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# THE RELATIONSHIP BETWEEN CHRONIC KIDNEY DISEASE AND FRAILTY IN GERIATRIC PATIENTS: A SYSTEMATIC REVIEW

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**Abstract:**

***Objectives:*** *This systematic review synthesizes current evidence on the prevalence of frailty in geriatric patients with chronic kidney disease (CKD), the impact of CKD on frailty development and progression, and the potential mechanisms underlying the relationship between the two conditions.* ***Methods:*** *To discover the pertinent literature, a thorough search was conducted across four main databases: PubMed, MEDLINE, and Embase.* ***Results:*** *We included thirteen studies with a total of 25,191 patients and 11,809 (46.9%) were males. The reported follow-up duration ranged from 3 months to 4 years. The prevalence of frailty among elderly CKD patients ranged from 11.9% to 86% with a total prevalence of 9351 (37.1%). Frailty among elderly CKD patients significantly increased, and higher baseline frailty was linked to higher death. Independent of other confounding factors, these individuals had a significantly higher risk of frailty/pre-frailty when they had increasing age, CKD, MetS, high CKD stage, significant proteinuria, and low serum albumin level, higher concentrations of cystatin C, lower 25OHD, albumin, hemoglobin concentrations, depression, decreased social support, and eGFR. Frailty is linked to increased rates of malnutrition, decreased physical performance, HRQoL, and mental and cognitive problems.* ***Conclusion:*** *Among patients with CKD, frailty is a significant predictor of death, hospitalization, and falls. According to our research, keeping an eye on these patients' frailty conditions and incorporating that data into a thorough evaluation can help to better direct the therapeutic care of this group. Despite the fact that we discovered a connection between frailty and unfavorable outcomes in CKD, this conclusion should be interpreted cautiously due to the paucity of relevant studies in the literature. Lastly, admitting frailty ought to start conversations with patients about their preferences for future care.*

***Keywords: Chronic kidney disease; Frailty; Geriatric patients; Comorbidities; Physiological reserve.***

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## BACKGROUND

CKD and frailty are two common conditions that often coexist in geriatric patients, leading to a significant impact on their overall health and quality of life. Understanding the relationship between these two conditions is crucial for healthcare providers in order to provide optimal care and management for this vulnerable population. In this systematic review, we will explore the current literature on the relationship between CKD and frailty in geriatric patients [1].

CKD is a progressive condition characterized by a gradual loss of kidney function over time. It is a common condition in older adults, with prevalence increasing with age. CKD can lead to a number of complications, including cardiovascular disease, anemia, bone disorders, and electrolyte imbalances. Frailty, on the other hand, is a state of increased vulnerability to stressors due to decreased physiological reserves, leading to a higher risk of adverse health outcomes such as falls, hospitalizations, and mortality [2].

Several studies have shown a strong association between CKD and frailty in geriatric patients. Studies have shown that frailty prevalence among dialysis-dependent CKD patients is greater than 60%, the prevalence of frailty in the population of older adults living in the community is reported to be 11%. The ARIC Study (Atherosclerosis Risk in Communities) found a high correlation between frailty and increasing renal impairment. Moreover, frailty has been frequently demonstrated to be connected to an increased risk of mortality and hospitalisation, and it is independently linked to unfavourable clinical outcomes in all stages of CKD. These findings suggest that there is a bidirectional relationship between CKD and frailty, with each condition potentially exacerbating the other [2, 3].

The mechanisms underlying the relationship between CKD and frailty are not fully understood, but several potential pathways have been proposed. One possible explanation is the presence of chronic inflammation in both CKD and frailty, leading to a cycle of worsening health outcomes. Another possible mechanism is the impact of CKD-related complications, such as anemia and electrolyte imbalances, on frailty status. Additionally, the presence of CKD can lead to decreased physical activity and muscle wasting, contributing to the development of frailty in older adults [4].

