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The relationship between comorbidity, anemia and response to erythropoiesis-stimulating agents in chronic hemodialysis

S. Anaya, F. Rivera, M. D. Sánchez de la Nieta, A. Carreño, C. Vozmediano, M. P. Alcaide, M. Arambarri, J. Nieto, G. Caparrós and I. Ferreras

Nephrology Unit. General Hospital of Ciudad Real.

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SUMMARY

Introduction: *Patients treated with haemodialysis have a high prevalence of co-morbidity that induces a elevate mortality risk. On the other hand, these patients have anaemia whose treatment is based in eritropoyesis stimulating agents. To date there are not enough studies to determine if co-morbidity alters erythropoietin response and the relationship between co-morbidity, response to treatment of anaemia and resistance to erythropoiesis-stimulating agents.* Objectives: *We have the following* Objectives: *i) to study the prevalence of associated diseases in patients treated with haemodialysis in our Hospital Unit and to evaluate the co-morbidity Charlson Index; ii) to know the degree of anaemia control, dose and response to erythropoiesis-stimulating agents, and iii) to determine the relationship with co-morbidity and anaemia treatment.* Patients and methods: *We designed a retrospective study in stable haemodialysis treated patients. We calculated the Charlson co-morbidity index adjusted to age and we analysed levels of haemoglobin in the 6 months before study, dose of erythropoiesis-stimulating agents and its resistance index defined as doses of erythropoiesis-stimulating agents/weight (kg)/week/haemoglobin (g/dL). The different variables included in Charlson index were considered as independent variables and the index to repose to erythropoiesis-stimulating agents as a dependent variable, using bivariant and multivariate statistical analysis.* Results: *We included 58 patients (31 males and 27 females), median age of 69.5 years (range 24-88), mean haemodialysis 83,7 months. Mean Charlson index was 7.4 ± 2.8 (range 2-13). Comorbidity-age Charlson index was 2 in 3.4% of patients; 10.3% had 3 or 4 points; 43.2% between 5 and 7 and 43.1% 8 or more. Mean haemoglobin levels was 11.7±1.2 g/dL. Mean erythropoiesis-stimulating agents dose was 163.7 ± 114.5 IU/kg/week and resistance index 14.1 ± 9.7. Most of patients (57%) had a IRE value higher than 10. Forteen patients (24%) had haemoglobin less than 11 g/dL, and 3 of them (5.1%) received erythropoiesis-stimulating agents more than 300 IU/kg/week. Nine subjects (15.5%) was treated with high dose of erythropoiesis-stimulating agents (> 300 IU/kg/week): 3 of them had Hb ≥ 11 g/dL and 6 had Hb < 11 g/dL. We did not found that the intensity of Charlson index is related with the degree of anaemia control or response to erythropoiesis-stimulating agents.* Conclusions: *Althought in our study the comorbidity index is high and the response to erythropoiesis-stimulating agents is inadequate, there is not relationship between these conditions.*

Key words: *Anaemia. Charlson index. Erythropoiesis-stimulating agents. Haemodialysis.*

Correspondence: *Sara Anaya Fernández*
Hospital General Ciudad Real
Tomelloso, s/n
13005 Ciudad Real
sara.anaya@senefro.org

