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PHASE ANGLE AND ITS CLINICAL RELEVANCE TO MALNUTRITION AND LOW-GRADE INFLAMMATION AMONG HEMODIALYSIS PATIENTS: A CROSS-SECTIONAL PERSPECTIVE

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Abstract

Background: Patients with chronic kidney disease (CKD) undergoing routine hemodialysis are prone to chronic inflammation and malnutrition, two interrelated conditions that worsen clinical outcomes. The phase angle obtained from bioelectrical impedance analysis (BIA) reflects cell membrane integrity and nutritional status and is suspected to correlate with inflammatory biomarkers such as TNF-α.

Objective: To analyze the relationship between phase angle and Dialysis Malnutrition Score (DMS) on TNF-α levels in routine hemodialysis patients.

Methods: A cross-sectional analytical study was conducted on 50 routine hemodialysis patients in a clinic in Semarang. Data collected included age, sex, duration of hemodialysis, BMI, skeletal muscle mass (SMM), DMS, phase angle, and TNF-α levels. Data were analyzed using Pearson correlation and multiple linear regression.

Results: The average age of participants was 52.38 years, and the average phase angle was 5.05. Pearson correlation showed a significant negative correlation between phase angle and TNF-α levels ($r = -0.587$; $p = 0.000$), while DMS showed a positive correlation ($r = 0.368$; $p = 0.009$). In the regression model, only phase angle was a significant predictor of TNF-α ($\beta = -0.471$; $p < 0.001$).

Conclusion: Phase angle has a significant negative correlation with TNF-α levels, suggesting its potential as a non-invasive marker for inflammation monitoring in hemodialysis patients. DMS was not significant in the multivariate model. Further studies are recommended to explore causal relationships and longitudinal assessments.

keywords : Hemodialysis, Phase Angle, TNF-α, Malnutrition, DMS, Chronic Inflammation

Introduction

Patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis (HD) often experience a combination of protein-energy wasting (PEW) and persistent low-grade systemic inflammation, which together contribute significantly to increased morbidity and mortality. This coexisting condition is widely

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known as the malnutrition–inflammation complex syndrome (MICS) and plays a critical role in adverse outcomes among dialysis patients.[1] In recent years, there has been a growing focus on identifying non-invasive, cost-effective, and clinically feasible biomarkers to assess nutritional and inflammatory status in HD patients. Phase angle (PhA), derived from a specialized bioelectrical impedance analysis (BIA) instrument, has emerged as a promising marker of cellular integrity, membrane stability, and body cell mass. Lower PhA values are frequently associated with loss of muscle mass, diminished cell vitality, and poorer survival outcomes in patients with chronic diseases, including those receiving dialysis. [2,3]

The main advantage of PhA measurement is that it is non-invasive, inexpensive, and quickly obtained with the patient simply sitting or lying down, thus offering a practical alternative to blood-based inflammatory assessments such as C-reactive protein (CRP) or tumor necrosis factor-alpha (TNF-α). This makes PhA particularly attractive for use in low-resource or high-volume dialysis settings where regular laboratory testing may not be feasible.[4] Chronic low-grade inflammation in hemodialysis patients has been linked to aging and the accumulation of disease burden and has become a significant concern in nephrology. In the HD patient population, inflammation is characterized by increased levels of pro-inflammatory cytokines, particularly TNF-α, which plays a role not only in inflammation but also in muscle catabolism, anorexia, and nutritional deterioration. [5,6]

Recent studies have demonstrated a significant inverse relationship between PhA and inflammatory cytokines, including TNF-α, suggesting that PhA could serve as a surrogate marker for both nutritional and inflammatory burden in this population.[7,8] Meanwhile, structured clinical tools such as the Dialysis Malnutrition Score (DMS) or Malnutrition-Inflammation Score (MIS) provide validated methods to assess nutritional risk in HD patients, though they remain semi-subjective and time-consuming.[9]

Despite increasing recognition of the clinical utility of PhA, there remains a lack of studies that explore the combined association between PhA, TNF-α levels, and malnutrition scores—especially in Indonesian populations. Understanding these interrelationships could support the development of simplified, non-invasive screening strategies for early detection of MICS and inflammaging. Therefore, the present study aims to evaluate the association between PhA, Dialysis Malnutrition Score, and serum TNF-α levels in patients undergoing maintenance hemodialysis. This study intends to assess PhA's potential role as a practical and accessible biomarker for

identifying patients at risk of malnutrition and inflammaging.

