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Patient-Reported Outcomes

Prevalence of Symptoms and Symptom Clusters of Patients on Dialysis in Uruguay

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ABSTRACT

Background: Patients on dialysis report high levels of symptom burden. The association of these symptoms may have an increased deleterious effect on the patients well-being. **Objective:** This study aimed to assess the prevalence of symptoms, to identify symptom clusters, and to describe the impact of concurrent symptoms on physical and emotional well-being in a sample of dialysis patients. **Methods:** Data of the first assessment of a longitudinal study aimed to assess patient-reported outcomes in dialysis were included here. The KDQOL-36 PCS, MCS and Symptom Subscale, the Hospital Anxiety and Depression Scales and the Epworth Sleepiness Scale were analyzed. The ICLUST procedure was followed for hierarchical cluster analyses. **Results:** Of the 512 eligible patients, 493 accepted to participate, 43.6 % were female, with mean age of 60.9 (SD=16.7). Treatment modality was HD in 87.6% of patients. Most prevalent and severe symptoms were muscle sores, cramps, washed out, dry skin, and itchy skin, Moderate to severe pain was reported by 25%, and daily somnolence by 12.4% of the patients. Five first level symptom clusters were identified as cutaneous, cardiac, digestive, sensory-motor, energy. Both, the presence of any cluster and cluster scores were significantly associated with lower physical and mental quality of life and a higher psychological distress. **Conclusions:** Our study confirms the presence of high symptom burden in dialysis patients in Uruguay. Several symptom clusters were identified having significant impact on the patients well-being. The identification of symptom clusters can help to understand common underlying pathways. It is possible that the management of symptom clusters may reduce symptom burden in these patients.

Keywords: dialysis, hierarchical cluster analysis, symptom clusters, Uruguay.

Introduction

There is an increasing concern over the study of the prevalence and severity of symptoms produced by end-stage renal disease (ESRD),[1] the comorbidities associated with it, and the effect of renal replacement treatments (RRTs). Several studies have shown that patients with ESRD suffer from a myriad of distressing symptoms,[2] and that the symptom burden increases in the advanced stages of the disease.[3,4] It was determined that symptom burden had a significant impact on functional status and quality of life,[5] which in turn were associated with morbidity and mortality in patients with ESRD,[6,7] concluding that better symptom management may possibly have a positive effect on global outcomes.

Many patients experience multiple concurrent symptoms during the disease trajectory, which may have a larger impact than do isolated symptoms. Symptom clusters were originally defined in patients with cancer as 3 or more concurrent symptoms related to one another.[8] This groundbreaking article highlighted the fact that frequent concurrent symptoms may have a synergistic effect on morbidity and functional capacity. It has been remarked that an understanding of symptom cluster in patients could help clinicians develop more comprehensive and useful assessment tools, as well as better-targeted and more effective interventions.[9] A review of studies aimed at identifying associations among symptoms in oncology found that symptom clusters (1) could be explained by common physiopathological pathways, (2) could be managed by a particular treatment strategy, or (3) might have detrimental effects on outcomes such as functional status, quality of life, costs, or morbidity and mortality.[10]

In the field of nephrology, only a few studies were carried out to describe concurrent symptoms[11,12]; to study the association of symptom clusters with functional status, depressive mood, and quality of life[13-15]; to depict the possible impact on mortality[16]; or to describe changes after renal transplantation.[17] Appendix Table 1 in

