

# UC Irvine

## UC Irvine Previously Published Works

### Title

Comparison of the malnutrition-inflammation score in chronic kidney disease patients and kidney transplant recipients

### Permalink

<https://escholarship.org/uc/item/10h6s06q>

### Authors

Molnar, MZ  
Carrero, JJ  
Carrero, JJ  
et al.

### Publication Date

2015-05-01

### DOI

10.1007/s11255-015-0984-2

### License

CC BY 4.0

Peer reviewed

# Comparison of the malnutrition–inflammation score in chronic kidney disease patients and kidney transplant recipients

Miklos Z. Molnar<sup>1</sup> · Juan J. Carrero<sup>2,3</sup> · Istvan Mucsi<sup>4</sup> · Adam Rempert<sup>5</sup> ·  
Connie M. Rhee<sup>6</sup> · Kamyar Kalantar-Zadeh<sup>6</sup> · Csaba P. Kovcsdy<sup>1,7</sup> ·  
Antonio C. Cordeiro<sup>8</sup>

Received: 20 January 2015 / Accepted: 13 April 2015 / Published online: 1 May 2015  
© Springer Science+Business Media Dordrecht 2015

## Abstract

**Background** Protein–energy wasting (PEW) is a common condition in patients with chronic kidney disease (CKD) including dialysis and kidney transplant recipients (TX) and frequently assessed with malnutrition–inflammation score (MIS). We hypothesized that (1) the MIS and PEW parameters are correlated with kidney function and (2) the MIS and PEW parameters are more severe in TX than in non-dialysis (ND) CKD patients with similar eGFR.

**Methods** In this study, we matched 203 ND-CKD and 203 TX patients from two independently assembled cohorts of patients based on estimated glomerular filtration rate (eGFR) and compared various PEW parameters between the two

groups using unadjusted and case-mix adjusted linear regression and conditional logistic regression analysis models.

**Results** In the combined cohort ( $n = 406$ ) of patients, the mean  $\pm$  SD age was  $57 \pm 12$  years; included 55 % men and 35 % diabetics; and demonstrated a mean  $\pm$  SD baseline eGFR of  $29 \pm 11$  ml/min/1.73 m<sup>2</sup>. The eGFR correlated positively with serum albumin ( $\rho = 0.26, p < 0.001$ ) and negatively ( $\rho = -0.33, p < 0.001$ ) with MIS. ND-CKD and TX patients had similar MIS, PEW parameters such as waist circumference, serum CRP, albumin, and leptin levels. After case-mix adjustment, TX status was associated with higher waist circumference (standardized coefficient: 0.187,  $p < 0.001$ ), lower BMI (standardized coefficient:  $-0.204, p < 0.001$ ), and lower SGA score (standardized coefficient: 0.156,  $p = 0.006$ ).

**Conclusions** We found associations between lower eGFR and various PEW measures in both the ND-CKD and TX populations. Additionally, we did not observe significant differences in the burden of PEW parameters between the CKD and TX populations.

✉ Miklos Z. Molnar  
mzmolnar@uthsc.edu

<sup>1</sup> Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center, 956 Court Ave., Room B216B, Memphis, TN 38103, USA

<sup>2</sup> Divisions of Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

<sup>3</sup> Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden

<sup>4</sup> Department of Medicine, Division of Nephrology, University Health Network, University of Toronto, Toronto, ON, Canada

<sup>5</sup> Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary

<sup>6</sup> Division of Nephrology and Hypertension, University of California Irvine Medical Center, Orange, CA, USA

<sup>7</sup> Nephrology Section, Memphis Veterans Affairs Medical Center, Memphis, TN, USA

<sup>8</sup> Department of Hypertension and Nephrology, Dante Pazzanese Institute of Cardiology, São Paulo, Brazil

**Keywords** Chronic kidney disease · Estimated glomerular filtration rate · Kidney transplantation · Malnutrition–inflammation score · Protein–energy wasting

## Introduction

Protein–energy wasting (PEW) is associated with adverse outcomes in various populations, including those with chronic obstructive pulmonary disease [1] and old age [2], or who have undergone surgery [3]. PEW is also frequently seen in chronic kidney disease (CKD) patients [4–6], those receiving maintenance dialysis [7, 8], and kidney transplant recipients [9–11]. PEW has been shown to be an independent and strong predictor of mortality [7, 12, 13], quality of

life (QOL) [7, 14], and morbidity [15–18] in both patients with CKD and end-stage renal disease (ESRD). While varying definitions of PEW have been utilized across studies [19], accurate ascertainment of PEW may be challenging, particularly in large cohorts.

In 2001, Kalantar-Zadeh et al. [20] developed the malnutrition–inflammation score (MIS, also called the Kalantar score), an efficient scoring system used to evaluate the severity of the malnutrition–inflammation complex syndrome (MICS) in patients receiving dialysis. The MIS has shown associations with nutritional and inflammatory measures, as well as with hospitalization and mortality risk in this population [20]. The MIS has also been validated in both CKD [21] and kidney transplant recipient samples [9]. Moreover, MIS was a strong predictor of adverse outcomes, including impaired QOL and mortality, in these latter groups [7, 13, 14].

The pathogenesis of PEW in non-dialysis (ND) CKD patients and kidney transplant recipients with moderate-to-severe kidney dysfunction remains unclear [22]. It has previously been shown that poor residual kidney or allograft function is one of the strongest predictors of PEW in these populations [16]. However, other factors may contribute to the development and severity of PEW, particularly in kidney transplant recipients, such as the prior history of dialysis therapy in most of these patients, which is in sharp contrast to ND-CKD patients; presence of a failing allograft (which may serve as a nidus of inflammation); use of immunosuppressive drugs; frequency of rejection episodes and the immunologic response against the allograft; and prolonged exposure to the inflammatory environment of CKD prior to receipt of kidney transplantation.

