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Risk factors associated with hyporesponse to erythropoietin in chronic kidney disease patients on hemodialysis who present anemia. A multicenter observational study.

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Abstract

Introduction: Anemia is common in patients with chronic kidney disease (CKD) and is associated with higher mortality and lower quality of life. The introduction of recombinant erythropoietin represented an advance in the management of anemia; however, an increase in the rate of cardiovascular disease and stroke was observed. Usually, anemia is partially corrected, with cases of hyporesponsiveness to treatment being found.

Methods: Observational, analytical, multicenter case–control study.

Results: Of 784 patients, 123 presented hyporesponsiveness (15.69%). The risk factors identified were: female sex (OR=2.188), age less than 50 years (OR=3.846), body mass index less than 23 kg/m² (OR=1.598), use of renin-angiotensin system blockers (OR=1.915), albumin less than 4.0 (OR=5.286), ferritin greater than or equal to 800 ng/ml (OR=4.775), transferrin saturation index (TSI) less than 20% (OR=5.803) and parathormone greater than or equal to 500 µ g/ml (OR=2.183). In the multivariate model, these variables were significant (P <0.05, R^2: 0.56) except for Diabetes and BMI (P >0.05).

Conclusion: Female sex, age less than 50 years, BMI less than 23 kg/m², ARB use, low albumin, elevated ferritin, low TSI, and elevated parathormone are risk factors associated with erythropoietin hyporesponsiveness.

Keywords:

Renal replacement therapy, hemodialysis, erythropoietin hyporesponsiveness, erythropoietin resistance, erythropoiesis-stimulating agents, anemia.

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Cchronic kidney disease (CKD) is recognized worldwide as a significant public health problem. It is estimated that between 4,902 and 7,083 million people with advanced CKD need renal replacement treatment. The estimated global incidence of CKD is 13.4% (11.7–15.1%) [1].

Due to its impact on cardiovascular risk, CKD directly contributes to the global burden of morbidity and mortality [1]. In Ecuador, CKD is the fifth cause of premature death and the fourth cause of general mortality, and it is estimated that between 6% and 7% of deaths in Ecuador are attributable to CKD [2]. In 2018, 17,484 patients were found on dialysis, or 567 per million inhabitants [3]. In its technical report, the National Directorate of Specialized Centers stated that by November 2022, there was a record of 21,394 patients in the Ecuadorian Registry of Dialysis and Renal Transplantation (REDT) [4].

Anemia is one of the leading causes of morbidity in individuals with advanced CKD [3]. Patients with chronic kidney disease frequently experience anemia, caused mainly by the decreased ability of kidney parenchyma cells to produce erythropoietin in the most severe stages. The primary treatment for anemia in patients with CKD on hemodialysis is erythropoiesis-stimulating agents; however, the response to these agents is affected by a wide range of factors, such as iron deficiency, secondary hyperparathyroidism, parameters related to hemodialysis (adequacy), systemic inflammation, malnutrition, and some other medications used to treat comorbidities [5].

Given that both low hemoglobin levels and high doses of erythropoiesis-stimulating agents are related to increased mortality, the presence of a state of this low response is closely related to a decrease in survival, largely dependent on high doses of erythropoiesis-stimulating agents rather than noncompliance with the hemoglobin target [5].

The incorporation of recombinant human erythropoietin in the treatment of anemia of renal origin has been the most significant advance in managing this complication in patients with CKD; however, a percentage of patients respond poorly or do not respond at all to this therapy [6].

Anemia has been associated with several unfavorable clinical outcomes and a significantly lower quality of life in patients with CKD. Before recombinant human erythropoietin is available, dialysis patients often require blood transfusions, which expose them to the risk of iron overload, transmission of viral hepatitis, and sensitization to human leukocyte antigen, all of which decrease their chances of receiving a successful transplant in the future [7].

Erythropoiesis-stimulating agents at doses greater than 6,000 units per week have been associated with a 1.2- to 1.5-fold increased risk of mortality [8]. Treatment to normalize hemoglobin levels in the general population can have adverse effects, so it is imperative to weigh the advantages and risks of interventions rationally [7].

