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Late nephrology referral influences on morbidity and mortality of hemodialysis patients. A provincial study

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SUMMARY

Objetive: *To evaluate the influence of late referral to nephrology of the patients with chronic renal failure in the morbimortality of the patients who start hemodialysis.*

Subjets and methods: *There were included in the study the patients who started hemodialysis (HD) as first form of treatment, and that survived at least three months in both hospitals of reference of the province of Huesca from january 1990 to december 2001. Patients who started HD after acute renal failure were excluded. Clinical and analytical data were determined for each patient at the start of HD and during the follow-up. Early (ER) and late referral (LR) were defined by the time of first nephrology encounter greather than or less than 4 months respectively, before HD initiation. Morbidity analysis (using multiple linear regression with rate of days of hospitalization as dependent variable) and global and anual during the first three years of follow-up survival analysis (using Cox proportional hazards regression) were carried out.*

Results*: A total of 139 patients (78%) started HD in the ER group and 39 (22%) in LR group. Mean follow-up was similar in both (ER = 34.43 ± 25.5 months; LR = 34.42 ± 28.37 months). At the start of dialysis LR was associated to higher proportion of temporary catheters, lower level of hematocrit and albumin, higher comorbidity and higher levels of urea and creatinine. Risk factors selected by the model in the morbidity analysis were index of comorbidity (CI), late referral, serum albumin, urea reduction ratio (URR) and hematocrit (R^2 = 0.334, F = 16.97, p < 0.005). The final equation of regression was: Rate of hospitalization's days = 101.12 + (2.45 x CI) - (12.11 x LR) - (11.57 x Alb.) - (0.43 x PRU) - (0.83 x Hto). Variables selected by Cox's regression model that were associated with survival throughout complete follow-up were hematocrit (RR = -0,207, CI 95% 0.726-0.910, p < 0.0005), index of comorbidity (RR = 0,265, CI 95% 1.066-1.594, p = 0.007), PRU (RR = -0,059, CI 95% 0.893-0.996, p = 0.038) and type of dialysis membrane (RR = 0,771, CI 95% 0.260-0.822, p = 0.007). Nevertheless, in successive models fitting after 12, 24 and 36 months of follow-up the variable LR influenced in an independent way survival first two years, losing his significance later.*

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Conclusion: *In our study patients of the group LR presented a worse clinical and metabolic situation at the beginning of the HD. Later there was demonstrated in this group a higher long-term morbidity and a lower survival the first two years.*

Key words: ***Chronic renal failure. Late referral. Hemodialysis. Morbidity. Survival.***

LA REFERENCIA TARDÍA AL NEFRÓLOGO INFLUYE EN LA MORBI-MORTALIDAD DE LOS PACIENTES EN HEMODIÁLISIS. UN ESTUDIO PROVINCIAL

RESUMEN

Objetivo*: Evaluar las repercusiones de la referencia tardía al nefrólogo de los pacientes con insuficiencia renal crónica en la morbi-mortalidad de los pacientes que inician hemodiálisis.*

Pacientes y métodos: *Se incluyó en el estudio a los pacientes que iniciaron hemodiálisis (HD) como primera forma de tratamiento, y que sobrevivieron al menos noventa días, en los dos hospitales de referencia de la provincia de Huesca (Hospital San Jorge de Huesca y Hospital de Barbastro) en el periodo comprendido entre el 1-1-1990 y el 31-12-2001. Se excluyeron los pacientes que iniciaron HD crónica tras presentar fracaso renal agudo. Se recogieron para el estudio variables clínicas como analíticas tanto al inicio de la HD como durante el seguimiento. Los pacientes se incluyeron en el grupo de referencia precoz (RP) o referencia tardía (RT) dependiendo de si se realizó un seguimiento en la consulta de nefrología previo al inicio de la HD mayor o menor de cuatro meses respectivamente. Se llevó a cabo un análisis de morbilidad mediante la construcción de un modelo de regresión lineal múltiple utilizando la tasa de días de ingreso por paciente-año como variable dependiente. También se realizó un análisis de supervivencia global y en los tres primeros años de seguimiento mediante el modelo de regresión de Cox.*

Resultados: *Un total de 139 pacientes (el 78%) iniciaron HD en el grupo de RP y 39 pacientes (el 22%) en el grupo de RT. El seguimiento medio fue similar en ambos grupos (RT = 34,43 ± 25,5 meses; RP = 34,42 ± 28,37 meses). Al inicio de la HD la RT se asoció de modo significativo a mayor porcentaje de catéteres temporales, menor nivel de hematocrito y de albúmina, mayor índice de comorbilidad y mayores niveles de urea y creatinina. Respecto a la morbilidad el análisis multivariante mostró como factores de riesgo independientes el índice de comorbilidad, la referencia tardía, la albúmina sérica, el porcentaje de reducción de la urea (PRU) y el hematocrito (R^2 = 0,334, F = 16,97, p < 0,005). La ecuación de regresión final fue la siguiente: Tasa de días de ingreso por paciente-año = 101,12 + (2,45 x índice de comorbilidad) – (12,11 x referencia tardía) – (11,57 x Albúmina) – (0,43 x PRU) – (0,83 x Hematocrito). En el análisis de supervivencia global tras el seguimiento completo el modelo de regresión de Cox seleccionó como variables independientes el hematocrito (RR = -0,207, CI 95% 0,726-0,910, p < 0,0005), el índice de comorbilidad (RR = 0,265, CI 95% 1,066-1,594, p = 0,007), el PRU (RR = -0,059, CI 95% 0,893-0,996, p = 0,038) y el tipo de membrana del dializador (RR = -0,771, CI 95% 0,260-0,822, p = 0,007). No obstante, tras ajustar sucesivos modelos al cabo de 12, 24 y 36 meses de seguimiento la variable RP influyó de modo independiente en la supervivencia los dos primeros años, perdiendo su significación los años posteriores.*

