Study Protocol and Statistical Analysis Plan

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Name: Construction of Symptom Network in Maintenance Hemodialysis Patients

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Objective

Through a cross-sectional questionnaire survey, a general information questionnaire and Dialysis Frequency, Severity, and Symptom Burden Index were used to investigate the frequency, severity, and degree of symptom distress in MHD patients, and to analyze the differences in symptom distress status between long and short dialysis age MHD patients. Using the R 4.2.2 software qgraph package, construct symptom networks for MHD patients of long and short dialysis age through network analysis. Analyze network centrality indicators, including intensity, closeness centrality, and mediation centrality, to identify core symptoms and compare if there are any differences between the two groups, aiming to lay the foundation for precise and efficient phased symptom management.

Background

End stage renal disease (ESRD) is caused by various kidney diseases, leading to irreversible decline in renal function. The main renal replacement therapy (RRT) for ESRD is hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation. Due to the impact of kidney supply on kidney transplantation, it is limited in clinical practice, and hemodialysis has become the most common method of RRT in most countries. According to the registration system of the Chinese Research Data Services (CNRDS), as of the end of 2021, there were 751098 dialysis patients and 155738 new patients in China, with an average dialysis age of 50.9 months. The proportion of patients with dialysis age greater than 5 years was 31.5%. There are a large number of hemodialysis patients with a longer dialysis age.

With the continuous development of dialysis technology, the survival rate of maintenance hemodialysis (MHD) patients is becoming higher and higher. However, MHD patients may experience various symptoms during long-term treatment, which is the main cause of discomfort and physical and mental health for patients. The physical and mental pain or torment experienced by patients due to the disease itself and/or the symptoms caused by treatment is called symptom distress. Multiple studies have shown that the incidence of symptom distress in MHD patients ranges from

13.75% to 91.5%, which is at a high level. Symptom distress is negatively correlated with the quality of life of MHD patients. Excessive symptom distress increases the cost of treatment and exacerbates the psychological burden on patients. Persistent symptom burden can significantly affect the quality of life of MHD patients and increase their mortality rate. MHD patients suffer from multiple symptoms at the same time. Li Jiuhong et al.'s research results show that MHD patients experience a total of 3-25 (13.12 ± 5.27) symptoms, which is similar to Weisbord et al.'s average of 9 symptoms. MHD patients experience a wide variety of symptoms, and how to accurately and effectively manage symptoms is the future research direction.

With the prolongation of dialysis treatment time for patients, some urea toxin that cannot be completely cleared by dialysis accumulates in the patient's body, which is closely related to discomfort symptoms such as itching, joint pain, and difficulty falling asleep. Ran Yuli et al. found that the dialysis age of MHD patients is negatively correlated with their physical function and role. With the prolongation of dialysis age, the physiological function of MHD patients will decrease to varying degrees, and various disease-related complications will also occur. The focus of symptom management will shift accordingly. Conducting grouping studies based on dialysis age for MHD patients has certain clinical significance. At present, domestic scholars use a 5-year hemodialysis period as the boundary, dividing dialysis age>5 years into long dialysis age, and dialysis age ≤ 5 years into short dialysis age. Hu Qian and others set up symptom management consultants to develop symptom management pathways and guide responsible nurses to implement symptom management for patients according to the pathway table. The results indicate that setting up symptom management consultants can reduce the incidence of symptoms in MHD patients, improve their quality of life, and improve patient satisfaction. A meta-analysis showed that aerobic exercise can improve several symptoms related to hemodialysis in adults receiving MHD, including restless leg syndrome, depressive symptoms, muscle spasms, and fatigue. Zhao Ying et al. used air wave pressure therapy to prevent dialysis related muscle spasms, Zuo et al. managed symptoms of fatigue through nurse led non drug multidisciplinary holistic care, Beerappa et al. improved sleep

disorders in MHD patients through aromatherapy, Guo Junjun et al. improved fatigue symptoms and alleviated sleep disorders in MHD patients through acupoint massage. When conducting symptom management for MHD patients, existing studies have not distinguished the age of dialysis, and currently, symptom management for MHD patients mainly focuses on a single symptom or symptom group, ignoring the interaction between multiple symptoms in the real world. In real clinical situations, patients often have multiple symptoms at the same time, and it is urgent to identify the core symptoms of patients to improve the accuracy and efficiency of symptom management.

