

Clinical Evaluation of Protein Energy Wasting in Maintenance Hemodialysis Patients

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Research

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Abstract

Background: Protein-energy wasting (PEW) is a common complication of maintenance hemodialysis (MHD) patients. This study aimed to explore the PEW evaluation method in MHD patients.

Methods: Clinical data, physical parameters, laboratory values, and a questionnaire survey of MHD patients were collected from PEW and non-PEW patients in our hospital from September to December 2019. Analysis of variance was used to assess the difference between the two groups. ROC analysis was used to compare the diagnostic efficacy of physical measurement and nutrition scores and find the appropriate evaluation criteria for clinical application.

Results: 1. There were statistically significant differences in many physical parameters between the two groups ($p < 0.05$). 2. ROC curve analysis showed that the diagnostic efficiency of a single physical measurement or nutritional score was not high, and multiple indexes should be combined. 3. The simplified Pew risk score formula was $27.4 + \text{abdominal circumference} + 0.4 * \text{main handgrip strength} - 3.2 * \text{body mass index} - 1.9 * \text{upper arm circumference}$, which had a sensitivity of 67.7% and specificity of 94.4% at AUC of 0.864 and cutoff of 0.043346.

Conclusion: A combination of abdominal circumference, main handgrip strength, BMI, and upper arm circumference could comprehensively evaluate PEW to improve the diagnostic efficiency.

Introduction

Protein-energy wasting (PEW) refers to a state of "malnutrition" in which various nutritional and metabolic abnormalities that occur in patients with chronic kidney disease (CKD) lead to a decrease in the body's protein-energy reserve^[1]. In maintenance hemodialysis (MHD) patients, the incidence of PEW can be as high as 22.4–75%^{[2][3]}. The hospitalization rates of MHD patients with mild, moderate, and severe malnutrition are 32.93%, 56.67%, and 83.33%, respectively, and the mortality rate is 3.66%, 6.67%, and 80.00%, respectively^[4].

In 2008, ISRN proposed a comprehensive four-aspect analysis method to determine whether a patient has PEW, including biochemical indicators, unexpected body mass loss, loss of muscle mass, as well as insufficient dietary protein and calorie intake^[6]. The current nutritional assessment methods used in clinical practice are still based on this standard, which requires clinicians to make comprehensive judgments based on medical history and various examination indicator, including laboratory inspection items (such as serum albumin, prealbumin, transferrin), and physical examination indicators (such as body mass, body mass index, anthropometric measurements, single/multi-frequency bioelectrical impedance analysis). Numerous nutritional assessment scales have been applied in clinics, such as Scored Patient-Generated Subjective Global Assessment (PG-SGA) provided by patients, nutritional risk screening 2002 (NRS2002), and malnutrition Universal screening tools (Malnutrition Universal Screening Tools, MUST). However, most of the scoring scales cannot simultaneously meet the clinical requirements

of reliability, low cost, non-invasive and convenient operation, so clinical applications are minimal. Therefore, we collected general information and laboratory test results of MHD patients in our hospital, conducted physical measurements and several questionnaire surveys based on the current research status, and compared the differences of the indicators between the two groups with or without PEW, the diagnostic efficacy of physical measurements and each questionnaire survey to find a more suitable evaluation method of multiple indicators for clinical application.

Methods

Ethics

This study was approved by the Ethics Committee of Tianjin Third Central Hospital. All research subjects have signed the informed consent.

Patient selection

There were 166 MHD patients in our hospital from September to December 2019. A total of 200 patients were screened, and 34 patients were excluded based on the inclusion criteria: age ≥ 18 years old and dialysis age ≥ 3 months as well as the exclusion criteria: patients with known malignant tumors, patients hospitalized for severe infection in the past month and patients with new cerebral infarction or cerebral hemorrhage in the past three months.

Research methods

Questionnaire survey

The researchers used a unified questionnaire to conduct on-site surveys of the research objects. The contents of the questionnaire include 1) general information such as gender, age, dialysis age, marital status, and education level; 2) the original disease status, including whether having diabetes and high blood pressure; 3) living conditions including daily defecation, daily sleep time, daily protein and staple food intake, weekly exercise time, whether there is stomatitis, and whether taking vitamins or amino acids.

Dialysis data collection

The patients' hemodialysis treatment information was collected, including weight before and after dialysis, blood pressure, ultrafiltration volume, dialysis method, blood flow and dialysis access.