Managing CKD and frailty in geriatric patients requires a comprehensive and multidisciplinary approach. Treatment strategies for CKD may include blood pressure control, management of electrolyte imbalances, and dietary modifications. For frailty, interventions may focus on physical exercise, nutrition, and social support. It is important for healthcare providers to recognize the relationship between CKD and frailty in geriatric patients and tailor their treatment plans accordingly [5].

Despite the increasing prevalence of CKD and frailty among geriatric patients, there is a lack of comprehensive understanding of the relationship between these two conditions. The impact of CKD on the development and progression of frailty in older adults remains poorly understood, hindering the development of effective strategies for the management and prevention of these interconnected health issues. Therefore, there is a critical need for a systematic review to synthesize existing evidence and identify gaps in knowledge to inform clinical practice and guide future research in this area.

The significance of the study lies in its potential to address a critical gap in understanding the complex interplay between two prevalent conditions in geriatric populations. By systematically reviewing the existing literature on the relationship between CKD and frailty, this study can provide valuable insights into the prevalence, impact, and potential mechanisms linking these two conditions. Understanding this relationship is crucial for improving the management and care of

geriatric patients with CKD, as frailty can significantly impact treatment outcomes, quality of life, and overall health status. The findings from this study can inform healthcare providers, policymakers, and researchers on the importance of considering frailty in the context of CKD management, leading to more tailored and effective interventions for this vulnerable population. Ultimately, the study's significance lies in its potential to contribute to the advancement of geriatric care and improve the overall health outcomes of older adults with CKD. Thus, the aim of this systematic review is to investigate the relationship between CKD and frailty in geriatric patients, with a focus on understanding the prevalence, impact, and potential mechanisms underlying this relationship.

**Study Objectives:**

1. To determine the prevalence of frailty in geriatric patients with chronic CKD.
2. To assess the impact of CKD on the development and progression of frailty in older adults.
3. To identify potential mechanisms linking CKD and frailty in geriatric populations.
4. To evaluate the existing evidence on interventions and management strategies for frailty in geriatric patients with CKD.

**Methods**

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6]. A comprehensive search of electronic databases, including PubMed, MEDLINE, and Embase, was conducted to identify relevant studies published in English. The search strategy included keywords related to CKD, frailty, and geriatric patients. Two independent reviewers screened the search results, selected eligible studies, extracted data, and assessed the quality of included studies using appropriate tools.

**Eligibility Criteria**

**Inclusion Criteria:**

1. Studies investigate the relationship between CKD and frailty in geriatric patients.
2. Studies involving geriatric patients aged 60 years and older.
3. Studies conducted between 2018-2024.
4. Studies published in English.
5. Studies that report on the prevalence, impact, mechanisms, interventions, or management strategies related to CKD and frailty.
6. Randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies.

**Exclusion Criteria:**

1. Studies that do not focus on geriatric patients.
2. Studies that do not specifically address the relationship between CKD and frailty.
3. Studies with participants younger than 60 years old.
4. Studies published in languages other than English.
5. Case reports, editorials, letters, and conference abstracts.
6. Studies with insufficient data or unclear methodology.

**Data Extraction**

The search results were verified using Rayyan (QCRI) [7] to ensure accuracy. Inclusion and exclusion criteria were applied to the search results to assess the relevance of titles and abstracts. Selected papers meeting the inclusion criteria underwent detailed scrutiny by reviewers. Any conflicts were resolved through discussion. A pre-prepared data extraction form was utilized to input relevant study details, such as titles, authors, study year, location, participants, gender, duration of diabetes, prevalence of dementia, and key outcomes. A separate document was created for the assessment of bias risk.

**Data Synthesis Strategy**

Summary tables were generated based on information extracted from relevant studies to provide a qualitative evaluation of the research findings and components. Once data for the systematic review is collected, the most effective approach for utilizing the information from the included studies will be determined.