Research Methods

This study is a quantitative, analytical, observational study with a cross-sectional approach. This approach was used to determine the relationship between phase angle values and levels of malnutrition and inflammation in patients undergoing routine hemodialysis. Cross-sectional studies allow for simultaneous data collection without intervention on the subjects, making them suitable for identifying correlations between variables. The target population was all chronic hemodialysis patients undergoing routine therapy for at least 3 months in a hemodialysis unit at a hospital or clinic partnering with the study. Inclusion criteria: Age ≥ 18 years, undergoing hemodialysis at least twice a week for ≥ 3 months, having comorbidities such as hypertension or diabetes mellitus or both, willing to participate and sign an informed consent. Exclusion criteria: Patients with acute conditions (severe infection, active cancer, severe mental disorders), patients who have more than 2 comorbidities other than hypertension and diabetes mellitus, patients with amputations or massive edema that could affect the accuracy of BIA measurements. The sampling technique used purposive sampling, based on inclusion and exclusion criteria. The research variables in this study consisted of :

1. Phase Angle (PhA) is a bioelectrical parameter that reflects cell membrane integrity and the distribution of intracellular versus extracellular water in the body. PhA is derived from Bioelectrical Impedance Analysis (BIA) measurements and physiologically indicates a person's cellular status—particularly active cell mass (body cell mass) and cell membrane condition. Technically, PhA is the angle formed between resistance (R) and reactance (Xc) in an alternating current measurement. This value reflects the cell membrane's capacity to store electrical charge and is thus an indicator of a person's vitality and nutritional status. The PhA data collection technique in this study was measured using a calibrated INBODY S-10 multifrequency Bioelectrical Impedance Analyzer (BIA) specifically designed for bedridden and hemodialysis patients. Measurements were performed in a

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supine position, with electrodes placed on the patient's hands and feet, following standard BIA measurement procedures. A higher PhA value indicates better cell integrity and function. Conversely, a lower value indicates cell membrane damage, inflammation, or malnutrition. Normal PhA values vary depending on age, gender, and clinical status. Generally, healthy adults have a PhA of 5° - 8°, while elderly individuals have a PhA of 4° - 6°. In dialysis patients, a PhA of < 5° indicates malnutrition. In a clinical context, PhA value < 4° is often considered a high-risk indicator of malnutrition, inflammation, and reduced quality of life, including mortality, especially in chronic patients such as those on hemodialysis, cancer, or in the intensive care unit (ICU).

2. The level of malnutrition is assessed using the Dialysis Malnutrition Score (DMS), which consists of seven assessment components (weight loss, food intake, gastrointestinal symptoms, functional capacity, assessment of fat and muscle tissue status, and subjective evaluation). Scores range from 7 to 35; the higher the score, the worse the nutritional status. The Dialysis Malnutrition Score (DMS) has a sensitivity of 94% and a specificity of 88% compared to the Subjective Global Assessment (SGA), which is currently the gold standard for general nutritional diagnosis. Research by Uy, Lim-Uy, and Chua (2018) demonstrated that the DMS is sensitive, practical, and simple in detecting malnutrition. This tool can be used rapidly in routine hospital assessments, making it useful for detecting malnutrition within minutes.[10] Validation of the Indonesia DMS questionnaire for Chronic Kidney Disease patients undergoing hemodialysis was conducted in the thesis of Edri Indah Yuliza Nur (2017) at Sebelas Maret University. The study concluded that the DMS is valid for detecting malnutrition in hemodialysis kidney failure patients in Indonesia.[11]
3. TNF-alpha levels were measured using venous blood samples (5 mL) collected from participants before a hemodialysis session, after an overnight fast of at least 8 hours. Serum TNF-α concentrations were measured using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) method, performed at the Prodia Clinical Laboratory, Indonesia, according to the manufacturer's protocol. Results were expressed in picograms per milliliter (pg/mL) and recorded for further statistical analysis. The normal value

of TNF-α in healthy subjects is 0.753 – 1.66 pg/mL.