In this historical cohort study, we hypothesized that (1) the MIS and PEW parameters are associated with residual kidney or allograft function and (2) the MIS and PEW parameters are more severe in kidney transplant recipients compared to their ND-CKD counterparts with similar kidney function. To test these hypotheses, we compared various parameters of PEW, including the MIS, waist circumference, BMI, serum albumin, leptin, and C-reactive protein (CRP) between 203 kidney transplant recipients and 203 CKD patients matched according to their estimated glomerular filtration rates (eGFR).

## Methods

### Patient populations and data collection

#### *Kidney transplant recipients*

All prevalent kidney transplant recipients 18 years of age or older ( $n = 1214$ ) receiving care from the Semmelweis

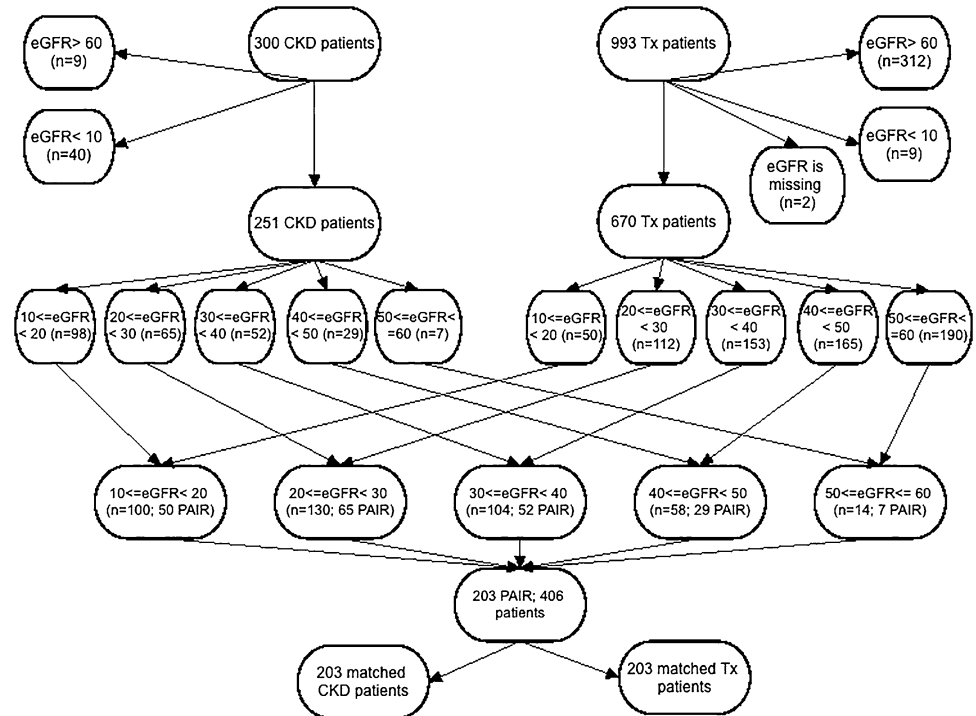
University Department of Transplantation and Surgery outpatient clinic in Budapest, Hungary, starting from the time of December 31, 2006, were invited to participate in the Malnutrition–Inflammation in Transplant—Hungary Study (MINIT-HU). Patients were excluded if they experienced acute rejection within the last 4 weeks, current hospitalization, kidney transplantation in the previous 3 months, acute infection, or bleeding at the time of study entry. Baseline assessments were conducted between February 1, 2007, and August 30, 2007 [9, 13, 16].

Patients' socio-demographic information and medical history, including age, gender, menopause status, etiology of CKD; transplantation-related data such as immunosuppressant medication use, weight, height, waist circumference; and comorbidity data such as the modified Charlson Comorbidity Index (CCI) [23] were obtained at the time of study enrollment. Patients' eGFRs were calculated using the four-variable modification of diet in renal disease (MDRD) study equation [24].

The study was approved by the Semmelweis University Ethics Committee (IRB No.: 49/2006). The study conformed to ICP Good Clinical Practices Guidelines and the Declaration of Helsinki. Prior to enrollment, patients received detailed written and verbal information regarding the aims and protocol of the study and gave written consent to participate.

#### *Chronic kidney disease patients*

ND-CKD patients' data were obtained from the “Malnutrition, Inflammation and Vascular Calcification (MIVC)” study [4, 21, 25, 26]. The MIVC cohort was comprised of 300 non-dialysis-dependent stage 3–5 CKD patients recruited from the Hypertension and Nephrology Division outpatient clinic at Dante Pazzanese Institute of Cardiology in Sao Paulo, Brazil, between the period of March, 2010 to March, 2013, among whom the median (IQR) age was 61 (53, 68) years; 63 % were men; and 57 % were current/prior smokers. The aim of MIVC was to evaluate the association between both traditional and novel uremic risk factors with cardiovascular morbidity and mortality in this population. Patients were excluded if they were <18 or >80 years old; had clinical signs of acute infection during the preceding month; had active cancer or liver disease; had history of immunologic disease; or were on any type of immunosuppressive medications at the time of study entry. The presence of CKD (defined as an eGFR < 60 ml/min/1.73 m<sup>2</sup>) was ascertained by 24-h urinary creatinine clearance. One physician (ACC) conducted the medical history interviews and performed chart reviews for all patients. The Dante Pazzanese Institute of Cardiology Ethics Committee approved the study, and informed consent was obtained from each patient.