Conclusiones: *En nuestro estudio los pacientes del grupo RT presentaron una peor situación clínica al inicio de la HD. Posteriormente se evidenció en este grupo una mayor morbilidad a largo plazo y una menor supervivencia los dos primeros años.*

Palabras clave: ***Insuficiencia renal crónica. Referencia tardía. Hemodiálisis. Morbilidad. Supervivencia.***

INTRODUCTION

Statistics show that incidence and prevalence of chronic renal failure have progressively increased in recent years and that this tendency will remain in the future, representing a number one health care and financial problem.[1, 2] Population starting on dialysis is increasingly older and has more associated cardiovascular risk factors, which conditions a greater likelihood of negative outcomes in terms of morbidity and mortality.[3] In spite of incessant technological advances and a better knowledge of management strategies, morbidity and mortality of hemodialysis patients still remain very high as compared to those in the general population.[4] These poor morbimortality outcomes have fueled the research on potentially modifiable factors associated to a greater risk.[5] Among which, we highlight those achieved on management of issues such as nutrition,[6] anemia,[7] dialysis dose,[8] osteodystrophy,[9] inflammation,[10] hypertension,[11], etc., that have partially lead to an improvement of clinical outcomes.

Within this strategy of continuous improvement, recently the number of published studies focused on describing new factors not taken into account so far, and that may influence on the outcomes of dialyzed patients, has increased. Among these factors, the initial clinical status of patients starting on HD stands out, which is largely the result of pre-dialysis care offered in a specialized nephrology clinic. In this regard, the concepts of early and late referral have been established, depending on the shorter or longer time the initial follow-up has taken.[12]

Currently, there are quite a number of published studies that have evaluated the consequences of late referral (LR). In general terms, these works confirm that LR is harmful for patients since they start on HD on a poorer condition, it increases costs, and it increases morbidity and mortality.[12-14]

We present the results from a study performed at a provincial level, which main goal was to evaluate the consequences of LR on morbimortality of patients starting on HD.

PATIENTS AND METHODS

Included in the study were all patients that started on HD in both reference hospitals of the province of Huesca, the San Jorge Hospital of Huesca and the Hospital of Barbastro, in the period comprised between 01/01/1991 and 12/31/2001. Excluded from the analysis were those patients not surviving on HD for longer than 90 days. We also excluded those patients that started on chronic HD after presenting acute renal failure.

The patients' clinical charts were retrospectively reviewed as well as their hemodialysis charts, from which the following data were gathered, constituting the different study variables:

- Gender
- Age (lifetime) at the start of replacement therapy.
- Date of HD onset
- Case origin (how the patient was referred to the Nephrology Department): primary care physician, urology, internal medicine, other specialists, CRF detected at the emergency room requiring starting on hemodialysis during the first hospital admission, another center, transplantation rejection.
- End-stage CRF (ESCRF) etiology: unknown, diabetic nephropathy, nephroangiosclerosis, autosomal dominant adult polycystic renal disease, chronic tubulointerstitial nephropathy, transplantation rejection, others.
- Initial vascular access: arterial-venous fistula, temporary catheter, funneled catheter, and vascular prosthesis.
- Early or late referral, considered as having being followed at a nephrology outpatient clinic for at least four months prior to start on dialysis (early referral; ER) or not (LR).
- Comorbidities at the start of HD, determined by calculating the Charlson's comorbidity index in each patient.[15] Since all patients were on renal replacement therapy (RRT), the minimum score for all of them is 2 points.
- Laboratory variables, measured at the beginning of RRT and further on a monthly basis for most of them (blood samples taken pre-dialysis): hematocrit, intact parathyroid hormone (iPTH), BUN, creatinine, calcium, phosphorus, bicarbonate, alkaline phosphatase, cholesterol, potassium, lymphocyte count, albumin, and uric acid. At San Jorge Hospital, albumin and cholesterol were determine every 3 months, and iPTH was determined every 6 months at both hospitals. The arithmetic mean for each one of these regular determinations in each patient was calculated.
- Variables related to hemodialysis treatment: type of membrane (cellulose, synthetic high-permeability; patients having used both were classified according to the type of membrane that was used in more than 50% of the sessions), percentage of urea reduction (PUR) as a parameter

of dialytic efficiency, vitamin D usage (as used or not used), and erythropoietin usage in units/kg/week. PUR was calculated by the following formula suing the Gotch and Sargent's urea kinetic model:[16]

PUR = 1 – (post-dialysis /pre-dialysis UREA) × 100

– In erythropoietin-treated cases, the erythropoietin resistance index (ERI) was calculated by the following formula:

ERI = epo dose (u/k/week) / hemoglobin (g/dL).

– Number of hospital admissions for any reason (including the initial admission if that happened, and also admissions related to problems with vascular access), and total number of admission days. With this latter datum and the follow-up time, we calculated the days of admission per patient-year index, by diving the total number of admission days by the follow-up time of in patients-year. In those patients with a follow-up time shorter than 12 months, the index was calculated by the following formula:

Standardized index = (12/time in months) × total admission days

– Follow-up time to death, renal transplantation, moving to another center, or study closure (31/12/2001). For the survival analysis, these latter three events were considered as incomplete or censored times.
– Death etiology: cardiovascular, infectious, neoplasic, hepatic-GI, unknown, and other.

The hemodialysis regimen was similar in all cases, with three weekly sessions between 3.5 and 4 hours, using bicarbonate in the dialysis bath, with a goal Kt/V greater than 1.

