J Renal Inj Prev. 2022; 11(3): e32031.

http://journalrip.com doi: 10.34172/jrip.2022.32031

Journal of Renal Injury Prevention

Is there any association between pentraxin-3, highly sensitive C-reactive protein and mannose-binding lectin with cardiovascular complications in hemodialysis patients?

Alireza Firouzjahi[1], Reyhaneh Ramezanzade[2], Simin Mouodi[3], Hossein Ghorbani[1], Karimollah Hajian Tilaki[4], Mehrdad Saravi[5], Roghayeh Akbari[6*]

[1]Department of Pathology, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran
[2]Department of Pathology, Faculty of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran
[3]Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
[4]Department of Epidemiology and Biostatistics, School of Public Health, Babol University of Medical Sciences, Babol, Iran
[5]Rouhani Hospital, Babol University of Medical Sciences, Babol, Iran
[6]Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

ARTICLE INFO

Article Type:
Original

Article History:
Received: 21 February 2022
Accepted: 19 May 2022
Published online: 31 May 2022

Keywords:
Kidney diseases
Hemodialysis
Cardiovascular diseases
Inflammatory factors

ABSTRACT

Introduction: The impact of cardiovascular disorders on morbidity and mortality of hemodialysis (HD) patients is considerable. Several markers have been investigated for renal disease and kidney transplantation.

Objectives: The aim of this study was to assess the correlation between three inflammatory biomarkers including pentraxin-3 (PTX-3), highly sensitive C-reactive protein (hs-CRP), and mannose-binding lectin (MBL) with cardiovascular disease (CVD) events and mortality in HD patients.

Patients and Methods: This longitudinal study was conducted on 18-80 years-old chronic kidney disease patients undergoing HD. The participants were followed every six months for 12 months and the occurrence of CVD events was determined with the calculation of left ventricular ejection fraction (LVEF) through echocardiography.

Results: Among 90 patients with a mean age of 54.0 ± 3.24 years, MBL and PTX-3 showed a significant correlation to detect CVD events (r=0.987; $P<0.001$). The mean PTX-3, MBL and hs-CRP levels were not significantly different among the three ejection fraction groups ($P>0.05$), since none of these markers reached statistical significance for the prediction of mortality ($P>0.05$). A significant correlation was found between PTX-3, MBL and hs-CRP, while all of these markers increased in patients with cardiovascular complications ($P<0.05$).

Conclusion: In our study, PTX-3, MBL and hs-CRP significantly increased in HD patients who had LVEF with decreasing value. The serum concentration of PTX-3 MBL and hs-CRP can be considered a diagnostic tool for early detection of CVD events in end-stage renal disease (ESRD) patients.

Implication for health policy/practice/research/medical education:
In a longitudinal study of a group of HD patients, we found a significant correlation between PTX-3, MBL and hs-CRP and all of these markers increased in patients with cardiovascular complications ($P<0.05$). The mean PTX-3, MBL and hs-CRP were not significantly different among the three ejection fraction groups ($P>0.05$) and none of these markers reached statistical significance for the prediction of mortality ($P>0.05$).

Please cite this paper as: Firouzjahi A, Ramezanzade R, Mouodi S, Ghorbani H, Hajian Tilaki K, Saravi M, Akbari R. Is there any association between pentraxin-3, highly sensitive C-reactive protein and mannose-binding lectin with cardiovascular complications in hemodialysis patients? J Renal Inj Prev. 2022; 11(3): e32031. doi: 10.34172/jrip.2022.32031.