**Fig. 1** Flow chart of the study cohort creation

### Final study cohort

The final study cohort was derived from the two independently assembled aforementioned cohorts (Fig. 1). After excluding ND-CKD and TX patients with an eGFR > 60 ml/min/1.73 m<sup>2</sup> and <10 ml/min/1.73 m<sup>2</sup>, 251 and 670 ND-CKD and TX patients remained, respectively. These ND-CKD and TX patients were matched (using a 10 ml/min/1.73 m<sup>2</sup> matching window) 1:1 according to baseline eGFR, resulting in 203 pairs and an overall cohort size of 406 patients ( $n = 203$  ND-CKD and 203 TX patients). We were not able to match 48 ND-CKD patients.

### Malnutrition–inflammation score (MIS)

To assess the MICS, we used the MIS, also known as the Kalantar score, developed, and validated by Kalantar-Zadeh et al. [20], which was measured at baseline. The MIS has ten components [change in end dialysis dry weight, dietary intake, gastrointestinal symptoms, functional capacity, comorbidities, decreased fat stores or loss of subcutaneous fat (according to SGA), signs of muscle wasting (according to SGA), BMI, serum albumin, and total iron-binding capacity], each with four levels of severity, from 0 (normal) to 3 (severely abnormal). The sum of the MIS components ranges from 0 (normal) to 30 (severely malnourished), in which a higher score reflects greater malnutrition and inflammation severity. In contrast to the original MIS, we did not include dialysis vintage in the comorbidity

component. Thus, the comorbidity component was scored as 0 if no comorbidities were present; 1 if there were mild comorbidities present and major comorbid conditions (MCCs) were absent (such as New York Heart Association Class III or IV congestive heart failure, severe coronary artery disease, acquired immunodeficiency syndrome, moderate-to-severe chronic obstructive pulmonary disease, and metastatic malignancies); 2 if moderate comorbidities were present, including one MCC; and 3 if multiple severe comorbidities were present, including two or more MCCs. Subjective global assessments (SGAs) were performed by an experienced physician according to conventional SGA guidelines [27].

### Laboratory data

In both study cohorts, laboratory data were extracted from the patients' charts and from the electronic database of the hospital at baseline and longitudinally at the time of each study visit. The following laboratory parameters were tabulated: hemoglobin (Hb), complete blood count, CRP, ferritin, cholesterol, phosphorous, parathyroid hormone (PTH), serum creatinine, blood urea nitrogen (BUN), and serum albumin. Serum samples were also collected at the time of the baseline assessment and stored at  $-70^{\circ}\text{C}$  for future use. From these samples, high sensitivity leptin levels were measured using immunoassay kits based on solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN) in both cohorts.

## Comorbidities

One of the most commonly used and validated comorbidity indices for the kidney transplant and ND-CKD populations is the CCI [28]. We used the modified CCI at baseline [23], which is a weighted scoring system based on the presence or absence of 17 variables. As one of these variables is the presence of moderate-to-severe renal disease (score = 2), the score may range from 2 to a maximum of 33. The presence of hypertension, which is not included in the CCI, was also separately assessed. In both cohorts, information on patients' smoking status and blood pressure was also collected at baseline.

## Statistical analyses

Data were summarized using proportions, mean  $\pm$  SD, or median (IQR) as appropriate. Continuous variables were compared using the Student's *t* test and Mann–Whitney *U* test according to data type. Logarithmic transformed variables were used where the distribution of the variable was not normal.

To compare various PEW parameters across the matched patient groups (TX vs. ND-CKD), we used both linear regression and conditional logistic regression analyses. In our multivariable linear regression and conditional logistic regression analyses, we adjusted for age, gender, and presence of diabetes based on the results of our bivariate analyses and previously published literature.

The associations between GFR examined as a continuous variable and various PEW parameters were flexibly modeled using fractional polynomials and restricted cubic splines. Variance inflation factors (VIF) were used to assess collinearity between independent variables. Model selection was guided by the minimization of the Akaike information criterion (AIC).

Statistical analyses were carried out using STATA 13.1 (StataCorp, College Station, TX) software. In all statistical analyses, two-sided tests were used, and the results were considered statistically significant if *p* was <0.05.

## Results

### Baseline characteristics

Baseline characteristics of patients according to their (1) stage of CKD and (2) ND-CKD versus TX status are shown in Table 1. Within each stage of CKD, ND-CKD patients were more likely to be older, to be diabetic, to have greater comorbidity burden and to have lower serum ferritin levels compared to TX recipients. Among those with stage 3 or 4 CKD, ND-CKD patients were more likely to be male

and to have higher serum creatinine and phosphorous levels compared to TX recipients. Other baseline characteristics were similar between ND-CKD and TX patients across each stage of CKD.

### Association between eGFR and nutritional parameters

Within both ND-CKD and TX patients, eGFR was negatively correlated with MIS (ND-CKD:  $\rho = -0.32$ ,  $p < 0.001$ ; TX:  $\rho = -0.35$ ,  $p < 0.001$ ) and with CRP (ND-CKD:  $\rho = -0.14$ ,  $p = 0.042$ ; TX:  $\rho = -0.16$ ,  $p = 0.027$ ). In contrast, moderate positive correlations were found between eGFR and serum albumin (ND-CKD:  $\rho = 0.25$ ,  $p < 0.001$ ; TX:  $\rho = 0.28$ ,  $p < 0.001$ ).

