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Handgrip strength is an independent predictor of renal outcomes in patients with chronic kidney diseases

Yu-Tzu Chang[1,*], Hung-Lien Wu[2,*], How-Ran Guo[3], Ya-Yun Cheng[3], Chin-Chung Tseng[1], Ming-Cheng Wang[1], Ching-Yuang Lin[4] and Junne-Ming Sung[1]

[1]Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, [2]Department of Nutrition, National Cheng Kung University Hospital, Tainan, Taiwan, [3]Department of Environmental and Occupational Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan and [4]Children's Medical Center, China Medical University Hospital, Taichung, Taiwan

Correspondence and offprint requests to: Junne-Ming Sung; E-mail: jmsung@mail.ncku.edu.tw
*Both authors contributed equally to this study.

Abstract

Background. In dialysis patients, protein-energy wasting (PEW) is associated with high mortality, and some indicators of PEW, such as serum albumin value, subjective global assessment (SGA) score and handgrip strength (HGS), may predict mortality. However, whether PEW is associated with poor renal outcomes and whether the indicators of PEW can predict renal outcomes in patients with non-dialysis-dependent chronic kidney disease (CKD-ND) is still unclear.

Methods. We enrolled 128 clinically stable patients with CKD-ND and followed up for 33.8 ± 9.2 months. Baseline characteristics, echocardiographic information, laboratory data, HGS, SGA scores, anthropometric parameters, bioimpedance analyses and other indicators of PEW were examined in relation to the risk of reaching renal composite end points of pre-dialysis mortality or dialysis-dependent end-stage renal disease.

Results. Twenty-six patients reached composite renal end points. Multivariate Cox regression analyses showed that HGS was an independent predictor of renal outcome in patients with CKD-ND of Stages 1–5 [$CKD_{1–5}$, hazard ratio (HR) = 0.90, P = 0.004] or advanced CKD-ND of Stages 3b [defined as estimated glomerular filtration rate (eGFR) of 30–44 mL/min/1.73m^2] to 5 ($CKD_{3b–5}$, HR = 0.91, P = 0.031), but not serum albumin, SGA score or other indicators of PEW. When the cutoffs were set at 24.65 kg in men with $CKD_{1–5}$, 20.15 kg in men with $CKD_{3b–5}$ and 10.15 kg in women with $CKD_{1–5}$ or $CKD_{3b–5}$, which were deduced from receiver-operating characteristics analyses, patients with lower HGS had significantly poor renal outcomes in Kaplan–Meier survival analyses in all subgroups and higher HR for reaching renal end points in multivariate Cox regression analyses in all subgroups except for women with $CKD_{3b–5}$, whose HR had marginal significance (HR = 3.78, P = 0.068) after adjusting for age and eGFR.

Conclusions. This is the first study demonstrating that HGS is an independent predictor of composite renal outcomes in CKD-ND patients. HGS can be incorporated to clinical practice for assessing nutrition status and renal prognosis in patients with CKD-ND.

Keywords: chronic kidney disease (CKD); handgrip strength (HGS); serum albumin; subjective global assessment (SGA)

Introduction

Individuals with chronic kidney disease (CKD), including non-dialysis-dependent CKD (CKD-ND) or dialysis-dependent end-stage renal diseases (ESRD), experience high cardiovascular and all-cause mortality rates [1, 2]. In dialysis patients, the high mortality rates are associated with protein-energy wasting (PEW) [3–5]. It is now clear that PEW is not only prevalent in dialysis patients but also in patients with CKD-ND [6, 7], and recent studies demonstrated that some indicators of PEW (such as serum albumin levels and percent of lymphocytes) are associated with cardiovascular events, cardiovascular mortality and all-cause mortality in CKD-ND patients [8–11], suggesting PEW have a great impact on clinical course of CKD-ND. However, most of

these studies did not report the pre-dialysis and post-dialysis mortalities separately [8–11], and there is little information about the association between the indicators of PEW and composite renal outcomes of pre-dialysis mortality or reaching ESRD in CKD-ND population. The assessment of composite renal outcomes is clinically relevant because there is a competition between pre-dialysis mortality and reaching ESRD in patients with CKD-ND, and the goal of clinical reno-protection strategies is to prevent both. It is feasible that PEW contributes to pre-dialysis mortality and rapid decline of renal function. As an example, PEW is strongly associated with cardiovascular disease (CVD) in patients with CKD-ND [8–11], and CVD is not only the leading cause of pre-dialysis mortality but also a strong risk factor for rapid decline of renal function [8–10, 12, 13].

CKD has emerged as a global public health burden. If PEW is clinically significant, identification of useful, easily performed and inexpensive tools to assess nutritional status is essential in clinical practice for the large population of patients with CKD-ND. Currently, several biochemical parameters (such as serum albumin and pre-albumin levels), anthropometric measurements, biophysical methods [such as bioimpedance (BIA), handgrip strength (HGS)], biochemical methods (such as dual energy X-ray absorptiometry) and nutritional scoring systems [such as Subjective Global Assessment of Nutrition(SGA)], which have been used clinically as nutritional assessment tools in dialysis patients, may be indicators of PEW. Among these, serum albumin value is the most commonly used and has a strong outcome predictability [5, 12], and SGA is suggested for the routine monitoring the nutritional status by the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [14] in dialysis patients. In addition, HGS measurement, a simple, easily performed, bedside test [15], has also emerged as a reliable tool to assess nutrition status and as a prognostic factor in dialysis patients [16–18]; however, use of these parameters as renal outcome predictors in patients with CKD-ND has not been established.

