Literature Review

Factors Associated with Fatigue in Chronic Kidney Disease Patients Undergoing Hemodialysis: A Systematic Review

Faktor yang Berhubungan dengan Kelelahan pada Pasien Gagal Ginjal Kronik yang Menjalani Hemodialisis: Sistematika Review

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ABSTRACT

Fatigue is the primary complaint most frequently reported by patients on hemodialysis. The importance of knowing the factors related to fatigue is a strategy that can be carried out by health workers in optimally applying interventions to reduce patient fatigue problems. This systematic review aimed to determine the factors associated with fatigue in patients undergoing hemodialysis. The systematic review method began by identifying research articles in the Pubmed, ProQuest, Ebsco, and ScienceDirect databases in 2011–2020. Review protocol was using PRISMA. Based on the results of the analysis, it was obtained 23 articles that discussed demographic factors, physiological factors, socioeconomic factors, situational factors, and psychological factors that could be associated with fatigue in hemodialysis patients. There is much to learn about fatigue in patients undergoing hemodialysis, including causative factors, assessment of severity, and effective management of fatigue so that it can be used as a benchmark for determining appropriate interventions.

Keywords: Chronic kidney disease, fatigue, hemodialysis

ABSTRAK

*Fatigue merupakan keluhan utama yang paling sering dilaporkan oleh pasien dengan hemodialisis. Pentingnya mengetahui faktor yang berhubungan dengan *fatigue* menjadi strategi yang dapat dilakukan oleh tenaga kesehatan dalam mengaplikasikan intervensi secara optimal untuk mengurangi masalah *fatigue* pasien. Sistematik review ini bertujuan untuk mengetahui faktor yang berhubungan dengan *fatigue* pada pasien yang menjalani hemodialisis. Metode sistematika review dimulai dengan mengidentifikasi artikel penelitian pada database Pubmed, ProQuest, Ebsco, dan ScienceDirect tahun 2011–2020. Protokol sistematik review menggunakan PRISMA. Hasil analisis didapatkan 23 artikel yang membahas faktor demografi, fisiologis, sosial ekonomi, situasional dan psikologis yang berhubungan dengan dengan *fatigue* pada pasien hemodialisis. Banyak hal yang harus dipelajari mengenai *fatigue* pada pasien yang menjalani hemodialisis, termasuk faktor penyebab, penilaian keparahan, dan manajemen *fatigue* yang efektif sehingga dapat menjadi tolak ukur untuk menentukan intervensi yang tepat.*

Kata Kunci: Gagal ginjal kronik, hemodialisis, kelelahan

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INTRODUCTION

The number of patients undergoing hemodialysis due to chronic kidney disease in 2010 increased by 2.62 million people worldwide, and it is predicted that it will double by 2030 (1). Data Report of the China Kidney Disease Network (CKNET) shows that in China the prevalence of hemodialysis increased rapidly by around 553,000 in 2015 (2). According to data from the Portuguese Nephrology Society, in 2015 there were 18,928 chronic kidney disease patients in Portugal, with 11,514 of them were enrolled in the dialysis program (3).

Although hemodialysis can help patients with kidney problems, long-term hemodialysis therapy can lead to complications and affect physical, psychological, social, spiritual, and emotional aspects that the individual cannot control (4,5). Hemodialysis patients come with various problems such as sleep disorders, neurological problems, physiological problems, poor quality of life, anxiety, depression symptoms, and fatigue (6). The results of research conducted by Ali & Taha (7) and Bossola et al (8) found that fatigue is one of the main complaints most often reported by patients with hemodialysis with a percentage of 78% to 83.8%.

The fatigue experienced by patients undergoing hemodialysis can be due to several factors. According to the theory of unpleasant symptoms put forward by Lenz et al (9), fatigue can be influenced by physiological factors, psychological factors, and situational factors. Meanwhile, according to Artom et al (10) and Jham et al (11), demographic factors and socioeconomic factors can also contribute to the development of fatigue, thus when describing the factors that can affect fatigue—they include demography, physiology, socioeconomic, situational, and psychological. These factors can also contribute to further complications of fatigue.

