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Erythropoietin Resistance Index in Hemodialysis Patients: A Single Moroccan Center Experience

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Abstract

Introduction: Anemia is a common disorder in dialysis patients. The use of high doses of erythropoiesis stimulating agents is associated with poor outcomes in this population. The aim of this study, was to describe the response of ESA treatment in hemodialysis patients and determine the factors that can influence this response. ***Materials and Methods*:** We compared the effectiveness of erythropoietin treatment using the erythropoietin resistance index (ERI). The patients were divided into two groups according to their ERI: group 1 with ERI>10 UI/kg/week/g/100 ml and group 2 ERI ≤10 UI/kg/week/g/100 ml. We evaluated the effects of the anthropometric, demographic, clinical, laboratory and dialytic factors on ERI. ***Results*:** We found that low BMI, low serum albumin, high C-reactive protein, high serum ferritin and high predialysis serum β2 microglobulin levels were associated with high ERI and a hyporesponsiveness to erythropoietin. A multivariate analysis was showed significant association between high ERI and low serum albumin (OR=0.56; p=0.02). ***Conclusion*:** This may provide new contribution into anemia management in Hemodialysis patients. However, more prospective studies with a larger sample population are needed to generalize our results.

Keywords: Anemia, Dialysis, Resistance, Erythropoietin, Morocco, Chronic Kidney Disease.

INTRODUCTION

Hemodialysis (HD) has proven its worth as a successful method for achieving long-term therapy of end- stage kidney disease, and improving the survival probability of those affected in a long-lasting manner [1]. In the kingdom of Morocco, the end-stage kidney disease is considered as a major health problem. Therefore, the prevalence of HD patients is presumed to have increased from 162 per million population (pmp) in 2004 to about 335,79 pmp in 2010 [2], while the latest statistics of the Moroccan Society of Nephrology showed that the number of dialyzed patients was 32250 in 2020 [3].

Anemia is a frequent disorder in dialysis patients [4]. Its incidence increases with the decline of renal function [4]. Moreover, anemia has a significant impact on the disease burden, considerably increasing mortality, morbidity and reducing the quality of life [5].

According to Kidney Disease Improving Global Outcomes guidelines in 2012, the target Hemoglobin in chronic kidney diseases patients is considered to be between 10 and 11.5 g/dl and the main causes of anemia in HD patients are erythropoietin deficiency and iron deficiency [6].

Although, treatment with recombinant human erythropoietin has improved the management of anemia in HD patients, a proportion of patients does not respond well to erythropoietin, which is defined as erythropoietin (EPO) hyporesponsive. Furthermore, the association between high Erythropoiesis-stimulating agents (ESA) doses used and higher mortality has been showed in many studies [7-11]. Therefore, there has been growing interest recently in defining the effective parameters and optimal ESA doses that will be beneficial HD patients to reach this hemoglobin target without increasing their mortality [12].

EPO hyporesponsiveness is a situation to describe the failure to reach the targeted hemoglobin despite higher than usual doses of EPO or a continuous need for higher doses to maintain achieved hemoglobin target. Erythropoiesis resistance index (ERI) is an important evaluation index to evaluate the EPO responsiveness which is calculated by the dose of EPO and the level of hemoglobin [13].

Previous studies have described many variables that may influence the response to EPO such as iron deficiency, dialysis adequacy, inflammatory response, secondary hyperparathyroidism, lower body mass index (BMI) and serum albumin level [14, 15].

The aim of this study, was to describe the response of ESA treatment in HD patients using ERI and determine the factors that can influence this response.

MATERIAL AND METHODS

We conducted between July and September 2024 in the Nephrology dialysis and Kidney Transplantation department of the Mohammed V teaching military Hospital in Rabat Morocco, a cross-sectional study.

Inclusion Criteria:

All chronic HD patients older than 18 years and treated by ESA at least three months.

Exclusion Criteria:

Patients with evidence of cancer, concurrent acute illness, pregnant or history of hematological disorders.

All the patients were treated by the post dilutional hemodiafiltration with Nikkiso DBB EXA and disposable high permeability membrane.

The flow rate ranged from 350-400 ml/mn and the dialysate flow was 500mL/min
All the patients had three weekly sessions four hours each.

Data were collected from medical records and by clinical examination. A proforma created for the study was used for data collection.

We used the ERI to evaluate the dose response ESA treatment.

For Epoetin, the ERI is calculated as the mean weekly epoetin dose per kg body weight divided by the average hemoglobin [16].

