NEPHROLOGY - ORIGINAL PAPER

Association of malnutrition with all-cause and cardiovascular mortality in patients with mild to severe chronic kidney disease undergoing coronary angiography: a large multicenter longitudinal study

Fei Gao[1] · Zhidong Huang[2,3] · JingJing Liang[4,5] · Yu Kang[2,3,11] · Yihang Ling[2,3] · Yibo He[2,3] · Jiahui Chen[6] · Daqing Hong[7] · Zewei Zhang[8] · Shanshan Xu[5] · Amanda Wang[9] · Xiaoming Yan[10] · Jin Liu[2,3] · Yong Liu[2,3] · Shiqun Chen[2,3] [ORCID] · Jiyan Chen[2,3]

Abstract

Purpose Evidence on the prognostic impact of malnutrition was focused on patients with advanced kidney disease. The relationships between malnutrition and all-cause and cardiovascular mortality in patients with different severity of chronic kidney disease (CKD) have not been adequately addressed. We aimed to reveal the prevalence of malnutrition and its prognostic value in patients with different severity of CKD undergoing coronary angiography (CAG).

Methods This was a multicenter, longitudinal, and retrospective cohort study of 12,652 patients with non-dialysis dependent CKD (defined as estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) undergoing CAG from five tertiary hospitals between January 2007 and December 2020. The controlling nutritional status (CONUT) score was applied to assess nutritional status. Cox regression models and competing risk Fine and Gray models were used to examine the relationships between malnutrition, all-cause and cardiovascular mortality. Further stratified analysis was performed according to baseline CKD severity (mild, moderate and severe, defined by eGFR < 30, 30–44 and 45–59 ml/min/1.73 m^2).

Results During a median follow-up of 5.5 years (interquartile range: 3.2 to 8.6 years), 3801 patients (30.0%) died, and 2150 (17.0%) definitely died of cardiovascular disease. After controlling for confounders, patients had higher all-cause mortality (mild, moderate, and severe *vs*. absent: HR 1.27, 95 CI % [1.17–1.39]; HR 1.54, 95 CI % [1.39–1.71]; HR 2.22, 95 CI % [1.78–2.77], respectively; P for trend < 0.001) and cardiovascular mortality (mild, moderate and severe *vs*. absent: HR 1.35, 95 CI % [1.21–1.52]; HR 1.67, 95 CI % [1.45–1.92]; HR 2.10, 95 CI % [1.55–2.85], respectively; *P* for trend < 0.001) with the severity of malnutrition. In further stratified analysis, a similar prognostic impact of malnutrition was observed in patients with mild to moderate CKD, while mild malnutrition did not seem to have a consistent effect on severe CKD patients.

Conclusion Malnutrition is common among patients with mild to severe CKD undergoing CAG and is strongly associated with increased risk of all-cause and cardiovascular mortality. Malnutrition seems to have a modestly stronger impact on mortality in patients with mild to moderate CKD.

This study was registered at Clinicaltrials.gov as NCT05050877.

Keywords Malnutrition · The CONUT score · Prevalence · All-cause mortality · Cardiovascular mortality · Chronic kidney disease

---

Fei Gao, Zhidong Huang, JingJing Liang, and Yu Kang have contributed equally to this work.

✉ Shiqun Chen
shiqunchen@126.com

✉ Jiyan Chen
chenjiyandr@126.com

Extended author information available on the last page of the article

Introduction

Chronic kidney disease (CKD) has become a worldwide health care burden with substantial morbidity and mortality [1, 2]. Cardiovascular disease (CVD) remains the leading cause of death in patients with CKD [3]. Traditional CVD risk factors are prevalent in patients with CKD but do not

fully explain the high incidence of cardiovascular events or the increased mortality rates in these patients [4, 5].

Accumulating evidence suggests that malnutrition plays a crucial role in the increasing risk of cardiovascular mortality in patients with renal insufficiency [6–9]. Comprehensive recommendations on managing nutritional derangements for patients with renal insufficiency have already existed in current management guidelines [10]. However, previous evidence on the prognostic impact of malnutrition was limited by small sample sizes and predominantly focused on patients undergoing dialysis or end-stage renal disease [6–8]. Recently, a multicenter prospective study of 2791 patients with CKD suggested that only geriatric nutritional risk index (GNRI) in the 3rd quartile had a weak association with decreased risk of cardiovascular events after adjusting for confounders, which may be limited by over censored events [9]. To date, the prevalence of malnutrition and its association with cardiovascular mortality among patients with CKD have not been reported in a large cohort, and the relationship between malnutrition and mortality in patients with different severity of CKD has not been adequately addressed.

There was no consensus on nutritional screening tools for patients with CKD [10]. Recently, the controlled nutritional status (CONUT) score has been widely confirmed as a stronger nutritional evaluation indicator for predicting mortality risk in the cardio-renal community [6, 11–13]. Compared to other nutritional assessment tools, the CONUT score has the advantage that it is well-validated and easy to use.

Accordingly, this study aimed to reveal the prevalence of malnutrition (based on the CONUT score) and its relationship with all-cause and cardiovascular mortality in patients with non-dialysis dependent CKD based on a larger multicenter longitudinal cohort study. Secondly, we aimed to investigate the prognostic impact of malnutrition on all-cause and cardiovascular mortality in different severity of CKD patients.

Methods

Study population

This was a multicenter, longitudinal and retrospective cohort study of 12,652 patients with non-dialysis dependent CKD undergoing coronary angiography (CAG) from five tertiary hospitals between January 2007 and December 2020 in CIN II (Cardiorenal Improvement II, ClinicalTrials.gov NCT05050877) study. A total of 145,267 patients undergoing CAG were initially evaluated, including patients admitted for an elective CAG examination and patients receiving an emergency CAG examination. Among them, 22,898 patients defined as CKD (estimated glomerular filtration rates [eGFR] < 60 mL/min/1.73 m^2) were initially included in the study. The exclusion criteria were as follows: (a) patients receiving dialysis or those who were unclear to have received it or not ($n = 7509$); (b) patients missing follow-up data ($n = 93$); (c) patients with history of cancer ($n = 318$); (d) patients aged < 18 years ($n = 0$); and (e) patients lacking essential data to calculate the CONUT score ($n = 2326$) (Fig. 1). The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Guangdong Provincial People's Hospital Institutional Review Board. All participating sites received institutional review board approval from their own ethics committees. Written informed consent was waived due to the retrospective nature of the current study.

Baseline data collection

The patient data were extracted from the electronic clinical management records system, which included demographic characteristics, medical history, laboratory examinations, and medications at discharge. Baseline levels of serum creatinine (Scr), albumin, total cholesterol, lymphocyte count and other biomarkers were measured before CAG. The follow-up information was accessed by matching the survival information from local Centers for Disease Control and Prevention.