RESUMEN

Introducción: **Los pacientes en hemodiálisis presentan un elevado número de patologías asociadas. Por otro lado, la mayoría reciben derivados eritropoyéticos como tratamiento de la anemia. No hay estudios que indiquen si el grado de comorbilidad influye en la respuesta a los derivados eritropoyéticos.** ***Objetivos:*** **Estudiar la comorbilidad de los pacientes de una unidad de hemodiálisis hospitalaria, cuantificarla mediante el índice de comorbilidad de Charlson, conocer el control de anemia, la respuesta a derivados eritropoyéticos y, finalmente, evaluar la relación entre comorbilidad y control y tratamiento de la anemia.** ***Pacientes y métodos:*** **Realizamos un estudio retrospectivo. Incluimos 58 pacientes en hemodiálisis del Hospital General de Ciudad Real. Recogimos datos de la historia clínica para calcular el índice de comorbilidad de Charlson. Analizamos las cifras de hemoglobina y las dosis de derivados eritropoyéticos en los seis meses previos y calculamos el índice de resistencia a derivados eritropoyéticos. Las distintas entidades incluidas en el índice de comorbilidad y el propio índice de comorbilidad se consideraron variables independientes y el índice de resitencia a derivados eritropoyéticos como variable dependiente, mediante análisis uni y multivariante.** ***Resultados:*** **Edad media 69,5 años; 53,4% varones; tiempo medio en hemdiálisis 83,7 meses. El índice de Charlson medio fue 5,2 ± 2,4 (2-11) y el ajustado a la edad 7,4 ± 2,8 (2-13). La hemoglobina media fue 11,7 ± 1,2 g/dL. El 24,1% presentaban hemoglobina inferior a 11 g/dL. La media del índice de resistencia a derivados eritropoyéticos fue 14,1 ± 9,7. No observamos que los valores del índice de Charlson se relacionaran con el grado de anemia ni con la resistencia a derivados eritropoyéticos.** ***Conclusiones:*** **En nuestra muestra existe una elevada comorbilidad asociada y un porcentaje importante de pacientes con anemia no controlada. No hemos encontrado relación entre la comorbilidad y el control de la anemia ni el grado de respuesta a derivados eritropoyéticos.**

Palabras clave: Anemia. Derivados eritropoyéticos. Hemodiálisis. Índice de Charlton.

INTRODUCTION

A high percentage of patients on renal replacement therapy with hemodialysis have other conditions not associated to the primary kidney disease, which are an important cause of morbimortality. The DOPPS study (**D**ialysis **O**utcomes and **P**ractice **P**atterns **S**tudy) gathers information about 8615 hemodialysis patients and finds a high prevalence of coronary heart disease, heart failure, cerebrovascular disease, and peripheral vascular disease, among others.[1] Assessment of these comorbidities may be quantified, expressed as the Charlson's index, either absolute or age-adjusted (AACI).[2,3] The utility of this comorbidity parameter has been confirmed in different studies[4,5] and its severity is related to higher health care expenditures, increased hospital admissions and hospitalization days.[6]

Most of the patients included in a dialysis program have anemia and its management with erythropoiesis-stimulating agents (ESA) has shown to be effective. The anemia is associated to increased mortality (independently of other associated conditions, quantified by means of AACI),[7] higher risk for hospitalization,[8] cardiovascular complications,[9] left ventricular hypertrophy,[10] lower quality of life,[11] and many other problems.[12,13] The European Guidelines on Anemia Management in Chronic Renal Disease, published in the year 2004, recommend hemoglobin levels ≥ 11 g/dL in these patients.[14] However, the results from DOPPS point out that a considerable percentage of patients have hemoglobin levels lower than this target value.[15] Resistance to ESA is considered when adequate hemoglobin levels are not achieved in spite of receiving high doses (rHuEPO > 300 IU/Kg/week or darbepoietin > 1.5 µg/kg/week).[14] However, the *"erythropoietin resistance index"* (ERI) is more appropriate to measure the degree of resistance to ESA, which is calculated as the weekly dose of ESA/weight (in kg)/Hb (in g/dL). An ERI value ≤ 10 is considered normal or desirable. Above this value, resistance to ESA is present and its time course indicates the degree of response to these agents. The EuCliD study, carried out among hemodialysis patients from several Spanish cities, finds an average ERI value of 9.3.[16] One of the most common causes of resistance to treatment is absolute or functional iron deficiency.[14,17,18] Other causes are: inflammation or infection, secondary hyperparathyroidism, aluminum poisoning, hemoglobinopathies, vitamin deficiencies, multiple myeloma, tumors, hyponutrition, hemolysis, infradialysis or the use of ACEIs.[14,19-21]

Given the high comorbidity in hemodialysis patients and the lack of response to anemia management with ESA we wonder: do associated pathologies in hemodialysis patients relate with the severity of anemia or with its response to ESA? The goals of our study are: i) to study the different pathologies presented by the in our hospital-based Hemodialysis Unit and their quantification by means of the AACI; ii) to know the degree of anemia control, the doses of ESA used, and the response to this therapy by means of ERI; and iii) to assess the relationship between AACI and hemoglobin levels, the dose of ESA, and the ERI.

