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Prognostic factors for death in patients with chronic kidney disease on hemodialysis

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SUMMARY

Chronic kidney disease (CKD) is considered a major and growing health problem, with a lower life expectancy among hemodialysis (HD) patients compared to the general population. This study aims to identify prognostic factors for death in CKD patients on hemodialysis. A

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prospective, analytical, observational cohort study was conducted at the Carlos Manuel de Céspedes Provincial General Hospital in the municipality of Bayamo, Granma province, from January 1, 2019, to December 31, 2022. The association of sociodemographic and clinical variables with death was determined using binary logistic regression. The main cause of death was septic shock, followed by cardiac arrhythmias and acute pulmonary edema. Factors associated with death were hemodialysis catheter use, blood glucose, hyperphosphatemia, and abnormal hematocrit, calcium, and albumin levels. The logistic regression model allowed us to identify prognostic factors for death in patients with CKD on hemodialysis based on data routinely available in clinical practice.

Keywords: Chronic kidney disease; Hemodialysis; Prognostic factors; Death.

SUMMARY

Chronic kidney disease (CKD) is considered a major and growing health problem; where the life expectancy of haemodialysis (HD) patients is lower compared to that of the general population. The aim of this study is to identify the prognostic factors for death in patients with CKD on haemodialysis. An observational, analytical, prospective cohort study was carried out at the "Carlos Manuel de Céspedes" provincial general hospital, in the municipality of Bayamo, Granma province, from January 1, 1999. From January 2019 to December 31, 2022. The association of sociodemographic and clinical variables with death was determined using binary logistic regression. The leading cause of death was septic shock, followed by cardiac arrhythmias and acute pulmonary edema. Factors Associated with Death These were the use of hemodialysis catheters, blood glucose, hyperphosphatemia, hematocrit, calcium and albumin alterations. The logistic regression model allowed us to identify the prognostic factors of death in patients with CKD on haemodialysis based on data commonly available in healthcare practice.

Keywords: Chronic kidney disease; Hemodialysis; Prognostic factors; Death.

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SUMMARY

Chronic kidney disease (CRD) is considered an important and growing health problem; where the life expectancy of two patients in hemodialysis (HD) is lower in comparison with the general population. The objective of this study is to identify the prognostic factors of death in patients with CKD on hemodialysis. An observational, analytical and prospective cohort study was carried out at the "Carlos Manuel de Céspedes" provincial general hospital, in the municipality of Bayamo, province of Granma, from January 1, 1999. From January 2019 to December 31, 2022. The association of sociodemographic and clinical variables such as Death was determined by binary logistic regression method. The main cause of death was septic shock, followed by cardiac arrhythmias and acute pulmonary edema. Factors Associated with Death Foram used hemodialysis catheters, glycemia, hyperphosphatemia, hematocrit, calcium and albumin alterations. The logistic regression model allows us to identify the prognostic factors of death in patients with CKD on hemodialysis based on data commonly available in healthcare practice.

Keywords: Chronic kidney disease; Hemodialysis; Prognostic factors; Morte.

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Introduction

Chronic kidney disease (CKD) develops slowly, progressively, and irreversibly, causing a set of signs and symptoms with a high risk of complications. In its terminal stage, renal replacement therapy is required. According to the latest Registry of the Spanish Society of Nephrology, the main causes of CKD are: diabetes mellitus (25.8%), unrelated diseases (14.9%), vascular diseases (14.6%), glomerulonephritis (14.1%), interstitial nephropathies (9.3%), other

diseases (8.7%), systemic diseases (5.2%), and polycystic disease or hereditary diseases in a lower percentage. (1,2)

Globally, CKD is becoming more common, with an overall prevalence of 11%-13%, with variations depending on socioeconomic status, ethnicity and social determinants of health, and is around 11% in developed countries. (3)

