Frailty at the beginning of dialysis; is it a prognostic factor?

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Abstract

Introduction: Frailty (F) refers to the cumulative organic damage caused by aging, as a consequence of a diminished physiological reserve. Frailty's prevalence is 73% in dialysis.

Objectives: Our aim was to identify the prevalence of F in patients starting hemodialysis (HD) or hemodiafiltration online (HDF) treatment to asses change in frailty during a six-month period of dialysis.

Patients and Methods: This prospective cohort study evaluated 67 incident patient starting-HD or HDF at one year, with a follow-up period of at least six months. The frailty was assessed by the Fried frailty method. According to this test, we divided the population in two groups: Pre-frail (0-2) and frail (3-5).

Results: Mean age was 64 years, 64% were male and 92% were treated with HD. A total of 35.8% of the patients were admitted to dialysis with a prosthetic or native fistula. The prevalence of F at the beginning of dialysis was 65.7%. The mean value of Charlson index (CHI) was 5.2 ± 2. There was a significant correlation between CHI and frailty test ($P<0.0001$). Basal F score (n=67) improved after 6 month (n=52): 3 (2-4) versus1 (1-2) ($P<0.0001$). Hematocrit (28 versus 32% $P=0.05$) and calcium levels (8.6 and 8.9 mg/dL, $P<0.002$) also increased after sixth-month. Global mortality was 7.5%. In the multivariate analysis CHI ($P<0.001$) and albumin ($P=0.003$) were frailty predictors.

Conclusion: The prevalence of F in patients who start dialysis therapy is high. There was an improvement in F score after six-month of dialysis treatment. Patients with higher F score had higher mortality with higher CHI.

Keywords: Dialysis, Sarcopenia, End-stage chronic renal disease

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Introduction

Historically, knowledge concerning aging was established upon the different biological mechanisms that lead to it, casting aside other matters unrelated to biology such as the psychosocial sphere (1). Following this new approach two principal syndromes where described, disability and comorbidity, which are now known to modify significantly quality of life (1). Disability in senile population was explained exclusively as a consequence of the underlying disease, without finding a physiopathological mechanism that accounted for it, in the absence of an established disease or its relationship with the process of aging itself (1). For this reason, over the past ten years, a new term has emerged, conceptualizing a new characteristic or phenotype, called frailty (1). This new phenotype or frailty syndrome, was first embraced by geriatricians to describe cumulative damage in multiple organic systems, produced by the process of aging itself (1-4). This leads to a state of diminished physiological reserve and tolerance to stressful insults, both internal and external (1-4). Therefore, frailty syndrome is defined as the cumulative damage of multiple organs and systems secondary to the mere process of

aging, which results in a diminished physiological reserve (30%) leading to an inadequate tolerance to internal and external insults (1-9). Woods et al describe four main risk factors for the development of frailty: physiological, comorbidity, socio-demographic and physiological (10). Frailty syndrome in chronic kidney disease (CKD) patients, without the need of renal replacement therapies (RRTs), account for the physiological dysfunction secondary to organic aging among other comorbidities (2,11). Furthermore, patients who require RRT, other factors such as uremic syndrome and pro inflammatory states are added alongside conditions characteristic to hemodialysis (HD) (vascular access type, dialysis dose (Kt/V), anemia, bone mineral metabolism etc.) (2,10). This syndrome affects a number of physiological areas such as the cognitive, emotional, nutritional, functional, strength, equilibrium, mobility and sleep. Moreover, it also has an impact in social aspects. This leads to the development of different diagnostic scores, to prevent and improve outcomes in patients suffering from frailty, which are now a new area of investigation (1). Overall, the Fried Frail test, is the most tested and applied, using five

■ **Implication for health policy/practice/research/medical education**

Frail is an undervalued condition associated with great mortality on dialysis. A lot of studies evaluated frail in cross sectional analysis. We studied incident patients admitted to dialysis. We assessed the frailty prevalence of patients starting hemodialysis or hemodiafiltration and followed these patients prospectively for 6 months. To our knowledge, there is a lack of prospective studies in this area.

different variables to score a patients as non-frail (0), pre frail (score 1-2) or frail (>3) (1,2,5,12-14). The prevalence of F accounts for 7% to 12% of general population and CKD at early stages and the incidence stands between 7% and 15%, accounting for different ethnic groups and methods applied to quantify the frailty (1,2). Frailty in population over forty years or older, varies between 42 and 73% with a frailty risk being 4 or 5 times greater than general population (2).