PATIENTS AND METHODS

We carried out a case-control retrospective study including all patients at the Hemodialysis Unit of the General Hospital of Ciudad Real, at March 1st of 2006, and having stayed on hemodialysis for at least 6 months.

We included 58 patients in total. We revised the clinical chart of each one of them and identified the pathologies present at the time of the study, pointing out those included in the Charlson's comorbidity index, according to the definitions established in the original article published in 1987.[2] The conditions included in the Charlson's comorbidity index are the following: myocardial infarction; congestive heart failure; arterial hypertension; peripheral vascular disease; cerebrovascular disease; dementia; chronic lung disease; connective tissue disease; peptic ulcer; mild, moderate or severe liver disease; diabetes with or without organic damage; Hemiplegia; leukemia; lymphoma; solid tumor with metastases; AIDS; and moderate or severe kidney disease. Once the comorbidity of the patients was known, we scored each condition according to what is indicated in Table I, the sum of all of them resulting in the Charlson's comorbidity index (CCI). Obviously, all of our patients had a score corresponding to "moderate or severe kidney disease" (2 points). To calculate the age-adjusted Charlson's comorbidity index (AACI), we added up one point for each decade of life over fifty years to the CCI value obtained. The values obtained (for both CCI and AACI) have been pooled into four categories of values: 1-2, 3-4, 5-7, or ≥ 8.

We also revised the laboratory results carried out in each patient over the 6 months prior to March 1st of 2006, and we obtained the mean hemoglobin levels (in g/dL) and hematocrit for that period. We recorded all treatments administered during the hemodialysis sessions during that time and the mean weekly dose of ESA. The conversion factor between doses of darbepoietin and rHuEPO is 200, i.e., 200 × µg of darbepoietin = IU of erythropoietin alpha or beta. We also calculated the mean dry weight for the last six months. Once the weight, ESA dose, and mean hemoglobin level for the last

Table I. Score assigned to each pathology for the calculation of AACI

Score	Pathology
1	Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic lung disease Connective tissue disease Ulcer Mild liver disease Diabetes
2	Hemiplegia Moderate or severe kidney disease Diabetes with organ damage Tumor Leukemia Lymphoma
3	Moderate or severe liver disease
6	Solid tumor with metastases AIDS

Table II. Prevalence of the variables considered in AACI

Variable	Number of patients (%)
Acute myocardial infarction	18 (31)
Heart failure	26 (44.8)
Peripheral vascular disease	17 (29.3)
Cerebrovascular disease	7 (12.1)
Dementia	3 (5.2)
Chronic lung disease	15 (25.9)
Connective tissue disease	0
Ulcer	8 (13.8)
Mild liver disease	10 (17.2)
Diabetes	22 (37.9)
Hemiplegia	5 (8.6)
Diabetes with organ damage	16 (27.6)
Tumor	8 (13.8)
Leukemia	0
Lymphoma	0
Moderate-severe liver disease	1 (1.7)
Solid tumor with metastases	0
AIDS	0

six months were calculated, we established the ERI, calculated as the mean weekly dose of erythropoietin (IU)/weight (kg)/Hb (g/dL). We categorized the patients into two groups depending on an ERI value higher or lower than 10.

