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Association between cognitive impairment and frailty in chronic kidney disease (CKD patients – A case control study

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Abstract

Aims & Objectives: To find the association between cognitive impairment and frailty in CKD Patients

Materials & Methods: A hospital based case control study was conducted among CKD patients above age 50 who presented to MES Medical college during 1st January 2021 to 31st December 2021. They were categorized into cases and controls in 1:1 ratio after satisfying fried frailty criteria. Sample size required was 114 with 57 cases and 57 controls. On fulfilment of the inclusion and exclusion criteria, all eligible patients were subjected to frailty assessment. All these patients underwent evaluation for mild neurocognitive impairment with Montreal Cognitive Assessment (MoCA)scale. Date entered and analysis done using SPSS software version 25.

Results: total of 114 patients enrolled in the study.57 cases and 57 controls. Both males and females were on equal proportion. Mean age of cases and controls were 68.65 ± 8.96 years and 63.96 ± 8.34 years, respectively. Results showed that following factors were associated with frailty in CKD patients: (MoCA) Score (p value<0.001), PHQ9 score (p value=0.001), Edmonton score (p value<0.001) Multivariable analysis identified Edmonton frailty score (p=0.002, OR =1.44, 95% CI 1.14-1.81)as a statistically significant predictor of frailty. Cases were having 1.44 times higher odds of having cognitive impairment and functional dependence than controls.

Conclusion: The study concluded thatCognitive impairment and functional dependence were more associated with frail cases compared to non-frail cases

Keywords: Chronic Kidney Disease**,**MOCA score, Edmonton score, Hemodialysis

Introduction

Global population ageing is rising, with an anticipated 2 billion individuals over the age of 65 in the world by 2050, up from 461 million in 2004. The process of ageing is the result of a lifetime accumulation of molecular and cellular damage brought on by several causes, which are controlled by a sophisticated network of maintenance and repair systems. [1]

As people get older, the rate at which their body's physiological function declines increases continuously. Yet, this pace of deterioration varies and is influenced by a variety of biological, psychological, genetic, and social factors.[2] Beyond a certain point of physiological decline, one develops a dependency, which may involve a dependence on a pharmaceutical, a mobility help, a sensory aid, a psychological aid, or even another. Because of this dependence's cumulative nature, those who have it are more susceptible to insults from unimportant illness or damage. This kind of physiological decline in the elderly is linked to a large death rate. Active or robust people, on the other hand, have a higher physiological reserve, which enables them to tolerate higher amounts of stress.

Frailty is a condition of increased susceptibility to stresses as a result of aging-related changes and the depletion of physiological reserves in the immunological, metabolic, and neuromuscular systems. Age-related losses in lean body mass, strength, endurance, balance, walking ability, and low activity are indicators of the condition. This is probably related to the diminished ability of the homeostatic system to endure stressors and the resulting vulnerabilities. The complex mechanisms of ageing, cumulative decline in several physiological systems, subsequent depletion of homoeostatic reserve, and vulnerability to disproportionate changes in health status following minor stressor events are thus important perspectives for healthcare professionals to take into account.[1]

Elderly people who are frail are more likely to fall, end up in the hospital, become disabled, and die. Frailty was also discovered to be a standalone predictor of these results. Although frailty and ageing are sometimes used interchangeably, it is now known that the two are not always connected. It is generally recognized that chronic illnesses or comorbidities accelerate the physiological ageing process and lead to frailty at a younger age than would be predicted. When two or more diseases are present, the chance of frailty increases, but not everyone who is weak has multi-morbidity. As a result, it is possible that frailty is either a physiological aspect of ageing or the final common pathway of a serious illness or comorbidity.

One of the fundamental ideas of ageing is sarcopenia, which greatly influences the frailty phenotype. Muscle deterioration begins in midlife and is caused by morphological and biochemical changes in ageing muscles that are sped up by inactivity or persistent inflammation. Weakness is a clinically significant signal of rising vulnerability to frailty and was the most prevalent early manifestation of the frailty phenotype. [3]

It's debatable whether or not frailty is an age-related phenomenon. Although older people are more prone to be feeble by nature, frailty can also occur in younger persons with low physical stamina and numerous comorbidities. These younger frail people have a higher risk of dying than those in their age group who are not frail.

