Limitations of serum albumin level as a marker of nutritional status in hemodialysis patients

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ABSTRACT

Introduction: Albumin is widely used to evaluate nutritional status. However, its usage on patients with chronic kidney disease (CKD) remains controversial. This study was conducted to determine whether serum albumin levels can be used indicator of nutritional status in end-stage CKD patients undergoing routine hemodialysis.

Methods: This cross-sectional study included 535 subjects who underwent hemodialysis twice per week in 2017 from three hospitals in Jakarta, Indonesia. Data were collected from the medical records of the subjects and analysed using descriptive statistics and mean comparisons of independent samples.

Results: Based on body mass index as a marker of nutritional status, the majority (85.9%) of subjects were not underweight. Almost an equal proportion of underweight subjects had normal serum albumin (15.1%) compared with hypoalbuminemia (14.4%). Hypoalbuminemia was found in 29.7% and 28.6% of non-underweight and underweight subjects, respectively. Moreover, there was no significant difference in serum albumin levels between underweight and non-underweight patients (p = 0.886, Mann-Whitney test).

Conclusions: Our data do not support a role for serum albumin level as a marker for nutritional status in CKD patients.

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INTRODUCTION

Malnutrition is a potential health problem for both adult and pediatric patients. Malnutrition contributes to increased morbidity and mortality rates, particularly among those with chronic pathological conditions. Malnutrition is also associated with increased healthcare cost. A study involving 709 adult patients, conducted in Brazil, reported a significantly higher incidence of medical complications in regions with higher rates of malnutrition (27%) compared with those with a lower prevalence of malnutrition (17%). Moreover, the mortality rate (12.4%) was also higher in patients with malnutrition than in those with good nutritional status (4.7%).[1]

Low nutritional status or malnutrition are often observed in patients with chronic kidney disease, usually in the form of protein-energy wasting (PEW), a medical condition in which there is a low level of protein, or backup energy, within the body. The leading cause of PEW is decreased functional capacity due to metabolic stress or inadequate nutritional intake. During chronic kidney disease, various mechanisms can lead to PEW, including non-specific inflammatory processes, nutritional loss, metabolic acidosis, and due to the use of dialyser membranes. These conditions resulted in increased protein catabolic process via suppression of the insulin/insulin-like growth factor 1 (IGF-1) molecular pathway; and activation of the ubiquitin-proteasome system.[2,3]

Although the measurement of albumin is established as a method to evaluate the nutritional status of patients with malnutrition, the predictive and diagnostic values of serum albumin in patients with chronic kidney disease remain controversial. The reason was due to the limited number of studies and because of the contributions of multiple confounding factors towards serum protein concentration. The relatively long half-life of albumin in plasma and its characteristic as an acute-phase protein make its levels particularly susceptible to physiological and pathological processes, such as infection, medication, and processes that alter the hepatic metabolism, among others. This study aimed to evaluate the association of serum albumin level and nutritional status and to determine whether serum albumin level is a suitable nutritional marker in end-stage chronic kidney disease patients undergoing routine hemodialysis twice per week.

METHODS

The study design was cross-sectional. The inclusion criteria applied for this study were those patients on routine hemodialysis twice per week in the relevant medical facilities at the time of the investigation. Subjects were excluded if they died or stopped hemodialysis treatment during the period of data collection. The minimum sample size was calculated based on a previous study by Takahashi et al. (2012), which investigated the combination of

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serum albumin, C-reactive protein, and body mass index (BMI) as predictors of long-term mortality in patients undergoing hemodialysis.[4,5] The study includes 535 subjects attending three hospitals with hemodialysis units in Jakarta-Indonesia (Cipto Mangunkusumo Hospital, Koja District Hospital, and Cengkareng District Hospital). Demographic and dialysis-related data were collected from the medical records. BMI calculation was conducted according to Asian BMI classification. The albumin cut-off in this study is 3.5 g/dL. The data gathering was conducted after the study process had been explained, and the subjects had signed informed consent. Patients were also provided with assurance about data confidentiality and their right to withdraw their participation from the study.

Data analysis include descriptive statistics (frequency, mean, median, mode, standard deviation, chi-square test) and mean comparisons by independent T-test or Mann-Whitney test (non-parametric data). Kolmogorov-Smirnov method used to define the normality of the data and Levene test used to asses homogeneity of variance. Results were considered statistically significant if p-values were < 0.05. Statistical analysis was performed with SPSS version 21.