The descriptive analysis of the qualitative variables is described as frequencies, and that for quantitative variables as means and standard deviations or medians, depending on their normal or abnormal distribution by the Kolmogorov-Smirnov test. The bi-variate analysis between the qualitative variables was done by the Chi-squared test. The relationship between qualitative and quantitative variables was done by using the Student's t test or ANOVA if the variables were normally distributed, or by means of non-parametric tests (Mann-Whitney or Kruskall-Wallis) in case of abnormal distribution of the quantitative variables. The relationship between quantitative variables was done by means of linear correlation. The multivariate analysis was done by using linear regression analysis. The data pertaining to the patients' clinical charts, hemodialysis regimes, and laboratory data were extracted from the Nefrosoft HD V3 software. With these data we created a database using SPSS V 8.0 software, with which we undertook the statistical analysis. A two-tailed p value < 0.05 was considered to be statistically significant.

RESULTS

We studied 58 patients, 31 males (53.4%) and 27 females (46.6%), with an age range of 24-88 years (median: 69.5 years). The etiology of kidney disease was diabetic nephropathy (24% of the cases); unknown (22%); glomerulonephritis (21%); nephroangiosclerosis/AHT (14%); pyelonephritis/chronic tubulointerstitial nephropathy (12%); polycystic renal disease (2%); and other (5%).

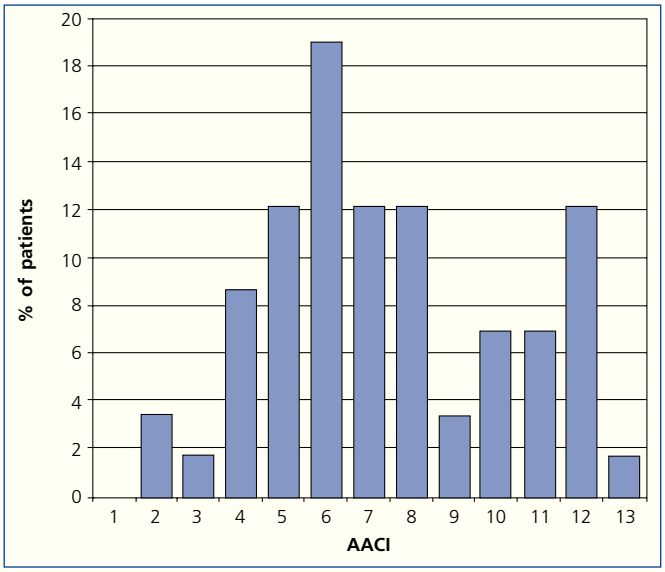

Figure 1. AACI values obtained in the sample and calculated according to the scoring system show in table I and adding up 1 point for each decade over fifty years of age. The mean AACI obtained was 7,4 ± 2,8.

Table II shows the frequency of the different pathologies defining the Charlson's index. The mean Charlson's index was 5.2 ± 2.4, and the CI adjusted by age (AACI) 7.4 ± 2.8.

We have only considered the AACI for the statistical analysis. Figure 1 shows the distribution of the different AACI values. These varied between 2 and 13; 3.4% of the patients had an age-adjusted Charlson's index of 2, 10.3% of 3 or 4; 43.2% between 5 and 7, and 43.1% ≥ 8.

The mean hemoglobin value was 11.7 ± 1.2 g/dL, with values comprised between 8.5 and 14.7 g/dL. All the patients were receiving erythropoiesis derivatives at the time of the study: 62.1% received epoietin alpha; 12.1%, epoietin beta, and 25.9% darbepoietin. Twenty-four point one percent of the patients (14) presented hemoglobin levels < 11 g/dL and only 3 (5.1%) of them met the criteria for resistance to ESA, according to the definition of the European guidelines, i.e., they were treated with more than 300 IU/week of erythropoietin. The remaining 11 patients with hemoglobin levels < 11 g/dL were being treated with doses below 300 IU/week. Six patients (10.3%) had hemoglobin levels > 11 g/dL, although they were receiving high doses of erythropoietin (> 300 IU/kg/week). In total, 15.5% of the patients (9) were treated with high doses of ESA: 3 maintained Hb ≥ 11 g/dL and 6 had Hb < 11 g/dL. The mean weekly dose of ESA was 163.7 ± 114.5 IU/kg, with values ranging from 18 to 500 IU/kg. The mean values of ERI found were 14.1 ± 9.7 IU/kg/week/Hb, ranging from 1.41 to 39.6. More than half (57%) of the patients had an ERI value above 10.