### Nutritional parameters in ND-CKD and TX groups

Across each stage of CKD, the MIS; waist circumference; and serum CRP, albumin, and leptin levels were similar in ND-CKD and TX patients (Table 1). However, BMI levels were significantly higher in ND-CKD patients compared to their TX counterparts across all CKD stages (Table 1).

Each MIS component was then compared between ND-CKD and TX patients (Table 2). Compared to TX recipients, ND-CKD patients reported greater weight loss in the preceding 3–6 months, worse appetite, and gastrointestinal symptoms. In contrast, the SGA was significantly worse in stage 4 and 5 TX recipients versus ND-CKD patients (Tables 1, 2).

### Regression analyses of the nutritional parameters

In univariate linear regression analyses, TX status was a predictor of lower BMI and higher (i.e., worse) SGA (reference: ND-CKD patients; Table 2). We then conducted multivariate analyses to assess whether ND-CKD versus TX status was a predictor of nutritional parameters independent of age, gender, and diabetes. In adjusted analyses, TX status was associated with higher waist circumference (standardized coefficient: 0.187;  $p < 0.001$ ), lower BMI (standardized coefficient:  $-0.204$ ;  $p < 0.001$ ), and higher SGA (standardized coefficient: 0.156;  $p = 0.006$ ) (Table 3). However, TX status was not associated with nutritional markers in the adjusted conditional logistic regression models (Table 4).

### Association of nutritional parameters and eGFR in ND-CKD and TX groups

We then compared the MIS, serum albumin level, BMI, and waist circumference between ND-CKD and TX patients across continuous eGFR levels using fractional polynomials and restricted cubic splines (Fig. 2). Between ND-CKD

**Table 1** Baseline characteristics of the 203 ND-CKD patients and 203 transplant recipients matched according to estimated glomerular filtration rate (eGFR)

	Stage 3: 60 ml/min > eGFR ≥ 30 ml/min			Stage 4: 30 ml/min > eGFR ≥ 15 ml/min			Stage 5: 15 ml/min > eGFR ≥ 10 ml/min		
	ND-CKD	TX	<i>p</i> value	ND-CKD	TX	<i>p</i> value	ND-CKD	TX	<i>p</i> value
<i>N</i>	88	88	N/A	94	95	N/A	21	20	N/A
Age (year; mean ± SD)	62 ± 10	53 ± 12	<0.001	61 ± 10	54 ± 11	<0.001	58 ± 10	48 ± 10	0.002
Sex (men; %)	73	50	0.002	61	39	0.003	52	50	0.879
Races (%)	51	91	N/A	47	96	N/A	52	95	N/A
Caucasian	13	0		15	0		29	0	
African-American	3	0		4	0		0	0	
Asian	33	0		34	0		19	0	
Pardo	0	9		0	4		0	5	
Roma									
eGFR (ml/min/1.73 m <sup>2</sup> ; mean ± SD)	40 ± 7	40 ± 7	0.990	23 ± 4	22 ± 4	0.844	12 ± 2	12 ± 2	0.837
Previous time on dialysis (month; median; IQR)	N/A	22; 12–38	N/A	N/A	20; 9–40	N/A	N/A	13; 7–36	N/A
Preemptive kidney transplantation (%)	N/A	5	N/A	N/A	2	N/A	N/A	0	N/A
<i>Nutritional/inflammatory parameters</i>									
MIS (median; IQR)	3; 2–5.5	3; 2–5	0.509	5; 3–7	4; 2–7	0.420	6; 5–9	7.5; 5–10	0.537
SGA part of MIS (median; IQR)	0; 0–0	0; 0–1	0.144	0; 0–0	1; 0–2	<0.001	0; 0–0	1; 0–2	0.037
Waist circumference (cm; mean ± SD)	98 ± 12	100 ± 13	0.440	96 ± 12	96 ± 16	0.925	96 ± 13	93 ± 13	0.548
BMI (kg/m <sup>2</sup> ; mean ± SD)	29.6 ± 5.4	27.0 ± 4.4	<0.001	29.3 ± 5.2	26.3 ± 5.2	<0.001	28.5 ± 4.6	25.1 ± 4.6	0.024
CRP (mg/l; median; IQR)	3.5; 1.4–8.1	3.7; 1.6–6.4	0.753	3.8; 1.0–7.9	2.9; 1.0–8.5	0.780	3.1; 0.9–12.0	4.3; 2.4–8.6	0.531
Serum albumin (g/l; mean ± SD)	40 ± 5	40 ± 4	0.659	38 ± 7	39 ± 4	0.742	36 ± 6	36 ± 5	0.827
Serum leptin (ng/ml; median; IQR)	20; 7–34	22; 10–37	0.375	19; 10–40	20; 6–51	0.754	14; 5–37	12; 3–41	0.597
<i>Comorbidities</i>									
Diabetes (%)	55	18	<0.001	47	21	<0.001	71	5	<0.001
Active smoking (%)	11	18	0.202	12	16	0.415	10	15	0.592
CCI (median; IQR)	6.5; 5–8	2; 2–4	<0.001	7; 5–8	2; 2–4	<0.001	6; 6–7	3; 2–3.5	<0.001
Peripheral vascular disease (%)	44	14	<0.001	48	14	<0.001	38	25	0.368
Previous cerebrovascular disease (%)	10	6	0.265	19	4	0.001	10	5	0.578
<i>Laboratory parameters</i>									
White blood cell count (10 <sup>9</sup> /l; mean ± SD)	7.6 ± 2.1	7.7 ± 2.3	0.975	7.8 ± 2.3	7.7 ± 2.6	0.968	7.1 ± 1.9	8.8 ± 2.6	0.028
Blood hemoglobin (g/l; mean ± SD)	133 ± 19	134 ± 17	0.724	125 ± 18	121 ± 13	0.051	109 ± 21	108 ± 16	0.835
Serum phosphorous (mmol/l; mean ± SD)	1.21 ± 0.22	1.06 ± 0.18	<0.001	1.35 ± 0.27	1.26 ± 0.25	0.013	1.43 ± 0.18	1.73 ± 0.42	0.006
Serum creatinine (ηmol/l; mean ± SD)	208 ± 51	149 ± 29	<0.001	292 ± 81	234 ± 56	<0.001	388 ± 109	400 ± 80	0.674
Serum cholesterol (mmol/l; mean ± SD)	4.7 ± 1.4	5.6 ± 1.2	<0.001	4.9 ± 1.5	5.8 ± 1.6	<0.001	4.9 ± 2.0	5.0 ± 1.3	0.887
Serum PTH (pg/ml; median; IQR)	102; 73–155	72; 53–117	0.002	162; 113–281	108; 72–181	<0.001	348; 249–441	268; 31–462	0.167
Serum ferritin (ng/ml; median; IQR)	123; 68–191	192; 81–435	<0.001	106; 53–205	207; 94–522	<0.001	115; 85–274	330; 158–915	0.002