Biochemical indicators collection

The past 3 months' data of the enrolled patients at the dialysis center were collected, including blood routine, liver and kidney function, electrolytes, parathyroid hormone, blood sugar, blood lipids, ferritin, transfer iron saturation, and other indicators.

Body measurement

All subjects were measured after dialysis, including height, weight, abdominal circumference, calf circumference, upper arm circumference (AC), triceps skinfold thickness (TSF), body mass index (BMI), and main handgrip strength. For measuring the abdominal circumference and calf circumference, let patients take a vertical standing posture and fully relax to distribute the weight evenly. Abdominal circumference is the length of the circle around the abdomen through the navel, and calf circumference is the length of the circle at the calf's thickest part. A standing posture with feet shoulder-width apart, hands drooping, and non-fistula side hands holding grips was for measuring the main handgrip strength. A skinfold thickness meter was used to measure the thickness of the triceps skinfold at the point 2 cm above the midpoint between the acromion and the olecranon of the non-fistula arm. A tape around the arm at the midpoint was used to measure the upper arm circumference.

All the above indicators were measured 3 times. If the measurement values were very close, their average was taken as the final result. If the measurement values were quite different, the average of the closest two was used as the final results.

Scoring scale

NS2002, PG-SGA and MUST scores were calculated for all participants.

PEW diagnostic criteria

Patients were diagnosed as PEW if they met at least one of the following criteria according to the recommendation by ISRNM in 2008. First, their biochemical indicators met serum albumin <3.8g/dL, serum pre-Alb<30mg/dL, and serum cholesterol<259 mmol/L; Second, they had unexpected body mass loss to BMI<23 kg/m², unintentional weight loss of 5% within 3 months, 10% weight loss within 6 months, or fat content< 10%; Third, their muscle mass loss reached 5% within 3 months or 10% within 6 months, upper arm midsection muscle circumference (AMC) decreased by > 10% or serum creatinine <618 μmol/L, where AMC (cm) = Upper arm circumference (cm)-3.14 × TSF (cm); Fourth, they had unintentional dietary protein intake <0.8 g·(kg·d)⁻¹ for at least 2 months or unintentional dietary energy intake <25 kcal·(kg·d)⁻¹ for at least 2 months. According to BMI, PEW was divided into 3 different levels: severe level with BMI≤18.5 kg/m²; moderate level with BMI 18.6-20.0kg/m² and mild level with BMI>20.0 kg/m²[6]. Because of insufficient accuracy in patients' long-term weight monitoring and the significant effects of water load of the dialysis interval on patients' BMI, post-dialysis BMI, which is relatively objective and easily accessible, was selected as the indicator for body mass reduction.

Statistical analysis

SPSS 26.0 software was used for statistical analysis. The measurement data conforming to the normal distribution were expressed as $\bar{x} \pm s$. T test was used to compare the measurement data of PEW patients and non-PEW patients, and the χ^2 test was used to compare the count data. ROC curve analysis was used

to evaluate the diagnostic efficacy of each scoring scale. A $p < 0.05$ indicates a statistically significant difference.

Results

Patient characteristics

A total of 166 patients were enrolled, including 100 males (60%) and 66 females (40%). Among them, 130 patients were in the PEW group (including 104 mild cases, 18 moderate cases, and 8 severe cases) and 36 patients in the non-PEW group. There was no statistical difference between the two groups in age, gender, dialysis age, dialysis blood flow, combined diabetes status, dialysis access, daily defecation, daily sleep, whether taking amino acids and antihypertensive drugs, and daily exercise status (Table 1).

Difference between non-PEW and PEW groups

Statistical analysis showed there were significant differences between the two groups in blood pressure, daily protein intake, vitamin intake, levels of uric acid, creatinine, and serum calcium, several physical indicators, including body weight, BMI, body surface area, abdominal circumference, triceps skinfold thickness, upper arm circumference, and calf circumference, and PG-SGA scores (all $p < 0.05$, Table 2). The rests were not significantly different.

Difference of diagnostic efficiency of indicators

The ROC curve analysis was used to evaluate the diagnostic efficacy of height, weight, BMI, body surface area, main handgrip strength, abdominal circumference, triceps skinfold thickness, upper arm circumference, calf circumference, NS2002, PG-SGA, and MUST scores. Statistical analysis shows that all these indicators' diagnostic efficacy is not high, with the highest being the PG-SGA score, which had the area under the AUC curve being only 0.558 (Table 3).