**Risk of Bias Assessment**

The Joanna Briggs Institute (JBI) [8] critical assessment criteria for studies reporting prevalence data were employed to evaluate research quality. This tool comprises nine questions, with a score of 1 assigned to affirmative responses and 0 to negative, ambiguous, or not applicable responses. Overall quality ratings of $< 4$, 5 to 7, and $\geq 8$ were considered as low, moderate, and excellent quality, respectively. Researchers independently assessed study quality, with any discrepancies resolved through discussion.

## RESULTS:

### Search results

After a thorough search, 713 study articles were found; 322 duplicates were eliminated. After 391 studies had their titles and abstracts screened, 312 were not included. Only four reports that were requested were not found. After screening 75 papers for full-text assessment, 42 were rejected due to incorrect study results, 17 were rejected due to incorrect population type, and 3 articles were editor's letters. This systematic review contained thirteen acceptable research papers. An overview of the procedure used to choose studies is provided in **Figure 1.**

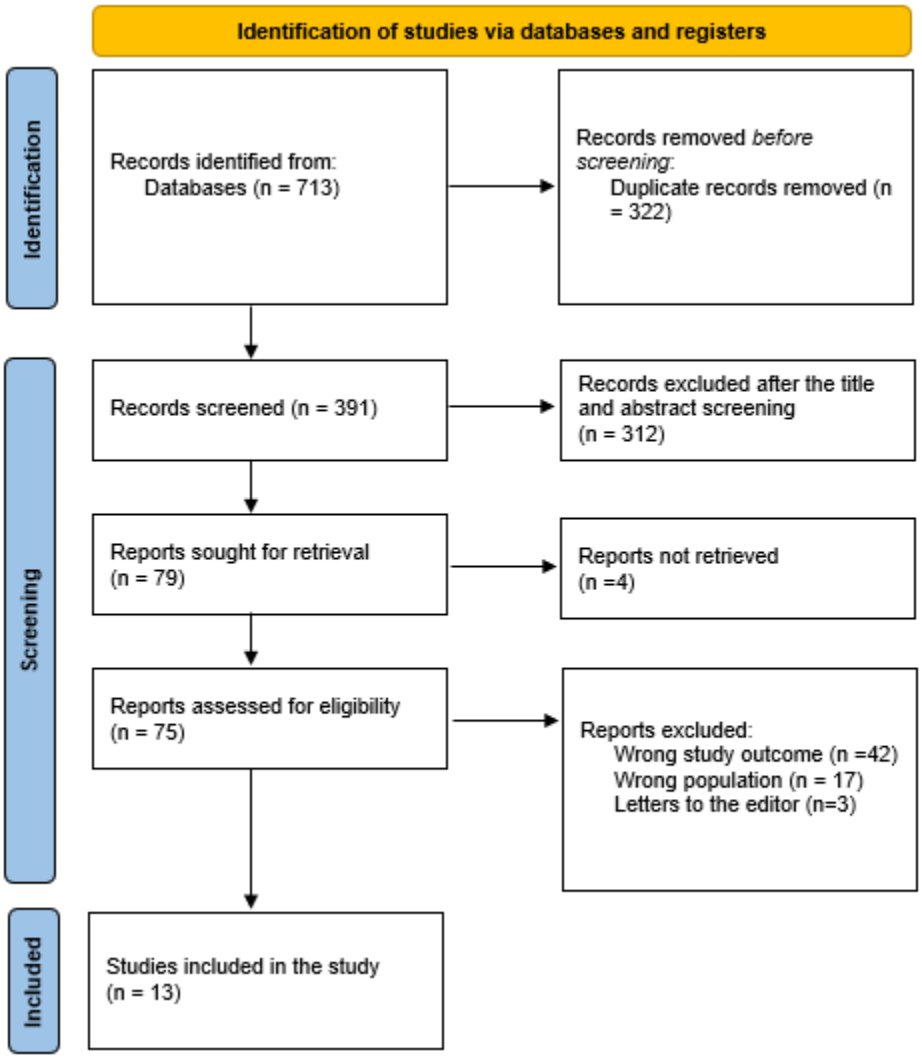


**Figure (1): Study selection is summed up in a PRISMA flowchart.**

**Characteristics of the included studies**

**Table (1)** presents the sociodemographic characteristics of the included study articles. Our results included thirteen studies with a total of 25,191 patients and 11,809 (46.9%) were males. Eight of the included studies were cross-sectionals [12, 13, 15-18, 20, 21] and five were prospective in nature [9-11, 14, 19]. Five studies were conducted in China [11, 13, 17, 18, 21], two in Australia [9, 21], two in Japan [14, 19], two in the United Kingdom [12, 15], one in Taiwan [10], and one in Italy [16].