Further complications of fatigue in patients on hemodialysis have been associated with poor quality of life and lower survival rates due to decreased physical and psychological activity (12,13). Research by Abd El-Nasser Ali (14) and Vasilopoulou et al (15) found that hemodialysis patients who have significant problems with fatigue and depression can also affect the poor quality of life. Poor quality of life in hemodialysis patients can increase cardiovascular and suicide risks, therefore this will become a big problem if not given proper management (13,16,17).

The importance of knowing the factors associated with fatigue is one of the strategies that can be used by health professionals in understanding and optimally applying interventions to reduce patient problems. Appropriate intervention can help patients manage fatigue thus it is important for improving the quality of life of patients with dialysis (12). However, the factors associated with fatigue in hemodialysis patients are still not comprehensively discussed, so this article aimed to determine the factors associated with fatigue in patients undergoing hemodialysis.

METHOD

Design

The design of this study was a systematic review that discussed the factors that cause fatigue in chronic kidney disease patients undergoing hemodialysis. The evaluation

used in this study was the PRISMA checklist as a component to select the studies that have been found so that they could be adjusted to the objectives of this systematic review.

Literature Search Strategy

Study adapted to PRISMA guidelines. A data-based literature search was carried out in June 2020 and the articles selected were articles of reputable journals. Publication from 2011-2020 were include in this study. The literature has been systematically reviewed for empirical evidence regarding factors associated with fatigue in chronic kidney disease patients undergoing hemodialysis. Search using the Pubmed, ProQuest, EBSCO, and ScienceDirect databases used a combination of the keywords of chronic kidney disease, fatigue, and hemodialysis with the Boolean AND, OR, and NOT search methods to get related articles that match the objectives of the systematic review.

Inclusion and Exclusion Criteria

The determination of inclusion and exclusion criteria was adjusted based on PICOS (population, intervention, comparators, outcomes, and study design). The inclusion criteria in this systematic review were studies that focus on the population undergoing hemodialysis, studies that discuss factors associated with fatigue or interventions that can affect fatigue in chronic kidney disease patients undergoing hemodialysis, studies that explain the outcomes of factors that can influence fatigue and studies that focus on cross-sectional, randomized controlled clinical trial, prospective cohort study, dan non randomized control trial. While the exclusion criteria were studies that focus on populations other than chronic kidney disease patients, studies that had no association with causes of fatigue in patients undergoing hemodialysis, and studies that include articles review.

Data Extraction

Extraction of data and information was in the form of authors, research objectives, population selection, research design, data analysis techniques, educational content, samples, year of publication, and language used from each study so that the correct study will be extracted according to the research objectives.

RESULTS

Characteristics of the Studies

The results of a review of 23 articles in this study are related to factors associated with fatigue in chronic kidney disease patients undergoing hemodialysis (Table 1). The number of samples from the articles found ranged from 37 samples to 511 samples with a total of 3,633 samples. Of the selected articles the research was conducted in China (26.08%, 6/23), Turkey (13.04%, 3/23), United States (13.04%, 3/23), Egypt (8.69%, 2/23), Japan (8.69%, 2/23), Italy (8.69%, 2/23), Iran (8.69%, 2/23), Netherlands (4.34%, 1/23), United Kingdom (4.34%, 1/23), and Greece (4.34%, 1/23). The articles found were published from 2011 to 2020 and all were written in English. The articles found were original research, namely cross-sectional (73.9%, 17/23), randomized controlled clinical trial (13.04%, 3/23), prospective cohort study (8.69%, 2/23), and non-randomized control trial (4.34%, 1/23).

