Cross-sectional Relationship Between Dietary Protein Intake, Energy Intake and Protein Energy Wasting in Chronic Kidney Disease Patients

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Short title: DPI, DEI and PEW in CKD patients

This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI
10.1017/S0007114524001041
The British Journal of Nutrition is published by Cambridge University Press on behalf of The Nutrition Society

Abstract:

The potential threshold for dietary energy intake (DEI) that might prevent protein-energy wasting (PEW) in chronic kidney disease (CKD) is uncertain. The subjects were non-dialysis CKD patients aged ≥ 14 years who were hospitalized from September 2019 to July 2022. PEW was measured by subjective global assessment (SGA). DEI and dietary protein intake (DPI) were obtained by 3-days diet recalls. Patients were divided into adequate DEI group and inadequate DEI group according to DEI ≥ 30 or < 30 kcal/kg/d. Logistic regression analysis and restricted cubic spline (RCS) were used in this study. We enrolled 409 patients, with 53.8% had hypertension and 18.6% had diabetes. The DEI and DPI was 27.63 ± 5.79 kcal/kg/day and 1.00 (0.90,1.20) g/kg/day, respectively. 69.2% of participants in inadequate DEI group. Malnutrition occurred in 18.6% of patients. Comparing to patients in adequate DEI group, those in inadequate DEI group had significantly lower total lymphocyte count (TLC), serum cholesterol (Chol) and low-density cholesterol (LDL), and a higher prevalence of PEW. For every 1kcal/kg/day increase in DEI, the incidence of PEW was reduced by 12.0% [odds ratio (OR): 0.880, 95% confidence interval (CI): 0.830 to 0.933, $P < 0.001$]. There was a nonlinear curve relationship between DEI and PEW (overall $P < 0.001$), and DEI ≥ 27.6 kcal/kg/d may have a preventive effect on PEW in CKD. Low DPI was also significantly associated with malnutrition, but not when DEI was adequate. Decreased energy intake may be a more important factor of PEW in CKD than protein intake.

Keywords: Chronic Kidney Disease, Dietary Energy Intake, Dietary Protein Intake, Protein-Energy Wasting.

Introduction:

Protein-energy wasting (PEW) is a frequent complication in chronic kidney disease (CKD) patients, especially in those with end-stage renal disease. Previous studies have reported a prevalence of PEW ranging from 17% to 85% [(1)]. PEW attenuates treatment response and increases poor prognosis in patients with CKD[(2)(3)]. Nutritional assessment scale to detect and manage PEW is suggested [(3)(4)]. Subjective global assessment (SGA) is a simple, inexpensive, and widely used nutritional scale that can be used by trained medical professionals. The utility of SGA in CKD has been recognized by researchers [(5)(6)(7)(8)].

Insufficient food intake caused by loss of appetite and dietary restriction is the direct adverse factor for PEW in CKD patients[(9)]. In a cross-sectional study, 56.6% of CKD patients did not reach the recommended energy intake[(10)]. Inadequate energy intake was correlated with renal progression and nutritional status [(10)(11)(12)]. The dietary energy intake (DEI) for CKD 1-5 patients, as recommended by KDOQI, is 25-35 kcal/kg/day[(4)]. The International Society for Renal Nutrition and Metabolism (ISRNM) recommends a daily energy intake of 30-35 kcal/kg/d for non-dialysis CKD patients [(13)]. Kopple JD et al. observed the maintenance of negative nitrogen balance with energy intake below 30 kcal/kg/ day in non-dialysis patients who consumed protein 0.55 to 0.60 g/kg/day [(14)]. No studies have investigated the minimum energy intake to prevent PEW in non-dialysis CKD.

A low-protein diet combined with keto acids can delay the progression of kidney disease and is therefore considered one of the strategies for the treatment of CKD [(4)(15)]. However, previous studies have different opinions on the effects of low-protein diet on nutritional indicators, and whether a low-protein diet increases the risk of PEW in patients is inconsistent in current studies [(12)(16)(17)(18)(19)]. In addition, no studies have considered energy intake when investigate the relationship between dietary protein intake (DPI) and PEW. Moreover, nutritional status in those studies were from biochemical or body-composition analyzers, which were insufficiently comprehensive.

