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Research Progress on Cognitive Frailty and Its Influencing Factors in the Elderly with Chronic Kidney Disease

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Abstract: *With the accelerated aging of the population, the prevalence of chronic kidney disease (CKD) is on the rise. Cognitive frailty (CF) is an important indicator of quality of life and quality of living in the elderly population, and has become a research hotspot in the nursing community at home and abroad. The prevalence of cognitive frailty in elderly CKD patients is significantly higher than that in the general population, and there is an urgent need to enhance the early identification and intervention of their cognitive frailty to reduce the occurrence of adverse health outcomes. The article describes the origin and development of the concept of cognitive frailty, assessment methods, epidemiology of cognitive frailty in elderly CKD patients, influencing factors, and recommended interventions, with a view to providing lessons for the standardized cognitive frailty assessment of elderly CKD patients and the development of long-term care plans.*

Keywords: *Chronic kidney disease; Cognitive frailty; Cognitive impairment; Review*

1. Introduction

Chronic kidney disease (CKD) has become a significant global public health issue due to its high prevalence, low awareness, poor prognosis, and substantial healthcare costs. In recent years, the number of CKD patients has steadily increased, with the prevalence rate among the elderly population reaching 32% to 37% [1]. As CKD progresses, older patients with CKD are more susceptible to cognitive frailty compared to the general elderly population, due to factors such as hemodynamic changes, vascular dysfunction, declining renal function, and reduced clearance of uremic toxins[2]. Cognitive frailty (CF) is characterized by the coexistence of physical frailty and cognitive impairment, excluding Alzheimer's disease (AD) and other types of dementia[3]. Currently, research on cognitive frailty in elderly CKD patients is limited in China, with cognitive impairment and frailty often studied as separate entities. Previous studies have indicated that frailty leads to adverse outcomes in elderly CKD patients, such as falls, hospitalization, and mortality[4]. The interaction between frailty and cognitive impairment creates a vicious cycle, significantly increasing the risk of adverse health outcomes in the elderly CKD population. Therefore, this paper aims to review the origin and development of the concept of cognitive frailty, its assessment methods, the epidemiology of cognitive frailty in elderly CKD patients, its influencing factors, and recommended intervention strategies. This review is intended to assist clinical healthcare professionals in the early identification of cognitive frailty in elderly CKD patients, provide guidance for developing scientific prevention and treatment plans, and further promote healthy aging.

2. The Origin and Development of the Concept of Cognitive Frailty

Cognitive frailty was first mentioned in 2001 by Paganini-Hill et al.[5] during an experiment investigating the relationship between the Clock Drawing Test and factors influencing Alzheimer's disease (AD). In 2013, the International Association of Gerontology and Geriatrics and the International Academy on Nutrition and Aging reached a consensus on the operational definition of cognitive frailty. They jointly proposed two diagnostic criteria for cognitive frailty[3]: (1) the

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simultaneous presence of physical frailty and cognitive impairment, with cognitive impairment being measured by a Clinical Dementia Rating (CDR) score of 0.5; (2) the exclusion of comorbid AD or other types of dementia.

To further innovate the conceptual framework and potential mechanisms of cognitive frailty, Ruan et al.[6] were the first to divide cognitive frailty into reversible CF and potentially reversible CF in 2015. The former refers to subjective cognitive decline and/or positive biomarkers in the absence of neurodegenerative diseases or other psychiatric disorders, while the latter is characterized by mild cognitive impairment (MCI). The introduction of these two subtypes demonstrated the reversibility of cognitive frailty and laid the foundation for future interventional studies aimed at promoting healthy aging. However, the concept of cognitive frailty has yet to reach a consensus, and future research is needed to further refine and deepen its definition.

3. Assessment of Cognitive Frailty

Currently, there is no unified diagnostic standard for cognitive frailty, and its screening and evaluation mainly rely on various scales. Clinically, the assessment of cognitive frailty often combines frailty and cognitive function assessments, but no universally accepted optimal combination of scales exists.

