Original Article

Comparative Analysis of Tools for Assessment of Protein–Energy Wasting in Chronic Kidney Disease Patients on Maintenance Hemodialysis

Abstract

Background: Patients with chronic kidney disease have muscle wasting, sarcopenia, and cachexia that contribute to frailty and morbidity. The present study assessed the prevalence of protein–energy wasting in dialysis-dependent chronic kidney disease population and evaluated the validity of various nutritional assessment tools in diagnosing protein–energy wasting. **Materials and Methods:** All patients above 18 years undergoing dialysis for more than 3 months without any active infection or malignancy were included in our study. Data from anthropometric measurements, dietary assessment, and blood investigations were collected. Protein–energy wasting was assessed by the International Society of Renal Nutrition and Metabolism 2008 criteria. Diagnostic validity of the nutritional assessment tools to predict protein–energy wasting was estimated by area under the curve, sensitivity, specificity, and accuracy statistics. **Results:** A total of 146 patients were studied. The prevalence of protein–energy wasting was 56.8%. Protein–energy wasting was significantly associated with socioeconomic status, hospitalization days, and catheter days. Normalized protein catabolism rate had the highest sensitivity (90.4%) for predicting protein–energy wasting. Malnutritional inflammatory score had the highest area under the curve (0.858), specificity (82.5%), and accuracy (82.2%). Mid-upper arm circumference, Dialysis Malnutrition Score, and albumin were also found to be significant predictors of protein–energy wasting. **Conclusion:** Lack of advanced equipment in suburban and rural centers to detect protein–energy wasting in India can be overcome by using the various stand-alone and combination nutrition assessment tools which have been validated in the present study.

Keywords: *Chronic kidney disease, Maintenance hemodialysis, Malnutrition, Malnutrition inflammation score, Nutritional assessment, Protein–energy wasting*

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Introduction

Protein–energy wasting (PEW) is a state of disordered catabolism resulting from metabolic and nutritional derangements in chronic disease states. Patients with chronic kidney disease (CKD), and end-stage renal disease (ESRD) in particular, have muscle wasting, sarcopenia, and cachexia, contributing to frailty and morbidity. A meta-analysis conducted by the International Society of Renal Nutrition and Metabolism (ISRNM) in 2018, which included an Indian study, estimated that the prevalence of PEW varies among countries and dialysis centers (around 18%–64%).[1] It also observed that the evaluation of PEW is hampered by a lack of standardized PEW definitions, variability of existing assessment tools, and differences in socioeconomic status (SES) among the countries. Thus, establishing proper screening tools was considered an important starting point.[1] Another meta-analysis conducted in 2021 estimated the worldwide prevalence of PEW to be from 35.2% to 50.6% and the prevalence in India as 56.7% based on nine studies.[2] Eight studies used Subjective Global Assessment (SGA) to assess the prevalence and one used Malnutrition Inflammation Score (MIS).[2] There is no accepted definition available for PEW. In 2008, ISRNM established readily usable criteria for PEW, which required multiple parameters for diagnosis.[3] Henceforth, various nutritional assessment tools and questionnaires have been developed aiming at rapid and effective diagnosis of PEW. However, various studies comparing the efficacy of various tools yield variable results. There is also a considerable lack of Indian data in this regard. Most Indian dialysis centers lack advanced equipment

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like body composition monitor and bioimpedance for nutritional assessment. So, effective alternate nutritional tools are necessary to screen/diagnose and consequently treat PEW in the Indian CKD population. The present study was undertaken to assess the prevalence of PEW in the dialysis-dependent CKD population and to determine the diagnostic validity of various nutritional assessment tools in diagnosing PEW.