Predictor selection

The previous analysis indicated that a single indicator, either a physical measurement or a scoring scale, could not evaluate PEW well. Thus, the binary logistic regression model with the combination of multiple indicators was used to find a method for PEW evaluation and calculate the predicted probability, including height, weight, BMI, body surface area, main handgrip strength, abdominal circumference, triceps skinfold thickness, upper arm circumference, calf circumference, NS2002, PG-SGA, MUST scores. The forward LR independent variable screening method indicated that only the combination of BMI, main handgrip, abdominal circumference, and upper arm circumference could predict whether the patient has PEW (Table 4) with the PEW predictive index

$\text{Logit}(p) = 6.641 - 0.567 * \text{BMI} + 0.067 * \text{Main handgrip strength} + 0.180 * \text{Abdominal circumference} - 0.345 * \text{AC}$. Re-analyzing the ROC curve of the PEW predictive index, $\text{Logit}(p)$, showed an $\text{AUC} = 0.864$, indicating the diagnostic efficiency is higher (Figure 1). However, the above formula is complicated and

not conducive to clinical use. Therefore, dividing both sides of the above formula by 0.18 and subtract 9.5 simplifies the formula as

Simplified formula of the PEW predictive index = $27.4 + \text{abdominal circumference} + 0.4 * \text{main handgrip strength} - 3.2 * \text{BMI} - 1.9 * \text{AC}$, with an AUC = 0.864, the cutoff value (Cut_{off}) calculated by the Youden index = 0.043346, which is approximately equal to 0, sensitivity = 67.7%, and specificity = 94.4%. In other words, when the PEW predictive index is greater than or equal to 0, we should consider the existence of PEW.

Discussion

Protein-energy wasting (PEW) is a common complication of maintenance hemodialysis (MHD) patients. It is closely related to the death of patients [5] and has attracted more and more attention. The causes of PEW are insufficient protein and caloric intake, insufficient dialysis, micro-inflammatory state, diabetes, volume overload, and metabolic acidosis. In addition, the ubiquitin-proteasome system, ghrelin, micro-RNAs, muscle cell apoptosis and regeneration defects, vitamin D deficiency and other cytokines and endocrine factors [6][7], are all reciprocal influence factors and could form a vicious circle, which will eventually lead to the clinical manifestations of fatigue and malaise in PEW patients [8][9]. In severe cases, it also increases the risk of depression [10].

Finding a single indicator for early screening and follow-up of PEW patients has always been a hot spot in the field of PEW. The currently used clinical practice methods for PEW evaluation still take the PEW diagnostic criteria proposed by ISRNM as the pure index, which requires clinicians to master anthropometry and dietary survey and analysis, and closely follow-up whether the patient has a decrease in body mass and muscle mass in the past 3 months. Therefore, its complexity also makes it impossible to operate in clinical applications.

We believe that physical measurement indicators are more precise and meaningful than laboratory indicators. Inoue [11] and other studies also indicated that excessive emphasis on controlling blood phosphorus could easily cause patients to have a PEW state and cause more significant harm to them than high phosphorus. At present, in addition to standard physical index measurements, there are many kinds of scores. In this study, the more commonly used NS2002, PG-SGA, and MUST scores are included. However, the ROC curve analysis showed that their diagnostic efficiency was not high: the highest was PG-SGA. For these scores, the area under the AUC curve was only 0.558. Nevertheless, logistic regression model analysis found that a combination of BMI, main handgrip strength, abdominal circumference, and upper arm circumference could predict whether the patient has PEW, but not others. At present, more and more studies have found that changes in muscle content could more intuitively reflect the nutritional status of patients [12]. For example, Gloria [13] found that muscle content and main grip strength have a linear and inverse relationship with PEW.

This study found that the PEW predictive index calculated as $27.4 + \text{abdominal circumference} + 0.4 * \text{main handgrip strength} - 3.2 * \text{BMI} - 1.9 * \text{AC}$, had a cut_{off} value of approximately equal to 0, meaning when

the PEW predictive index is greater than or equal to 0, we should consider the existence of PEW. Using this formula to substitute all patient data and re-analyze the ROC curve resulted in an AUC = 0.864, which has higher diagnostic efficiency. However, since the number of patients included in this study is still limited, it needs to be further confirmed in future clinical applications.