Factors that influence fatigue were found to be

demographic factors (52.17%, 12/23), physiological factors (60.8%, 14/23), socioeconomic factors (47.82%, 11/23), situational factors (43.47%, 10/23), and, psychological factors (47.8%, 11/23). The measuring instruments used were the fatigue scale (8.69%, 2/23), the fatigue severity scale (FSS) (21.7%, 5/23), the fatigue sleepiness exhaustion scale (4.34%, 1/23), SF-36 vitality subscale (8.69%, 2/23), the fatigue questionnaire (4.34%, 1/23), FACIT-F Scale (13.04%, 3/23), multidimensional fatigue inventory (4.34%, 1/23), dialysis symptom fatigue index (DSI) (8.69%, 2/23), the fatigue assessment scale (4.34%, 2/23), revised piper's fatigue scale (8.69%, 2/23), hemodialysis patients fatigue Scale (4.34%, 1/23), Iowa fatigue scale (IFS) (4.34%, 1/23), and the piper's fatigue scale (4.34%, 1/23).

Study Selection

Based on the results of literature searches through publications in four databases and using keywords, the researchers found 3575 articles that matched the keywords. Then the articles were checked for duplication and it was found 759 duplicated articles so they were excluded, and the remaining was 2816 articles. The researchers then conducted a screening based on the title and abstract of the study and obtained 82 articles that fit the objective of this study; these 82 articles were then screened in full text. The feasibility assessment of 82 articles based on the text as a whole and conformity to the eligibility criteria obtained 23 articles that can be used in this systematic review. The results of the study articles selection can be illustrated in the Flow Diagram using the PRISMA selection process below:

Image 1. Flowchart of articles selected on the systematic review, selection process using PRISMA

Demographic Factors

Based on the results of the study, it was found that demographic factors such as age that is more than 50 years, female gender, married status, lower education are associated with higher levels of fatigue in patients (18-21). Then, other factors such as black race and unemployed status have higher rates associated with the problem of fatigue (18,19). However, there is not enough evidence and research controversy remains to describe the association of these factors with fatigue in patients

undergoing hemodialysis. Several studies did not find a relationship between age, gender, marital status, occupation, race, and education with the level of fatigue in hemodialysis patients with a p-value >0.05 (8,17,19,22,23). However, other studies found a relationship between gender, marital status, occupation, and education with the level of fatigue with a p-value <0.05 (18,21,24).

Physiological Factors

The results of the analysis showed that patients who had sleep disorders (7), HB levels of <10 mg/dl (21), an average BUN of 44.1 mg/dl (25), mean hematocrit of 35%, mean albumin of 3.9 g/dl, mean creatinine of 9.7 mg/dl, mean calcium of 9.1 mg/dl (8), an average IL-6 with a value of 5.1 pg/ml, an average BMI value of 28.5 (19) had a higher level of fatigue. However, there were differences in research findings regarding physiological factors associated with fatigue. There are studies that found there is no relationship between BMI (r=0.019, p-value 0.833), albumin (r=0.071, p-value 0.567), hemoglobin (r=0.174, p-value 0.053) (26), calcium (coefficient correlation of 0.182, p-value 0.084) (27), sleep patterns (p > 0.05) (7), creatinine (p-value 0.807), hematocrit (p-value 1.000) (8), and bilirubin (p <0.05) (28) with fatigue. However, other studies found that there is a relationship between albumin (correlation coefficient of 0.223, p-value 0.040), creatinine (correlation coefficient of 0.347, p-value 0.001), urea (correlation coefficient of 0.322, p-value 0.012), and IL-6 (correlation coefficient of 0.660, p-value 0.001) (27), BMI p-value <0.05) (29), hemoglobin (p-value 0.048), and sleep quality (p-value 0.003) (19) with fatigue.

Socioeconomic Factors

In general, several studies found that low physical activity (18), smokers and ex-smokers (19), living in urban areas (23), low family income (24), and families with nuclear family structures and difficult economic status (17) are associated with higher levels of fatigue. There are studies that found there is no relationship between physical activity carried out for 2 months (p-value 0.24) (30), smoking status (p-value 0.24) (19), family structure (p-value 0.13), tea consumption (p-value 0.321), coffee consumption (p-value 0.38), smoking (p-value 0.74), and alcohol consumption (p-value 0.276) (17) with fatigue. However, other studies found that there is a relationship between physical activity (p-value <0.05) (18,29), living area (p-value 0.002) (23), treatment method cost (p-value 0.001), family income (p-value 0.001) (24), economic status (p-value 0.006) (17) with fatigue.