Materials and Methods

The present study was a cross-sectional, observational, validation study conducted over 3 months in a tertiary care hospital in southern Tamil Nadu from June to September 2022. The eligibility criteria and the methods applied were based on the 2020 Kidney Disease Outcome Quality Initiative (KDOQI) clinical practice of nutrition guidelines.[4] Patients above 18 years of age who had been on hemodialysis for at least 3 months and signed informed written consent were included in the study. Patients with acute infection at the time of presentation, patients with temporary access catheter, patients with malignancy at the time of presentation, and patients who refused to give informed written consent were excluded from the study. Predesigned, pretested, interviewer-administered semi-structured questionnaire for demographic and epidemiological data was used (SES was calculated by the modified Kuppuswamy scale).[5] The study was undertaken following the process depicted in Figure 1. Ethical approval to conduct the study was obtained from the Institutional Ethics Committee of Tirunelveli Medical College and Hospital (ID no. 20222395). Eligible patients were enrolled after getting informed written consent from them.

Anthropometric measurements: Patients' body weight and height were measured using the spider 505 platform weight scale and stand-alone stadiometer, respectively. The body mass index (BMI) of patients was computed using the formula weight (kg)/(height × height) (m^2) based on dry weight. A monthly weight assessment was used to determine whether the weight loss was significant. As an indicator of fluid compliance, interdialytic weight gain (IDWG) was calculated by subtracting the postdialysis weight of the previous dialysis session from the predialysis weight.[6] Mid-upper arm circumference (MUAC) of the nonfistula arm was measured using a flexible, nonstretchable measuring tape at the midpoint of the upper arm, between the acromion and the olecranon process, after completion of the dialysis session. Waist–hip ratio (WHR) was assessed by taking the waist circumference and hip circumference using a measuring tape postdialysis. All measurements were taken postdialysis on three separate occasions at monthly intervals by trained dialysis technicians.

Dietary assessment was made by the 24-h dietary recall and 7-day dietary records on three separate occasions at a monthly interval. Dietary energy intake (DEI) and dietary protein intake (DPI) were calculated using this data and compared to the required DEI and DPI as per the readily usable criteria of ISRNM.[3]

Biochemical parameters such as blood urea, serum creatinine levels, serum lipid profile, liver function test, albumin, hemogram, C-reactive protein, total iron-binding capacity (TIBC), transferrin, and urine creatinine after dialysis (urea and creatinine before and after dialysis) were collected on three separate occasions at a monthly interval.

The above investigations were used to calculate measures such as urea reduction ratio (URR), Kt/V using Daugirdas formula,[7] normalized protein catabolism rate (NPCR) using Lightman simple formula,[8] and simplified creatinine index using creatinine kinetic modeling.[9]

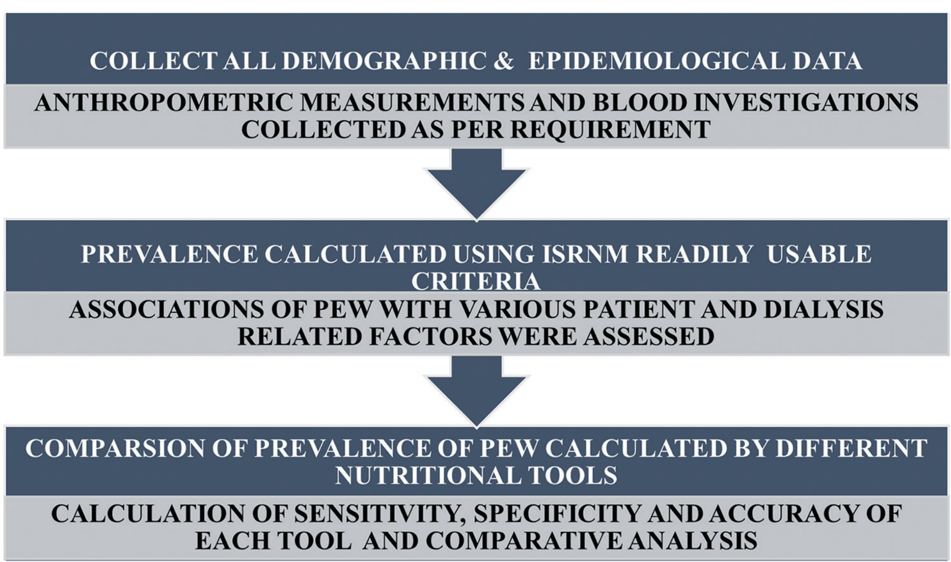

Figure 1: Sequence of the study process.