Conclusions

In summary, protein-energy wasting is a common comorbidity in maintenance hemodialysis patients, and its incidence is getting higher and higher as the course of the disease progresses^[14]. The study revealed the importance of physical measurement indicators by comparison between PEW and non-PEW groups. A comprehensive evaluation of abdominal circumference, upper arm circumference, main handgrip strength, and other indicators can further assist in the clinical assessment of PEW status. In short, early diagnosis and timely intervention of PEW are essential measures to improve the quality of life of maintenance hemodialysis patients.

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Tables

Table 1 General situations of non-PEW and PEW groups				
Variables		Non-PEW (n=36)	PEW (n=130)	P values
Age	(years, $\bar{x} \pm s$)	60.000±9.610	61.680±10.189	p=0.378
Gender	Male (100, 60%)	22, 61.1%	78, 60%	p=0.904
	Female (66, 40%)	14, 38.9%	52, 40%	
Dialysis age	(Months, $\bar{x} \pm s$)	59.06±31.735	74.34±64.758	p=0.051
Dialysis blood flow	(ml/min, $\bar{x} \pm s$)	233.330±18.822	233.690±17.659	p=0.915
Combined diabetes	(52, 31.3%)	10, 27.8%	42, 32.3%	p=0.699
Dialysis access	Arteriovenous fistula	32, 88.9%	114, 87.7%	p=1.000
	Hemodialysis catheter	4, 11.1%	16, 12.3%	
Daily defecation	≥ 1	28, 77.8%	100, 76.9%	p=0.914
	< 1	8, 22.2%	30, 23.1%	
Daily sleep	≥ 6h	20, 55.6%	64, 49.2%	p=0.502
	< 6h	16, 44.4%	66, 50.8%	
Taking amino acids	14, 8.4%	2, 5.6%	12, 9.2%	p=0.716
Antihypertensive drug kinds	≥ 2	22, 61.1%	60, 46.2%	p=0.112
	< 2	14, 38.9%	70, 53.8%	
Types of antihypertensive drugs	≥ 90 min	16, 44.4%	56, 43.1%	p=0.884
	< 90 min	20, 55.6%	74, 56.9%	
Long-term bed rest	52, 31.3%	12, 33.3%	40, 30.8%	p=0.769
Note: p<0.05, statistically different				

Table 2 Difference between non-PEW and PEW groups				
Variables		Non-PEW (n=36)	PEW (n=130)	P values
Blood pressure	<140/90	24 (66.7%)	42 (32.3%)	p=0.000
	>140/90	12 (33.3%)	88 (67.7%)	
Daily protein intake	>0.8 g/kg/g	36 (100%)	42 (32.3%)	p=0.000
	<0.8 g/kg/d	0 (0%)	88 (67.7%)	
Vitamin intake	26, 15.6%	10 (27.8%)	16 (12.3%)	p=0.024
Body weight	(kg, $\bar{x} \pm s$)	76.367±11.486	64.908±13.292	p=0.000
BMI	($\bar{x} \pm s$)	26.915±2.684	22.972±3.653	p=0.000
Body surface area	(m ² , $\bar{x} \pm s$)	1.845±0.185	1.725±0.190	p=0.001
Main hand grip strength	(kg, $\bar{x} \pm s$)	23.900±10.574	21.506±7.304	p=0.119
abdominal circumference	(cm, $\bar{x} \pm s$)	93.890±8.485	86.600±11.379	p=0.000
TSF	(mm, $\bar{x} \pm s$)	1.322±0.718	0.985±0.498	p=0.001
AC	(cm, $\bar{x} \pm s$)	27.889±3.379	24.400±3.170	p=0.000
Calf circumference	(cm, $\bar{x} \pm s$)	32.861±3.259	30.469±3.474	p=0.000
Uric acid	(mmol/l, $\bar{x} \pm s$)	438.89±73.177	404.86±101.724	p=0.027
Creatinine	(umol/l, $\bar{x} \pm s$)	1000.83±171.839	866.26±255.695	p=0.003
Calcium levels	(mmol/l, $\bar{x} \pm s$)	2.144±0.139	2.230±0.196	p=0.015
NRS2002	($\bar{x} \pm s$)	1.61±0.903	1.82±1.440	p=0.421
PG-SGA	($\bar{x} \pm s$)	3.17±2.091	4.09±3.358	p=0.045
MUST	($\bar{x} \pm s$)	0.44±0.695	0.62±1.177	p=0.273
Note: p<0.05, statistically different; AC upper arm circumference; TSF, triceps skinfold thickness; BMI, body mass index.				

