ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211348

Serum Prealbumin: a potential predictor of Right Ventricular Dysfunction in patients receiving programmed hemodialysis

Murat Gok[1*], Alparslan Kurtul[2], Gökay Taylan[1], Emel Işıktaş Sayılar[3], Kenan Yalta[1]

SUMMARY

OBJECTIVE: Prealbumin has been a reliable marker to predict protein energy malnutrition and hypercatabolic state. In this analysis, we particularly aimed to investigate the potential association between serum prealbumin levels and right ventricular dysfunction in patients receiving programmed hemodialysis.

METHODS: A total of 57 subjects were included in the analysis. The subjects were then categorized into two groups: right ventricular dysfunction (n=18) and non-right ventricular dysfunction (n=39) groups. In all patients, detailed transthoracic echocardiography (following hemodialysis) were performed along with the evaluation of complete blood count, routine biochemistry parameters, and, in particular, serum prealbumin levels.

RESULTS: Mortality rate at 3 years was found to be significantly higher in the right ventricular dysfunction group (p=0.042). Serum prealbumin levels were also significantly lower in the right ventricular dysfunction group compared with the non-right ventricular dysfunction group (23.83±8.50 mg/dL versus 31.38±6.81 mg/dL, p=0.001). In the receiver operating characteristics curve analysis, a prealbumin cutoff value of <28.5 mg/dL was found to predict right ventricular dysfunction, with a sensitivity of 67% and a specificity of 62% (area under the curve: 0.744). In the correlation analysis, a moderate yet significant positive correlation was demonstrated between serum prealbumin and tricuspid annular plane systolic excursion (r=0.365, p=0.005).

CONCLUSION: This study suggests that low serum prealbumin might serve as a potential predictor of right ventricular dysfunction (and its clinical consequences) in patients receiving programmed hemodialysis.

KEYWORDS: Hemodialysis. Malnutrition. Prealbumin. Mortality. Right ventricular dysfunctions.

INTRODUCTION

Chronic renal failure (CRF) is generally regarded as a progressive loss of nephron mass in an irreversible manner[1] and might potentially result in end-stage renal failure (ESRF) after a certain period. In contrast, ESRF inevitably necessitates life-saving renal replacement therapies, including renal transplantation, peritoneal dialysis, and hemodialysis (HD)[1]. In particular, malnutrition is commonly encountered in patients receiving programmed HD (mild-to-moderate and severe malnutrition in 33% and 6–8% of patients, respectively)[2]. Malnutrition has also been a common problem in heart failure (HF) and has a strong link with unfavorable outcomes[3]. Moreover, malnutrition in patients with CRF might lead to a variety of cardiovascular complications that are held responsible for increased morbidity and mortality[4]. To date, left ventricular (LV) functions have been the focus of interest in patients with CRF. However, implications of right ventricular dysfunction (RVD) remains to be further established in these patients[5]. Interestingly, HD might significantly increase the risk of RVD largely due to the hemodynamic impact of brachial arteriovenous fistula that leads to a state of left-to-right shunt with consequent increases in cardiac preload[6].

Clinically, there have been many methods to evaluate malnutrition in HD patients. In this setting, assessment of weight loss, anorexia, vomiting, body mass index, upper arm muscle circumference, and handgrip strength might aid in the gross evaluation of malnutrition in these patients. Moreover, certain biochemical parameters including albumin, prealbumin, transferrin, and insulin-like growth factor might more objectively predict an existing malnutrition[7]. Specifically, prealbumin has been regarded as a marker of nutritional and inflammatory status, and accordingly, low serum levels of this marker might be associated with unfavorable outcomes in the setting of HF[7]. Importantly, RVD has been recently suggested as a predictor of cardiovascular death, both in the settings of HF and programmed HD[8].However, the association of prealbumin with

[1]Trakya Üniversitesi, Cardiology Department – Edirne, Turquia.
[2]Hatay Mustafa Kemal Üniversitesi, Cardiology Department – Antakya, Turquia.
[3]Ufuk Üniversitesi, Dr. Rıdvan Ege Hastanesi, Nephrology Department – Çankaya/Ankara, Turquia.
*Corresponding author: drmuratg@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on January 11, 2022. Accepted on March 05, 2022.