Situational Factors

In situational factors, it was found that the length of time in undergoing hemodialysis with an average of above 6 years, has comorbid diseases (8,18,26) such as cardiovascular and diabetes mellitus (26), the frequency of hemodialysis of 3 times a week (22,24), has disease complications (21,24) have a higher rate of fatigue, but the relationship with fatigue is not clear enough. There are studies that found there is no relationship between comorbid diseases (p-value 0.938) (8), length of time in undergoing hemodialysis (r = -0.154, p-value 0.086), diabetes mellitus (r = 0.128, p-value 0.157), the frequency of dialysis (F = 2.156, p-value 0.119) (22), and cardiovascular disease (r = 0.151, p-value 0.092) (26) with fatigue in hemodialysis

patients. However, other studies found that there is a relationship between cardiovascular disease (standard error of 2.15, p-value 0.01) (19), comorbid diseases (p-value 0.001) (17), the frequency of dialysis (mean 260.00, p-value <0.001) (24) with fatigue.

Psychological Factors

The psychological factors most commonly found in cases of fatigue are depression and anxiety. Moderate to severe depression levels were found to be in line with the incidence of fatigue (7,27). Meanwhile, the higher the anxiety score, the higher the symptoms of fatigue (20,24). There is a study that found that there is no relationship between depression (p-value 0.07) and fatigue. However, other studies found there is a relationship between anxiety and depression (p-value <0.05) (20,29) with fatigue.

DISCUSSION

Demographic factors such as age that is more than 50 years, lower education, female gender, and married status are associated with have high levels of fatigue (17,24). However, there is still inconclusive and insufficient evidence because there are still differences in research findings. Regarding age, there are many convincing findings that found the increase of age will contribute to fatigue (17,18,21). This is because patients with older age experience decreased physical function, especially in the kidneys, which is a triggering factor for fatigue. Regarding gender, most studies have found no association with fatigue, this may be due to the large sample size from several studies and the unbalanced distribution between women and men so that this needs to be further proven. Varied results are found in educational status and marital status, so further exploration is needed to obtain consistent results.

Table 1. Summary of included studies

First Authors	Cause Factors	Tools	Study Design	n	Result
Bai (2015) (18)	- Demographics: Age, gender, education, marital status, employment status - Socio-economy: physical activity - Situational: comorbid disease, long undergoing hemodialysis	The Fatigue Scale	Cross-sectional	193	There was relationship between age, employment status, marital status, physical activity with fatigue. There was no relationship between sex, education, length of undergoing hemodialysis, comorbid disease with fatigue
Ali (2017) (7)	- Demographics: age and education - Physiological: Sleep patterns - Psychological: Depression	Fatigue Severity Scale (FSS)	Cross-sectional	105	There was no relationship between sleep patterns, age, education and depression with fatigue However, based on several dimensions of sleep pattern factors, there is a relationship between sleep during the day and sleep latency with fatigue
Abdel-Kader (2014) (25)	- Physiological: sleep patterns - Psychological: anxiety, stress, mood	Fatigue Sleepiness Exhaustion Scale	Prospective Cohort Study	55	There was relationship between anxiety and mood with fatigue. There was no relationship between sleep patterns and stress with fatigue
Bossola (2018) (8)	- Demographics: Age, gender - Physiological: hemoglobin, albumin, creatinine, hematocrit, calcium - Situational: comorbid disease, length of undergoing hemodialysis - Psychological: the level of anxiety	SF-36 Vitality Subscale	Cross-sectional	137	There was relationship between the level of anxiety and fatigue There was no relationship between hemoglobin, albumin, creatinine, hematocrit, calcium, age, sex, comorbid disease and length of undergoing hemodialysis with fatigue.
Chilcot (2016) (29)	- Physiology: Body Mass Index (BMI) - Socio-economy: physical exercise - Psychological: anxiety and depression	Fatigue Severity Scale (FSS)	Cross-sectional	174	There was relationship between BMI, physical exercise, anxiety and depression with fatigue
Bossola (2014) (27)	- Demographics: Age, gender, marital status - Physiology: Body Mass Index (BMI), albumin, creatinine, urea, hemoglobin, calcium, interleukin 6 (IL-6) - Situational: length of undergoing hemodialysis - Psychological: depression, anxiety	SF-36 Vitality Subscale	Cross-sectional	100	There was relationship between age, anxiety, albumin, creatinine, depression, urea and IL-6 with fatigue There was no relationship between sex, marital status, length of undergoing hemodialysis, BMI, hemoglobin, calcium with fatigue
Fukuda (2015) (31)	- Physiological: Nutrition	The Fatigue Questionnaire	Randomized controlled clinical trial	173	There was effect of nutrition on fatigue in hemodialysis patients