We hypothesized that PEW is associated with poor composite renal outcomes in patients with CKD-ND. The aim of the present study is to evaluate the renal outcome predictability of various potential indicators of PEW, including HGS, SGA score, serum albumin and other nutritional markers, in patients with CKD-ND, for testing the hypothesis and identifying useful indicator(s) for clinical patient care.

Subjects and methods

Study design and participants

We conducted a prospective observational study to evaluate the association between potential indicators of PEW and the composite renal outcomes in patients with CKD-ND in the Nephrology Outpatient Unit of National Cheng Kung University Hospital, Tainan, Taiwan. This study protocol was approved by the Ethics Committee at the institute, and informed consent was obtained from each enrolled patient. From 1 July to 31 December 2005, patients with CKD-ND, who had received multidisciplinary CKD education (focused on lifestyle, nephrotoxin avoidance, dietary principles and pharmacological regimens) every 3 months for at least a half year were eligible to enroll. Exclusion criteria included age <18 or >75, inability to communicate with examiners, arthritis or neuromuscular diseases involving bilateral hands, an acute illness necessitating admission within the previous 6 months, malignancy diagnosed before enrollment, Class III or IV congestive heart failure (CHF), severe nephrotic syndrome [defined as an increase of body weight (BW) of $\geq$5 kg from baseline due to heavy proteinuria], intercurrent steroid therapy, gastrointestinal disease (such as ulcerative colitis and Crohn's disease) or other severe organ failure that may influence nutritional data or survival time.

GFR was estimated (eGFR) using an Isotope Dilution Mass Spectrometry -traceable formula derived by the Modification of Diet in Renal Disease (MDRD) study group: eGFR $= 175 \times (\text{serum creatinine})^{1.154} \times \text{age}^{0.203} \times (0.742$ if female) [19]. CKD was staged according to National Kidney Foundation (NKF) guidelines with minor modifications as the following: eGFR (mL/min/1.73m^2) of 45–59 was assigned to CKD Stage 3a, and eGFR of 30–44 was assigned to CKD Stage 3b. In addition, all enrolled patients with CKD Stages 1 and 2 were required to have urine albumin-to-creatinine ratio $>$ 30 (mg/g). For the final statistical analysis, we further defined three groups: $CKD_{1–5}$ group, patients with CKD-ND Stages 1–5; $CKD_{1–3a}$ subgroup, patients with CKD Stages 1–3a; $CKD_{3b–5}$ subgroup, patients with CKD-ND Stages 3b–5.

Patients were followed up every 1–3 months till 31 December 2008. The end point was composite renal end point of pre-dialysis mortality (mortality before commencing long-term dialysis) or reaching ESRD (uremia receiving long-term dialysis). The indications of starting long-term dialysis, which were consistent with the clinical practice and the recommendations of the National Health Insurance of Taiwan, were eGFR $\leq$5 or serum creatinine level $\geq$10 mg/dL or the presence of uremic symptoms [20]. Since the use of nephrotoxic agents may affect the renal outcomes, participants with an episode of documented drug-related (such as herbal medicine or non-steroid anti-inflammatory drugs) or contrast media-related acute deterioration of renal function (defined arbitrarily as an increase in serum creatinine of $\geq$25% from the baseline [21]) during the follow-up period would be excluded from statistic analyses.

Clinical assessments and data collection

We collected baseline clinical data [such as age, sex, height, BW, clinical etiology of CKD if possible, comorbidities, blood pressure, use of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II-receptor blockers (ARBs)], laboratory measures [such as serum creatinine, albumin, C-reactive protein (CRP), total cholesterol, complete blood counts, urine routines, urine total protein to creatinine ratio and albumin to creatinine ratio], anthropometric information and various potential indicators of PEW [such as body mass index, waist/hip ratio, mid-arm circumference (MAC), triceps skinfold thickness (TSF), mid-arm muscle circumference (MAMC), mid-arm muscle area (MAMA), SGA, BIA analyses, HGS and pinch strength (PS)]. For the laboratory tests, fasting blood and urine samples were obtained from each patient within 1 month after enrollment and were performed in the Department of Clinical Pathology, National Cheng Kung University Hospital, by means of routine methods. The daily urine protein loss was estimated by urine total protein to creatinine ratio. All patients received echocardiograms studies performed within 3 months after enrollment, which were used to estimate CHF (defined as an ejection fraction of $<$50%) or left ventricular hypertrophy (LVH, defined as left ventricle mass index $\geq$125 g/m^2 in men and 100 g/m^2 in women). CVD was defined as a previous history of CHF, LVH, ischemic heart disease (including prior history of angina, myocardial infarction, coronary artery bypass grafting and percutaneous cardiac catheter intervention) or cerebrovascular disease (including prior history of transient ischemic attack and stroke).