Questionnaires for assessing nutrition: Nutritional adequacy was graded by Malnutrition Universal Screening Tool (MUST),[10] 7-point SGA score,[11] Dialysis Malnutrition Score (DMS),[12] and the Malnutritional Inflammatory Score (MIS).[13]

Pulmonary hypertension (PHT) was diagnosed with an echocardiogram by a cardiologist based on the European Society of Cardiology (ESC)/European Respiratory Society (ESC/ERS) guidelines.[14]

All the data collected were used to calculate the prevalence of PEW using ISRNM 2008 criteria.[3] It comprises the following major categories: biochemical parameters (low albumin, low prealbumin, low serum cholesterol), low body weight (BMI of less than 23, weight loss), low total body fat (less than 10%), reduction in the muscle mass of patients (muscle wasting, decreased MUAC, appearance of creatinine), and low protein/energy intake (low DPI, low DEI).[3] If the patients had minimum of three among the four major categories (with minimum of one test being positive in each major category), then they can be diagnosed with kidney disease–related PEW.[3]

Prevalence of PEW, factors associated with PEW, and the diagnostic validity of MUAC, MUST, SGA, DMS, MIS, NPCR, albumin, and simplified creatinine index in predicting PEW were the outcomes assessed in the study.

Analysis was conducted using IBM Statistical Package for the Social Sciences (SPSS) v26.0. Categorical variables were expressed as frequency and proportion. Mean with standard deviation was calculated for continuous variables of interest. The normality of the continuous variables was tested by the Kolmogorov–Smirnov test and was found to be not normally distributed. Hence, the Mann–Whitney test was used to test the significance of the difference in continuous variables between PEW and non-PEW patients. The significance of the association between the PEW status and the categorical variables was tested by the Chi-square test. For the tools with continuous data (MUAC, MUST, DMS, MIS, NPCR, albumin, SCI), the area under the curve (AUC) was calculated by the receiver operator characteristic (ROC) curve. Ideal cut-offs to predict PEW were obtained by Youden index for the tools which had a significant AUC. The sensitivity, specificity, and accuracy of the tests were calculated for the tools based on these cut-offs for each tool. PEW in SGA was categorized according to the category of the patients (mild malnutrition to severe malnutrition were included under PEW category). The PEW diagnosis based on the ISRNM 2008 criteria was considered the gold standard. A P value of <0.05 was considered statistically significant.

Results

A total of 146 patients were included in the study. The baseline clinical, anthropometrical, and biochemical characteristics of the included patients are enumerated in Table 1. The age of the participants was 40.9 + 12.6 years; 104 (71%) were males and 42 (29%) were females. Among the patients, 19.9% had diabetes. The mean dialysis vintage was 15.2 months. Among the patients, 77.4% belonged to a lower middle SES and 61% had PHT. The average dietary intake based on 24-h dietary recall and 7-day dietary records was 994.3 kcal of energy/36 g of protein and 1010.2 kcal of energy/40 g of protein, respectively [Table 1].

PEW based on ISRNM criteria (2008)

The prevalence of PEW was 56.8%. Although most of the patients in the study were males, the proportion of PEW was higher in females (61.9%) than males (54.8%) [Supplementary Table 1].

The association of various factors related to patients, dialysis, mortality, and morbidity with PEW is presented in Table 2. Age had an inverse relationship with PEW among the patients in the study, that is, patients with PEW were significantly younger than non-PEW patients (P = 0.048). A linear regression model was run between the calorie intake and protein intake and the age of the patients. Calorie intake was found to have a significant association with the age of the patients (β = 0.170, P = 0.040). Hence, we adjusted the calorie intake of patients in a logistic regression model to ascertain the association between PEW and age and found that the significance of the association between PEW and age was not retained (P = 0.144). Data from the current study showed DEI as the maximum in lunch and DPI as the maximum in breakfast.