Understanding the risks involved in the use of high doses of erythropoiesis-stimulating agents, early identification of factors that may be related to an inadequate response to treatment with erythropoiesis-stimulating agents, and limitations in achieving target levels of hemoglobin are needed to improve the outcomes of patients with CKD on hemodialysis. Some of these factors are modifiable, allowing early interventions to be implemented to avoid complications associated with high doses of erythropoiesis-stimulating agents, especially morbidity and mortality.

The objective of the present study was to establish the risk factors associated with hyporesponsiveness to treatment with erythropoietin in a population of patients with chronic kidney disease on hemodialysis in hemodialysis centers from January to December 2019.

Materials and methods

Kind of investigation

The present study is based on an observational, analytical, multicenter case-control design and documentary-based, secondary source study through collecting and analyzing data obtained from records anonymized from the source.

Scenery

Six hemodialysis centers from the complementary health network participated: Nefromedic, Clínica de los Riñones Menydial, located in Ibarra, Quito, Ambato, Riobamba North, and Riobamba South. The study period was January 1, 2019, to December 31, 2019.

Universe and sample

The universe of the study corresponds to the anonymized documentary records of patients diagnosed with chronic kidney disease who received hemodialysis at the complementary health network dialysis centers and the same patients who had

anemia and received treatment with erythropoietin during the study period.

To develop the study, the following definitions are used:

The cases corresponded to the records of patients with chronic kidney disease who received hemodialysis and who presented anemia with a hyporesponse to treatment with erythropoietin, defined by the need for doses of erythropoietin greater than or equal to 200 IU/kg/week during the period described.

The controls correspond to the records of patients with chronic kidney disease who received hemodialysis and who presented anemia with an adequate response to treatment with erythropoietin, defined by the need for doses of erythropoietin less than 200 IU/kg/week during the period described.

Sample size

The present study has a case-control design for which the statistical formula for calculating the sample size was as follows:

$$n=(Z_{\frac{\alpha}{2}}\sqrt{(m+1)p(1-p)}+ Z_{\beta}\sqrt{mP_1(1-P_1)+P_2(1-P_2)})^2/\, m(P_1-P_2)^2$$

An association coefficient (OR) of 3 was significantly different from 1. According to previous studies and estimates, the prevalence of hyporesponsiveness to treatment with agents of erythropoiesis stimulants ranges from 12.5% to 30.3% [5-7]. A presumption of exposed controls of 70% is estimated, with a proportion of cases of 0.87, a confidence level of 95%, and 90% power. For this study, 113 cases and 113 controls were needed; however, the entire population was included, which included 123 cases and 661 controls who met the inclusion and exclusion criteria, respectively, to guarantee adequate operationalization of the variables.

Inclusion criteria

Patients older than 18 years of age with a diagnosis of advanced chronic kidney disease, who were receiving hemodialysis at least three months before data collection, and who presented anemia while receiving treatment with erythropoietin (dose greater than or equal to 200 IU/kg/week for more than three consecutive months) or doses less than 200 IU/kg/week) during the study period were included.

Exclusion criteria

Patients with incomplete data, those hospitalized in the last three months before data collection, or those who received blood transfusions in the previous three months were excluded.

Variables

The following variables were taken into account: response to erythropoietin, age, sex, history of diabetes mellitus, hypothyroidism, body mass index, parathormone, ferritin, transferrin saturation index, albumin, urea reduction rate, KT/V, time on hemodialysis, renin-angiotensin system blockers and death. The dependent variable was the response to erythropoietin. Two groups of patients (responders and hypo-responders) were defined according to whether they met the inclusion and exclusion criteria for cases and controls.

Techniques and instruments

The data were collected from the anonymized documentary records of patients treated in the dialysis centers of the complementary health network to be physically tabulated in an information collection form, which was created as an instrument for this research work.

The anonymized database contains patient demographic data, anthropometry, medications administered each month (erythropoietin, iron, ACEIs, and ARA II), clinical laboratory parameters, dialysis treatment records, and the adequacy parameters and comorbidities of the dialysis units. Anonymized records were obtained, establishing a monthly sequence of the doses of erythropoietin alfa used. The medical charts show the value of erythropoietin in monthly accumulated international units; therefore, conversion was carried out until the dose of erythropoietin was obtained per kilogram and week (IU/kg/wk).