RVD in the setting of CRF remains to be elucidated. In this study, we aimed to focus on the potential link between serum prealbumin and RVD in patients receiving programmed HD.

METHODS

The study comprised a total of 57 patients who were categorized into two groups: patients with RVD (RVD group) and those without RVD (non-RVD group). RVD and non-RVD groups were composed of 18 and 39 patients, respectively. Particular inclusion criteria were as follows: the need for a programmed HD, being at the age of >18 years, having a history of programmed HD in a dialysis center three times a week for at least 3 months, and having no active infection, malignancy, or left HF. In contrast, patients with secondary causes of RVD (including chronic obstructive pulmonary disease, morbid obesity, pulmonary hypertension [primary and secondary forms], and pulmonary thromboembolism) were excluded from the study. The subjects were under regular clinical follow-up on an annual basis. Annual clinical, laboratory (e.g., prealbumin and C-reactive protein [CRP]), and transthoracic echocardiographic (TTE) examinations were regularly filled in follow-up forms. Thereafter, the results were statistically analyzed. In particular, the potential relationship between RVD and serum prealbumin levels was investigated in these patients. The study protocol conformed to the Declaration of Helsinki and was endorsed by the local Ethics Committee. The committee waived the informed consent due to the retrospective nature of the study.

In all patients, TTE and Doppler echocardiographic examination were performed with a 3.5-MHz transducer. Calculation of left ventricular ejection fraction (LVEF) was performed on apical two- and four-chamber views using the modified Simpson's method. Evaluation of RV functions was performed based on tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and E/E′. RVD was defined as a TAPSE value of ≤15 mm[9]. Patients with severe tricuspid regurgitation were also excluded as the evaluation of RV systolic functions by TAPSE method might not be proper in the setting of severe tricuspid regurgitation.

Statistical analysis

All statistical analyses were done by using SPSS software (IBM SPSS Statistics for Windows, version 21.0; Armonk, NY, USA). Continuous variables with a normal distribution were expressed as mean±standard deviation, and variables with non-normal distribution were expressed as median (interquartile range). Categorical variables were presented as number (percentage). Statistical analysis between the two groups involved Student's t-test for normal data and Mann-Whitney U test for non-normal data. Categorical variables were compared by chi-square test. Pearson's correlation was used for analyzing correlation between serum prealbumin and TAPSE. Receiver operating characteristic (ROC) curve was utilized to evaluate the cutoff value for serum prealbumin in predicting RVD. A p-value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of both groups are presented in Table 1. There were no significant diversities between the two groups in terms of age; gender; duration of HD; body mass index; serum levels of phosphate, aluminum, magnesium, uric acid, albumin, creatinine, and lipid parameters;

Table 1. Comparison of the two groups with regard to baseline clinical and laboratory data.

Variable	Right ventricular dysfunction		p-value
	No (n=39)	Yes (n=18)	
Age (years)	59.7±13.1	64.4±15.2	0.240
Male gender, n (%)	23 (59.0)	9 (50.0)	0.526
Duration of hemodialysis (year)	5 (2-8)	6 (3–9)	0.356
Hypertension, n (%)	22 (56.4)	9 (50.0)	0.625
Diabetes mellitus, n (%)	15 (38.4)	7 (38.8)	0.972
Active smoking, n (%)	16 (41.0)	9 (50.0)	0.728
BMI (kg/m^2)	23.9±2.9	25.1±7.9	0.469
Serum albumin (mg/dL)	3.80±0.41	3.77±0.38	0.810
Serum creatinine (mg/dL)	7.44±1.50	6.97±2.56	0.437
Total cholesterol (mg/dL)	166±34	165±20	0.898
LDL cholesterol (mg/dL)	103±27	100±18	0.692
HDL cholesterol (mg/dL)	34±11	40±11	0.100
Triglyceride (mg/dL)	176±96	158±78	0.549
Serum prealbumin (mg/dL)	31.38±6.81	23.83±8.50	0.001
Serum uric acid (mg/dL)	5.33±0.76	5.51±0.95	0.495
Serum aluminum (mg/dL)	15.6±9.7	15.2±7.2	0.882
Serum magnesium (mg/dL)	2.23±0.27	2.14±0.29	0.327
Serum phosphate (mg/dL)	5.11±1.33	4.85±1.26	0.216
Serum CRP (mg/dL)	0.80 (0.40–1.60)	1.45 (0.95–3.30)	0.023
Mortality for 3 years follow-up, n (%)	3 (7.7)	5 (27.8)	0.042

BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CRP: C-reactive protein.

and histories of diabetes, hypertension, and active smoking. Serum CRP levels appeared to be higher in the RVD group compared with the non-RVD group (p=0.023). Moreover, mortality at 3 years was also significantly higher in the RVD group (p=0.042). In particular, serum prealbumin levels appeared to be lower in the RVD compared with the non-RVD group (23.83±8.50 mg/dL versus. 31.38±6.81 mg/dL, p=0.001) (Figure 1).

Echocardiographic parameters including pulmonary artery systolic pressure (PASP), TAPSE, E/E′ ratio, and FAC values also significantly differed between the groups. RVD group had higher values of PASP and E/E′ ratio (p=0.001 and 0.034, respectively) along with lower values of TAPSE and FAC (p<0.001 for both) (Table 2). In the ROC curve analysis, a prealbumin cutoff value of <28.5 mg/dL was found to predict RVD with a sensitivity of 67% and a specificity of 62% (area under the curve: 0.744) (Figure 2).

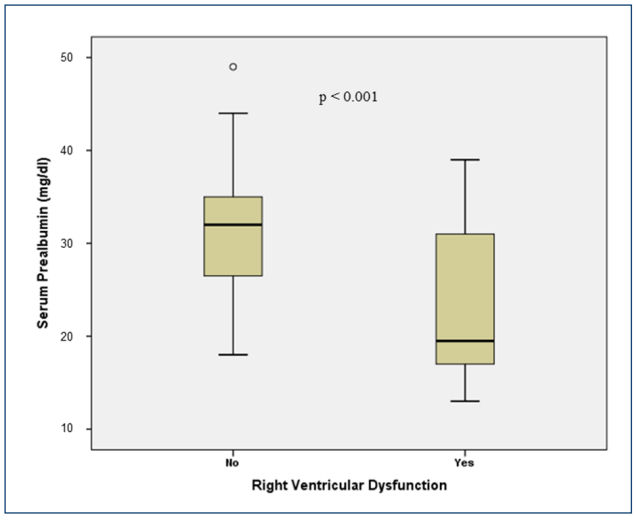

Figure 1. Comparison of serum prealbumin levels between the two groups.

Table 2. Comparison of the two groups with regard to baseline echocardiographic parameters.

	Right ventricular dysfunction		p-value
	N (n=39)	Yes (n=18)	
LVEF (%)	60±5	58±9	0.138
Right ventricular function parameters			
TAPSE	21.3±4.2	12.8±1.9	<0.001
Fractional area change (%)	44.1±6.3	33.4±8.6	<0.001
Left atrial volume (mL)	145±56	130±44	0.358
E/E′ ratio	16±6	22±7	0.034
PASP (mmHg)	30.9±4.9	37.7±9.2	0.001

LVEF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion.

The correlation analysis exhibited a moderate positive correlation between serum prealbumin and TAPSE values (r=0.365, p=0.005) (Figure 3).