Objectives
Our aim was to identify the prevalence of frailty in patients starting HD or hemodiafiltration online (HDF) treatment. To asses change in frailty during a six-month period of dialysis

Patients and Methods
Study design
The study was designed as a single-centered prospective cohort study evaluating 67 incident patients starting HD or HDF between December 2017 and December 2018 with a follow up period of at least six months.

Inclusion criteria
- Incident patients (>18 years) starting HD or online high volume HDF.

Exclusion criteria
- Patients treated with other forms of RRT (peritoneal dialysis or kidney transplant)
- Patients denial to perform the frailty test

Variables
The quantitative and qualitative variables for each patient where obtained from the EUCLID (European Clinical Database) database, an online program for data recollection of patients admitted for chronic RRT of Fresenius dialysis centers. Demographic data such as age, gender, cause of renal insufficiency, comorbidities, cardiovascular disease (considered as coronary artery disease, peripheral artery disease or the presence of aortic aneurysm), Charlson index (CHI) adjusted by age and validated for dialysis, RRT modality (HD or HDF), type of vascular access at entry (graft or native fistula or catheter, either permanent

or transient). The weight taken into account was measured with BCM (Body Composition Monitor) after two weeks of treatment trying to account for the possible bias of fluid overweight or malnutrition. Blood sample analysis [albumin, creatinine, urea, PCR, ferritin, ferremia, transferrin, transferrin saturation percentage, hematocrit, calcium, phosphorus, intact parathyroid hormone (iPTH) and vitamin D were measured at the beginning and after six months of treatment.

Fragility measurement
Frailty was measured by the Fried Frail method which considers five physical variables (Table 1).
The test was first performed in the examination room before the first dialysis session and at month six. According to the obtained score the study population was divided into two groups:
1. Pre-frail: 0 to 2 points
2. Frail: 3 to 5 points

Non-frail patients were included in the pre-frail group to facilitate the statistical analysis at baseline due to the small number of patients (2 non-frail patients younger than 24 years).

Ethical issues
The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of CEMIC University Institute of Medical Sciences approved this study. Accordingly, written informed consent was taken from all participants before any intervention.

Statistical analysis
The qualitative variables are described as percentages; the quantitative variables are expressed in means and medians with their standard deviation (SD) or interquartile range (IQR) as appropriate. Frailty was considered as a quantitative discrete variable for significance analysis with a minimum score of 0 and a maximum score of 5 points, distributed in two groups according to the score, pre-frail (0-2 points) and frail (3-5 points). This was considered at enrolment and at month six. The descriptive variables considered for each group where included according to clinical criteria and literature review, considering mortality and morbidity predictors in patients with RRT. Adjusted risk indices and confidence intervals of 95% (IC of 95%) with a P value <0.05 were used to establish statistical significance. For the analysis of comparison of continuous quantitative variables between admission and sixth month for the two groups, the Wilcoxon non-parametric test was used.

Results
A total of 67 patients initiated RRT. At month six, 52 patients (77.6%) completed the study. Five patients died (7.5%), four were transferred to other dialysis center (6%), one patient recovered renal function and five (7.5%)

Table 1. Frailty test according to Fried frail (Cardiovascular Heart Study)

Component	Physical Method	Score	
		Yes	No
Low weight	Unintentional weight loss ≥4.5 kg in the past year.	1	0
Exhaustion	According to CES-D 2 parameters: How often did you feel exhausted? **0.** Rarely or not (less than 1d), **1.** With certain frequency (1-2 d), **2.** Moderate frequency (3-4 d) **3.** Most of the time. **2-3** in the score, it is positive.	1	0
Physical Activity	Short version of the Minnesota Leisure Time Activity questionnaire 2011,* stratified by sex: <383 kcal/wk men <270 kcal/wk women	1	0
Walking time	Based on a 4.5 m walking distance; stratified by sex and height. **Men** Height: walking time ≤173 cm: ≥7 s >173 cm: ≥6 s **Women** Height ≤159 cm ≥7 s >159 cm ≥6 s	1	0
Grip strength	By men/women BMI: Men BMI Dynamometer** ≤24 kg/m² ≤ 29 kg 24.1-26 kg/m² ≤ 30 kg 26.1-28 kg/m² ≤ 31 kg >28 kg/m² ≤ 32 kg Women: ≤23 kg/m² ≤ 17 kg 23.1-26 kg/m² ≤17.3 kg 26.1-29 kg/m² ≤18 kg >29 kg/m² ≤ 21 kg	1	0
Results	0: No frail 1-2: Pre Frail 3 -5: Frail		