Based on previous studies in which the possibility of restoring the responsiveness to erythropoiesis-stimulating agents of less than or equal to 4 months was determined [8 - 10], it was decided to consider patients with hyporesponses who warranted a higher dose of erythropoietin or equal to 200 IU/kg/week for a period greater than or equal to 3 consecutive months from the baseline. The baseline dose was defined as the month when the erythropoietin dose was increased to 200 IU/kg/week or more.

The data from the registry correspond to those presented in the month corresponding to the baseline. In the case of bimonthly or quarterly examinations, the last reported values were taken according to the schedule of laboratory examinations required by the Ministry of Public Health of Ecuador as a health control entity. The data of the controls were taken from a random month as long as they completed at least three months of hemodialysis.

The information obtained corresponds to data correlated in previous studies as risk factors, described in this work's

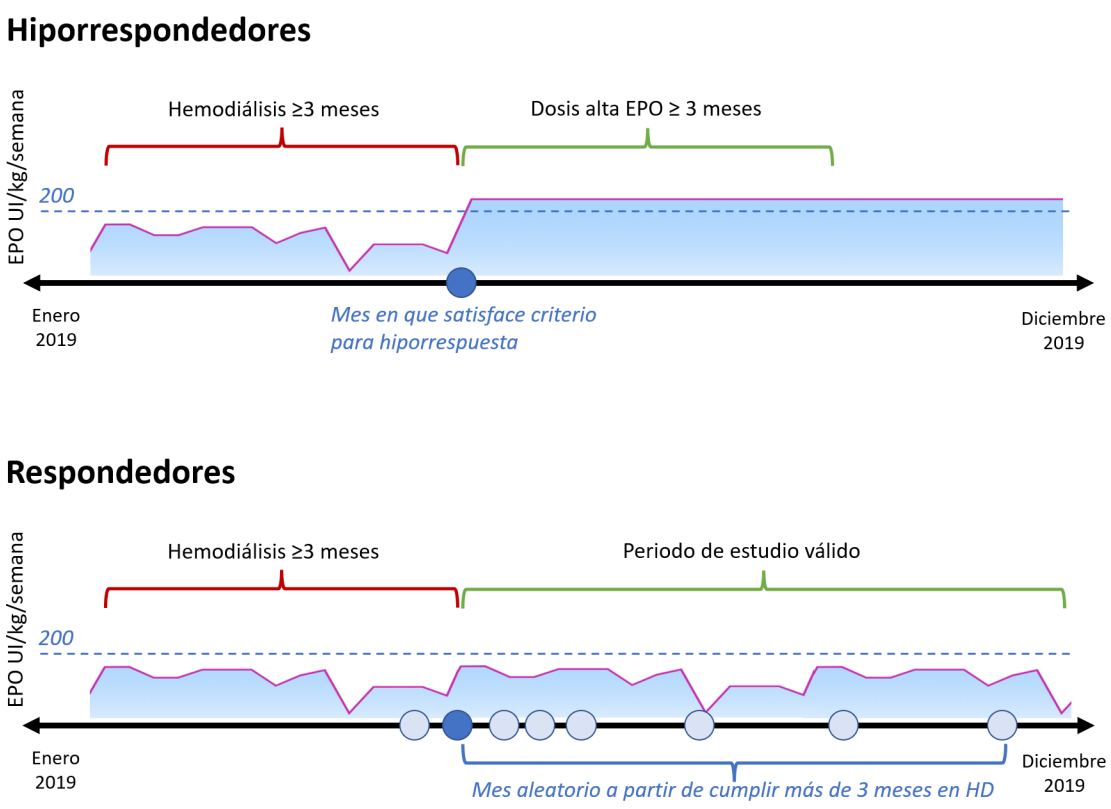
reference framework. Figure 1 represents the selected records according to earlier methods.

Information analysis

The digital database was analyzed with the SPSS statistical program in version 25. One control was taken for each patient. The normality of the distribution of each quantitative variable was determined using the Kolmogorov–Smirnov normality test. Quantitative variables with a normal distribution are expressed as the mean and standard deviation; quantitative variables with a nonnormal distribution are described as the median and 10th-90th percentiles; and qualitative variables are expressed as numbers and percentages.