Malnutrition screening tools

The CONUT score was developed by Ulibarri et al. [14] in 2005 as a screening tool for the nutritional status of hospitalized patients. It takes into account serum albumin, total cholesterol, and total lymphocyte count. A score of 0 to 1 is considered normal; scores of 2 to 4, 5 to 8, and 9 to 12 reflect mild, moderate, and severe malnutrition, respectively (Supplemental Table S1).

Endpoint and clinical definition

The endpoints were all-cause death and cardiovascular death. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [15], and CKD was defined as eGFR < 60 mL/min/1.73 m^2 [16]. Mild, moderate, and severe CKD were defined as subjects with an eGFR < 30, 30–44 and 45–59 ml/min/1.73 m^2. Anemia was defined as a hematocrit < 39% (male) or < 36% (female). Congestive heart failure (CHF) was defined as New York Heart Association class > 2 or Killip class > 1 [17]. Acute myocardial infarction (AMI), diabetes mellitus (DM), and hypertension were defined according to the 10th Revision Codes of the International Classification of Diseases (ICD-10).
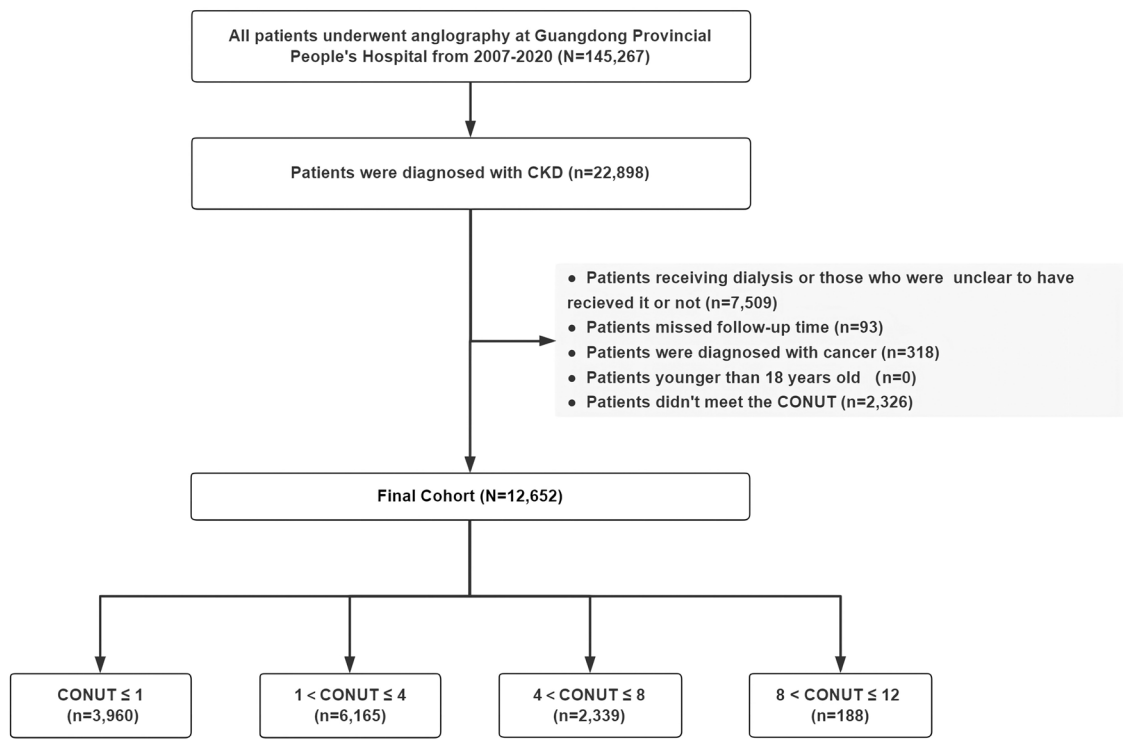
Fig. 1 Study flow chart

Statistical analysis

Demographic characteristics, complications, laboratory findings, and discharge medications were described for patients with CKD undergoing CAG in different groups stratified by nutritional status. For the baseline characteristics, continuous variables were summarized as mean and standard or median and quartiles deviation as appropriate. Categorical variables were described as frequencies and percentages. Student t-tests and non-parametric tests (Kruskal–Wallis) were used to compare normally and non-normally distributed variables, respectively. Differences in categorical variables were compared using the chi-square test. The distribution of patients with different renal functions was described by density curves for different nutrition stratified groups. Relationship between all-cause and cardiovascular mortality and malnutrition was analyzed by restricted cubic spline (RCS). Time-to-event data were presented graphically using Kaplan–Meier curves and compared with a log-rank test. The association between nutritional statuses and all-cause mortality was assessed by multivariate Cox regression models, adjusted for age, sex, percutaneous coronary intervention (PCI), comorbidities including DM, AMI, CHF, anemia, hypertension, and laboratory test including low density lipoprotein cholesterol (LDL-C). We generated cumulative incidence function (CIF) curves for competing risk of cardiovascular death. Gray's tests were used to assess

differences in cardiovascular mortality. For cause-specific mortality analyses, we further excluded individuals with unknown causes of death. The association between cardiovascular mortality and nutritional status was examined using competing risk Fine and Gray models, adjusted for the same confounders. Mortality due to other causes were treated as competing risks. We calculated linear P for trend and P for interaction. Further analysis was conducted by using stratification based on the baseline level of kidney function (eGFR < 30, 30–44 and 45–59 ml/min/1.73 m^2) [18] and by evaluating effect modification through interaction terms for the respective categories. Data management and statistical analyses were performed by R version 4.0.3. We considered a two-sided P value < 0.05 statistically significant.

Result

Baseline characteristics

Among the 12,652 patients with CKD undergoing CAG (the mean age was 69.0 ± 9.5 years, 31.5% were women) were included, 8692 (68.7%) had malnutrition, of which 48.7%, 18.5%, and 1.5% patients had mild, moderate, and severe malnutrition, respectively. Based on the CONUT score, patients in worse nutritional status groups were significantly older, were more likely to be male, and had a higher

prevalence of AMI, CHF, PCI, anemia, hypertension, DM and stroke. They also were more likely to have a lower concentration of LDL-C, as well as a lower proportion of receiving statins and angiotensin converting enzyme inhibitors or angiotensin receptor blocker (ACEI or ARB). More data on the baseline characteristics of the study population are shown in Table 1.

Malnutrition and the baseline level of kidney function

The malnutrition prevalence of patients with mild to severe CKD ranges from 64.2% to 83.3%. The prevalence of moderate and severe malnutrition increases with higher severity of CKD from 14.6% and 0.7 to 32.4% and 4.7%, respectively.