The incidence of PHT was significantly higher in PEW patients (71.1%) than non-PEW patients (47.6%) (P = 0.004). Patients with PEW had a higher incidence of hospitalization per month (P = 0.001) as well as per year (P = 0.004) [Table 2]. All four patients who died during the study period had a diagnosis of PEW (100%). Five of the 146 patients (3.4%) had permanent catheters, while 96.6% were on fistulas. All those five permanent catheter patients had PEW. Patients with PEW also had significantly higher catheter days in the past than the ones without PEW. No association was found between hepatitis C virus (HCV) status (P = 0.791), coronavirus disease 2019 (COVID-19) status (P = 0.247), and PEW status. Dialysis vintage, adequacy parameters (Kt/V and URR), and WHR did not show any significant association. Weight, BMI, lean body mass, and MUAC were significantly lower among PEW patients [Table 2].

Diagnostic validity of the nutritional assessment tools in predicting PEW

The ROC curves revealed that MUAC, DMS, MIS, NPCR, and albumin had a significant AUC for predicting PEW (P < 0.05) [Table 3, Figures 2 and 3]. MIS was

Table 1: Baseline characteristics of patients included in the study

Variable	All patients		PEW		Non-PEW	
	Mean	SD	Mean	SD	Mean	SD
Age	40.9	12.6	38.9	13.3	43.4	11.2
SBP	148.8	25.4	146.3	27.3	152.2	22.6
DBP	87.9	16.1	87.2	18.3	88.9	12.7
Dialysis vintage	15.2	22.4	14.1	22.8	16.7	22.0
Kt/V	1.3	0.4	1.3	0.5	1.3	0.4
Urea reduction ratio	62.5	12.7	61.6	14.3	63.5	10.2
Mean interdialytic weight gain	2.4	0.9	2.5	0.9	2.4	0.9
Height	159.3	9.2	159.5	9.3	159.1	9.2
Weight	51.0	10.1	47.4	9.5	55.8	9.0
BMI	20.0	3.5	18.3	3.1	22.1	2.7
Lean body mass	41.7	8.6	39.5	8.2	44.5	8.3
Mid-upper arm circumference	19.8	4.6	18.7	4.5	21.2	4.2
Hb	7.0	1.6	6.8	1.6	7.3	1.5
Hospitalization last month	6.5	8.3	8.3	9.3	4.1	6.2
Hospitalization per year	10.8	15.1	14.4	17.5	6.1	9.4
Albumin	3.4	0.6	3.3	0.6	3.6	0.6
Prealbumin	30.8	1.2	28.6	1.3	31.2	1.1
Cholesterol	115.0	35.3	102.9	37.4	130.9	24.9
TGL	111.5	51.1	97.6	38.8	129.8	59.3
HDL	40.1	11.1	38.8	10.9	41.8	11.3
LDL	108.7	28.9	110.2	26.2	106.7	32.3
TG:HDL ratio	3	1.6	3	1.6	3	1.6
Catheter days	36.0	18.1	40.7	19.6	29.8	13.8
Required dietary intake	1256.3	250.0	1179.9	222.7	1357.0	250.0
Actual dietary intake 24 h	994.3	161.6	947.1	155.0	1056.5	149.7
Actual dietary intake 7 days	1012.2	167.1	961.7	159.0	1078.8	154.9
EF	58.7	11.9	58.7	12.6	58.7	10.9
WHR	0.9	0.1	0.9	0.1	0.9	0.1

BMI=body mass index, DBP=diastolic blood pressure, EF=ejection fraction, Hb=hemoglobin, HDL=high-density lipoproteins, LDL=low-density lipoproteins, PEW=protein–energy wasting, SBP=systolic blood pressure, SD=standard deviation, TGL=triglycerides, WHR=waist–hip ratio

found to have the highest AUC (0.858, $P < 0.001$). The efficacy of these tools assessed by calculating sensitivity, specificity, and accuracy has been presented in Table 4. Individually, NPCR had the highest sensitivity (90.4%), while MIS was the most specific tool (82.5%) as well as the most accurate tool to predict PEW (82.2%) [Table 4]. SGA or DMS in combination with NPCR was found to have the highest sensitivity (98.8%). MIS + NPCR had the highest diagnostic accuracy among the combination of the tools (78.1%) [Table 4].