Table III shows the values for the different variables related with comorbidity and their relationship with ERI. We did not find any correlation between any of them and ERI.

Figure 2 shows the relationship between the comorbidity evaluated by means of the AACI and the response to the different erythropoiesis derivatives assessed by ERI. The values of the different response or resistance indexes for the different AACI values (20.9 IU/kg/week/g/gL for AACI of 2; 23.3

Table III. The relationship between the different variables and resistance to erythropoiesis derivatives

	ERI ≥ 10 N: 33	ERI < 10 N: 22	Odds ratio	p
Age	65.12 ± 15.63	68.59 ± 13.9		0.403**
Gender (M/F)	17/16	12/10	0.88	0.825*
Etiology of renal failure	% within the group			
- Diabetes	18.2% (6)	31.8% (7)		
- Unknown	21.2% (7)	27.3% (6)		
- Glomerulonephritis	27.3% (9)	9.1% (2)		0.529*
- Nephroangiosclerosis	15.2% (5)	13.6% (3)		
- Interstitial	12.1% (4)	9.1% (2)		
- Polycystic renal disease	3% (1)	0		
- Other	3% (1)	9.1% (2)		
Time on hemodialysis (months)	93.46 ± 97.17	69.59 ± 63.56		0.315**
Myocardial infarction	27.3%	36.4%	0.65	0.475*
Congestive heart failure	39.4%	54.4%	0.54	0.269*
Peripheral vascular disease	24.2%	31.8%	0.68	0.537*
Cerebrovascular disease	9.1%	18.2%	0.45	0.322*
Dementia	6.1%	4.5%	1.35	0.808*
Chronic lung disease	24.2%	27.3%	0.853	0.8*
Connective tissue disease	0%	0%		
Ulcer	15.2%	13.6%	1.13	0.876*
Mild liver disease	15.2%	18.2%	0.8	0.766*
Diabetes	30.3%	45.5%	0.52	0.252*
Hemiplegia	9.1%	4.5%	2.1	0.525*
Diabetes with organ damage	21.2%	31.8%	0.57	0.376*
Tumor w/o metastases	9.1%	18.2%	0.45	0.322*
Leukemia	0%	0%		
Lymphoma	0%	0%		
Moderate or severe liver disease	3%	0%		
Solid tumor with metastases	0%	0%		
AIDS	0%	0%		
Type of ESA (α/β/darbe)	63.6%/6.1%/30.3%*	59.1%/22.7%/18.2%*		0.158*

* Chi 2.
** *t*-Student or Man-Withney.

IU/kg/week/g/gL for AACI of 3-4; 11.9 IU/kg/week/g/gL for AACI 5-7, and 13.2 IU/kg/week/g/gL for AACI ≥ 8) do not show statistically significant differences (p = 0.276).

The patients with hemoglobin levels < 11 g/dL presented an AACI value slightly higher (8 ± 3.3) as compared with those with hemoglobin levels ≥ 11 g/dL (7.3 ± 2.7). We did not find statistically significant differences between these results.

In the multivariate analysis we did not find either a relationship between the comorbidity and ERI.

DISCUSSION

The prevalence of hemodialysis patients in Spain is 425 per million population.[22] Many of these patients present a considerable number of associated pathologies, as has been shown in DOPPS.[1] When we compared the characteristics of the 2,590 patients belonging to European centers from the DOPPS study with those obtained in our study (table IV), we observed that the prevalence of myocardial infarction, cerebrovascular disease, and peptic ulcer is similar. By contrast, we have found a higher percentage of heart failure, peripheral vascular disease, chronic lung disease, and diabetes in our sample, as compared with the data reported in DOPPS. The MAR study (**M**orbidity and mortality **A**nemia **R**enal study),[7,23] which is a prospective study assessing a representative sample of hemodialysis patients in Spain, gathers data on cardiovascular