**Table 1** continued

	Stage 3: 60 ml/min > eGFR ≥ 30 ml/min			Stage 4: 30 ml/min > eGFR ≥ 15 ml/min			Stage 5: 15 ml/min > eGFR ≥ 10 ml/min		
	ND-CKD	TX	<i>p</i> value	ND-CKD	TX	<i>p</i> value	ND-CKD	TX	<i>p</i> value
<i>Blood pressure</i>									
Systolic blood pressure (mmHg, mean ± SD)	155 ± 31	140 ± 20	0.002	151 ± 30	147 ± 22	0.343	159 ± 28	144 ± 24	0.070
Diastolic blood pressure (mmHg, mean ± SD)	82 ± 17	83 ± 12	0.693	80 ± 15	85 ± 13	0.015	83 ± 15	84 ± 12	0.958

*BMI* body mass index, *CCI* Charlson Comorbidity Index, *CRP* C-reactive protein, *GFR* glomerular filtration rate, *IQR* interquartile range, *MIS* malnutrition–inflammation score, *ND-CKD* non-dialysis-dependent chronic kidney disease, *PTH* parathormone, *SD* standard deviation, *SGA* subjective global assessment, *TX* transplant

**Table 2** Distribution of each MIS component in the CKD and transplant cohort

	<i>p</i> value	CKD				TX					
		Median (IQR)	0	1	2	3	Median (IQR)	0	1	2	3
MIS1: change in end dialysis dry weight	<0.001	0 (0–2)	65	1	12	22	0 (0–1)	70	5	15	10
MIS2: dietary intake	<0.001	1 (0–1)	48	31	21	0	0 (0–0)	89	10	1	0
MIS3: gastrointestinal symptoms	0.035	1 (0–1)	50	38	12	0	0 (0–1)	59	35	5	1
MIS4: functional capacity	<0.001	0 (0–0)	86	12	1	1	0 (0–1)	58	38	4	0
MIS5: comorbidities	<0.001	1 (1–1)	14	77	9	0	1 (0–1)	36	46	16	2
MIS6: decreased fat stores or loss of subcutaneous fat (according to SGA)	<0.001	0 (0–0)	84	6	8	2	0 (0–1)	62	31	6	1
MIS7: signs of muscle wasting (according to SGA)	0.079	0 (0–0)	83	10	6	1	0 (0–1)	74	19	6	1
MIS8: body mass index	0.034	0 (0–0)	99	1	0	0	0 (0–0)	93	5	1	1
MIS9: serum albumin	0.022	0 (0–1)	51	30	13	6	1 (0–1)	40	44	12	4
MIS10: serum total iron-binding capacity	0.002	0 (0–0)	84	12	2	2	0 (0–1)	70	20	9	1

Values represent the percentage of patient in each category. Each MIS component has possible score of 0–3 (0 is the best, and 3 is the worst) *MIS* malnutrition–inflammation score, *IQR* interquartile range

**Table 3** Comparison of various PEW parameters between TX and ND-CKD patients (reference: ND-CKD patients) using linear regression models

Outcome variables	TX versus ND-CKD status							
	Unadjusted				Adjusted <sup>a</sup>			
	<i>R</i> <sup>2</sup>	Coefficient for TX	95 % CI of coefficient	<i>p</i> value	<i>R</i> <sup>2</sup>	Coefficient for TX	95 % CI of coefficient	<i>p</i> value
MIS	0.0019	−0.28	−0.90; 0.35	0.383	0.0259	0.17	−0.69; 0.73	0.963
Waist circumference	0.0001	0.32	−2.31; 2.95	0.814	0.1387	5.03	2.24; 7.83	<0.001
BMI	0.0752	−2.85	−3.83; −1.87	<0.001	0.0944	−2.12	−3.22; −1.01	<0.001
SGA part of MIS (MIS6 and MIS7)	0.0130	0.28	0.04; 0.51	0.021	0.0349	0.38	0.11; 0.64	0.006
Serum Ln CRP	0.0001	0.02	−0.24; 0.29	0.867	0.0192	0.14	−0.17; 0.44	0.378
Serum albumin	0.0008	0.30	−0.72; 1.32	0.561	0.0298	0.11	−1.04; 1.26	0.851
Serum Ln leptin	0.0001	0.02	−0.22; 0.27	0.847	0.1645	−0.13	−0.23; 0.13	0.325