Table 1 Baseline characteristics according to nutrition status

Characteristics	Malnutrition Groups					P value	% Std. Diff		
	Overall	Absent	Mild	Moderate	Severe		Mild vs. absent	Moderate vs. absent	Severe vs. absent
	(N = 12,652)	(n = 3960)	(n = 6165)	(n = 2339)	(n = 188)				
Demographic characteristics									
Age, year	69.0 ± 9.5	67.3 ± 9.5	69.5 ± 9.4	70.3 ± 9.6	70.2 ± 9.8	< 0.001	22.8	31.9	29.7
Female, n (%)	3987 (31.5)	1507 (38.1)	1870 (30.3)	575 (24.6)	35 (18.6)	< 0.001	16.3	29.4	44.2
Complication									
Severity of CKD						< 0.001			
45 ≤ eGFR < 60	7926 (62.7)	2838 (71.7)	3875 (62.9)	1156 (49.4)	57 (30.3)		18.9	46.7	90.8
30 ≤ eGFR < 45	3315 (26.2)	887 (22.4)	1638 (26.6)	726 (31.0)	64 (34.0)		9.7	19.6	26.1
eGFR < 30	1411 (11.2)	235 (5.9)	652 (10.6)	457 (19.5)	67 (35.6)		16.9	41.7	78.7
AMI, n (%)	2042 (16.1)	377 (9.5)	962 (15.6)	635 (27.2)	68 (36.2)	< 0.001	18.4	46.8	66.9
CHF, n (%)	2684 (21.2)	586 (14.8)	1235 (20.0)	769 (32.9)	94 (50.0)	< 0.001	13.8	43.4	81.2
Anemia, n (%)	6160 (48.7)	1224 (30.9)	3117 (50.6)	1659 (70.9)	160 (85.1)	< 0.001	40.8	87.4	131.4
Hypertension, n (%)	8650 (68.4)	2743 (69.3)	4251 (69.0)	1541 (65.9)	115 (61.2)	0.003	0.7	7.2	17.1
DM, n (%)	5375 (42.5)	1605 (40.5)	2626 (42.6)	1057 (45.2)	87 (46.3)	0.002	4.2	9.4	11.6
Pre-MI, n (%)	751 (5.9)	218 (5.5)	379 (6.2)	147 (6.3)	7 (3.7)	0.265	2.7	3.3	8.5
Stroke, n (%)	988 (7.8)	266 (6.7)	476 (7.7)	226 (9.7)	20 (10.6)	< 0.001	3.9	10.8	14.0
PCI, n (%)	7714 (61.0)	2295 (58.0)	3807 (61.8)	1496 (64.0)	116 (61.7)	< 0.001	7.8	12.3	7.6
Laboratory findings									
WBC, 10^9/L	7.95 ± 2.6	7.9 ± 2.2	7.8 ± 2.5	8.2 ± 3.1	9.5 ± 3.8	< 0.001	6.0	11.3	49.6
Hemoglobin, g/L	126.7 ± 19.4	133.6 ± 17.1	126.6 ± 18.2	116.8 ± 20.5	107.2 ± 20.5	< 0.001	39.4	89.0	139.4
LDL-C, mmol/L	2.7 ± 0.9	3.2 ± 0.9	2.6 ± 0.9	2.4 ± 0.9	1.9 ± 0.7	< 0.001	63.8	94.2	164.6
HDL-C, mmol/L	1.0 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	0.9 ± 0.3	0.8 ± 0.3	< 0.001	31.4	54.4	107.8
Lymphocyte, 10^9/L	1.7 ± 0.7	2.1 ± 0.6	1.7 ± 0.6	1.3 ± 0.6	0.9 ± 0.3	< 0.001	63.9	142.5	244.9
Albumin, g/L	35.2 ± 4.5	38.5 ± 2.6	35.2 ± 3.5	30.4 ± 3.5	24.6 ± 3.0	< 0.001	107.3	268.5	497.5
CHOL, mmol/L	4.5 ± 1.2	5.1 ± 1.1	4.3 ± 1.1	3.9 ± 1.1	3.3 ± 0.8	< 0.001	75.8	114.7	194.4
eGFR, mL/min/1.73 m^2	46.0 ± 11.6	48.6 ± 9.9	46.2 ± 11.4	42.3 ± 13.0	35.9 ± 14.8	< 0.001	22.7	54.3	100.7
SCr, μmol/L	1.6 ± 0.7	1.4 ± 0.5	1.6 ± 0.7	1.8 ± 0.9	2.3 ± 1.6	< 0.001	18.5	43.3	68.5
Medications									
CCB, n (%)	3310 (26.8)	1081 (27.7)	1593 (26.4)	592 (26.2)	44 (26.8)	0.506	2.8	3.3	1.9
ACEI or ARB, n (%)	8675 (70.2)	2797 (71.6)	4275 (70.9)	1500 (66.4)	103 (62.8)	< 0.001	1.5	11.2	18.8
Beta-blockers, n (%)	9194 (74.4)	2891 (74.0)	4528 (75.1)	1659 (73.5)	116 (70.7)	0.244	2.6	1.2	7.3
Statins, n (%)	10,548 (85.4)	3330 (85.3)	5179 (85.9)	1914 (84.8)	125 (76.2)	0.004	1.9	1.4	23.1
Endpoints									
All-cause death, n (%)	3801 (30.0)	890 (22.5)	1854 (30.1)	940 (40.2)	117 (62.2)	< 0.001	17.3	38.9	87.9
Cardiovascular death, n (%)	2150 (17.0)	475 (12.0)	1054 (17.1)	555 (23.7)	66 (35.1)	< 0.001	14.5	31.0	56.6

AMI acute myocardial infarction, *CHF* chronic heart failure, *PCI* percutaneous coronary intervention, *DM* diabetes mellitus, *MI* myocardial infarction; *WBC* white blood cell, *TRIG* triglycerides, *LDL-C* low density lipoprotein cholesterol, *HDL-C* high density lipoprotein, *CHOL* cholesterol, *ALB* albumin, *SCr* serum creatinine, *CCB* calcium channel blockers, *ACEI* Angiotensin Converting Enzyme Inhibitors, *ARB* angiotensin receptor blocker
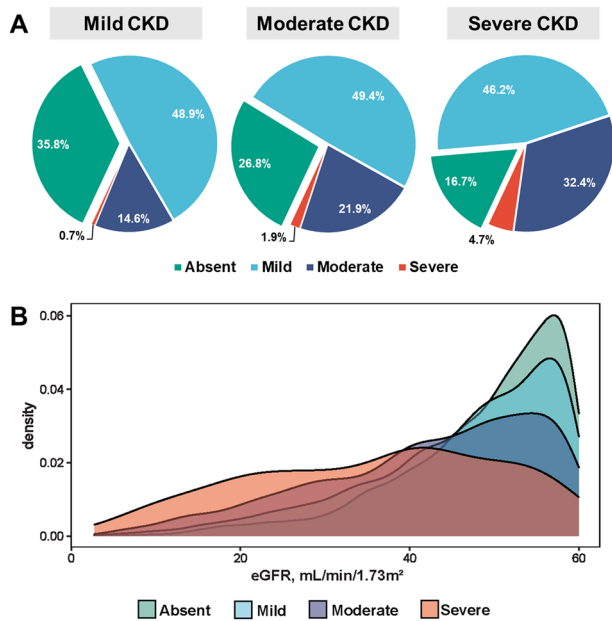
Fig. 2 The association of malnutrition with a baseline level of kidney function, **A** The proportion of various degrees of malnutrition in patients with mild to severe chronic kidney disease; **B** The population distribution of eGFR in different nutritional statuses.