Modified from: Johansen et al.[4]

CESD-2: Epidemiological Center for Depression Studies, BMI: Body Mass Index, MET: unit of measure for metabolic index defined as the amount of heat emitted by a person at rest per square meter of skin equivalent to 50 kcal/ h/m²

*Calculation by METS (resting metabolic unit) for each physical activity with the formula: kcal/week: METS × KG × Time in hours × days a week of the activity.

The activities carried out 3 months prior to admission to hemodialysis were considered, ruling out baseline activities (dressing, personal hygiene, sleeping, physiological functions) and taking into account those that imply moderate light intensity (1-1.5 METS) (1.6-3 METS). and great intensity (more than 6 METS)

** Instrument to measure force, based on the deformation capacity of elastic bodies.

received a kidney transplant (Figure 1).

Mean age was of 67 ± 17 years, 43 (64%) were male. The follow-up period since RRT until end of study, death, renal transplant or transfer to other dialysis facility was 5.9 months (5.7-6.4). Considering patients with two or more renal risk factor (being hypertension the most prevalent in our cohort) as multifactorial etiology for renal insufficiency, this accounted for the leading cause of CKD with 48% of the patients (n=32). Regarding comorbidities, 26.8% of the patients where diabetic, 88% had hypertension and 32.8% presented with some extent of cardiovascular disease. Prior to enrolment 5 patients were treated with ketoanalogues supplements and diet. Thirty-five patients did not have prior nephrological care (late referral) and 32 had nephrological care and received erythropoiesis stimulator agents and secondary hyperparathyroidism treatment such as calcium and vitamin D supplements. We did not find statistical difference in frailty (3.0 ± 1.3 vs 3.2 ± 1.3, $P = 0.48$) and CHI (5.03 ± 1.8 versus. 5.52 ± 2.1, $P = 0.31$) between patients according to prior nephrological care (Table 2).

The median estimated glomerular filtration rate (eGFR) at entry was 6.9 (5-10) mL/min/ 1.73 m2. The median value of hematocrit and serum albumin were 28% (17-33%) and 3.7 g/dL (2.4-4.9 g/dL) respectively. HD accounted for the most common renal replacement modality with 62 patients (92%) and transient catheters were the most common vascular access n= 37 (55%). The median body mass index was 26 kg/m² (14.8-40 kg/m²). The median for CHI at enrolment was 5.2 (2-10). We found a significant improvement in hematocrit and serum calcium at month six. Regarding treatment modalities, 29% of the patients (n = 15) remained in HD and 71% changed to HDF during the study. In contrast with the data presented at enrolment at the end of the trial prothesis and native fistulas were the most common vascular access accounting for 86.5% of the patients while 13.5% had a permanent catheter. The median score of frailty at dialysis entry was of three (2-4) versus one (1-2) at month six ($P < 0.0001$). The prevalence of F at the beginning of the study accounted for 65.7% of the population, in contrast in the 52 patients who remained in the study until completion, the frailty prevalence descended to 19% with a corresponding increase to 81% of pre-frail patients ($P < 0.0001$).

No patient with involuntary weight loss was observed. The respective medians for each frail parameter at month six where: Walking speed 5.5 (3-9), grip strength 23 (10-50), exhaustion 0.3 (0-3) and physical activity 1734 (197.6-7159) kcal/wk. Walking for leisure was the physical activity most commonly observed in the study.