STATISTICAL ANALYSIS

– *Descriptive statistic and exploratory analyses:* an analysis of epidemiological characteristics, mean indexes and biological markers was conducted. Quantitative variables are described as mean ± 1 standard deviation (SD). A univariate analysis was carried out to determine significant differences in certain variables of patients in groups LR and ER.

Categorical variables were analyzed by the Chi-squared test. If the required conditions for performing this test were not met, the Fisher exact test was done. The Student's t test was used for comparison of quantitative variables with a normal distribution. In the case the variables did not fit into a normal distribution, the non-parametric Mann-Whitney's test was used.

– *Morbidity analysis:* those variables significantly relating to the days of admission per patient-year index were identified by a simple linear regression analysis. Then, a multivariate analysis was done using the multiple regression model, with the number of admission days per patient-year index as the dependent variable. The selection of variables to be included in the initial model was done according to the results from the univariate analysis, including those with statistical significance. After variables introduction into the model, the analysis was performed using a step-wise regression model with an inclusion and exclusion criteria of $p < 0.05$ and $p > 0.10$, respectively, and tolerance > 0.01.

– *Survival analysis:* survival of patients form the LR and ER was analyzed by the Kaplan-Meier method and comparing the estimated survival curves by the log-rank test. A multivariate analysis was done using the proportional hazard regression model (Cox's regression model) to detect possible prognostic variable associated with survival after complete follow-up, and three other analyses to assess the impact of late referral on survival within the first three years on HD. For the initial modeling, the selection of included variables was done in the same way according to the results from the univariate analysis. Variable management in the model was carried out following a forward step-wise selection procedure (sequential inclusion) based on the odds ratio probability. probabilidad del estadístico de la razón de verosimilitud.

In previous analyses, when using laboratory variables, we used mean values for all determinations performed on each patient throughout the follow-up time, except for LR and ER groups comparison at start of HD and for the multivariate analysis of late referral impact for the first three years. In the latter cases, the patients' initial laboratory parameters were analyzed (the last laboratory test done before the first hemodialysis session).

All these analyses were done using the statistical package software SPSS 10.0. A p value < 0.05 was considered as being statistically significant.

RESULTS

One hundred and ninety one patients in total started on HD treatment at the San Jorge Hospital of

Huesca (100 patients) and at the Hospital of Barbastro (91) patients, between 01/01/1990 and 31/12/2001. Of these, 13 cases were excluded from the analysis, 11 for not surviving at least for 90 days on therapy, and two because of loss of laboratory results. The mean follow-up time after dialysis onset was 36.31 ± 28.2 months (median: 26.96 months). Patients' mean age was 59.57 ± 15.05 years (95% CI 57.55-61.58), range 71 years (13- 84). Sixty-one percent were male patients, and 38.2% females. As for CRF etiology, diabetic nephropathy accounted for 22.5% of the cases, nephropathies of unknown origin 18.5%, tubulointerstitial nephropathies 14.6%, glomerulonephritis 12.4%, nephroangiosclerosis 11.2%, polycystic renal disease 12.9%, and other etiologies 7.9%. Patients distribution by initial vascular access type was as follows: 59.8% started on HD through an arterial-venous fistula, 36.2% through a temporary catheter, 2.9% through a funneled catheter, and 1.1% through a vascular prosthesis. Fifty-two percent of the patients used cellulose membranes versus 48% that used high permeability synthetic membranes.

Figure 1 shows the origin of the cases, i.e., how patients were referred for the first time to the Nephrology Department. The greatest percentage (33.9%) was referred to the nephrology outpatient clinic by his/her primary care physician. The reason for referral was mainly the finding of raised BUN and plasma creatinine values or for arterial hypertension. It is remarkable that 10.9% of the patients were detected when they attended the emergency room, already presenting at that time and end-stage chronic renal failure that motivated the implementation of hemodialysis therapy during that first hospital admission with no previous control by a nephrologist. Fifty point tow percent of the patients were referred from other centers located outside the province of Huesca, and they already knew the existence of their chronic renal failure. The remaining patients are distributed as follows: 10.9% referred by the urologist, a percentage similar for other specialists (GI specialists, reumathologists, respiratory specialists, etc.), wit the exception for Internal Medicine specialists that diagnosed 7.9% of the cases. Another 7.9% of the cases were detected at the emergency room as non-ESCRF not known until that moment. Finally, a minority of cases (2.4%) entered into a chronic hemodialysis program after chronic rejection of the renal graft. Taken altogether, these data show that 50% of the patients that started on HD were diagnosed for the first time at the Hospital as having CRF.

At the time of study closure, 60 patients (33.7%) had died, 50 (28.1%) had received a renal transplantation, 67 (37.6%) continued on HD, and only one patient (0.6%) had been transferred to another