3.1. Physical Frailty Assessment

The primary scales used to assess physical frailty in elderly CKD patients include the Fried Frailty Phenotype (FFP), the Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight (FRAIL) scale, and the Tilburg Frailty Indicators (TFI). The FFP[7] integrates subjective responses from the patients with objective measurements and is one of the most widely used frailty assessment tools. The FRAIL scale[8] is simple, quick, and does not require specialized equipment, making it ideal for large-scale, rapid screening. The TFI[9] is suitable for comprehensive frailty assessment in various settings, such as hospitals, nursing homes, and communities.

3.2. Cognitive Function Assessment

Cognitive function is primarily assessed using the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). The MMSE[10] is widely used in China due to its simplicity and ease of use. The MoCA[11], with its higher sensitivity, can serve as an auxiliary tool for the early diagnosis of mild cognitive impairment (MCI), providing a more comprehensive evaluation of cognitive functions.

3.3. Biomarker Assessment

Biomarker-based assessments, involving laboratory and imaging techniques, are gradually becoming a new trend. Current studies show that hippocampal subfield atrophy and white matter hyperintensities are closely associated with cognitive frailty[12-14]. The sarcopenia index (SI) has also been linked to both sarcopenia and cognitive function[15]. In elderly CKD patients, biomarkers of renal tubular injury, such as kidney injury molecule-1 (KIM-1) and monocyte chemoattractant protein-1 (MCP-1), as well as angiogenesis biomarkers, may serve as early warning indicators of cognitive frailty[12, 16]. Although biomarker assessments are costly and less feasible for widespread use, they offer high accuracy and allow for early, objective diagnosis.

4. Epidemiology of Cognitive Frailty in Elderly Patients with Chronic Kidney Disease

There is a lack of research on cognitive frailty in elderly CKD patients both domestically and internationally, and currently, only a limited amount of epidemiological evidence is available. Due to variations in study populations, regions, and assessment tools, the reported prevalence rates of cognitive frailty in China show considerable heterogeneity. A cross-sectional study conducted in Guangdong Province, using the Fried frailty phenotype and MMSE, found a prevalence rate of cognitive frailty of 21.9% in elderly CKD patients[17]. In another study conducted in Beijing, which employed the FRAIL scale and MMSE for assessment, the prevalence of cognitive frailty among elderly CKD patients was 15.2% [18]. Notably, the prevalence of cognitive frailty varies across CKD

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stages 1 to 5, with rates of 4.7%, 7.5%, 13.8%, 18.5%, and 21.4%, respectively. Researchers have observed that as CKD progresses, the prevalence of cognitive frailty gradually increases, with the highest rates seen in dialysis patients. However, a study from the United States, which evaluated 324 hemodialysis patients using the Fried frailty phenotype, a modified MMSE, and the Trail Making Test, reported a prevalence of frailty combined with cognitive impairment of only 4.6% [19].

5. Influencing Factors of Cognitive Frailty in Elderly Patients with Chronic Kidney Disease

The current research on cognitive frailty in elderly CKD patients is still insufficient, with cognitive impairment and frailty often studied as independent topics. The factors influencing cognitive frailty can be classified into five categories: sociodemographic factors, psychosocial factors, behavioral factors, physical health factors, and CKD-related factors.

5.1. Sociodemographic Factors

Age, gender, and educational level have been shown to be closely associated with cognitive frailty in elderly CKD patients. Many studies have indicated[17, 18, 20] that advanced age not only accelerates the progression of CKD but also increases the occurrence of cognitive frailty. With aging, physiological functions decline, brain white matter shrinks, and brain cells atrophy, leading to impaired cognitive function and learning abilities, thus increasing the risk of cognitive frailty. Elderly female CKD patients are at a higher risk of developing cognitive frailty compared to males[16], possibly due to estrogen deficiency after menopause, which leads to skeletal muscle cell apoptosis and neuron damage, triggering cognitive frailty. A low level of education is another significant risk factor for cognitive frailty in elderly CKD patients[17], as those with less education often engage in fewer intellectual activities, have limited knowledge of disease prevention, poor health management, and lower treatment adherence, resulting in poorer cognitive and physical health.

