Araştırma Makalesi
Research Article

Association of monocyte-to-lymphocyte ratio and practical nutritional indicators in peritoneal dialysis patients

PERİTON DİYALİZ HASTALARINDA MONOSİT-LENFOSİT ORANI VE PRATİK NUTRİSYONEL BELİRTEÇLERİ ARASINDAKİ İLİŞKİ

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ABSTRACT

Background: This study aimed to analyze the association between monocyte-to-lymphocyte ratio (MLR) and nutritional indicators in peritoneal dialysis (PD) patients

Methods: Among the 228 maintenance PD patients 44 of those were included in this retrospective analysis. The geriatric nutrition risk index (GNRI) was calculated using serum albumin and body weight, and the prognostic nutrition index (PNI) was calculated using serum albumin and lymphocyte count. Monocyte-to-lymphocyte ratio (MLR) and nutritional indicators were analyzed using Spearman correlation and linear regression analysis.

Results: During the follow-up of 25 months, median GNRI and PNI values showed an increase from a median baseline GNRI of 86.7 (IQR, 92.9, 104.9) to 100.5 (IQR, 92.7, 109.0) (p=0.03) and PNI values of baseline 43.1 (IQR, 41.0, 46.3) to 46.1 (IQR, 39.1, 50.5) (p=0.02). MLR showed a decrease from the baseline median value of 0.38 (IQR, 0.28, 0.58) to 0.36 (IQR, 0.29, 0.47) p=0.03. There were no changes in leukocyte and hs-CRP levels. There were statistically significant negative correlations between MLR and PNI (rs -0.452; p=0.002), GNRI (rs -0.400 p=0.008), and BMI (rs -0.308; p=0.04). No significant correlation was observed with albumin levels (rs =0.221; p=0.154). MLR was statistically significantly associated with GNRI, PNI, and body mass index (BMI) except albumin, however, hs-CRP level was only associated with serum albumin in both univariate and multivariate regression analysis.

Conclusion: This study indicates that the higher MLR values were associated with lower GNRI and PNI values in PD patients. MLR may help clinicians to identify the nutritional status of this population.

Keywords: Monocyte-to-lymphocyte ratio, geriatric nutrition risk index, prognostic risk index, nutrition, peritoneal dialysi

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DEU Tıp Derg 2024;38(3): 179-188
J DEU Med 2024;38(3): 179-188
doi: 10.18614/deutip.1424254

Gönderim tarihi / Submitted:23.01.2024
Kabul tarihi / Accepted: 20.09.2024

ÖZ

Giriş: Bu çalışma periton diyaliz (PD) hasta grubunda klinik pratikte kullanılan nutrisyon belirteçleri ile monosit-lenfosit arasında ilişkiyi değerlendirmeyi hedeflemiştir.

Gereç ve Yöntem: 228 PD hastasından 44 hasta bu çalışmaya dahil edilmiştir. Geriatrik nutrisyon indeksi (GNRI) serum albumin düzeyi ve kilo, prognostik nutrisyon indexi (PNI) serum albumin düzeyi ve lenfosit sayısı , monosit - lenfosit oranı (MLR) ise tam kan sayımı sonuçlarına göre hesaplanmıştır. MLR ve nutrisyon belirteçleri arasındaki ilişki spearman korelasyon analizi ve lineer regresyon analizi kullanılarak incelenmiştir.