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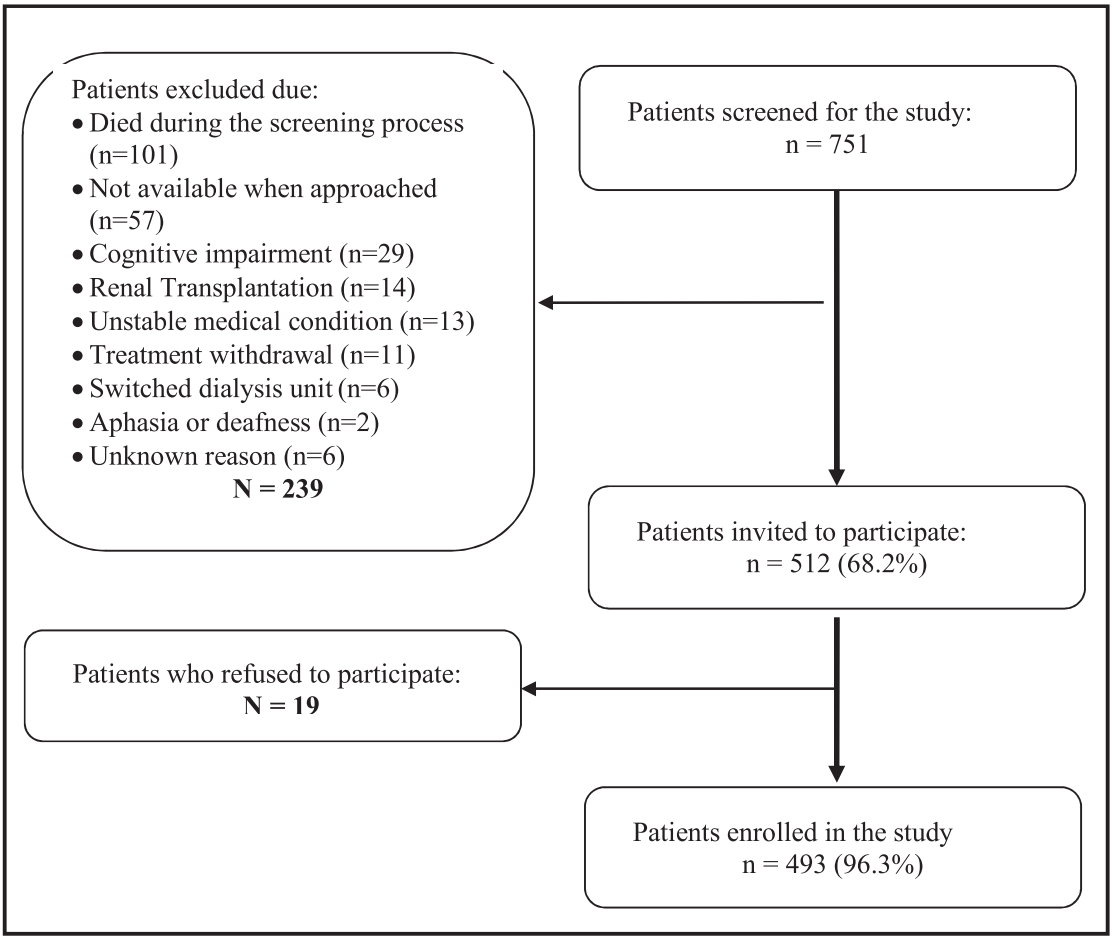

Fig. 1 – Flow chart of the data collection process.

Supplemental Materials found at 10.1016/j.vhri.2018.10.003 provides the characteristics of these studies, including aims, methodology, and main outcomes. Most of the studies used principal-component analysis for symptom clustering. None of them included Latin-American Spanish-speaking patients.

The present study aimed at assessing the prevalence of symptoms, identifying symptom clusters, and studying the impact of symptom clusters on physical and mental well-being in a sample of patients on dialysis in Uruguay. Although the scope of research is limited to a national sample of patients, it provides a reference that could be considered by other researchers in the region. In addition, an original aspect of our study was that the method used for setting symptom clusters was a hierarchical cluster analysis (HCA).

Methods

The study sample consisted of a large prospective observational cohort of incident and prevalent patients on RRTs for ESRD from 11 dialysis centers, 7 from the capital city Montevideo and 4 from other parts of the country. All patients from the participating centers who were fluent in Spanish, 18 years or older, and undergoing either hemodialysis (HD) or peritoneal dialysis (PD) were invited to participate. Patients with cognitive impairment (Mini-Mental State Examination[18] score of <20 points) or severe psychiatric disorders or who were unable to sign an informed consent were excluded. Incident patients were approached 3 months after starting dialysis once clinical stability had been obtained; prevalent patients were approached on the anniversary of their admission for dialysis. Patients filled out the questionnaires during the dialysis session via self-administration. A research assistant was available for those patients who required interview administration. The recruitment process is shown in Appendix Figure 1 in Supplemental Materials found at 10.1016/j.vhri.2018.10.003.

