Systematic Review Article

Influencing Factors for Malnutrition in Chronic Kidney Disease Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

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This study reviewed the evidence on influencing factors for malnutrition in Chronic Kidney Disease (CKD) patients. A systematic search of PubMed, Web of Science, EMBASE, Cochrane Library, China National Knowledge Infrastructure, and Wanfang Data Knowledge Service Platform for English and Chinese language observational studies published from 1966 to 2022 was conducted. RevMan 5.4.1 software was used for statistical analysis. A total of 13 observational studies with 7,790 study participants were included in the systematic review and meta-analysis. Seven risk factors and two protective factors related to malnutrition were identified. Age (OR=1.29; 95% CI:1.03-1.61), required feeding assistance (OR=3.33: 95% CI:2.55-4.35), living status (with family) (OR=0.49; 95% CI:0.34–0.71), protein intake (OR=0.89; 95% CI:0.85-0.94), comorbidities (OR=1.78; 95% CI:1.03-3.07), long dialysis duration (OR=1.61; 95% CI:1.16-2.24), inadequate dialysis (OR=1.25; 95% CI:1.12-1.40), hemoglobin level (OR=1.84; 95% CI:0.92-3.66), and depression (OR=3.44; 95% CI:2.21-5.34) were associated with an increased influence of malnutrition among CKD patients. This review provides comprehensive evidence of potential influencing factors of malnutrition among CKD patients.

INTRODUCTION

Chronic Kidney Disease (CKD) is a general term used for heterogeneous disorders that affect renal structure and function. At present, malnutrition has emerged as a prevalent clinical complication among CKD patients. Malnutrition is an imbalance between nutrient intake and requirement, leading to deficits in energy, protein, or micronutrients that can adversely impact growth, development, and other critical outcomes (Becker *et al.* 2014). The prevalence of malnutrition among CKD patients in stages 3 to 5 is estimated to range from 11% to 54% worldwide (Carrero *et al.* 2018).

Malnutrition is a life-threatening problem for CKD patients, because has been linked to various adverse health outcomes, heightening the risk of morbidity, mortality, and overall disease burden among CKD patients. It is also an important risk factor for the malignant progression of CKD (Iorember 2018).

Due to the exact pathogenesis of malnutrition in CKD patients is complex, malnutrition often goes undetected and untreated (Barril *et al.* 2022). Therefore, identification of potentially modifiable influencing factors on malnutrition is critical for early implementation of effective interventions. However, in previous studies, the influencing factors for malnutrition are varied, and sometimes the results were inconsistent (Windahl *et al.* 2018; Omari *et al.* 2019; Namuyimbwa *et al.* 2018). In this light, we have conducted a systematic review and meta-

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analysis to assess malnutrition factors among CKD patients. This aims to identify these factors early, allowing us to take protective measures to reduce malnutrition occurrence, thereby improving CKD patients' health.

METHODS

Design, location, and time

The design of this study was a systematic review on published articles from 1966 to 2022, using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines throughout all the processes (PRISMA 2020). The review protocol was registered in PROSPERO 2022 (CRD42022353103). The inclusion criteria of this review includes: 1) peerreviewed observational studies written in English and Chinese; 2) the study population age was 18 and above, diagnosed with CKD; 3) focusing on influencing factors for malnutrition, and 4), used valid and reliable parameters or instruments to evaluate malnutrition. While the exclusion criteria were includes:1) incomplete study results or have only single-factor analysis results reported; and 2) literature with a "low" quality rating (a score of < four corresponds to low quality).

Data collection

Data sources and search strategies. Six electronic databases, namely, PubMed, Web of Science, EMBASE, Cochrane Library, China National Knowledge Infrastructure, and Wanfang Data Knowledge Service Platform, were used to search for related articles.

Data extraction and quality appraisal. The EndNote X9 reference manager software was utilized for collecting and organizing search results and eliminating duplicate articles. Initial screening of study titles was conducted independently by two qualified reviewers based on accessibility criteria, followed by abstract screening. Subsequently, a re-evaluation was performed to determine the inclusion of studies in the meta-analysis, considering the full text. Discrepancies were resolved via discussions involving a third reviewer, facilitating consensus (Rimbawan *et al.* 2022).