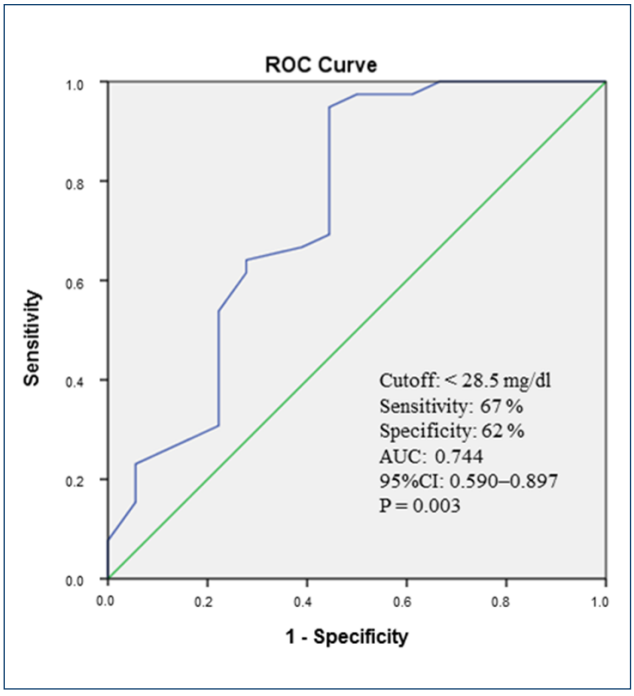

Figure 2. Receiver operating characteristics curve analysis of prealbumin in the prediction of right ventricular dysfunction.

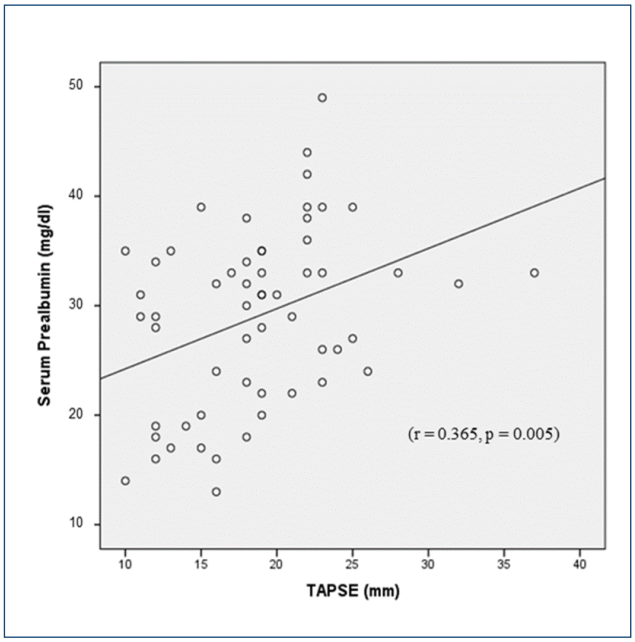

Figure 3. Pearson's correlation analysis between serum prealbumin and tricuspid annular plane systolic excursion.

DISCUSSION

In the present analysis, we have demonstrated a significant association between low serum prealbumin levels (a marker of malnutrition) and RVD (a predictor of low quality of life with consequent mortality) in a population of HD patients.

To date, two major types of malnutrition have been described in patients with CRF. The first type is characterized by low serum albumin levels possibly attributable to the reduced intake of energy and protein as a consequence of uremic toxicity. The second type generally presents with low prealbumin levels due to protein catabolism, increased resting energy expenditure, and significant increments in oxidative stress and pro-inflammatory cytokine levels (e.g., CRP)[10]. In HD patients, these two types are typically observed in combination[11]. Of note, emerging hyperinflammatory state generally marks the initiation of complications in HD patients. This hyperinflammation is largely attributable to the associated uremia that elicits a significant imbalance between pro-inflammatory and anti-inflammatory milieu largely through induction of pro-inflammatory cytokine production[12]. Accordingly, CRP levels are well known to be high in these patients, potentially leading to an increased cardiovascular mortality as well[13]. Specifically, we were able to demonstrate even higher levels of serum CRP in HD patients with RVD. Importantly, this suggests that an existing RVD might have important implications in the generation of a more substantial inflammatory response in HD patients. However, the issue of whether RVD serves as the cause or consequence (or both) of hyperinflammation still needs to be established in this context.