For Darbepoetin, we calculated the ERI as the mean weekly darbepoetin dose (multiplied by 200) per kg body weight divided by the average hemoglobin [17].

The patients were divided into two groups according to their ERI:
Group 1: with ERI > 10 U/kg/week/g/100ml
Group 2: with ERI ≤ 10 U/kg/week/g/100ml

The effects of the following factors on ERI were assessed such:

- Anthropometric and demographic data (sex, age, BMI calculated as the weight in kilograms divided by the square of the height in meters. and duration of HD).
- Clinical and laboratory parameters, (hemoglobin levels, transferrin saturation index), ferritin levels, C reactive protein, serum albumin, serum calcium, serum phosphorus, intact parathyroid hormone, vitamin D).
- Dialytic parameters (intra- dialytic weight gain, ekT/V, mean of convection volume, predialysis serum β2-microglobulin levels).

Statistical analysis was recorded using IBM SPSS Statistics software version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages and quantitative variables were presented as the mean and standard deviation or median and interquartile range for variables with symmetric and non-symmetric distributions, respectively. Categorical variables were compared with the λ2 test and quantitative variables were compared with Student's t-test or the Mann–Whitney test. Binary logistic regression analysis was used to evaluate the association between higher ERI and outcome variables A P value <0.05 was considered statistically significant.

Ethical approval for our study was provided by the institution ethics committees (MMTH/IEC/55/2024) and consent was obtained from all patients. This study was performed out in accordance with the Declaration of Helsinki, 2013.

RESULTS

Of the 50 hemodialysis patients, 42 were included in this study.

The mean age was 62.7 ± 16.8 years old, 28 (66,7 %) were female and 14 (33.3%) were male. The mean of BMI was 25.5 ± 4.1Kg/m^2.

The causes of end stage renal disease were diabetic and vascular nephropathies in 15 (35.7%) patients, chronic interstitial nephritis in 11 (26.2%) patients, chronic glomerulonephritis in 5 (11.9%) patients and various kidney diseases in 12 (28.5%) patients.

More than 30 (73.8%) patients had an average of hemoglobin greater than 10 g/dl and the target of hemoglobin (10.0-11.5 g/dL) was achieved.

81% of patients were treated by using darbepoetin and 19% by epoetin α and the mean ERI was 9.9 ± 4.1 U/kg/week/g/100ml.

17 (40.48 %) patients had an ERI > 10 U/kg/week/g/100ml (group 1) and 25 (59.52%) patients had an ERI ≤ 10 U/kg/week/g/100ml (group2).

Table 1 describes the baseline anthropometric, demographic, clinical, dialytic and laboratory characteristics of our patients.

Tables 2,3 and 4 describes demographic, clinical, dialytic and laboratory characteristics in our patients according the ERI groups.

We found that low BMI (p= 0.02), low serum albumin (p<0.001), high C-reactive protein (p=0.001), high serum ferritin (p=0.02) and high predialysis serum β2 microglobulin levels (p=0.04) were associated with high ERI and a hyporesponsiveness to erythropoietin. Whereas, no impact was found between the two groups in age, sex, duration of dialysis, serum calcium and others parameters.

In multivariate binary logistic regression analysis, high ERI levels was associated with low serum albumin (OR=0.56; p=0.02), while BMI, C-reactive protein, serum ferritin and predialysis serum β2-microglobulin levels were not statistically associated, as showen in Table 5.

Table1: Anthropometric, demographic, clinical, dialytic and laboratory parameters in our study

Parameters *	**Results (N=42)**
Age (years) mean ± SD	59.4 ± 15.7
Hemoglobin (g/dl) mean ± SD	11.07 ± 1.16
ERI (U/kg/week/g/100ml) mean ± SD	9.9 ± 4.1
Duration on dialysis (months) median (Interquartiles)	126 (69-219)
Serum Calcium (mg/l) mean ± SD	84.6 ± 12.6
Serum Phosphorus (mg/l) mean ± SD	39.9 ± 12.56
PTHi (pg/ml) median (Interquartiles)	464 (275.2-940.7)
Vitamin D (nmol/l) mean ± SD	27.5 ± 8.1
Hemoglobin(g/dl) mean ± SD	11.07 ± 1.16
Serum ferritin (ng/ml) mean ± SD	464.6 ± 310.9
Transferrin saturation index (%) mean ± SD	29.5 ± 10.9
C reactive protein (mg/l) median (Interquartiles)	4.1 (1.9 – 8.2)
Serum albumin (g/l) mean ± SD	37.14 ± 3.53
eKT/v mean ± SD	1.53 ± 0.2
Interdialytic Weight gain (kg) median (Interquartiles)	2 (1.5-2.5)
Convective Volume (liter) mean ± SD	24.2 ± 1.56