All ethical issues had been reviewed according to the latest version of the Declaration of Helsinki. Ethical clearance was obtained from the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia (Number of Letter: 0612/UN2.F1/ETIK/2018).

RESULTS

In total, 535 samples were obtained from the medical facilities. However, based on the removal of specific samples due to incompleteness of the medical records, and data availability, there were some differences between the numbers of samples analysed for each variable in this study. Due to insufficient completeness of medical records, only 254 of 535 samples had serum albumin data.

As detailed in table 1, the subjects in this study were recruited evenly from the three medical facilities. The overall subject who underwent hemodialysis in this study were non-underweight (86%) and were mostly within the normal range of BMI (49.2%).

Demographic and dialysis-related data were presented in table 2. There were more male (303, 56.6%) than female (232, 43.4%) patients. Additionally, among the 80 underweight patients, most were male (51, 63.8%), while 29 (36.2%) were female. Similarly, of 455 non-underweight patients, 252 (55.4%) were male and 203 (44.6%) were female. Complete date of birth information was available for 454 patients who underwent hemodialysis in Cipto Mangunkusumo, Koja District, and Cengkareng District Hospitals in 2017. Most patients were aged between 31 and 60 years (333, 73.3%). Among 69 underweight patients, most were aged between 31 and 60 years old (43; 62.3%), as were the majority of non-underweight patients (290; 75.3%). Furthermore, among 80 underweight patients, 29 (36.3%) underwent dialysis with reusable membranes and 51 (63.7%) with single-use membranes. Similarly, among the non-underweight group (n = 453), 176 (38.9%) were dialysed with reusable membranes and 277 (61.1%) with single-use membranes. The mean (sd) BMI value for patients included in this study was 20.74 (7.83) kg/m²; the median (range) was 22.3 (13.2–38.47) kg/m²; and the mode was 22.46 kg/m². After classification based on the BMI category as underweight and non-underweight, the mean BMI for each group were 16.78 and 23.94, respectively. Among 254 patients with complete information, the mean (standard deviation), median (range), and mode serum albumin levels were 3.95 (1.97), 3.96 (1.2–8.89), and 3.8 g/dL, respectively. As detailed in Table 2, most patients (181 patients; 71.3%) had normal albumin levels, while the remaining 73 patients (28.7%) had hypoalbuminemia. Additionally, of the 37 underweight patients, only 11 (29.7%) had hypoalbuminemia and the

Table 1 Nutritional Status of Patients Based on Body Mass Index Classification

Body Mass Index	Cipto Mangunkusumo National Referral Hospital, N (%)	Koja District Hospital, N (%)	Cengkareng District Hospital, N (%)	Total (%)
Underweight	29 (14.1)	20 (12.5)	31 (18.34)	80 (17.6)
Non-underweight	177 (85.9)	140 (87.5)	138 (83.1)	455 (85)
Normal	116 (56.3)	87 (62.1)	60 (36.1)	263 (57.8)
Overweight	42 (20.4)	27 (19.3)	34 (20.5)	98 (21.5)
Obese	19 (9.2)	26 (18.6)	44 (26.5)	94 (20.7)
Total	206 (38.5)	160 (30)	169 (100)	535 (31)

The calculated percentage is column percentage.

Table 2   Characteristics of the study population who underwent hemodialysis in 2017

Variable	Total [n (%)]	Underweight [n (%)]	Non-underweight [n (%)]
Sex			
Male	303 (56.6)	51 (63.8)	252 (55.4)
Female	232 (43.4)	29 (36.2)	203 (44.6)
Age (years, n = 454)			
< 19	4 (0.8)	2 (2.9)	2 (0.5)
19–30	26 (5.7)	8 (11.6)	18 (4.7)
31–60	333 (73.3)	43 (62.3)	290 (75.3)
> 60	91 (20.2)	16 (23.2)	75 (19.5)
Types of dialysis membrane			
Reusable	205 (38.5)	29 (36.3)	176 (38.9)
Non-reusable	328 (61.5)	51 (63.7)	277 (61.1)
Vascular access			
Arteriovenous fistula (Cimino)	269 (72.3)	42 (73.7)	227 (72.1)
Tunnel catheter	57 (15.3)	8 (14)	49 (15.6)
Femoral	36 (9.7)	7 (12.3)	29 (9.2)
Double lumen catheter	10 (2.7)	0 (0)	10 (3.2)
Status of Infection			
Infection	312 (71.2)	48 (75)	264 (70.6)
No infection	126 (28.8)	16 (25)	110 (29.4)
Albumin levels (n=254)			
Hypoalbuminemia	73 (28.7)	11 (29.7)	62 (28.6)
Normal	181 (71.3)	26 (70.3)	155 (71.4)
Mean Albumin, g/dL (SD)	3.95 (1.97)	4.04	3.81