In this study, we aimed to identify the association between DEI, DPI, and PEW as assessed by SGA, and to evaluate dose-response relationship between DEI and PEW in CKD. In addition, we further investigated the relationship between DPI and PEW in different DEI subgroups.

Methods:

Participants

This was a cross-sectional study conducted in nephrology department of Sun Yat-Sen Memorial Hospital, and CKD stages 1-5 inpatients ≥ 14 years from September 2019 to July 2022 were enrolled. Those undergoing dialysis and renal transplantation were excluded. Besides, patients with acute or severe illnesses (e.g., acute gastroenteritis, acute heart failure, active infection, or respiratory failure), patients with conditions that increase catabolism (e.g., cancer or thyroid dysfunction), and patients who were unable to complete the three-day dietary survey were also excluded. The study was approved by the ethics Committee of Sun Yat-sen Memorial Hospital and the approval number was SYSKY-2022-491-01.

Measurement and data collection

The data collected included gender, age, comorbidities, laboratory indicators, anthropometric indicators, SGA score and dietary indicators. Comorbidities included a history of hypertension and diabetes mellitus (DM). Fasting blood samples were collected from patients on the second day of admission and were tested using automated instruments. Anthropometric measurements, SGA score, and dietary intake assessment were conducted during hospitalization by a trained dietitian in the department of clinical nutrition.

Laboratory indicators. Routine laboratory data were obtained, including hemoglobin (Hb), total lymphocyte count (TLC), serum creatinine (Scr), urine acid (UA), serum bicarbonate (CO_2), glucose (Glu), total cholesterol (Chol), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), albumin (Alb), serum ferritin (SF). We calculated estimated glomerular filtration rate (eGFR) using the CKD Epidemiology Collaboration (CKD-EPI) equation and CKD stages were defined according to the KDIGO 2012 clinical practice guideline for evaluation and management of CKD[(20)].

SGA score. SGA scale consists of five historical components and three physical examinations. Historical components included weight change in the last 6 months and the last 2 weeks, changes in dietary intake, symptoms of gastrointestinal, functional capacity, and comorbidities affecting nutritional requirements. Physical examinations contained subcutaneous fat (orbital fat pads, triceps, biceps, and chest), muscle wasting (temporal,

clavicle, shoulder, interosseus, scapula, interosseus, quadriceps, and gastrocnemius) and edema/ascites. According to the subjective and objective nutritional status, SGA was scored and patients were divided into well nourished (A) group, moderate malnutrition (B) group, and severe malnutrition (C) group. Patients with score B and C were defined as PEW [21].

Anthropometric indicators. Body mass index (BMI) was calculated by dividing weight (kilograms, kg) by the square of the height (meters, m). Waist-to-hip ratio (WHR) referred to waist circumference in centimeter (cm) divided by hip in cm and circumferences measured by the authors of the study.

Dietary intake assessment. Three-days dietary recalls were performed to obtain DEI and DPI for patients. The dietitian asked patients in detail about their diet of the three days before enrollment, including the type and amount of food, oil and salt in each meal, and snacks. Daily total dietary energy and protein was calculated according to Chinese Food Composition Table (6th edition). DEI and DPI was equal to the daily energy and protein intake divided by ideal body weight (IBW). IBW for male (kg)= (height (cm) – 100) × 0.9; IBW for female (kg) = IBW (male) – 2.5. Patients with DEI < 30kcal/kg/day and ≥ 30kcal/kg/day were considered as inadequate DEI group and adequate DEI group, respectively.

Statistical Analysis

Data were presented as mean±standard deviation (SD) for normally distributed variables median (interquartile range, IQR) for non-normally distributed variables, and n(%) for categorical variables. Continuous variables were compared between the two groups with the use of student's t-test or one-way ANOVA. The comparison of proportion of male, hypertension, DM, and PEW between DEI adequate and inadequate groups was tested with χ^2. Multivariate logistic regression model was performed to identify independent relationships between DEI, DPI and PEW. Models between DPI and PEW in different DEI groups were also analyzed to explore whether the relationship between DPI and PEW was affected by energy intake. Adjusted factors in multivariate model were indicators with *P* less than 0.05 in univariate analysis, including eGFR, Hb, Lym, Alb and SF. Restricted cubic spline (RCS) analysis with 4 knots was performed using R language (version 6.2.0) to explore dose-response relationship between DEI and PEW. Differences were considered statistically significant if a p

value < 0.05. All statistical analysis, unless RCS analysis, were performed using SPSS (version 25.0). In addition, to identify the reliability of our results, we set alpha to 0.5 and calculated the power of this study by PASS (version 11) based on the sample size and the proportion of PEW in both groups.