*BMI* body mass index, *CI* confidence interval, *CRP* C-reactive protein, *MIS* malnutrition–inflammation score, *ND-CKD* non-dialysis-dependent chronic kidney disease, *PEW* protein–energy wasting, *SGA* subjective global assessment, *TX* transplant

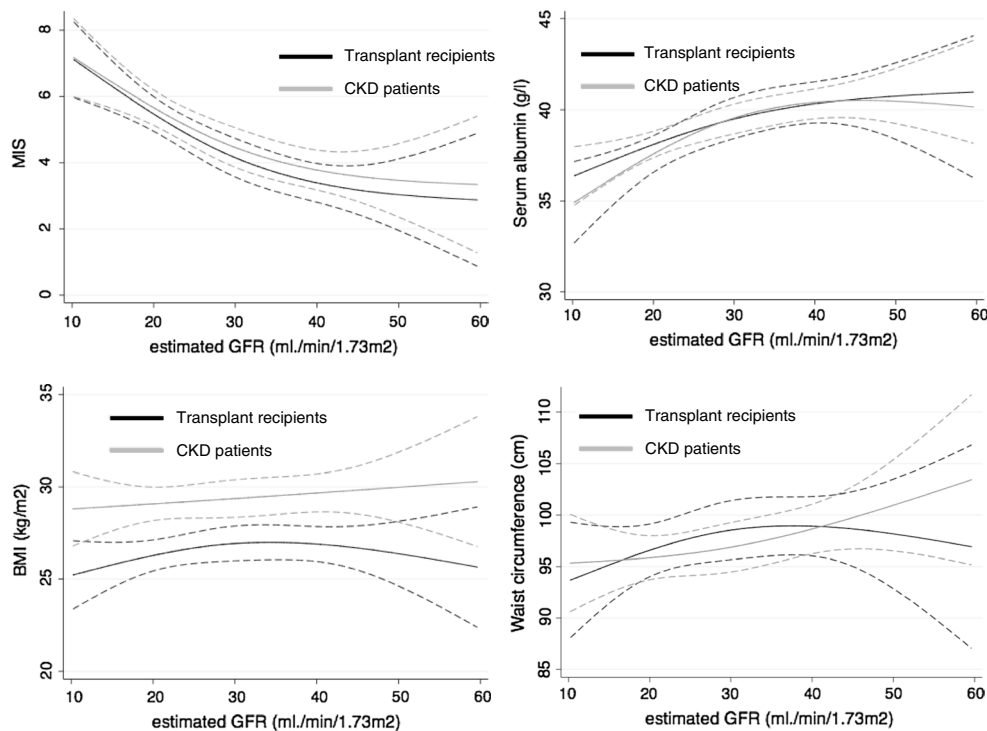
<sup>a</sup> Adjusted for age, sex, and presence of diabetes

**Table 4** Comparison of various PEW parameters between TX and ND-CKD patients (reference: ND-CKD patients) using conditional logistic regression models

Outcome variables	TX versus ND-CKD (reference)					
	Unadjusted			Adjusted <sup>a</sup>		
	OR for TX	95 % CI of OR	<i>p</i> value	OR for TX	95 % CI of OR	<i>p</i> value
BMI <23 kg/m <sup>2</sup>	3.43	1.89–6.22	<0.001	1.56	0.68–3.55	0.291
SGA part of MIS $\geq 2$	1.48	0.89–2.46	0.130	1.80	0.91–3.59	0.093
Serum albumin <38 g/l	1.15	0.75–1.74	0.523	1.17	0.70–1.96	0.541

BMI body mass index, CI confidence interval, MIS malnutrition–inflammation score, ND-CKD non-dialysis-dependent chronic kidney disease, OR odds ratio, SGA subjective global assessment, TX transplant

<sup>a</sup> Adjusted for age, sex, and presence of diabetes

**Fig. 2** Associations between eGFR and various PEW markers using fractional polynomials and restricted cubic splines in ND-CKD and transplant patients

and TX patients, the MIS, serum albumin levels, and waist circumferences overlapped across the entire eGFR range. However, BMI levels were significantly higher in ND-CKD patients versus TX recipients between the eGFR range of 10–60 ml/min/1.73 m<sup>2</sup> (Fig. 2).

## Discussion

In this study, we compared the severity of PEW components in ND-CKD and TX patients. Our findings showed that various PEW parameters, including nutritional/

inflammatory markers such as serum albumin and the MIS, are higher in patients with lower eGFR irrespective of their CKD or TX status. The other salient observation was that the severity of PEW components was similar in CKD and TX patients.

To our knowledge, this is the first study to show an inverse correlation between eGFR and PEW parameters (e.g., MIS and CRP) in both ND-CKD and TX patients. Recently, Cuppari et al. [5] showed a strong negative association between kidney function and prevalence of PEW (as assessed by SGA) in 922 CKD patients. We have also previously shown these associations in prevalent kidney



transplant recipients [16]. We find notable in our study that, along this line and using spline models, eGFR examined as a continuous variable showed a similar and potent association with serum albumin and MIS values across the entire eGFR range in both CKD and TX patients (Fig. 2).