The Newcastle–Ottawa Scale (NOS) (Stang 2010) was used to evaluate the quality of the case-control and cohort studies. Cross-sectional studies were conducted using Joanna Briggs Institute (JBI) Tool (Munn *et al.* 2015)

to assess quality. For NOS and JBI scores, a score <four is considered low quality, four to six is medium quality, and \geq seven is high quality. Studies were included with scores \geq four.

Data analysis

Statistical analysis was conducted employing RevMan 5.4.1 software. To gauge the heterogeneity among the included studies, the I² statistics was employed. When $p\ge0.1$ and I² \le 50%, indicative of homogeneity among studies, a fixed-effects model was used for description. Conversely, a random-effects model was employed for depiction in cases of substantial inter-study heterogeneity. Sensitivity analysis was conducted to evaluate the influence of individual studies on the overall effect estimation. The significance level was set at p<0.05.

RESULTS AND DISCUSSION

A total of 5,462 articles were searched, and 4,845 articles remained after eliminating duplicates. After screening by title and abstract, 277 articles remained. The full text was read to exclude 264 articles, and 13 articles were finally included. The screening process is shown in Figure 1. In total, the combined patient sample



Figure 1. PRISMA flow chart of study selection process

encompassed 7,790 individuals, with samples size ranging from 53 to 2,151 patients. The detailed characteristics are summarized in Table 1.

The 10 possible influencing factors related to malnutrition were analyzed. Age was estimated as a risk factor for malnutrition among CKD patients based on five studies (Namuyimbwa *et al.* 2018; Omari *et al.* 2019; Wang *et al.* 2016; Windahl *et al.* 2018; Hwang *et al.* 2009). The pooled data under random model showed an OR of 1.29 (95% CI:1.03–1.61; p=0.02), with substantial heterogeneity ($I^2=87\%$, p<0.01) (Table 2). Forest plot of age is presented in Figure 2 (A).

Investigators in two studies reported on relationships between the required feeding assistance and malnutrition among CKD patients (Boaz *et al.* 2019; Zhu *et al.* 2020).With an OR of 3.33 (95% CI:2.55–4.35; p<0.01), the required feeding assistance showed a significant trend towards higher malnutrition risk, under fixedeffect model (I²=0, p=0.70) (Table 2). Forest plot of required feeding assistance is shown in Figure 2 (B).

Living status (with family) (I²=0, p=0.49) was regarded as a protective factor associated with malnutrition, based on two included studies (Omari *et al.* 2019; Zhu *et al.* 2020). Analysis was conducted by fixed-effect model, with an OR of 0.49 (95% CI:0.34–0.71; p<0.01), presenting statistical significance (Table 2). Forest plot of living status (with family) is displayed in Figure 2 (C).

Data on CKD patients with protein intake were available from three studies with a pooled OR of 0.89 (95% CI:0.85–0.94; p<0.01) from the fixed-effect model with I²=0 (p=0.97) (Wang *et al.* 2012; Windahl *et al.* 2018; Dahl *et al.* 2022) (Table 2). Meta-analysis results showed that higher protein intake as a protective factor against malnutrition in CKD patients. Forest plot of protein intake is shown in Figure 2 (D).

Two studies which examining the impact of comorbidities on the nutritional conditions among CKD patients were pooled in the analysis (Omari *et al.* 2019; Wang *et al.* 2012), revealing comorbidities as significance risk factors for CKD (OR=1.78; 95% CI:1.03–3.07; p=0.04; fixedeffect model). No between-study heterogeneity was found, with I²=0 (p=0.44) (Table 2). Forest plot of this analysis on comorbidities is presented in Figure 2 (E). Based on data from three research (Omari *et al.* 2019; Wang *et al.* 2016; Zhu *et al.* 2020), CKD patients with lengthy dialysis duration had a substantial relationship with malnutrition. The OR was 1.61 (95% CI:1.16–2.24; p=0.01, fixed-effect model), with no between-study heterogeneity (I²=0, p=0.64) (Table 2). Forest plot of long dialysis duration is illustrated in Figure 2 (F).

Inadequate dialysis (Li *et al.* 2018; Wang *et al.* 2016; Wang *et al.* 2012) was estimated as a risk factor for malnutrition based on three studies, yielding an OR of 1.25 (95% CI:1.12–1.40; p<0.01, random model). Statistical heterogeneity was high between studies (I²=60%, p=0.08) (Table 2). Forest plot of inadequate dialysis is presented in Figure 2 (G).