Assessments of nutritional status and potential indicators of PEW

We applied a modified SGA with a 7-point scale and a single renal dietitian, who has worked in this field for 20 years, assessed the nutritional status of all patients. The actual BW and height on the day of assessment was used. Anthropometric measurements include TSF used skinfold calipers (Lange Skinfold Caliper Beta Technology Inc., Cambridge, MD); MAC measured by a stretchable measuring tape, MAMC equals MAC (centimeter) $-$ 3.14 $\times$ TSF (millimeter)/10 and MAMA equals (MAMC^2/4π). Muscle strength as HGS test was measured by Lafayette Hand Dynamometer (Model 78010; Lafayette Instrument Co., Lafeyette, IN). HGS was measured 3 times for both left and right hands with patients in a standing position using a dynamometer in units of kilograms. Patients held the dynamometer at thigh level and were encouraged to squeeze the instrument as hard as possible for 3 s. The maximum grip strength among all measurements was used for the present study. PS test was measured by pinch gage (Pinch Gauge Operating Instruction; B & L Engineering Pinsco Inc., Tusia, CA). Single frequency bioimpedance (Bodystat1500; Bodystat Limited, Douglas, Isle of Man) was used to estimate body composition when patients were resting in a supine position.

Statistical analyses

Continuous variables were presented as mean ± standard deviation (SD). Comparisons of variables with normal distribution were assessed by using Student's *t*-test, and comparisons of nonparametric data were assessed by Mann–Whitney *U*-test. The categorical variables were presented as number of case (percentage) and compared using the chi-squared test. Cox proportional hazards analysis was used to evaluate the impact of patients' baseline parameters on renal composite outcome. Since the gender may influence HGS, receiver-operating characteristic curves (ROC curves) were used to evaluate outcome predictability of HGS by comparing the areas under curve (AUCs) between unadjusted and adjusted (for serum albumin and SGA) and to set the cutoffs of HGS to predict renal outcomes in different gender subgroups, including men with $CKD_{1–5}$, women with $CKD_{1–5}$, men with $CKD_{3b–5}$ and women with $CKD_{3b–5}$. Kaplan–Meier survival analysis with the log-rank test and multivariate Cox proportional hazards analysis were subsequently performed to evaluate the renal survival difference and hazard ratio (HR) for reaching end points by using different cutoffs values of HGS in different subgroups, respectively. In $CKD_{1–5}$ men and women subgroups, we constructed the final Cox's models by starting with a full model with all relevant predictor variables and then keeping those with $P \leq 0.2$; thus, age, eGFR, the presence of CVD, systolic blood pressure (SBP) and urine daily protein loss were included in the final models. In $CKD_{3b–5}$ subgroups, only age and eGFR were put into final models because of the limitation of sizes. A P-value <0.05 was considered significant. Statistical analyses were performed with SPSS 17.0 statistical software (SPSS Inc., Chicago, IL).

Results

There were 164 CKD-ND patients eligible and 31 patients refused to participate. Five patients withdrew because of drug-related or contrast media-induced acute renal function deterioration. No patients were lost to follow-up or received preempive kidney transplantation. Finally, there were 128 patients entering the statistic analysis. Among them, 9 had CKD Stage 1, 35 had CKD Stage 2, 18 had CKD Stage 3a, 17 had CKD Stage 3b, 31 had CKD Stage 4 and 18 had CKD-ND Stage 5 when enrolled. During the follow-up period, 26 participants reached the end point: 10 patients had pre-dialysis mortality and 16 reached ESRD. The causes of death included CVD ($n = 5$; including coronary heart diseases, $n = 2$; heart failure, $n = 1$; aortic dissection, $n = 1$ and

Table 1. Baseline clinical characteristics of the study populations[a]

