Predictors of erythropoietin response in nondiabetic end-stage renal-disease patients on hemodialysis

Muhammad R. Abdel Hammed[a], Mohammed Ali Tohammy[b], Samah Ahmed Mohammed[c], Walaa Hosni Ibrahim[b], Mostafa Faisal Mohammad[a]

Departements of [a]Internal Medicine and Haematology, [b]Internal Medicine and Nephrology, Faculty of Medicine, Assiut University, Asyut, Egypt, [c]Departement of Internal Medicine, El Eman General Hospital, Asyut, Egypt

Correspondence to Samah Ahmed Mohammed, Department of Internal Medicine, EL Eman General Hospital, Assiut, Egypt.
Tel: +010095838501;
e-mail: 91.ahmed@gmail.com

Received 19 April 2021
Revised 13 June 2021
Accepted 07 December 2021
Published 26 December 2022

Journal of Current Medical Research and Practice
2022, 7:310–315

Background
Erythropoietin (EPO) resistance is an essential health problem in end-stage renal-disease patients as it is associated with increased mortality. Despite combined intravenous iron usage, anemia exists substantially in the majority of patients, indicating the presence of other pathophysiological mechanisms such as inflammation that could lead to EPO resistance.

Objectives
To evaluate neutrophil-lymphocytic ratio (NLR) and platelet-lymphocytic ratio (PLR) as possible predictors of EPO resistance in nondiabetic patients on hemodialysis (HD).

Patients and methods
Fifty patients aged from 18 to 70 years old were diagnosed as end-stage renal disease and on HD regularly for more than 6 months and are receiving EPO therapy for at least more than 2 months. EPO dosing and intravenous iron supplementations given to HD patients and response assessment were following the 2012 Kidney Disease Improving Global Outcome guidelines. EPO resistance was assessed using EPO-stimulating agent (ESA) hyporesponsiveness index (EHRI), calculated as EPO weekly dose divided by body weight (kg) divided by hemoglobin level (Hb) and correlation with NLR, PLR, and C-reactive protein (CRP) was analyzed. EPO hyporesponsiveness (nonresponders) was diagnosed when we need to increase ESA doses up to 50% higher than the dose at which they were stable to maintain a steady Hb concentration after the first month of EPO treatment on weight-based dosing or after treatment with continuous EPO doses.

Results
Nonresponders to EPO had significantly higher EHRI, NLR, PLR, and CRP in comparison with responders. EHRI had a weak positive correlation with NLR ($r = 0.18$, $P = 0.20$), whereas it had a strong positive correlation with PLR ($r = 0.65$, $P = 0.001$). PLR at the cutoff point <116.5 has 90% sensitivity and 70% specificity for prediction of response to EPO therapy with overall accuracy that was 82% (area under curve [AUC]=0.79).

Conclusion
Inflammation is a major contributor in EPO resistance. CRP and PLR could represent cheap and simple parameters to predict response to EPO therapy in nondiabetic HD patients.

Keywords:
anemia, end-stage renal disease, erythropoietin, hemodialysis, nondiabetic

J Curr Med Res Pract 7:310–315

2357-0121

Introduction

Anemia is a frequently seen complication in end-stage renal disease (ESRD) due to loss of kidney function. Severe anemia has deleterious effects on health as it increases cardiovascular and mortality risk in hemodialysis patients [1]. Anemia is defined as hemoglobin values less than 13.0 g/dl in males and 12.0 g/dl in females in patients with chronic kidney disease (CKD) aged >15 years by the Kidney Disease Improving Global Outcome (KDIGO) group [2].

Human recombinant erythropoietin (EPO) has become the standard of care for anemia in individuals with chronic renal disease since its debut. The drug decreased the need for blood transfusion, thus reducing complications of iron overload, transmission of blood-borne infections, and cardiac complications [3].

EPO resistance is defined as failure to achieve target hemoglobin in individuals receiving more than 300 IU/kg/week of EPO or those who require such large doses to achieve goal levels [1,2].

Many factors are responsible for EPO resistance in CKD patients in the presence of sufficient iron stores such as

inflammation, inadequate dialysis, infection, malnutrition, and hyperparathyroidism. Investigating predictors of EPO resistance related to those factors is running by several studies [3]. EPO-stimulating agent (ESA) hyporesponsiveness index (EHRI) is an effective method for evaluation of EPO hyporesponsiveness, and it is calculated by dividing the dose of EPO/week by the body weight in kilograms divided by hemoglobin (Hb) [4].