Measures

The Kidney Disease Quality of Life 36 items (KDQOL-36)[19] is the shorter version of the KDQOL short form,[20] which makes it easier to apply and reduces the burden of administration while maintaining the psychometric properties of the longer version. A previous study in South American patients showed good reliability and validity.[21] The generic module of the KDQOL-36 consists of 12 items from the Medical Outcome Study short form 12. The items are recoded and aggregated so that 2 summary measures are calculated: the physical component summary (PCS) and the mental component summary (MCS). The PCS and the MCS are standardized for the US population norms so that the population mean corresponds with a 50-point score and an SD of 10 points.[22,23] The specific module has 24 items grouped into 3 subscales specific to renal patients: Symptoms (12 items), Burden of the renal disease (4 items), and Effects of the renal disease on daily life (8 items). The scores are transformed into a range from 0 to 100, with higher scores meaning better health status for that dimension.

Eleven physical symptoms listed in the KDQOL-36 were included in the analyses: muscle soreness, chest pain, itchy skin, dry skin, shortness of breath, faintness or dizziness, lack of appetite, "washed out" or "drained," numbness in extremities, nausea, and upset stomach. The item "problems with the vascular access or peritoneal catheter" was excluded. The response categories ranged from "extremely bothered" (0 points) to "not bothered at all" (100 points) during the last 4 weeks. Symptoms and clusters were rated as "present" if any score other than 100 was endorsed. Symptom scores and cluster mean scores of 50 points or lower were rated as "moderate to severe."

Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS),[24] a brief, reliable self-reported measure of anxiety and depression in hospitalized and ambulatory medical patients, also used in primary care and research, consisting of 7 items for anxiety (HADS-A) and 7 for depression (HADS-D). Cutoff scores of more than 8 points in the HADS-A and HADS-D proved to be appropriate to identify cases of anxiety disorder and depression, respectively.[25] The Spanish version of the HADS is available from the publisher (GL Assessment, www.gl-assessment.co.uk).

Pain was assessed using the visual analogue scale. Functional status was rated using the Eastern Cooperative Oncology Group Performance Status Rating, a 5-point scale[26] ranging from a 0 score (asymptomatic and fully ambulatory) to 4 (not being able to leave bed), which was filled out by the patient. Clinical and laboratory data were obtained from the Uruguayan Registry of Dialysis. Sociodemographic data were collected from the patients. Socioeconomic status was assessed using the Graffar Social Stratification Scale.[27] This instrument rates the occupation, level of education, household income, and housing, grouping the patients into 5 levels: (1) upper class, (2) upper middle class, (3) middle class, (4) middle low class, and (5) low class.

The Epworth Sleepiness Scale[28] was used to assess the impact of sleep disorders. The questionnaire asks about the possibility of falling asleep during 8 common daily situations. Categories of daily somnolence were as follows: 0 to 6 points: no daily somnolence; 7 to 13 points: light; 14 to 19 points: moderate; and 20 to 24 points: severe daily somnolence.

Statistical Analyses

Symptom clusters were defined as 2 or more associated and coexistent symptoms. The all-possible symptom approach was used to select the symptoms for cluster identification. The main characteristics of this method, as opposed to those of the most common symptom approach, are that (1) researchers target all potential

Table 1 – Sociodemographic characteristics of the sample.