(Fig. 2A) From the perspective of malnutrition stratified (no malnutrition, mild, moderate and severe malnutrition), with the deterioration of nutritional status, the number of patients with poorer renal function increases (Fig. 2B).

Malnutrition and clinical outcomes

During a median follow-up of 5.5 years (interquartile range: 3.2 to 8.6 years), 3801 patients (30.0%) died, and 2150 (17.0%) definitely died of cardiovascular disease. The all-cause mortality of absent *vs.* mild *vs.* moderate *vs.* severe malnutrition was 22.5% *vs.* 30.1% *vs.* 40.2% *vs.* 62.2% and cardiovascular mortality of absent *vs.* mild *vs.* moderate *vs.* severe malnutrition: 12.0% *vs.* 17.1% *vs.* 23.7% *vs.* 35.1% in patients with CKD undergoing CAG (Table 1). RCS analysis suggested an approximately linear increase in the risk of all-cause and cardiovascular mortality as the CONUT score increased. (Fig. 3) Kaplan–Meier curves for all-cause mortality and cumulative incidence function curves for cardiovascular mortality according to groups of nutritional status and corresponding univariate analysis, are shown in Fig. 4A, B, respectively. After controlling for confounders, patients had higher all-cause mortality (mild, moderate and severe *vs.* absent: HR 1.27, 95 CI % [1.17–1.39]; HR 1.54, 95 CI % [1.39–1.71]; HR 2.22, 95 CI % [1.78–2.77], respectively; P for trend < 0.001) and cardiovascular mortality (mild, moderate and severe *vs.* absent: HR 1.35, 95 CI % [1.21–1.52]; HR 1.67, 95 CI % [1.45–1.92]; HR 2.10, 95 CI % [1.55–2.85], respectively; *P* for trend < 0.001) with

Fig. 3 All-cause and cardiovascular mortality risk across malnutrition severity in patients with CKD undergoing CAG, Restricted cubic spline depicts the hazard ratio of malnutrition based on the CONUT score for all-cause (left) and cardiovascular mortality (right) in patients with CKD; The bar chart shows the frequency of the CONUT score from 1 to 12 (scores of 0 to 1 are considered normal and 2 to 4, 5 to 8, and 9 to 12 reflect mild, moderate, and severe malnutrition, respectively). Adjusted for the following factors (plot settings): age, sex, acute myocardial infarction, congestive heart failure, percutaneous coronary intervention, diabetes mellitus, hypertension, anemia, low density lipoprotein cholesterol, angiotensin converting enzyme inhibitors or angiotensin receptor blocker, beta blocker, calcium channel blockers and statins
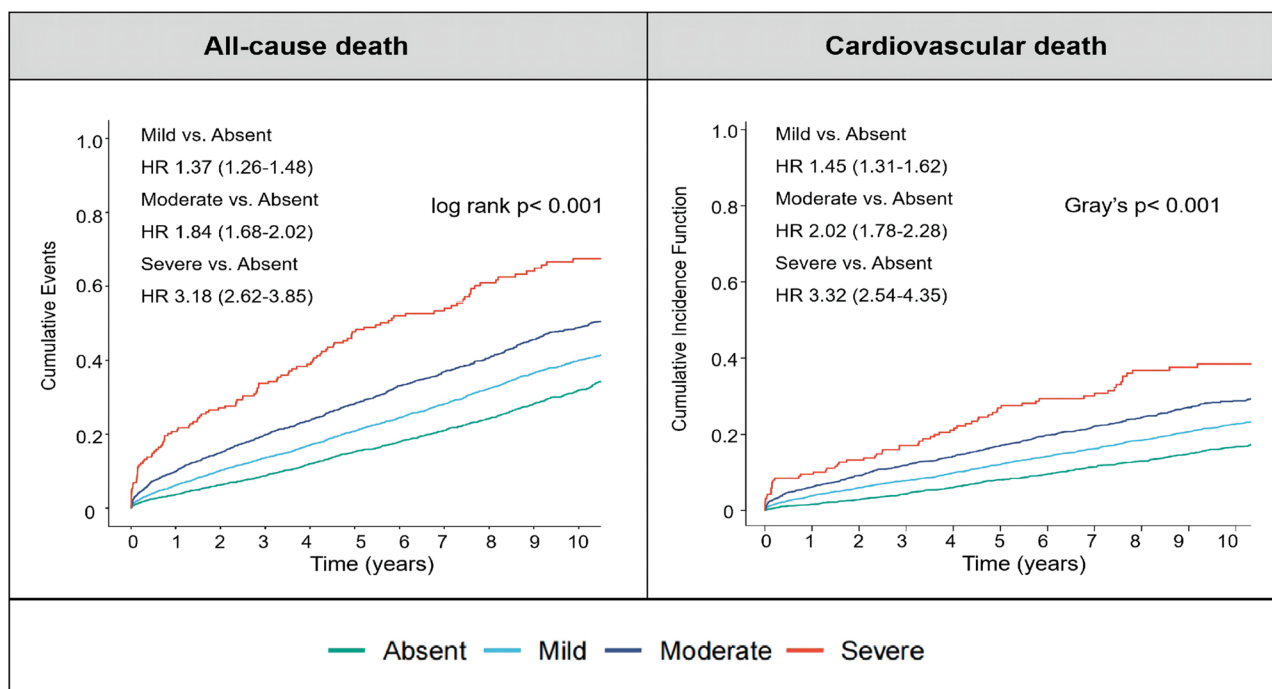
Fig. 4 Malnutrition severity and risk of all-cause and cardiovascular mortality, Kaplan–Meier and cumulative incidence function curves for all-cause death (left) and cardiovascular death (right) according to groups of nutritional status defined by the CONUT score, respectively

the severity of malnutrition. (Table 2). RCS analyses were further conducted in patients with mild to severe CKD, we found the associations of the CONUT score and risk of all-cause and cardiovascular mortality tend to weaken as kidney function declines. We noted an interaction between mild to severe CKD and the CONUT score for cardiovascular mortality (*P* for interaction < 0.05), but not for all-cause mortality (Fig. 5). Kaplan–Meier curves for all-cause mortality and cumulative incidence function curves for cardiovascular mortality in patients with mild to severe CKD are showed in Supplemental Figure S1. In addition, a similar prognostic impact of different malnutrition severity on all-cause and cardiovascular mortality was observed in patients with mild to moderate CKD (eGFR 30 mL/min/1.73 m^2). However, in patients with severe CKD (eGFR < 30 mL/min/1.73 m^2), mild malnutrition did not seem to have a consistent effect on all-cause mortality and cardiovascular mortality (Fig. 6).