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Many research conducted over the past 20 years have confirmed the validity of several frailty assessment techniques. The Fried Frailty Phenotype, the Frailty Index as defined by Rockwood et al., the PRISMA 7 test, the timed Up-and-go test, the Edmonton Frail Scale, and numerous other tests are among the most often utilized. These tests are extremely valuable when used in large-scale community evaluations or in the OPD clinic environment because they are mostly based on brief clinical assessments and self-reported questionnaires.

Aging causes a gradual decline in many physiological systems, which leaves people with less physiological reserve and more susceptibility to stress.[4,5]

Frailty is a complex condition marked by a lack of reserve, a high susceptibility to physical stressors like sickness or trauma, and an elevated risk of poorer clinical outcomes. It results from the cumulative and sustained degradation of several physiological systems, which may also be brought on by a decline in mental health and a lack of social support.

It is believed that the accumulation of many deficiencies across various systems serves as the foundation for the emergence of frailty.[6]

Chronic kidney disease (CKD) is a state of accelerated metabolic aging, evidenced by accumulation of advanced glycation end products, oxidative stress, chronic inflammation, insulin resistance, vascular calcification, and osteoporosis.[5]

It is unclear exactly how frailty and chronic kidney disease (CKD) are related. Inflammation has been linked to frailty in many chronic diseases, according to a thorough investigation by Jeffery et al. This raises the possibility that frailty has a "shared pathophysiology."[7]

Worldwide, chronic kidney disease (CKD) is a growing public health concern. According to the Global Burden of Disease study, CKD will be the leading cause of death for over 1.4 million people worldwide in 2019, up 20% from 2010.[4]

According to estimates by Fried and colleagues, the prevalence of frailty ranges from 7% of people over 65 to 40% of people over 80. [2] Frailty is more common in dialysis-dependent CKD patients than in the general population, with rates ranging from 14% to 73%, according to recent studies. [8] The prevalence of frailty among patients with stages 1 through 4 of CKD is almost 14%, more than twice as high as that of older persons living in the community.[9]

It is believed that a number of variables, such as protein energy wasting, anemia, acidosis, and hormonal imbalances, contribute to the occurrence of frailty in CKD patients. [10] Figure 2 shows the epidemiology of sarcopenia and frailty.[11]

Frailty phenotype rises with age: 65-69 years 4%, 70-74 years 7%, 75-79 years 9%, 80-84 years 16%, and more than 85 years 26%. It is statistically more common in women (9.6%) than in men (5.2%).[12]

Even in younger people, Johansen et al.13 discovered a significant correlation between frailty and end-stage renal illness. The Dialysis Morbidity and Mortality Wave 2 cohort of 2,275 dialysis patients was evaluated, and it was discovered that two thirds of them were fragile. Frailty was linked to hospitalization and death, regardless of age, comorbidities, or laboratory measurements obtained during dialysis.[2, 13-15]

The Atherosclerosis Risk in Communities (ARIC) Study demonstrated that frailty is directly proportional to the progressive renal dysfunction.[16]

Frailty has been defined as a phenotype of reduced physiological reserves and diminished ability to respond

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to stressors and has been found to be associated with falls, hospitalization, and death.[14]

The criteria for defining frailty were the Short Physical Performance Battery (SPPB), Frailty Index, and Frailty Phenotype. By measuring the capacity to stand in three positions, the time it takes to stand up from a seated position five times, and the time it takes to walk a short distance, SPPB assesses the degree of impairment. [14,17] A assessment instrument called the Frailty Index focuses mostly on self-reported impairments or co-occurring medical issues. The Frailty Index of a patient is calculated by dividing the total number of clinical markers examined by the number of clinical impairments identified.[14,18]

According to the Fried Criteria, the frailty phenotype is a multifaceted illness that is typically present in kidney patients. It determines frailty based on the existence of severe impairment in 3 of the 5 categories, including weariness, sluggishness, weakness, weight loss, and poor activity. 2 Cognitive function has recently been added.[19]

Patients are classified as frail if they have three or more of the five characteristics, pre-frail if they have one or two, and fit or robust old patients if they have none.[2]

Chronic kidney disease: Is defined as abnormalities of kidney structure or function, present for >3months, with implications for health.[20]

Criteria for CKD (Either of the following present for>3months)

Markers of kidney damage (one or more):

-Albuminuria (AER>30mg/24hours; ACR>3Omg/g (>3mg/mmol)

-Urine sediment abnormalities

-Electrolyte and other abnormalities

-Abnormalities detected by histology

-Structural abnormalities detected by imaging

-History of kidney transplantation.

