cardiac-related problems" or "cardiac-pulmonary symptoms" [27,29]. Symptoms common to the "uraemic" cluster were lack of appetite, feeling squeezed, feeling weak or dizzy, and difficulty breathing. Fatigue or muscle weakness was common in the "energy/vitality" or "sensory discomfort" clusters. Finally, in the "cardiac-related problems" or "cardiac-pulmonary symptoms" clusters, we find chest pain as a common symptom.

4. Discussion

4.1. Summary

This systematic review aims to describe the symptom clusters of KF patients. Scientific evidence indicates that some of the symptoms experienced by patients with CKD are presented in clusters. Symptom clusters can be defined as the presence of two or more concurrent symptoms that, with the same cause, occur independently of other symptoms. Providing treatment in clusters produces a passive relief of the cluster symptoms. This treatment allows healthcare staff to develop personalized treatment strategies [33].

Therefore, through this systematic review, we aimed to provide further information on the symptom clusters that appear in KF patients.

4.2. Study population

The population sample included in the selected articles was variable. The sample included haemodialysis patients (2263 patients) [16–18,26–30], peritoneal dialysis patients (659 patients) [16–18,28], supportive care patients (101 patients) [13,16], and grade IV CKD patients (69 patients) [16].

The articles tended to focus on exploring KF patients, except for one article, which included grade IV CKD patients [16]. Sample selection differences may be due to patients' accessibility. In fact, a systematic review that assessed KF patients' quality of life indicated that about 80 % of individuals received kidney replacement therapy through haemodialysis [34]. Another systematic review reported a higher age, chronic pathologies, and higher mortality in KF patients with supportive care treatment [35], which may explain why most patients in the sample were in haemodialysis treatment.

4.3. Cluster analysis and extraction method

Symptom clusters were extracted using principal component analysis [17,27–29], exploratory factor analysis [16,18], or Pearson's correlation coefficient, alone [26] or in conjunction with Spearman's correlation coefficient [30].

Pearson's correlation coefficient was applied to evaluate symptom association through Cronbach's alpha, calculated to test internal validity and internal consistency. Symptom correlation was measured using Pearson's correlation coefficient, and multiple linear regression was performed to measure the relationship between symptoms and patients' characteristics [26]. High values of Pearson's correlation coefficient indicate a low probability of randomly obtaining the data ($Rp > 0.74$). Pearson's correlation coefficients could establish factor coincidences but never cause-effect relationships between factors [36]. Pearson's correlation coefficient values range from −1 (negative correlation) to 1 (positive correlation) [37]. In addition to Pearson's correlation coefficient, Spearman's correlation coefficient was used because it does not require a normal distribution of the variables [37]. In this way, both methods can be used to evaluate correlations between symptoms [30].

Articles that used principal component analysis opted for the Kaiser-Meyer-Olkin measure of sample adequacy or Bartlett's test of sphericity and varimax rotation [17,27,29]. Thong et al. [28] did not mention the methods for the extraction of components. Some studies extracted the components by eigenvalue, scree plot, and factor loads [17,29], while others used the Kaiser-Guttman rule, scree plot, and theoretical soundness [27]. Main component analysis is often used to reduce the number of shared variables [38]. Factor loads <0.40 are considered low loads; a small sample size could lead to low factor loads. Larger samples reached more precise solutions [39]. All articles found factor loads ≥ 0.40 except in a haemodialysis sample of one article (factor load 0.364) [17]. Using an orthogonal rotation method such as varimax assumes independence between factors; using oblique rotation methods assumes independence between data [38,39].

The remaining articles applied exploratory factor analysis using Kaiser-Meyer-Olkin sample adequacy, Bartlett's sphericity test, eigenvalues ≥ 1, and oblique rotation methods, establishing a factor load cutoff point at 0.50 [16,18]. Using an oblique rotation method avoids assuming independence between the extracted factors [38,39]. The establishment of a 0.50 cutoff point is consistent with the achievement of medium factor loads (factor load >0.40) [39]. As methodological differences, one article maintained symptoms despite the factor loads charging into more than one symptom cluster [16], while in another article, if a symptom charged simultaneously into more than one symptom cluster, it was eliminated in the cluster with a minor factor load [18].