Discussion

To our knowledge, this was the largest multicenter, longitudinal cohort study to report the prevalence of malnutrition (based on the CONUT score) in patients with different severity of CKD undergoing CAG. The current study was also the first to examine the prognostic value of malnutrition for all-cause and cardiovascular mortality in this population. The findings of our study were that (1) malnutrition

was common among patients with CKD undergoing CAG, affecting about 70 percent of patients regardless of the level of kidney function; (2) patients with severe malnutrition had a twofold increased risk of all-cause and cardiovascular mortality than those with normal nutritional status, and all-cause and cardiovascular mortality increased with higher severity of malnutrition; (3) stratified analysis by renal dysfunction status showed that malnutrition had a higher impact on all-cause and cardiovascular mortality in mild to moderate CKD patients.

The comprehensive, well-validated, and easy-to-use tool to identify patients at malnutrition risk is critically needed by the cardio-renal community. Previous studies reported that nutritional screening tools, such as the Mini-Nutritional Assessment (MNA) and subjective global assessment (SGA), could identify patients with renal insufficiency at risk of malnutrition [19, 20]. However, carrying out assessments in a large sample is difficult because of subjective evaluations. For patients with renal insufficiency who underwent CAG, cardiologists usually determine their nutritional status based only on serum albumin levels. However, serum albumin provides limited information about the complex nature of the underlying nutritional problem in the setting of renal insufficiency [21, 22]. Moreover, high cholesterol levels have been preconceived by cardiologists as a poor cardiovascular prognostic factor, even though the cholesterol paradox has been found when patients with poor renal function are malnourished [23]. Compared with other nutritional

Table 2 Adjusted hazard ratio of malnutrition for all-cause and cardiovascular mortality in patients with CKD undergoing CAG

	All-cause death		_P_ for trend	Cardiovascular death		_P_ for trend
	aHR (95% CI)	_P_ value		aHR (95% CI)	_P_ value	
Absent	Ref	–	<0.001	Ref	/	<0.001
Mild	1.27 (1.17–1.39)	<0.001		1.35 (1.21–1.52)	<0.001	
Moderate	1.54 (1.39–1.71)	<0.001		1.67 (1.45–1.92)	<0.001	
Severe	2.22 (1.78–2.77)	<0.001		2.10 (1.55–2.85)	<0.001	
Age, year	1.02 (1.02–1.03)	<0.001		1.02 (1.01–1.02)	<0.001	
Female	0.81 (0.75–0.87)	<0.001		0.87 (0.79–0.96)	0.007	
AMI	0.95 (0.86–1.05)	0.324		0.89 (0.78–1.02)	0.093	
CHF	1.46 (1.35–1.58)	<0.001		1.67 (1.50–1.86)	<0.001	
PCI	0.90 (0.83–0.97)	0.006		0.88 (0.80–0.98)	0.018	
_DM_	1.24 (1.16–1.32)	<0.001		1.48 (1.35–1.62)	<0.001	
Hypertension	0.99 (0.91–1.06)	0.702		0.95 (0.86–1.06)	0.360	
Anemia	1.22 (1.14–1.31)	<0.001		1.35 (1.16–1.57)	<0.001	
Stroke	1.26 (1.12–1.41)	<0.001		1.33 (1.21–1.46)	<0.001	
LDL-C	1.13 (1.09–1.17)	<0.001		1.16 (1.10–1.21)	<0.001	
ACEI or ARB	0.87 (0.81–0.94)	<0.001		0.88 (0.79–0.98)	0.015	
β-blocker	1.06 (0.98–1.14)	0.175		1.10 (0.98–1.22)	0.095	
CCB	0.99 (0.91–1.06)	0.708		1.00 (0.91–1.11)	0.940	
Statins	0.89 (0.80–0.98)	0.019		0.95 (0.83–1.10)	0.520	

Adjusted for age, sex, acute myocardial infarction, congestive heart failure, percutaneous coronary intervention, diabetes mellitus, hypertension, anemia, low density lipoprotein cholesterol, angiotensin converting enzyme inhibitors or angiotensin receptor blocker, beta blocker, calcium channel blockers and statins

assessment tools, the CONUT score consisting of total cholesterol, serum albumin, and lymphocyte count has the advantage that it is a well-validated and easy-to-use nutritional assessment tool which comprehensively considers all conditions described above. Recently, Roubín et al. have explored the prognostic consequences of malnutrition in patients with acute coronary syndrome based on the CONUT score, the Nutritional Risk Index (NRI), and the Prognostic Nutritional Index (PNI), and they recommend the use of the CONUT score [11]. Yang et al. have evaluated the effect of objective nutritional indexes, (i.e., the CONUT score, PNI and GNRI) on all-cause mortality and new-onset major adverse cardiovascular events (MACE) in peritoneal dialysis patients, and they suggest that the CONUT score and PNI may provide more useful predictive values than GNRI [6]. However, clinical cardiologists are unaware that screening for malnutrition based solely on albumin misses some high-risk patients. Accordingly, the first lesson that derives from our study is that clinical cardiologists need to use comprehensive nutritional assessment tools to screen CKD patients undergoing CAG for malnutrition. The CONUT score is a comprehensive, well-validated and easy-to-use tool to identify patients at risk of malnutrition.