Bulgular: 25 aylık takip süresince, ortanca GNRI ve PNI değerleri istatistiksel olarak anlamlı yükselme göstermiştir [ortanca bazal GNRI 86,7 (IQR, 92,9, 104,9) 'den 100,5 (IQR, 92,7, 109,0) (p=0,03) ve PNI değerleri bazal 43,1 (IQR, 41,0, 46,3) 'den 46,1 (IQR, 39,1, 50,5) (p=0,02)]. MLRdüzeyi istatistiksel olarak anlamlı düşüş izlenmiştir [ortanca bazal 0,38 (IQR, 0,28, 0,58) 'den 0,36 (IQR, 0,29, 0,47) p=0,03]. Lökosit ve hs-CRP düzeylerinde anlamlı değişiklik izlenmemiştir. MLR ile PNI (rs -0,452; p=0,002), GNRI (rs -0,400 p=0,008), ve Vücut kitle indeksi (VKİ) (rs -0,308; p=0,04) değerleri arasında istatistiksel olarak anlamlı negatif korelasyon saptanırken, serum albumin düzeyi ile korelasyon izlenmemiştir (rs =0,221; p=0,154) Hem tek değişkenli hem çok değişkenli lineer regresyon analizinde, MLR düzeyleri ile GNRI, PNI ve VKI arasında istatistiksel olarak anlamlı ilişki tespit edilirken serum albumin düzeyi ile herhangi bir ilişki tespit edilmemiştir. Serum hs-CRP düzeyi ise sadece serum albumin düzeyi ile ilşkili bulunmuştur.

Tartışma: Bu çalışma da PD hasta grubunda yüksek MLR düzeyleri düşük GNRI ve PNI düzeyleri ile ilişkili tespit edilmiştir. Klinik pratikte sıklıkla kullandığımız tam kan sayımından elde edilen MLR düzeyi PD populasyonunun nutrisyonel durumunu gösterir basit bir belirteç olarak kullanılabilir.

Anahtar Kelimeler : Monosit-lenfosit oranı, geriatrik nutrisyon risk indeksi , Prognostik risk indeksi, nutrisyon, periton diyalizi

Patients receiving chronic dialysis, irrespective of the dialysis modality, experience nutritional derangements termed protein-energy wasting (PEW) (1). Despite improvements in disease management and peritoneal dialysis (PD) prescriptions, poor survival of PD patients, especially those with PEW, persists more than in the general population (2).

The measurement of the nutritional condition of these patients varies and easy tools are still under research in many fields (1,3,4). Body mass index (BMI) and serum albumin levels are determined by several factors such as volume expansion, redistribution, and active inflammation. The geriatric nutrition risk index (GNRI), was first described by Bouillane et al (5) and includes both biochemical and anthropometric components. GNRI has previously been studied for either hemodialysis (HD) and PD patients by single or sequential measurements and found as simple and useful nutritional predictor for mortality (6-8). The prognostic nutrition index (PNI) is an inflammation-based nutrition marker and was first studied on perioperative patients (9-10). Recently PNI was also examined in continuous ambulatory peritoneal dialysis patients (CAPD) and reported as an independent predictor for mortality (11).

Inflammation is the most important amplifier for the development of PEW which might result in an increment of inflammation and lead to the vicious circle in PEW pathogenesis (12). C-reactive protein, a traditional inflammatory marker, is associated with nutritional markers in PD patients which demonstrates the close

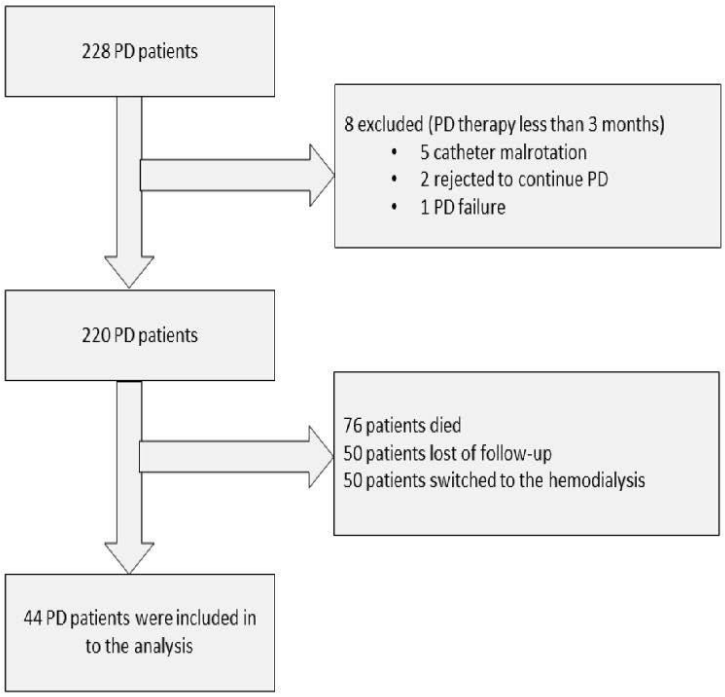
association between inflammation and PEW (13). However, elevated hs-CRP levels might frequently seen in dialysis patients due to infectious conditions, volume overload, PD catheter, or disease by itself even without PEW. The monocyte-to-lymphocyte ratio (MLR) is a cost-effective marker of inflammatory response that can be obtained from a complete blood count. MLR has been studied as a prognostic indicator in PD patients (14-15).