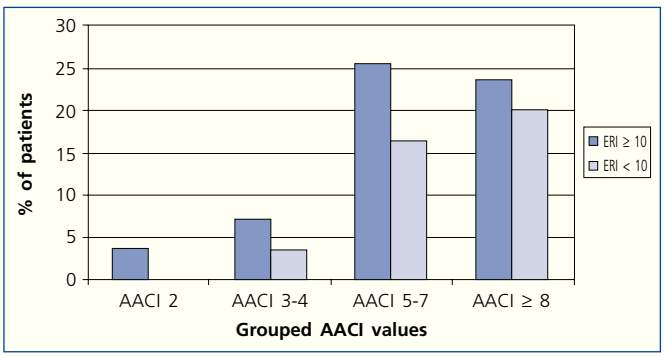

Figure 2. AACI values by ERI above or below 10. We did not find statistically significant differences between the AACI values of patients with ERI ≥ 10 and ERI < 10.

TablE IV. Data on the prevalence of the different pathologies in patients from European dialysis centers in Europe (DOPPS)[1], Spain (MAR)[23] and our center

	DOPPS[1] (Europe) n = 2,590	MAR[23] (Spain) n = 1,710	General Hospital of Ciudad Real n = 58
Age	60.2 años	64.4	69.5 años
Males (%)	57.6	60	53.4
Acute myocardial infarction (%)	29.4	16.7	31
Heart failure (%)	25	13.9	44.8
Peripheral vascular disease (%)	22.5	5.5	29.3
Cerebrovascular disease (%)	13.7	2	12.1
Dementia (%)	ND	ND	5.2
Chronic lung disease (%)	10.7	ND	25.9
Connective tissue disease (%)	ND	ND	0
Ulcer (%)	17.6	ND	13.8
Mild liver disease (%)	ND	ND	17.2
Diabetes (%)	20.1	25.9	37.9
Hemiplegia (%)	ND	ND	8.6
Diabetes with organ damage (%)	ND	ND	27.6
Tumor (%)	ND	ND	13.8
Leukemia (%)	ND	ND	0
Lymphoma (%)	ND	ND	0
Moderate-severe liver disease (%)	ND	ND	1.7
Solid tumor with metastases (%)	ND	ND	0
AIDS (%)	0.2	ND	0

ND: Data not available or not corresponding with the definitions used to calculate the Charlson's index.

comorbidity and anemia control from 1,710 patients. When comparing these data from those from our study (table IV), we confirmed a higher prevalence of cardiovascular pathology such as acute myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, and diabetes.

In 1987, Charlson validated the comorbidity index associated to age (AACI) to predict the mortality within ten years.[2] This index was later on used in hemodialysis patients.[4,5] In the already mentioned MAR study[7,23] the mean value obtained for the AACI was 6.5 ± 2.3, which is slightly lower than that found in our work (7.4 ± 2.5). Of the patients included in our study, only 8 did not show comorbidity associated to chronic kidney disease, i.e., their CCI score was only of 2 (the score corresponding to kidney disease). The 50 patients remaining had some other pathology of those included in the Charlson's index, which reflects the high prevalence of associated conditions in our sample of hemodialysis patients.