Table3. Difference of diagnostic efficiency of indicators					
Test Result Variable(s)	Area	Std. Error (a)	Asymptotic Sig. (b)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Height	0.488	0.057	0.82	0.377	0.599
Weight	0.243	0.042	0	0.161	0.325
BMI	0.174	0.034	0	0.108	0.24
Body surface area	0.329	0.05	0.002	0.232	0.427
Main hand grip strength	0.501	0.054	0.987	0.396	0.606
Abdominal circumference	0.288	0.047	0	0.197	0.38
TSF	0.347	0.051	0.005	0.247	0.447
AC	0.22	0.043	0	0.135	0.305
Calf circumference	0.302	0.05	0	0.204	0.399
NRS2002	0.508	0.053	0.888	0.404	0.611
PG-SGA	0.558	0.05	0.29	0.459	0.656
MUST	0.498	0.053	0.975	0.395	0.601

Table 4. Predictor selection of logistic regression model						
	B	Std. Error	Wald	df	Sig.	Exp (B)
BMI	-0.567	0.157	12.986	1	0	0.567
Main hand grip strength	0.067	0.033	4.209	1	0.04	1.07
Abdominal circumference	0.18	0.055	10.861	1	0.001	1.198
AC	-0.345	0.125	7.693	1	0.006	0.708
Constant	6.641	1.988	11.158	1	0.001	765.568

AC, upper arm circumference; BMI, body mass index.

Figures

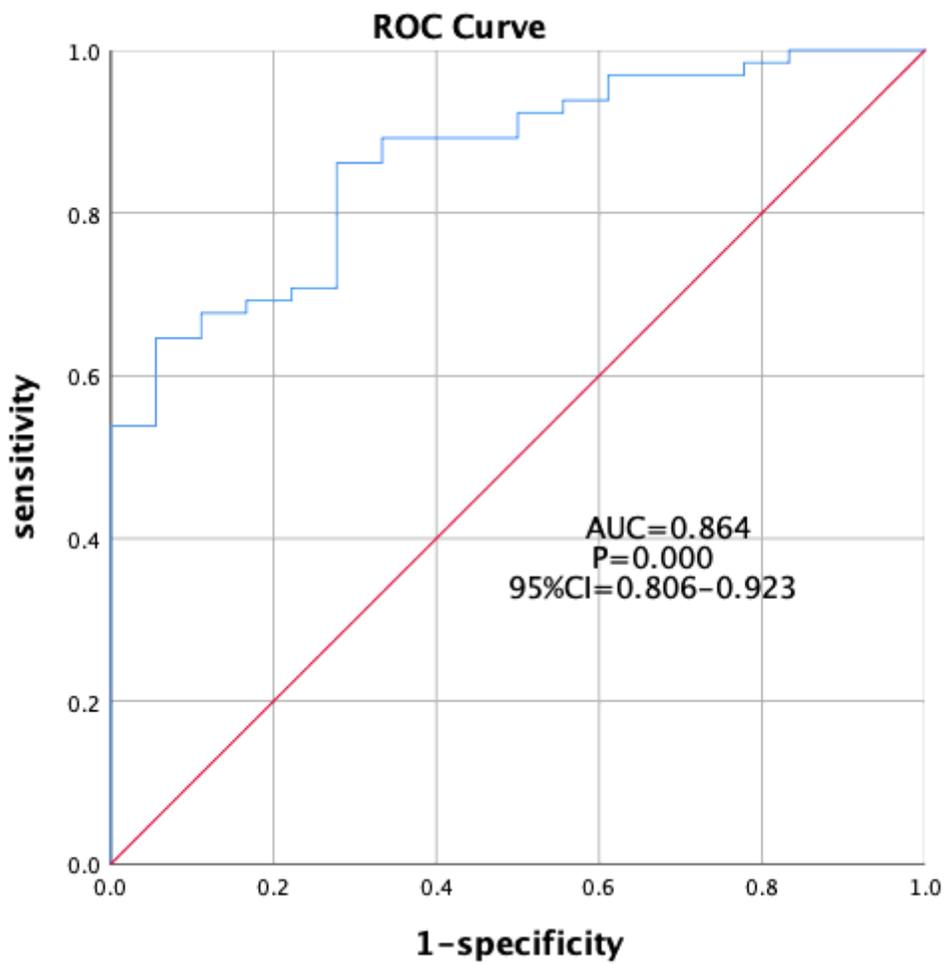


Figure 1

The ROC curve of the PEW predictive index