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

Murat Gok1*, Alparslan Kurtul2, Gökay Taylan1, Emel Işıktaş Sayılar3, Kenan Yalta1

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 manner1 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 outcomes3. Moreover, malnutrition in patients with CRF might lead to a variety of cardiovascular complications that are held responsible for increased morbidity and mortality4. 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 patients5. 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 preload6.

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 malnutrition7. 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 HF7. Importantly, RVD has been recently suggested as a predictor of cardiovascular death, both in the settings of HF and programmed HD8. However, the association of prealbumin with

1Trakya Üniversitesi, Cardiology Department – Edirne, Turquia.
2Hatay Mustafa Kemal Üniversitesi, Cardiology Department – Antakya, Turquia.
3Ufuk Üniversitesi, Dr. Redvan 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 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; 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.

| 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/m²)                     | 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±8.81                   | 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 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).

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

**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±6                         | 37±9    | 0.001   |

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

---

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

**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). In HD patients, these two types are typically observed in combination. 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. Accordingly, CRP levels are well known to be high in these patients, potentially leading to an increased cardiovascular mortality as well. 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. 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. In the specific context of RVD, PASP and endothelial dysfunction were previously suggested to be associated with RVD. 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. Accordingly, CRP levels are well known to be high in these patients, potentially leading to an increased cardiovascular mortality as well. 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.

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. Ikawami 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;250:529-36. 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, Hassans 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-Quitijano JM, Gordillo-Moscoco 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/10.1159/0004444129

9. Venner C, Selton-Suty C, Hutin O, Erpelding ML, Aliot E, Juilfire 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/10.1016/S0959-6646(02)00322-2

11. Locatelli F, Fouque D, Heimbberger O, Druke TB, Cannata-Andia 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. Zygis M, 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.1755-6866.2011.00201.x

13. Pawlaczuk 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. Molfinno 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. Paneri F, Gregori M, Ciavarella GM, Scarfatti S, Di 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