Bivariate analysis of the groups was performed to compare the dependent variable corresponding to "response to treatment with erythropoietin" with the other variables included in the study (age, sex, body mass index, time on dialysis, ferritin, transferrin saturation index, KT/V, hours of dialysis treatment, urea reduction rate, hypothyroidism, parathormone, albumin, and renin-angiotensin system blockers); the $\chi 2$ test was used for the comparison of qualitative variables, and Student's t-test was employed for the comparison of quantitative variables. Tables (2x2) were made to obtain odds ratios (ORs), considering a result > one as a positive association to determine exposure as a risk factor.

Figure 1. Procedure for inclusion of cases and controls.



The values of each calculated OR are presented with their respective 95% confidence intervals.

A binary logistic regression was performed using the variable "Response to treatment with erythropoietin" as the dependent variable for the multivariate analysis. The independent variables that were significant in the bivariate analysis were included in the study.

The quantitative variables were categorized into age, time on hemodialysis, ferritin, body mass index, transferrin saturation, albumin, urea reduction rate, and KT/V to convert them into dichotomous variables. The cutoff values of these variables are based on the results of previous studies and comparisons of the means of the case and control groups. For all the statistical analyses, a significance level of 5% at an alpha error was used ($P = 0.05$).

Results

Study participants

The study included 784 patients, and erythropoietin alfa was used as the only erythropoiesis-stimulating agent. Of the 784 patients who received treatment with erythropoietin, 123 had a hyporesponse (15.69%, 95% CI 6.829-16.44) during the study period, and 661 were classified as responders.

Table 1. General characteristics of the study population.

	Responders n= 661	Underresponders n= 123	*P* value
Female Sex	254 (38.4%)	71 (57.7%)	<0.001*
Age (years)	63 (40-78)	50 (28-74)	<0.001*
Time on hemodialysis (months)	28 (5-76)	29 (7-75)	0.385
Body mass index (kg/m²)	23.7 (19.46-29.69)	22.98 (19.03 –27.73)	0.005*
Body mass index classification			
Under weight	35 (5.3%)	6 (4.9%)	
Normal	383 (58%)	85 (69.1%)	
Overweight	182 (27.5%)	27 (22%)	
Obesity	61 (9.2%)	5 (4.1%)	
Erythropoietin dose (IU/kg/week)	89.41 (42.3-150.62)	247.42 (215.7-343.94)	<0.001*
Comorbidities			
Diabetes	226 (34.2%)	30 (24.4%)	0.033*
Hypothyroidism	30 (4.5%)	6 (4.9%)	0.869
Medicines			
Use of SRA Blockers	244 (36.9%)	65 (52.8%)	<0.001*
Factors related to hemodialysis			
Urea reduction rate (%)	70.11 (62.30-78.13)	70.00 (65.00 - 75.80)	0.716
Kt/v	1.5 (1.2-1.82)	1.5 (1.29-1.71)	0.465
Vascular access (Catheter)	70 (10.6%)	15 (12.2%)	0.648
Laboratory parameters			
Albumin (g/dL)	4.32 (3.79-4.6)	3.96 (3.41-4.29)	<0.001*
Hemoglobin (g/dL)	11.3 (10.0-12.6)	10.0 (8.4-11.0)	<0.001*
Hematocrit (%)	33.3 (29.5-37.17)	29.5 (24.78-32.45)	<0.001*
Ferritin (ng/ml)	723.93 (118.45-1761.82)	1350.9 (538.68-2000)	<0.001*
Transferrin saturation (%)	34.00 (22.00-47.37)	30.21 (11.48-50.40	<0.001*
Parathormone (µg/ml)	356.48 (132.2-1081.44)	511.3 (146.5-2030.2)	<0.001*

*P value: statistically significant. SRA: Renin Angiotensin System.