Prevalence of PEW based on the Youden index-based cut-offs of the nutritional assessment tools

The prevalence of PEW was calculated for the tools based on the ideal cut-offs determined by the ROC curve and is presented in Supplementary Table 1. The prevalence varied from 35.6% with MUAC to about 78.1% with SGA. The prevalence also varied across males and females between the various tools evaluated in the study. Among males, it ranged from 39.4% (MUAC) to 90.4% (SGA + NPCR), while among females, it ranged between 26.2% (MUAC) to 95.2% (SGA + NPCR) [Supplementary Table 1].

Discussion

The prevalence of PEW among the patients from the index study (56.8%) was the same as that of the estimate from the most recent meta-analysis, which assessed the prevalence of malnutrition in the Indian population as 56.7%.[2] The prevalence of PEW was also comparable to that reported by Harvinder *et al.*,[15] that is, 59%. Our estimate was lower than the prevalence calculated in the Indian population by ISRNM 2018 meta-analysis (61%–80%).[1] Ours was a government-run center providing dialysis free of cost. Hence, the study population predominantly belonged to lower and lower middle SES.

In the present study, 89.7% of the patients had an actual DEI lower than the required intake. A recent Indian Council of Medical Research study concluded that the Indian diet had lower calorie and protein content than a standard EAT Lancet diet.[16] However, currently, there is no Indian data

Table 2: Association of PEW with patient- and dialysis-related factors

	PEW status	*n*	Mean rank	*P*
Age	PEW	83	67.48	**0.048**
	No PEW	63	81.44	
	Total	146		
Height	PEW	83	74.72	0.688
	No PEW	63	71.89	
	Total	146		
Weight	PEW	83	57.87	**<0.001**
	No PEW	63	94.10	
	Total	146		
BMI	PEW	83	52.66	**<0.001**
	No PEW	63	100.95	
	Total	146		
Weight loss	PEW	83	72.96	0.858
	No PEW	63	74.21	
	Total	146		
Lean body mass	PEW	83	63.19	**0.001**
	No PEW	63	87.08	
	Total	146		
Hospitalizations in the last year	PEW	83	83.28	**0.001**
	No PEW	63	60.61	
	Total	146		
Hospitalization in the last month	PEW	83	81.98	**0.004**
	No PEW	63	62.33	
	Total	146		
Catheter days	PEW	83	84.99	**<0.001**
	No PEW	63	58.36	
	Total	146		
WHR	PEW	83	70.43	0.311
	No PEW	63	77.55	
	Total	146		
Mid-upper arm circumference	PEW	83	63.05	**0.001**
	No PEW	63	87.26	
	Total	146		
Mean interdialytic weight gain	PEW	83	74.45	0.755
	No PEW	63	72.25	
	Total	146		
TG/HDL ratio	PEW	83	73.08	0.890
	No PEW	63	74.06	
	Total	146		
SBP	PEW	83	68.50	0.098
	No PEW	63	80.09	
	Total	146		
DBP	PEW	83	70.96	0.396
	No PEW	63	76.84	
	Total	146		
PHT	PEW	83	57.87	**<0.001**
	No PEW	63	94.10	
	Total	146		

Continued.

Table 2: Continued

	PEW status	*n*	Mean rank	*P*
Kt/V	PEW	83	72.31	0.696
	No PEW	63	75.07	
	Total	146		
Urea reduction ratio	PEW	83	72.45	0.730
	No PEW	63	74.89	
	Total	146		

BMI=body mass index, DBP=diastolic blood pressure, HDL=high-density lipoproteins, PEW=protein–energy wasting, PHT=pulmonary hypertension, SBP=systolic blood pressure, TGL=triglycerides, WHR=waist–hip ratio. *P* values set in bold indicate statistical significance

Table 3: AUC and the ideal cut-offs for the nutritional assessment tools in predicting PEW