SD: standard deviation, iPTH: intact parathyroid hormone, ERI: Erythropoiesis resistance index
*Non-symmetric distributions quantitative parameters were expressed by median (Interquartiles) and symmetric distributions quantitative parameters were expressed by mean ± SD

Table 2: Demographic and clinical Characteristics of patients in the both ERI groups

Variables *	**Group 1 (N=17)**	**Group 2 (N=25)**	**P value**
Age (years) mean ± SD	62.71 ± 16.82	57.28 ± 14.9	0.27**
Female sex n (%)	11 (39.3)	17 (60.7)	0.82***
BMI (Kg/m^2) mean ± SD	23.81 ± 4.48	26.77 ± 3.53	0.02**
Diabetes mellitus n (%)	4 (33.3)	8 (66.7)	0.73***
History of heart disease n (%)	9 (50)	9(50)	0.27***
Antihypertensives used n (%)	4 (40)	6 (60)	0.63***
History of left ventricular hypertrophy n (%)	6 (46.2)	7 (53.8)	0.43***

SD: standard deviation, BMI: Body mass index
*Categorical variables were expressed as frequencies and percentages and symmetric quantitative variables were expressed by mean ± SD.
**Symmetric distributions quantitative variables were compared with Student's t-test
***Association between categorical variables was tested using Chi-square test while Fischer exact test was used when expected cell count was less than 5

Table 3: Laboratory Characteristics of patients in the both ERI groups

Variables *	Group 1 (N=17)	Group 2 (N=25)	P value
Serum Calcium (mg/l) mean ± SD	80.29 ± 17.58	87.6 ± 6.7	0.06**
Serum Phosphorus (mg/l) mean ± SD	40.82 ± 13.3	39.4 ± 12.28	0.72**
iPTH (pg/ml) Médian (Interquartiles)	499 (351-1103,5)	408 (211-846)	0.32***
Vitamin D (nmol/l) mean ± SD	28.75 ± 10.62	26.9 ± 7.33	0.73**
Serum ferritin (ng/ml) mean ± SD	597.18 ± 381.26	374.52 ± 217.53	0.02**
Transferrin saturation index (%) mean ± SD	28.5 ± 11.81	30.28 ± 10.5	0.627**
Serum albumin (mg/l) mean ± SD	34.94 ± 3.21	38.64 ± 2.94	<0.001**
C reactive protein (mg/l) Médian (Interquartiles)	8 (4.3-18.8)	2.56 (1.45-5.1)	0.001***

SD: standard deviation, iPTH: intact parathyroid hormone

*Non-symmetric distributions quantitative variables were expressed by median (Interquartiles) and symmetric quantitative variables were expressed by mean ± SD

**Symmetric distributions quantitative variables were compared with Student's t-test

***Non-symmetric distributions quantitative variables were compared with the Mann–Whitney test

Table 4: Dialytic Characteristics of patients in the both ERI groups

Variables*	Group 1 (N=17)	Group 2 (N=25)	P value
Duration on dialysis (months) median (Interquartiles)	96 (53-168)	156 (84-270)	0.07***
Interdialytic Weight gain (kg) median (Interquartiles)	2 (1.5-2.5)	2 (1.9-2.5)	0.11***
Predialysis serum β2-microglobulin (mg/l) mean ± SD	30.12 ± 5.51	26.58 ± 27	0.04**
eKT/V mean ± SD	1.54 ± 0.19	1.52 ± 0.22	0.66**
Convective volume (liter) mean ± SD	24.01 ± 1.62	24.33 ± 1.54	0.531**

SD: standard deviation

*Non-symmetric distributions quantitative variables were expressed by median (Interquartiles) and symmetric quantitative variables were expressed by mean ± SD