Results

Study patients and comparison of groups

The median age of 409 participants was 46.0 (33.0,57.0) years, with 50.1% male, 53.8% had hypertension and 18.6% had DM. The median eGFR was 48.92 (15.09,94.46) ml/min/1.73m^2. The stages 1-5 of CKD were 28.9%, 16.9%, 15.4%, 14.9%, and 24.0%, respectively. The etiologies of CKD include primary glomerular disease (72.4%), diabetic nephropathy (10.0%), hereditary nephropathy (2.7%), hypertensive nephropathy (2.2%), lupus nephritis (2.0%), gouty nephropathy (1.0%), and others (9.7%). DEI and DPI was 27.63 ± 5.79 kcal/kg/day and 1.00 (0.90,1.20) g/kg/day, respectively. Of the total sample, 69.2% (n=283) were classified as belonging to the inadequate DEI group, while the remaining 30.8% (n=126) were categorized as having sufficient DEI. The prevalence of malnutrition, as assessed by SGA, was found to be 18.6%, comprising of 9.5% in the adequate DEI group and 22.6% in the inadequate DEI group. Additionally, the study demonstrated a high statistical power of 0.91, indicating that the sample size was sufficient.

As can been seen in Table 1, patients with lower DEI had significantly lower TLC and higher prevalence of PEW. The levels of Chol and LDL was significantly increased in adequate DEI group. Other indicators, including age, gender, rates of hypertension and DM, BMI, WHR, MAMC, Hb, eGFR, UA, CO_2, Glu, TG, Alb and SF, were not different between two groups.

Relationship between DEI, DPI and PEW

After adjustment for eGFR, Hb, TLC, Alb and SF, multivariate logistic regression model showed that DEI was an independent factor of PEW (Table 2). For every 1 kcal/kg/ day increase in DEI, the incidence of PEW decreased by 12.0% (OR=0.880, 95% CI=0.830-0.933, $P < 0.001$). As for DPI, it was also significantly related to PEW, the incidence of PEW reduced by 9.69% for every 0.1g/kg/day increased in DPI (OR=0.031,95% CI=0.008-0.119, $P < 0.001$). However, the effect of DPI on PEW disappeared in subgroup with adequate DEI ($P > 0.05$), and remained in inadequate DEI subgroup (OR=0.006,95% CI=0.001-0.043, $P < 0.001$).

Dose-response relationship between DEI and PEW

Unadjusted RCS analysis showed a nonlinear decreasing relationship between DEI and the risk of PEW (overall $P < 0.001$; Figure 1A). Multivariable RCS model showed the curve between DEI and risk of malnutrition was similar to the curve in unadjusted model (overall $P < 0.001$, Figure 1B). DEI > 27.6 kcal/kg/day significantly lowered the risk of PEW.

Discussion

In this cross-sectional study, the prevalence of malnutrition was 18.6% and patients with DEI < 30 kcal/kg/day accounted for 69.2%. Low DEI was a significant predictor of PEW and DEI > 27.6 kcal/kg/day may prevent PEW in non-dialysis CKD patients. Low DPI was also significantly related with PEW, but the effect missed in patients with DEI ≥ 30 kcal/kg/day.

Mechanisms in decreased calorie and protein intake are integrated, including anorexia, dietary restrictions, alterations in organs involved in nutrient intake, depression, and inability to obtain or prepare food [9]. It is common for patients with CKD to have actual DEI lower than dietitian recommendations. Huang et al. defined recommended energy according to KDOQI guideline [22], and founded 56.6% of CKD patients had energy intakes less than 90% of recommended levels [10]. In another study involving 100 patients with CKD, only three patients met the recommended daily energy intake[23]. A significant proportion of patients in this study also had inadequate energy intake, potentially attributed to the tendency among Chinese individuals to prioritize dietary control upon discovering disease, while neglecting timely access to scientific diet guidance. More attention should be paid to the importance of scientific dietary guidance in clinical practice, with an emphasis on initiating such guidance as early as possible.