Tool	AUC (95% CI)	*P*	Cut-offs
MUAC	0.666 (0.577–0.755)	**0.001**	≤18.5
MUST	0.481 (0.386–0.576)	0.691	NA
DMS	0.776 (0.701–0.852)	**<0.001**	≥4
MIS	0.858 (0.795–0.920)	**<0.001**	≥8
NPCR	0.784 (0.703–0.866)	**<0.001**	≤1.075
Albumin	0.677 (0.588–0.766)	**<0.001**	≤3.55
Simplified creatinine index	0.530 (0.434–0.625)	0.538	NA

AUC=area under the curve, CI=confidence interval, DMS=Dialysis Malnutrition Score, MIS=Malnutrition Inflammation Score, MUAC=mid-upper arm circumference, MUST=Malnutrition Universal Screening Tool, NPCR=normalized protein catabolic rate, PEW=protein–energy wasting. *P* values set in bold indicate statistical significance

to compare the distribution of DEI and DPI patterns found in our study. Although the unadjusted analysis revealed an association between increasing age and PEW, the association was lost when adjusted for the calorie intake of the patients. Thus, the association found between PEW and increasing age in the univariate analysis might be due to reduced calorie intake.

In our study, MUST was found to have an insignificant predictive capacity for PEW detection among CKD patients. In line with our findings, past studies had concluded MUST as a low-sensitivity tool for detecting PEW in CKD patients on dialysis.[17,18] MUAC, as a stand-alone nutritional marker, had a specificity of 79.4%, but a low sensitivity of 47%. As a single anthropometric measure, there is a significant correlation with PEW as observed in other similar studies.[19,20] Nevertheless, the lower sensitivity observed in our study warrants a cautious usage of MUAC in the current settings.

DMS and MIS had shown a better sensitivity (80% and 81.9%, respectively). However, the specificity of MIS was higher, which, in turn, increased the accuracy of MIS (82.2%) over DMS (72.6%). This was comparable to