Characteristic	N	%	Characteristic	N	%
Sex			Source income		
Male	277	56.4	Live off investments	17	3.8
Female	214	43.6	Honoraria or utilities	119	26.5
Age (y)	60.9 (16.7)		Regular salary	183	40.8
Range	18-96		Paid per job, small business	35	7.8
Marital status			Social welfare	95	21.2
Married	231	47.1	Family monthly income ($)		
Unmarried couple	27	5.5	Mean ± SD	661 ± 550	
Divorced/separated	80	16.3	Median	500	
Widow	81	16.6	Range	0-3502	
Single	71	14.5	Profess religion		
Family living			No	268	55.4
Lives alone	59	12	Yes	216	44.6
Lives with family	399	81.5	Type of religion		
Lives with others	20	4.1	Catholic	148	68.8
Lives in institution	12	2.4	Protestant	3	1.4
Level of education			Evangelic	47	21.9
Primary school incomplete	11	2.3	Jewish	4	1.9
Primary school complete	181	37.2	Afro-Uruguayan	1	0.5
High school incomplete	197	40.5	Other	12	5.5
High school complete	67	13.8	Occupation		
College/university	30	6.2	Professional, businessman, executives	26	5.6
Employment			Commerce, producer, technicians	37	7.9
Full-time	51	10.6	Small business, services	105	22.5
Part-time	36	7.6	Skilled worker	131	28
Retired	319	66.6	Day laborer, handyman	168	36
Social welfare	1	0.2	Housing		
Unemployed	13	2.7	Optimal conditions, luxurious	2	0.4
Medical leave	12	2.5	Optimal conditions, nonluxurious	87	18.1
Others	47	9.8	Good sanitary conditions	279	58.1
Performance status			Shortcoming sanitary condition	101	21
0	237	48.6	Inadequate sanitary environment	11	2.3
1	109	22.3	Graffar interpretation		
2	114	23.4	Upper class	18	3.8
3-4	28	5.7	Upper middle	47	9.7
			Middle	141	29.4
			Middle low	231	48.1
			Low	43	9

symptoms that patients might experience to identify clusters rather than including only the most frequent symptoms; (2) clusters are obtained by statistical analysis, instead of assuming clusters on the basis of previous empirical studies; (3) several clusters can be identified, not only those defined by the researcher; and (4) clusters can include a larger number of symptoms.

The analytic technique used to define clusters was an HCA. Item cluster analysis[29] was used to group symptoms into clusters. This method uses an algorithm that hierarchically links symptoms, which can help understand how symptoms relate to one another. For each cluster, reliability was estimated by means of the α (split half correlation) and β (mean of the correlations of the worst split half) coefficients. The clusters were combined if both coefficients increased in the new cluster.

The advantage of this technique with regard to models of multiple regression, or to exploratory or confirmatory factor analysis, is that it retains the original values of the observed variables without information loss and, in turn, allows for setting an item hierarchy by cutting the tree of aggregation at different levels, something highly useful when working with composite scales as in the case of the present study.

An individual symptom cluster score was created for each of the symptom clusters identified by HCA, consisting of the mean score for all symptoms included in the cluster. These scores ranged from 0 (worst perceived) to 100 (best perceived).

Simple linear regression analysis was used to study the association among variables, considering each symptom cluster and cluster scores as independent variables and considering health-related quality of life (HRQOL) evaluated by the PCS and MCS scores of the KDQOL-36 short form 12 scale as well as depression and anxiety assessed with the HADS as dependent variables. Two regression models were studied, one introducing symptom clusters as dummy variables (present = 1) and the other including cluster scores as continuous variables.

Ethical Considerations

The project was approved by the institutional review boards of the participating institutions. Patients were extensively informed about the characteristics of the research, participated voluntarily, and signed informed consent forms.

Results

Appendix Figure 1 in Supplemental Materials shows a flowchart of the data collection process. Of the 512 eligible patients, 493 accepted to participate (96.3% response rate), with a mean age of 60.9 ± 16.7 years (range 18-96 years); 43.6% were females and 47.1% were married, with relatively low education (only 20% completed high school or university) and low income (49.0% ranked in middle low or low socioeconomic classes). Most were retired (66.6%) and fully ambulatory (70.9% reported Eastern Cooperative Oncology Group Performance Status 0-1) (Table 1).

Table 2 – Biological variables.