5.2. Psychosocial Factors

Studies by Chang et al. indicate that depression and lack of social support significantly affect the level of cognitive frailty in elderly CKD patients[18]. Depression is the most common psychological problem in these patients due to factors such as prolonged illness, heavy financial burdens, loss of social function, frequent dialysis, and hospitalization, and it has been proven to be related to the occurrence of cognitive frailty[18]. Anne et al. found that lack of social support is a risk factor for cognitive frailty in elderly CKD patients[21]. A lack of social support may reduce opportunities for verbal communication and physical activity, slowing down movement and thought processes, thereby increasing the risk of cognitive frailty.

5.3. Behavioral Factors

Elderly CKD patients often experience a decline in daily activity levels and engage in unhealthy lifestyle habits. Studies show that elderly CKD patients with reduced grip strength and slower gait are not only at risk of decreased physical mobility but also of developing mild cognitive impairment[22, 23]. Reduced physical activity leads to a decline in physical function, accelerating frailty and promoting cortical atrophy, thus increasing the risk of cognitive frailty. Poor sleep quality is another common issue among elderly CKD patients due to nighttime dialysis care, depression, or anxiety. Research indicates that sleep disturbances accelerate the progression of frailty and cognitive impairment[24], with factors such as long sleep duration (≥9 hours), poor sleep quality, difficulty falling asleep, short sleep duration, and long nap times increasing the risk of cognitive frailty[25, 26]. Smoking accelerates brain aging, with metals in cigarette smoke accumulating in tissues and bodily fluids, causing heavy metal toxicity, which speeds up physical frailty[23] and cognitive impairment[27]. Additionally, studies show that excessive alcohol consumption increases the risk of cognitive impairment and frailty, suggesting that overdrinking raises the likelihood of developing cognitive frailty[28].

5.4. Physical Health Factors

5.4.1. Multimorbidity

Studies suggest that the more chronic diseases elderly CKD patients suffer from, the higher their risk of cognitive frailty[18]. This is likely due to the presence of multiple chronic conditions, which leads

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to a decline in physical function, reduced physiological reserves, and cognitive impairment, increasing the risk of cognitive frailty. Moreover, polypharmacy in the context of multimorbidity significantly raises the risk of adverse drug reactions, further damaging both physical and cognitive functions, thus making cognitive frailty more likely to occur

5.4.2. Malnutrition

Malnutrition plays a crucial role in the development of cognitive frailty in elderly CKD patients[17]. Due to dietary restrictions, loss of appetite, and prolonged dialysis, these patients often suffer from insufficient intake of protein and calories, making them prone to malnutrition. Long-term nutritional deficiency inhibits neuron regeneration in the brain and leads to weight loss, muscle dysfunction, falls, and immune system impairment, all of which increase the risk of cognitive frailty. Serum albumin is a key indicator of a patient's nutritional status. Research by Gopinathan et al. suggests that low albumin levels increase the incidence of cognitive frailty in elderly CKD patients[29]. Albumin can regulate oxidative stress and promote brain repair after injury, helping to maintain cognitive function[30]. According to Yamamoto et al.[31], low serum albumin levels reduce muscle strength and mass, accelerating the development of frailty.

5.5. CKD-Related Influencing Factors

5.5.1. Estimated Glomerular Filtration Rate (eGFR)

Research suggests that a decline in estimated glomerular filtration rate (eGFR) is one of the primary risk factors for cognitive frailty in elderly CKD patients[18]. Regarding cognitive impairment, the degree of eGFR reduction is closely linked to cognitive dysfunction. When eGFR falls below 60 mL/min/1.73 m², for every 10 mL/min/1.73 m² decrease in eGFR, the risk of cognitive decline increases by 11% [32]. However, this conclusion remains controversial. A cohort study by Helmer et al.[33], which followed patients for seven years, found that the rate of eGFR decline was associated with cognitive ability, but low eGFR levels were not directly linked to cognitive decline. Additionally, a 12-year follow-up study[34] indicated that proteinuria, rather than eGFR-based renal impairment, predicted poor memory function. The discrepancies in findings could be due to the heterogeneity of study populations. Future research may focus on identifying the threshold level of eGFR decline that contributes to cognitive frailty in elderly CKD patients.