Decreased GFR: -GFR <60ml/min/1.73m2

Cognitive Impairment in CKD

Epidemiology of Cognitive Impairment in CKD:

The prevalence of cognitive impairment and dementia in people with ESRD is more than twice as high as it is in people who live in communities.A loss in one or more important brain functions, such as memory, learning, focus, and decision-making, is referred to as cognitive impairment.[21] More than predicted cognitive deterioration with ageing, but not one that interferes with day-to-day life. [22]Low cognitive function is linked to low health literacy, less effective drug use, poor physical and mental health, and higher death and morbidity rates. [22]Patients undergoing haemodialysis (HD) frequently experience depression. According to studies, depressive symptoms are prominent in 20–30% of HD patients.[23]

As people with CKD have a higher risk of cerebrovascular disease, a higher burden of cardiovascular risk factors like diabetes, hypertension, and dyslipidemia, metabolic dysregulation, and direct effects of kidney disease, a number of potential mechanisms have been postulated that may link CKD with cognitive impairment.[24,25]There are three levels of cognitive impairment: mild, moderate, and severe. When severe impairment affects a person's ability to live independently and with daily activities, it is often dementia.[21]When compared to the general population, people with proteinuria or CKD (eGFR 60ml/min/1.73m2) are more likely to experience cognitive impairment. 21 Cognitive dysfunction is correlated with the duration of kidney disease rather than the severity of renal impairment.[26]

Based on diagnostic techniques and CKD stage, the prevalence of cognitive impairment in CKD patients

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ranges from 10 to 40%. Those receiving dialysis had a higher risk of cognitive impairment.Both albuminuria and low estimated GFR (eGFR) are independent risk factors for cognitive impairment. Albuminuria is the biggest risk factor in patients with greater eGFR, while advanced CKD patients' eGFR is the strongest risk factor.[21]Out of 374 dialysis patients, 13% had normal cognitive function, 50% had mild cognitive impairment, and 37% had severe cognitive dysfunction, according to a study by Murray et al. [27]In contrast to the general population, dialysis patients have a higher prevalence of cognitive impairment, according to a comparative study by Sarnak et al.[28]In cross-sectional and longitudinal studies, respectively, cognitive impairment and incident cognitive impairment were more prevalent in CKD patients compared to individuals without CKD, according to a comprehensive review by Etgen et al. [29].

However, one study[29] suggested that there is a similar high prevalence of cognitive impairment in peritoneal dialysis compared with HD, indicating that the dialysis modality is not the only contributing factor in the pathogenesis of CKD related cognitive impairment. There are few studies comparing the dialysis modality and its association with cognitive impairment. [21] Even if kidney transplantation plays a protective effect, returning to normal cognitive function is virtually impossible.[30]There are few research on the effects of cognitive impairment, but those that do imply that patients who are on maintenance HD and have cognitive impairment need more time with dialysis personnel, spend most of the time in hospitals, and have a high mortality risk.[21]

Chronic illnesses, particularly chronic renal failure, are linked to an underlying inflammatory process that considerably speeds up the frailty cycle's advancement. Because to the morbidity and physiological changes linked to CKD, patients with CKD are more than twice as likely to report decreased physical activity as those without CKD. Frailty is more common in CKD patients, which may be caused by malnutrition, dialysis need, comorbidities, advancing age, or psychosocial problems. Frailty may also appear in CKD patients considerably earlier than is typical for their age group.6This study aims to find the association between cognitive impairment and frailty in CKD patients.