After dividing the population into frail (FR) and pre-frail (PF) groups, we stratified age in three groups from 18 to 39; 40 to 61 and 62 years or older and observed that patients in the last group had more prevalence of frailty ($P < 0.0001$). We did not find significant differences between genders. Median eGFR in the FR group 8.1 mL/min (1.5-17) was greater than in the PF group: 7.1 mL/min (2-14) ($P < 0.0001$). CHI median in the FR group was higher six (2-10) than PF group: 2 (4-7) ($P < 0.0001$). Serum albumin levels were lower in FR group ($P < 0.03$).
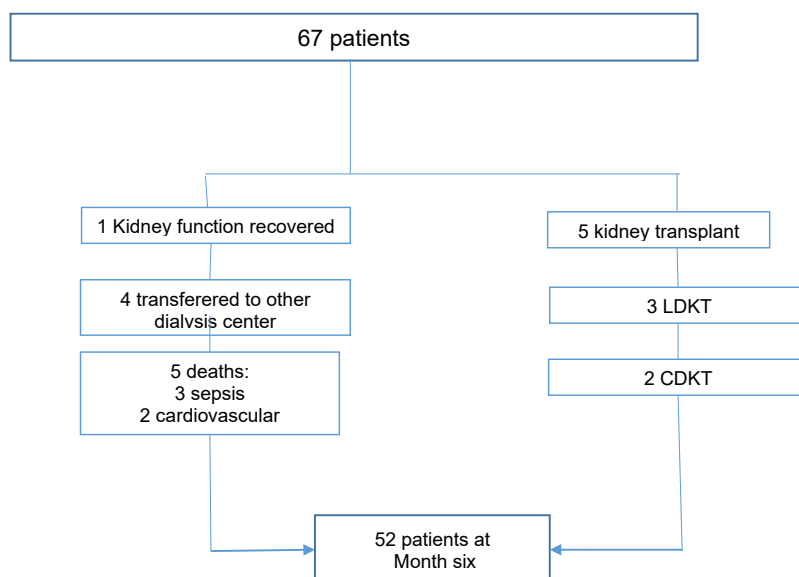
Figure 1. Follow up at six months. LDKT: living donor kidney transplant, CDKT: cadaveric donor kidney transplant.

We observed five (11.4 %) deaths in the FR group compared with no deaths in PF group (*P*<0.01). Causes of death were cardiovascular (n= 2) and infectious (n=3). The frail group also had a lesser number of kidney transplants (*P*=0.02; Tables 3 and 4**).**

The frailty test had a significant statistical correlation with the CHI, (r=0.54; *P*<0.0001) suggesting that patients with greater number of comorbidities are more frailty (Figure 2). In the linear multivariate analysis, CHI (*P*<0.0001) and serum albumin (*P*<0.003) were the only predictors of frailty (Table 5)**.**

Discussion

In the present study, the prevalence of frailty in patient's incident in RRT was 67.5% using the Fried frail score by the physical method. This data is similar to the prevalence reported in Bao et al (73%) counting with a population of 1576 patients who initiate dialysis from Comprehensive Dialysis Study (CDS) using the Fried Frail score criteria by the self-reported method (15). The prospective study by Bárbara et al including 95 patients on pre-dialysis, showed a prevalence of F for patients over 65 years of 44% using the Groningen Frailty Indicator (GFI) test, the Identification of Seniors at Risk-Hospitalized Patients (ISAR-HP) and the Veiligheids management system (VMS). This prevalence compared with the Fried Frail self-report test had lower sensitivity and specificity (GFI 89% / 57%, ISAR-HP 83% / 77% and VMS 77% / 67% respectively) (16). Several studies report that the prevalence of F is modified according to the method used to measure it, as well as gender, age, and comorbidities. Leaving aside these variations, the Fried Frail test by the physical method has a high sensitivity and specificity compared to other techniques in the incident population on dialysis, especially in patients older than 40 years. Based on the above, we have chosen this method to evaluate our patients. A significant improvement in frailty status, hematocrit and calcemia was observed during the follow-up. We believe it was due to better medical control (monthly control), therapeutic compliance, improvement in nutritional status and physical state which we think accounts for the optimization of the internal environment and the elimination of blood toxins, hence we do not consider that this finding represents a selection biases.