**Table (2)** presents the clinical characteristics. The reported follow-up duration ranged from 3 months [16] to 4 years [9]. The prevalence of frailty among elderly CKD patients ranged from 11.9% [18] to 86% [9] with a total prevalence of 9351 (37.1%). Frailty among elderly CKD patients significantly increased, and higher baseline frailty was linked to higher death [9]. Independent of other confounding factors, these individuals had a significantly higher risk of frailty/pre-frailty when they had increasing age [9-21], CKD, MetS [10], high CKD stage, significant proteinuria, and low serum albumin level [11, 15], higher concentrations of cystatin C, lower 25OHD, albumin, hemoglobin concentrations [12], depression, decreased social support [17], and eGFR [17-19]. Frailty is linked to increased rates of malnutrition, decreased physical performance, HRQoL, and mental and cognitive problems [15, 16].

***Table (1): Sociodemographic characteristics of the included participants.***

| Study | Study design | Country | Participants | Mean age | Males (%) |
|---|---|---|---|---|---|
| **King et al., 2023 [9]** | Prospective observational study | Australia | 98 | 76.3 ± 7.3 | 54 (55%) |
| **Chao et al., 2020 [10]** | Prospective observational study | Taiwan | 2862 | 73.4 ± 6.7 | 1279 (45%) |
| **Wang et al., 2023 [11]** | Prospective observational study | China | 774 | 64-72 | 511 (66%) |
| **Smith et al., 2021 [12]** | Cross-sectional | UK | 300 | 74 ± 7.1 | 214 (71%) |
| **Weng et al., 2023 [13]** | Cross-sectional | China | 560 | 83.4 | 428 (76.4%) |
| **Yoshida et al., 2020 [14]** | Prospective cohort | Japan | 310 | 83.1 | 166 (54.6%) |
| **Nixon et al., 2020 [15]** | Cross-sectional | UK | 90 | 73 ± 11 | 45 (50%) |
| **Vettoretti et al., 2020 [16]** | Cross-sectional | Italy | 112 | 80 ± 6 | 78 (70%) |
| **Chang et al., 2022 [17]** | Cross-sectional | China | 1015 | 82 ± 8.6 | 607 (59.8%) |
| **Yang et al., 2024 [18]** | Cross-sectional | China | 177 | 70.8 ± 8.8 | 92 (51.9%) |
| **Inoue et al., 2021 [19]** | Prospective cohort | Japan | 630 | 70-84 | 315 (50%) |
| **Walker et al., 2023 [20]** | Cross-sectional | Australia | 17759 | 75.1 ± 4.6 | 7737 (44%) |
| **Wang et al., 2024 [21]** | Cross-sectional | China | 504 | 70.5 ± 6.4 | 283 (56.2%) |