The calculated percentage is column percentage.

Table 3   Serum Albumin Levels of The Study Population According to Type of Dialyzer Membrane and Infection Status

Characteristic	Hypoalbuminemia N (%)	Normal Albumin Level N (%)
Dialyser Membrane		
Single-use	47 (21.8%)	169 (78.2%)
Reusable	36 (67.9%)	17 (32.1%)
Infection Status		
No infection	41 (32.5%)	83 (67.5%)
Infection	18 (22.2%)	63 (77.8%)

The calculated percentage is row percentage

remaining 26 (70.3%) had normal serum albumin levels. Meanwhile, among the 217 non-underweight patients, 62 (28.6%) had hypoalbuminemia and 155 (71.4%) had normal albumin levels.

The characteristics of the study population with serum albumin data, in terms of the type of dialyser membrane used and the presence of infection, were also analysed (Table 3). In total, there were 216 samples from patients who underwent dialysis with single-use membranes and 53 from those using reusable membranes. Most subjects using single-use dialyser membrane had normal serum albumin levels (78.2%), with low levels of serum albumin in only 21.8% of these subjects. In contrast, 67.9% of samples from patients using reusable dialyser membranes had low serum albumin levels. Based on infection status, 77.8% and 67.5% of subjects with or without infections, respectively, had normal albumin levels.

Table 4 Chi-square test for an association between subject serum albumin levels and Nutritional Status

| | BMI Classification | | | | | |
| | Underweight | | Not underweight | | Total | |
Serum albumin level	n	%	n	%	n	p-value
Hypoalbuminemia	11	29.7	62	28.6	73	0.847
Normal	26	70.3	155	71.4	181	
Total*	37	14.6	217	85.4	254	

*the percentage calculated was row percentage, other percentages were column percentage

Table 5 Association between serum albumin level and nutritional status of patients who underwent hemodialysis at Cipto Mangunkusumo, Koja District, and Cengkareng District Hospitals in 2017

Variable	p-value	Mean Rank Underweight	Mean Rank Non-Underweight
Albumin as Nutritional status	0.886	37 (Mean rank: 126.24)	217 (Mean rank: 127.71)

Next, we tested whether there was an association between BMI classification and serum albumin levels in study subjects, and the result was non-significant (p = 0.847; chi-square test) (Table 4).

Mann-Whitney Test was performed since the data was not normally distributed (Kolmogorov-Smirnov, p>0,05). We also found no significant difference (p-value > 0.05; Mann-Whitney test) between the mean rank of underweight patients (126.24) and that of non-underweight patients (127.71). Therefore, we conclude that there was no significant difference in serum albumin levels between underweight and non-underweight patients who underwent hemodialysis twice per week in this study (Table 5).

DISCUSSION

The use of serum albumin levels as a marker to assess nutritional status, especially in patients undergoing hemodialysis, remains controversial. The advantages of serum albumin levels as a diagnostic tool for malnutrition are that they are simple and affordable to measure and that the results are highly reproducible. Serum albumin levels also respond consistently to follow-up intervention after their measurement, and levels remain stable following surgery. In contrast, the disadvantages of serum albumin level measurement include the existence of numerous factors that can influence albumin levels in the serum, specifically inflammatory responses, infection status, hepatic abnormalities, medication, sepsis, and history of previous trauma (e.g., burn injuries).[6]