We also observed that frailty increases proportionally to age (group 40-61 years, 18% and >62 years 82%), as occurred in the cross-sectional study by Johansen et al with incidents in HD that are part of the longitudinal Dialysis Morbidity and Mortality Study (DMMS), where the prevalence in those under 40 years of age was 44.4%, in those aged 60 to 70, 74.2% and 80 or more 78.8% (12). The high prevalence of frailty in patients requiring dialysis compared to the healthy population over 50 years (7 to 17%) according to cross-sectional CHS studies (Cardiovascular Health Study and SHARE STUDY (Study, Survey of Health, Aging and Retirement in Europe), is an important observation with potential clinical benefits its diagnosis and early prevention (1). The cohort of patients with a score for FR had a mortality of 11.4% compared to 0% in the pre-frail patients. It is reasonable to expect that mortality could increase with a longer period of observation, as demonstrated by the prospective study by McAdams-DeMarco et al in 146 HD patients in whom mortality was 40% at 3 years of follow-up, also associating a 3-fold higher risk of death independently compared to non-frailty patients in HD (RR: 2.6; 95% CI: 1.04-6.49, *P*=0.04) (17). In the present study, the F measured by the Fried Frail physical method test had a significant correlation with the age-adjusted CHI at the start of RRT (r = 0.54, *P*<0.0001). However, a retrospective study by Kim et al using the claim frailty index (CFI) test in

Table 2. Characteristics at baseline and at month 6

Variables	Baseline n = 67 (%)	Month 6 n = 52 (%)	P
Demographics			
Age	64 ± 17		
Male, n (%)	43 (64)		
Causes of CKD			
Glomerulonephritis	9 (13.4)		
Hypertension	14 (20.8)		
Multiple myeloma	4 (6)		
Multifactorial*	32 (48)		
Polycystic renal disease.	5 (7.4)		
Obstructive uropathy**	3 (4.4)		
Laboratory values			
CKD-EPI, mL/min/1.73 m^2	6.9 (5-10)		
Albumine, mg/dL	3.7 (2.4-4.9)	3.9 (3-7.9)	0.2
Urea, mg/dL	197 (43-654)	135 (84.4-214)	0.04
PCR, mg/dL	1.1 (0.2-3.4)	5.3 (0.1-33)	0.01
Transferrin, ng/dL	183.7 (105-272)	192 (128-331)	0.1
Transferrin saturation, %	24.8 (9-69)	27.3 (6-83)	0.3
25-OH, mg/dL	18 (11.7-27.7)	Not measured	
Calcium, mg/dL	8.6 (6.9-10.7)	8.8 (7.3-10)	<0.002
Phosphorus, mg/dL	5.5 (1.2-10.5)	5.8 (1.5-9.6)	0.9
Hematocrit, %	28 (17-33)	32.7 (19.3-44.8)	0.05
Dialysis modality, n (%)			
Hemodialysis	62 (92)	15 (29)	<0.001
Online hemodiafiltration	5 (8)	37 (71)	
Vascular access, n (%)			
Transient catheter	37 (55)		
Permanent catheter	6 (9)	7 (13.5)	<0.01
Prosthetic or native fistula	24 (36)	45 (86.5)	
Other			
BMI (kg/m^2)	26 (14.8-40)		
Charlson Index	5.2 (2- 10)		
Kt/V***		1.5 (0.9-2.2)	

* It was considered multifactorial with 2 or more comorbidities at the same time, except that the cause of CKD was evidenced by imaging methods, renal biopsy or bone marrow.
** Prostatic hypertrophy, there was no other related cause.
*** Kt/V dialysis quality and efficacy measurement parameter K: urea clearance in dialysis process, T: dialysis time and V: urea distribution volume.

Table 3. Parameters of frailty at admission and sixth month

| Frailty test	Admission n= 67	Sixth month n= 52	P
Frailty (median)	3 (2-4)	1 (1-2)	<0.0001
Frail, n (%)	44 (65.7%)	10 (19%)	<0.0001
Pre-frail, n (%)	23 (34.3%)	42 (81%)	