ALB, as evaluated in three studies, was identified as a potential risk factor for malnutrition in CKD patients (Guligowska *et al.* 2020; Li *et al.* 2018; Wang *et al.* 2016). In the overall pooled estimate with random model, the ALB factor played a statistically significant negative role (OR=0.70; 95% CI:0.44–1.10; p=0.13) with severe between study heterogeneity ($I^2=94\%$, p<0.01) (Table 2). Forest plot of ALB is shown in Figure 2 (H).

Hb was significantly associated with malnutrition among CKD patients, based on two studies (Boaz *et al.* 2019; Namuyimbwa *et al.* 2018). The OR was 1.84 (95% CI:0.92–3.66; p=0.08, random model), with high between study heterogeneity (I²=62%, p=0.11) (Table 2). Forest plot of Hb is presented in Figure 2 (I).

Presence of a depression significantly correlated with malnutrition in CKD patients (OR=3.44; 95% CI:2.21–5.34; p=0.08) under fixed-effect model in all three selected studies (Boaz *et al.* 2019; Czira *et al.* 2011; Namuyimbwa *et al.* 2018), with no between-study heterogeneity of $I^2=0$ (p=0.55) (Table 2). Forest plot of depression is presented in Figure 2 (J).

The fixed-effects model and the randomeffects model were employed to combine the effects sizes separately. The values of the combined effects of the two models are close to each other, which indicates that the results are more reliable. However, the results of the two models of ALB are inconsistent (Table 3). The fixed effects model results in OR=0.93; 0.90-0.97; p<0.01. The random effects model results in OR=0.70; 0.44-1.10; p=0.13, indicating that the results are unstable.

Table 1. Characteristic of included studies

Study	Study country (study design)	Sample size (study setting)	Gender (M/F)	Age (Year)	Screening parameter or tools	Prevalence of malnutrition	The stage of CKD	Influence factorsa	Quality
Guligowska et al. (2020)	Austria, Germany, Israel, Italy, The Netherlands, Poland, Spain (Cohort)	2,151 (Outpatient)	932/1,219	79.5±5.90	MNA and serum albumin	44.00%	Stage 2–5	4, 13	8
Lynch et al. (2013)	America (Cohort)	1,846 (Center)	764/981	57.8±14.10	Dry weight, mid-arm muscle circumference, and triceps skinfold thickness.	-	Stage 5	14	8
Windahl et al. (2018)	Germany, Italy, Netherland, Poland, Sweden, United Kingdom (Cohort)	1,334 (Clinics)	874/460	76	7-point SGA	21.00%	Stage 4–5	1, 3, 9, 15	6
Boaz et al. (2019)	Israel (Cross-secrtion-	378 (Center)	197/181	-	BMI and serum albumin	46.30%	Stage 5	6, 10,16	5
Dahl <i>et al.</i> (2021)	Norway (Cross-scrtional)	53 (Hospital)	39/14	62	NRS2002	26.00%	Stage 5	9, 17, 18	6
Czira et al. (2011)	Hungary (Cross-sectional)	973 (Outpatient)	555–418	51±13.00	MIS	28.50%	Stage 5	3	5
Hwang <i>et al.</i> (2009)	Korea (Cross-sectional)	110 (Outpatient)	46/64	58.6±1.00	Triceps skinfold thickness and Mid-arm muscle circumference	42.70%	Stage 5	19	4
Namuyimbwa et al. (2018)	Uganda (Cross-sectional)	182 (Outpatient clinic and wards)	56/126	33	BMI, serum albumin, Mid upper arm circumference	68.60%	Stage 1–5	1, 6, 20, 21, 22, 23	8
Omari <i>et al.</i> (2019)	Palestine (Cross-sectional)	174 (Hospital)	91/83	57.7±12.80	MIS	65.00%	Stage 5	1, 2, 7, 11, 24	7
Zhu et al. (2020)	China (Cross-sectional)	278 (Hospital)	163/115	68.78±4.23	PG-SGA	40.65%	Stage 5	3, 7, 10, 11, 25	5
Wang et al. (2012)	China (Cross-sectional)	125 (Hospital)	79/46	68.2±4.70	SGA	48.80%	Stage 5	2, 8, 9	6
Wang et al. (2016)	China (Cross-sectional)	114 (Hospital)	71/43	51.63±13.26	MQSGA	48.20%	Stage 5	1, 4, 5, 7, 8	5
Li <i>et al.</i> (2018)	China (Cross-sectional)	72 (Hospital)	39/33	42.14±11.50	SGA	79.17%	Stage 5	4, 8	5