Tx modality (HD) n (%)	413 (83.6)
(PD) n (%)	81 (16.4)
Mean Time in dialysis months (SD)	66.8 (75.4)
Median Time in dialysis months (Interquartile range)	46.3 (24.0-85.1)
Mean Kt/V (SD)	1.3 (0.6)
Kt/V > 1.20 n (%)	261 (69.6)
Mean Urea g/l (SD)	1.3 (0.3)
Urea >1.7g/l n (%)	31 (8.3)
Mean Haematocrit (SD)	33.9 (4.6)
Mean Haemoglobin g/l (SD)	11.2 (1.5)
Haemoglobin >10g/l n (%)	329 (87.7)
Mean Serum calcium mg/dL (SD)	8.5 (1.0)
Serum calcium >10.5 n (%)	0 (0.0)
Mean Ferritin mc/ml (SD)	296.9 (302.2)
Mean Albumin g/l (SD)	2.4 (1.9)
Albumin >3.5 g/l n (%)	217 (57.9)
Mean Total cholesterol (mmol/l) (SD)	172.2 (46.1)
Mean Systolic Blood Pressure (mmHg) (SD)	130.1 (15.2)
Diabetes n (%)	84 (23.9)
Current smoking n (%)	57 (12.4)

HD indicates hemodialysis; PD, peritoneal dialysis.

As for the clinical and laboratory data (Table 2), treatment modality was HD in 83.6% of patients, mean time in treatment was 66.8 ± 75.4 months (median 46.3 months; interquartile range 24.0-85.1), and 23.9% of patients had diabetes.

The mean number of symptoms reported was 2.3 ± 2.7 (median 3.5). Only 24 patients (4.8%) were asymptomatic when answering the questionnaire, 207 (41.9%) reported 1 to 3 symptoms, 188 (38.1%) reported 4 to 6 symptoms, 69 (14%) reported 7 to 9 symptoms, and 6 (1.2%) reported 10 to 11 symptoms.

Most prevalent symptoms endorsed in the KDQOL-36 Symptoms Scale were muscle soreness (59.0%), cramps (57.1%), washed out (51.1%), dry skin (48.6%), and itchy skin (43.7%), as presented in Table 3. These symptoms were also the most frequently

Table 3 – Prevalent symptom: prevalence of categories moderate to severe endorsed for each symptom, and symptom mean scores.

Symptom	Symptom present (%)	Moderate to severe (%)	Symptom score, mean ± SD	Median
Muscle soreness	58.7	20.8	70.1 ± 31.4	75
Cramps	57.1	14.5	74.2 ± 28.6	75
Washed out	51.1	13.7	75.9 ± 28.8	75
Dry skin	48.6	18.0	75.5 ± 30.4	100
Itch	43.7	13.9	78.9 ± 28.5	100
Numbness of extremities	31.8	11.0	84.4 ± 27.4	100
Nausea/vomiting	28.6	6.3	87.0 ± 23.4	100
Lack of appetite	22.5	6.4	89.2 ± 22.6	100
Shortness of breath	21.2	4.5	90.5 ± 20.9	100
Faintness	19.2	2.7	92.1 ± 18.1	100
Chest pain	15.3	3.9	92.9 ± 18.7	100