Parameters	Total ($n = 128$)	Reaching renal composite end point		P-value[b]
		No ($n = 102$)	Yes ($n = 26$)	
Age (year)	60.7 ± 14.8	60.3 ± 14.0	62.5 ± 18.0	0.491
Height (cm)	159.2 ± 7.3	158.8 ± 7.4	160.4 ± 7.2	0.329
BW (kg)	62.9 ± 10.7	62.7 ± 10.9	63.6 ± 9.8	0.725
Male/female (*n*)	60/68	46/56	14/12	0.425
CKD stage [*n* (%)]				
Stages 1–3a	62 (48.4%)	59 (57.8%)	3 (11.5%)	<0.0001
Stages 3b–5	66 (51.6%)	43 (42.2%)	23 (88.5%)	
Past medical history [*n* (%)]				
Chronic glomerulonephritis	34 (26.6%)	30 (29.4%)	4 (15.4%)	0.148
Tubulointerstitial nephritis	36 (28.1%)	29 (28.4%)	7 (26.9%)	0.879
ADPKD	7 (5.5%)	6 (5.9%)	1 (3.9%)	0.684
Hypertensive nephrosclerosis	8 (6.3%)	7 (6.9%)	1 (3.8%)	0.571
DM	45 (35.1%)	33 (32.4%)	12 (46.2%)	0.188
CVD	36 (28.1%)	22 (21.6%)	14 (53.8%)	0.001
Renal survival time during the study period (month)	33.8 ± 9.2	37.6 ± 3.6	18.9 ± 11.6	<0.0001
SBP (mmHg)	130.0 ± 15.7	127.6 ± 14.8	137.6 ± 17.0	0.007
Diastolic blood pressure (mmHg)	74.5 ± 10.6	74.7 ± 10.7	73.5 ± 10.5	0.630
Use of ACEIs/ARBs [*n* (%)]	70 (54.7%)	61 (59.8%)	9 (34.6%)	0.021
Education level [*n* (%)]				
Junior high school or below	62 (48.4%)	47 (46.1%)	15 (57.7%)	0.290
Senior high school or above	66 (51.6%)	55 (53.9%)	11 (42.3%)	
Blood urea nitrogen (mg/dL)	33 ± 11.2	27.2 ± 9.2	55.8 ± 25.9	<0.0001
Cr (mg/dL)	2.0 ± 0.4	2.0 ± 0.9	3.7 ± 1.7	<0.0001[c]
eGFR (mL/min)	46.6 ± 28.2	53.0 ± 26.6	21.6 ± 12.3	<0.0001[c]
Calcium (mg/dL)	9.5 ± 0.6	9.6 ± 0.5	9.2 ± 0.8	0.040
Phosphate (mg/dL)	4.1 ± 0.8	3.9 ± 0.6	4.5 ± 1.0	0.002
Sodium (mmol/L)	140.6 ± 3.4	140.5 ± 3.5	141.0 ± 3.2	0.542
Potassium (mmol/L)	4.4 ± 0.5	4.3 ± 0.4	4.5 ± 0.7	0.165
Glucose (mg/dL)	112.1 ± 51.5	114.9 ± 50.3	112.3 ± 58.1	0.863
Albumin (g/dL)	4.3 ± 0.37	4.3 ± 0.3	4.0 ± 0.5	0.003
Urine daily protein loss (g/day)	1.6 ± 2.7	1.0 ± 1.6	3.9 ± 4.4	0.004
White blood cell (1000/mm^3)	7.0 ± 2.4	6.9 ± 2.6	7.4 ± 1.5	0.420
Hematocrit (%)	35.4 ± 5.4	37.1 ± 7.4	31.4 ± 4.4	0.001
Total cholesterol (mg/dL)	203.1 ± 40.7	203.4 ± 40.1	201.8 ± 44.0	0.868
Triglyceride (mg/dL)	168.4 ± 116.7	167.8 ± 121.8	171.2 ± 93.4	0.899
High-density lipoprotein cholesterol (mg/dL)	45.3 ± 14.1	46.3 ± 13.9	41.1 ± 14.6	0.166
Low-density lipoprotein cholesterol (mg/dL)	119.9 ± 38.8	120.1 ± 39.7	118.7 ± 35.8	0.899
CRP (mg/L)	3.6 ± 3.5	3.2 ± 3.1	5.3 ± 4.9	0.021[c]

[a]ADPKD, autosomal dominant polycystic kidney disease; All data are expressed as mean ± SD.
[b]P-values for comparisons between patients with and without reaching renal composite end point by Students' *t*-test for parametric data.
[c]P-values for comparisons between patients with and without reaching renal composite end point by Mann–Whitney *U*-test for nonparametric data.

Table 2. The anthropometric parameters, muscle strength and nutritional markers of the study populations[a]

Parameters	Total ($n = 128$)	Reaching renal composite end point		P-value
		No ($n = 102$)	Yes ($n = 26$)	
BMI (kg/m^2)	24.9 ± 4.1	24.9 ± 4.0	24.9 ± 4.6	0.984
IBW (kgw)	55.8 ± 5.1	55.6 ± 5.2	56.7 ± 5.1	0.334
MAC (cm)	28.0 ± 3.6	28.1 ± 3.5	27.8 ± 4.1	0.699
TSF (mm)	21.7 ± 9.2	21.5 ± 8.9	22.5 ± 10.7	0.641
MAMC (cm)	21.3 ± 3.4	21.5 ± 3.5	20.8 ± 3.3	0.358
MAMA (cm^2)	36.9 ± 11.4	37.4 ± 11.6	35.1 ± 10.7	0.363
HGS (kg)	21.9 ± 9.9	23.2 ± 9.6	16.9 ± 9.8	0.004
Male ($n = 60$)	28.0 ± 9.4	30.1 ± 8.1 ($n = 46$)	21.2 ± 10.3 ($n = 14$)	0.001
Female ($n = 68$)	16.5 ± 6.8	17.5 ± 6.5 ($n = 56$)	11.9 ± 6.5 ($n = 12$)	0.008
PS (kg)	6.0 ± 2.1	6.2 ± 2.2	5.4 ± 2.0	0.095
SGA (score)	5.1 ± 1.0	5.3 ± 0.9	4.6 ± 1.2	0.011
Waist (cm)	84.6 ± 10.7	84.0 ± 10.8	86.8 ± 10.5	0.249
Hip (cm)	96.5 ± 8.1	96.4 ± 7.5	96.9 ± 10.0	0.788
Waist/hip ratio	0.88 ± 0.07	0.87 ± 0.08	0.90 ± 0.06	0.113
Body fat (%)	27.1 ± 9.9	27.6 ± 9.7	25.3 ± 10.8	0.232
BIA data				
Total fat in body (kg)	17.4 ± 7.2	17.4 ± 7.2	16.4 ± 8.3	0.524
Lean body mass (kg)	45.2 ± 9.2	45.2 ± 9.5	47.2 ± 7.7	0.327
Total body water (kg)	33.3 ± 7.4	33.3 ± 7.4	35.4 ± 6.1	0.217
Total body water (%)	54.3 ± 9.0	53.9 ± 9.0	56.9 ± 9.0	0.179
Lean body mass (%)	73.8 ± 7.0	73.6 ± 7.4	74.9 ± 3.7	0.265
Resistance (Ω)	523.3 ± 125.9	532.2 ± 129.5	489.0 ± 106.8	0.180
Reactance (Ω)	84.4 ± 44.3	87.6 ± 43.7	72.2 ± 45.2	0.166
Phase angle	9.3 ± 4.8	9.5 ± 4.7	8.5 ± 5.0	0.334