5.5.2. Proteinuria

A study by Chang et al. involving 1,015 elderly CKD patients found that proteinuria is a key predictor of cognitive frailty[18]. Elevated proteinuria levels are associated with increased white matter hyperintensities and brain atrophy, thereby raising the risk of cognitive frailty. It is worth noting that a rapid decline in eGFR combined with persistent proteinuria has greater predictive value for cognitive frailty than eGFR decline alone[35, 36].

5.5.3. Dialysis

Research by Chen et al.[27] indicated that compared to elderly CKD patients not undergoing dialysis, those on dialysis had a higher prevalence of cognitive frailty. The duration and frequency of dialysis were found to be correlated with the occurrence of cognitive frailty. Previous studies have shown that hemodialysis is a risk factor for frailty[37], as the acute hemodynamic changes induced by hemodialysis may increase the risk of brain atrophy, thereby affecting cognitive function[25]. However, the relationship between the type of dialysis and cognitive function remains debated. For example, Bin et al.[38] found that peritoneal dialysis patients experienced more severe cognitive impairment than those undergoing hemodialysis. Conversely, a meta-analysis involving 195,774 patients[39] concluded that peritoneal dialysis patients demonstrated better cognitive function. Therefore, more research is needed to clarify the relationship between dialysis types and cognitive frailty, potentially through large-scale data analysis.

5.5.4. Anemia

Anemia is one of the common complications of CKD and can lead to reduced erythropoiesis and decreased hemoglobin levels. Existing research shows that lower hemoglobin levels are closely associated with cognitive frailty in elderly CKD patients[20]. A decrease in hemoglobin levels restricts oxygenation to peripheral tissues, reducing brain tissue metabolism and neuronal activity, which in turn leads to cognitive decline. Additionally, anemia induces fatigue, reduces muscle mass and strength, and contributes to the onset of frailty.

Firstly, this may be related to the limited oxygenation of peripheral tissues due to low hemoglobin levels[37]. Studies have pointed out that lower hemoglobin levels are associated with reduced cerebral

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blood flow, which decreases brain tissue metabolism and neuronal activity[38]. Prolonged hypoxia affects the excitatory expression of iron channels, leading to neurodegenerative changes. Both factors contribute to cortical atrophy[39], and anemia is also a contributing factor to physical frailty, further increasing the risk of cognitive frailty. Secondly, anemia is associated with chronic diseases and inflammation. Increased levels of inflammation in the elderly are related to hippocampal shrinkage, which raises the risk of cognitive impairment. Thirdly, some studies suggest that anemia increases the risk of white matter hyperintensities, which are linked to cognitive dysfunction.

6. Conclusion

Cognitive frailty has become a new hotspot in the field of international nursing, while domestic research on this topic is still in its early stages. The concept and assessment tools for cognitive frailty are not yet unified, with screening and evaluation mainly based on various scales. These methods are labor-intensive, difficult to standardize, and vary across study populations and settings, making it challenging to ensure the accuracy of evaluation results. Additionally, there is a general lack of precise, specific multi-omics indicators. Future research should focus on developing fast, simple, and standardized tools for assessing cognitive frailty, constructing a "gold standard" based on objective indicators, and further standardizing the application of these tools across different populations and settings.

Cognitive frailty is prevalent among the elderly CKD population, but research on this topic remains scarce both domestically and internationally, and most studies are cross-sectional. Future research should aim to conduct large-scale epidemiological studies on cognitive frailty in elderly CKD patients to enrich the body of evidence. Prospective studies are needed to clarify the causal relationship between cognitive frailty and its influencing factors, providing a foundation for the development of targeted intervention strategies for cognitive frailty in elderly CKD patients.

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