Data were analyzed using SPSS 26 statistical software. Univariate analysis was used to describe respondent characteristics. Bivariate analysis was performed using the Pearson or Spearman correlation test, depending on the data distribution, to assess the relationship between PhA and DMS with TNF-α levels. The analysis can be continued with multiple linear regression to determine the simultaneous influence and contribution of each variable. This research has received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Diponegoro University, under No. 25/EC/KEPK/FK-UNDIP/I/2022.

Result

Table 1. Characteristics of Research Subjects

Characteristics of Research Subjects (n =50)	***Mean ± standart deviation; median (min-max)***	***p-value***
Age; years	52,38±4,54; 53,0 (45,0-60,0)	0,200*
Gender		
- Male	33 (66%)	
- Female	17 (34%)	
Hemodialysis Duration; month	29,04±10,42; 28,0 (12,0-50,0)	0,200*
IMT ; kg/m^2	22,80±2,56; 22,75 (18,5-28,3)	0,200*
DMS ; total score	10,56±1,87; 10,5 (7-14)	0,076*
SMM; kg	24,15±3,84; 24,0 (17,8-33,3)	0,099*
PhA, ^{0}	5,05±1,12; 4,95 (2,6-7,7)	0,200*
TNF – α ; pg/mL	3,03±0,99; 2,99 (1,41-5,88)	0,151*

Note :
*Kolmogorov-Smirnov data normality test

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The study was conducted on 50 routine hemodialysis patients at a hemodialysis clinic in Semarang. The majority of subjects were male (33 people) (66%), and 17 were female (34%). The average age of the study subjects was 52.38, with the youngest being 45 years old and the oldest being 60. The average duration of routine hemodialysis was 29.04 months, with the shortest being 12 months and the longest being 50 years. The average Body Mass Index (BMI) was 22.8 kg/m^2, with 6 subjects being overweight, 10 subjects being obese, and the remainder having normal nutritional status. Objective measurements using BIA revealed an average skeletal muscle mass (SMM) of 24.15 kg, with a low range of 17.8 kg and a high range of 33.3 kg. The average phase angel was 5.050, with a minimum value of 2.60 and a maximum of 7.70. Nutritional status measurements using the DMS yielded an average of 10.56 subjects, indicating good nutritional status. Blood measurements, which measured TNF-α levels as a marker of inflammation, yielded an average value of 3.03 pg/mL for all subjects, with the lowest level at 1,411 pg/mL and the highest at 5,883 pg/mL.

Table 2. Correlation Analysis of PhA and DMS Score on TNF-α levels

Variabel	r	p-value
PhA	-0,587	0,000**
DMS score	0,368	0,009**

Note : **Pearson Correlation Test

The correlation test showed that both variables were significantly related to TNF-α levels. PhA was significantly negatively correlated with a value of -0.587, indicating a strong correlation

Table 3. Results of Multiple Linear Regression Analysis

Table 3.1. Model Summary Table

Dependent Variable : TNF Alfa ; Variabel Independen: PhA, DMS

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.595	0.354	0.327	0.815

Coefficient of Determination ($R^2 = 0.354$)

The model explained 35.4% of the variation in TNF-α influenced by PhA and DMS. The remaining 64.6% was explained by other variables outside the model.

Table 3.2 ANOVA

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	17.110	2	8.555	12.879	0.000
Residual	31.220	47	0.664		
Total	48.330	49			

Model Significance Test (ANOVA: p = 0.000)

The simultaneous regression model was significant ($p < 0.05$), meaning that at least one of the independent variables significantly affected TNF-α

Table 3.3 Regression Coefficients

Variabel	B (Unstd)	Std. Error	Beta (Std)	t	Sig.	95% CI Lower	95% CI Upper	VIF
Konstanta	4.790	1.165	-	4.113	0.000	2.447	7.133	-
DMS	0.059	0.071	0.112	0.834	0.408	-0.083	0.202	1.301
PhA	-0.471	0.118	-0.533	-3.989	0.000	-0.708	-0.233	1.301

DMS: Not significant (p = 0.408), meaning changes in DMS scores had no significant effect on TNF-α levels.

PhA: Significant (p = 0.000), with a negative coefficient (-0.471). This means that every 1-unit increase in Phase Angle decreases TNF-α levels by 0.471 units, indicating a strong negative relationship.