Here we aimed to evaluate the association between inflammation and nutrition by using clinically practical markers such as MLR and GNRI, PNI, serum albumin levels, and BMI among maintenance PD patients.

MATERIALS AND METHODS

We have screened 228 patients, who had been under follow-up at our PD clinic between 1992 and 2023 and 44 of those were included in this retrospective analysis. Patients under PD for less than 3 months, under active peritonitis or any infection, malignancy, or documented cardiovascular disease, who were lost of follow-up, death, or switched to hemodialysis, and patients under 18 years were all excluded from the analysis Figure 1.

Figure 1: Study Flowchart



Follow-up time was recorded until the last visit to our PD clinic. All demographic characteristics, baseline and the last visit laboratory analysis such as blood urea nitrogen (BUN), creatinine, sodium, potassium, albumin, calcium, phosphorus, hemoglobin, leukocyte, lymphocyte, and monocyte counts were recorded. BMI, GNRI, and PNI were obtained at baseline and the last visit. GNRI values were calculated by using the serum albumin levels and body weight of the patients (5).

GNRI=(1.489xalbumin[g/L]) + (41.7 x [body weight/ideal body weight])

The PNI was calculated using serum albumin and absolute lymphocyte count levels (16).

PNI=10 × ALB (g/dL) + 0.005 × ALC (per μL)

The study was approved by the local Ethics Committee (decision number: 2023/16-07). All informed consent from patients has been obtained and stored in our PD outpatient clinic.

Statistical Analysis

All analyses have been performed using SPSS version 24 (IBM Corp., Armonk, NY, USA). All values are expressed as mean± standard deviation (SD) or median with interquartile range (IQR) depending on their distribution and categorical variables such as numbers and frequencies. The Wilcoxon analysis was performed to compare repeated variables at baseline and last visit including nutritional and inflammatory parameters. The correlation between nutrition and inflammation was evaluated using Spearman correlation analysis. The association was examined with univariate and multivariate linear regression analysis adjusting by age and gender. Logarithmic transformation was performed for the abnormally distributed variables to ensure normality before regression analysis. A two-sided p-value <0.05 was considered significant.

RESULTS

All demographics of the study population are depicted in Table 1. The mean (±SD) age was 60±13 years and 57 % of the patients were female. The median duration of PD time was 25 (IQR, 14, 60) months. The most common primary disorders were diabetes mellitus (23%) and glomerulonephritis (23 %) followed by hypertension. (18%). Sixty percent of the patients were under automated peritoneal dialysis (APD). The baseline permeability in the peritoneal equilibration test (PET) showed that the average level is the most common result in our patients (high average 39%, low average 39 %). The baseline weekly peritoneal Kt/V was 1.95 (IQR, 1.71, 2.25) and residual kidney function was 46.9 (IQR, 36.0, 60.2) mL/min/1.73 m2. The last visit evaluation did not show significant changes (p=0,86 for Kt/V, p=0.18 for residual kidney function) (Table 1).