In Cuba, crude mortality in dialysis has decreased in recent years from 42% in 2001 to 23% in 2011. (4) In 2021, a rate of 14.1 was reported due to glomerular and renal diseases. (5)

CKD is classified into five stages according to the reduction in glomerular filtration rate. Preventing progression from stage I to V represents a challenge for healthcare systems, professionals, and, above all, for the patient, who is required to attend regular medical checkups, follow a restricted diet, and take medications daily. However, patients diagnosed with stage V CKD experience increased survival when treated with renal replacement therapy, either HD, peritoneal dialysis, or kidney transplant. (6,7)

Furthermore, the life expectancy of HD patients is lower compared to the general population. In recent years, despite technical advances in HD, survival has not improved. This is due to the increasing age and cardiovascular comorbidity of these patients. Furthermore, there are notable differences in morbidity and mortality across countries, and the negative role of prognostic factors for cardiovascular mortality in these patients is recognized. (8)

Although several researchers have addressed the factors associated with mortality in patients with CKD on HD, studies in the province are scarce. This motivated this research, which aimed to identify prognostic factors for death in patients with CKD on hemodialysis.

Methods

A prospective, analytical, observational cohort study was conducted in patients with CKD on hemodialysis treated at the Nephrology Service of the Carlos Manuel de Céspedes Provincial

General Hospital in the municipality of Bayamo, Granma province, from January 1, 2019, to December 31, 2022.

All patients aged 18 years or older, of both sexes, who received hemodialysis treatment at the institution where the study was conducted were included. Patients who died from motor vehicle accidents and those who dropped out of the program were excluded.

The sample size for the study was determined using the EPIDAT 4.2 statistical program. The following parameters were used to estimate the sample size: 95% confidence interval, 80% study power, 55.0% risk in exposed patients, 40.0% risk in unexposed patients, and 1.3% relative risk. Mortality from the disease was estimated based on the literature, in this case, at 8.7%. Based on these characteristics, a minimum sample size of 295 patients was calculated, and the decision was made to investigate 342 patients.

Dependent variable: death.

Independent variables: age (years completed), male sex; type of vascular access (hemodialysis catheter). All were operationalized as nominal dichotomous qualitative variables (0) absent and (1) present.

Biological markers (quantitative): hematocrit in L/L, calcium inmmol/L, phosphorus in mmol/L,serum albumin in g/L, total proteins in g/L, blood glucose in mmol/L, creatinine in µmol/L, urea in mmol/L.

Statistical analysis began with a comprehensive characterization of the sample, including a description of all variables. For qualitative variables, the absolute and relative frequencies (percentages) of the different categories were determined. For quantitative variables, the means, medians, and standard deviations were obtained, as well as the maximum and minimum values for each distribution.

For comparisons between deceased and living patients, Pearson's chi-square test was calculated (for qualitative variables) and Student's t-test was used for quantitative variables, provided the latter was normally distributed; or the Mann-Whitney U test was used for quantitative variables with a non-normal distribution. A univariate strategy was used to

identify prognostic factors based on estimating the percentages of deaths and then the incidence ratio or relative risk (RR) of death; point estimates and 95% confidence interval estimates of the RR were obtained. For each variable, the hypothesis that the population RR was actually equal to or greater than 1.3 was tested with a significance level of less than 0.05. The multivariate strategy was based primarily on fitting a binary logistic regression model, first using the "drop-in" method (evaluating possible interactions between variables) with all those variables that constituted predictors of mortality in the univariate analysis; and then using the "forward stepwise" method. The logistic regression function was fitted using the maximum likelihood method. The Hosmer-Lemeshow chi-square goodness-of-fit statistic was also applied.

This process was performed using the algorithm included in the SPSS statistical package, version 25.0 for Windows. Before being included in the study, each patient, or failing that (in cases of significant impairment of consciousness or severe aphasia), their family member, was asked for verbal and written informed consent. The study was approved by the Hospital's Scientific Council and Ethics Committee.