[a]BMI, body mass index; IBW, ideal BW.

ischemic bowel disease, $n = 1$), septic shock ($n = 2$), acute pancreatitis ($n = 1$), malignancy with sepsis ($n = 1$) and massive gastrointestinal bleeding ($n = 1$).

Baseline clinical characteristics of patients with or without reaching renal composite end points

Tables 1 and 2 showed the baseline data, measurements of various potential indicators of PEW and the results of the statistical analysis. Patients reaching renal end points had more advanced renal disease, higher SBP, higher CVD prevalence, and fewer patients used ACEIs/ARBs. They also had higher blood urea nitrogen, creatinine and phosphate levels, while having lower eGFR, calcium and hematocrit levels, than patients not reaching end points. Furthermore, their serum albumin levels were lower ($P = 0.003$) and daily urine protein losses were heavier ($P = 0.004$).

Among various potential indicators of PEW, only HGS ($P = 0.004$) and SGA scores ($P = 0.011$) were significantly different between patients with and without reaching composite renal end points. Average HGS by age-, sex- and CKD group-specific categories were shown in Supplementary Figure S1. Data of the health control group were deduced from a Japanese population-based study, which included persons 35–74 years of age [22]. A gradual decrease was found in both sexes when the age increased in $CKD_{1–3a}$ and $CKD_{3b–5}$ patients (trend tests, all $P < 0.05$). There were significant differences of HGS between men and women according to age-, sex- and CKD group-specific categories (*t*-tests, all $P < 0.05$); however, there was no significant difference in HGS values between $CKD_{1–3a}$ and $CKD_{3b–5}$ subgroups in both sexes in all categories (*t*-tests, all $P > 0.05$). We also noted that HGS correlated with MAMA, MAMC, SGA scores and serum albumin levels though not as strong (Supplementary Table S1). In addition, we observed that malnourished patients (SGA 1–5) had significantly lower HGS than well-nourished participants (SGA 6–7) (20.3 ± 9.7 versus 24.7 ± 9.8 kg, $P = 0.02$).

Assessment of the outcome predictability of clinical parameters and indicators of PEW in patients with $CKD_{1–5}$ and $CKD_{3b–5}$

We subsequently analyzed the potential risk factors predicting the composite renal outcomes deduced from Tables 1 and 2. Blood urea nitrogen, calcium, phosphate and hematocrit values, which were significantly different between patients with or without reaching renal end points, were not included in risk factor analysis because they were significantly associated with eGFR levels by Pearson's correlation analysis and they were not significantly associated with the composite renal end point by Cox regression analysis after adjusted eGFR (Supplementary Tables S2-A and S2-B). Age, sex and the presence of diabetes were included since previous studies suggested that they had a potential impact on renal outcomes [9, 10, 13]. Participants with mild renal failure ($CKD_{1–3a}$) were less likely to reach renal end points during the follow-up period and tend to have higher HGS, which might confound the statistical results, so we evaluated the potential risk factors in both the $CKD_{1–5}$ group as a whole CKD population and $CKD_{3b–5}$ subgroups as a high risk group in terms of reaching composite renal endpoints. Univariate Cox regression analyses showed HGS, eGFR level, CVD history, use of ACEIs/ARBs, SGA scores, SBP, serum albumin value, serum CRP value

Table 3. Univariate Cox regression model for identifying the potential risk factors for reaching renal composite end point in various populations[a]

	CKD Stages 1–5 ($n = 128$)		CKD Stages 3b–5 ($n = 66$)	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (year)	1.01 (0.98–1.04)	0.491	1.01 (0.98–1.04)	0.756
Sex	1.37 (0.63–2.96)	0.425	1.38 (0.61–3.13)	0.438
Cr (mg/dL)	2.30 (1.84–2.86)	<0.0001	2.15 (1.65–2.81)	<0.0001
eGFR (mL/min)	0.93 (0.90–0.96)	<0.0001	0.87 (0.82–0.92)	<0.0001
CVD	3.51 (1.62–7.60)	0.001	3.80 (1.66–8.69)	0.002
Use of ACEI/ARB	0.34 (0.15–0.78)	0.012	0.58 (0.23–1.48)	0.255
HGS (kg)	0.93 (0.89–0.98)	0.002	0.94 (0.90–0.99)	0.015
SGA	0.53 (0.37–0.77)	0.001	0.57 (0.40–0.82)	0.002
SBP (mmHg)	1.03 (1.01–1.06)	0.005	1.03 (1.01–1.06)	0.016
DM	1.55 (0.72–3.36)	0.263	1.64 (0.72–3.75)	0.238
Albumin (g/dL)	0.13 (0.05–0.34)	<0.0001	0.21 (0.07–0.61)	0.004
Urine DPL (g/day)	1.16 (1.09–1.24)	<0.0001	1.12 (1.05–1.20)	0.001
CRP (mg/L)	1.03 (1.02–1.05)	<0.0001	1.03 (1.01–1.04)	0.009