**Table (2): Clinical characteristics and outcomes of the included studies.**

| Study | Follow-up duration (years) | Frailty diagnostic tool | Frailty prevalence | Main outcomes | JBI |
|---|---|---|---|---|---|
| **King et al., 2023 [9]** | 4 | 84 (86%) | Frailty index (FI) | Over four years, frailty significantly increased, and higher baseline frailty was linked to higher death. Starting dialysis had a beneficial impact on QOL from baseline to follow-up but had no effect on the trajectory of FI. | Moderate |
| **Chao et al., 2020 [10]** | NM | 494 (17.3%) | Study of Osteoporotic Fractures (SOF) | Independent of other confounding factors, these individuals had a significantly higher risk of frailty/pre-frailty when they had increasing age, CKD, and MetS. Furthermore, participants over 85 years of age negated the correlation between MetS and frailty/pre-frailty, while higher CKD stages emphasized the association. | Moderate |
| **Wang et al., 2023 [11]** | 36.5 (months) | 259 (33.5%) | FI | Even before dialysis, sarcopenia and frailty are common in older adults with CKD. A higher risk of frailty was found to be independently correlated with sarcopenia. Frailty should be evaluated in patients with advanced age, sarcopenia, high CKD stage, significant proteinuria, and low serum albumin level. | Low |
| **Smith et al., 2021 [12]** | 1 | 234 (78%) | NM | Compared to the overall older population, the group of patients with advanced CKD had a higher prevalence of frailty. Higher concentrations of cystatin C, lower 25OHD, albumin, hemoglobin concentrations, and older age were all linked to frailty. | Moderate |
| **Weng et al., 2023 [13]** | 2.92 | 278 (49.6%) | Rockwood frailty index | This study's key conclusion was that frailty was more common in older adults with CKD and diabetes. Research has demonstrated the synergistic impact of CKD, frailty, weak handgrip strength, and prolonged timed up-and-go-on survival in senior diabetic patients. | Moderate |
| **Yoshida et al., 2020 [14]** | 27.3 (months) | 103 (33.2%) | Rockwood frailty index | Dialysis patients who are frail have a dismal outlook. Comorbidities, diet, and particularly geriatric syndrome were linked to frailty. | Moderate |
| **Nixon et al., 2020 [15]** | 1 | 19 (21.1%) | Frailty Phenotype (FP) | In patients with CKD Stages 4 and 5, frailty is independently linked to lower HRQOL; the most important frailty phenotype component influencing HRQOL is self-perceived tiredness. | High |

| | | | | | |
|---|---|---|---|---|---|
| **Vettoretti et al., 2020 [16]** | 1 | 50 (45%) | FP | FP is 45 percent common in elderly people with CK and is linked to increased rates of malnutrition, decreased physical performance, and mental and cognitive problems. | Moderate |
| **Chang et al., 2022 [17]** | 3 (months) | 154 (15.2%) | FRAIL scale (FS) | Among elderly CKD patients, cognitive frailty was highly prevalent. The disease was associated with independent risk variables such as advanced age, comorbidities, depression, decreased social support, eGFR, and albuminuria. | Moderate |
| **Yang et al., 2024 [18]** | NM | 10 (11.9%) | FS | Frailty and prefrailty were prevalent in CKD patients who did not receive dialysis. In this sample, frailty was correlated with daily step counts, BMI, and eGFR. | Moderate |
| **Inoue et al., 2021 [19]** | NM | 252 (40%) | Kihon Checklist Score | In patients with chronic renal disease, pre-frailty and frailty were more common. Urinary protein data is added to eGFR, strengthening the correlation between CKD and frailty. | Moderate |
| **Walker et al., 2023 [20]** | NM | 7323 (41%) | Fried | When it comes to understanding the onset of frailty in older persons, albuminuria may be more significant than eGFR. More research is necessary to fully understand the complex link between albuminuria (which may be a biomarker for vascular inflammation), aging, increasing CKD, and frailty. | High |
| **Wang et al., 2024 [21]** | NM | 91 (18%) | FP | In older patients with CKD, depression is a mediating factor in the connection between sleep problems and physical frailty. | Moderate |

