Symptom Clusters in Hemodialysis : Insights from a Multicenter Analysis Using Tetrachoric Correlations

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1 Introduction

Patients receiving maintenance hemodialysis experience a substantial and multidimensional symptom burden that affects physical, psychological, and functional well-being [1, 2, 3, 4, 5]. Systematic reviews and observational studies consistently demonstrate that these symptoms rarely occur in isolation; instead, they aggregate into reproducible clusters encompassing psychological, gastrointestinal, musculoskeletal/pain, sleep-related, cutaneous, and uremic domains [6- 12]. These clusters have been linked to impaired quality of life, diminished self-management, and adverse clinical outcomes [7, 11, 13, 14, 15]. Beyond their descriptive utility, symptom clusters may also hold prognostic significance. In a landmark analysis, Amro et al. [16] showed that uremic symptom clusters—rather than individual symptoms—were independently associated with higher mortality risk, suggesting that inter-symptom relationships carry meaningful clinical information and warrant deeper investigation within the hemodialysis population.

Characterizing these clusters is critical for understanding patients' lived experience, anticipating clinical trajectories, and guiding interventions that are more effective than symptom-by-symptom management [7, 12, 16, 17, 18]. Across recent studies, the most frequently reported symptoms include fatigue, pruritus, dry skin, sleep disturbances, pain, gastrointestinal complaints, and psychological symptoms such as anxiety and depression [3, 6, 7, 8, 9, 10, 14, 18]. Network analyses and systematic reviews repeatedly identify similar clusters—psychological, sleep-related, uremic, neurological, gastrointestinal, dermatological, and pain clusters [6, 7, 8, 9, 10, 11, 19,]. Notably, Chang et al. identified four major clusters, with the psychological cluster exerting the greatest impact on health-related quality of life [6].

These clusters have been robustly associated with poorer functioning, greater psychological distress, and reduced physical and social well-being [11, 17, 14, 18, 16]. Their reproducibility and relative stability underscore the need for routine, structured assessment and a multidimensional, patient-centered management approach. Integrating symptom-cluster evaluation into routine practice may support more targeted care strategies and improve self-management, adherence, and overall well-being among patients on hemodialysis [7, 12, 15, 20].

Methodological advancements—including network analysis and factor-analytic techniques—have refined the detection of latent symptom structures in hemodialysis cohorts [6, 7, 9]. However, most studies rely on ordinal symptom scores. Only a minority employ tetrachoric correlations, which are well suited to dichotomous symptom data and may more accurately reflect latent interdependencies. Another major knowledge gap concerns the relationship between symptom patterns and comorbidities. Although comorbid conditions such as cardiovascular disease, diabetes, and pulmonary disorders are widespread in the hemodialysis population, their influence on symptom clustering remains inconsistent. Several large cohorts have reported only weak associations between comorbidity burden and symptom expression [15, 18], raising the possibility that symptom clustering reflects intrinsic patient-reported experiences rather than disease-driven phenotypes.

The need to address symptom burden in dialysis care has been reaffirmed by the KDIGO Controversies Conference on Symptom Management, which highlighted that fatigue, pain, pruritus, sleep disturbance, and emotional distress are common, disabling, and insufficiently recognized in routine nephrology practice. KDIGO therefore recommended routine structured symptom assessment and emphasized that symptoms should be considered core clinical outcomes [21].

Increasing evidence also points to important sex-related disparities in symptom experience. Women undergoing hemodialysis consistently report higher levels of fatigue, psychological distress, and somatic symptoms. In our ePROMs study [22], female sex was independently associated with elevated stress (OR 2.27, 95% CI 1.00–5.14; p=0.05) and prolonged post-dialysis fatigue recovery (OR 2.7, 95% CI 1.05–6.92; p=0.04). These findings align with broader international data: according to the OECD's 2025 patient-reported indicator surveys, women consistently report lower physical and mental health scores, poorer well-being, and reduced social functioning—typically 6–15% lower—than men, with the smallest sex difference observed for self-management confidence [23]. Despite this, few nephrology studies have examined whether sex differences influence the structure of symptom clusters.

In 2025, Guerraoui et al. published the Concordance Study in *Clinical Kidney Journal*, a large multicenter cross-sectional study embedded within the French REIN registry. This study compared symptoms reported by hemodialysis patients using the Dialysis Symptom Index (DSI) with clinician-perceived symptoms, revealing a high symptom burden and marked patient–clinician discordance [3].

The present work is a secondary analysis of the Concordance Study dataset. Building on the original findings, this analysis aims to deepen understanding of symptom organization and determinants in hemodialysis using multivariate and correlation-based approaches. Specifically, our objectives were :

1. **to identify and characterize symptom clusters** using tetrachoric correlations and hierarchical clustering;
2. **to examine associations between symptoms (and clusters) and comorbidity burden**, while assessing potential **sex-specific patterns** in symptom expression.

Through this secondary analysis, we aim to clarify the internal architecture of symptom co-occurrence, identify key demographic drivers such as sex, and generate evidence supporting cluster-informed, individualized approaches to symptom assessment and management in routine nephrology care.

2 Methods

2.1 Study Design and Population

This study is a secondary analysis of data from the Concordance Study, a multicenter, prospective, observational investigation conducted between 2023 and 2024 across six dialysis centers in France.

The primary study evaluated concordance between symptoms self-reported by adults undergoing maintenance hemodialysis (≥18 years, dialysis vintage ≥3 months) and symptoms identified by dialysis nurses and nephrologists. All participants provided written informed consent. Data were collected as part of routine clinical care. The study protocol was approved by institutional review boards at participating centers and was conducted in accordance with the Declaration of Helsinki.