[a]DM, diabetic mellitus; DPL, daily protein loss; CI, confidence interval.

and daily urine protein loss are significant prognostic indices for renal outcomes (Table 3, all $P < 0.05$). Neither age nor diabetes was a significant predictor.

Since three potential indicators of PEW, including serum albumin value, HGS and SGA score, were significant predictors in a univariate model, we further assessed their outcome predictability by multivariate Cox survival analysis. Table 4 showed that HGS was an independent outcome predictor (HR, 95% confidence interval = 0.90, 0.84–0.97 in $CKD_{1–5}$ group and 0.91, 0.83–0.99 in $CKD_{3b–5}$ subgroup, respectively); whereas, serum albumin level and SGA score were not significantly associated with renal outcomes. In addition, we evaluated outcome predictability of HGS by using ROC curve analysis. As shown in Supplementary Figure S2, adjusting for SGA and serum albumin for ROC curves of HGS would not increase prediction powers significantly in different subgroups, indicating HGS was the major nutritional marker for predicting composite renal outcomes.

Assessment of outcome predictability of HGS for different cutoffs

We defined the cutoffs with outcome predictability of HGS by ROC curves of different subgroups. The sensitivity and specificity were 80.4 and 57.1% for the HGS cutoff of 24.65 kg in men with $CKD_{1–5}$, 87.5 and 58.3% for the cutoff of 10.15 kg in women with $CKD_{1–5}$, 95 and 50% for the cutoff of 20.15 kg in men with $CKD_{3b–5}$ and 87.5 and 58.3% for the cutoff 10.15 kg in women with $CKD_{3b–5}$ (all $P < 0.05$). Kaplan–Meier survival curves analyses showed patients with HGS lower than different cutoffs set for all subgroups had significantly poor renal outcomes (Figure 1, all $P < 0.05$). Multivariate Cox regression analyses showed patients with HGS lower than cutoffs had higher HR for reaching renal end points in all subgroups except for women with $CKD_{3b–5}$, whose HR had marginal significance (HR = 3.78, P = 0.068) after adjusting for age and eGFR (Table 5).

Table 4. Multivariate Cox regression models for evaluating the impacts of various nutritional markers on renal outcomes in different patient subgroups[a,b]

		CKD Stages 1–5 ($n = 128$)		CKD Stages 3b–5 ($n = 66$)	
Models	Variables	HR (95%CI)	P-value	HR (95%CI)	P-value
A	HGS	0.90 (0.84–0.97)	0.004	0.91 (0.83–0.99)	0.031
B	SGA	0.72 (0.44–1.19)	0.203	0.59 (0.33–1.05)	0.071
C	Albumin	0.40 (0.09–1.86)	0.242	0.93 (0.14–6.28)	0.937

[a]Models A, B and C all included DM, CVD, use of ACEI/ARB, sex, age, eGFR, SBP, DPL and CRP as independent variables, in addition to HGS in Model A, SGA in Model B and albumin in Model C.
[b]DPL, daily protein loss; Cr, creatinine; CI, confidence interval.

Discussion

The present study showed that HGS, but not other potential indicators of PEW examined, is a valid predictor of composite renal outcomes in all CKD-ND subgroups, suggesting PEW is one of the underlying mechanisms leading to pre-dialysis mortality or reaching ESRD rapidly. These findings underline the importance of nutritional assessments and suggest that HGS measurement can be used as a reliable and inexpensive tool in clinical practice to assess the nutrition status of patients with CKD-ND. HGS measurement will be very useful especially when a dietician is not available such as in local outpatient clinics or in areas with limited medical resources.

In the present study, serum albumin value was not significantly associated with renal outcomes in patients with $CKD_{1–5}$ or $CKD_{3b–5}$ after adjustment for multiple risk factors (Table 4). Serum albumin was significantly associated with renal outcome in univariate analyses; however, serum albumin lost its outcome predictability after adjusting for urine protein loss and eGFR, suggesting that the renal outcome predictability of serum albumin is largely dependent on the urine protein loss and eGFR in CKD-ND patients. Contradictory to our results, Kovesdy *et al.* [11] found that a serum albumin level <3.7 g/dL was independently associated with poor composite renal outcomes (pre-dialysis mortality and ESRD) in their patients with CKD-ND. This discrepancy might be explained by different study populations. We excluded patients with severe comorbidities or acute illness necessitating admission within 6 months before enrollment, resulting in total mortality (including both pre-dialysis and post-dialysis mortality) of 40.1/1000 and 64.3/1000 patient-year in patients with $CKD_{1–5}$ and $CKD_{3b–5}$, respectively; whereas, Kovesdy *et al.* [11] studied 1220 men (most of whom had CKD Stages 3 and 4) enrolled without specific excluding criteria over a period of 16.5 years, resulting in a mortality rate of 125/1000 patient-year. Since serum albumin is highly influenced by inflammatory status, it is possible that the renal outcome predictability of low serum albumin level in the study population of Kovesdy *et al.* [11] reflected more prevalent comorbidities or acute illnesses.