## DISCUSSION:

The prevalence of frailty in patients with CKD was found to be relatively high (37.1%) in this comprehensive study, and it rose as kidney function declined. Adverse health outcomes were significantly predicted by frailty, especially in individuals with severe stages of CKD. Frailty among elderly CKD patients significantly increased, and higher baseline frailty was linked to higher death [9]. **Mei *et al.*** conducted a meta-analysis of 22,788 CKD patients and reported a higher risk of frail and prefrail patients (41.8%) [22]. Sarcopenia, protein-energy wasting (PEW), and inflammation were potential risk factors for death among fragile individuals with CKD [23, 24]. Research has indicated that people with CKD are more likely to develop sarcopenia and eventual physical frailty due to the unavoidable loss of amino acids and protein during dialysis and the decreased dietary protein intake of these patients [25]. Long-term muscle loss may also contribute to a decline in bodily functions and raise the chance of death for CKD patients [26].

Frailty has long been thought to be an age-related condition, but according to **Kallenberg *et al.*** [27], it actually represents biological and phenotypic age rather than chronological age [28]. Furthermore, **Kojima *et al.*** [29] discovered that young patients with prefrailty had a higher chance of recovering and returning to health. However, patients with CKD under the age of 60 have not received enough attention in the literature currently in publication. As a result, we highly recommend that more research be done to clarify the significance of prefrailty and frailty in younger CKD patients. Significantly, our review verified that, despite the fact that dialysis patients typically have worse physical conditions, frailty raises the risk of death in CKD patients whether or not they receive it [30]. It could be explained by the fact that there is a dearth of research on the fragility of non-dialysis CKD and that symptoms in early CKD are not always evident or simple to identify.

This review reported that independent of other confounding factors, these individuals had a significantly higher risk of frailty/pre-frailty when they had increasing age [9-21], CKD, MetS [10], high CKD stage, significant proteinuria, and low serum albumin level [11, 15], higher concentrations of cystatin C, lower 25OHD, albumin, hemoglobin concentrations [12], depression, decreased social support [17], and eGFR [17-19]. Frailty is linked to increased rates of malnutrition, decreased physical performance, HRQoL, and mental and cognitive problems [15, 16]. A similar systematic review by **Chowdhury *et al.* [31]** reported that a lower glomerular filtration rate was associated with a higher incidence of frailty. There was a correlation between frailty and a higher risk of hospitalization and death.

In the elderly population, low levels of 25(OH)D have been linked to frailty [32, 33]. In the kidney's proximal tubule, 25(OH)D is hydroxylated to produce the more potent 1,25-dihydroxyvitamin D [1,25(OH)2 D] [34]. Deficits in 1,25(OH)2D are common in people with CKD because levels of the vitamin decline with increasing renal impairment [35]. Research indicates that vitamin D may influence contractile muscle performance and muscle metabolism by directly acting on skeletal muscle via genomic and non-genomic mechanisms [35].

We suggest that the FP be evaluated in subsequent research involving patients with advanced CKD in order to facilitate more precise comparisons and conclusions. As of right now, the choice to start renal replacement treatment should be taken in consultation with each patient, taking into account their perceived risks and advantages in light of the scant data that is now available. In the absence of a clear consensus, patient desire and unique circumstances should determine the modality used if a patient chooses renal replacement treatment. We think that by acknowledging frailty in these conversations, a meaningful opportunity is presented to ascertain the patients' intentions regarding their future care.

This systematic review has both inherent strengths and limitations. It includes a wide variety of CKD groups, such as dialysis patients, community members who do not get dialysis, and recipients of kidney transplants. With 25,191 patients, the total sample size is substantial. Nonetheless, there was a great deal of heterogeneity throughout the studies due to variations in the frailty evaluation techniques used in each.

## CONCLUSION:

Among patients with CKD, frailty is a significant predictor of death, hospitalization, and falls. According to our research, keeping an eye on these patients' frailty conditions and incorporating that data into a thorough evaluation can help to better direct the therapeutic care of this group. Despite the fact that we discovered a connection between frailty and unfavorable outcomes in CKD, this conclusion should be interpreted cautiously due to the paucity of relevant studies in the literature. Lastly, admitting frailty ought to start conversations with patients about their preferences for future care.

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