***Corresponding author**: Roghayeh Akbari, Email: roghayeh.akbari@yahoo.com, r.akbari@mubabol.ac.ir

Original

Introduction

Choosing the best treatment approach for patients with end-stage renal disease (ESRD) on hemodialysis (HD) is an important issue and prevention and control of its comorbidities are common challenges in the management of these patients (1). Cardiovascular disease (CVD), as the main cause of mortality and morbidity in these patients (2-4), has been reported in more than 50% of HD patients. In addition, the mortality rate due to CVD in these patients may be up to 20 times higher than the general population (2). In recent years, the association between immune response and inflammatory process with cardiovascular events has been reported in ESRD patients (5,6). Pentraxin-3 (PTX-3), highly sensitive C-reactive protein (hs-CRP) and mannose-binding lectin (MBL) are the most common inflammatory biomarkers whose association with CVD and mortality in ESRD patients has been reported (4,7,8). C-reactive protein, as an acute-phase reactant, is primarily synthesized in the liver and plays an important role in the inflammatory process. It has several homologs and is a member of the pentraxin family (9). PTX-3, a long PTX, is expressed in most cell types in response to inflammatory cytokines. Increased level of PXT-3 has been reported in critically ill patients such as HD individuals (5,10,11). MBL is a genetically determined biomarker that can activate the complement immune system and has been shown to affect the endothelial function and the clinical course of CVD in ESRD patients (6,12-14).

Objectives

Considering different results in previous studies about the association between hs-CRP, PTX-3 and MBL in patients undergoing HD, this study was carried out to evaluate this association.

Patients and Methods

Study design

This longitudinal study was conducted on ESRD patients undergoing HD referring to the HD center affiliated with Babol university of medical sciences. Inclusion criteria were an age of 18-80 years, receiving HD for at least six months and written informed consent to participate in the study. Patients with a medical history of myocardial infarction, cerebrovascular accident or hospital admission one month ago, pulmonary embolism, pericarditis, severe pulmonary hypertension, surgery, malignancy or severe inflammatory disease, diabetic foot and receiving steroids or non-steroidal anti-inflammatory drugs and immunosuppressives were excluded. Furthermore, the patients who presented these conditions during the study have been excluded.

The sample size was determined based on the study power of 0.8, a 95% confidence interval and the effect size of the three examined biomarkers for the occurrence of cardiovascular events or death in the study population.

For each person, age, gender, blood pressure, smoking status, medications, previous history of urinary tract infections and angina pectoris were recorded. Recruited patients were examined at the baseline and every six months for 12 months. In each medical visit performed every six months, the patients underwent echocardiography and left ventricular ejection fraction (LVEF) as an indicator of cardiovascular complications was calculated. Ejection fraction value in the range of 50-55% was considered normal and lower values were classified as a low range. Based on LVEF results, the patients were categorized into three groups; low LVEF with a decreasing value, low LVEF with a constant value, and normal LVEF.

At the beginning of the study, a blood sample was obtained from the patients after 12 hours of fasting. hs-CRP was determined by immunoturbidimetric assay using Pars-Azmoon laboratory kits. PTX-3 and MBL were assessed by ELISA (enzyme-linked immunosorbent assay) by human PTX-3 and Human Mannose-Binding Lectin kits, respectively.

Statistical methods

SPSS software package version 16.0 was used for data analysis. Paired *t* test, Wilcoxon signed-rank test, Pearson's correlation coefficient and receiver operating characteristic (ROC) curve were employed for data analysis. To assess the normal distribution of variables, the Kolmogorov-Smirnov test was employed. *P* values less than 0.05 were considered to be statistically significant.

Results

Ninety patients between 19 to 86 years and a mean age of 54.0 ± 3.24 years including 51.1% male and 48.9% female were participated. The flow diagram of the participants is shown in Figure 1. At the baseline examination, 84 (93.3%) cases reported a previous history of hypertension; 39 (43.3%) diabetes mellitus; 34 (37.9%) hyperlipidemia and 20 (22.2%) of them were smoker.

The mean PTX-3, MBL and hs-CRP in three ejection fraction groups has been presented in Table 1. In the three groups of LVEF, the mean serum level of the biomarkers were not significantly different ($P > 0.05$).

The area under the ROC curves for diagnostic accuracy of these three biomarkers in the occurrence of cardiovascular complications has been presented in Table 2 and Figures 2 and 3. Data showed that all of the three biomarkers (PTX-3, MBL, and hs-CRP) had a significant area under the curve for precise differentiation and diagnosis between the patients with low LVEF with a decreasing value and normal LVEF patients ($P < 0.05$).