Table 1: Demographic Characteristics and Laboratory Values of Study Population

	n=44
Age (years, mean±SD)	60±13
Gender (n, %)	
Male	19 (43%)
Female	25 (57%)
PD duration time (months) (median, IQR)	25 (14,60)
Primary Disorder (n, %)	
Diabetes Mellitus	10 (23%)
Hypertension	8 (18%)
Polycystic Kidney Disease	6 (14%)
Glomerulonephritis	10 (23%)
Nephrolitiasis	2 (4%)
Other	1 (2%)
Unknown	7 (16%)
PD Modality (n,%)	
APD	26 (60%)
CARD	18 (40%)
Baseline PET results	
High	4 (8%)

High-average	17 (39%)
Low	6 (14%)
Low-average	17 (39%)
Baseline weekly peritoneal Kt/V(median, IQR)	1.95 (1.71, 2.25)
Baseline residual kidney function (ml/min/1,73m^2, median IQR)	46.9 (36.0, 60.2)
Last Visit PET results	
High	3 (7%)
High-average	20 (45%)
Low	4 (9%)
Low-average	17 (39%)
Last Visit weekly peritoneal Kt/V(median, IQR)	1.97 (1.74, 2.14)
Last visit residual kidney function (ml/min/1,73m^2, median IQR)	50.6 (42.0, 59.6)

SD; standard deviation, **IQR;** interquartile range, **PD**; peritoneal dialysis, **APD;** automated peritoneal dialysis, **CAPD;** continuous ambulatory peritoneal dialysis, **PET**; the peritoneal equilibration test

The comparison of the baseline and final visit biochemical parameters showed that the median serum BUN, serum potassium, and serum phosphorus levels statistically significantly decreased (p<0.01 for all) (Table 2).

Table 2: Laboratory, Nutritional, and Inflammatory Results of the Patients

	Baseline (n=44)	Last Visit (n=44)	P value
BUN (mg/dL, median, IQR)	67.1 (50.7, 83.0)	49.1 (41.0, 56.4)	<0.01
Creatinine (mg/dL, median, IQR)	5.7 (4.3, 8.3)	6.7 (4.7, 8.1)	0.87
Sodium (mmol/L, median, IQR)	139 (136, 140)	137 (135, 140)	0.06
Potassium (mmol/L, median, IQR)	4.7 (4.2, 5.3)	4.1 (3.7, 4.3)	<0.01
Calcium (mg/dL, median, IQR)	8.9 (8.3, 9.3)	8.8 (8.3, 9.3)	0.35
Phosphorus (mg/dL, median, IQR)	5.3 (4.6, 6.2)	4.6 (4.0, 5.2)	<0.01
Hemoglobine (g/dL, median, IQR)	11.0 (9.6, 11.9)	11.3 (10.7, 12.2)	0.06
Parathyroid hormone (pg/mL, median, IQR)	325 (174, 549)	361 (250, 681)	0.08
Ferritin (ng/mL, median, IQR)	192 (80, 403)	213 (111, 542)	0.28
Nutritional Parameters			
Serum albumin (g/dL, median, IQR)	3.9 (3.2, 4.1)	3.5 (3.3, 3.7)	0.05
BMI (kg/m2, median, IQR)	25. 6 (23.0, 28.2)	25.2 (22.9, 29.0)	0.81
GNRI (median, IQR)	86.7 (92.9, 104.9)	100.5 (92.7,109.0)	0.03
PNI (median, IQR)	43.1 (41.0, 46.3)	46.1 (39.1, 50.5)	0.02
Inflammatory Parameters			
hs-CRP (mg/L, median, IQR)	8.5 (1.9, 30.1)	8.6 (2.4, 20.6)	0.47
White Blood Cell (10^3/uL, median, IQR)	7300 (6200, 9875)	7600 (6500, 9200)	0.74
MLR (median, IQR)	0.38(0.28, 0058)	0.36 (0,29, 0,47)	0.03

IQR; interquartile range, **BUN;** blood urea nitrogen, **BMI;** body mass index, **GNRI;** geriatric nutrition risk index, **PNI;** prognostic nutrition index, hs-**CRP**; high sensitive C-reactive protein**, MLR;** monocyte to lymphocyte ratio