While most of the PEW parameters were similar between ND-CKD and TX patients, some differences in nutritional and inflammatory parameters were detected between these two groups. First, we observed differences in body composition of ND-CKD and TX patients. While the BMI was significantly lower in TX versus ND-CKD patients, we found that waist circumference, a strong predictor of mortality [29], was higher in TX recipients. This may suggest that TX patients may have greater visceral fat tissue and lower muscle mass than their ND-CKD counterparts. These findings were corroborated with the SGA, which showed lower subcutaneous fat tissue and lower muscle mass in TX patients versus their ND-CKD counterparts (Table 2). Such differences may be explained by the use of particular drugs in TX patients that influence body anthropometry, such as steroids, but also by differential dietary habits and lifestyle. The previous time of dialysis in our TX patients can be another explanation for these observed differences. It has been shown that longer time on dialysis increases the inflammatory cytokines, which can lead further to PEW [30–32]. We also observed that transplant patients reported greater appetite versus ND-CKD patients based on the MIS findings (Table 2). This difference in appetite is unlikely to be explained by uremia, as ND-CKD and TX patients were matched according to eGFR; furthermore, serum leptin and CRP levels did not differ between the two groups. While differences in socio-demographics, comorbidity burden, and administered drugs may again explain these observed disparities, further studies are needed to confirm findings and to explore mechanistic pathways for this observed difference.

Several limitations of our study deserve mention. First, patients were recruited from two centers in Hungary and Brazil, which may limit generalizability to other populations, particularly with regard to dietary habits and lifestyle. However, the negative association between PEW prevalence and eGFR was nearly identical in these diverse cohorts, supporting this association may be robust across different populations. Second, while we were able to match ND-CKD and TX patients on the basis of eGFR, we had limited ability to match patients on the basis of age, gender, diabetes, and other key confounders due to small sample size. However, as an attempt to address residual confounding, we adjusted for these variables in our multivariate models. Third, tests were conducted in two different centers, which may limit their comparability. Lastly, the patients who declined participation or were excluded from

the study may have differed from the included participants, which could increase risk of selection bias.

## Conclusions

In summary, our study demonstrated strong associations between eGFR and severity of PEW components in both ND-CKD and TX populations. Additionally, we found similar PEW parameters between the ND-CKD and TX populations, but potentially important differences in body habitus between these two groups. We hope such observations will stimulate further studies aiming to confirm findings and explore the underlying pathways for the GFR–PEW association in these populations.

**Acknowledgments** JJC acknowledges grant support from the Swedish Research Council and Stockholm County Council (ALF). MIVC cohort was supported by grants by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (Process number: 2010/16593-2), Adib Jatene's Foundation, and the Swedish Research Council.

**Conflict of interest** None.

## References

1. Karadag F, Kirdar S, Karul AB, Ceylan E (2008) The value of C-reactive protein as a marker of systemic inflammation in stable chronic obstructive pulmonary disease. *Eur J Intern Med* 19:104–108
2. Carriere I, Dupuy AM, Lacroux A, Cristol JP, Delcourt C (2008) Biomarkers of inflammation and malnutrition associated with early death in healthy elderly people. *J Am Geriatr Soc* 56:840–846
3. Nakamura K, Moriyama Y, Kariyazono H, Hamada N, Toyohira H, Taira A, Yamada K (1999) Influence of preoperative nutritional state on inflammatory response after surgery. *Nutrition* 15:834–841
4. Amparo FC, Cordeiro AC, Carrero JJ, Cuppari L, Lindholm B, Amodeo C, Kamimura MA (2013) Malnutrition-inflammation score is associated with handgrip strength in nondialysis-dependent chronic kidney disease patients. *J Ren Nutr* 23:283–287
5. Cuppari L, Meireles MS, Ramos CI, Kamimura MA (2014) Subjective global assessment for the diagnosis of protein-energy wasting in nondialysis-dependent chronic kidney disease patients. *J Ren Nutr* 24(6):385–389
6. Ikizler TA, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K, Kuhlmann MK, Stenvinkel P, TerWee P, Teta D, Wang AY, Wanner C (2013) International Society of Renal N, Metabolism: prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int* 84:1096–1107
7. Rambod M, Bross R, Zitterkoph J, Benner D, Pithia J, Colman S, Kovesdy CP, Kopple JD, Kalantar-Zadeh K (2009) Association of malnutrition-inflammation score with quality of life and mortality in hemodialysis patients: a 5-year prospective cohort study. *Am J Kidney Dis* 53:298–309