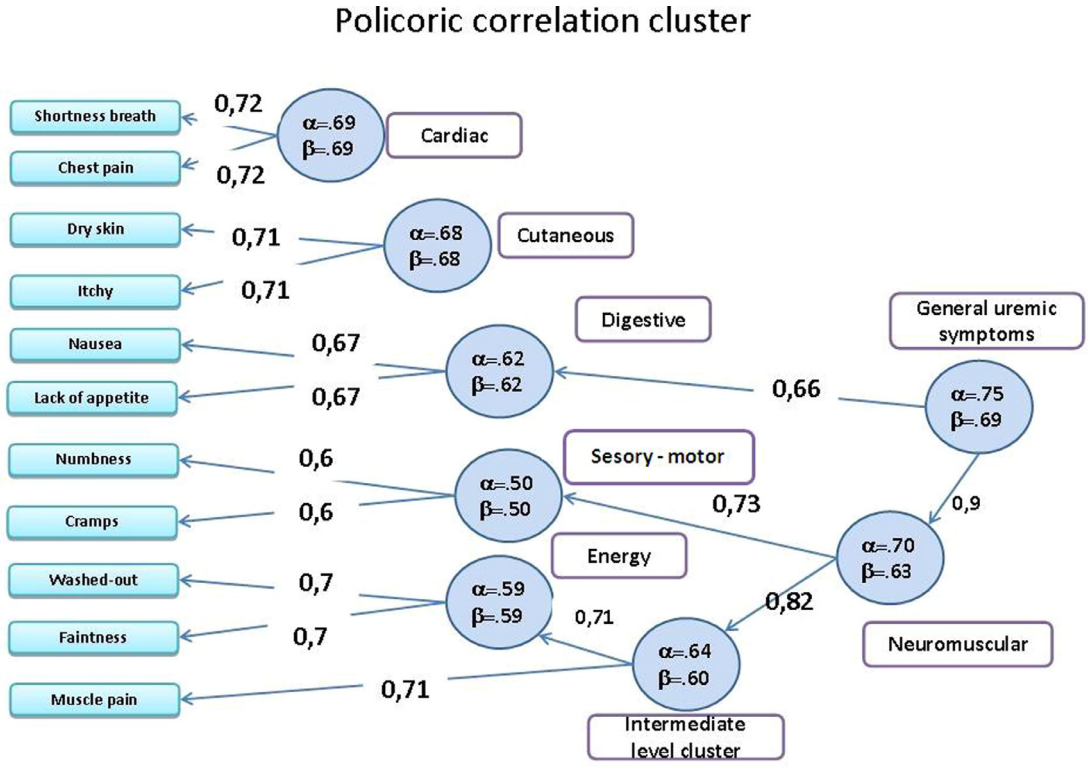

Fig. 2 – Symptom clusters using polychoric correlations.

endorsed as moderate or severe and obtained the lowest mean scores.

As for other symptoms, 12.4% of patients (n = 54) reported mild to severe daily somnolence as an evidence of sleep disturbance, 24% (n = 94) had a positive screening for anxiety (8.9% moderate to severe), and 24.3% (n = 95) had a positive screening for depression (11.8% moderate to severe). As for satisfaction with sexual functioning, although 38.1% (n = 181) reported experiencing some adverse effects, 13.8% endorsed the categories "very much" or "extremely bothered" in the item "How much does kidney disease bother you in your sexual life?" (included in the KDOQOL-36 Effect subscale).

Figure 2 shows the clusters obtained. Five first-level clusters of symptoms were identified as "cutaneous" (itchy and dry skin), "cardiac" (chest pain and shortness of breath), "digestive" (nausea and lack of appetite), "sensory-motor" (numbness and cramps), and "energy" (washed out and faintness). The results showed a second-level cluster that included the symptoms of the sensory-motor and energy clusters plus muscle soreness into a "neuromuscular cluster," and finally a third-level grouping was formed by 7 symptoms called "uremic symptoms cluster." The frequency of each cluster, cluster mean scores, and frequency of cluster scores in the range of moderate to severe are presented in Table 4, together with the α coefficients for each cluster. The

Table 4 – Prevalence of clusters and moderate/severe cluster scores.

Clusters	Symptom	Cluster present (%)	Moderate to severe (%)	Cluster score, mean ± SD	ICLUST α coefficient
		First-level clusters			
Cutaneous	Dry skin, itch	27.7	8.6	77.2 ± 29.5	0.68
Neuropathic	Numbness, cramps	22.0	3.9	79.3 ± 28.4	0.50
Energy	Washed out, faintness	14.1	1.6	84.0 ± 25.4	0.59
Digestive	Nausea, lack of appetite	11.2	1.6	88.1 ± 23.0	0.62
Cardiac	Shortness of breath, chest pain	8.4	0.6	91.7 ± 19.9	0.69
		Intermediate-, second-, and third-level clusters			
Intermediate	Washed out, faintness, muscle soreness	12.1	0.4	79.4 ± 28.3	0.64
Neuromuscular	Numbness, cramps, washed out, faintness, muscle soreness	4.5	0.2	79.4 ± 17.1	0.75
Uremic	Numbness, cramps, washed out, faintness, muscle soreness, nausea, lack of appetite	1.8	0.0	82.1 ± 14.9	0.70

ICLUST indicates item cluster analysis.

Table 5 – Descriptive analyses of the instruments.