Notably, malnutrition is common among patients with mild to severe CKD. More relevantly, people with poorer kidney function are more likely to have poor nutritional status. Recently, Guligowska et al. reported a similar result that decreased eGFR was associated with increased risk of malnutrition, which was assessed by albumin level or MNA in elderly subjects aged ≥ 75 years [24] Few large cohort studies have reported the prevalence of malnutrition in CKD patients. A meta-analysis of the global prevalence of malnutrition (defined by subjective global assessment or malnutrition-inflammation score) in kidney disease, which was from contemporary studies between 2000 and 2014, reported that malnutrition prevalence of patients with CKD stages 3–5 ranges from 11 to 54% in five studies including 1776 patients. In addition, the 25th–75th percentiles range in malnutrition prevalence of patients on maintenance dialysis was from 28 to 54% in ninety studies including 16,434 patients [25]. Evidence on the prevalence of malnutrition was limited by small sample sizes and predominantly focused on patients undergoing dialysis. Our study is a multicenter cohort study including more than 12,000 patients with CKD undergoing CAG and may provide more solid evidence on the prevalence of malnutrition in patients with CKD. In our study, the malnutrition prevalence of patients with mild to severe CKD ranged from 64.2 to 83.3%, and the prevalence of moderate to severe malnutrition ranged from 15.3 to 37.1%. Given the high prevalence rate, clinical cardiologists should pay attention to this condition and screening routinely for malnutrition in patients with CKD hospitalized in cardiology department.
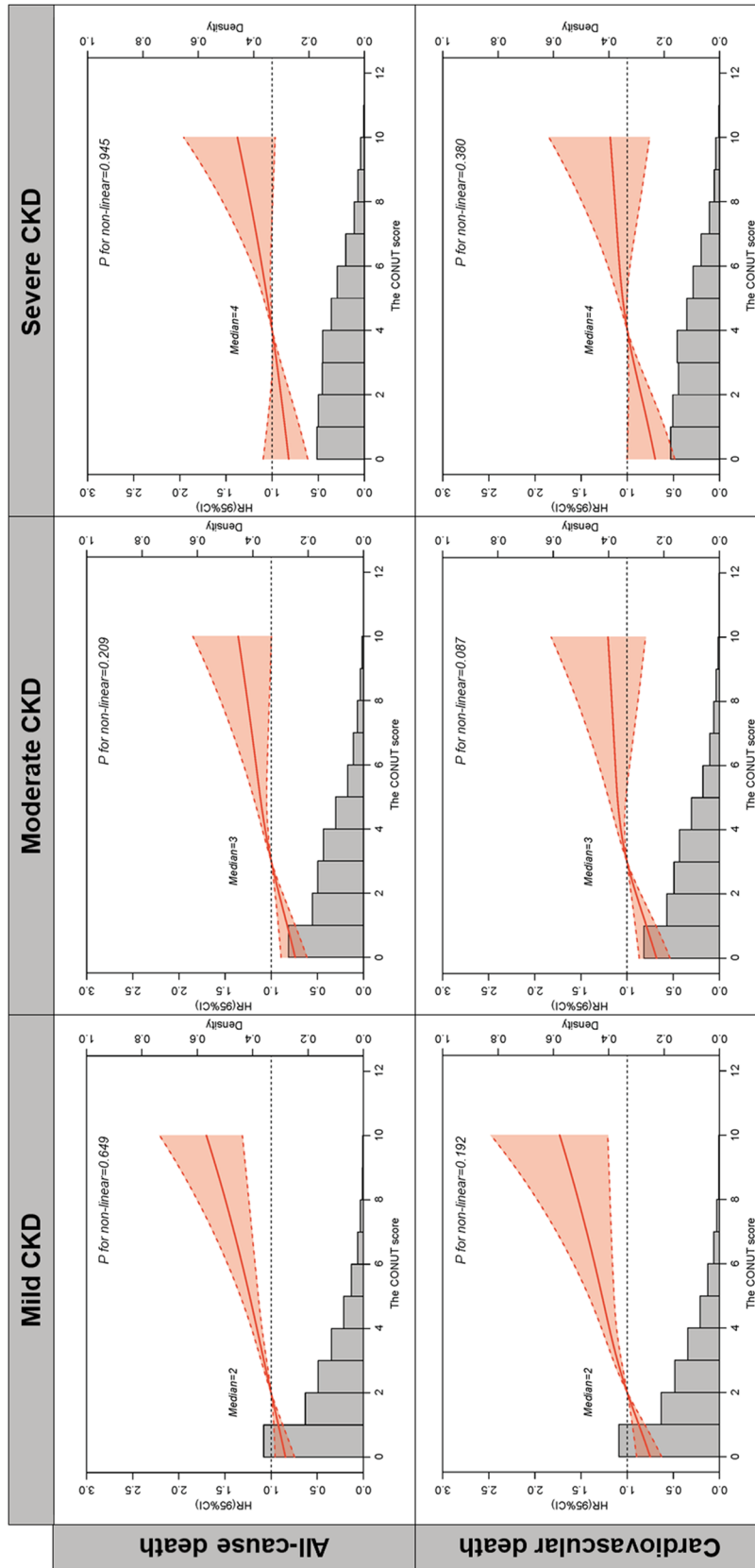
Fig. 5 Restricted cubic spline depicting the relationship of the Controlling Nutritional Status (CONUT) score with risk of all-cause and cardiovascular mortality in different severity of CKD patients undergoing CAG. Adjusted for the following factors (plot settings): age, sex, acute myocardial infarction, congestive heart failure, percutaneous coronary intervention, diabetes mellitus, hypertension, anemia, low density lipoprotein cholesterol, angiotensin converting enzyme inhibitors or angiotensin receptor blocker, beta blocker, calcium channel blockers and statins. *P* for interaction > 0.05 (on all-cause death) and *P* for interaction = 0.04 (on cardiovascular death)

Categories (eGFR,ml/min1.73m²)	Events/Total (%)	All-cause death			Events/Total (%)	Cardiovascular death		
		HR(95%CI)	Forest plots	P for trend		HR(95%CI)	Forest plots	P for trend
eGFR ≥45								
Absent	557/2838 (19.63)	Ref			269/2660 (10.11)	Ref		
Mild	1007/3875 (25.99)	1.23 (1.10–1.37)		<0.001	522/3587 (14.55)	1.31 (1.12–1.54)		<0.001
Moderate	401/1156 (34.69)	1.43 (1.23–1.65)			210/1062 (19.77)	1.47 (1.19–1.82)		
Severe	57/35 (61.40)	2.04 (1.39–2.98)			19/47 (40.43)	2.24 (1.35–3.71)		
30≤ eGFR <45								
Absent	250/887 (28.18)	Ref			151/823 (18.35)	Ref		
Mild	573/1638 (34.98)	1.22 (1.05–1.43)		<0.001	346/1519 (22.78)	1.23 (1.01–1.50)		0.004
Moderate	304/726 (41.87)	1.35 (1.12–1.63)			191/664 (28.77)	1.44 (1.13–1.82)		
Severe	35/64 (54.69)	2.00 (1.36–2.94)			16/53 (30.19)	1.43 (0.78–2.61)		
eGFR <30								
Absent	83/235 (35.32)	Ref			55/223 (24.66)	Ref		
Mild	274/652 (42.02)	1.22 (0.94–1.58)		0.001	186/602 (30.90)	1.20 (0.88–1.65)		0.013
Moderate	235/457 (51.42)	1.45 (1.11–1.91)			154/411 (37.47)	1.45 (1.04–2.03)		
Severe	47/67 (70.15)	1.79 (1.17–2.75)			31/57 (54.39)	1.54 (0.91–2.59)		

Fig. 6 Forest plot demonstrating the hazard ratio of malnutrition for all-cause and cardiovascular mortality in different severity of CKD patients undergoing CAG. The bar chart shows the population density of the CONUT score from 1 to 12. Adjusted for age, sex, acute myocardial infarction, congestive heart failure, percutaneous coronary intervention, diabetes mellitus, hypertension, anemia, low density lipoprotein cholesterol, angiotensin converting enzyme inhibitors or angiotensin receptor blocker, beta blocker, calcium channel blockers and statins