**Symmetric distributions quantitative variables were compared with Student's t-test

***Non-symmetric distributions quantitative variables were compared with the Mann–Whitney test

Table 5: Binary Logistic Regression for hyporesponsiveness to erythropoietin

Variables	Univariate analysIs OR (95% IC)	P value	Multiivariate analysIs OR (95% IC)	P value
BMI (kg/m^2)	0.82 (0.69-0.98)	0.03	0.75 (0.56-1.01)	0.06
Serum albumin (g/l)	0.65 (0.49-0.87)	0.01	0.56 (0.96-1.15)	0.02*
Serum ferritin (ng/ml)	1.01 (1-1.02)	0.04	1.01 (0.99-1.02)	0.14
C reactive protein (mg/l)	1.10 (0.99-1.22)	0.07	1.05 (0.96-1.15)	0.22
Predialysis serum β2-microglobulin (mg/l)	1.14 (0.99 1.27)	0.06	1.18 (0.9-1.54)	0.23

BMI: Body mass index, OR: Odds ratio

*p-value of < 0.05 was considered significant

Table 6: The mean of The ERI in studies

Studies	Countries and years	Number of patients	Mean of ERI (U/kg/week/g/100ml)
Juan M.Lopez-Gomez *et al*., [19]	Spain (2008)	1710	10.2
Fayez Hejaili *et al*., [20]	Saudi Arabia (2017)	250	10.96
Fatemah Saleh Bin Saleh *et al*., [21]	Saudi Arabia (2018)	130	11
Xiangxue Lu *et al*., [18]	China (2020)	276	12.57
Our Study	Morocco	42	9.9

DISCUSSION

Two variables were used to evaluate the outcomes of patients treated by ESA for anemia such as hemoglobin level and ESA doses. The ERI allows us to describe the response to EPO treatment in a simple way by observing a single parameter. A higher ERI indicated a hyporesponsiveness to erythropoietin, whereas a lower ERI indicated a better responsiveness. In addition, this index allows us to compare groups of patients in different circumstances and to describe the effect of different treatments in the same HD patient. Furthermore, A high ERI is an important predictor of all-cause and cardiovascular mortality [18].

In our study, including 42 HD patients, using EPO to maintain a range of Hb according KDIGO

guidelines, we found that 75% of our patients have an average of hemoglobin greater than 10 g/dl and the target of hemoglobin was achieved and the mean of ERI was 9.9 ± 4.1 UI/kg/week/g/100ml.These findings were in agreement with previous publications observing range of ERI between 10 and 13 UI/kg/week/g/100ml, as showen in Table 6 [18-21].

Although, iron deficiency is the usual causes of EPO hyporesponsiveness [13]. The current routine use of parenteral iron therapy was a major reason to consider the other causes of high ERI such a malnutrition and an inflammatory state. In our study, we did not evaluate the all the nutritional parameters of the HD patients. However, we found that HD patients with low BMI, low serum albumin, high serum CRP level and high serum ferritin were associated with significantly high ERI. These results confirm that the malnutrition-inflammation complex can contribute to a decreased to EPO response. Therefore, nutritional parameters were closely related to inflammation state and atherosclerosis and though common mediators such as TNFα and IL6, it may play a fundamental role in the response to EPO treatment [22].

In the past few years, three studies elucidated an association between the resistance to ESA in HD patients and low BMI [15-24]. Our findings indicated that better responses to EPO treatment were achieved in HD patients with high BMI. This association may reflect a modulated response in patients with higher BMI mediated by autocrine regulation. Leptin, which is higher in obese HD patients, has been found to stimulate erythropoiesis [24]. Obesity and higher BMI also provides protection against malnutrition.

Several studies have found that lower Kt/v was associated with ESA hyporesponsiveness. In our study all of patients had high Kt/v and the effect of the dose of dialysis have been probably camouflaged [25].

The use of online hemodiafiltration with high convective volume has been related with reduced EPO needs [15-26]. In our study, all patients were treated by the post dilutional hemodiafiltration and we found that high predialysis serum β2-microglobulin levels was associated with high ERI and no impact were described about the convective volume. Whereas, in multivariate binary logistic regression analysis, high ERI levels was only associated with low serum albumin (OR=0.56; p=0.02). Therefore, in HD patients serum albumin is not only an indicator of nutritional status, but also has been reported to be a good predictive variable of response to EPO treatment [27].

Physiologically, in the general population several studies found that women have lower hemoglobin than men, which is explicated to the effect of estrogens and androgens on erythropoiesis [28], these findings were confirmed in HD patients by other studies revealed that female sex was associated with EPO hyporesponsiveness [19-29]. However, in our study we found no significant association between the gender and the response to EPO.

Previous studies have shown that older age and secondary hyperparathyroidism were associated with higher ERI [19]. Thus, hyperparathyroidism inhibits erythropoiesis secondary to bone marrow fibrosis and has been described as a predictive factor for increased the ERI [30]. However, in this study neither age or hyperparathyroidism had any relationship on the ERI.