Total leukocytic count and platelets give a crude and sensitive assessment of inflammatory status. The platelet–lymphocyte ratio (PLR) and the neutrophil–lymphocyte ratio (NLR) are markers of systemic inflammation and are considered as prognostic factors for many diseases such as inflammatory diseases, cardiovascular diseases, and cancer [5–8].

This study evaluates the correlation of NLR and PLR with EHRI and identifies their potential as possible predictors of EPO response in nondiabetic hemodialysis patients.

Patients and methods

This is a cross-section study conducted at the Hemodialysis Unit of Assiut University Hospital between May 2018 and May 2019. In total, 50 ESRD adult patients on regular hemodialysis thrice weekly for more than 6 months were recruited as they were receiving EPO therapy in a dose of 20 000 IU per week for at least 2 months. Erythropoiesis-stimulating agent used in all patients was Epoetin alfa. EPO dosing and intravenous iron supplementations given to HD patients were following the 2012 KDIGO guidelines.

This study was approved by the Medical Ethical Committee, Faculty of Medicine, Assiut University, and it was conducted according to the provisions of the Declaration of Helsinki Approval number: 17101209. Informed consent was obtained from the participants before participation.

Diabetes, hepatitis B or C infection, acute disease, bleeding within 2 months, iron deficiency (serum ferritin values less than 30 ng/ml suggest iron deficiency according to KDIGO anemia guidelines), overt infection or inflammation, history of hospital admission within the last 3 months, history of blood transfusion within the last 3 months, and hematologic malignancy are all exclusion criteria.

The patients were given a complete medical history and a comprehensive clinical examination. Lab parameters at the start were done as routine investigation in Assiut University Hospitals. Laboratories including complete blood count, ferritin, serum iron, albumin, calcium, hepatitis B and C markers, phosphorus, the levels of parathyroid hormone, C-reactive protein (CRP), serum creatinine, and blood urea nitrogen (BUN) were all measured. The NLR was determined by dividing the total number of neutrophils by the total number of lymphocytes. Platelet count separated by lymphocytic count yielded the PLR (absolute). The target hemoglobin of 11 gm/dl was used to determine response and patients with EPO resistance need to increase EPO up to 50% higher than the dose at which they were stable to maintain a stable Hb concentration after 1 month of EPO therapy on weight-based dosing or after using high doses of EPO to maintain a stable Hb concentration [2]. EHRI was calculated by dividing the dose of weekly EPO by body weight in kilograms divided by Hb [9].

Statistical analysis

SPSS was used to examine the data (Statistical Package for the Social Science, version 20). Nominal data were reported as a percentage, whereas continuous data were given as a mean or median. The χ^2 test was used to compare the nominal data of the different groups in the study, and the Student *t*-test was used to analyze the mean of two different groups. The independent risk factors for EPO-treatment response were identified using multivariate regression analysis. The association between EHRI and NLR and PLR was determined using the Pearson correlation. The diagnostic accuracy of NLR and PLR in predicting EPO responsiveness was assessed using an ROC curve. The level of confidence was preserved at 95%, and the *P* value was considered significant if it was less than 0.05.

Results

The mean age of all patients was 45.46 ± 15.88 years and 50% were males. Mean duration of hemodialysis was 5.67 ± 2.45 years in all patients. The most frequent cause of ESRD was chronic glomerulonephritis in 35 (70%) patients (8 patients had past history of schistosomiasis, and 27 had undetermined causes). Other causes are hypertension (12%), obstructive uropathy (12%), and polycystic kidney disease (6%).

EPO given for all enrolled patients (rHuEPO, SEDICO Pharmaceutical Company) was 100 IU/kg/week, subcutaneous injection, after 1 month of treatment and according to Hb level with cutoff point 11, we have two groups:

(1) Responders included 30 patients in whom Hb level was above 11 gm/dl.
(2) Nonresponders included 20 patients in whom Hb level was below 11 gm/dl.

Baseline laboratory data of the studied groups are shown in Table 1. Both groups of patients, either responders or nonresponders, had insignificant differences as regarding baseline data with exception of:

(1) Responders had significantly higher Hb (12.01 ± 1.50 vs. 9.37 ± 1.30 g/dl, $P < 0.001$) and hematocrit values (36.73 ± 6.17 vs. 31.93 ± 3.58%, $P < 0.001$) in comparison with nonresponders.
(2) CRP was significantly higher among nonresponders compared with responders (12.75 ± 3.83 vs. 9.20 ± 4.51 mg/dl, $P < 0.001$).

