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Frailty syndrome in patients with chronic kidney disease at a dialysis Centre from Santander, Colombia

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Background & aims. Frailty syndrome, characterized by loss of functional reserves and vulnerability to acute stressors, conditionate a higher risk of adverse outcomes and mortality. Its prevalence is mainly high (65%) in patients with End Stage Kidney Disease, receiving renal replacement therapy.
Methods. Cross-sectional study with a non-probabilistic sampling of adult patients with chronic kidney disease stage 5 that initiated renal replacement therapy at a dialysis centre from Santander, Colombia. The main objective was to estimate the prevalence of frailty syndrome and to describe the clinical and functional characteristics of the studied population. The frailty syndrome was defined through the FRAIL Questionnaire.
Results. Sixty-six subjects were included. The median age was 65 years (IQR 58-69). 54.55% were frail. The median age in frail patients was higher than the one in non-frail (p = 0.019). The prevalence of frailty syndrome was higher in women than in men (p = 0.045). Frail patients had a higher Charlson comorbidity index (p =< 0.01). The mean serum creatinine, parathyroid hormone (PTH), and albumin were lower in frail patients, with statistically significant differences.
Conclusions. The prevalence of frailty in patients that initiate renal replacement therapy in Santander, Colombia, is similar to that reported in other latitudes. Although the FRAIL Scale is based on the self-report, it counts with studies that endorse its reproductivity. Albumin and creatinine serum levels are decreased in subjects with frailty syndrome, behaving as frailty biomarkers in our research.

Key words: frailty, end stage kidney disease, comorbidity, outcome assessment, health care

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INTRODUCTION

The frailty syndrome is a clinical entity that mainly affects older adults, characterized by the inability to overcome everyday events or acute stressors because of the vulnerability generated by the decreased physiological reserve and organic dysfunction related to the age [1]. Various studies have also documented that the frail patient has a higher risk of adverse outcomes, compared with the one pre-frail or vigorous [2]. Kojima, et al. described that frail patient has almost twice risk of presenting falls and hip

fracture (OR, 1.84; CI 95%, 1.43 to 2.38), as well as a higher number of hospitalizations for any cause (OR, 1.9; CI 95%, 1.74 to 2.07), and death (OR, 2.34; CI 95%, 1.77 to 3.09) [3-5].

Multiple definitions of frailty syndrome have been proposed, as well as methods for its classification and diagnosis. One of the most popular is the one proposed by Fried, et al. in 2001 [6]. In general, the assessment must include aspects as the presence of unintentional weight loss, sarcopenia, low physical activity, slow walking speed, self-reported exhaustion, and weakness. The International Conference on Frailty and Sarcopenia Research (ICFSR) recommends screening instruments as the FRAIL Questionnaire, the Clinical Frailty Scale (CFS), or the Edmonton Scale [7,8]. The prevalence of frailty in over 65 years old is estimated between 7-12%, and increases proportionally with age, being close to 25% in over 85 years old [9]. The number and severity of comorbidities that suffer an individual behave as an additional risk factor to develop frailty syndrome [10].

Chronic kidney disease is a condition commonly associated with frailty syndrome [11]. Diverse studies even report a prevalence of 67.7% in patients that depend on dialysis [12]. On the other hand, the globally increased expectation of life is related directly to a higher prevalence of non-transmissible chronic diseases, such as chronic kidney disease. According to high account statistics in Colombia, the prevalence of chronic kidney disease is between 2-3% in the general population, and the one of end-stage kidney disease on dialysis is 68 cases per 100,000 people, mostly older adults at risk of having frailty syndrome [13].

Considering chronic kidney disease as a frequent public health issue, its common association with frailty syndrome, and, therefore, a higher risk of adverse outcomes, this study was designed. The aim of this research is to analyse the socio-demographic and clinical variables of patients who initiate haemodialysis or peritoneal dialysis due to end-stage kidney disease. The FRAIL scale was applied for the diagnosis of frailty syndrome from June 01, 2019, to March 31, 2020, at a dialysis centre in Santander, Colombia.