Our study has certain limitations, such it's a single-center study with a small sample size. Furthermore, this is a cross-sectional study, which excludes any conclusion regarding factors associated with high ERI.

CONCLUSIONS

In this study, we showed that the hyporesponsiveness to erythropoietin treatment was associated to low albumin concentration. Therefore, this may provide new contribution into anemia management in HD patients. However, more prospective multicentric studies with a larger sample population are needed to generalize our results and to analysis others confounding factors.

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REFERENCES

1. O'connor, N. R., & Corcoran, A. M. (2012). End-stage renal disease: symptom management and advance care planning. *American family physician*, *85*(7), 705-710.
2. Benghanem, G. M. (2010). Renal replacement therapies for end- stage renal disease in North Africa. *Clin Nephrol*, *1*, S17-9.
3. Alaoui, A. C., Elomari, M., Qarmiche, N., Kouiri, O., Chouhani, B. A., El Rhazi, K., ... & Tachfouti, N. (2023). Management of Chronic Kidney Disease in Morocco: A Cost-of-Illness Study. *Cureus*, *15*(6).
4. Li, Y., Shi, H., Wang, W. M., Peng, A., Jiang, G. R., Zhang, J. Y., ... & Chen, N. (2016). Prevalence, awareness, and treatment of anemia in Chinese patients with nondialysis chronic kidney disease: first multicenter, cross-sectional study. *Medicine*, *95*(24), e3872.
5. Stenvinkel, P., Heimbürger, O., Lindholm, B., Kaysen, G. A., & Bergström, J. (2000). Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). *Nephrology Dialysis Transplantation*, *15*(7), 953-960.