Table 1. Summary of included studies (Cont.)

First Authors	Cause Factors	Tools	Study Design	n	Result
Jham (2013) (19)	<ul style="list-style-type: none"> - Demographics: age, gender, race, education, marital status, employment status - Physiological: sleep patterns, albumin, BMI, hemoglobin, albumin - Socioeconomic: smoking status - Situational: cardiovascular disease, diabetes mellitus - Psychological: depression 	FACIT-F Scale	Cross-sectional	173	<p>There was relationship between albumin levels, hemoglobin, sleep patterns, albumin, cardiovascular disease and depression with fatigue</p> <p>There was no relationship between age, sex, race, education, marital status, employment status, diabetes mellitus, BMI, smoking status with fatigue.</p>
Salehi (2020) (30)	<ul style="list-style-type: none"> - Socio-economy: physical exercise 	Multi dimensional Fatigue Inventory	Randomized controlled clinical trial	37	<p>There was no effect of giving physical exercise in the first and second months on fatigue in hemodialysis patients</p> <p>There was effect of physical exercise at the third month on fatigue in hemodialysis patients</p>
Hintistan (2018) (22)	<ul style="list-style-type: none"> - Demographics: age, gender, education, marital status, employment status - Socioeconomic: smoking status - Situational: duration of hemodialysis, frequency of hemodialysis within 1 week 	Dialysis Symptom Index Fatigue (DSI)	Cross-sectional	194	<p>There was relationship between gender, marital status, education, employment status, with fatigue</p> <p>There was no relationship between age, smoking status, duration of hemodialysis, frequency of hemodialysis, with fatigue</p>
Royani (2017) (20)	<ul style="list-style-type: none"> - Demographics: age, gender, education, marital status, employment status - Physiological: hemoglobin, systolic blood pressure - Situational: length of undergoing hemodialysis - Psychological: anxiety, depression 	Fatigue Severity Scale (FSS)	Cross-sectional	165	<p>There was relationship between anxiety and depression with fatigue</p> <p>There was no relationship between hemoglobin levels, systolic blood pressure, length of undergoing hemodialysis, age, sex, education, marital status, employment status and fatigue.</p>
Sheshad (2019) (32)	<ul style="list-style-type: none"> - Socio-economy: physical activity 	Dialysis Symptom Index Fatigue (DSI)	Cross-sectional	48	There was relationship between physical activity with fatigue
Kodama (2020) (26)	<ul style="list-style-type: none"> - Physiological: BMI, albumin, C-reactive protein, hemoglobin, physical function - Situational: post dialysis, length of undergoing hemodialysis, cardiovascular disease, diabetes mellitus 	The Fatigue Scale	Cross sectional	126	<p>There was relationship between post dialysis and physical function with fatigue</p> <p>There was no correlation between length of undergoing hemodialysis, diabetes mellitus, cardiovascular disease, BMI, albumin, C-reactive protein, hemoglobin with fatigue.</p>
Wang (2015) (33)	<ul style="list-style-type: none"> - Psychological: depression 	FACIT-F Scale	Cross-sectional	187	There was relationship between depression with fatigue
Zyga (2015) (23)	<ul style="list-style-type: none"> - Demographics: education - Socio-economic: Residence 	The Fatigue Assessment Scale	Cross-sectional	129	<p>There was relationship between residence and work with fatigue</p> <p>There was no relationship between education with fatigue</p>
Zuo (2018) (24)	<ul style="list-style-type: none"> - Demographics: ethnicity, marital status, employment status, education - Physiological: albumin, urea, sleep patterns - Socio-economy: cost of treatment methods, physical exercise, family income - Situational: complications of disease, frequency of dialysis - Psychological: anxiety, depression 	Revised Piper's Fatigue Scale	Cross-sectional	511	There was relationship between ethnicity, marital status, employment status, education, cost of treatment methods, physical exercise, complications of disease, frequency of dialysis, anxiety, depression, family income, albumin, urea, sleep patterns with fatigue