Measurement of nutrition and inflammation

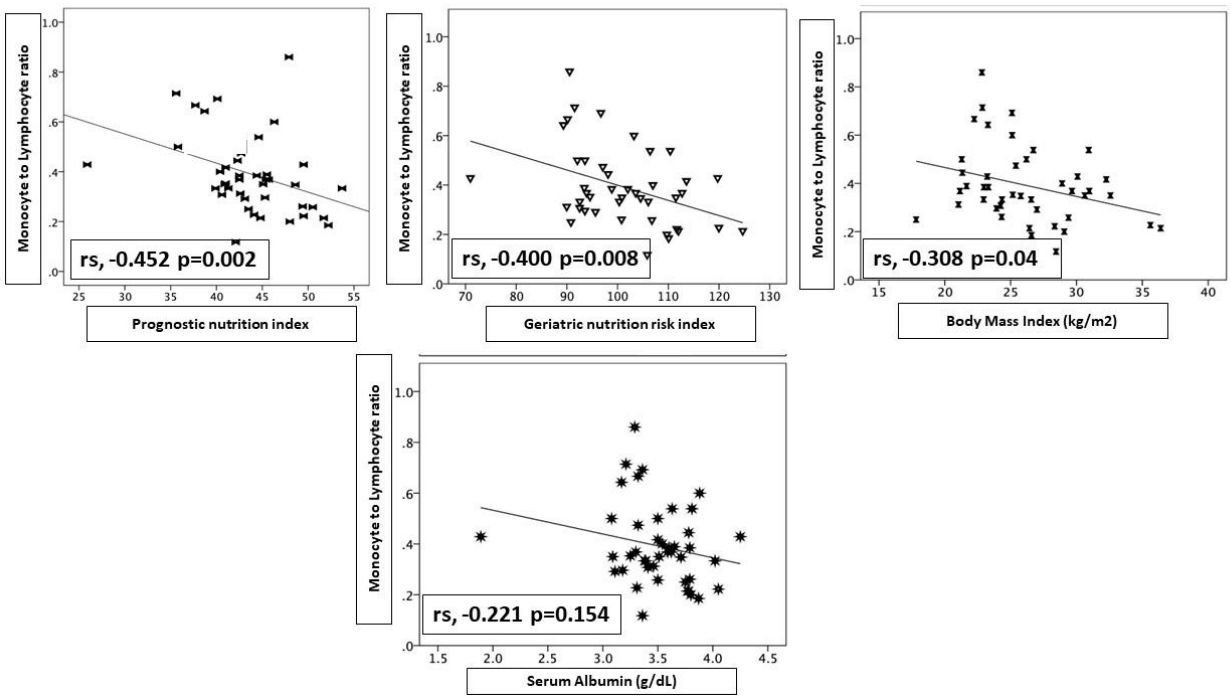
The summary of the nutritional indicators is presented in Table 2. During the median follow-up of 25 months, median GNRI and PNI values showed a statistically significant increase from a median baseline GNRI of 86.7 (IQR, 92.9, 104.9) to 100.5 (IQR, 92.7, 109.0) (p=0.03) and PNI values of baseline 43.1 (IQR, 41.0, 46.3) to 46.1 (IQR, 39.1, 50.5) (p=0,02). No significant changes were observed in median BMI and serum albumin levels.

Regarding the inflammatory parameters, there were no significant differences for hs-CRP and leukocyte levels in comparison between baseline and last follow-up visits, However, the MLR showed a statistically significant decrease from baseline median value of 0.38 (IQR, 0.28, 0.58) to 0.36 (IQR, 0.29, 0.47) p=0.03.

The Association Between MLR and Nutritional Indicators

Figure 2 shows the Spearman correlation analyses between the MLR and nutritional indicators.