With the development of information technology, big data analysis technology, and the innovation of complex scientific research concepts in the real world, the concept of symptom networks is gradually replacing the previous research paradigm that focuses on individual symptoms and must control other variables. Symptom network is a collective representation of symptoms related to a patient's disease, and based on complex network analysis to quantitatively study the correlation between different symptoms. It studies the network structure, nodes, and network indicators composed of individual symptoms to reflect the interaction mechanism of symptoms in the real world and provide precise intervention targets. Discovering core symptom targets through symptom networks can improve the management efficiency and intervention accuracy of symptom management, evolving from the working mode of "having multiple symptoms and providing multiple sets of intervention measures" to "identifying intervention targets and providing intervention measures targeting target symptoms". Since Fried et al. first proposed the concept of symptom networks in 2015, the research paradigm of symptom networks has been applied in psychopathology, chronic disease symptom management, long-term follow-up of tumors, and patient self-management. Lin et al. constructed a self-reported psychological and neurological symptom network for head and neck cancer patients through network analysis. The results showed that network analysis clarified the interrelationships between five psychological and neurological symptoms, and identified depression as the core symptom. It is recommended to develop symptom

management measures for depression in clinical practice. Han et al. constructed symptom networks for autism and schizophrenia. Yang Hongli et al. applied symptom networks to HIV infected individuals and identified fatigue as the core symptom. They suggested that when HIV infected individuals have multiple symptoms at the same time, high-intensity and precise intervention on fatigue can reduce the transmission of fatigue as a mediating bridge in the symptom network, reduce the severity of fatigue symptoms, and also alleviate the severity of other symptoms. As mentioned above, symptom network analysis can identify core symptoms, and changing these core symptoms may be an important entry point for changing the entire network. In practical clinical work, implementing key interventions by nurses on core symptoms can more effectively improve other related symptoms and improve intervention efficiency. Applying symptom networks to the field of symptom management is a promising and precise technology in real-world clinical settings.

This study has developed a symptom distress questionnaire for maintenance hemodialysis patients. Previous literature on symptom distress and symptom management in MHD patients has been reviewed. Whether there are differences in symptom distress among MHD patients of different dialysis ages, and how to identify the core symptoms of MHD patients of different dialysis ages through symptom networks to improve the accuracy and effectiveness of intervention are all directions that need to be studied in the future. The research hypotheses of this study are: ① There are differences in the frequency, severity, and degree of symptom distress between long and short dialysis age MHD patients; ② By using network analysis methods to construct symptom networks for long and short dialysis age MHD patients, identify the core symptoms of different dialysis age MHD patients. Based on literature review and clinical experience, it is assumed that the core symptoms of long dialysis age MHD patients are itching or dry skin, while the core symptoms of short dialysis age MHD patients are fatigue or dry mouth.

Contents

① Understanding the current status of symptom distress in maintenance hemodialysis patients through cross-sectional questionnaire survey

② Comparative analysis of symptom distress in maintenance hemodialysis patients with long and short dialysis age

2. Construction of symptom network and core symptom recognition for maintenance hemodialysis patients

① A multicenter study on the current status of symptom distress in maintenance hemodialysis patients

② Construct symptom networks for long-term, short-term, and all maintenance hemodialysis patients using network analysis based on cross-sectional survey data from multiple centers

③ Identify and analyze the core symptoms of long dialysis age, short dialysis age, and all maintenance hemodialysis patients based on network centrality parameters

Methods

Participants

Convenient sampling method was used to select MHD patients from six blood purification centers, including the East, West, South, Baoshan Branch, Ningbo Hangzhou Bay Branch, and Punan Hospital of Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine.

(1) Inclusion criteria: ① Age not less than 18 years old; ② Regular hemodialysis time greater than or equal to 3 months; ③ The dialysis plan did not change within one month; ④ Informed consent and voluntary participation in this study.