Table 1. Summary of included studies (Cont.)

First Authors	Cause Factors	Tools	Study Design	n	Result
Yang (2017) (21)	<ul style="list-style-type: none"> - Demographics: age, employment status, education, marital status - Physiological: sleep disorders, hemoglobin, albumin - Situational: complications of disease, frequency of dialysis, length of time on hemodialysis 	Revised Piper's Fatigue Scale-Chinese Version	Cross-sectional	130	<p>There was relationship between age, occupation, education, sleep disorders, albumin, disease complications, dialysis frequency with fatigue</p> <p>There was no relationship between marital status, length of undergoing hemodialysis and hemoglobin levels with fatigue</p>
Wang (2016) (17)	<ul style="list-style-type: none"> - Demographics: age, gender, marital status, education, employment status - Physiological: BMI, hemoglobin, albumin, sleep patterns - Socio-economic: family structure, tea consumption, coffee consumption, smoking, alcohol, physical exercise, economic status - Situational: length of undergoing hemodialysis, frequency of dialysis, comorbid diseases 	FACIT-F Scale	Cross-sectional	345	<p>There was relationship between age, physical exercise, economic status, employment status, comorbid diseases, sleep patterns with fatigue</p> <p>There was no relationship between gender, BMI, marital status, family structure, tea consumption, coffee consumption, alcohol smoking, education, length of undergoing hemodialysis, dialysis frequency, hemoglobin, albumin with fatigue.</p>
Wu (2014) (34)	<ul style="list-style-type: none"> - Situational: physical exercise 	Haemodialysis Patients Fatigue Scale	Non Random Control Trial	172	There was effect of physical exercise on fatigue in patients undergoing hemodialysis
Huisman (2011) (28)	<ul style="list-style-type: none"> - Physiological: hemoglobin, albumin, bilirubin, creatinine - Psychological: depression anxiety 	Fatigue Severity Scale (FSS)	Prospective Cohort Study	75	<p>There was relationship between depression and anxiety with fatigue</p> <p>There was no relationship between levels of hemoglobin, albumin, bilirubin, creatinine with fatigue</p>
Turk (2018) (35)	<ul style="list-style-type: none"> - Situational : restless leg syndrome 	Fatigue Severity Scale (FSS)	Cross-sectional	220	There was relationship between restless leg syndrome and fatigue
Soliman (2015) (36)	<ul style="list-style-type: none"> - Demographics: gender, marital status, residence, education, employment status - Socio-economy: Physical exercise 	Iowa Fatigue Scale (IFS)	Randomized controlled clinical trial	30	<p>There was relationship between physical exercise with fatigue</p> <p>There was no relationship between gender, marital status, residence, education, employment status with fatigue</p>
Karakan (2011) (37)	<ul style="list-style-type: none"> - Physiological: Serum potassium, Serum phosphorus - Psychological: Depression 	The Piper's Fatigue Scale	Cross-sectional	154	There was relationship between serum potassium, serum phosphorus and depression with fatigue