In contrast, cardiac cachexia is well known to be associated with malnutrition and systemic inflammation in patients with HF[14]. Furthermore, cytokines including interleukin-6 might not only alter intestinal permeability and elicit cardiac cachexia but also have an important pathogenetic role in the genesis and perpetuation of HF[14]. In the specific context of RVD, PASP and endothelial dysfunction were previously suggested to be associated with RVD[15,16]. More specifically, RVD has gained a significant reputation as a predictor of cardiovascular mortality both in the settings of HF and HD[8]. As previously mentioned, lower levels of prealbumin (a marker of nutritional and inflammatory status) appear to have a strong link with unfavorable outcomes in the setting of HF[7]. Prealbumin has also been shown to be associated with nutrition and inflammation in HD patients[17]. Notably, prevalence of RVD is significantly higher in HD patients and is regarded as the fundamental cause of mortality in patients with ESRF[18]. In this study, we have uncovered the potential link between low prealbumin levels (that indirectly denotes malnutrition) and RVD in HD patients. Furthermore, rate of mortality appeared to be substantially higher in patients with RVD at 3 years. This increased mortality might not only be due to the direct consequences of right HF (e.g., arrhythmogenesis and progressive hypoperfusion) but also be strongly associated with the underlying hyperinflammatory state. In this context, systemic inflammation is well known to be associated with a variety of cardiovascular events, including induction of acute coronary syndromes and malignant arrhythmogenesis[19]. In this setting, evaluation of serum prealbumin may potentially help predict an existing RVD and its clinical consequences in HD patients. This might also enable to implement patient-specific management strategies in an effort to improve overall prognosis.

Study limitations

The relatively small cohort of patients possibly arises as the most significant limitation. The utility of afterload-dependent parameters including TAPSE might be regarded as another limitation. However, this challenge was partially mitigated through acquisition of calculations right after HD. Moreover, the mean TAPSE values were calculated by two cardiologists to enhance the objectivity of method. More importantly, the diagnostic power of prealbumin for the prediction of RVD was only moderate. However, it might possibly have a higher predictive value in larger cohorts. Finally, we were not able to evaluate other inflammation markers that might also have important implications in this setting.

CONCLUSIONS

In patients receiving programmed HD, prealbumin (an indirect indicator of malnutrition) may potentially predict an existing RVD that might be associated with unfavorable outcomes. Therefore, serum prealbumin, as an important prognostic marker, may be evaluated at regular intervals in these patients.

ACKNOWLEDGMENT

The authors received no financial support for the research, authorship, and/or publication of this article.

AUTHORS' CONTRIBUTIONS

MG: Data curation, Methodology, Writing – original draft, Writing – review & editing. **AK:** Data curation, Methodology, Writing – review & editing. **GT:** Data curation, Methodology **EIS:** Data curation, Software, Validation, Writing – original draft. **KY:** Data curation, Writing – original draft, Writing – review & editing.