Another highlight of this study is that higher severity of malnutrition is strongly associated with increased all-cause and cardiovascular mortality in patients with CKD undergoing CAG. Evidence on the prognostic impact of malnutrition was limited by small sample sizes and predominantly focused on patients undergoing dialysis or end-stage renal disease. Previous studies showed that malnutrition assessed by MNA or SGA was an independent and strong risk factor for all-cause mortality in dialysis patients [26, 27]. As with subjective nutritional indexes, objective nutritional indexes have similar prognostic effects. A retrospective, single-center study of 252 Chinese has demonstrated that malnutrition using the CONUT score is associated with increased all-cause mortality in patients undergoing peritoneal dialysis [28]. Similarly, Panichi et al. have shown that malnutrition assessed by the GNRI is a significant predictor of mortality in patients receiving hemodialysis. However, cardiovascular events did not differ among the GNRI quartiles in the study of Panichi et al. [29]. Recently, Xiong et al. have performed a multicenter prospective study which showed that malnutrition defined by GNRI was associated with renal progression, cardiovascular events, and all-cause mortality in a cohort of 2791 patients with CKD [9]. However, the relationship between GNRI and cardiovascular events trended to be non-significant after a fully adjusted multivariate analysis. Moreover, for patients with different severity of CKD, the associations between malnutrition, all-cause and cardiovascular mortality have been scarcely reported. We further demonstrated that higher severity of malnutrition assessed by the CONUT was significantly associated with an increased risk of cardiovascular mortality. Malnutrition, inflammation, and atherosclerosis (MIA) syndrome are possible explanations for the association between malnutrition and higher cardiovascular mortality risk in patients with CKD [30]. Chronic inflammation is a common condition of CKD. Inflammation can induce additional catabolism and anorexia in CKD patients, leading to protein-energy wasting (PEW), impaired nutritional status and higher risk of cardiovascular diseases and mortality [31]. In a 5-year follow-up of 310 Swedish patients, mortality was greater in patients with a C-reaction protein (CrP) > 10 mg/l and a worse nutritional status [32]. Moreover, we also explored the relationships between malnutrition, all-cause and cardiovascular mortality in patients with different severity of CKD, and found that malnutrition had a higher impact on all-cause and cardiovascular mortality in patients with mild to moderate CKD, while mild malnutrition did not seem to have a consistent effect on all-cause mortality and cardiovascular mortality in patients with severe CKD. Thereinto, no significant difference in the risk of cardiovascular mortality was observed between no malnutrition and severe malnutrition in patients with moderate CKD (eGFR 30–44 mL/min/1.73 m^2). We speculated that the statistical power was diminished in that the number of cardiovascular deaths was limited in severely malnourished patients with moderate CKD. The likely explanation is that patients with more advanced stages of CKD were more likely to be weaker and their conditions were poorer, thereby associated with a relatively high risk of mortality at baseline. Thus, the contribution of malnutrition to mortality is diminished in this setting.

The results from our study could have the following clinical implications. The CONUT score is an objective nutritional index which uses only three inexpensive laboratory values routinely measured in the cardiology department and is very easy to calculate, as well as can be widely used to identify mortality risk in CKD patients undergoing CAG. A recent longitudinal study of advanced CKD inpatients at nutritional risk found that individualized nutrition education had long-term improvements in nutritional status, reduced hospital admissions, and improved survival [33]. Our findings suggest that individualized nutrition education may also improve long-term prognosis in patients with CKD, and may even be more beneficial in patients with mild to moderate CKD. Further investigation is needed to prospectively evaluate the efficacy of nutritional interventions on outcomes in patients with mild to moderate CKD.

Study limitations

This is a retrospective observational study with the subsequent disadvantages secondary to its nature, so our inferences did not reflect direct causality. Besides, we only adopted the CONUT score as the assessment tool for malnutrition. Due to the retrospective nature of the study, certain baseline variants had relatively a high missing rate, such as body mass index and waist to hip circumference, which could help us apply alternative and comprehensive nutritional assessment tools to understand the nutritional status and verify our findings in this population. Furthermore, nephrotic syndrome is a possible cause for patients with hypoalbuminemia. Due to proteinuria was not routinely tested in this population, patients with nephrotic syndrome could not be easily recognized and excluded in this study. Similarly, chronic inflammation is prevalent and linked with impaired nutritional status and in CKD patients, but it could not be properly recognized and adjusted during the analysis, because inflammation markers such as serum C-reaction protein (CrP) were not routinely tested in this population. Lastly, we only evaluated preoperative nutritional indexes and did not record changes during the follow-up period, and the effect of nutritional support was also neglected. Well-designed and well-executed future studies are needed to examine the predictive validity of the CONUT score in general CKD patients.

Conclusions

Malnutrition is common among patients with CKD undergoing CAG regardless of the level of kidney function. Higher severity of malnutrition is strongly associated with higher all-cause mortality and cardiovascular mortality in patients with CKD undergoing CAG, and this correlation appears to be stronger in patients with mild to moderate CKD.

Declarations

References

1. Cockwell P, Fisher LA (2020) Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet 395(10225):709–733
2. Shlipak MG, Tummalapalli SL, Boulware LE, Grams ME, Ix JH, Jha V, Kengne AP, Madero M, Mihaylova B, Tangri N et al (2021) The case for early identification and intervention of chronic kidney disease: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. Kidney Int 99(1):34–47
3. Saran R, Robinson B, Abbott KC, Bragg-Gresham J, Chen X, Gipson D, Gu H, Hirth RA, Hutton D, Jin Y et al (2020) US renal data system 2019 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 75(1 Suppl 1):A6-a7
4. Longenecker JC, Coresh J, Powe NR, Levey AS, Fink NE, Martin A, Klag MJ (2002) Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. J Am Soc Nephrol 13(7):1918–1927
5. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, Sarnak MJ (2007) The framingham predictive instrument in chronic kidney disease. J Am Coll Cardiol 50(3):217–224
6. Yang Y, Zhou H, Zhang P, Chao W, Zou Y, Yang M (2020) Evaluation of objective nutritional indexes as predictors of worse outcomes in peritoneal dialysis patients. Nutrition 79–80:110963

7. Xiong J, Wang M, Zhang Y, Nie L, He T, Wang Y, Huang Y, Feng B, Zhang J, Zhao J (2018) Association of geriatric nutritional risk index with mortality in hemodialysis patients: a meta-analysis of cohort studies. Kidney Blood Press Res 43(6):1878–1889

8. Kiuchi A, Ohashi Y, Tai R, Aoki T, Mizuiri S, Ogura T, Aikawa A, Sakai K. (2016) Association between Low Dietary Protein Intake and Geriatric Nutrition Risk Index in Patients with Chronic Kidney Disease: A Retrospective Single-Center Cohort Study. Nutrients 8 (10).