Table 2. Bivariate analysis of factors associated with the presence of hyporesponsive to erythropoietin: General characteristics

	Cases n= 123	Controls n= 661	OR (95%CI)	*P* value
Sex woman vs man	71 (57.7%)	254 (38.4%)	2,188 (1,480-3,233)	<0.001*
Age (years) <50 vs. ≥50	56 (45.5%)	118 (17.9%)	3,846 (2,560-5,778)	<0.001*
Time on Hemodialysis (months) <28 vs. ≥28	65 (52.8%)	327 (49.5%)	1.145 (0.779-1.683)	0.492
Body mass index (kg/m²) <23 vs. 23	62 (50.4%)	257 (38.9%)	1,598 (1,086-2,352)	0.017*
Comorbidities				
Diabetes	30 (24.4%)	226 (34.2%)	0.621 (0.399-0.966)	0.033*
Hypothyroidism	6 (4.9%)	30 (4.5%)	1.079 (0.439-0.504)	0.869
Medicines				
Blockers of the Renin Angiotensin system	65 (52.8%)	244 (36.9%)	1,915 (1,300-2,822)	<0.001*
Treatment parameters				
Urea reduction rate (%) <70%	8 (6.5%)	40 (6.1%)	1,080 (0.493-2,367)	0.848
Ktv <1.3	13 (10.6%)	66 (10.0%)	1,065 (0.568-1,998)	0.843
Vascular Access Catheter	15 (12.2%)	70 (10.6%)	1.173 (0.647-2.124)	0.599
Laboratory parameters				
Albumin <4.0 g/dL	67 (54.5%)	122 (18.5%)	5,286 (3,523-7,930)	<0.001*
Ferritin ≥800 ng/ml	98 (79.7%)	298 (45.1%)	4,775 (2,999-7,603)	<0.001*
Transferrin Saturation <20%	36 (29.3%)	44 (6.7%)	5,803 (3,539-9,513)	<0.001*
Parathormone ≥500 µg/ml	62 (50.4%)	210 (31.8%)	2,183 (1,479-3,223)	<0.001*

*P value: statistically significant.

Table 3 . Multivariate analysis of factors associated with hyporesponsive to erythropoietin.

	β	*P* value	OR	(95%CI)
Female Sex	0.672	0.007	1959	1,199 – 3,201
Age <50 years	1,447	<0.001	4,249	2,419 – 7,465
BMI <23 kg/m²	0.012	0.963	1,012	0.607 – 1.688
Albumin <4.0 g/dl	2,355	<0.001	10,533	6,080 – 18,250
Ferritin ≥800 ng/ml	1986	<0.001	7,284	4,059 – 13,069
Transferrin Saturation <20%	2,226	<0.001	9,265	4,797 – 17,894
Parathormone ≥500 µg/ml	0.636	0.011	1,889	1,160 – 3,077
Diabetes	-0.247	0.405	0.781	0.437 – 1.397
Blockers of the Renin Angiotensin system	0.809	0.002	2,246	1,333 – 3,787

*P value: statistically significant.

Characteristics of the study groups

There were differences in the hypo responder group, which included a significantly higher proportion of women, older age, and greater use of antihypertensive renin-angiotensin system blockers. Additionally, there was a lower prevalence of diabetes among hyporesponders (Table 1). There was no difference in the factors related to the hemodialysis process between the groups; they had the same Kt/V, the same urea reduction rate, or the exact incidence of vascular access via catheters (Table 1).

According to the laboratory parameters, the hypo-responders had lower serum ALB, hemoglobin, transferrin saturation, ferritin, and parathyroid hormone levels (Table 1).

Main results

The risk factors associated with hyporesponsiveness were female sex, age less than 50, body mass index less than 23 kg/m2, and renin-angiotensin system blockers. Diabetes, as the cause of chronic kidney disease, was a protective factor (Table 2). Within the treatment parameters, there were no associated factors. Among the laboratory test results, the risk factors were hypoalbuminemia, hyperferritinemia, secondary hyperparathyroidism, and a low transferrin saturation percentage (Table 2).

Multivariate analysis

For the multivariate analysis, a logistic regression model was used. The R^2 value of the model was 0.564. The variables included in the model were sex, age, body mass index, albumin concentration, ferritin concentration, transferrin saturation, parathyroid hormone level, presence of diabetes, and use of renin-angiotensin system blockers (Table 3).

Discussion

In the present study, risk factors associated with a hyporesponse to treatment with erythropoietin were investigated in patients with chronic kidney disease who were receiving hemodialysis and who presented with anemia. Anonymized records from 6 different dialysis centers were included in this multicenter study. The risk factors were female sex, age less than 50 years, an albumin concentration less than 4.0 g/dl, a ferritin concentration greater than or equal to 800 ng/ml, a transferrin saturation less than 20%, a parathyroid hormone level greater than or equal to 500 µg/ml and the use of renin–angiotensin system blockers.