-: Not provided; *1: Age; 2: Comorbidites; 3: Depression; 4: ALB: Low Blood Albumin; 5: CRP: Creactive Protein; 6: Hb: Hemoglobin; 7: Long dialysis duration; 8: Inadequate dialysis; 9: Protein intake; 10: Requires feeding assistance; 11: Living status (with family); 12: Creatinine; 13: eGFR: estimated Glomerular Filtration Rate; 14: Taste perception; 15: Sex (Female); 16: Increased delivered dialysis dose; 17: Energy intake; 18: Pre-albumin; 19: Family history of chronic renal failure; 20: Being single; 21: Catholic religion; 22: Chronic kidney disease stage; 23: LDL: Low Density Lipoproteins; 24: The number of chronic medications; 25: Dialysis frequency; BMI: Body Mass Index; NRS2002: Nutritional Risk Screening 2002; MIS: Malnutrition–Inflammation Score; SGA: Subjective global assessment; PG-SGA: Scored patient-generated subjective global assessment; MQSGA: Modified Quantitative Subjective Global Assessment

Factors influencing malnutrition among CKD patients

Factors	n	Heterogeneity test		Model	OR	95% CI	р
		I ² (%)	р				
Age	5 (Namuyimbwa <i>et al.</i> 2018; Omari <i>et al.</i> 2019; Wang <i>et al.</i> 2016; Windahl <i>et al.</i> 2018; Hwang <i>et al.</i> 2009)	87	<0.01	Random	1.29	(1.03–1.61)	0.02
Requires feeding assistance	2 (Boaz et al. 2019; Zhu et al. 2020)	0	0.70	Fixed	3.33	(2.55–4.35)	< 0.01
Living status (with family)	2 (Omari et al. 2019; Zhu et al. 2020)	0	0.49	Fixed	0.49	(0.34–0.71)	< 0.01
Protein intake	3 (Wang <i>et al.</i> 2012; Windahl <i>et al.</i> 2018; Dahl <i>et al.</i> 2022)	0	0.97	Fixed	0.89	(0.85–0.94)	< 0.01
Comorbidities	2 (Omari et al. 2019; Wang et al. 2012)	0	0.44	Fixed	1.78	(1.03–3.07)	0.04
Long dialysis duration	3 (Omari <i>et al.</i> 2019; Wang <i>et al.</i> 2016; Zhu <i>et al.</i> 2020)	0	0.64	Fixed	1.61	(1.16–2.24)	<0.01
Inadequate dialysis	3 (Li <i>et al.</i> 2018; Wang <i>et al.</i> 2016; Wang <i>et al.</i> 2012)	60	0.08	Random	1.25	(1.12–1.40)	< 0.01
ALB	3 (Guligowska <i>et al.</i> 2020; Li <i>et al.</i> 2018; Wang <i>et al.</i> 2016)	94	< 0.01	Random	0.70	(0.44–1.10)	0.13
Hb	2 (Boaz et al. 2019; Namuyimbwa et al. 2018)	62	0.11	Random	1.84	(0.92–3.66)	0.08
Depression	3 (Boaz <i>et al.</i> 2019; Czira <i>et al.</i> 2011; Namuyimbwa <i>et al.</i> 2018)	0	0.55	Fixed	3.44	(2.21–5.34)	0.04

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ALB: Low Blood Albumin; Hb: Hemoglobin; OR: Odds Ratio; CI: Confidence Interval

Protective factors against malnutrition

Protein intake was demonstrated to a protective risk factor of malnutrition among CKD patients according to our analysis (Wang *et al.* 2012; Windahl *et al.* 2018; Dahl *et al.* 2022). However, given the prolonged duration of CKD, patients with enduring dietary limitations often harbor concerns about protein consumption. They tend to instinctively avoid high-protein foods, even when their dietary restrictions post-dialysis are not as stringent (Kiuchi *et al.* 2016). Low protein diets could retard the progression of CKD but worsened the nutritional status of patients (Noce *et al.* 2016).