We observed that Lym counts were significantly decreased in insufficient calorie intake group. TLC is a traditional and frequently used nutritional indictor, which decreases in malnourished patients[24]. It has been shown that CKD patients with nutritional risk had significantly lower TLC compared with CKD patients without nutritional risk[25]. The present study also found that TLC was significantly decreased in patients with PEW than in those without PEW [1.39(0.97,2.01) *vs* 1.80(1.28, 2.37), $P<0.001$]. There was no significant difference in Alb between the DEI sufficient group and the DEI insufficient group in our study.

Patients with low DPI may experience decreased albumin [18][26]. However, the results of the KNOW-CKD study found no difference in Alb between the two non-low-protein groups[19]. Table 1 showed that although there was a clear difference in DPI between the two groups, DPI was greater than 0.8g/kg/day in both groups. This may account for the lack of difference in albumin between the two groups in this study.

Serum lipids, including Chol and LDL, were significantly elevated in adequate DEI group. Similarly, Yang et al. reported that patients with higher DEI had higher serum Chol levels in hemodialysis patients[27]. Dietary cholesterol intake was higher in the DEI sufficient group than in the DEI insufficient group [310.7(199.4,450.6) mg/day *vs* 293.7(156.3, 436.8) mg/day, *P*=0.047, not shown in Tables]. Dietary cholesterol could lead to elevated serum cholesterol, which had been demonstrated in animal model [28]. Human metabolic studies have also found a positive correlation between dietary cholesterol and serum cholesterol[29][30]. However, other confounding factors that affect blood lipids, such as lipids-lowering drugs and exercise, were not considered in our study. Lipids metabolism is impaired due to inflammation and oxidative stress, and dyslipidemia is prevalent in CKD [31][32]. The relationship between DEI, dietary lipid intake and blood lipids in CKD patients deserves further investigation. It also reminds us to consider possible lipid effects when formulating the recommended energy intake for patients.

Patients with CKD often suffer from PEW. There are various scales used to identify malnutrition. The simple and widely used SGA scale was performed in this study. The prevalence of PEW in our study was slightly higher than the 11% to 18% reported in previous studies using SGA scale [1]. Moreover, we observed patients in inadequate energy group were more likely to develop PEW. DEI is identified as a crucial determinant of nutritional status. However, the detailed relationship between DEI and PEW was not explored in CKD, the DEI threshold capable of predicting PEW is unknown. In this study, multivariate logistic regression analysis found that higher DEI intake was associated with greater protection against PEW. Moreover, we observed that the lowest DEI to prevent PEW was 27.6 kcal/kg/day. The identified cutoff value in our study was found to be below the recommended range of dietary energy intake as per previous guidelines[4] [13], prompting us to question whether our population necessitates adherence to the current caloric intake recommendations. We believe that more studies with larger sample size are needed in the future to establish nutritional guidelines

suitable for Chinese CKD patients.

Nutrition guidelines for CKD suggest low DPI for preventing from renal progression[4]. Studies are limited as to whether low-protein diets lead to malnutrition. Hahn et al. systematically reviewed the RCT studies of low-protein diet in patients with CKD and found that only 15 studies focused on the effect of DPI on PEW, of which 12 had no evidence of PEW, and 3 studies had a small number of patients with PEW in DPI and non-DPI groups. Therefore, there were insufficient data to compare the risk of PEW between low-protein and non-low-protein groups [16]. This may be due to the good baseline nutritional status and methods of evaluating PEW in the previous study. Lee et al. found that the risk of PEW significantly increased as DPI decreased, especially in those with DPI < 0.94 g/kg/day[19]. We also demonstrated that low DPI per se was a predictor of malnutrition. Nevertheless, lower DPI did not increase the risk of PEW in group with adequate calorie intake.

Our results suggest that adequate energy intake rather than protein intake is more vital for the prevention of PEW, which confirms the nutritional safety of low-protein diet to a certain extent. Some limitations existed in this study. There may be recall bias in dietary assessment using the 3-day recalls method. We used 30kcal/kg/ day as the energy intake standard for grouping, without considering age, BMI, diabetes, CKD stage and other factors. The study was cross-sectional, and the causal relationship between DEI, DPI and PEW cannot be explored.