4.4. Measuring instruments

Several validated instruments were used to measure the occurrence of symptoms in patients with KF, such as the Kidney Disease Quality of Life Short Form-36 [17,28], the Dialysis Symptom Index [30], the Chronic Kidney Disease Symptom Burden Index [16], and the Palliative Care Outcome Scale – Symptoms [40]. In addition, some symptom lists created by the articles' authors were used to evaluate the presence of symptoms [26,27,29].

The Kidney Disease Quality of Life Short Form-36 and the Palliative Care Outcome Scale – Symptoms are considered gold standards for assessing the quality of life of CKD patients [32] and the presence of symptoms in KF patients, respectively [40]. The Dialysis Symptom Index was validated [41] and adapted for many languages [42,43]. The Chronic Kidney Disease Symptom Burden Index consists of an adaptation of the Dialysis Symptom Index and evaluates symptoms in grade IV CKD and KF patients [44].

Surveys are common in scientific studies and are employed to measure complex processes. By using validated surveys, researchers ensure that the results they obtain are reliable. The psychometric properties of a scale inform researchers how reliable the survey is [45]. That is the reason why researchers should select validated scales, which ensure that generalizable results are produced.

4.5. Clusters of symptoms

The "gastrointestinal problems" cluster included symptoms such as nausea and vomiting [17,18,27,29,30]. However, some studies included nausea and vomiting in the "uraemic" cluster [16,28], while another study did not make reference to nausea or vomiting at all [26].

Symptoms of muscle pain or numbness of extremities were included in the "neuromuscular symptoms/problems" or "mobility index" cluster [16,17,26,28]. Joint pain was included in the "pain/comfort" cluster [27] or in the "pain system" cluster, while numbness of feet was included in the "neurologic system" cluster [30] or in the "electrolyte imbalance" cluster [29]. However, some studies did not include these symptoms at all [18].

The symptoms that composed the "uraemic" cluster were lack of appetite, feeling squeezed, feeling weak or dizzy, and difficulty breathing [16,28]. Difficulty breathing was also included in the "cardiac-related problems" or "cardiovascular symptoms" clusters [27,29]. In addition, shortness of breath was included in conjunction with dizziness in the "fluid volume symptoms" cluster [17]. Weakness was included in "cluster 1" [18], and shortness of breath, weakness, and dizziness were included in the "cardiopulmonary system", "sleep system", and "neurologic system" clusters, respectively [30]. Some articles included symptoms such as feeling tired or lack of energy in the "fatigue/sleep index" cluster [26].

Symptoms included in the "sexual symptom concerns" or "endocrine system" cluster were a low interest in sex and difficulty becoming sexually aroused [17,26,30].

The "skin problems" or "dermatologic system" cluster included symptoms such as dry or itchy skin [16,28,30]. Some studies included itchy skin in the "miscellaneous symptoms" or "pain/comfort" clusters [26,27].

Besides the inclusion of fatigue or muscle weakness in the "energy/vitality or "sensory discomfort" cluster [27,29], weakness was included in "cluster 1" [18] and in the "sleep system" cluster [30]. In addition, muscle weakness was included in the "mobility index" cluster [26].

Finally, chest pain was included in the "cardiac-related problems" or the "cardiac-pulmonary symptoms" cluster [27,29]; the same symptom was also included in several other clusters, such as the "uraemic" [16], "fluid volume symptoms" [17], "neuromuscular

problems" [28], and "pain system" [30] clusters.