Instrument	Cronbach α	Mean ± SD (range)	Median (interquartile range)
KDQOL-36 Effect subscale	0.73	72.7 ± 20.7 (0-100)	75 (62.5-87.5)
KDQOL-36 Burden subscale	0.77	53.9 ± 30.6 (0-100)	56.25 (31.2-75.0)
KDQOL-36 Symptom subscale	0.72	82.4 ± 14.1 (0-100)	85.42 (75.0-91.7)
KDQOL-36 PCS	–	40.7 ± 10.9 (16-65)	41.44 (31.9-50.7)
KDQOL-36 MCS	–	49.5 ± 11.4 (12-84)	51.80 (41.2-58.9)
Instrument	**Cronbach α**	**N**	**%**
VAS pain (moderate to severe)	–	140	25.0
Epworth daily somnolence (mild to severe)	0.68	54	12.4
HADS anxiety positive screening ≥8 points	0.62	95	24.3
HADS depression positive screening ≥8 points	0.72	94	24.0

HADS indicates Hospital Anxiety and Depression Scale; KDQOL, Kidney Disease Quality of Life 36 items; MCS, mental component summary; PCS, physical component summary; VAS, visual analogue scale.

cutaneous, sensory-motor, and energy symptom clusters were the most frequent and severe ones. The Cronbach α of the total Symptom Scale was 0.93.

Table 5 presents the results of the KDQOL-36 PCS, MCS, Effect, Burden, and Symptom Scales, as well as the frequency of the HADS-A and HADS-D scores.

The linear regression analysis showed statistically significant negative regression coefficients between the presence of symptom clusters (dummy variables) and the PCS scores of the KDQOL-36, showing worst HRQOL if the symptom clusters were present. Similar results were observed for most clusters and the KDQOL-36 MCS, HADS-A, and HADS-D scores, with only a few exceptions. In addition, positive β coefficients were statistically significant between cluster scores and there were larger PCS scores (Table 6).

Discussion

Although RRTs are available in all Latin-American countries, the possibility of being included in a treatment plan differs between countries. Although in certain countries, such as in Uruguay, treatments are available to the whole population, in others acceptance is restricted because of lack of dialysis units, reduced budgets, age limitations, certain comorbidities (ie, cancer, AIDS, and

Table 6 – Linear regression analyses between clusters and the outcome variables.

	PCS		MCS		HADS anxiety score		HADS depression score	
Clusters	**β^***	**P value**	**β^***	**P value**	**β^***	**P value**	**β^***	**P value**
Association between symptom cluster (as dummy variables [presence = yes]) and outcome variables								
Symptom clusters								
Cardiac	−0.159	.000	−0.089	.049	0.068	.141	0.103	.025
Cutaneous	−0.243	.000	−0.090	.047	0.179	.000	0.136	.003
Digestive	−0.203	.000	−0.148	.001	0.280	.000	0.240	.000
Neuropathic	−0.183	.000	−0.220	.000	0.173	.000	0.169	.000
Energy	−0.243	.000	−0.241	.000	0.336	.000	0.230	.000
Intermediate	−0.260	.000	−0.208	.000	0.321	.000	0.209	.000
Neuromuscular	−0.130	.004	−0.154	.001	0.224	.000	0.136	.003
Uremic	−0.152	.001	−0.112	.013	0.137	.003	0.070	.127
Association between symptom cluster scores (as continuous variables) and outcome variables								
Cluster scores								
Cardiac	0.231	.000	0.208	.000	−0.134	.004	−0.130	.005
Cutaneous	0.245	.000	0.158	.000	−0.237	.000	−0.134	.004
Digestive	0.217	.000	0.278	.000	−0.315	.000	−0.244	.000
Neuropathic	0.258	.000	0.247	.000	−0.241	.000	−0.224	.000
Energy	0.402	.000	0.377	.000	−0.382	.000	−0.337	.000
Intermediate	0.462	.000	0.399	.000	−0.442	.000	−0.366	.000
Neuromuscular	0.443	.000	0.394	.000	−0.420	.000	−0.359	.000
Uremic	0.427	.000	0.419	.000	−0.441	.000	−0.372	.000

HADS indicates Hospital Anxiety and Depression Scale; KDQOL, Kidney Disease Quality of Life 36 items; MCS, mental component summary; PCS, physical component summary.