Conclusion:

In CKD patients, energy intake had a greater effect on PEW than protein intake, and dietary energy intake ≥ 27.6 kcal/kg/day may prevent malnutrition.

Author contributions : Participants enrollment and data collection, QH, RZ, FQ, and WL; Data analysis and manuscript writing, QH, RZ, and JW; Anthropometric and dietary intake assessment, FH, and CC; Study design and guidance, manuscript revision, QY and CC. All authors contributed significantly to the conduct of the study and approved the final manuscript

Fundings and Acknowledgement : We thank the support from National Natural Science Foundation of China (82270743), National Key R&D Program of China (No. 2021YFC2009400) and Natural Science Foundation of Guangdong Province (2021A1515010801).

Ethics approval and consent to participate: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the ethics committee of Sun Yat-Sen Memorial hospital (Approval Number: SYSKY-2022-491-01), exempt from informed consent was agreed from ethics committee.

Data Availability Statement: The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations: PEW, protein-energy wasting; CKD, chronic kidney disease; SGA, subjective global assessment; DEI, dietary energy intake; ISRNM, International Society for Renal Nutrition and Metabolism ; DPI, dietary protein intake; DM, diabetes mellitus; Hb, hemoglobin; TLC, total lymphocyte count; Scr, serum creatinine; UA, urine acid; CO2, serum bicarbonate; Glu, glucose; Chol, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Alb, albumin; SF, serum ferritin. eGFR, estimated glomerular filtration rate; CKD-EPI, CKD Epidemiology Collaboration; BMI, body mass index; WHR, waist to hip ratio; IBW, ideal body weight; SD, standard deviation; IQR, interquartile range; RCS, restricted cubic spline.

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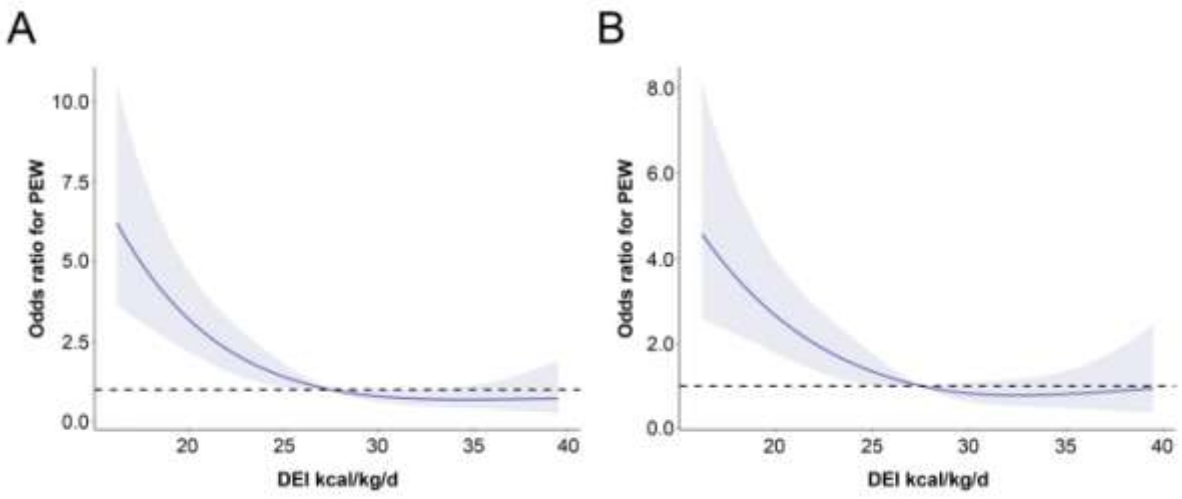

Figure 1: Dose-response analysis showed a nonlinear decreasing curve relationship between DEI and PEW, DEI ≥ 27.6 kcal/kg/day may reduce the risk of PEW in CKD: (A) unadjusted analysis (overall $P < 0.001$); (B) multivariate adjusted for age, gender, Scr, hemoglobin, total lymphocyte count, albumin, and serum ferritin (overall $P < 0.001$)

Table1. Clinical characteristics of individuals and comparisons between subgroups