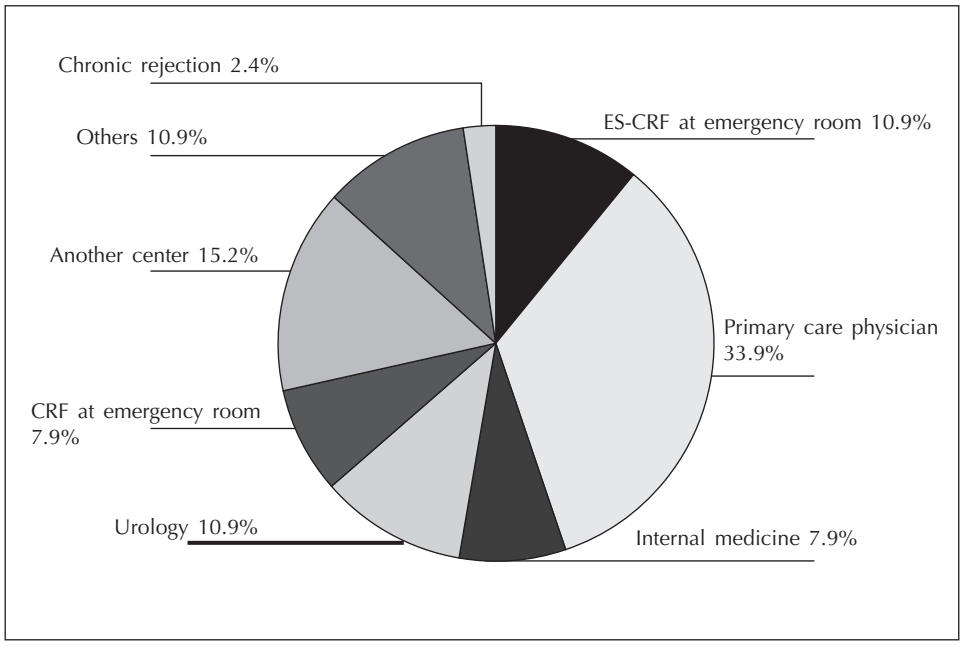

Fig. 1.—Origin of the cases.

center abroad the province. As for the etiology of deaths, 45.2% were of cardiovascular origin, and 22.6% were infectious, the remaining distributing among the other causes.

Late referral impact analysis

Thirty-nine patients (22%) were included in the LR group and 139 patients (78%) in the ER group. Mean follow-up time was similar between groups (LR = 34.43 ± 25.5 months; ER = 34.42 ± 28.37 months). Table I shows the clinical and laboratory characteristics of patients from both groups at the time of starting on HD. There were no significant differences for age, gender, and CRF etiology. A greeter proportion of cases in the LR group started on HD through a temporary catheter and their comorbidity index was greater. Besides, the LR group had significantly lower hematocrit and albumin levels, contrary to urea and creatinine levels, which were increased. There were no significant differences in the remaining laboratory parameters.

Table II shows the mean of laboratory parameters after complete follow-up of patients and the comparison of other parameters between groups. The LR group had significantly lower hematocrit level and higher serum potassium levels as compared to the ER group. There were also differences in erythropoietin-administered doses, the erythropoietin resistance index, the admission days per patient-year index, and in the percentage of deceased patients

Table I. Clinical and laboratory characteristics of patients at hemodialysis onset

	Referral to nephrology		
	Late n = 39	Early n = 139	Significance
Gender (age, %)	66.7	60.2	ns
Age at HD onset (years)	61.4 ± 15	58.58 ± 15	ns**
HD onset with catheter (%)	81.3	25.2	p < 0.0001
Diabetic nephropathy	25.6	21.6	
Polycystic renal disease	10.3	13.7	
Unknown	15.4	19.4	
Glomerular	10.3	12.9	ns
Nephroangioesclerosis	15.4	10.1	
Nefroangioesclerosis	10.3	15.8	
Tubulointerstitial	12.9	6.5	
Other			
Comorbididy index	6.71 ± 2.3	5.93 ± 2.1	p = 0.028**
Patients on EPO (%)	8	24	p = 0.026
Uric acid mg/dL	7.06 ± 7.1	6.86 ± 6.9	ns*
Urea mg/dL	227.23 ± 102.7	184.54 ± 57	p = 0.038**
Creatinine mg/dL	10.22 ± 4.3	8.28 ± 2.2	p = 0.037**
Alkaline phosphatase IU/l	86.00 ± 88	79.23 ± 79	ns**
Potassium mEq/L	5.23 ± 0.96	4.98 ± 0.77	ns**
Bicarbonate mEq/L	21.67 ± 5.1	21.84 ± 3.7	ns*
Albumin g/dL	3.23 ± 0.56	3.54 ± 0.41	p = 0.004**
Calcium mg/dL	8.55 ± 1	8.88 ± 0.9	ns*
Phosphorus mg/dL	5.90 ± 2.3	5.75 ± 1.5	ns*
Cholesterol mg/dL	186.75 ± 53	183.72 ± 40	ns*
Hematocrit %	23.9 ± 4.4	27.4 ± 4.5	p < 0.0001**
iPTH pg/mL	425 ± 437	401 ± 350	ns**
Lymphocyte count x 10^6/l	1.586 ± 451	1.513 ± 434	ns**

ns, not significant difference. *Student's t test. **Mann Whitney's U test.

Table II. Comparison of both groups after complete follow-up. Mean values of laboratory variables are shown

	Referral to nephrology		
	Late n = 39	Early n = 139	Significance
Uric acid mg/dL	6.47 ± 0.95	6.45 ± 1.04	ns*
Urea mg/dL	159.82 ± 31.27	157.1 ± 27.6	ns*
Creatinine mg/dL	10.02 ± 2.4	9.42 ± 2.2	ns*
Alkaline phosphatase IU/l	87.13 ± 47.2	89.2 ± 57.6	ns**
Potassium mEq/l	5.6 ± 0.6	5.23 ± 0.6	p = 0.0**
Bicarbonate mEq/l	22.35 ± 2.2	22.25 ± 2	ns *
Albumin g/dL	3.46 ± 0.45	3.55 ± 0.33	ns*
Calcium mg/dL	9.02 ± 0.66	9.22 ± 0.64	ns*
Phosphorus mg/dL	5.86 ± 1.05	6 ± 1.08	ns*
Cholesterol mg/dL	168.33 ± 35.43	179.61 ± 39	ns*
Hematocrit %	29.1 ± 2.97	31.12 ± 2.83	p < 0.0001*
iPTH pg/mL	343.6 ± 300.6	435 ± 407	ns**
Lymphocyte count x 10^6/l	1.586 ± 451	1.513 ± 434	ns**
PUR	66.3 ± 7.6	67.9 ± 8.2	ns*
U/kg/week epo in HD	101.43 ± 43	80.25 ± 47	p = 0.012*
EPO resistance index	11.19 ± 5.02	7.83 ± 5.04	p = 0.001*
HPM (%)	46	49	ns
Admission days per patient year-index	29.46 ± 37	10.64 ± 13.54	p < 0.0001**
Died during follow-up (%)	51	29	p = 0.009
Transplanted (%)	18	31	ns
On HD at 12-31-2001 (%)	31	40	ns

epo, erythropoietin. NS, not significant difference. PUR, Percentage of urea reduction. HPM, high-permeability membrane. *Student's test. **Mann Whitney U test.