Pearson's correlation between PTX-3 and MBL (r=0.987; $P < 0.0001$) represented a significant correlation between these two biomarkers, while both of them increased in patients with cardiovascular complications. Moreover, significant correlations were found between PTX-3 and hs-CRP (r=0.250; $P = 0.017$) and MBL and hs-CRP

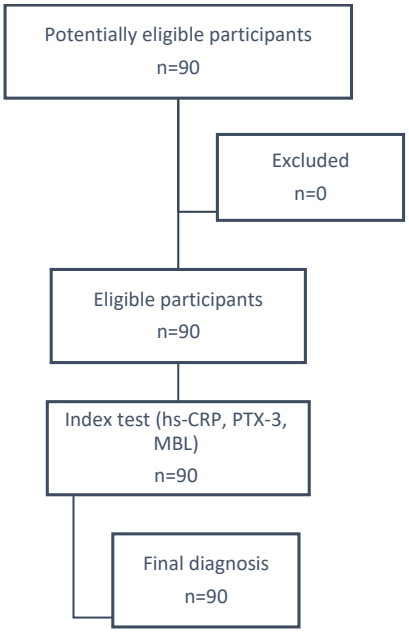

Figure 1. The flow of participants through the study.

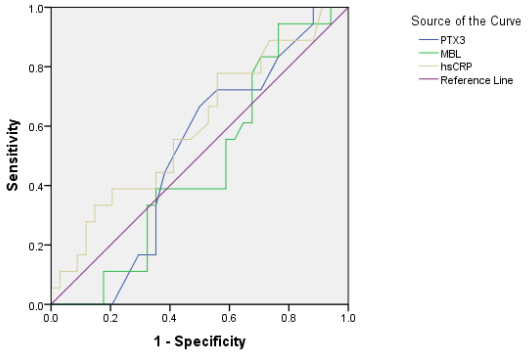

Figure 2. Diagnostic accuracy of PTX-3, MBL and hs-CRP in ESRD patients undergoing hemodialysis with low ejection fraction (with a decreasing value) compared with normal EF individuals.

(r=0.232; $P=0.028$).

The area under the ROC curves for diagnostic accuracy of these three biomarkers in mortality of the patients undergoing HD was presented in Figure 4. The results showed that PTX-3 with a sensitivity of 0.62 (95% CI: 0.45-0.79; $P=0.127$), MBL with a sensitivity of 0.65 (95% CI: 0.47-0.82; $P=0.066$) and hs-CRP with a sensitivity of 0.61 (95% CI: 0.46-0.76; $P=0.165$) had no significant accuracy for detection of mortality.

Discussion

Our study showed that PTX-3, hs-CRP, and MBL can be presented as useful biomarkers to determine CVD in patients undergoing HD; although, PTX-3 and MBL are suggested as better indicators for detection of severity and disease progression. None of the three biomarkers had significant accuracy for the prediction of mortality in these patients.

Honda et al, reported interleukin-6 (IL-6) level as the most reliable predictor of cardiovascular disease and mortality in patients with ESRD (4). EEl Sebai et al reported higher plasma PTX-3 levels in HD cases compared to ESRD patients without HD (5). Sjöberg et al, reported that higher PTX3 levels could predict incident chronic kidney disease in older adults (10). Patients with CVD had higher plasma PTX3 levels than those without CVD in the study by Xu et al, study. They also concluded that high plasma PTX3 level was positively and independently associated with CVD and the correlation between PTX3 and CVD was higher than hs-CRP in patients with hs-CRP >3 mg/L (11). Accordingly, Poppelaars et al represented MBL as a useful biomarker to predict cardiovascular events in HD

Table 1. PTX-3, MBL and hs-CRP in patients with ESRD undergoing hemodialysis divided into three groups of ejection fraction

Examined biomarker	Mean ± SD			*P* value
	Low EF with a decreasing value (n=38)	Low EF with a constant value (n=18)	Normal EF (n=34)	
PTX-3 (ng/mL)	12.2±2.5	3.7±0.1	8.1±2.7	0.10
MBL (ng/mL)	931.3±161.3	394.1±17.1	640.1±159.9	0.08
hs-CRP (mg/L)	25.0±3.9	19.6±5.4	14.1±3.1	0.12