9. Xiong J, Wang M, Wang J, Yang K, Shi Y, Zhang J, Zhang B, Zhang L, Zhao J (2020) Geriatric nutrition risk index is associated with renal progression, cardiovascular events and all-cause mortality in chronic kidney disease. J Nephrol 33(4):783–793

10. Fiaccadori E, Sabatino A, Barazzoni R, Carrero JJ, Cupisti A, De Waele E, Jonckheer J, Singer P, Cuerda C (2021) ESPEN guideline on clinical nutrition in hospitalized patients with acute or chronic kidney disease. Clin Nutr 40(4):1644–1668

11. Raposeiras Roubín S, Abu Assi E, Cespón Fernandez M, Barreiro Pardal C, Lizancos Castro A, Parada JA, Pérez DD, Blanco Prieto S, Rossello X, Ibanez B et al (2020) Prevalence and prognostic significance of malnutrition in patients with acute coronary syndrome. J Am Coll Cardiol 76(7):828–840

12. Seo M, Yamada T, Tamaki S, Morita T, Furukawa Y, Iwasaki Y, Kawasaki M, Kikuchi A, Kawai T, Abe M et al (2019) Prognostic significance of serum cholinesterase in patients with acute decompensated heart failure: a prospective comparative study with other nutritional indices. Am J Clin Nutr 110(2):330–339

13. Sze S, Pellicori P, Zhang J, Weston J, Clark AL (2021) The impact of malnutrition on short-term morbidity and mortality in ambulatory patients with heart failure. Am J Clin Nutr 113(3):695–705

14. Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, González P, González B, Mancha A, Rodríguez F, Fernández G (2005) CONUT: a tool for controlling nutritional status first validation in a hospital population. Nutr Hosp 20(1):38–45

15. Aguiar-Souto P, Ferrante G, Del Furia F, Barlis P, Khurana R, Di Mario C (2010) Frequency and predictors of contrast-induced nephropathy after angioplasty for chronic total occlusions. Int J Cardiol 139(1):68–74

16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. Ann Intern Med 130(6):461–470

17. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW et al (2004) A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 44(7):1393–1399

18. Bansal N, Hyre Anderson A, Yang W, Christenson RH, deFilippi CR, Deo R, Dries DL, Go AS, He J, Kusek JW et al (2015) High-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and risk of incident heart failure in patients with CKD: the chronic renal insufficiency cohort (CRIC) study. J Am Soc Nephrol 26(4):946–956

19. Tsai AC, Wang JY, Chang TL, Li TY (2013) A comparison of the full mini nutritional assessment, short-form mini nutritional assessment, and subjective global assessment to predict the risk of protein-energy malnutrition in patients on peritoneal dialysis: a cross-sectional study. Int J Nurs Stud 50(1):83–89

20. Khor BH, Tiong HC, Tan SC, Abdul Rahman R, Abdul Gafor AH (2020) Protein-energy wasting assessment and clinical outcomes in patients with acute kidney injury: a systematic review with meta-analysis. Nutrients 12(9):2809

21. Jeejeebhoy KN (1998) Nutritional assessment. Gastroenterol Clin North Am 27(2):347–369

22. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA et al (2019) Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 48(1):16–31

23. Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, Tracy RP, Powe NR, Klag MJ (2004) Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. JAMA 291(4):451–459

24. Guligowska A, Corsonello A, Pigłowska M, Roller-Wirnsberger R, Wirnsberger G, Ärnlöv J, Carlsson AC, Tap L, Mattace-Raso F, Formiga F et al (2020) Association between kidney function, nutritional status and anthropometric measures in older people: the screening for CKD among older people across Europe (SCOPE) study. BMC Geriatr 20(Suppl 1):366

25. Carrero JJ, Thomas F, Nagy K, Arogundade F, Avesani CM, Chan M, Chmielewski M, Cordeiro AC, Espinosa-Cuevas A, Fiaccadori E et al (2018) Global prevalence of protein-energy wasting in kidney disease: a meta-analysis of contemporary observational studies from the international society of renal nutrition and metabolism. J Ren Nutr 28(6):380–392

26. de Mutsert R, Grootendorst DC, Boeschoten EW, Brandts H, van Manen JG, Krediet RT, Dekker FW (2009) Subjective global assessment of nutritional status is strongly associated with mortality in chronic dialysis patients. Am J Clin Nutr 89(3):787–793

27. Brzosko S, Hryszko T, Kłopotowski M, Myśliwiec M (2013) Validation of mini nutritional assessment scale in peritoneal dialysis patients. Arch Med Sci 9(4):669–676

28. Zhou H, Chao W, Cui L, Li M, Zou Y, Yang M (2020) Controlling Nutritional Status (CONUT) score as immune-nutritional predictor of outcomes in patients undergoing peritoneal dialysis. Clin Nutr 39(8):2564–2570

29. Panichi V, Cupisti A, Rosati A, Di Giorgio A, Scatena A, Menconi O, Bozzoli L, Bottai A (2014) Geriatric nutritional risk index is a strong predictor of mortality in hemodialysis patients: data from the Riscavid cohort. J Nephrol 27(2):193–201

30. Maraj M, Kuśnierz-Cabala B, Dumnicka P, Gala-Błądzińska A, Gawlik K, Pawlica-Gosiewska D, Ząbek-Adamska A, Mazur-Laskowska M, Ceranowicz P, Kuźniewski M (2018) Malnutrition, inflammation, atherosclerosis syndrome (mia) and diet recommendations among end-stage renal disease patients treated with maintenance hemodialysis. Nutrients 10(1):69

31. Fouque D, Pelletier S, Mafra D, Chauveau P (2011) Nutrition and chronic kidney disease. Kidney Int 80(4):348–357

32. Avesani C, Carrero J, Axelsson J, Qureshi AR, Lindholm B, Stenvinkel P (2006) Inflammation and wasting in chronic kidney disease: partners in crime. Kidney Int 70:S8–S13

33. Pérez-Torres A, González García ME, Ossorio-González M, Álvarez García L, Bajo MA, Del Peso G, Castillo Plaza A, Selgas R. (2021) The Effect of Nutritional Interventions on Long-Term Patient Survival in Advanced Chronic Kidney Disease. Nutrients 13 (2) 621

Authors and Affiliations

Fei Gao[1] · Zhidong Huang[2,3] · JingJing Liang[4,5] · Yu Kang[2,3,11] · Yihang Ling[2,3] · Yibo He[2,3] · Jiahui Chen[6] · Daqing Hong[7] · Zewei Zhang[8] · Shanshan Xu[5] · Amanda Wang[9] · Xiaoming Yan[10] · Jin Liu[2,3] · Yong Liu[2,3] · Shiqun Chen[2,3] [ORCID] · Jiyan Chen[2,3]

[1] Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China

[2] Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China

[3] Department of Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China

[4] Department of Cardiology, Shunde Hospital, Southern Medical University, Foshan, China

[5] The Second School of Clinical Medicine, Southern Medical University, Guangzhou, China

[6] Department of Pharmacy, Guangdong Pharmaceutical University, Guangzhou, China

[7] Department of Nephrology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu 610072, China

[8] Department of Public Health, Guangdong Medical University, Dongguan, China

[9] The George Institute for Global Health, UNSW, Sydney, Australia

[10] Department of Information Technology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China

[11] Shantou University Medical College, Shantou 515041, China