4.6. Clinical implications and interventions for symptom cluster management

The identification of symptom clusters in KF has clinical relevance, and this research could facilitate the development of adequate intervention strategies, simplifying the treatment offered to patients and even reducing the side effects of treatments [46]. Symptom clusters may share a biological aetiology, and their resolution can relieve accessory symptoms [47]. The symptom clusters may arise because of a shared aetiology, symptoms that trigger the generation of other symptoms, or the side effects of treatments [48]. For KF patients, the symptom burden produces a worse quality of life, lower productivity, and increased morbidity or mortality. In cancer patients, evidence supporting the benefits of treatment based on symptom clusters is increasing [49–51]. Applying this type of treatment to KF patients would provide health professionals with different strategies for symptom management [16]. There is some evidence showing that KF symptoms are similar to symptoms found in advanced stages of several other diseases, such as cancer, chronic obstructive pulmonary disease, congestive heart failure, and AIDS [12,52]. Patients are often more interested in treatments that reduce the severity of symptoms than in treatments that prolong life expectancy [47]. Knowledge of symptom clusters improves the health outcomes of patients, allows the anticipation or investigation of related symptoms, and improves treatment efficiency [48]. The “uraemic” and “neuromuscular” clusters have been associated with variations in the physical status of patients, and offering management interventions to those clusters would improve the functional status of patients and, at the same time, their psychological well-being [17].

Treatment offered based on symptom clusters is complex but beneficial for patients. Various interventions have been shown to improve patients’ quality of life with a non-pharmacological approach based on psychoeducation, physical exercise, sensory therapy, or artistic and cognitive strategies for learning self-control techniques such as relaxation or directed imagination [48,53,54]. Non-pharmacological strategies are based on symptom appearance or symptom exacerbation due to drug use, so non-pharmacological treatment can be used as a reliable complementary treatment [54] In addition, it has been shown that patients prefer non-pharmacological techniques adapted to their needs. Therefore, healthcare teams should consider implementing non-pharmacological techniques in addition to pharmacological ones [48].

4.7. Strengths and limitations

To perform this systematic review, we carried out an exhaustive and independent bibliographic search. The PRISMA standards were followed [24]. The systematic review was properly recorded in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42023388061. The articles were selected according to the STROBE initiative checklist [25]. The articles were selected by two authors, and if they did not agree, a third author decided on the inclusion or exclusion of the article.

The main weakness was that it was not possible to perform a meta-analysis due to the methodology used in the articles analysed. In addition, the restriction to articles written in English or Spanish meant that not all articles on KF symptom clusters could be considered.

5. Conclusions

The aim of this systematic review was to provide a scientific approach to what is known about clusters of symptoms in KF. Nowadays, scientific studies tend to show that offering treatment based on clusters of symptoms is better than treatment based on isolated symptoms, thereby improving the quality of life of patients and avoiding the occurrence of unpleasant symptoms. The most frequent symptom clusters in KF were, in order of frequency, "gastrointestinal problems" (nausea or vomiting), "neuromuscular symptoms/problems" (fatigue or muscle weakness), "sexual symptom concerns" (low interest in sex or difficulty becoming sexually aroused), and "skin problems" (dry skin or skin itching). "Uraemic" (lack of appetite, feeling squeezed, feeling weak or dizzy, and difficulty breathing), "energy/vitality" (fatigue or muscle weakness), and "cardiac-related problems" (chest pain) clusters were less frequent.

Knowing the symptom clusters in KF constitutes the first step in establishing personal strategies for managing symptomatology in KF patients, instead of managing isolated symptoms. The treatment based on cluster symptoms is more effective and produces relief of associated symptoms. The identification of symptom clusters in KF has clinical relevance, and this research could facilitate the development of adequate intervention strategies, simplifying the treatment offered to patients and even reducing the side effects of treatments. Further investigations should examine treatment lines based on symptom cluster management in KF patients.

CRediT authorship contribution statement

Jaime Gomariz-Ruiz: Writing – original draft, Validation, Supervision, Methodology, Investigation. **David Pérez-Cruzado:** Writing – review & editing, Writing – original draft, Funding acquisition, Data curation, Conceptualization. **Daniel Gutiérrez-Sánchez:** Writing – review & editing, Data curation, Conceptualization.

Registration

The protocol for this systematic review was recorded in the International Prospective Register of Systematic Reviews (CRD42023388061).

Ethics declarations

No applicable to this systematic review.

Data and code availability

No data was used for the research described in the article.

Funding sources

No founding sources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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