The mean hemoglobin level obtained in our patients (11.7 g/dL) is similar to that reported in other studies performed in Spain and Europe (table V). The European guidelines on anemia management in chronic kidney disease[14] recommend that at least 85% of the patients in hemodialysis units should have hemoglobin levels ≥ 11 g/dL. In our center, this value is lower: 24% of the patients studied did not reach the target hemoglobin level, which is not reached in other European or Spanish regions either, according to several epidemiologic studies (table V). In DOPPS,[24] only 53% of the European patients included had hemoglobin levels ≥ 11 g/dL. In Spain,[23] 31.2% of the hemodialysis patients present hemoglobin levels < 11 g/dL. Thus, we may state that, in spite of the revolution that has represented the use of ESA for managing anemia in renal failure, we still are far from an adequate anemia control in these patients, especially if we analyze the percentage of patients out of range. In our work, we have found that one fourth of the patients have an Hb level below the recommended one, and in addition more than half of them (57%) have an ERI value > 10. This value indicates that certain patients with normal hemoglobin levels receive therapies falling within the range of resistance to ESA, or said in other terms, they reach adequate hemoglobin levels at the expense of high doses of ESA. For this reason, we believe it is better to assess the response to ESA by using the ERI than just using the concept of resistance that only contemplates the absolute doses not corrected by the hemoglobin level.[25,26] The use of high doses of ESA may normalize the hemoglobin level in spite of existing a certain degree of resistance to these therapies. In our study, 21% of the patients with hemoglobin levels ≥ 11 g/dL received very high doses of ESA. In the EuCliD study,[16] which includes 4,426 hemodialysis patients, the ERI is assessed in patients on hemodialysis program for longer than 6 months, obtaining an average value of 9.3; in our study, the average ERI value is higher (14.1). In EuClid, it is reported that the ERI was higher when ESA were used intravenously as compared to their subcutaneous administration (11.6 *vs* 9.6). In our case, all patients received their treatment intravenously, and we observed that if we compare them with those patients included in EuCliD only treated with intravenous ESA, the ERI value obtained in our center still is higher (14.1 in our center and 11.63 in EuCliD). That is to say, the response to erythropoiesis derivatives in our patients is lower than that shown in other dialysis units in Spain. We have not included in our study the description of the parameters known to affect the response to erythropoiesis derivatives because it was out of the goals defined at the beginning of this text, such as iron deficiency (absolute or functional), malnourishment, inflammation, infradialysis, and others. In spite of this important limitation, we have found either an "excess of therapy" in our Unit or a decreased response to ESA. Had we only used the

Table V. Mean hemoglobin level and adherence to European guidelines in several studies

	Location	Mean hemoglobin level (g/dL)	Patients with Hb > 11 g/dL
EuCliD[16]	Spain	11.8 ± 1.4	69.2%
Renal Anemia Group[25]	Spain	11.3 ± 1.4	78.8%
MAR[23]	Spain	11.7 ± 1.5	68.8%
ESAM-2003[27]	Europe	11.5 ± 1.4	66%
DOPPS[24] (Europe)	Europe	11.6 ± 1.4	53%
General Hospital of Ciudad Real	Ciudad Real	11.7 ± 1.2	76%
Recommendations from the European guidelines (EBPG)[14]		**≥ 11**	**85%**

hemoglobin levels to assess the appropriate anemia management in these patients, it may be that we would be masking those resistant or over-treated cases that only show up when we carry out comparisons with the index of response to ESA. Among the biases in our work, we may point out that it is a retrospective study and that the sample gathered is based on patients included in a hospital-based dialysis program. Thus, it gathers information on those complex patients, more aged, with severe associated pathologies, and with a higher number of conditions promoting resistance to erythropoiesis derivatives.

When we carried out the analysis in the different AACI groups and studied in each one of them the degree of anemia control and response to erythropoiesis derivatives, we did not find significant differences (fig. 2). We have found that resistance to erythropoietin, measured through ERI, is similar in the different comorbidity groups established, with no statistical significance (p = 0.276).

We did find a relationship between the different variables measuring the associated pathology in hemodialysis patients and the ERI values (table III). According to our study results, the degree of comorbidity has not an influence on the response of these patients to ESA, although these data ought to be compared with those of patients from other extra-hospital hemodialysis units that usually have a lower comorbidity level. This relationship has not been previously studied, and our group believes that this aspect is relevant given the high number of comorbidities present in hemodialysis patients. According to our study, we may thus affirm that there exists a relationship between the comorbidity presented by these patients and appropriate anemia control or response to erythropoiesis derivatives assessed by means of ERI.

We conclude that in spite of finding high comorbidity indexes and out of control anemia with increased resistance to ESA in the patients included in our hemodialysis program, it seems there is not a clear-cut relationship between these variables. It is very likely that the response to ESA may depend on other factors not related with the conditions determining the comorbidity.

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