METHODS

Design and population

Cross-sectional study with a convenience non-probabilistic sampling from all patients over 18 years old with end-stage kidney disease on dialysis, who initiate haemodialysis or peritoneal dialysis within three months before the recruiting of the study, at a dialysis centre from the Bucaramanga metropolitan area from June 01, 2019, to March 31, 2020.

Variables

We registered socio-demographic such as age, sex, origin, and occupation, as well as past medical history and relevant comorbidities. Also, the values of the main laboratory test at admission, which includes serum creatinine, blood urea nitrogen, intact PTH, haemoglobin, corrected calcium, and serum albumin. In addition, the detection of frailty syndrome was made by the application of the self-reported FRAIL questionnaire in the Spanish version.

Definitions

The frailty diagnosis was realized by the FRAIL Scale, accompanied by researches. The scale is validated to Spanish [14]. This tool asses five clinical variables, including weakness, resistance, slow walking speed, unintentional weight loss, and number of comorbidities. Each variable detected add 1 point to the scale. To consider the point that corresponds to the comorbidity item, the assessed subject must have at least 5 from the following chronic debilitating diseases: arterial hypertension, diabetes mellitus, cancer, chronic obstructive pulmonary disease, ischemic heart disease, heart failure, angina, asthma, arthritis or arthrosis, stroke and chronic kidney disease. The subject is considered frail having 3 or more points, pre-frail with 1 or 2 points, and vigorous if the score is zero. With the purpose of better interpretations of the results, we defined the non-frail category, grouping patients classified as pre-frail and vigorous.

Data processing

For the information collection and construction of the database, the software Microsoft Excel 2016 was used. To ensure the confidentiality of people´s data, we assigned alphanumeric codes for the collection and analysis of the information.

Statistical analysis

The socio-demographic and clinical variables are expressed as frequencies, percentages, median, or mean, considering their magnitude and dispersion measures (interquartile range, standard deviation, or variance). Besides, we applied t student test or Wilcoxon, depending on normality distribution, to explore the relation and significance of the quantitative variables with the presence of frailty. For categoric variables, Chi2 or Fisher exact were used, according to the number of events per category. The data analysis was realized by the Statistical program STATA 14.0.

Ethical aspects

This study complies with the principles of the Declaration of Helsinki, local regulatory standards, and universal guidelines for good clinical practice. The protocol

was evaluated and approved by the research ethics committee of the Industrial University of Santander. As it is a merely descriptive study, without interventions of any kind, it is considered risk-free. All subjects authorized entry to the study by signing an informed consent, after ample and sufficient explanation of the objectives and scope of the study.

RESULTS

Sixty-six (66) subjects were evaluated. The median age was 65 years (IQR 58-69). 63.6% were men. 81.8% of the participants were from the urban area. 54.55% were classified as frail, 37.9% pre-frail, and only the 7.6% were vigorous. Stratifying demographic variables by the degree of frailty, the median age of the frail patients was higher compared with non-frail ones (66 years IQR 62-72 *versus* 61.5 years IQR 51-66; p 0.0190). 2.8% of the frail subjects were men, however, the prevalence of frailty was higher in the female group (70.8%), compared with the male one (45.2%), p 0.045. The socio-demographic variables according to the severity of frailty are shown in Table I (Socio-demographic characteristics in frail and non-frail patients).

Stratifying the prevalence of frailty by age group, we registered that subjects over 60 years old presented a higher proportion of frailty syndrome (28/45 (62.2%)), compared with the 41-60 years group (8/16 (50%)), p 0.0190; we did not have frail patients under 40 years old.

Arterial hypertension was the most common comorbidity in the studied population. On the other hand, we observed a higher Charlson comorbidity index on frail patients, as well as a higher proportion of heart disease, compared with non-frail ones, 7 SD ± 2.09 *versus* 5.5 ± 2.32, p < 0.01, and 36.1% *versus* 6.7%, p < 0.01, respectively. Also, the prevalence of diabetes mellitus, ischemic heart disease, stroke, and peripheric arterial disease of the frail patients were higher, compared to non-frail ones, without s statistically significant differences. The comorbidities prevalence according to the severity of frailty is shown in Table II (Prevalence of comorbidities and past medical history, by frail and non-frail).