Figure 2: The scatter blott graphs of the correlation between the monocyte-to-lymphocyte ratio and nutritional parameters



There were statistically significant negative correlations between MLR and PNI (rs -0.452; p=0.002), GNRI (rs -0.400 p=0.008), and BMI (rs -0.308; p=0.04). No significant correlation was observed with serum albumin level (rs 0.221; p=0.154). There was a statistically significant negative correlation between hs-CRP and the serum albumin level (rs -0,466; p=0,002). Although negative correlations were observed between hs-CRP and GNRI, PNI, and BMI, the associations did not reach statistical significance (rs -0,144; p=0,35 for GNRI, rs -0,003; p=0.98 for PNI, and rs-0,106; p=0,49 for BMI) In the linear regression analysis, MLR was all statistically significantly associated with GNRI, PNI, and BMI, except serum albumin levels. However, hs-CRP level was only associated with serum albumin levels. After adjusting the analysis for age and

gender the associations did not change. The summary of the results is depicted in Table 3.

Table 3: Univariate and Multivariate Linear Regression Analyses Between inflammation and nutritional indicators

	GNRI		PNI		Albumin		BMI	
Univariate Analysis								
	B coefficient	P	B coefficient	P	B coefficient	P	B coefficient	P
MLR	-26.047(-44.858, -7.236)	0.008	-11.794 (-21.107, 2.482)	0.01	-0.522 (-1.249, 0.204)	0.15	-7.902 (-15.600, -0.204)	0.04
hs-CRP	-0.130(-0.375, 0.115)	0.29	-0.057(-0.146, 0.033)	0.208	-0 .424 (-0.015, -0.003)	0.005	-0.002 (-0.075, 0.071)	0,95
Multivariate Analysis*								
MLR	-24.008(-42.667, -5.350)	0.01	-11.146(-20.554, -1.737)	0.02	-0.391(-1.070,0.288)	0.25	-7.990(-15.863, -0.118)	0.04
hs-CRP	-0.134(-0,303, 0,036)	0.11	-0.043 (-0.128,0.043)	0.32	-0.009(-0.015, -0.002)	0.007	0.006(-0.006,0.007)	0.87

*Adjusted by age, gender, MLR, and hs-CRP

MLR; monocyte to lymphocyte ratio, hs-CRP; high-sensitive C-reactive protein, GNRI; geriatric nutrition risk index, PNI; prognostic nutrition index, BMI; body mass index

DISCUSSION

Protein-energy wasting and inflammation are interrelated in dialysis settings (17).To the best of our knowledge, this is the first report that evaluates the association between inflammation and nutrition by using practical parameters, MLR as an inflammatory marker, GNRI, and PNI as nutritional indicators in PD patients. The main finding of this study was that higher levels of MLR are associated with lower levels of GNRI, PNI, and, BMI. The traditional inflammatory marker, hs-CRP is only significantly negatively associated with serum albumin levels. The association between MLR and nutritional indicators persisted even after adjustment of age, gender, and hs-CRP levels in regression analysis.

Protein-energy wasting is an important health consequence in the PD population (17). All end-stage renal disease (ESRD) guidelines including PD recommends regular evaluation of nutritional status with clinical and laboratory markers. However, the optimal measurement method is still under debate (12). Most of the scores that are used in nutrition require many laboratory and clinical information that should be obtained from the patients. It is always not possible to obtain detailed information. The follow-up of the patient will be optimal if the laboratory markers are cheap, easily obtainable, and sensitive to specific clinical condition. Hence, the usefulness of markers such as GNRI and PNI besides serum albumin and BMI became an area of interest in many disorders including ESRD patients.

The prevalence of PEW in previous studies varied between 28-65%, particularly, in the pre-dialysis period (189. Since uremia and uremia-related factors such as decreased absorption of nutrients due to the oedematous gut, metabolic acidosis, oxidative stress, and inflammation are closely interrelated with the development of PEW, AND starting adequate dialysis might reverse this negative effect in this population (19). In our study, regarding the GNRI and PNI levels, patients became in a more favorable state without any significant change in BMI, during the follow-up of 25 months. This would be the false positive finding of the patient selection in our analyses since, we excluded all patients who had, any history of infections including peritonitis, malignancy, or documented cardiovascular disease that might also affect nutritional status. Although serum albumin levels showed a slight decrease in the last visit of the patients, it should be kept in mind that albumin by itself is highly sensitive to any

conditional changes such as age, subclinical inflammation, and liver disease that we could not be able to document at that time. One of the significant results of our study is the negative correlation between serum albumin and hs-CRP level which is a traditional finding. However, the null association between MLR and albumin levels along with hs-CRP and GNRI, PNI levels are conclusive about the utility of serum albumin levels by itself as a sufficient marker for evaluation of nutrition.