The prevalence of hyporesponsiveness was 15.69% for this group. In other studies, it has been reported to be 12.5-30.3% [11]. In this study, female sex was a risk factor for hyporesponsiveness, with an OR of 2.188 according to the bivariate analysis and 1.959 according to the multivariate model. This condition gives the female sex almost twice the probability of presenting an inadequate response to treatment with erythropoietin, the results of which agree with other studies of hypo responder patients, in which the prevalence of pregnancy was 56% [12]. Several studies, which included 7,009 patients in Iran, found that male sex was the predominant sex among the evaluated group of patients who achieved target hemoglobin levels (>10 g/dL) [5]. There tends to be a greater incidence of CKD with advancing age, but among women with CKD, anemia is more common at younger ages [13]. A likely explanation is the more significant iron deficiency present in menstruating women, sex hormones, and perhaps poor nutritional intake[14].

Patients aged less than 50 years were approximately four times more likely to have a hyporesponse (OR=3.846 and OR=4.249) in the present study. Similar results were described in a multicenter cross-sectional survey by Nafar et al. The mean age of patients who did not reach hemoglobin goals (>10 g/dL) was 55.7 ± 15.3 years greater than that of patients who did reach the hemoglobin goal (57.8 ± 14.7); this association between older age and improved hemoglobin levels was statistically significant ($P < 0.001$)[5].

Bivariate analysis revealed that patients with a body mass index less than 23 kg/m² were almost 1.6 times more likely to exhibit hyporesponsiveness. Multivariate analysis did not reveal statistical significance. In this regard, a cross-sectional study carried out by Locatelli et al., which aimed to evaluate the response to treatment with erythropoietin, revealed that patients who had a lower response rate to erythropoietin had a greater mean mass index than did those who had a higher response rate to erythropoietin (body mass index) (24.9 ± 4.3 vs. 21.3 ± 3.8 kg/m²) [6]. In contrast, two studies found no significant difference in mean body mass index between hypo responders and hypo responders to erythropoietin [5, 6].

This study showed that patients with a serum ALB concentration less than 4.0 g/dL were 2.3 to 5 times more likely to exhibit hyporesponsiveness (according to multivariate and bivariate analyses, respectively), and these differences were statistically significant. These results agree with previous studies [6], assuming that an outstanding nutritional status is essential for responding to erythropoietin.

There are numerous epidemiological studies described in the current literature that show a paradoxical association between obesity and increased survival, with increased mortality rates in dialysis patients who had a BMI less than 25 kg/m² [15]. Within the definitions of malnutrition and protein-energy wasting issued by a panel of experts from the International Society of Renal Nutrition and Metabolism (ISRNM), we considered albumin levels less than 3.8 g/dl and a BMI less than 23 kg/m^2. These criteria are used in nutritional assessment studies for patients with CKD on hemodialysis [14]. The identification of BMI <23 kg/m2 and albumin <4.0 g/dL as risk factors for hyporesponse to treatment with erythropoietin can be explained by the diagnosis of protein-energy wasting, beyond the

traditional cutoffs of malnutrition, such as low weight based on WHO BMI (<18.5 kg/m ^{2}) or hypoalbuminemia (<3.5 g/dL). Additionally, adipose tissue secretes leptin, which has been shown to stimulate human erythroid development in vitro [16]. In a study of 479 African American CKD patients on hemodialysis, erythropoietin requirements were reduced, and erythropoietin resistance improved in patients with high total adipose and subcutaneous adipose tissue[16].