The review incorporates two studies that have demonstrated living with family as a protective factor against malnutrition among CKD patient (Omari *et al.* 2019; Zhu *et al.* 2020). Silva *et al.* (2016) emphasized the significant impact of family and social support on the physical and mental health of individuals with CKD, consequently affecting their nutritional status (Silva *et al.* 2016). Additionally, the current research highlights that emotional and financial support provided by family members can enhance quality of life, foster healthy behaviors, improve adherence to nutritional guidance, and decrease the risk of malnutrition among patients (Kiajamali *et al.* 2017).

Risk factors for malnutrition

Among the various studies incorporated in the review, five investigations have consistently demonstrated that age stands out as a prominent risk factor for malnutrition among CKD patients (Namuyimbwa *et al.* 2018; Omari *et al.* 2019; Wang *et al.* 2016; Windahl *et al.* 2018; Hwang *et al.* 2009). Notably, older CKD patients face a higher susceptibility to malnutrition compared to other age groups. These reasons include dietary

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Figure 2. Forest plot of meta-analysis of influcing factors for malnutrition in chronic kidney disease patients

restrictions, frailty, cognitive decline, diminished gastrointestinal function, tooth loss, reduced appetite, deteriorated taste perception (Kiuchi *et al.* 2016).

CKD patients' condition of requiring feeding assistance was reported as a risk factor for malnutrition based on two studies (Zhu *et al.* 2020; Boaz *et al.* 2019). Generally, this condition indicates poor independent living skills. Furthermore, patients exhibiting better independent living skills tended to take a more

proactive approach in maintaining and enhancing their own health (Zhu *et al.* 2020).

Comorbidities have been identified as risk factors for malnutrition in CKD patients (Omari *et al.* 2019; Wang *et al.* 2012). Rhee *et al.* (2015) demonstrated that among patients with nephropathy, inadequate glycemic control independently correlated with markers indicative of malnutrition (Rhee *et al.* 2015). Similar associations were found that diabetics undergoing hemodialysis exhibited reduced food intake

Factors influencing malnutrition among CKD patients

Factors		Fixed model		Random model			
		95% CI	р	OR	95% CI	р	
Age (Namuyimbwa et al. 2018; Omari et al. 2019; Wang et al. 2016; Windahl et al. 2018; Hwang et al. 2009)	1.06	(1.02–1.11)	<0.01	1.29	(1.03–1.61)	0.02	
Protein intake (Wang et al. 2012; Windahl et al. 2018; Dahl et al. 2022)	0.89	(0.85–0.94)	<0.01	0.89	(0.85–0.94)	< 0.01	
Requires feeding assistance (Boaz et al. 2019; Zhu et al. 2020)	3.33	(2.55–4.35)	< 0.01	3.33	(2.55–4.35)	< 0.01	
Living status (with family) (Omari et al. 2019; Zhu et al. 2020)	0.49	(0.34–0.71)	< 0.01	0.49	(0.34–0.71)	<0.01	
Comorbidities (Omari et al. 2019; Wang et al. 2012)	1.78	(1.03–3.07)	0.04	1.78	(1.03–3.07)	0.04	
Long dialysis duration (Omari <i>et al.</i> 2019; Wang <i>et al.</i> 2016; Zhu <i>et al.</i> 2020)	1.61	(1.16–2.24)	< 0.01	1.61	(1.16–2.24)	< 0.01	
Inadequate dialysis (Li <i>et al.</i> 2018; Wang <i>et al.</i> 2016; Wang <i>et al.</i> 2012)	1.25	(1.12–1.40)	< 0.01	1.35	(1.09–1.68)	< 0.01	
ALB (Guligowska <i>et al.</i> 2020; Li <i>et al.</i> 2018; Wang <i>et al.</i> 2016)	0.93	(0.90–0.97)	< 0.01	0.70	(0.44–1.10)	0.13	
Hb (Boaz et al. 2019; Namuyimbwa et al. 2018)	1.52	(1.19–1.93)	< 0.01	1.84	(0.92–3.66)	0.08	
Depression (Boaz et al. 2019; Czira et al. 2011; Namuyimbwa et al. 2018)	3.44	(2.21–5.34)	0.04	3.44	(2.21–5.34)	< 0.01	

 Table 3. Sensitive analysis of influence factors for malnutrition in chronic kidney disease patients

ALB: Low Blood Albumin; Hb: Hemoglobin; OR: Odds Ratio; CI: Confidence Interval

compared to non-diabetic counterparts, directly contributing to compromised nutritional status (Bataille 2017).