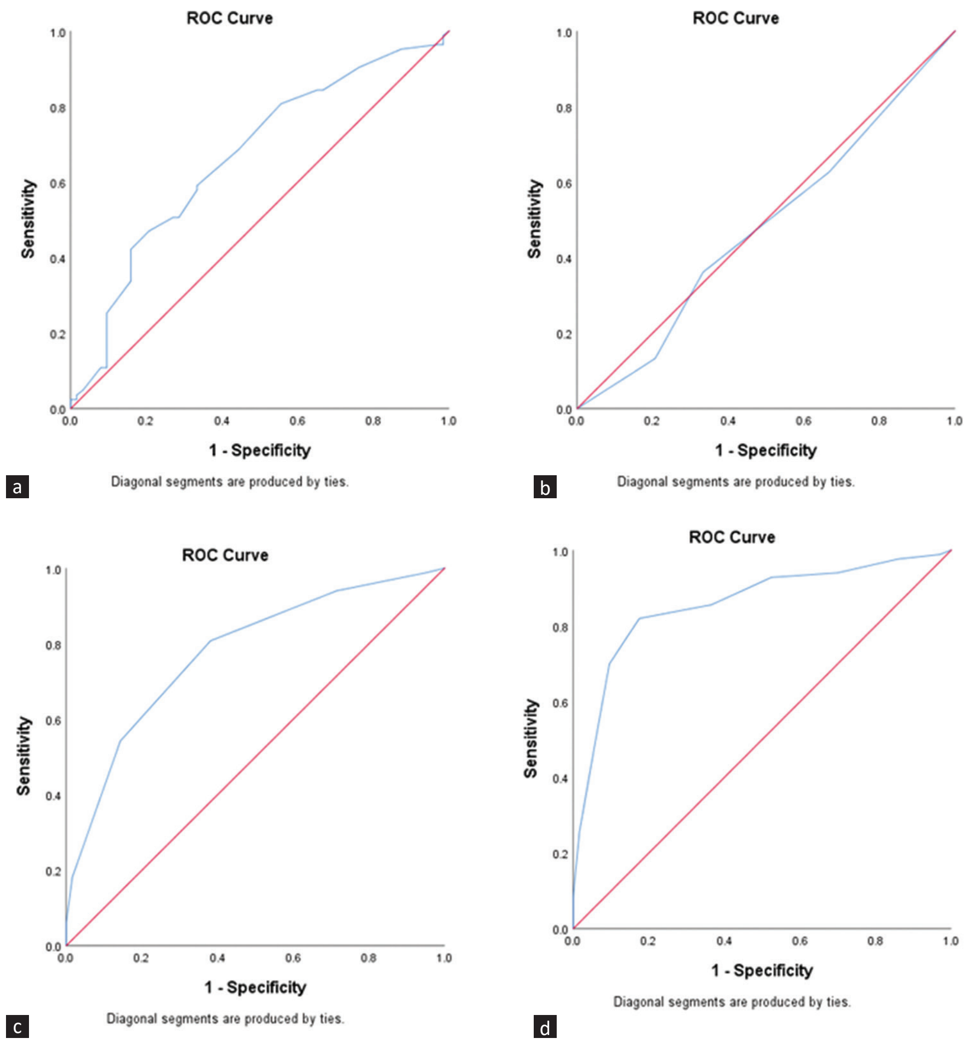

Figure 2: ROC curves for predicting PEW: (a) MUAC, (b) MUST, (c) DMS, (d) MIS. DMS = Dialysis Malnutrition Score, MIS = Malnutrition Inflammation Score, MUAC = mid-upper arm circumference, MUST = Malnutrition Universal Screening Tool, PEW = protein–energy wasting, ROC = receiver operator characteristic.

Table 4: Diagnostic accuracy of the nutritional assessment tools in predicting PEW

Tool	Sensitivity (%)	Specificity (%)	Accuracy (%)
MUAC	47	79.4	62.2
SGA	71.1	69.9	55.4
DMS	80.7	61.9	72.6
MIS	81.9	82.5	82.2
NPCR	90.4	65.1	79.5
Albumin	77.1	58.7	69.2
SGA + NPCR	98.8	17.5	63.7
DMS + NPCR	98.8	41.3	74
MIS + NPCR	97.6	52.4	78.1

DMS=Dialysis Malnutrition Score, MIS=Malnutrition Inflammation Score, MUAC=mid-upper arm circumference, NPCR=normalized protein catabolic rate, PEW=protein–energy wasting, SGA=Subjective Global Assessment

data from previous studies.[12,13,15] As a stand-alone tool, SGA was found to have lower diagnostic validity than the combination of MIS and DMS. Overall, our findings showed that MIS was better than any other stand-alone or combination of tools in detecting PEW among CKD patients.

NPCR is the most sensitive tool for detecting PEW (90.4%), albeit with a slightly lower accuracy (79.5%) than MIS. Similar findings were obtained in a recent study which compared NPCR with albumin, prealbumin, and transferrin and found NPCR to be a superior marker of nutritional status.[21] A combination of NPCR with multiple questionnaires was attempted, and a combination of NPCR with MIS had the best accuracy (78.1%) among the combinations. Yet, stand-alone MIS (82.2%) and NPCR (79.5%) had better accuracy than the combined MIS and NPCR. No data is available in the existing literature to compare the diagnostic validity of the combination of tools.

The current KDOQI 2020 states that serum albumin can be used as an isolated marker for mortality in PEW. Hence, it was tested separately in the present study.[4] Serum