Concerning the modality of dialysis in which patients entered renal replacement therapy, we found 54% of patients (81.8%) who initiated with haemodialysis, only one had arteriovenous fistula, the remaining ones started with a transient catheter of haemodialysis. Twelve subjects (18.2%) entered the peritoneal dialysis program. Most of the participants (78.8%) initiated renal replacement therapy in the context of a dialytic emergency, without differences according to the frailty status, Figure 1.

In Table III (Laboratory values by frail and non-frail patients) are grouped relevant values of laboratory according to the frailty status. We found that creatinine, albumin, and intact PTH values were lower in patients with frailty syndrome compared to non-frail ones, with statistically significant differences.

DISCUSSION

In our study, the prevalence of Frailty Syndrome in subjects who initiated renal replacement therapy was 55.55%, measured through the FRAIL Scale, which was higher than the one reported by Lee, et al. (34.8%),

Table I. Socio-demographic characteristics in frail and non-frail patients.

	All patients (n = 66)	Frail patients (n = 36)	Non-frail patients (n = 30)	P value
Variable				
Age, median (IQR)	65 (58-69)	66 (62-72)	61.5 (51-66)	0.019
Sex, n (%)				0.045
Male	42 (63.6)	19 (52.8)	23 (76.7)	
Female	24 (36.4)	17 (47.2)	7 (23.3)	
Origin, n (%)				0.523
Rural	12 (18.2)	8 (22.2)	4 (13.3)	
Urban	54 (81.8)	28 (77.8)	26 (86.7)	
Occupation, n (%)				
Home	21 (31.8)	15 (41.7)	6 (20)	
Retired	8 (12.1)	6 (16.7)	2 (6.7)	
Trader	6 (9.1)	0 (0)	6 (20)	
Agriculture	4 (6.1)	3 (8.3)	1 (3.3)	
Other	27 (40.9)	12 (33.3)	15 (50)	

Table II. Prevalence of comorbidities and past medical history, by frail and non-frail.				
	All patients (n = 66)	Frail patients (n = 36)	Non-frail patients (n = 30)	P value
Comorbidity/ Past medical history				
Charlson Comorbidity Index, mean (SD)	6.33 (± 2.3)	7 (± 2.09)	5.53 (± 2.32)	< 0.01
Arterial hypertension, n (%)	56 (84.9)	30 (83.3)	26 (86.7)	0.745
Diabetes mellitus, n (%)	48 (72.7)	29 (80.6)	19 (63.3)	0.118
Ischemic heart disease, n (%)	16 (24.2)	12 (33.3)	4 (13.3)	0.084
Congestive heart failure, n (%)	15 (22.7)	13 (36.1)	2 (6.7)	< 0.01
Peripheric arterial disease, n (%)	12 (18.2)	8 (22.2)	4 (13.3)	0.523
Stroke, n (%)	5 (7.6)	3 (8.3)	2 (6.7)	1
Chronic obstructive pulmonary disease, n (%)	4 (6.1)	2 (5.6)	2 (6.7)	1

Table III. Laboratory values by frail and non-frail patients.

	All patients (n = 66)	Frail patients (n = 36)	Non-frail patients (n = 30)	P value
Variable				
BUN, mean (SD)	55.87 (± 18.9)	55.68 (± 21.4)	56.09 (± 15.7)	0.9307
Serum creatinine, median (IQR)	5.33 (3.95-7.1)	4.84 (3.71-5.94)	7.01 (5.16-7.9)	< 0.01
Haemoglobin, mean (SD)	9.6 (± 1.35)	9.63 (± 1.37)	9.58 (± 1.36)	0.8941
Corrected serum calcium, median (IQR)	8.78 (8.3- 9.18)	8.95 (8.6-9.18)	8.64 (7.9-9.14)	0.0558
Serum albumin, mean (SD)	3.45 (± 0.6)	3.31 (± 0.61)	3.61 (± 0.56)	0.0446
Serum PTHi, median (IQR)	232.8 (165.4- 372.1)	218.1 (149.7-315)	271.85 (207.9-471)	0.0432

BUN: blood urea nitrogen; PTHi: intact Parathormone.