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Discussion

This study aimed to analyze the relationship between phase angle and DMS scores and TNF-α levels in routine hemodialysis patients. Based on the results, the average age of the study subjects was 52.38 years, with an average hemodialysis duration of 29.04 months. The nutritional status of most respondents was within the normal range, but a proportion were overweight and obese.

Relationship of PhA to TNF-α

Correlation analysis showed that phase angle had a significant negative correlation with TNF-α levels ($r = -0.587$; $p = 0.000$). Regression results also supported this finding, where phase angle was a significant predictor with a regression coefficient of $\beta = -0.471$ ($p < 0.001$), meaning that each one-unit increase in phase angle was associated with a decrease in TNF-α levels of 0.471 pg/mL.

Phase angle is a bioimpedance parameter that indicates cell membrane integrity and intracellular hydration status. Higher values indicate healthier cell status and good membrane integrity. Recent studies have shown that phase angle negatively correlates with inflammatory biomarkers, including TNF-α and IL-6, especially in patients with advanced chronic kidney disease. [12,13] The findings of this study strengthen the evidence that phase angle can be used as a non-invasive indicator of chronic inflammatory status in dialysis patients.

Furthermore, the coefficient of determination ($R^2 = 0.354$) indicates that the combination of phase angle and DMS score explains approximately 35.4% of the variation in TNF-α levels. This implies that phase angle plays a significant role in influencing inflammatory status and has the potential to be a clinical screening tool in nephrology and nutrition clinics.

DMS Score and TNF-α Levels

DMS showed a significant positive correlation with TNF-α bivariately ($r = 0.368$; $p = 0.009$), but was not significant multivariately in a multiple linear regression model ($\beta = 0.059$; $p = 0.408$). This indicates that although DMS correlates with TNF-α, its role in predicting inflammatory cytokine levels becomes less dominant when controlled for with phase angle.

The DMS score assesses a patient's nutritional status through clinical parameters such as weight loss, gastrointestinal status, and physical examination. However, a limitation of the DMS lies in its inability to directly measure inflammation.[14,15] This may explain why its contribution to TNF-α variance is weaker than phase angle, which is quantitative and sensitive to changes in cell integrity.

Clinical Implications

These findings underscore the importance of phase angle as a simple yet informative clinical assessment tool for evaluating the risk of inflammation and malnutrition in hemodialysis patients. Integrating phase angle measurements into clinical nutrition management may aid in the early detection of chronic inflammation and more targeted nutritional interventions [14,16]

Conclusion and Recomendations

This study demonstrates a significant relationship between phase angle and TNF-α levels in patients on routine hemodialysis. Phase angle was shown to have a strong and statistically significant negative correlation with TNF-α levels, indicating that the better the patient's cell membrane integrity and cellular status, the lower the level of systemic inflammation (as indicated by TNF-α levels). Conversely, the DMS score, although positively correlated bivariately with TNF-α, did not show a significant effect in the multiple linear regression model, indicating its limitations in independently predicting inflammatory status.

Therefore, phase angle can be considered a potential indicator in monitoring the inflammatory and nutritional status of hemodialysis patients, given its non-invasive, sensitive nature, and ease of access through bioimpedance technology.

It is recommended to add other variables that also influence inflammatory status, such as IL-6, hsCRP, and oxidative status, to obtain a more comprehensive picture of inflammation. Studies with larger sample sizes and involving multiple hemodialysis centers would improve the external validity and generalizability of the results. Future research could stratify subjects based on nutritional status, dialysis duration, or the presence of comorbidities such as diabetes and hypertension, to determine whether the effect of phase angle on TNF-α is consistent across groups. Further studies should also evaluate the impact of nutritional interventions, anti-inflammatory supplements, or physical exercise on increasing phase angle and decreasing TNF-α.

Acknowledgment

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Competing Interest

The authors declare that there are no competing interests related to the study

List Of Abbreviations

HD : Hemodialysis
ESRD : end-stage renal disease
PEW : Protein Energy Wasting

MICS : malnutrition–inflammation complex syndrome
PhA : Phase Angle
BMI : Body Mass Index
DMS : Dialysis Malnutrition Score
BIA : Bio Impedance Analysis
CRP : C-Reactive Protein
TNF-α : Tumor Necrosis Factor alpha

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