Table 2 shows NLR, PLR, and EHRI in studied patients. It was noticed that

(1) NLR was significantly higher in nonresponders (2.29 ± 0.88 vs. 1.83 ± 0.75, $P = 0.04$). Also, PLR was significantly higher in nonresponders (151.17 ± 84.03 vs. 84.45 ± 26.66, $P < 0.001$).
(2) Nonresponders had significantly higher EHRI in comparison with responders (11.13 ± 2.95 vs. 7.93 ± 3.51, $P < 0.001$).

Table 3 shows that EHRI had no correlation with NLR, whereas it showed significant correlation with PLR ($r = 0.65$ and $P < 0.001$) (Fig. 1).

Based on the current study, NLR <2.7 has 87% sensitivity and 40% specificity for prediction of EPO response with accuracy 68%, whereas PLR <116.5 has 90% sensitivity and 70% specificity for prediction of EPO response with overall accuracy that was 82%, AUC = 0.79 (Fig. 2).

In multivariate regression analysis for prediction of EPO response [Table 4], the only predictor for response to EPO therapy was PLR (odds ratio = 2.11, 95% confidence interval = 1.23–4.55, $P < 0.001$) with adjusted R^2 0.44.

Discussion

Management of anemia in ESRD is challenging for both hematologists and nephrologists. EPO resistance represents a major health issue in such disease population. Several factors other than iron deficiency can be associated with EPO hyporesponsiveness in dialysis patients [10]. The current study demonstrates that inflammation is a major contributor for EPO resistance in nondiabetic HD patients with higher inflammatory indices such as CRP, NLR, and PLR reported in nonresponders.

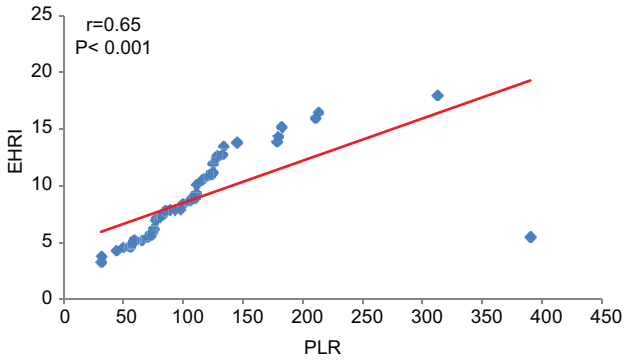
In our study, age, and sex were not predictive of EPO resistance. In a comparative study of Adult and Pediatric Dialysis Cohorts 2009, EPO was required more in younger ages due to higher inflammatory

Table 1 Baseline laboratory data in the studied groups

Variable	Responders (*n*=30)	Nonresponders (*n*=20)	*P*
Age in years	41±2.5	45±3.5	0.23
Sex, female, *N* (%)	14 (46.6)	11 (55)	0.43
CBC			
Hemoglobin (g/dl)	8.78±1.20	9.32±1.50	0.34
Hematocrit value (%)	30.84±4.65	31.25±5.03	0.40
Hemoglobin (g/dl)[a] after a month	12.01±1.50	9.37±1.30	**<0.001**
Hematocrit value (%)[a] after a month	36.73±6.17	31.93±3.58	**<0.001**
MCV (fl)	97.16±26.29	87.45±13.88	0.13
MCH (g/dl)	27.85±4.75	28.50±1.39	0.55
Platelets ($\times 10^9$/l)	180.30±60.79	188.75±58.23	0.62
Leukocytes ($\times 10^9$/l)	6.33±1.67	5.38±1.06	0.20
Neutrophils ($\times 10^9$/l)	3.73±0.84	3.78±0.86	0.84
Lymphocytes ($\times 10^9$/l)	1.96±0.75	1.99±0.77	0.87
KFTs			
Urea (mmol/l)	89.33±52.07	96.85±61.36	0.64
Creatinine (mmol/l)	945.16±199.84	932.15±269.90	0.17
Calcium^{+2} (mg/dl)	8.61±0.55	8.61±0.69	0.99
Phosphorus^{+4} (mg/dl)	5.36±2.13	5.01±1.68	0.53
Parathormone (pg/ml)	600.63±287.54	532.15±363.56	0.46
Albumin (mg/dl)	40.43±2.48	37.16±8.43	0.06
Iron studies			
Serum iron (µg/dl)	120.93±35.16	112.35±32.36	0.38
Serum ferritin (mg/l)	3986.16±987.56	3736.01±888.56	0.72
TIBC (µg/dl)	259.30±89.56	235.25±48.06	0.46
CRP (mg/dl)	9.20 ± 4.51	12.75 ± 3.83	**<0.001**