Results

In patients with CKD on hemodialysis, the main cause of death was septic shock (74 patients; 29.02%), followed by cardiac arrhythmias and acute pulmonary edema, results shown in Table 1.

Table 1. Causes of death in patients with chronic kidney disease on hemodialysis.

Direct cause	No	%
Septic shock	74	29.02
Cardiac arrhythmias	64	25.10
Acute pulmonary edema	23	9.02
Hemorrhagic stroke	21	8.24

Hypovolemic shock	12	4.71
Mixed shock	11	4.31
Acute respiratory failure	10	3.92
Uremic encephalopathy	9	3.53
Covid-19	5	1.96
Cardiogenic shock	5	1.96
Acute myocardial infarction	4	1.57
Other causes	17	6.67

Other causes of death included: ischemic stroke, multiple myeloma, lung neoplasia, bladder neoplasia, aneurysm, bacterial bronchopneumonia, fluid and electrolyte imbalance, mixed encephalopathy, infective endocarditis, gynecological neoplasia, testicular tumor.

Qualitative variables were compared between both groups of patients in relation to the probability of death; however, only the use of a hemodialysis catheter stood out for its contribution from an etiopathogenic perspective (Table 2).

Table 2. Comparison between living and deceased patients with chronic kidney disease on hemodialysis from the entire sample. Qualitative variables.

Variables	**Deceased n=255**	**Alive n=87**	**Total n=342**	**p***
Male sex	145	55	200	0.0414
Hemodialysis catheter	193	32	225	0.0000

*Pearson's chi-square.

When comparing quantitative variables, significant differences were observed in seven of them. The following stood out for their etiopathogenic contributions: glucose, phosphorus, hematocrit, albumin, and age (Table 3).

Table 3. Comparison between living and deceased patients with chronic kidney disease on hemodialysis from the entire sample. Quantitative variables.

Variables	Deceased (n=255) mean/median (standard	Living (n=87) mean/median (standard	p

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	deviation)	deviation)	
Age	62.69/63 (11.06)	52.11/53 (12.94)	0.0000
Hematocrit	0.26/0.27 (0.07)	0.30/0.3(0.04)	0.0000
Calcium	2.33/2.36(0.73)	2.14/2.1(0.57)	0.0365
Phosphorus	2.11/1.9 (1.00)	1.38/1.27(0.73)	0.0000
Albumin	33.4/33(5.72)	34.1/34 (4.15)	0.0000
Blood glucose	6.24/5.6(2.81)	4.89/4.8 (1.28)	0.0000
Creatinine	774.22/759(308.67)	862.13/856(253.29)	0.0034
Urea	18.39/16.4(7.00)	16.51/15.6(5.58)	0.1510
Total proteins	69.60/69(10.15)	73.87/73 (9.67)	0.5901

Univariate analysis showed a relationship between the variables and the likelihood of death. Of the total variables studied, only six were associated with the risk of death, reaching an RR ≥1.3. The most important factors were the use of a hemodialysis catheter, blood glucose, hyperphosphatemia, and altered hematocrit (Table 4).

Table 4. Results of the univariate analysis of the variables under study.

Variable	RR	p	95% CI	
			Lower	Superior
Hemodialysis catheter	5.35	0.0000	4.01	7.12
Blood glucose ≥ 6.2 mmol/L	3.89	0.0000	3.03	4.98
Phosphorus≥ 1.9mmol/L	3.50	0.0000	2.55	4.79
Hematocrit <0.30 L/L	2.81	0.0000	2.17	3.65
Albumin <35 g/L	1.66	0.0000	1.29	2.14
Calcium≥ 2.6mmol/L	1.31	0.0365	1.02	1.62
Urea ≥ 7.8 mmol/L	1.20	0.1510	0.94	1.54
Total protein < 70 g/L	0.91	0.5901	0.69	1.21
Male sex	0.76	0.0414	0.59	0.98
Creatinine ≥ 200 µmol/L	0.68	0.0034	0.53	0.88
Age	0.20	0.0000	0.16	0.26

When the logistic regression model was fitted to the data to assess the independent value of the various prognostic factors, the number of factors was reduced to six. The most independent factor was the use of a hemodialysis catheter, followed by blood glucose and increased phosphorus levels, all significantly (p = 0.000). (Table 5)

Table 5. Multivariate logistic regression model. Stepwise regression results (forward method).