According to the present study, patients with a blood ferritin level greater than or equal to 800 ng/ml are approximately 5 to 7 times more likely to have a hyporesponse to erythropoietin. These results agree with those published in a cohort of 6645 European patients with CKD receiving hemodialysis and who received treatment with erythropoiesis-stimulating agents[17]. Patients were grouped according to ferritin levels; in this way, those with ferritin levels greater than 800 were three times more likely to have a hyporesponse, and those with ferritin levels between 500 and 799 were twice as likely (OR=3.46 and OR=2.21, respectively) [17]. The serum ferritin concentration is known to be positively correlated with inflammatory markers (C-reactive protein and interleukin-6)[18]. In inflammatory states, an increase in ferritin levels occurs independently of iron status [18]. Proinflammatory cytokines such as tumor necrosis factor-alpha and interleukins 1, 6, and 10 can induce ferritin expression and stimulate iron storage within macrophages, thereby reducing the level of circulating iron and the availability of iron for use by erythroid cells [9]. International guidelines for managing iron deficiency anemia recommend iron supplementation up to an upper limit between 500 and 800 ng/ml to avoid iron overload [18].

Another study reported a less than 20% transferrin saturation level in patients with a hyporesponse to erythropoietin. This triggered an increase of between 5 and 9 times the risk in patients treated with erythropoietin. In agreement with these results, Cizman et al. reported a more significant percentage of patients with a TRF saturation less than 20% in the hypo responder group (26.5% vs. 10.9%) and even a lower mean TRF saturation value in hypo responders (27.7 ± 13.2 vs. 32.9 ± 14.0%) [12]. Other studies have not shown this difference [17, 19]. Studies that address functional iron deficiency are associated with absolute iron deficiency combined with a hyporesponse to erythropoietin; there is a more excellent distribution of functional iron deficiency among patients who do not reach the target hemoglobin levels, both for those who presented absolute deficiency (15.8% vs. 12.9%) and for those with a functional deficit (40.5% vs. 36.7%), both with a *P* value <0.001[5]. Functional iron deficiency may be related to the administration of erythropoiesis-stimulating agents or inflammatory blockade of available iron in the pathophysiology of anemia in patients with chronic disease. In the first case, total body iron stores are adequate. Nevertheless, the release of iron from stores into circulation is not rapid enough to provide sufficient iron to support the increased erythropoietic rate driven by erythropoiesis-stimulating agents.

On the other hand, in chronic disease, there is an underlying inflammatory state mediated partly by hepcidin, whose levels are elevated in CKD patients and increase as the glomerular filtration rate decreases. Hepcidin reduces the ability of reticuloendothelial cells and hepatocytes to recruit iron stores for erythropoiesis [20]. Absolute iron deficiency was defined by severely reduced or absent iron stores in the bone marrow, liver, and spleen. This may be due to decreased iron absorption and increased iron loss (1-3 g/year). This iron loss is due to gastrointestinal bleeding resulting from the combination of gastritis and platelet dysfunction and, in addition, a higher rate of blood loss during dialysis related to frequent phlebotomies and blood remaining in the dialysis tubing that contributes to the loss of iron [20]. An excessive iron load can induce hepcidin and suppress erythropoiesis; judicious and accurate regulation of the serum iron and ferritin status appears necessary [5].

The use of drugs that inhibit the renin-angiotensin system, including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ARBs), has been associated with hyporesponsiveness to erythropoietin treatment [5, 15]. In this study, 52.8% of the hyporesponding patients used these drugs as antihypertensive therapy. This condition gave patients an approximately twofold-fold greater probability of presenting this condition according to both the bivariate and multivariate models (OR=1.9 and OR=2.2). However, there have been at least 16 observational cohort studies in which approximately half of the patients demonstrated a neutral effect, and the other half demonstrated a deleterious effect of angiotensin-converting enzyme inhibitors on the responsiveness to agents. Erythropoiesis stimulants, however, seem to be helpful in trying to modify antihypertensive therapy with these drugs by using antihypertensives of a different class in patients in whom it is suspected that these could be the cause of their inadequate response [15].

In this study, patients with parathormone levels equal to or greater than 500 µg/ml were approximately twice as likely to present as hyporesponsive according to both the bivariate and multivariate analyses (OR=2.18 and OR=1.8, respectively). These findings have already been reported in small [10,

12] and large [17, 20] cohort studies; in contrast, other studies have noted that there are no significant differences [5]. The mechanisms by which excess parathyroid hormone (PTH) can slow the response to erythropoietin include direct inhibition of erythropoiesis, induction of spinal fibrosis with the consequent annulment of erythropoietic tissue, and inhibition of erythropoietin synthesis [11]. Epidemiological studies have suggested that women undergoing dialysis have higher serum PTH levels than men do, which is interesting considering that the population of hypo responders in the present study had a more significant proportion of women. However, in another study, the association between female sex and higher PTH levels could not be demonstrated [21].