EF, Ejection fraction; PTX-3, Pentraxin-3; MBL, Mannose-binding lectin; hs-CRP: Highly sensitive C-reactive protein

Table 2. Area under the ROC curves for PTX-3, MBL and hs-CRP in the occurrence of cardiovascular complications in ESRD patients undergoing hemodialysis, based on the comparison of each low EF group with normal EF patients

Comparison of each low EF group with normal EF patients	Examined Biomarker	The area under the ROC curve	95% CI	*P* value
Low EF with a decreasing value (n=38)	PTX-3 (ng/mL)	0.72	0.60-0.84	0.001
	MBL (ng/mL)	0.72	0.60-0.84	0.001
	hs-CRP (mg/L)	0.66	0.53-0.78	0.019
Low EF with a constant value (n=34)	PTX-3 (ng/mL)	0.50	0.35-0.66	0.91
	MBL (ng/mL)	0.46	0.30-0.62	0.70
	hs-CRP (mg/L)	0.59	0.43-0.76	0.25

EF, Ejection fraction; PTX-3, Pentraxin-3; MBL, Mannose-binding lectin; hs-CRP: Highly sensitive C-reactive protein

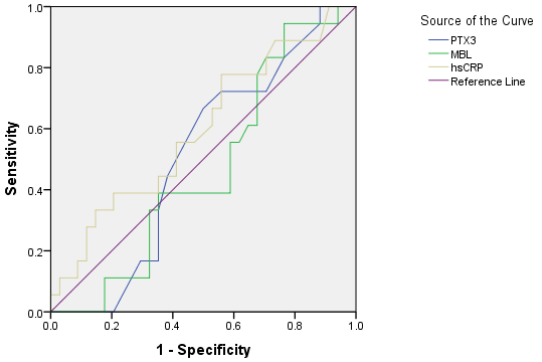

Figure 3. Diagnostic accuracy of PTX-3, MBL and hs-CRP in ESRD patients undergoing hemodialysis with low ejection fraction (with a constant value) compared with normal EF individuals.

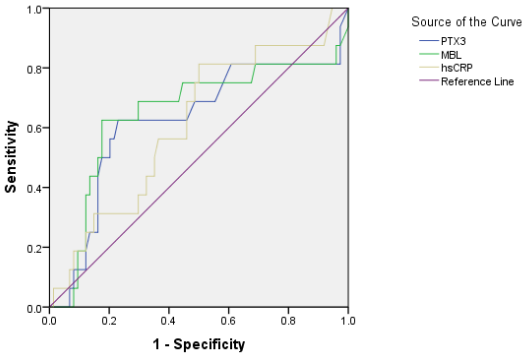

Figure 4. Diagnostic accuracy of PTX-3, MBL and hs-CRP in mortality of patients with ESRD undergoing hemodialysis compared to other HD patients.

patients and found that CVD was more prevalent in HD patients with low MBL level. They also found, low MBL level was independently associated with increased CVD. This study also showed no association between low MBL levels and mortality (6).

In this study, serum concentration of hs-CRP, PTX-3 and MBL indicated accurate differentiation between the patients with low-LVEF with a decreasing value and normal LVEF patients. These results may suggest that when LVEF is normal, the serum level of CRP is low. However, when LVEF decrease or has a decreasing value because of any damage in cardiac muscle, serum hs-CRP level increases. PTX-3 and MBL were only elevated in patients with decreasing values of LVEF. Cardiovascular events may occur and progress as a result of inflammation.