We also found that SGA was not significantly associated with renal outcomes in patients with $CKD_{1–5}$ or $CKD_{3b–5}$ after adjusted for multiple risk factors (Table 4). It is not

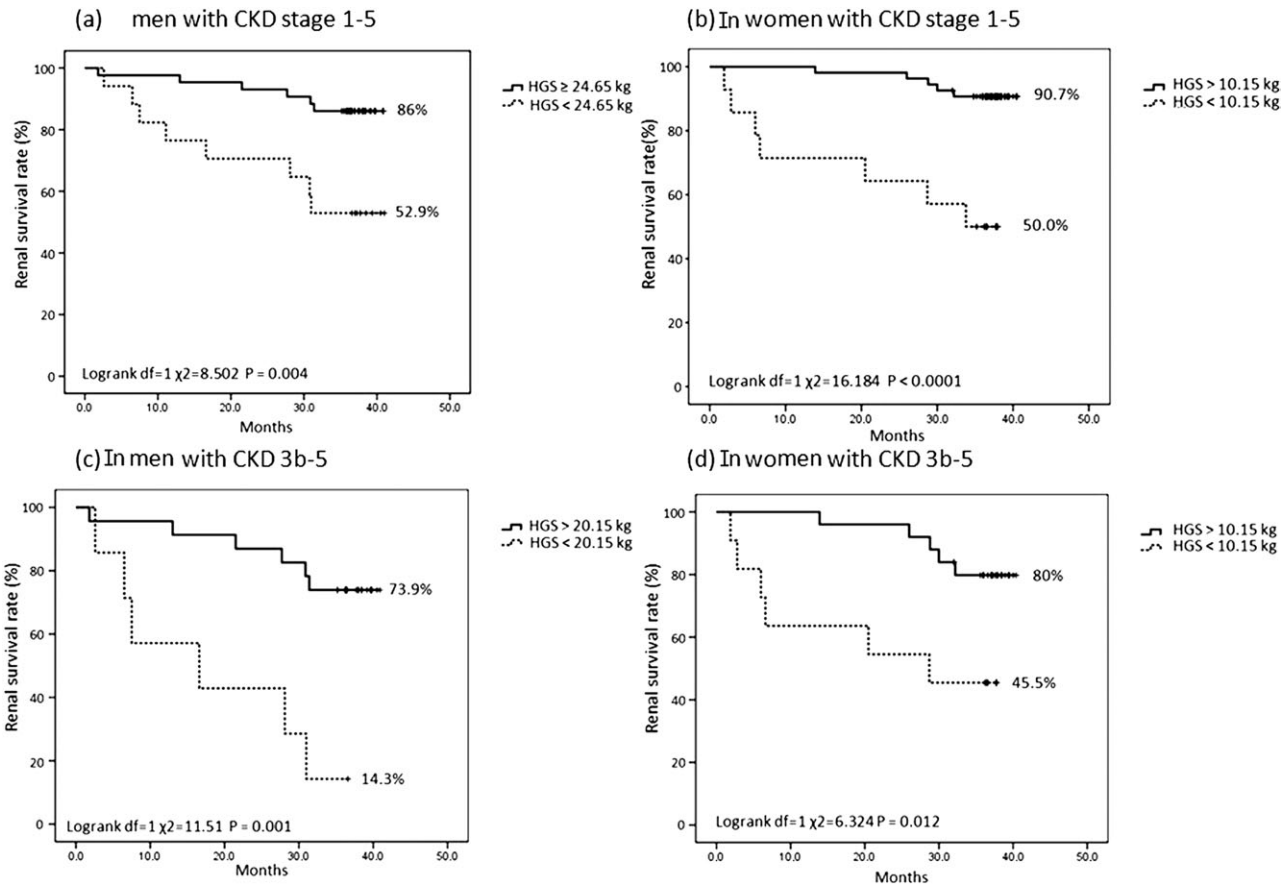

Fig. 1. Kaplan–Meier survival analyses for the composite renal outcomes in non-dialysis-dependent chronic kidney patients with different cutoffs of HGS.

Table 5. HRs for reaching composite renal end points using different cutoffs of HGS

Subgroups	HR[a]	P-value	HR[b]	P-value	HR[c]	P-value
CKD Stages 1–5						
Men ($n = 60$)						
HGS > 24.65 kgw	1.0	0.007	1.0	0.008	1.0	0.027
HGS < 24.65 kgw	4.27 (1.48–12.34)		4.55 (1.49–13.87)		4.57 (1.13-17.08)	
Women ($n = 68$)						
HGS > 10.15 kgw	1.0	0.001	1.0	0.020	1.0	0.039
HGS < 10.15 kgw	7.48 (2.37–23.65)		4.56 (1.27–16.41)		5.939 (1.10–32.19)	
CKD Stages 3b–5						
Men ($n = 30$)						
HGS > 20.15 kgw	1.0	0.003	1.0	0.045		
HGS < 20.15 kg	5.97 (1.87–19.09)		3.72 (1.03–13.41)			
Women ($n = 36$)						
HGS > 10.15 kgw	1.0	0.020	1.0	0.068		
HGS < 10.15 kgw	4.12 (1.25–13.58)		3.78 (0.91–15.81)			