Data are presented as a mean (SD). CBC, full blood-image CRP stands for C-reactive protein; KFTs, kidney-function tests; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; TIBC, Total iron binding capacity. [a]After 1 month of EPO therapy. *P* value was important if 0.05.

Figure 1



Correlation of erythropoietin-stimulating agent hyporesponsiveness index with platelet-lymphocytic ratio.

Table 2 NLR, PLR, and EHRI in enrolled patients

Variable	Responders (*n*=30)	Nonresponders (*n*=20)	*P*
NLR	1.83±0.75	2.29±0.88	0.04
PLR	84.45±26.66	151.17±84.03	<0.001
EHRI	7.93 ± 3.51	11.13 ± 2.95	<0.001

Mean is used to represent data (SD). If the *P* value was less than 0.05, the result was statistically significant. EHRI, erythropoietin hyporesponsiveness index; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

Table 3 Correlation of EHRI with NLR and PLR

	r	*P*
NLR	0.18	0.20
PLR	0.65	<0.001

Data are expressed in terms of *r* (correlation strength) and *P* (significance of correlation). If the *P* value was less than 0.05, the result was considered meaningful. EHRI, erythropoietin hyporesponsiveness index; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

Table 4 Univariate and multivariate regression analysis for prediction of response

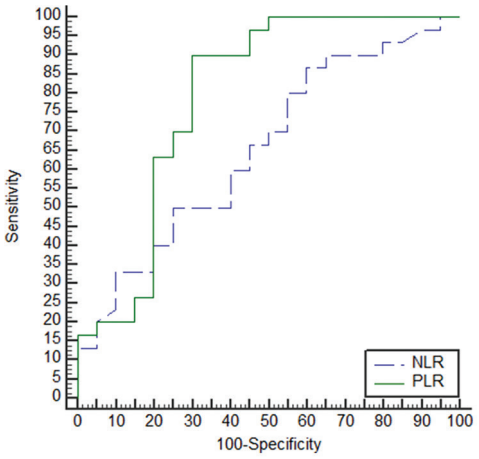
	Univariate regression analysis		Multivariate regression analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	0.22 (0.11-0.49)	0.11		
CRP	0.55 (0.22-1.11)	0.22		
NLR	1.22 (0.99-1.44)	0.09		
PLR	1.99 (1.54-3.33)	0.0	2.11 (1.23-4.55)	<0.001

P value was significant if <0.05. CI, confidence interval; CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio; OR, odds ratio; PLR, platelet/lymphocyte ratio.

stress, nutritional deficits, and disproportionate blood loss. Adult females have greater need of EPO may be due to iron deficiency with menstrual cycles or androgenic erythropoiesis stimulation in males. However Beati *et al.* (2011) and Schneider *et al.* (2013) found that male sex was identified as one of the clinical parameters for EPO resistance [13, 14, 15].

The present research showed CRP levels to be considerably greater in nonresponders than in responders. Patients with high CRP levels had a rapid

Figure 2



Diagnostic accuracy of neutrophil-lymphocytic ratio and platelet-lymphocytic ratio for prediction of erythropoietin response.

decline in hemoglobin levels and increased EPO doses, which results in an increase in EPO hyporesponsiveness, according to the Dialysis Outcomes and Practice Patterns Study, which analyzed 12 389 hemodialysis patients between 2009 and 2018.

This report demonstrated that nonresponders had a considerably higher NLR and much greater PLR. In comparison with responders, nonresponders had a considerably higher EHRI that showed negligible connection with NLR, despite having a strong positive connection with PLR. Some reports showed NLR and PLR to be correlated with EPO resistance in HD patients; however, ESRD in such studied cohorts was mainly due to diabetic nephropathy. In concurrent with our findings, Taymez *et al.* (2016) found that logarithmically converted EHRI was only connected with Hb (r=–0.381, P = 0.0001) and PLR (r = 0.227, P = 0.021), but not with NLR. Antihypertensive medicine use and PLR were found to be independent factors of logarithmically converted EHRI [16, 17].