Materials & Methods

Study protocol was approved by the Institutional ethics committee of MES Medical College, Perinthalmanna (IEC/MES/12/2020) dated 5/12/2020 and written informed consent was obtained from all study participants. This Case control study was conducted among the Patients attending Outpatient and Inpatient departments of MES Medical College, Perinthalmanna between January 1 2021 to December 31 2021 where included.

Working Definition

Chronic Kidney Disease (CKD): Is defined as abnormalities of kidney structure or function, present for >3months, with implications for health.[5]

Criteria for diagnosis of CKD (Either of the following present for>3months)

Presence of Markers of kidney damage (one or more):

- Albuminuria (AER>30mg/24hours; ACR>3Omg/g (creatinine >3mg/mmol)
- Abnormal urine sediments
- Electrolyte and other abnormalities
- Abnormal kidney histology
- Structural abnormalities detected by imaging
- History of kidney transplantation.
- Decreased GFR: -GFR <60ml/min/1.73m2

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Frailty[1]:

Fried frailty phenotype:

-Hand grip strength in bottom 20% of healthy elderly distribution*

-walking speed in bottom 20% of healthy elderly distribution*

-Self-reported exhaustion

-physical inactivity

-at least 4.5kg weight loss within 1 year

Patient is defined as frail if 3 or more factors are present; 1-2 factors indicate a pre frail state.

Case selection: After meeting the inclusion and exclusion requirements, all qualified patients underwent a frailty assessment using the Fried et al phenotype and the Edmonton Frailty scale. According to the assessment described above, the patient was included in the study if it was determined that they were frail.

Control: Non frail as well as pre frail patients considered as controls.

Patients diagnosed with chronic kidney disease with CrCL less than 60 mL/min were older than 50 and enrolled in the study. The following patients were excluded from the study: those with functional disability following a stroke, those with active CNS infections, those with a history of substance abuse, those taking medications that affect neurological and psychological performance, those unable to understand instructions related to the evaluation of neuro-cognition, those with active or past history of malignancy, and those unable to provide written informed consent.

Sample size was calculated using Open-Epi version 3.01. Following assumptions were made to calculate the sample size for unmatched case-control study.

Two-sided confidence level (1-alpha): 95

Power (% chance of detecting): 80

Ratio of Controls to Cases: 1

Hypothetical proportion of controls with exposure: 28

Hypothetical proportion of cases with exposure: 53.85

Least extreme Odds Ratio to be detected: 3.00.

Sample Size Cases: 57

Sample Size Controls: 57

Total sample size: 114

Samples were recruited through Convenient sampling.

Data collection:

All patients over the age of 50 with a known diagnosis of stable CKD admitted to the medical ward and attending the MES Medical College's outpatient department were assessed for eligibility after providing written informed permission. All eligible patients who met the inclusion and exclusion criteria underwent a frailty assessment using the Fried et al phenotype and the Edmonton Frailty scale. The patient was treated as a case if the aforementioned assessment revealed that they were fragile. Patients who were neither pre-frail nor frail were used as a control. All of these individuals had their depression and mild neurocognitive impairment measured using the PHQ-9 and MOCA scales, respectively (Patient Health Questionaire-9). A systematic case record form was used to capture data on demographics, the length of the patient's renal disease, comorbidities, and biochemical markers such the CBC, RFT, LFT, electrolytes, TSH, and Vitamin D levels (where available). To rule out any substantial confounding factor, each patient had a thorough physical examination.

Fried Frailty Phenotype

Frailty was defined according to the Fried et al phenotype as the presence of three or more of the following conditions: unintended weight loss (4.5 kg in the preceding year), self-reported weariness, weakness

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(grip strength), slow walking speed, and low physical activity.

Edmonton Frailty Scale

The Edmonton Frail Scale, is a bedside frailty screening scale based on the following Domains:

cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance.

MoCA (Montreal Cognitive Assessment) Scale

The MoCA, which consists of 13 tasks testing the following eight cognitive domains: visuospatial/executive, naming, memory, attention, language, abstract, delayed recall, and orientation, was given to each participant to complete in either Malayalam or English. The sum of the scores from the 13 tasks was used to determine the final score. A score of 26 out of a possible 30 points indicated cognitive impairment. Any participant with 12 or fewer years of formal schooling received an additional point.

Data Analysis

Data analysis was done using SPSS 25 software package.