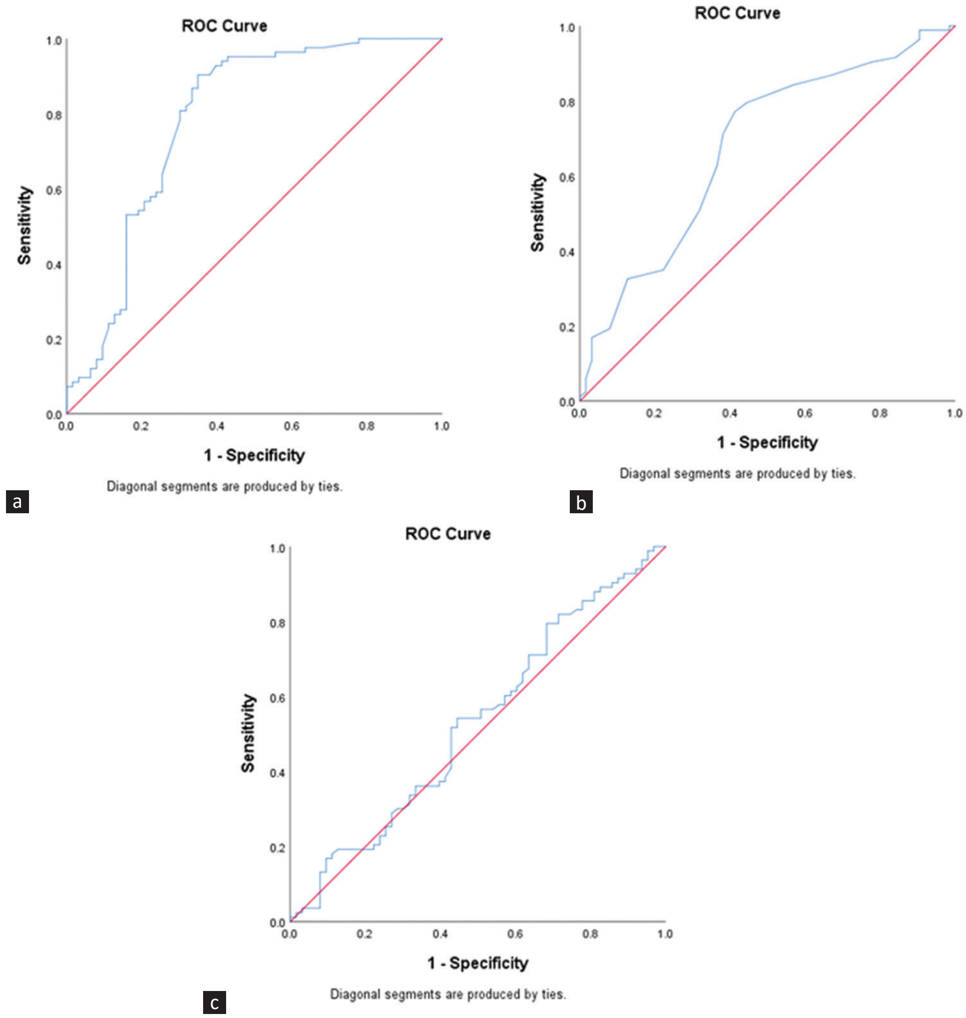

Figure 3: ROC curves for predicting PEW: (a) NPCR, (b) albumin, (c) simplified creatinine index. NPCR = normalized protein catabolic rate, PEW = protein–energy wasting, ROC = receiver operator characteristic.

albumin of the patients had a sensitivity and specificity of 71.1% and 61.1%, respectively, with an accuracy of 69.2%, indicating the scope to be used as a potential marker for PEW. While a recent study compared the simplified creatinine index with PEW identified by ISRNM criteria and found it to be an effective assessment tool,[22] the index study found it to be a nonsignificant tool to predict PEW among the studied patients.

Thus, from our study, it can be concluded that NPCR is the most sensitive tool and MIS is the most specific tool to detect PEW. The simplest method was to apply NPCR initially as a screening tool followed by the calculation of MIS, which could predict PEW with higher accuracy. The strength of this study was that it compared multiple nutritional assessment tools in the same cohort with standard conditions. The present study was not devoid of limitations. A higher proportion of males in the study population might have impacted the overall prevalence of the PEW in the current study. The generalizability of the findings is limited owing to the single-centric nature of the study.

Conclusion

PEW was prevalent among 56.8% of CKD patients on hemodialysis, which included predominantly people from a low SES. Lower SES, catheter days, hospitalization days per month and per year, and PHT had a significant association with PEW. Nutritional assessment tools such as MUAC, DMS, MIS, NPCR, and serum albumin were significant predictors of PEW. Among the nutritional assessment tools, MIS had the highest accuracy in predicting PEW.

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Conflicts of interest

There are no conflicts of interest.

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