	B*	DS	β†	Next.	‡ Exp(B)	95% Confidence Interval (95% CI) for Exp (B)	
Variables						Lower	Superior
Hemodialysis catheter	2,627	0.543	23,365	0.000	13,831	4,767	40,127
Calcium	1,401	0.803	3,043	0.018	4,061	1,481	16,414
Blood glucose	2,175	0.169	1.79	0.008	8,170	3,580	41,840
Phosphorus	1,829	0.828	4,879	0.027	6,226	1,229	31,543
Hematocrit	1,812	0.634	6,174	0.004	6,120	1,768	21,189
Albumin	1,719	0.728	4,879	0.029	6,026	1,209	30,453
Constant	3,080	0.715	18,541	0.000	0.046		

* Estimated coefficients from the logistic regression model †Standardized coefficients. ‡ OR adjusted for other variables.

Discussion

The risk of death in patients with CKD on hemodialysis is high. There are several causes of death in these patients. The main cause is cardiovascular disease (35% to 48%), (9,10) since it is known that 30% to 45% of individuals who reach this stage have advanced cardiovascular complications, and the second cause of death is infectious causes (28% to 34%). (11,12) This differs from the findings of the present study, where the causes were reversed; this could be related to the increase in infectious diseases during this period.

Tapia (13) found that overall survival did not vary according to the decade of admission to a chronic hemodialysis program, advanced age and the use of catheters were associated with a lower survival of the patient cohort over a 20-year follow-up period. This does not fully

coincide with the results obtained in the present study, where advanced age was not related as an adverse factor in our patients.

Central venous catheters are an effective vascular access for hemodialysis; they are used relatively frequently, despite the recommendations of the KDOQI and the guidelines of the Spanish Society of Nephrology (SEN), which limit their use to very specific clinical situations that preclude the use of other types of venous access. However, these catheters are not free of complications and their lifespan is limited. The main complications are infection, blood flow deficit, coagulation, and thrombosis. (14-16)

Fiterre Lacis and Rajoy Fernández GE (14,17) in their article, propose that there is a relationship between the type of infection and the type of vascular access, and it directly influences the risk of presenting infectious episodes. It represents the most important risk factor in the development of bacteremia and infections.In the present study, the use of a hemodialysis catheter was the most independent factor, closely related to the first direct cause of death in our series.

According to Colombijn et al., (18) cardiovascular mortality in patients with CKD is related to traditional risk factors (e.g., age, hypertension, diabetes, dyslipidemia, and smoking) and non-traditional risk factors associated with CKD, such as chronic inflammation, anemia, and mineral metabolism disorders.

In the sample studied, it is observed that patients with calcium-phosphorus product alterations have a high probability of presenting with cardiovascular disease. Among the factors that favor these alterations are elements of uremia, which includes anemia, malnutrition and hypoalbuminemia, increased oxidative stress and chronic inflammatory state, and chronic volume overload. (19) For Hu and collaborators, (20) this causes vascular calcification and the consequent increase in wall stiffness, hypertension, left ventricular hypertrophy, hypoperfusion of cardiac tissue and cardiovascular mortality.