8. Gracia-Iguacel C, Gonzalez-Parra E, Perez-Gomez MV, Mahillo I, Egido J, Ortiz A, Carrero JJ (2013) Prevalence of protein–energy wasting syndrome and its association with mortality in haemodialysis patients in a centre in Spain. *Nefrologia* 33:495–505
9. Molnar MZ, Keszei A, Czira ME, Rudas A, Ujszaszi A, Haromszeki B, Kosa JP, Lakatos P, Sarvary E, Beko G, Fornadi K, Kiss I, Rempert A, Novak M, Kalantar-Zadeh K, Kovesdy CP, Mucsi I (2010) Evaluation of the malnutrition-inflammation score in kidney transplant recipients. *Am J Kidney Dis* 56:102–111
10. ter Wee PM (2013) Protein energy wasting and transplantation. *J Ren Nutr* 23:246–249
11. Tatal E, Sezer S, Uyar ME, Bal Z, Demirci BG, Acar FN (2013) Evaluation of nutritional status in renal transplant recipients in accordance with changes in graft function. *Transplant Proc* 45:1418–1422
12. Kovesdy CP, George SM, Anderson JE, Kalantar-Zadeh K (2009) Outcome predictability of biomarkers of protein–energy wasting and inflammation in moderate and advanced chronic kidney disease. *Am J Clin Nutr* 90:407–414
13. Molnar MZ, Czira ME, Rudas A, Ujszaszi A, Lindner A, Fornadi K, Kiss I, Rempert A, Novak M, Kennedy SH, Rosivall L, Kovesdy CP, Mucsi I (2011) Association of the malnutrition-inflammation score with clinical outcomes in kidney transplant recipients. *Am J Kidney Dis* 58:101–108
14. Ujszaszi A, Czira ME, Fornadi K, Novak M, Mucsi I, Molnar MZ (2012) Quality of life and protein–energy wasting in kidney transplant recipients. *Int Urol Nephrol* 44:1257–1268
15. Czira ME, Lindner AV, Szeifert L, Molnar MZ, Fornadi K, Kelemen A, Laszlo G, Mucsi I, Keszei AP, Kennedy SH, Novak M (2011) Association between the malnutrition-inflammation score and depressive symptoms in kidney transplanted patients. *Gen Hosp Psychiatry* 33:157–165
16. Molnar MZ, Czira ME, Rudas A, Ujszaszi A, Haromszeki B, Kosa JP, Lakatos P, Beko G, Sarvary E, Varga M, Fornadi K, Novak M, Rosivall L, Kiss I, Rempert A, Goldsmith DJ, Kovesdy CP, Mucsi I (2011) Association between the malnutrition-inflammation score and post-transplant anaemia. *Nephrol Dial Transplant* 26:2000–2006
17. Kim JC, Kalantar-Zadeh K, Kopple JD (2013) Frailty and protein–energy wasting in elderly patients with end stage kidney disease. *J Am Soc Nephrol* 24:337–351
18. Molnar MZ, Bunnapradist S, Huang E, Krishnan M, Nissen AR, Kovesdy CP, Kalantar-Zadeh K (2012) Association of pre-transplant erythropoiesis-stimulating agent responsiveness with post-transplant outcomes. *Nephrol Dial Transplant* 27:3345–3351
19. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevino-Becerra A, Wanner C (2008) A proposed nomenclature and diagnostic criteria for protein–energy wasting in acute and chronic kidney disease. *Kidney Int* 73:391–398
20. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH (2001) A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *Am J Kidney Dis* 38:1251–1263
21. Amparo FC, Kamimura MA, Molnar MZ, Cuppari L, Lindholm B, Amodeo C, Carrero JJ, Cordeiro AC (2014) Diagnostic validation and prognostic significance of the malnutrition-inflammation score in nondialyzed chronic kidney disease patients. *Nephrol Dial Transplant*. doi:10.1093/ndt/gfu380
22. Carrero JJ, Stenvinkel P, Cuppari L, Ikizler TA, Kalantar-Zadeh K, Kaysen G, Mitch WE, Price SR, Wanner C, Wang AY, ter Wee P, Franch HA (2013) Etiology of the protein–energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr* 23:77–90
23. Jassal SV, Schaubel DE, Fenton SS (2005) Baseline comorbidity in kidney transplant recipients: a comparison of comorbidity indices. *Am J Kidney Dis* 46:136–142
24. Levey A, Greene T, Kusek J, Beck G, Group MS (2000) A simplified equation to predict glomerular filtration rate from serum creatinine {Abstract}. *J Am Soc Nephrol* 11:155A
25. Cordeiro AC, Qureshi AR, Lindholm B, Amparo FC, Tito-Paladino-Filho A, Perini M, Lourenco FS, Pinto IM, Amodeo C, Carrero JJ (2013) Visceral fat and coronary artery calcification in patients with chronic kidney disease. *Nephrol Dial Transplant* 28(Suppl 4):152–159
26. Cordeiro AC, Lindholm B, Sousa MG, Picotti JC, Nunes GJ, Santana MR, Grimaldi W Jr, Amparo FC, Amodeo C, Carrero JJ (2014) Reliability of electrocardiographic surrogates of left ventricular mass in patients with chronic kidney disease. *J Hypertens* 32:439–445
27. Enia G, Sicuso C, Alati G, Zoccali C (1993) Subjective global assessment of nutrition in dialysis patients. *Nephrol Dial Transplant* 8:1094–1098
28. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40:373–383
29. Kovesdy CP, Czira ME, Rudas A, Ujszaszi A, Rosivall L, Novak M, Kalantar-Zadeh K, Molnar MZ, Mucsi I (2010) Body mass index, waist circumference and mortality in kidney transplant recipients. *Am J Transplant* 10:2644–2651
30. Segall L, Moscalu M, Hogas S, Mititiuc I, Nistor I, Veisa G, Covic A (2014) Protein–energy wasting, as well as overweight and obesity, is a long-term risk factor for mortality in chronic hemodialysis patients. *Int Urol Nephrol* 46:615–621
31. Carrero JJ, Chmielewski M, Axelsson J, Snaedal S, Heimbürger O, Barany P, Suliman ME, Lindholm B, Stenvinkel P, Qureshi AR (2008) Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. *Clin Nutr* 27:557–564
32. Johansen KL, Kaysen GA, Young BS, Hung AM, da Silva M, Chertow GM (2003) Longitudinal study of nutritional status, body composition, and physical function in hemodialysis patients. *Am J Clin Nutr* 77:842–846