Physiological factors associated with disturbed levels of hemoglobin, BUN, hematocrit, creatinine, IL-6, and BMI levels are associated with factors of fatigue (8,19,25). However, some research findings are still different related to factors related to fatigue. The state of anemia is related to fatigue in general due to a lack of oxygen supply that enters the cells, which is a trigger to fatigue. Individuals with chronic kidney disease have a target of maintaining hemoglobin levels of 10 to 11.5 g/dL (38). Increased levels of BUN and creatinine can affect fatigue due to accumulated body metabolic waste which can trigger a state of malaise (39). Increased IL-6 is also associated with fatigue but research by Bossola et al (40) found that there was no significant relationship between IL-6 levels and fatigue, however, in general serum IL-6 levels were proven to increase in patients with fatigue. The lack of statistical significance can be attributed to the small sample size. Meanwhile, BMI is associated with excess body weight that

triggers fatigue in chronic kidney disease patients undergoing hemodialysis (39).

The socioeconomic factors most often associated with fatigue are low physical activity and a history of smoking and alcohol consumption (17,18,22,29). Most of the studies found that decreased physical activity is closely related to fatigue. Several studies found the effect of physical activity on reducing levels of fatigue in patients undergoing hemodialysis (34,36). Physical activity can be associated with increased blood flow to the muscles, increasing the number of capillaries and increasing the area and surface of the capillaries so as to reduce fatigue in patients. Then related to a history of smoking and alcohol consumption in general, there are higher numbers of patients experiencing fatigue. However, there is no strong evidence yet and there are still differences from some of the research results, thus it remains to be explored further (17,22).

In situational factors, there are several studies that reveal that the length of time in undergoing hemodialysis with more than 5 years, has comorbid diseases and complications such as cardiovascular disease and diabetes mellitus, has more frequency of hemodialysis, and has disease complications (8,18,21,24,26) have a higher incidence of fatigue in patients on hemodialysis. However, the mechanism mentioned from several studies related to situational factors with the incidence of fatigue is still unclear, so this still needs to be further proven. In general, hemodialysis patients report higher levels of fatigue when they have been on hemodialysis for a long time which is associated with intradialysis hypotension, whereas patients who have comorbid disease will add more burden and stress to the individual. Patients with stage 4 and 5 of kidney disease who suffer from hypertension and diabetes mellitus have a higher rate of fatigue than patients who do not have comorbidities (39).

The most common psychological factors found in research are depression and anxiety (20,24,33). Most of the studies found that there is a relationship between psychological factors and fatigue, although there were still differences in the results of the research which might be due to the relatively small sample factor. In general, depression and anxiety are associated with peripheral activation of immune-inflammatory pathways that can contribute to neurological inflammation and ongoing neuroprogressive changes including decreased neuroplasticity, neurogenesis, increased neurodegeneration, and reduced expression of neurotransmitters (e.g., serotonin, noradrenaline). Therefore, It has been shown that

activated immune-inflammatory pathways such as interleukin-6 (IL-6) can contribute to the fatigue experienced by individuals with chronic kidney disease (27,41).

The implication that can be learned from the factors that cause fatigue in patients undergoing hemodialysis is to facilitate health practitioners to manage fatigue, especially those associated with the most dominant causative factor. Besides, health practitioners can identify the patient population undergoing hemodialysis who have the most potential to experience fatigue which can result in a decrease in quality of life and increase the risk of death to make sure that prevention can be carried out more quickly so as not to cause more complex problems.

The study's findings concluded that there were several factors contributing to fatigue, but there were still some discrepancies between the findings, which may be attributed to variations in respondent characteristics, sample size, and study design methods, necessitating further research to determine the causative factors of fatigue. There is much to learn about fatigue in patients undergoing hemodialysis, including causal factors, assessment of severity, and effective management of fatigue so it is important to study fatigue-related issues more specifically to apply to patients. Further identification of fatigue can be used as a benchmark to determine appropriate interventions that can be provided by health workers to produce fatigue management following the dominant causative factors that can be applied to patients undergoing hemodialysis.

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