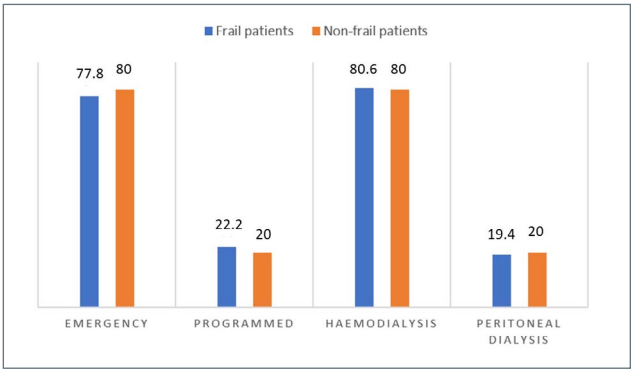

Figure 1. Modality and clinical context at the beginning of renal replacement therapy, according to frailty status (%).

measured through a scale directed by an interviewer, with the items from the Fried phenotype as a reference [15]. Also, using a self-reported scale, Johansen, et al. found in a subgroup of patients (2275) from the Dialysis Morbidity and Mortality Wave 2 Study (DMMS), that 67.7% met the criteria for frailty syndrome [12,16,17]. In the population from Latin America are few studies that have been published. One study from Chile found that 83% of patients initiated haemodialysis or peritoneal dialysis in frail or pre-frail status, according to FRAIL Scale, less than the 92.4% from our research [18]. In contrast, McAdams, et al. using the same Fried´s criteria, found a prevalence of frailty of only 19.5% in patients taken to kidney transplantation [19], merely logical findings due to selection bias related to the priority of vigorous subjects to transplantation.

We used the FRAIL Scale for the diagnosis and classification of frailty syndrome, considering it is a self-report instrument, validated to Spanish, and easy to apply. Besides, it counts with robust studies that confirm the reproductivity of its results compared to the methods which use objective measurements, even using it in population with chronic kidney disease [20].

Despite the clear association between frailty and chronic kidney disease, different registers show variability in the reported prevalence, which could be explained by the heterogenicity of the characteristics from the population (age, sex, comorbidities, and time at dialysis). Also, there are differences between the instruments or measurement scales of frailty, not necessarily comparable [6,21,22].

In our study, stratifying frail patients by age group, we found that almost 65% of them over 61 years were frail, higher to the proportion reported by Lee for that group (48.5%) [15], but less than the one described by Johansen, et al. (76%) [12]. On the other hand, we found that 22.2% of our frail patients were under 60 years old,

which have a different trend compared with the report made by Johansen and Lee for the same age group, 48.3%, and 46.8%, respectively [12,15]. Considering that most of the prevalent and incident population with end-stage kidney disease in dialysis is over 60 years old, the risk of having frailty syndrome is higher for these people.

Johansen et al. also concluded that, independently from the age group, the female group with chronic kidney disease in dialysis were more susceptible to frailty syndrome [12]. Lee, et al. reported the prevalence of frail women in 53.9% [15], a lower percentage compared with the one found in our register, which is close to 70% (p. 0.045), similar to the analysis of McAdams, et al. with a higher perception of frailty in women [23].

It is well known that to initiate dialysis in a non-planned way carries a higher risk of adverse outcomes. In that way, the study of Gorriz in 5 hospitals reported for the beginning of the renal replacement therapy as an emergency, higher length of stay at the beginning and during the first six months of dialysis ($p < 0.001$), as well as higher mortality to six months (10.2% *versus* 3.2% $p = 0.015$, log Rank test), and mortality to three years (24.2% *versus* 36.9% $p = 0.006$, log Rank test) [24]. The percentage of subjects from our study who initiated renal replacement therapy in a non-planned way was 78.8%, which supposed higher risk of adverse outcomes, contrary to that found by Sanabria, et al. in Bogota, considering that 88% of the patients initiated programmed renal replacement therapy [25]. Equally, all patients from this research who entered non-programmed haemodialysis did it through a transitory catheter, similar to that reported in other studies [24-26].