2.2 Symptom Assessment

Symptoms were assessed using the Dialysis Symptom Index (DSI), a validated self-administered instrument that captures 30 common physical and psychological symptoms in hemodialysis patients.

Each symptom was coded dichotomously (present = 1, absent = 0). A total symptom count was calculated for each participant. Sociodemographic and clinical characteristics—including age, sex, dialysis vintage, and comorbidities—were extracted from electronic medical records.

2.3 Data Preparation and Quality Control

The initial dataset included 256 patient records. Data integrity was evaluated by screening for missing values and outliers. Twenty-four records with incomplete symptom data were excluded, yielding a final analytical sample of 232 patients. No additional inconsistencies were identified following internal validation and cross-checks.

2.4 Symptom and Comorbidity Grouping

Symptom Families

To enhance interpretability and reduce dimensionality, DSI symptoms were aggregated into eight clinically coherent families based on prior literature and expert consensus. A symptom family was considered present if the participant reported ≥1 symptom within that category:

- **Cardiopulmonary:** swelling of the legs, cough, shortness of breath
- **Gastrointestinal:** nausea, constipation, vomiting, decreased appetite, diarrhea
- **Pain-related:** muscle cramps, chest pain, muscle soreness, joint or bone pain
- **Neurological:** concentration difficulties, headache, numbness/tingling in feet, Dizziness
- **Endocrine/Sexual:** decreased interest in sex, difficulty becoming sexually aroused
- **Sleep-related:** trouble falling asleep, restless legs, trouble staying asleep, fatigue or lack of energy
- **Psychological:** nervousness, worrying, irritability, anxiety, sadness
- **Dermatological:** dry mouth, dry skin, itching

This categorization enabled the exploration of correlations both at the individual-symptom level and at the family level.

Comorbidity Groups

Comorbidities were categorized into major clinical domains to capture patterns of multimorbidity:

- **Cardiovascular:** ischemic cardiomyopathy or myocardial infarction, heart failure, peripheral arterial disease, stroke or transient ischemic attack, arrhythmias, abdominal aortic aneurysm
- **Pulmonary:** chronic respiratory failure or long-term oxygen therapy
- **Digestive:** cirrhosis or chronic liver disease
- **Endocrine/Diabetes:** diabetes mellitus (any type)
- **Cancer:** active malignancy

Each comorbidity group was treated as a binary variable (present/absent). This classification enabled correlation testing between symptom families and comorbidity profiles.

2.5 Symptom Frequency Analysis

A univariate descriptive analysis was performed to quantify the frequency of individual symptoms and symptom families. This provided an overview of symptom burden and highlighted the most prevalent versus less common symptoms prior to exploring inter-symptom associations. Frequencies and proportions were summarized in tabular format, with descriptive comparisons by age, sex, and comorbidity status.

2.6 Tetrachoric Correlation Analysis

Associations between binary symptom variables were evaluated using tetrachoric correlation, which estimates the correlation between two dichotomous variables under the assumption of an underlying bivariate normal distribution. Tetrachoric coefficients (r_t) range from –1 to +1, with higher values indicating stronger positive co-occurrence. This method provides more accurate estimates of latent associations than Pearson or Spearman correlations for binary indicators.

A complete tetrachoric correlation matrix was generated for individual symptoms and symptom families. Pairwise correlations were inspected to identify symptom pairs with strong associations ($r_t > 0.5$). Distance matrices ($1 - r_t$) were subsequently constructed for use in clustering analyses.

2.7 Interpretation of the Tetrachoric Correlation Matrix

Correlation coefficients were interpreted as strong ($r_t > 0.5$), moderate (0.3–0.5), or weak (<0.3). Strongly correlated symptoms tended to cluster together, suggesting shared physiological or experiential mechanisms (e.g., fatigue, sleep disturbance, appetite loss). Weak correlations indicated relatively independent symptom manifestations. Negative correlations—rare in this dataset—suggested mutual exclusivity or reversed binary coding. The tetrachoric matrix thus provided a robust foundation for exploring latent symptom structure in hemodialysis patients.

Overall, the tetrachoric correlation matrix provided a robust framework for identifying symptom clusters and characterizing the latent structure of symptom co-occurrence in the hemodialysis population.

2.8 Exploratory Cluster Identification

Latent symptom structures were explored using hierarchical agglomerative clustering (Ward's minimum-variance method) applied to distance matrices derived from tetrachoric correlations. Dendrograms and cluster memberships were visually inspected to identify clinically interpretable clusters characterized by high within-cluster and low between-cluster correlation.

Cluster robustness was examined through complementary Multiple Correspondence Analysis (MCA), which provided an alternative multidimensional representation of symptom co-occurrence. Symptom clusters consistently reproduced across both methods were considered the most reliable and clinically meaningful.

This dual approach (tetrachoric correlation + MCA) enabled the identification of symptom clusters consistent across methods and clinically meaningful in the hemodialysis context.

2.9 Statistical Analysis

All analyses were performed using Python, for tetrachoric correlations and the *stats* package for hierarchical clustering.

An analysis of the frequency distribution of individual symptoms was conducted to summarize the prevalence of each symptom within the study population. This univariate analysis provided a descriptive overview of common and rare symptoms, informing subsequent correlation analyses.

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as frequency (percentage).

Building on this frequency overview, tetrachoric correlation analysis was used to examine the associations between symptoms, as well as between symptom families.

The tetrachoric correlation is a statistical measure used to estimate the correlation between two binary variables, assuming an underlying continuous distribution.

The value for a tetrachoric correlation can range from -1 to 1 where:

- **-1** indicates a strong negative correlation between the two variables.
- **0** indicates no linear correlation
- **1** indicates a strong positive correlation between the two variables

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