In a study of inflammation in ESRD patients, Turkmen *et al.* (2013) found a relation between NLR and PLR with tumor-necrosis factor (TNF) and interleukin (IL)-6 and showed that this was a part of inflammation. They also concluded that PLR was a better marker for inflammation than NLR [18].

Moreover, in a study by Jerome *et al.* (2017), a positive correlation between NLR and CRP was found (HD: r = 0.47, P < 0.001), whereas it was inversely correlated with albumin (r=–0.51, P < 0.001). However, high NLR was associated with a nonsignificant increased ERI. Again, in a large cohort study 2017 from the United States, NLR but not PLR, was beneficial in predicting

mortality in those patients along with demographics, comorbidities, and serum albumin [19, 20].

Recently, Shah *et al.* (2020) found that in patients with ESRD not on dialysis, both PLR and NLR were higher in those with high sensitive–CRP levels (>3 mg/l), compared with patients with low–high sensitive–CRP levels (≤3 mg/l) and were both positively correlated with high sensitive–CRP (rs = 0.377, P = 0.000 for NLR; rs = 0.161, P = 0.001 for PLR).

Li *et al.* (2020) recognized that NLR or PLR with a cutoff value of 5.07 or 163.80 that indicated sensitivity and specificity were 65.67 and 66.37% (AUC = 0.69) or 57.21 and 57.52% (AUC = 0.55), respectively. This is quite similar to our study, where we found that NLR at the cutoff point <2.7 has 87% sensitivity and 40% specificity for prediction of response to EPO therapy with overall accuracy that was 68%, whereas PLR at the cutoff point <116.5 has 90% sensitivity and 70% specificity for prediction of response to EPO therapy with overall accuracy that was 82% [21].

EPO resistance is linked to inflammation in hemodialysis patients, that causes elevated amounts of IL-1,6, interferon-gamma, and TNF-alpha, which alter iron regulation by upregulating hepcidin and decreasing the bone marrow response to ESA and/or producing erythrocyte hemolysis [11].

Identification of inflammation as the etiology of EPO resistance could guide EPO and IV iron treatment. This can assist in selecting patients who may benefit from emerging medicines for treating anemia that are less influenced by the inflammatory process, such as hypoxia-induced prolyl-hydroxylase inhibitors [12].

Our study had certain limitations, such as the fact that it was a cross-section single-center study with a small number of patients and that the results were interpreted based on a single laboratory measurement, which may not reflect the relationship over time. The relationship with other inflammatory indicators such as IL-6 and TNF was not investigated. As a result, a well-designed prospective study is required to further clarify the situation.

Conclusion

Inflammation contributes significantly to EPO resistance in nondiabetic HD patients. CRP and PLR can represent cheap and simple parameters to predict response to EPO therapy in hemodialysis patients. NLR also can be used in prediction of response to EPO therapy in HD patients but with less accuracy and sensitivity than PLR.

Acknowledgements

Ethics approval and consent to participate: The study protocol was approved by the Ethics Review Board of the Faculty of Medicine, Assiut University, and informed consent was obtained from all participants according to the Declaration of Helsinki.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions:

MRA performs study design and concept, questionnaire design, data collection, data analysis, data interpretation, and drafting. MAT made substantial contributions to the design of the work, the acquisition, analysis, and interpretation of data, and was a major contributor in revising the paper. SAM is the corresponding author, has a major role in collecting the data and laboratory investigations of the patients in the study, writing the paper, and the statistical analysis of the data. WHI involved in questionnaire design, data collection, data analysis, data interpretation, and drafting. MFM performs questionnaire design, data collection, data analysis, data interpretation, and drafting, and was a major contributor in revising the paper.

All authors have read and approved the paper.

Abbreviations:

CRP, (c-reactive protein); EHRI, (erythropoietin hyporesponsiveness index); EPO, (erythropoietin); ESA, (erythropoietin-stimulating agents); ESRD, (end-stage renal disease); Hb, (hemoglobin); HD, (hemodialysis); NLR, (neutrophil-lymphocytic ratio); PD, (peritoneal dialysis); PLR, (platelet-lymphocytic ratio); rHuEPO, (recombinant human erythropoietin).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Sibbel SP, Koro CE, Brunelli SM, Cobitz AR. Characterization of chronic and acute ESA hyporesponse: a retrospective cohort study of hemodialysis patients. BMC Nephrol 2015; 16:144.