6. McMurray, J., Parfrey, P., Adamson, J. W., Aljama, P., Berns, J. S., Bohlius, J., ... & Weiss, G. (2012). Kidney disease: Improving global outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney International Supplements*, 279-335.
7. Kim, I. Y., Kim, J. H., Kim, M. J., Lee, D. W., Hwang, C. G., Han, M., ... & Lee, S. B. (2018). Low 1, 25-dihydroxyvitamin D level is associated with erythropoietin deficiency and endogenous erythropoietin resistance in patients with chronic kidney disease. *International Urology and Nephrology*, *50*, 2255-2260.
8. Drüeke, T. B., Locatelli, F., Clyne, N., Eckardt, K. U., Macdougall, I. C., Tsakiris, D., ... & Scherhag, A. (2006). Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *New England Journal of Medicine*, *355*(20), 2071-2084.
9. Singh, A. K., Szczech, L., Tang, K. L., Barnhart, H., Sapp, S., Wolfson, M., & Reddan, D. (2006). Correction of anemia with epoetin alfa in chronic kidney disease. *New England Journal of Medicine*, *355*(20), 2085-2098.
10. Besarab, A., Bolton, W. K., Browne, J. K., Egrie, J. C., Nissenson, A. R., Okamoto, D. M., ... & Goodkin, D. A. (1998). The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *New England Journal of Medicine*, *339*(9), 584-590.
11. Pfeffer, M. A., Burdmann, E. A., Chen, C. Y., Cooper, M. E., De Zeeuw, D., Eckardt, K. U., ... & Toto, R. (2009). A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *New England Journal of Medicine*, *361*(21), 2019-2032.
12. Drüeke, T. B., & Parfrey, P. S. (2012). Summary of the KDIGO guideline on anemia and comment: reading between the (guide) line (s). *Kidney international*, *82*(9), 952-960.
13. Coyne, D. (2010). "It's time to compare anemia management strategies in hemodialysis," *Clinical Journal of the American Society of Nephrology*, *5*(4), 740–742
14. Szczech, L. A., Barnhart, H. X., Sapp, S., Felker, G. M., Hernandez, A., Reddan, D., ... & Singh, A. K. (2010). A secondary analysis of the CHOIR trial shows that comorbid conditions differentially affect outcomes during anemia treatment. *Kidney International*, *77*(3), 239-246.
15. El-Kannishy, G. M., Megahed, A. F., Tawfik, M. M., El-Said, G., Zakaria, R. T., Mohamed, N. A., ... & Sayed-Ahmed, N. A. (2018). Obesity may be erythropoietin dose-saving in hemodialysis patients. *Kidney Research and Clinical Practice*, *37*(2), 148.
16. Chait, Y., Kalim, S., Horowitz, J., Hollot, C. V., Ankers, E. D., Germain, M. J., & Thadhani, R. I. (2016). The greatly misunderstood erythropoietin resistance index and the case for a new responsiveness measure. *Hemodialysis International*, *20*(3), 392-398.
17. Aljama, P., Bommer, J., Canaud, B., Carrera, F., Eckardt, K. U., Hörl, W. H., ... & Wikström, B. (2001). Practical guidelnes for the use of NESP in treating renal anaemia. *Nephrology Dialysis Transplantation*, *16*(suppl_3), 22-28.
18. Lu, X., Zhang, J., Wang, S., Yu, Q., & Li, H. (2020). High Erythropoiesis Resistance Index Is a Significant Predictor of Cardiovascular and All-Cause Mortality in Chinese Maintenance Hemodialysis Patients. *Mediators of inflammation*, *2020*(1), 1027230.
19. López-Gómez, J. M., Portolés, J. M., & Aljama, P. (2008). Factors that condition the response to erythropoietin in patients on hemodialysis and their relation to mortality: New strategies to prevent cardiovascular risk in chronic kidney disease. *Kidney International*, *74*, S75-S81.
20. Hejaili, F., Hafeez, E., Bhutto, B., Al Turki, L., Alsuwida, A. K., Raza, H., & Al-Sayyari, A. (2017). Variables affecting darbepoetin resistance index in hemodialysis patients. *Saudi Journal of Kidney Diseases and Transplantation*, *28*(4), 737-742.
21. Saleh, F. S. B., Naji, M. N., Eltayeb, A. A., Hejaili, F. F., & Al Sayyari, A. A. (2018). Effect of thyroid function status in hemodialysis patients on erythropoietin resistance and interdialytic weight gain. *Saudi Journal of Kidney Diseases and Transplantation*, *29*(6), 1274-1279.
22. Rattanasompattikul, M., Molnar, M. Z., Zaritsky, J. J., Hatamizadeh, P., Jing, J., Norris, K. C., ... & Kalantar-Zadeh, K. (2013). Association of malnutrition–inflammation complex and responsiveness to erythropoiesis-stimulating agents in long-term hemodialysis patients. *Nephrology Dialysis Transplantation*, *28*(7), 1936-1945.
23. do Sameiro-Faria, M., Ribeiro, S., Rocha-Pereira, P., Fernandes, J., Reis, F., Bronze-da-Rocha, E., ... & Santos-Silva, A. (2013). Body mass index and resistance to recombinant human erythropoietin therapy in maintenance hemodialysis patients. *Renal failure*, *35*(10), 1392-1398.
24. Vega, A., Ruiz, C., Abad, S., Quiroga, B., Velázquez, K., Yuste, C., ... & López Gómez, J. M. (2014). Body composition affects the response to erythropoiesis-stimulating agents in patients with chronic kidney disease in dialysis. *Renal failure*, *36*(7), 1073-1077.
25. Movilli, E., Cancarini, G. C., Vizzardi, V., Camerini, C., Brunori, G., Cassamali, S., & Maiorca, R. (2003). Epoetin requirement does not depend on dialysis dose when Kt/N> 1.33 in patients on regular dialysis treatment with cellulosic membranes and adequate iron stores. *Journal of Nephrology*, *16*(4), 546-551.
26. Maduell, F., Navarro, V., Torregrosa, E., Rius, A., Dicenta, F., Cruz, M. C., & Ferrero, J. A. (2003). Change from three times a week on-line hemodiafiltration to short daily on-line

hemodiafiltration. *Kidney international*, *64*(1), 305-313.

27. Macdougall, L. G., Moodley, G., Eyberg, C., & Quirk, M. (1982). Mechanisms of anemia in protein-energy malnutrition in Johannesburg. *The American Journal of Clinical Nutrition*, *35*(2), 229-235.
28. Murphy, W. G. (2014). The sex difference in haemoglobin levels in adults—mechanisms, causes, and consequences. *Blood reviews*, *28*(2), 41-47.
29. Daza, J. C., & Cuchi, G. U. (2019). Gender differences in dose of erythropoietin to maintain hemoglobin target in hemodialysis patients. *Indian Journal of Nephrology*, *29*(3), 160-165.
30. Al-Hilali, N., Al-Humoud, H., & Ninan, V. T. (2007). Does parathyroid hormone affect erythropoietin therapy in dialysis patients? *Med Princ Pract*, *16*(1), 63–67.