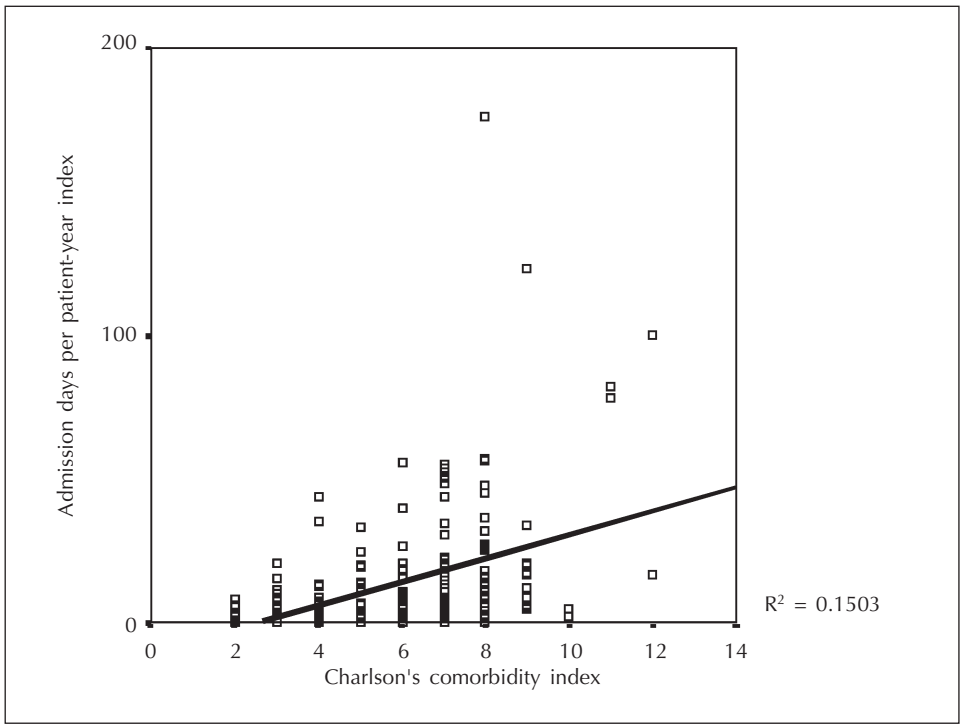

Fig. 2.—Association between comorbidity index and admission days index (p < 0.0001).

during the follow-up. All these differences favored the ER group.

Figure 2 shows the Kaplan-Meier survival curves for both groups. The log-rank test is close to statistical significance (p = 0.06). Median survival for the LR group was 53.36 months (95% CI = 34.73-71.98), whereas for the ER group it was 75.50 months (IC 95% = 55.12-92.14).

Morbidity analysis

The variables that showed a significant linear association with the admission days per patient-year were identified by means of a simple regression analysis. For the comorbidity index (p < 0.0001) (Figure 3) and the erythropoietin resistance index (p = 0.0030) the linear association between both variables is positive, as happens with age (p = 0.015) and potassium (p = 0.006). As for serum albumin (p < 0.0001) (Figure 4) and PUR (p = 0.008) the linear association is negative, as also happens with late referral (p < 0.0001), vitamin D therapy (p = 0.013) and hematocrit (p < 0.0001).

When introducing into a multiple linear regression model all selected variables from the previous univariate analysis, the following variables remained significant (table III): morbimortality index, serum albumin, previous management by the nephrology department, PUR, and hematocrit.

The regression equation that eventually predicts the admission days index is as follows (R^2= 0.334, F = 16.97, p < 0.005):

Admission days per patient-year index = 101.12
+ (2.45 ± Comorb. index) – (12.11 ± Late referral)
- (11.57 ± ALB.) – (0.43 ± PUR) – (0.83 × HTC)

It just suffices to replace the values of the five variables for a given patient to obtain the index prediction by the model. The late referral variable is a binary one, taking the naught value for the LR group and the one value for the ER group.