Several inflammatory markers have been assessed as potential candidates for the enhancement of cardiovascular risk evaluation (15). We found a significant correlation between PTX-3 and MBL. Both of them increased in patients with progressive cardiac disorders; however, the correlation between PTX-3 and hs-CRP and MBL with hs-CRP, although significant, was weaker. It might be related to the pathway of immune system response and several times for the elevation of these markers in human blood circulation. C-reactive protein is an acute-phase protein and its plasma level increases by acute phase stimuli. However, PTX-3 may not be detectable in the early stages of inflammation. This factor also increases several hours following inflammation (16). Turker et al assessed the serum level of hs-CRP and uric acid in 200 patients with moderate to severe mitral valve regurgitation and found a significant correlation between uric acid and LVEF. They also found higher serum level of uric acid correlated to more severe mitral regurgitation; whereas hs-CRP was not correlated with these parameters (17). Karakas et al concluded that PTX-3 was more tightly associated with the complexity and severity of CAD than hs-CRP and additionally reported it as an independent predictor for CAD (18). These results are similar to our study in which hs-CRP was not correlated with LVEF and was not a predictive factor for mortality. Moreover, Dubin et al evaluated 986 cases with stable coronary heart disease and concluded that each unit increase in log PTX-3 at baseline was associated with an 80% increased risk of mortality, a 50% increased risk of cardiovascular events (myocardial infarction, stroke, or CVD death) and an 80% higher risk of incident heart failure (19). The study by Poppelaars et al, showed that a low-MBL level is associated with a higher risk for future cardiovascular events and presented MBL as a useful indicator for the prediction of CVD in HD patients (6).

Conclusion

In our study PTX-3, MBL and hs-CRP showed a significant increase in HD patients who had low LVEF with decreasing value. We found no significant correlation between these biomarkers and patient mortality.

Limitations of the study

We had some limitations in this study. We did not estimate the glomerular filtration rate; in addition, long-term follow up of the patients were not performed. Repeated measurement of these biomarkers over a longer period can help accurate evaluation of their diagnostic value in predicting disease progression and mortality.

Acknowledgments

A part of this study was published in the congress abstract of the 17th International Congress of Nephrology, Dialysis, and Transplantation held in Tabriz, Iran, 2019 (http://www.ijkd.org/index.php/ijkd/article/download/5207/1101).

Authors' contribution

Conceptualization: RA and AF. Methodology: RA. Validation: RA and KHT. Formal Analysis: KHT. Investigation: RA, RR, SM and HG. Data Curation: RR, SM and HG. Writing Original Draft Preparation: HG and SM. Writing Review and Editing: RA. Supervision: RA and AF. Project Administration: RA and AF. Funding Acquisition: RA and AF. All authors have read the

manuscript, revised it critically for important intellectual content and approved the final version of the article to be published.

Availability of data and materials

Data supporting the results reported in the article can be found by academic researchers via sending an email to the corresponding author at roghayeh.akbari@yahoo.com.

Conflicts of interest

The authors declare no competing interests.

Ethical issues

The research followed the tenet of the Declaration of Helsinki. The study protocol has been approved by the Ethics Committee of Babol university of medical sciences with registration code: MUBABOL.HRI.REC.1396.28. Written informed consent was obtained from all participants prior to study. This study was conducted as the pathology specialty thesis of Reyhaneh Ramezanzade at this university (Thesis# 3947).

Consent for publication

All participants gave written informed consent for their personal or clinical details along with any identifying images to be published in this study.

Funding/Support

This study is a result of the pathology thesis of Reyhaneh Ramezanzade and, it was financially supported by Babol university of medical sciences, Babol, Iran (Grant #960356).