2 Kanbay M, Perazella MA, Kasapoglu B, Koroglu M, Covic A. Erythropoiesis stimulatory agent-resistant anemia in dialysis patients: review of causes and management. Blood Purif 2010; 29:1–12.

3 Alves MT, Vilaça SS, Carvalho MdG, Fernandes AP, Dusse LMSA,

Gomes KB. Resistance of dialyzed patients to erythropoietin. Rev Bras Hematol Hemoter 2015; 37:190–197.

4 Mallick S, Rafiroiu A, Kanthety R, Iqbal S, Malik R, Rahman M. Factors predicting erythropoietin resistance among maintenance hemodialysis patients. Blood Purif 2012; 33:238–244.

5 Qin B, Ma N, Tang Q, Wei T, Yang M, Fu H, *et al*. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Mod Rheumatol 2016; 26:372–376.

6 Delcea C, Buzea CA, Dan GA. The neutrophil to lymphocyte ratio in heart failure: a comprehensive review. Rom J Intern Med 2019; 57:296–314.

7 Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, *et al*. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 2014; 106:dju124.

8 Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, *et al*. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014; 23:1204–1212.

9 Bamgbola OF. Pattern of resistance to erythropoietin-stimulating agents in chronic kidney disease. Kidney Int 2011; 80:464–474.

10 Gluba-Brzózka A, Franczyk B, Olszewski R, Rysz J. The influence of inflammation on anemia in CKD patients. Int J Mol Sci 2020; 21:725.

11 Shah HH, Uppal NN, Fishbane S. Inflammation and erythropoiesis-stimulating agent hyporesponsiveness: a critical connection. Kidney Med 2020; 2:245–247.

12 Sanghani NS, Haase VH. Hypoxia-inducible factor activators in renal anemia: current clinical experience. Adv Chronic Kidney Dis 2019; 26:253–266.

13 Bamgbola OF, Kaskel FJ, Coco M. Analyses of age, gender and other risk factors of erythropoietin resistance in pediatric and adult dialysis cohorts. Pediatr Nephrol 2009; 24:571–579.

14 Schneider A, Schneider MP, Scharnagl H, Jardine AG, Wanner C, Drechsler C. Predicting erythropoietin resistance in hemodialysis patients with type 2 diabetes. BMC Nephrol 2013; 14:67.

15 Panichi V, Rosati A, Bigazzi R, Paoletti S, Mantuano E, Beati S, *et al*. Anaemia and resistance to erythropoiesis-stimulating agents as prognostic factors in haemodialysis patients: results from the RISCAVID study. Nephrol Dial Transplant 2011; 26:2641–2648.

16 Karaboyas A, Morgenstern H, Fleischer NL, Vanholder RC, Dhalwani NN, Schaeffner E, *et al*. Inflammation and erythropoiesis-stimulating agent response in hemodialysis patients: a self-matched longitudinal study of anemia management in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Kidney Med 2020; 2:286–296.

17 Taymez DG, Ucar E, Turkmen K, Ucar R, Afsar B, Gaipov A, *et al*. The predictive value of platelet/lymphocyte ratio in hemodialysis patients with erythropoietin resistance. Ther Apher Dial 2016; 20:118–121.

18 Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Akbas EM, Ozbicer A, *et al*. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int 2013; 17:391–396.

19 Pineault J, Lamarche C, Bell R, Lafrance J-P, Ouellet G, Leblanc M, *et al*. Association of neutrophil-to-lymphocyte ratio with inflammation and erythropoietin resistance in chronic dialysis patients. Can J Kidney Health Dis 2017; 4:2054358117735563.

20 Catabay C, Obi Y, Streja E, Soohoo M, Park C, Rhee CM, *et al*. Lymphocyte cell ratios and mortality among incident hemodialysis patients. Am J Nephrol 2017; 46:408–416.

21 Li P, Xia C, Liu P, Peng Z, Huang H, Wu J, *et al*. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in evaluation of inflammation in non-dialysis patients with end-stage renal disease (ESRD). BMC Nephrol 2020; 21:511.