COMORBIDITIES

This study found a mean Charlson comorbidity index of 7 (± 2.09) for frail patients, which is higher than the one for non-frail patients (5.53 ± 2.32), $p < 0.01$. These results are consistent with those Garcia, et al. described, a higher Charlson comorbidity index in frail versus non-frail patients (7.9 *versus* 4.7, $p < 0.001$) [27]. Still, there are variations with the results of Rubio, et al. in which they did not find differences between the Charlson comorbidity index for frail and non-frail patients (8.61 ± 1.28, *versus*, 8.39 ± 1.36, p 0.55) [28]. Besides, Huidobro, et al. did not observe differences between the Charlson comorbidity index for frail and pre-frail patients, comparing the dialysis modality [18].

More frequent comorbidities of frail patients from our study were arterial hypertension and diabetes mellitus. Likewise, diabetes mellitus in Lee, et al. research was the most common comorbidity, with a proportion of 51% [15]. Although this proportion seems low, it is related to the lower prevalence of diabetes mellitus for the general population of Korea, in contrast with the one for Latin America, which is much higher and tends to rise [29-31].

LABORATORY TEST

Even when the haemoglobin value has been proposed as a frailty marker in the general population, this does not seem to apply to subjects with end-stage kidney disease that start dialysis [32,33]. Despite 93.8% of patients admitted to our research had anemia, there were no statistically significant differences comparing haemoglobin levels between frail and non-frail people (9.63 SD ± 1.37 *versus* 9.58 SD ± 1.36; p 0.8941). These findings are similar to the ones reported by Lee, et al. what indicate that haemoglobin is not an adequate biomarker of frailty for dialysis-dependents patients [15].

Several studies have shown a correlation between hyperparathyroidism, muscle-skeletal frailty, and falls in frail elderly [34,35]. Considering the higher cut-off point for intact PTH to de diagnosis of hyperparathyroidism in end-stage kidney disease compared with the general population, those results are not easy to extrapolate to the people on renal replacement therapy. That is why the capacity of this variable to predict frailty and the risk of adverse outcomes in patients with end-stage kidney disease is not completely clear. We found in our study lower values of intact PTH on frail patients compared with the non-frail ones, with a statistically significant difference. These results are similar to the description of Liu, et al. who did not find a correlation between levels of intact PTH and frailty [36]; further studies are required on frail population with end-stage kidney disease for this reason.

One of the topics of interest to future researches in frailty syndrome is to determine the existence of biomarkers that predict adverse outcomes on patients with end-stage kidney disease and frailty syndrome. Garcia et al. found a correlation of hypoalbuminemia with frailty, independently of the scale used to its diagnosis [27]. Moreover, Johansen, et al. found a direct relationship between the severity of hypoalbuminemia and the risk of frailty syndrome [12]. In this study, lower values of serum albumin on frail patients compared with non-frail ones, with a statistically significant difference, although it was not designed to find frailty syndrome predictors.

This study provides knowledge concerning the prevalence, as wells as the clinical and socio-demographic variables of patients with frailty syndrome who depend on renal replacement therapy from Santander, Colombia. Plus, allow exploring clinical and laboratory variables

that eventually estimate the relationship between frailty and renal replacement therapy. For the above reason, the study is considered a pioneer that incentives the active search of patients with frailty syndrome.

Within the limitations of the study, it is worth mentioning that the diagnosis of frailty syndrome depends on the operative definition used. The FRAIL scale, based on a self-reported questionnaire, could get away from the frailty phenotype proposed by Fried, which uses objective measurements to evaluate strength, resistance, slowing, among others. Besides, the study´s objectives and the sample size do not let to estimate associations between clinical, socio-demographic, and laboratory findings, with the severity of frailty. It is relevant to design prospective investigations with a higher sample size to determine the association between laboratory variables and prognosis factors.

To recognize the frailty syndrome on patients who receive haemodialysis or peritoneal dialysis is a challenge that the treating physician assumes assessing patients with the recent beginning of renal replacement therapy. Interdisciplinary and multi-component recommendations for these patients must be designed, such as physical rehabilitation, nutritional, psychological, and social, aiming to impact favourably on their long-term prognosis and quality of life. The findings allow us to recommend the inclusion of the FRAIL instrument within the comprehensive assessment of adults starting the dialysis program to timely identification of frailty syndrome.

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