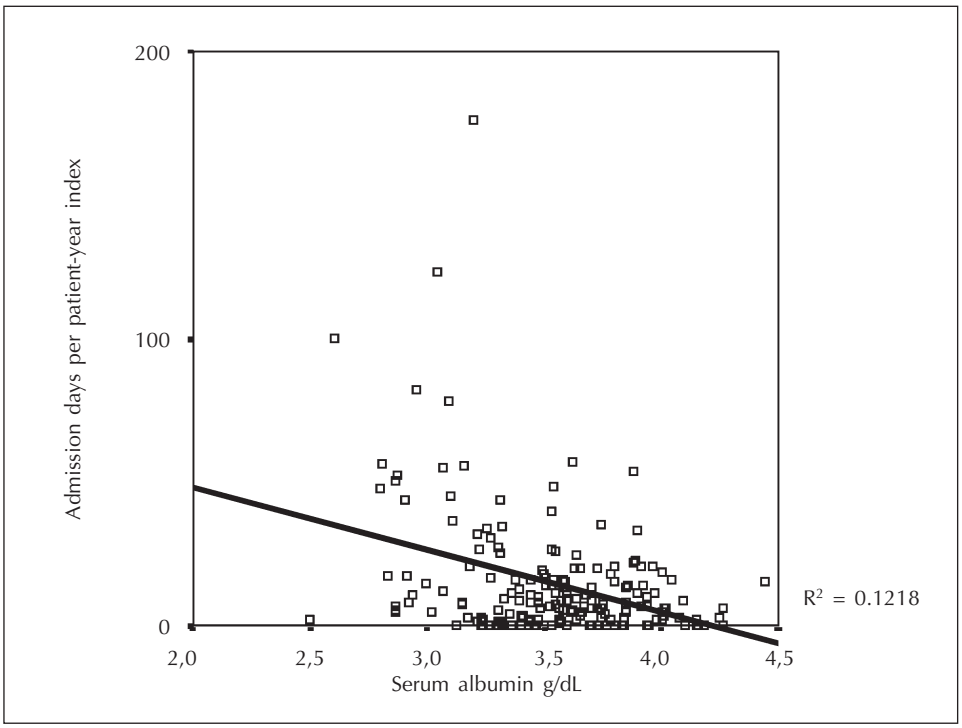

Fig. 3.—Association between albumin admission days index ($p < 0.0001$).

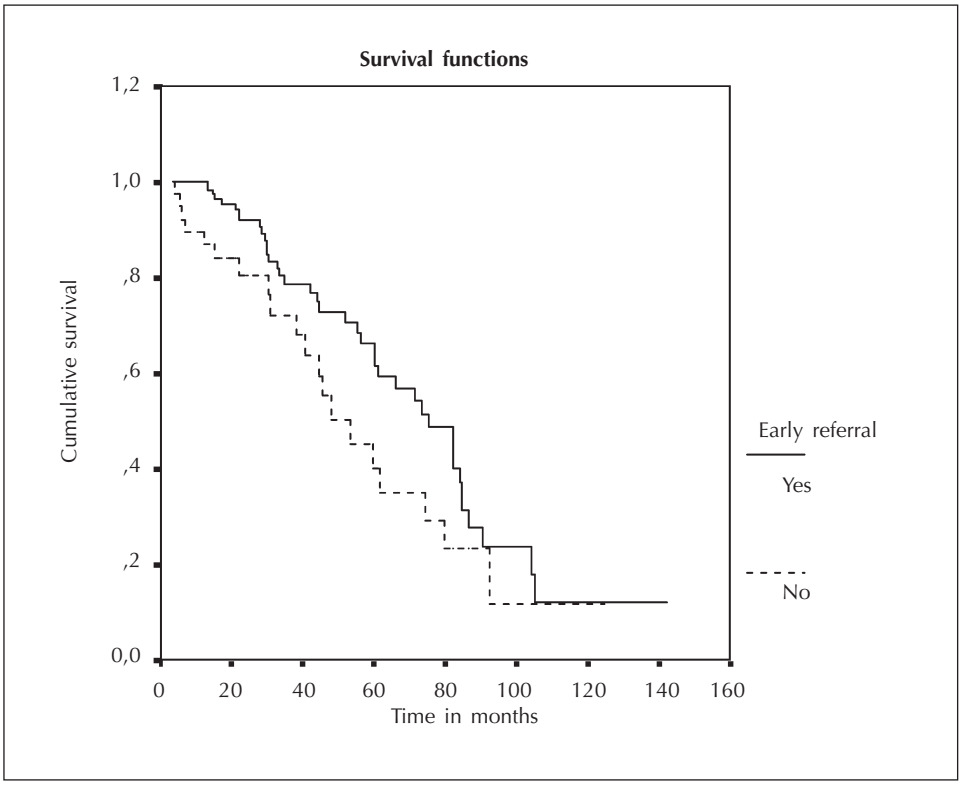

Fig. 4.—Survival curves for LR and ER groups. Log-rank = 0.06.

Table III. Morbidity analysis. Selected variables by the final multiple linear regression model

	Non-standardiez coefficients	Significance	95% confidence interval for B	
			Upper limit	Lower limit
(Constant)	101,118	< 0.0005	53,601	148,635
Charlson's comorbidity index	2,445	< 0.0005	1,190	3,699
Late referral	-12,111	< 0.0005	-18,132	-6,091
Serum albumin g/dL	-11,565	0.002	-18,768	-4,361
PUR	-0.428	0.031	-.816	-.039
Hematocrit	-0.826	0.049	-1,648	-.004

PUR, percentage of urea reduction.

Table IV. Survival analysis. Variables remaining statistically significant with the multivariate Cox's regression model after complete follow-up

Variable	Coefficient B	exp (B)	Significance	95% CI of exp (B)	
				Lower	Upper
Hematocrit	-0.207	0.813	< 0.0005	0.726	0.910
Comorbidity index	0.265	1.303	0.007	1.066	1.594
PUR	-0.059	0.943	0.038	0.893	0.996
Membrane	-0.771	0.463	0.007	0.260	0.822

PUR, percentage of urea reduction.

Survival analysis

After introducing into a univariate Cox regression model, the variables that showed a significant association with mortality after complete follow-up were: albumin, age, vitamin D therapy, hematocrit, comorbidity index, PUR, membrane type, and start of HD with temporary catheter. Three other variables were close the a significance level: the parathyroid hormone (p = 0.087), the erythropoietin resistance index (p = 0.059), and late referral (p = 0.061).

The previous 11 variables were simultaneously introduced into a Cox regression model. Finally, those still having significance after statistical adjustment are: the comorbidity index, hematocrit, PUR, and type of dialyzer membrane (table IV).