The median and interquartile range were calculated for quantitative data including MOCA score, PHQ-9 score, CrCl, and other scores. Man-Whitney To find statistically significant differences between the observed median in the two groups, the U test was used. pertaining to numerical data with a normal distribution To establish the statistical significance, the Student's T test was used. To determine statistical significance for qualitative data, the percentage was determined and the Chi Square test was run. A p value of <0.05 was taken as statistically significant. Data was compared between the two groups to detect statistical significance of the risk factors for frailty by univariate analysis. statistically significant data underwent multivariate analysis with logistic regression for evaluating association of individual risk factors.

Results

During the study period, a total of 114 CKD patients were included in the study. They were categorised to cases and controls in the ratio of 1:1 by using fried frailty criteria. 54 of them were analyzed as cases and the rest were represented as controls. The data was tabulated in MS Excel worksheet and analyzed using SPSS software version 25.

Table 1: Gender distribution

Gender	Group		Total
	Cases (%)	Controls (%)	
Female	24(50)	24(50)	48(100)
Male	33(50)	33(50)	66(100)
Total	57 (50)	57(50)	114(100)

The gender distribution among cases showed equal proportion of males and females in both cases and controls.

Table 2: Age of the study population

Age	
Mean ± SD	
Cases	Controls
68.65±8.96	63.96±8.34

Table 3: Comparison of Edmonton frailty scale score between cases and controls

Group	Edmonton frailty scale score		p-value
	Mean ±SD	Median (Q1, Q3)	
Cases n=57	8.96±3.66	10(6,12)	<0.001
Controls n=57	4.47±2.51	4(3,5)	

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The mean and median values of Edmonton frailty scale score in cases were **8.96±0.3.66** and **10(6,12),** that in Control group were **4.47±2.51** and **4(3,5)** respectively. Result shows median distribution of Edmonton frailty scale score significantly different between Cases and controls. (**p<0.001**). Control showed a lower score than cases, and this difference is statistically significant.

Table 4: Comparison of MOCA score between cases and controls

Group	MOCA Score		p - value
	Mean ± SD	Median (Q1, Q3)	
Cases n=57	14.86±6.66	15(10,21)	<0.001
Controls n=57	20.72±5.05	20(16,26)	

The mean and median MOCA scores for cases are **14.86±6.66 and 15(10,21),** while they are **20.72±5.05** and **(16,26)** in the control group The median distribution of MOCA scores between cases and controls is significantly different, according to the results (**p <0.001**). The difference between the control and the cases was higher, and it was statistically significant.

Table 5: Multivariate analysis

Variable	B	SE	Wald	p-value	OR	95 CI for OR	
						Lower	Upper
Edmonton Frailty scale	0.365	0.177	9.66	0.002	1.44	1.14	1.81

In order to identify the significant predictors for frailty, multivariate analysis with logistic regression was performed. The results of the multivariate analysis showed Edmonton frailty scale score is the most significant predictor of frailty with p value **0.002**which also indicates Functional dependency and cognitive impairment. odds ratio(95%CI) was **1.44(1.14,1.81).** that is frail CKD patients had 1.44 times higher odds of having cognitive impairment and functional dependence than robust CKD patients

Discussion

After satisfying inclusion criteria this study included 114 patients in the Outpatient and Inpatient departments of MES Medical College. Patients were categorised to cases and controls in the ratio of 1:1 after scoring fried frailty criteria.

Age

With an equal proportion of men and women, cases were found to be slightly older than controls in this investigation, with mean ages of 68.65 ± 8.96 years and 63.96 ± 8.34 years, respectively. This was consistent with Mansur et al. [31]'s demographics, which showed that participants were 41% female and 59% male with a mean age of 61± 11.5. Our study's age group, represented by Reese et al.[32], had a mean age of 65±8 years. The major prospective study by Roshanravan et al.[5], where the mean age was 5913 years, is another study with comparable demographics. Hart et al.'s[33] study only included male participants, and the study's elder age group had a mean age of 74 5.9 years. In the study by Dalrymple et al.[34], there were 41% men and 59% women, with a mean age of 75.