[a]Univariate Cox's regression.
[b]Cox's regression adjusted for age and eGFR.
[c]Cox's regression adjusted for age, eGFR, CVD, SBP and urine DPL.

surprising that SGA has some limitations assessing the severity of PEW and thus failed to predict renal outcomes. Muscle weakness and wasting are important components of PEW since degradation of muscle protein is the main source of amino acids for protein synthesis and gluconeogenesis during starvation or several acute or chronic illnesses [23, 24]; in addition, the inflammatory status of PEW may independently diminish the muscle strength even when the muscle mass is still relatively well preserved [24, 25]. Therefore, assessments of PEW should include measurements of muscle mass and function [23, 24]. The SGA evaluates nutritional status by encompassing the patient's history and physical examination, but no functional measurement.

Since measure of muscle compartment is often difficult by traditional methods, measurement of HGS may be an appropriate strategy. HGS has been shown to correlate with force measurements exerted by different muscle groups, underlining its usefulness in assessing the functional status of general muscles. In patients with ESRD, HGS is shown to be a reliable nutritional marker in both hemodialysis and peritoneal dialysis patients [17, 26], and low HGS predicts mortality [16–18, 27]. In addition, HGS was associated with arterial stiffness [28] and predicted circulatory congestion in peritoneal dialysis patients [29]. In patients with CKD-ND, HGS was demonstrated to correlate with other nutritional markers, e.g. lean body mass and SGA scores [24, 27]. In the present study, we further demonstrated that HGS independently predicted the composite renal end points. Other nutritional indicators such as MAMA, MAMC, serum albumin levels and SGA scores all failed to predict renal outcomes independently. This suggests that HGS uniquely reflects skeletal muscle function additional to muscle mass that is not captured by other nutritional indices and contributes to renal outcome predictability of HGS.

Several potential mechanisms may be involved in the association between low HGS, as an indicator of PEW, and poor composite renal outcomes in CKD-ND patients. Firstly, inflammatory cytokines, such as CRP, interleukin-6 and tumor necrosis factor-α, and concurrent malnutrition and muscle wasting may worsen patient outcome by aggravating CVD and arterial stiffness and increasing susceptibility to infection [30, 31]. In addition, CVD and arterial stiffness would accelerate the decline of renal function in CKD-ND patients [13, 32]. Secondly, the components of PEW, such as inflammation, acidosis, vitamin D deficiency and accumulation of 'uremic toxins', appear to decrease insulin sensitivity and muscle phosphatidylinositol 3-kinase activity, leading to activation of caspase 3 and the ubiquitin proteasome pathway and subsequent muscle wasting [33, 34]. It was recently reported that insulin resistance is not only a risk factor of CVD but also of the rapid progression of CKD [35]. It should be mentioned that Castaneda *et al.* [36, 37] showed in a randomized controlled trial of patients with moderate CKD consuming a low-protein diet that 12 weeks of resistance exercise training decreased serum CRP and interleukin-6 levels, accompanied by a significant improvements in protein utilization and nutritional status (mid-thigh muscle area, type I and II muscle fiber cross-sectional area and serum prealbumin). In addition, they also demonstrated that resistance exercise training could improve glycemic control in older adults with type 2 diabetes [38]. This suggests that the possible interactions between inflammation, insulin resistance and muscle wasting and resistance exercise training to increase muscle strength and mass can potentially attenuate the severity of PEW by reducing inflammation and insulin resistance. Further studies are needed in this field.

There are several limitations worth noting in our study. Firstly, the sample size is relatively small, which may affect defining the cutoffs of HGS for renal outcome predictability. However, although the CIs were wide in Table 5, the P-values were significant except in women with $CKD_{3b–5}$, whose HR had marginal significance (HR = 3.78, P = 0.068) after adjusting for age and eGFR. In addition, the HRs obtained through a series of models were similar for each subgroup. Taking together, these data suggest acceptable statistic power but small sample size in these models. Furthermore, we cannot analyze the predictability of HGS on pre-dialysis mortality and reaching ESRD separately due to the limitation of size. Secondly, we enrolled clinically stable patients with CKD-ND; thus, the findings in the present study might not be generalized to CKD-ND patients with acute illness or severe comorbidities. Thirdly, we could not study the dynamic changes of various indicators of PEW and further explore their impacts.

In conclusion, we show that low HGS is an independent predictor of the composite renal outcome in CKD-ND patients. Based on our findings, we recommend the measurement of HGS can be incorporated to clinical practice to assess the degree of PEW and renal outcome in patients with CKD-ND. Further studies with larger sample sizes are warranted to define the cutoffs of HGS for outcome predictability and to evaluate whether strategies to increase HGS, such as resistance exercise training, can improve renal outcomes in CKD-ND patients.

Supplementary data

Supplementary Figures 1–2 and Tables 1–2 are available online at http://ndt.oxfordjournals.org/.

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