For Charlson's comorbidity index, the Exp (B) value = 1.303 indicates that in our patient population the death risk increases by 30% for each point the index is increased. Thus, exp(B) is equivalent to the relative risk.

The three other variables present an exponential coefficient lower than 1. For its interpretation, it is easier to consider the inverse value (1/exp(B)) that indicates the increase in risk rate for each 1-unit decrease in the variable. For hematocrit, 1/0.813 = 1.23 indicates that the risk increases by 23% for each 1 point decrease in its value. For PUR 1/0.903 = 1.06 indicates a 6% risk increase for each one point reduction of this index of dialysis efficacy. Finally, in the case of the variable type of membrane, the inverse of the exponential value 1/0.463 = 2.16 indicates that patients dialyzed with cellulose membranes have a mortality risk 2.16 times higher as compared to those patients dialyzed with high-permeability synthetic membranes.

To elucidate whether late referral is a variable independently influencing on HD patients' survival, a multivariate analysis was performed creating three Cox regression models to assess the survival prog-

Table V. Survival analysis. Significant variables with Cox's regression at 12, 24 and 36 months of follow-up

Variable	Coefficient B	exp (B)	Significance	95% CI of exp (B) Lower	Upper
		12 months of follow-up			
Late referral	-4.8	0.008	0.010	0.009	0.73
Comorbidity index	0.59	1.8	0.004	1.2	2.73
		24 months of follow-up			
Late referral	-1.3	0.27	0.017	0.098	0.75
Comorbidity index	0.65	1.91	< 0.0001	1.46	2.5
		36 months of follow-up			
Comorbidity index	0.51	1.7	< 0.0001	1.28	2.18
Age	0.06	1.1	0.0025	1.01	1.12
Temp. catheter	-0.77	0.46	0.052	0.21	1.01

nostic factors at 12, 24, 36 months, respectively. Table V shows the analysis results.

At 12 months of follow-up, the only variables that showed significance in the multivariate analysis were the comorbidity index (RR = 1.8, 95% CI = 1.20-2.73, p = 0.004) and LR (RR = 0.008, 95% CI = 0.009-0.73, p = 0.010). At 24 months of follow-up, the variables selected by the model remained the same, the comorbidity index (RR = 1.91, 95% CI = 1.46-2.5, p < 0.0005) and LR (RR = 0.272, 95% CI = 0.098-0.75, p = 0.017). At 36 months of follow-up, the comorbidity index remains as a significant variable (RR = 1.67, 95% CI = 1.28-2.18, p < 0.0005) together with age (RR = 1.061, 95% CI = 1.01-1.12, p = 0.0025) and start of HD with a temporary catheter (RR = 0.46, 95% CI = 0.21-1.01, p = 0.052), although this latter variable is close to the significance limit. In this model, LR is no longer a statistically significant variable.

DISCUSSION

There is increasing awareness among nephrology professionals of the importance of quality of care during the pre-dialysis period. There are a number of studies that have evaluated the hypothesis that early referral of CRF patients to the nephrology department will translate in improved clinical outcomes. Most of these studies have been performed in other countries[17-35] with very few done in Spain, so far. For that reason, we believe that our study contributes to increase the existent evidence on this issue in our country. It is generally seen from these studies that patients that been early referred start on dialysis in better clinical and metabolic conditions: a greater percentage through a permanent vascular access, they present a lesser degree of anemia and hyponutrition, a better management of calcium-phosphorus metabolism, lesser metabolic acidosis, a lesser water overload. This will later have an impact on better clinical outcomes and lower costs, with lower number of hospital admissions, especially during the early phase, and more importantly, on a greater likelihood for survival. Some studies have even shown that better outcomes proportionally increase with the longer duration of pre-dialysis follow-up by a nephrologist.[24,30] However, it is worth noting that not all authors have seen this benefit of ER in terms of mortality.[21,27,29]

In spite of all this, there still exist no consensus when defining late referral. For some authors, LR occurs when patient management could have been improved if contact with the nephrology specialist had occurred sooner.[39] Of course, this definition is too confusing, and in clinical practice, this time interval during which the patient could have been appropriately managed by a nephrologist during the pre-dialysis period varies according to different authors. It has been thus defined as less than 1 month,[26,28,29] less than 3 months,[19-21,32] less than 4 months,[17,25,27,30] and less than 6

months.[24,36,37] This discrepancy spreads also to scientific societies. For instance, the Canadian Society of Nephrology defines ER as the follow-up that occurs for at least one year prior to dialysis onset,[40] whereas others, such as the US National Institutes of Health set up their cut-off point at 4 months.[41] This latter definition seems to be the more frequently employed in recent works and it is the one we have adopted. As a result, in our study, only 22% of the patients were referred late to the nephrologist. This figure is somewhat lower than that published by other foreign authors that used the same definition criterion and that establish it between 29% and 34%.[17, 25, 27, 30] In our country, in a previous study the prevalence was 23.74% but set up the cut-off point at 6 months.[36] Another Spanish study assessed starting dialysis electively or not, independently of ER or LR, including 48.6% of the patients starting in a non-elective way.[38] Also in our country, according to a recent report from the INESIR study, 26.8% of the patients starting on dialysis were managed by a nephrologist for a period longer than 6 months, and 32.5% have not previously been managed by a any kind of physician.[37]

The causes for late referral are several, among which we highlight the lack of appropriate communication between primary care physicians and nephrologists, the perception by some doctors of dialysis uselessness in elderly or diabetic patients, the lack of perception of the importance of nephrology care during the pre-dialysis period, and the consideration of nephrologists as just dialysis providers by some other specialists.[13] Besides, there exist other reasons mainly considered as inevitable and that in some series represent up to 50% of the cases:[33] patients presenting a non-resolved acute renal failure or a rapidly progressing glomerulonephritis, patients not compliant with medical indications or that refuse doing the check-ups until they reach a critical condition, asymptomatic patients until very advanced phases of chronic renal failure and, for that reason, they were not detected earlier, and patients not previously controlled by any kind of physician.