References

1. O'Shaughnessy MM, Erickson KF. Measuring comorbidity in patients receiving dialysis: can we do better? Am J Kidney Dis. 2015;66:731-4. doi: 10.1053/j.ajkd.2015.07.001. PMID: 26210068.
2. Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. Nephrol Dial Transplant. 2018;33:iii28-34. doi: 10.1093/ndt/gfy174.
3. Kobayashi S. Cardiovascular Events in Hemodialysis Patients: Challenging against Vascular Calcification. Ann Vasc Dis. 2017;10:1-7. doi: 10.3400/avd.ra.17-00006.
4. Honda H, Qureshi AR, Heimbürger O, Barany P, Wang K, Pecoits-Filho R, et al. Serum albumin, C-reactive protein, interleukin 6, and fetuin a as predictors of malnutrition, cardiovascular disease, and mortality in patients with ESRD. Am J Kidney Dis. 2006;47:139-48. doi: 10.1053/j.ajkd.2005.09.014.
5. EEl Sebai AA, El Hadidi ES, Abdel Al H, El Sayed EY. Pentraxin-3 in hemodialysis patients: Relationship to comorbidities. Saudi J Kidney Dis Transpl. 2016;27:701-9. doi: 10.4103/1319-2442.185226.
6. Poppelaars F, Gaya da Costa M, Berger SP, Assa S, Meter-Arkema AH, Daha MR, et al. Strong predictive value of mannose-binding lectin levels for cardiovascular risk of hemodialysis patients. J Transl Med. 2016;14:236. doi: 10.1186/s12967-016-0995-5.
7. Russa D, Pellegrino D, Montesanto A, Gigliotti P, Perri A, Russa A, et al. Oxidative Balance and Inflammation in Hemodialysis Patients: Biomarkers of Cardiovascular Risk? Oxid Med Cell Longev. 2019;2019:8567275. doi: 10.1155/2019/8567275.
8. Kuswardhani RT, Wiradharma KG, Kandarini Y, Widiana GR, Martadiani ED. Factors associated with carotid intima-media thickness in patients on maintenance hemodialysis. Int J Gen Med. 2018;12:1-6. doi: 10.2147/IJGM.S178276.
9. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol. 2018;9:754. doi: 10.3389/fimmu.2018.00754.
10. Sjöberg B, Qureshi AR, Heimbürger O, Stenvinkel P, Lind L, Larsson A, et al. Association between levels of pentraxin 3 and incidence of chronic kidney disease in the elderly. J Intern Med. 2016;279:173-9. doi: 10.1111/joim.12411.
11. Xu Y, Ding X, Zou J, Liu Z, Jiang S, Xu S, et al. Plasma pentraxin 3 is associated with cardiovascular disease in hemodialysis patients. Ren Fail. 2011;33:998-1004. doi: 10.3109/0886022X.2011.618969.
12. Hornum M, Bay JT, Clausen P, Melchior Hansen J, Mathiesen ER, Feldt-Rasmussen B, et al. High levels of mannose-binding lectin are associated with lower pulse wave velocity in uraemic patients. BMC Nephrol. 2014;15:162. doi: 10.1186/1471-2369-15-162.
13. Satomura A, Fujita T, Yanai M, Kumasaka K, Uehara Y, Okada K, et al. Functional mannose-binding lectin levels in patients with end-stage renal disease on maintenance hemodialysis. J Innate Immun. 2012;4:293-300. doi: 10.1159/000334601.
14. Ishii M, Ohsawa I, Inoshita H, Kusaba G, Onda K, Wakabayashi M, et al. Serum concentration of complement components of the lectin pathway in maintenance hemodialysis patients, and relatively higher levels of L-Ficolin and MASP-2 in Mannose-binding lectin deficiency. Ther Apher Dial. 2011;15:441-7. doi: 10.1111/j.1744-9987.2011.00936.x.
15. Bridgman AC, Qureshi AA, Li T, Tabung FK, Cho E, Drucker AM. Inflammatory dietary pattern and incident psoriasis, psoriatic arthritis, and atopic dermatitis in women: A cohort study. J Am Acad Dermatol. 2019;80:1682-1690. doi: 10.1016/j.jaad.2019.02.038.
16. Ma YJ, Garred P. Pentraxins in Complement Activation and Regulation. Front Immunol. 2018;9:3046. doi: 10.3389/fimmu.2018.03046.
17. Turker Y, Ekinozu I, Turker Y, Akkaya M. High levels of high-sensitivity C-reactive protein and uric acid can predict disease severity in patients with mitral regurgitation. Rev Port Cardiol. 2014;33:699-706. doi: 10.1016/j.repc.2014.03.014.
18. Karakas MF, Buyukkaya E, Kurt M, Motor S, Akcay AB, Buyukkaya S, et al. Serum pentraxin 3 levels are associated with the complexity and severity of coronary artery disease in patients with stable angina pectoris. J Investig Med. 2013;61:278-85. doi: 10.2310/JIM.0b013e31827c2971.
19. Dubin R, Li Y, Ix JH, Shlipak MG, Whooley M, Peralta CA. Associations of pentraxin-3 with cardiovascular events, incident heart failure, and mortality among persons with coronary heart disease: data from the Heart and Soul Study. Am Heart J. 2012;163:274-9. doi: 10.1016/j.ahj.2011.11.007.