Lengthy dialysis duration has identified as a notable risk factor for malnutrition in CKD patients across three studies (Omari *et al.* 2019; Wang *et al.* 2016; Zhu *et al.* 2020). The catabolic process, which accelerates the significant of large amounts of nutrients, may explain the higher prevalence of malnutrition during extended dialysis duration (Jankowska *et al.* 2017). Salame *et al.* (2018) emphasized that extended periods of dialysis lead to significant protein and amino acid loss, and if not replaced in a timely manner, the patient's nutritional status deteriorates over time (Salame *et al.* 2018).

Inadequate dialysis stands as one of the risk factors for malnutrition among CKD patients in three studies (Li *et al.* 2018; Wang *et al.* 2016; Wang *et al.* 2012). The high incidence of malnutrition in patients undergoing inadequate dialysis may be attributed to the ineffective removal of uremic toxins, resulting in altered taste sensations among patients, affecting appetite, food intake, consequently resulting

in malnutrition (Hara *et al.* 2018). Therefore, patients receiving dialysis should be provided with the recommended dialysis dose to avoid inadequate treatment (Iorember 2018).

Two different studies (Boaz *et al.* 2019; Namuyimbwa *et al.* 2018) within this review have consistently identified Hb as a risk factor for malnutrition. Their findings revealed a substantial association between hemoglobin levels below 11.5 g/dL and a threefold higher prevalence of malnutrition when contrast to individuals with hemoglobin levels at or above 11.5 g/dL (Namuyimbwa *et al.* 2018). The discrepancy might stem from malnourished CKD patients experiencing reduced bone marrow responsiveness to erythropoietin (Weir 2021).

Depression has emerged as a significant risk factor for malnutrition in CKD patients based on findings from three studies (Boaz *et al.* 2019; Czira *et al.* 2011; Namuyimbwa *et al.* 2018). Gebrie & Ford (2019) highlighted that patients with CKD frequently experience negative mood states, and as renal function deteriorates, the incidence of depression tends to rise (Gebrie & Ford 2019). A pivotal link between depression and malnutrition exists due to the common manifestation of reduced appetite, a prevalent symptom of depression. Consequently, as patients consume less food, the likelihood of malnutrition escalates (Türk *et al.* 2020).

Strengths and limitations of the review

The key strength of this study lies in its pioneering role as the first systematic review and meta-analysis investigating the factors influencing malnutrition in individuals with CKD. Additionally, all articles included in this review/ meta-analysis can be considered as moderate to high quality studies, enhancing the credibility and reliability of the findings.

Nonetheless, several limitations must be acknowledged. Firstly, certain influencing factors were only documented in a limited number of studies, precluding their incorporation into a meta-analysis to establish their impact on malnutrition. Additionally, high heterogeneity was observed in the results of some studies, as a result of differences in the study populations.

Implications for clinical practice

The early detection and recognition of malnutrition among CKD patients by clinicians and nursing staff hold significant importance within clinical practice. Effective identification of malnourished patients and subsequent enhancement of their nutritional status hinge on addressing the associated factors of malnutrition and promptly initiating targeted interventions. Concurrently, there is a call for diligent exploration into the mechanisms through which various factors contribute to the emergence of malnutrition in CKD patients.

CONCLUSION

This meta-analysis delved into the array of factors influencing malnutrition among CKD patients. The findings underscore that several factors, including age, the need for feeding assistance, living arrangements (with family), protein intake, comorbidities, prolonged dialysis duration, inadequate dialysis, Hemoglobin (Hb) levels, and depression, significantly contribute to the risk of malnutrition among CKD patients. Notably, living with family and adequate protein intake emerge as protective factors against malnutrition within this patient population. Moreover, this review did not confirm ALB as a risk factor for malnutrition. Thus, it's crucial to conduct prospective studies with larger sample sizes to conclusively validate or refute this result.

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DECLARATION OF CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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