Variable	Total	Inadequate DEI	Adequate DEI	*P* value
n	409	283	126	
Age (years)	46.0 (33.0,57.0)	45.0(32.8,57.0)	46.0(34.5,55.0)	0.961
Male (n/%)	207 (50.1)	136(48.1)	71(56.3)	0.075
Hypertension (n/%)	220 (53.8)	151(53.4)	69(54.8)	0.407
DM (n/%)	76 (18.6)	51(18.0)	25(19.8)	0.365
BMI (kg/m^2)	23.07±3.55	23.04±3.71	23.14±3.18	0.789
WHR	0.89±0.14	0.88±0.08	0.91±0.21	0.062
DEI (Kcal/kg/d)	27.63±5.79	24.76±3.80	34.07±4.03	< 0.001*
DPI (g/kg/d)	1.00 (0.90,1.20)	0.90(0.80,1.10)	1.20(1.10,1.33)	< 0.001*
PEW (n/%)	76 (18.6)	64(22.6)	12(9.5)	0.001*
Hb (g/L)	115.31±25.09	114.38±25.64	117.40±23.78	0.265
TLC (*10^9/L)	1.73 (1.22,2.30)	1.67(1.19,2.21)	1.92(1.29,2.45)	0.026*
Scr (umol/L)	127.50(78.8,346.3)	129.0(79.0,345.5)	122.0(72.0,355.5)	0.892
eGFR ($ml/min/1.73m^2$)	48.92 (15.09,94.46)	48.71(14.94,94.90)	51.16(16.55,94.24)	0.977
UA (umol/L)	414.00 (343.00,504.50)	406.0(341.3,504.8)	424.0(344.5,504.0)	0.973
CO_2 (mmol/L)	22.60±3.62	22.47±3.81	22.87±3.13	0.306
Glu (mmol/L)	4.60 (4.20,5.10)	4.60(4.20,5.10)	4.60(4.20,5.30)	0.524
Chol (mmol/l)	5.11 (4.35,6.16)	5.05(4.23,5.92)	5.41(4.61,6.75)	0.032*
TG (mmol/L)	1.42 (0.99,1.95)	1.41(0.98,1.91)	1.47(1.02,2.05)	0.212
HDL (mmol/L)	1.21 (0.98,1.48)	1.19(0.97,1.43)	1.25(0.99,1.55)	0.115
LDL (mmol/L)	3.22 (2.67,4.02)	3.17(2.59,3.86)	3.45(2.85,4.37)	0.035*

Alb (g/L)	33.52±7.52	33.66±7.61	33.20±7.32	0.571
SF (ug/L)	165.95 (73.68,328.23)	167.50(69.78,364.55)	150.65(82.15,281.55)	0.793

*P< 0.05 was considered statistically significant

DEI: dietary energy intake; DM: diabetes mellitus; BMI: body mass index; WHR: waist to hip ratio; DPI: dietary protein intake; PEW: protein-energy wasting; Hb: hemoglobin; TLC: total lymphocyte count; Scr: serum creatinine; eGFR: estimated glomerular filtration rate; UA: urine acid; CO2: serum bicarbonate; Glu: glucose; Chol: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; Alb: albumin; SF: serum ferritin.

Table2. Multivariable logistic regression analysis of DEI, DPI to PEW

		Model 1			Model 2			Model 3		
		OOR	95%CI%	*P*	OR	95%CI	*P*	OR	95%CI	*P*
DEI		0.865	0.820-0.911	<0.001*	0.869	0.823-0.917	<0.001*	0.880	0.830-0.933	<0.001*
DPI		0.025	0.007-0.083	<0.001*	0.030	0.009-0.104	<0.001*	0.031	0.008-0.119	<0.001*
Inadequate DEI subgroup	DPI	0.007	0.001-0.037	<0.001*	0.008	0.001-0.046	<0.001*	0.006	0.001-0.043	<0.001*
Adequate DEI subgroup	DPI	1.582	0.111-22.494	0.735	1.868	0.109-31.948	0.666	1.422	0.054-37.755	0.834

Model 1: Unadjusted;

Model 2: Adjusted by Model 1 + age + gender + Scr;

Model 3: Adjusted by Molde 2 + Hb + TLC + Alb + SF

*P< 0.05 was considered statistically significant