The published evidence indicates a lack of data supporting the use of serum albumin levels for diagnostic and evaluation of malnutrition in subjects either with or without specific pathological conditions. For example, a meta-analysis of 63 studies of the effects of starvation on healthy subjects, involving a total of 2125 patients, showed that serum albumin levels remain normal in most subjects with an extreme history of starvation (mean BMI <12 kg/m^2 or duration of starvation > 6 weeks) and clinical manifestations of malnutrition.[7] Another case-control study comparing 14 subjects with anorexia nervosa with 15 healthy subjects showed that there was no significant variation between the serum albumin levels in the two groups after one year of follow-up, indicating a lack of diagnostic utility of serum albumin level as an indicator for malnutrition.[8]

There have been few reports of assessment of the value of serum albumin levels as a nutritional marker in patients with end-stage chronic kidney disease undergoing routine hemodialysis. Plasma protein concentration can be affected by several factors, including the rate of protein synthesis, fractional catabolic rate (FCR), the volume of distribution, or loss of proteins due to external factors. Under conditions of protein restriction, decreased FCR is a homeostatic response to decreased serum albumin concentrations. In contrast, in patients undergoing routine hemodialysis, this homeostatic response does not occur because of the multiple inflammatory responses commonly observed in patients with end-stage renal failure (particularly those with known source of infection).[9] In another observational study of patients undergoing routine hemodialysis, conducted by Kaysen et al., low serum albumin levels were significantly associated with systemic inflammation but did not exhibit any significant relationship with inadequate nutritional status.[10]

The results of this study also demonstrate no significant correlation between serum albumin

levels and nutritional status (p-value = 0.886), indicating that serum albumin levels cannot be used as a useful diagnostic tool to determine malnutrition in patients with end-stage chronic kidney disease who undergo routine hemodialysis twice per week. Incomplete availability of serum albumin data may have contributed to these findings. It is due to serum albumin level and the patient's height are not routinely measured in Indonesian hemodialysis units. The low number of underweight patients may have also influenced the abnormal data distribution at Cipto Mangunkusumo, Koja District, and Cengkareng District Hospitals (Table 1).

In the past, low serum albumin levels have been considered as a potential indicator of low nutritional status. However, our results do not support this hypothesis. Instead, in this study, hypoalbuminemia was more common among non-underweight subjects (29.7%) than underweight subjects (28.6%). This study has several limitations, including the use of different types of dialyser membranes, which may be a confounding factor. The use of semi-permeable membranes to clear solutes through diffusion and ultrafiltration processes are affected by the type of membrane used: low-flux (membranes with lower water permeability) and high-flux (membranes with higher water permeability). The use of high-flux membranes is more effective for the removal of molecules of moderate to large sizes (10000–15000 Daltons), such as inflammatory proteins and lipoproteins.[11] Hence, it could be argued that the results may be confounded by the type of membranes used in the hemodialysis process. We found that hypoalbuminemia was more common in subjects undergoing dialysis with single-use membranes compared to those using reusable membranes (Table 3). However, similar results were also found in subjects with normal albumin levels, thus suggesting that these findings may be insignificant. These findings may be attributable to the higher proportion of single-use membrane users in the study population or the higher number of total serum albumin level data points for subjects undergoing dialysis with single-use membranes. Another potential confounding factor was the infection status. However, the conclusion about the association between serum albumin levels cannot be drawn out since the number of subjects who did not have any infection and with normal serum albumin level is also higher compared to the number of subjects with the presence of infection and hypoalbuminemia (Table 3).

The primary limitation of this study is the incompleteness of the data, particularly the serum albumin levels. Although data were collected in three medical centres (one of which is a national teaching and top referral hospital in Indonesia), the amount of data was insufficient, due to lack of routine measurement of serum albumin levels in patients undergoing regular hemodialysis.

CONCLUSION

Despite the presence of multiple confounding factors, which could theoretically affect levels of serum albumin, this study support showed that serum albumin levels are not significantly associated with nutritional status (based on BMI classification) in patients with end-stage chronic kidney disease undergoing routine hemodialysis. Further studies to confirm these results may include cohort studies, with subjects specifically chosen to undergo routine examinations with 1 year of follow-up during their routine hemodialysis processes, to ensure the collection of sufficient data. We also recommend comparisons of the use of albumin as a nutritional marker in end-stage chronic kidney disease patients undergoing routine hemodialysis with use of other nutritional laboratory markers, such as pre-albumin, transferrin, or retinol-binding protein, to identify other more effective nutritional markers.

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CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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