Edmonton frailty score

In cases, the mean and median values of the Edmonton Frailty Scale score were 8.960.3.66 and 10(6,12), respectively, while they were 4.472.51 and 4(3,5) in the Control group. The median distribution of scores on the Edmonton Frailty Scale between cases and controls is considerably different, according to the results. (p<0.001). The difference between the scores for the control and the cases is statistically significant. Frail patients were 1.44 times more likely than controls to

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have cognitive impairment and functional dependency, according to multivariate analysis and logistic regression.Out of 374 dialysis patients, 13% had normal cognitive function, 50% had mild cognitive impairment, and 37% had severe cognitive dysfunction, according to a study by Murray et al. [27]A comparative investigation by Sarnak et al.[28] found that dialysis patients had a higher prevalence of cognitive impairment than the general population.

In cross-sectional and longitudinal studies, Etgen et al. [29] discovered that CKD patients were more likely to experience cognitive impairment than non-CKD individuals. These findings agreed with the current research.Another study by Berger et al. [35] showed that early-stage CKD is accompanied by cognitive abnormalities, and that these alterations advance differently for various cognitive domains as the disease worsens and eGFR decreases. This is a list of further studies with related conclusions.

Study authors	Study design	Cognitive outcome	Result
Buchman et al[150]	Longitudinal study-886 patients CKD: eGFR<60 mL/min/1.73m2	Cognitive function	Decline in renal function was associated with decline in memory
Helmer et al[151]	Longitudinal: 7839 CKD: eGFR<60 mL/min/ 1.73m2	Incident dementia	No increased risks of cognitive decline or dementia were associated with low eGFR level.
Kurella et al [80]	Longitudinal: 3075 CKD: eGFR<45, 45-59, <60 mL/ min/1.73m2	Cognitive impairment	More advanced stages of CKD (eGFR<45) were associated with increased risk for cognitive impairment.
Seliger et al [152]	Longitudinal: 3349 Inverse of serum creatinine 1/SCr. Elevated SCr: <1.3 mg/ dL if female or <1.5 mg/dL if male	Incident dementia	Elevated serum creatinine was associated with a higher risk of incident dementia among participants with good baseline health.
Present study	Case control 150 CKD: eGFR<60 mL/min/ 1.73m2 Edmonton frail score	Cognitive impairment	frail patients were 1.44 times more likely to have cognitive impairment and functional dependence than controls

MOCA score

In the current research The mean and median MOCA scores for the cases are respectively 14.86±6.66 and 15(10,21), while in the control group they are respectively 20.72±5.05 and (16,26). The results show that there are substantial differences in the median distribution of MOCA scores between patients and controls (p 0.001). Comparing the control with the cases revealed a larger and statistically significant difference. In all cognitive domains, especially memory recall and executive functioning, HD patients outperformed controls in a case control study by Tiffin-Richards et al.36. The MoCA showed good correlation and had a sensitivity of 76.7% and a specificity of 78.6% for identifying patients with cognitive impairment.

In the CRIC COG Study by Yaffe et al. [24], it was discovered that people with more severe renal illness had lower baseline cognitive performance measured across various domains, even after adjusting for a number of possible confounders, including demographic traits and pertinent comorbidities. Results from a cross-sectional study by Kurella Tamura M et al[25] were associated with

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those of the current investigation. Independent of confounding variables, CKD was linked to a higher prevalence of cognitive impairment (odds ratio, 1.23; 95% confidence interval, 1.06 to 1.43). For every 10 mL/min/1.73 m2 decrease in eGFR below 60 ml/min/1.73 m2 in individuals with CKD, the prevalence of cognitive impairment rose by 11% (odds ratio, 1.11; 95% confidence interval, 1.04 to 1.19). The following were some of the study's flaws: The ages of the cases and controls were not matched. Participants were not followed up to determine how the individuals' frailty was progressing, and the educational status of the participants was a confounding factor. We suggest Early frailty assessment of otherwise healthy CKD patients may assist us in starting therapies that enhance quality of life. Due to the fact that earlier frailty assessment might lessen the burden of functional reliance, depression, and neural cognitive impairment in CKD patients..

Conclusion

Cognitive impairment and functional dependence were more associated with frail cases compared to non frail cases

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