The prognostic nutrition index is a good marker by combining both serum albumin levels and lymphocyte count (20). In previous studies, PNI has a positive correlation with nutritional indicators such as hemoglobin and BMI levels in this population (21). The low levels of PNI reflect poor nutritional status. The cutoff level was reported between 40 to 50 in different disease conditions (20-22). Few studies have evaluated the optimal cutoff level of PNI reflecting PEW in the PD population and it is still not well validated (23). The median PNI value in our report is in the favorable range compared to the earlier reports (21,23,249. Formerly, GNRI was analyzed in PD patients, and serial measurements especially worsening levels have been found a risk factor for poor outcomes in these patients 86,25,26). Lower GNRI values are an indicator for PEW and seem like have no observation bias compared to the other assessment methods. It has been reported that the GNRI levels under 92 are representative of malnutrition (27). To take as a reference of this value, our study population is mostly in well nutritional classification. This is possibly related to the patients that we enrolled having no documented concomitant active major disorder that might aggravate to development of PEW.

The inflammatory response can be presented by the blood values of leukocytes, lymphocytes, monocytes, hs-CRP levels, and also serum albumin levels. MLR is an inexpensive, easily calculated marker (149 and has been studied in different disease states, including hemo and PD patients, and found an independent risk factor for all-cause and cardiovascular mortality (15,28,29). All these previous studies including the dialysis population have focused on the prognosis of the patient rather than the relation with nutritional status. Although, in our study, both baseline and last visit measurements of MLR are relatively higher compared to the previous publications (>0,.21), we observed a significant decrease in MLR levels accompanied by no change in CRP in the last visit, which let us conclude the possible renal replacement therapy related improvement on inflammatory status.

Here we demonstrated that MLR is negatively correlated with nutritional indicators such as GNRI, PNI, and BMI levels. Also, both univariate and age, gender adjusted multivariate linear regression analysis showed a significant association between MLR and nutritional indicators. We could not find any PD studies investigating the relationship between MLR and nutritional indicators using GNRI and PNI in the literature. Our observation may reflect the plausible relationship in PD patients between nutrition and inflammation by using easy parameters, even in a subclinical state. To our knowledge, this is one of the most meaningful studies on PD patients to evaluate the relationship between MLR and nutritional indicators such as GNRI and PNI levels.

Some limitations of this study should be acknowledged. Owing to the retrospective design and relatively small sample size limit to conclude the cause-effect relationship between nutrition and inflammation. However, given the prevalence of PD as renal replacement therapy and the difficulties to find relatively homogenous patients in this population, we can still conclude that the sampling of this study might reflective for all PD patients. Here, we also used the last visit parameters in both correlation and regression analysis rather than baseline parameters. Although both baseline and final visit assessments were similar in our patients, we preferred to use the same time point calculations in analyses, since the clinically non-diagnosed physical conditions at different time points might affect the inflammatory and nutritional status of this dynamic patient population.

In conclusion, this study demonstrated that the higher MLR values were associated with lower GNRI and PNI values in maintenance PD patients. Further large sample-sized studies are needed to confirm these results and to explore the potential cause of the lack of the association between hs-CRP levels and GNRI and PNI or whether MLR is more sensitive than hs-CRP. Nevertheless,

our findings have led us to suggest that MLR might be a useful marker, easily available in routine clinical practice for predicting the nutritional status of PD patients.

Funding

This research did not receive any specific grant from funding agencies

Declaration of Conflicting Interest

All authors declare that there is no conflict of interest.

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