(2) Exclusion criteria: ① Previous or current mental illness; ② Cognitive impairment; ③ Acute cardiovascular and cerebrovascular disease; ④ Acute infection period; ⑤ Complications such as severe cerebrovascular sequelae and tumors.

(3) Sample size and calculation method: The Dialysis Frequency, Severity, and Symptom Burden Index for dialysis patients used in this study includes a total of 30 symptoms. When constructing a symptom network model, the threshold parameters

that need to be estimated are 30, paired association parameters are $30 \times \frac{(30-1)}{2} = 435$, and the total parameters are $30 + 435 = 465$. Therefore, the sample size needs to be at least 465. Considering 10% of invalid samples, the sample size of this study is at least $465 \div (1 - 10\%) = 517$.

Instruments

General Information Questionnaire: Designed by the researchers themselves, including laboratory examination indicators such as gender, age, dialysis age, marital status, educational level, work status, residential status, medical expense payment method, economic burden, primary disease, comorbidities, recent medication, hemoglobin, etc.

Dialysis Frequency, Severity, and Symptom Burden Index(DFSSBI) : DFSSBI is an adaptation of the Dialysis Symptom Index (DSI) developed by Weisbord et al., using the symptom management theory model as the theoretical framework, by American scholars Danquah et al., which increases the frequency of symptoms and the degree of distress in two dimensions. This scale has been proven to have good reliability and validity in foreign countries. Cronbach's α The coefficient is 0.923, the content validity coefficient is 0.939, and the retest reliability is 0.83. It has good internal consistency, stability reliability, and structural validity. The scale consists of 30 items, including 25 physiological symptoms such as fatigue, dry skin, itching, etc; Psychological symptoms include sadness, irritability, tension, etc., totaling 5 symptoms. The appearance of symptoms is obtained in the form of "having" and "not having". The frequency and severity of occurrence are evaluated using a Likert 4 level score, with values ranging from "occasional/mild" to "always/very" ranging from 1-4 points. The degree of distress is evaluated using a Likert 5 level score, with values ranging from 0-4 points from "no impact" to "very serious" ranging from 0-360 points. The higher the score, the heavier the individual's burden of symptoms. Zhou Xiaojuan et al. used the Chinese version of DFSSBI to investigate the symptom burden of hemodialysis patients, and their Cronbach's α The coefficient is 0.89, and the retest reliability is 0.91, indicating that the scale is suitable for application in domestic

hemodialysis patients.

Data Collection

Before the investigation, obtain the consent of the hospital ethics committee and departments, explain and communicate with the survey subjects. On dialysis day, researchers will use unified guidelines to explain the research purpose and explain the answer methods and precautions for each question to the survey subjects. The questionnaire is filled out by the patient themselves. For survey subjects who are unable to independently complete the questionnaire, the researcher can collect data through one-on-one Q&A. Collect and check for any missing items on the spot, and promptly supplement and complete them.

Statistical Analysis Plan

Enter the collected information into the database established by Epidata 3.1, and after verification, import it into SPSS 21.0 software for data analysis. The patient's gender, marital status, education level, work status, and other counting data are described using frequency and percentage. Age, hemoglobin, blood phosphorus, and other measuring data that meet normality are represented by mean and standard deviation, while those that do not meet normality are represented by median and interquartile spacing. The symptom distress scores of MHD patients with different characteristics were tested for normality and homogeneity of variance. If they obey the normal distribution and have the same variance, t-test and analysis of variance were used. Otherwise, nonparametric rank sum test was used. Use R4.2.2 software qgraph package for network analysis to generate complex network descriptions of the relationship between symptoms. Use network centrality indicators such as strength, tight centrality, and mediation centrality to represent the degree of interconnection of symptom networks. The intensity reflects the total direct connection between symptoms and other symptoms, that is, the ability of symptoms to affect other symptoms; The closeness centrality reflects the reciprocal of the distance between symptoms and other symptoms, that is, the core position of symptoms in the network; Mediation centrality reflects the number of shortest paths through the symptom, which serves as a bridge between the symptoms in the network.