Concerning the parameters associated with hemodialysis treatment, the urea reduction rate, Kt/V, and type of vascular access were not significantly different (OR=1.08, OR=1.06, and OR=1.17, respectively) (P >0.05). Other studies have shown significant differences concerning dialysis dose [5]. This finding could be affected by the smaller body size of the patients and the lower availability of high-flux dialytic membranes [5].

No significant difference in the duration of hemodialysis was found between the two groups (OR=1.145; P =0.492). Similarly, Santos et al. found no significant difference in the length of time on hemodialysis between the hyporesponder and responder groups (49 months vs. 47 months), with P = 0.989 [20].

Anemia tends to be more severe in patients with diabetes mellitus and can develop in earlier stages of chronic kidney disease [21], even independently of the CKD stage [22]. This study revealed the opposite trend, with an OR of 0.621; however, according to the multivariate model, there was no significant association (P =0.405). The explanations for these findings may be due to selection bias since studies of diabetic patients indicate that they have a high incidence of diabetic foot disease, an increased risk of infections, osteomyelitis, and ischemia in the extremities; these processes involve a greater rate of hospitalization and may have been subject to exclusion according to the criteria of this study[23]. Second, diabetic patients on dialysis tend to have a greater body mass index, yet multiple studies suggest that at the same time, they have a greater risk of malnutrition [24]; additionally, body composition measured by bioimpedance is reported in patients with diabetes to have a more significant mean body fat percentage (26.05% vs 28.52%; P =0.235) and a greater visceral fat area (72.41 vs 93.02; P =0.04) than did those in the nondiabetic group [25]. With its consequent more excellent leptin production, this greater adiposity could justify a better response to erythropoietin.

A limitation of this study is the difficulty in obtaining representative samples of the study population. This may be because CKD patients receiving hemodialysis constitute a heterogeneous group in terms of demographic characteristics, comorbidities, and risk factors involved. In addition, access to records from other regions of Ecuador could have been improved. Another limitation is the retrospective design, which limits longitudinal studies' ability to understand the findings during anemia better. Furthermore, in the present study, there were no sensitive markers of inflammation, such as C-reactive protein or hepcidin levels; moreover, only the association between ferritin levels and the pathophysiology of inflammation was recorded.

Conclusion

The analysis of the study population revealed a 15.69% prevalence of hyporesponsiveness to treatment with erythropoietin. It was possible to identify the risk factors present in patients with chronic kidney disease on hemodialysis that are related to a hyporesponsive to treatment with erythropoietin: female sex, age less than 50 years, a BMI less than 23 kg/m² and the use of blockers of the renin-angiotensin system. Regarding laboratory parameters, low albumin levels, high ferritin levels, a TRF saturation of less than 20%, and high parathormone levels were found to be risk factors associated with a hyporesponse to erythropoietin.

Abbreviations

ARB: Blocker of the renin-angiotensin system
ERC: Chronic Kidney Disease.
BMI: body mass index.
OR: odds ratio.
PTH: Parathyroid hormone

Supplementary information

The supplementary materials have not been provided.

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Does not apply.

Author contributions

Carlos Eduardo Pérez: Data curation, Formal analysis, Funding acquisition, Research, Methodology, Project management, Resources, Software, Writing – original draft.
Jorge Fabián Chonata: conceptualization, supervision, validation, visualization, writing, review, and editing.
Jorge Washington Velez: Conceptualization, Supervision, Validation, Visualization, Writing: review and editing.
All the authors read and approved the final version of the manuscript.

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The studies, laboratory tests, and intradialytic measurements constituted the regular activity of the hemodialysis unit and were not a cost to the patients. The authors provided the administrative costs of this research.

Availability of data or materials
The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available upon justified academic request.

Statements

Ethics committee approval and consent to participate
The protocol for this research was analyzed and approved by the Research Ethics Committee of the Central University of Ecuador.

Consent for publication
Patient photographs, tomography scans, or X-ray studies were not needed.

Conflicts of interest
The authors declare no conflicts of interest.

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