* Standardized regression coefficient.

drug addiction), or geographical barriers. The universal access to dialysis treatments in our country, with the inclusion of elderly people and patients with a more impaired health status at the start, in addition to higher survival rates in dialysis, has posed a great concern about the symptom burden and impact on quality of life imposed by RRTs.[30,31] The present study aimed at describing the symptom burden of a sample of Uruguayan patients on HD and PD, the way symptoms are grouped in clusters, and the impact they have on quality of life and psychological distress. To our knowledge, this is the first study of its kind in South American patients.

According to the Uruguayan Registry of Dialysis,[32] the sociodemographic characteristics of our sample, the distribution of treatments (HD and PD), and the frequency of comorbidities such as diabetes are similar to the population on RRT in the country.

The number of symptoms reported by the patients was high, with a median of 3.5 symptoms. Previous studies identified the same symptoms as the most frequent and most severe symptoms. Even when the symptom burden was high, the KDQOL-36 burden of disease subscale was rated with the lowest scores.

HCA identified five 2-symptom clusters: cutaneous, neuropathic, energy, digestive, and cardiac. The cutaneous cluster was present in 27% of the sample, being the most frequent and disturbing symptom association. Frequency and severity of other clusters were lower. In fact, second- and third-level symptom clusters were endorsed by a small number of patients.

Previous studies carried out in the field of oncology showed large variations in the number of clusters and the type of symptoms included in them. Studies of symptom clusters in patients on dialysis proved to be more consistent in the clusters identified. Compared with the results by Amro et al[15], we identified 3 well-differentiated clusters: skin, neuromuscular, and uremic. Nevertheless, there were considerable differences in cluster composition because, in our study, numbness and cramps were included as uremic, whereas shortness of breath and chest pain remained as a separate cardiac cluster.

In our study, the presence of any symptom cluster (first-, second-, and third-level) was significantly associated with lower scores in the KDQOL-36 PCS, showing the impact that symptom burden has on the physical component of HRQOL. Similar associations were observed when using cluster scores. The presence of a cluster and the rating of cluster scores were associated with worst mental well-being as shown by the KDOQOL-36 MCS, HADS-A, and HADS-D, with the only exception of the cardiac cluster. The observation supports the conclusion that it could be useful to include symptom clusters or cluster scores as independent variables in outcome studies in dialysis.

It is worth mentioning that in similar studies carried out with the same instrument in patients on dialysis, only some clusters could be identified as having significant impact on physical or mental well-being. It is possible that HCA is a more robust method to identify clinically significant symptom clusters.

Initially, theoretical frameworks available to guide our understanding of symptom clusters were developed in the field of oncology.[33] We used the Symptom Management Model that includes 3 dimensions of symptoms: experience, management strategies, and outcomes related to symptom status. According to Barsevick,[33] this approach may not address the following issues: which symptom is more or less important (most frequent vs more severe vs more disturbing), how to identify which of the multiple symptoms should be included as part of a cluster, and which symptom groups should be categorized as symptom clusters. In our study, only the experience dimension (perception, frequency, and severity) was considered for symptom clustering. The outcomes dimension was used to set the validity of the clusters. As for the second objection, only the symptoms included in a standardized symptom checklist frequently used in patients on dialysis were used for the analyses. The HCA was followed as to set which symptoms are included in a cluster.

As a limitation of the study, there may be distressing complaints that were not included in the analyses, such as global pain, sexual dysfunction, or sleep problems. Although these variables were assessed in our study, we decided not to include them in the cluster analyses to make our results more comparable with those of previous studies in the field. Information on symptomatic therapies was not recorded during the study, so no conclusions can be made on the relationship of symptom clusters and ongoing treatments.

Conclusions

This is the first study of its kind carried out in a South American sample of patients on dialysis. We could identify several clinically significant symptom associations on the basis of a robust statistical method such as an HCA. It is possible that managing symptom clusters rather than single symptoms may reduce symptom burden in patients on dialysis. In turn, we expect that further studies could lead to identifying common physiopathological pathways on the basis of the way symptoms are associated, and using treatments targeting associated symptoms.

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Supplemental Materials

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