When analyzing how our patients were carriers of renal failure, we observed that half of the cases were detected at a hospital setting, and that only a third of them were referred to the clinic by their primary care physician. Thus, until recently, in our province, renal failure detection has greatly depended on the hospital and its specialists to the detriment of primary care centers and primary care physicians. This obviously an abnormal situation that has started to be rectified in recent years after improving the communication circuits between both health care levels. In our province, there is no outpatient nephrology program and these data show to what extent its implementation and generalization are justified, as the Spanish Society of Nephrology has longer been advocating.[42]

In our study, patients from the LR group reached dialysis in poorer conditions than those from the ER group. They presented higher anemia levels, partially because they were treated with erythropoietin less frequently during the pre-dialysis period. They also showed lower albumin levels and higher creatinine and urea levels. Their comorbidity index was higher and they required a temporary catheter as a first vascular access more frequently. These data are in agreement with those reported by others.[17,22,24,25,27,36,38] When comparing the course of laboratory parameters, the LR group had higher mean potassium levels and lower hematocrit, this latter datum correlating with requirement of higher doses of erythropoietin and with higher erythropoietin resistance index.

In the morbidity analysis, the late referral variable was one of the one chosen for the final multivariate model, indicating that in our patient population that started on hemodialysis this variable independently affected on hospital admission index during further follow-up. In the survival analysis, although the LR variable was not included into the final Cox regression model after complete follow-up, it did show a statistical significance in multivariate models constructed with follow-up times at 12 and 24 months, respectively. This would indicate that the death risk becomes similar between both groups once the initial phase of entry into dialysis is overcome. Although, as some authors point out, this mortality course may be explained by a survival bias, the so-called «survivors depletion phenomenon», that is to say, those patients more susceptible to the effects of an inappropriate preparation for dialysis die in excess at the beginning, whereas those better prepared have greater likelihood of survival.[32] Further, after a depletion of these «susceptible» patients, survival in the LR group becomes similar to that in the ER group. This concept would also imply that the associations between mortality and early or late referral would derived only from the mortality excess of the LR group during the first months. In previous Spanish studies, survival was analyzed by using the Kaplan Meier test but with no statistical adjustment for other variable. In the study by Ga-

llego *et al.,* there were no differences in LR patients' progression with regards to greater morbidity or mortality. In the study by Gorriz, they do find survival differences within 3 years and also in hospital admissions, although these ones were computed during the first 6 months. By contrast, in our study, we carried out a longer follow-up and we performed a statistical adjustment for other possible confounding variables.

Our morbidity and survival multivariate analysis selected variables that may be considered classical and that had been previously described in other studies including a high number of patients. It is remarkable that in spite of the relatively small sample size of our study, these variables can show significance, which indicates their power as predictors in hemodialysis patients and their usefulness in daily clinical practice with no need to lie on monitoring of other more expensive and difficult to obtain variables. In the case of three of them (by order of statistical power, hematocrit, comorbidity index, and PUR), they were predictive both of morbidity and mortality, indicating the profitability of the information provided by its monitoring in clinical practice.

Our study presents some limitations. The first one derives from its observational and retrospective design, a limitation that is shared by most of the studies published on this issue and that subtracts quality of the scientific evidence derived from them. On the other hand, we cannot rule out that survival differences might be due to the so-called advance diagnosis bias. This bias implies that mistaken conclusions may be derived from a study in which patients are included at different stages of their disease, so that the longer survival for some of them may be simply due to an earlier registration of the cases. In the dialysis setting, this bias relates to the effect by which survival measurement at the beginning of renal replacement therapy apparently increases in patients with higher residual renal function, that is, at an earlier stage of the disease natural history, as compared to those starting dialysis with lower residual renal function. In our study, we had no available patients' creatinine clearance at the time of HD onset. In a recent study designed to counteract the advance diagnosis bias, survival was compared in between two groups of patients from the time they presented an estimated creatinine clearance of 20 mL/min and not from the time of dialysis onset.[43] The early onset group (119 patients) started on dialysis with an average creatinine clearance of 10.4 mL/min whereas the late onset group (116 patients) did so with an average creatinine clearance of 6.7 mL/min. There was not a benefit in terms of survival by initiating dialysis earlier, on the opposite, the Cox regression model showed a significant negative correlation between creatinine clearance at the beginning of dialysis and survival (RR = 1.1; p = 0.02), that is to say, patients that started on dialysis with lower creatinine clearance levels had a tendency for a longer survival. This relationship was still significant when variables such as gender, age, diabetes presence, initial vascular access, hemoglobin, serum albumin, leucocyte count, Khan comorbidity index, and creatinine clearance at dialysis onset were added into the model. From these results, it derives that the supposed benefit of early dialysis onset still is controversial nowadays.

To conclude, the results from our study show how late referral to the nephrologist of CRF patients has an effect on poorer clinical and metabolic conditions at dialysis onset, and it furthers follows in increased patient morbidity and mortality during their continuance on hemodialysis. These results strengthen the evidence of how important is early disease detection, for which the coordinated work of primary care physicians and reinforcement of extra-hospital nephrology units. Only in this way we will be able to reduce the number of patients lately referred and assure a quality of care to patients during the pre-dialysis period, which will allow them reaching the onset of renal replacement therapy with the best available preparation.

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