3642 volunteer older adults with different comorbidities showed that this was significantly higher than the CHI to predict disability (0.62-0.72 viruses. 0.58-0.66, $P \leq 0.01$) and morbidity (0.58 viruses. 0.66, $P \leq 0.01$), not so to predict mortality (0.68 vs. 0.68; $P = 0.5$) or hospitalization (0.58 vs. 0.54, $P = 0.07$) (14). In our study there was a decrease in the percentage of patients with F after sixth month of RRT (65.7 vs. 19%), improvement in walking speed time (5.5 versus 6 m/s) and in the exhaustion (0.3 vs. 2.5 points), increased physical activity (1734 vs. 493 kcal/wk) and increased grip strength (23 versus 20 kg). The vast majority of studies on F in dialysis patients evaluate this population with cross-sectional studies; however, a study by Lee et al showed similar data to our work (18). Forty-six incident patients older than 65 years undergoing HD were evaluated with a comprehensive geriatric assessment (CGA) frailty score, obtained a 32,6% of frailty (defined as a CGA >10). This group observed that in the CGA index carried out in 29 (60.4%) patients at 12 months they showed an improvement in the median score, being at baseline 8 versus 6 a year ($P < 0.001$) (18). To our knowledge, there is no literature on other studies showing the prevalence of F at the start of dialysis with a follow-up after 6 or 12 months. We find important to state the idea that the manifestations of the uremic syndrome can overlap with the frailty syndrome, sharing several of its symptoms, such as exhaustion, weight loss and decrease in muscle mass. This could support the fact that in the first months a significant improvement is evident in the initiation of RRT patients with uremic symptoms. This would not be the case in frail patients for whom RRT may worsen, improve slowly or maintain their symptoms (19). That is why, in view of the false positives that can occur for the diagnosis of F at the beginning of RRT, we consider necessary to evaluate more diagnostic tools of greater specificity and, in the same way highlight the need of prospective studies with longer times.

Table 4. Variables in frail and Pre-frail groups

Variable	Frail n= 44	Pre-Frail n= 23	P
Age	74 (40-91)	48 (18-77)	<0.001
Groups by age			
18-39	0	7 (30.5%)	
40-61	8 (18 %)	11(47.8%)	<0.0001
>62	36 (82%)	5 (21.7%)	
Male gender	28 (63.6 %)	15(65.2%)	0.36
eGFR, mL/min	8.1 (1.5-17)	7.1(2-14)	<0.0001
Charlson Index	6 (2-10)	2 (4-7)	<0.0001
Albumin	3.6 (2.4-4.5)	4 (2.8-4.9)	0.03
PCR	1.15	2.7	0.05
Kidney transplant	0	5	0.02
Deaths	5	0	0.01

Table 5. Multivariate linear regression (Dependent variable: fragility)

Variable	OR	P	95% CI	
Sex	0.70	0.472	3.62	2.72
Charlson Index	0.479	<0.0001	0.19	0.45
Albumin	- 0.319	<0.003	-1.47	-0.32
CKD-EPI	0.117	0.309	-0.44	0.13
Calcium	0.345	0.520	0.25	1.22
Phosphorus	- 0.92	0.440	-0.26	0.11
Urea	0.47	0.701	-0.003	0.005
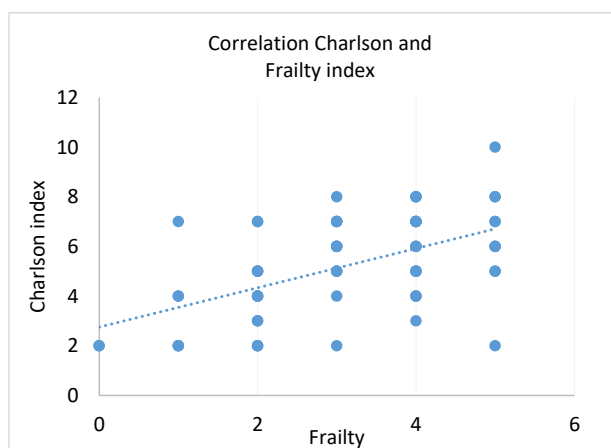
Figure 2. Correlation histogram between Frailty Index and Charlson (r= 0.54, $P<0.0001$).

Conclusion

The prevalence of frailty in patient's incident starting two different dialysis modalities was 67.5%. There was an improvement in frailty test after six months of dialysis. Mortality in patients with frailty was related with lower levels of albumin and an increased CHI.

Limitations of the study

The main limitation of this study is the number of patients at the beginning of the trial, which was not sufficiently representative for extracting conclusive results. The follow up period was only of six months, which limits the observations on the long-term behavior of frailty. It may be argued that the loss of 22 % of data (n = 15) may affect this study validity, but we think that the results would not be much different with lesser loss of data. Nevertheless, the strength of this study resides in the follow up and re-evaluation of the majority of patients after six months of having initiated a dialysis therapy

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due was generate by the authors in an excel program, but are available from the corresponding author on reasonable request.

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