REFERENCES

1. Nahas M. Progression of Chronic Renal Failure. In: Floege J, Johnson RJ, Feehally J, editors. Comprehensive Clinical Nephrology. Missouri: Mosby; 2000. p. 67.1. https://doi.org/10.1016/C2009-0-46539-5
2. Kopple JD. Effect of nutrition on morbidity and mortality in maintenance dialysis patients. Am J Kidney Dis. 1994;24(6):1002-9. https://doi.org/10.1016/s0272-6386(12)81075-4
3. Iwakami N, Nagai T, Furukawa TA, Sugano Y, Honda S, Okada A, et al. Prognostic value of malnutrition assessed by Controlling Nutritional Status score for long-term mortality in patients with acute heart failure. Int J Cardiol. 2017;230:529-36. https://doi.org/10.1016/j.ijcard.2016.12.064
4. Stenvinkel P. Inflammation in end-stage renal failure: could it be treated? Nephrol Dial Transplant. 2002;17(Suppl 8):33-8;discussion40. https://doi.org/10.1093/ndt/17.suppl_8.33
5. Koga S, Ikeda S, Matsunaga K, Naito T, Miyahara Y, Taura K, et al. Influence of hemodialysis on echocardiographic Doppler indices of the left ventricle: changes in parameters of systolic and diastolic function and Tei index. Clin Nephrol. 2003;59(3):180-5. https://doi.org/10.5414/cnp59180
6. Said K, Hassan M, Farouk M, Baligh E, Zayed B. Right ventricular function after creation of an atriovenous fistula in patients with end stage renal disease. Heart Lung Circ. 2019;28(6):884-92. https://doi.org/10.1016/j.hlc.2018.04.282
7. Rao P, Reddy GC, Kanagasabapathy AS. Malnutrition-inflammation-atherosclerosis syndrome in chronic kidney disease. Indian J Clin Biochem. 2008;23(3):209-17. https://doi.org/10.1007/s12291-008-0048-9
8. López-Quijano JM, Gordillo-Moscoso A, Viana-Rojas JA, Carrillo-Calvillo J, Mandeville PB, Chevaile-Ramos A. Clinical and echocardiographic factors associated with right ventricular systolic dysfunction in hemodialysis patients. Cardiorenal Med. 2016;6(3):230-6. https://doi.org/10.1159/000444129
9. Venner C, Selton-Suty C, Huttin O, Erpelding ML, Aliot E, Juillière Y. Right ventricular dysfunction in patients with idiopathic dilated cardiomyopathy: prognostic value and predictive factors. Arch Cardiovasc Dis. 2016;109(4):231-41. https://doi.org/10.1016/j.acvd.2015.10.006
10. O'keefe A, Daigle NW. A new approach to classifying malnutrition in the hemodialysis patient. J Ren Nutr. 2002;12(4):248-55. https://doi.org/10.1053/jren.2002.35322
11. Locatelli F, Fouque D, Heimburger O, Drüeke TB, Cannata-Andía JB, Hörl WH, et al. Nutritional status in dialysis patients: a European consensus. Nephrol Dial Transplant. 2002;17(4):563-72. https://doi.org/10.1093/ndt/17.4.563
12. Zyga S, Christopoulou G, Malliarou M. Malnutrition-inflammation-atherosclerosis syndrome in patients with end-stage renal disease. J Ren Care. 2011;37(1):12-5. https://doi.org/10.1111/j.1755-6686.2011.00201.x
13. Pawlaczyk K, Oko A, Lindholm B, Czekalski S. Malnutrition – inflammation – atherosclerosis (MIA syndrome) in patients with renal failure]. Pol Merkur Lekarski. 2003;15(88):334-41;discussion341-3. PMID: 14974361
14. Stenvinkel P, Heimbürger O, Lindholm B, Kaysen GA, Bergström J. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant. 2000;15(7):953-60. https://doi.org/10.1093/ndt/15.7.953
15. Santosh S, Chu C, Mwangi J, Narayan M, Mosman A, Nayak R, et al. Changes in pulmonary artery systolic pressure and right ventricular function in patients with end-stage renal disease on maintenance dialysis. Nephrology (Carlton). 2019;24(1):74-80. https://doi.org/10.1111/nep.13183
16. Dubin RF, Guajardo I, Ayer A, Mills C, Donovan C, Beussink L, et al. Associations of macro- and microvascular endothelial dysfunction with subclinical ventricular dysfunction in end-stage renal disease. Hypertension. 2016;68(4):913-20. https://doi.org/10.1161/HYPERTENSIONAHA.116.07489
17. Molfino A, Heymsfield SB, Zhu F, Kotanko P, Levin NW, Dwyer T, et al. Prealbumin is associated with visceral fat mass in patients receiving hemodialysis. J Ren Nutr. 2013;23(6):406-10. https://doi.org/10.1053/j.jrn.2013.02.007
18. Paneni F, Gregori M, Ciavarella GM, Sciarretta S, De Biase L, Marino L, et al. Right ventricular dysfunction in patients with end-stage renal disease. Am J Nephrol. 2010;32(5):432-8. https://doi.org/10.1159/000320755
19. Yalta T, Yalta K. Systemic Inflammation and Arrhythmogenesis: A Review of Mechanistic and Clinical Perspectives. Angiology. 2018;69(4):288-96. https://doi.org/10.1177/0003319717709380