The results of a 2017 meta-analysis by Hou et al., (21) including 9 cohort studies and 1,992,869 HD patients, showed that both higher and lower phosphorus levels were

associated with an increased risk of all-cause mortality. Based on this evidence, the KGIDO guidelines suggest restricting the dose of calcium-based phosphate binders. (18,20) The results of the meta-analysis by Jamal et al., (22) involving 4622 patients from 11 randomized trials, showed that the use of non-calcium-based phosphate binders is associated with a lower risk of all-cause mortality compared with the use of calcium-based phosphate binders (hazard ratio 0.78, 95% CI 0.61–0.98).

CKD is characterized by decreased peripheral insulin sensitivity, decreased insulin secretion, changes in the levels of several substances such as leptin, cytokines, or changes typical of CKD (hyperparathyroidism, activation of the renin-angiotensin system, anemia, vitamin D deficiency, inflammatory state, among others) that increase the vulnerability of these patients to hyperglycemia and hypoglycemia. (23,24)

Glucose homeostasis is severely impaired in patients with CKD, who are at high risk for both hyperglycemia and hypoglycemia. Both high and low blood glucose levels are associated with increased morbidity and shorter survival in this patient group. Factors associated with an increased risk of hypoglycemia in patients with CKD include decreased renal gluconeogenesis, altered metabolic pathways (including altered drug metabolism), and decreased insulin clearance. On the other hand, decreased glucose filtration and excretion and inflammation-induced insulin resistance are predisposing factors for hyperglycemic episodes.[23,24]

The reasons why the incidence of CKD is influenced by hematocrit are unclear. It could be due to exacerbation of pre-existing kidney disease or an increased incidence of kidney damage or kidney disease. It is well known that hypoxia causes kidney damage. Systemic hypoxia leads to a restoration of balance between the antidiuretic and antinatriuretic influences of the renin-angiotensin system and the diuretic and natriuretic influences of atrial natriuretic peptide. Hypoxic stimulation may lead to increased renal sympathetic activity. Systolic and/or diastolic dysfunction may occur early in essential hypertension, and kidney disease and congestive heart failure (CHF) may cause glomerulopathies. (25)

Early detection and appropriate treatment of such dysfunction can delay the progression of both kidney disease and heart failure. The development of CHF in patients with essential hypertension has been shown to be one of the most powerful predictors of CKD. In patients with chronic hypoxia, an increased hematocrit is considered a causal factor in the pathogenesis of glomerulopathy in CHF and cor pulmonale. (25)

There are multiple studies that have shown an association between mortality and low albumin. In

In this study, more than 90% of the deceased showed figures below 30 g/L. Considering that serum albumin is an indicator of nutritional status, it is likely that the greater

mortality observed in this group is due to nutritional deficiency which in turn favors the increased infections. Serum albumin is a negative acute-phase reactant of inflammation, so a low albumin level could be indicative of an inflammatory state, probably infectious or otherwise, that may be associated with increased mortality. (26,27) A Cuban study observed serum albumin levels below 35 g/L in 25% of patients. (27)

CastleVelarde et al., (28) in a study to determine the association between hypoalbuminemia and hypophosphatemia with the subjective global assessment scale (SGA) type C in patients with chronic kidney disease on hemodialysis; found differences between SGA and albumin ($p<0.001$) and phosphorus ($p=0.040$).

Conclusions

A logistic regression model was developed to identify prognostic factors for death in CKD patients on hemodialysis, based on data routinely available in clinical practice. The most important factors were the use of a hemodialysis catheter, calcium, glucose, phosphorus, hematocrit, and albumin levels.

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Conflicts of interest

The authors have no conflicts of interest.

Authorship contribution

Dr. Liannis Batista Causa: Developed the original idea for the topic; developed the methodological design of the research; and contributed to the writing of the paper and the bibliography review.

Dr. C. Yurisnel Ortiz Sánchez: Formulated and evaluated the objectives; performed statistical processing.

Dr. Libiannis Batista Cause:He contributed to the writing of the work and the review of the bibliography.

Dr. Oslaidis Bárzaga Pérez:He contributed to the writing of the work and the review of the bibliography.