Original article

Influencing Factors in the Survival of Dialysis Patients in El Salvador

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Abstract
Introduction. The chronic kidney disease is responsible for approximately 2.4 million deaths worldwide, in El Salvador during 2019 death rate was 72.9 for 100 000 habitants, five year survival in patients after starting dialysis was between 39 and 60 % depending on the country. **Objective.** Analyze the factors that influence the five years survival in patients after starting renal replacement therapy in El Salvador. **Methodology.** It is a retrospective cohort study from patients included in dialysis and renal replacement therapy national registry from January 2016 to February 2023, the start point for the following was the initiation of dialysis, the event of interest was patient´s death, the Kaplan-Meier method was used to determine one year and five year survival; and Cox regression with Royston-Parmar model was used to analyze the factors that influence survival. **Results.** The study included 7088 patients, one and five-years survival was 79.5 % (CI 95 %: 78.6-80.5) and 50.6 % (CI 95 %: 49.1-52.1) respectively. The Cox regression for age of treatment initiation resulted in a hazard ratio of 1.02 (CI 95 %: 1.01-1.02), while for farmers, the hazard ratio was 1.09 (CI 95 %: 1.00-1.18), for hypertensive etiology the hazard ratio was 0.7 (CI 95 %: 0.64-0.78). **Conclusion.** Data suggest that age of treatment initiation, and jobs related to agriculture were associated with less five year survival in dialysis patients.

Keywords
Chronic Renal Insufficiency, Dialysis, Survival Analysis.

Resumen
Introducción. La enfermedad renal crónica es responsable de aproximadamente 2,4 millones de defunciones a nivel mundial. La supervivencia a los cinco años después de iniciar diálisis se encuentra entre un 39 a 60 % dependiendo del país. **Objetivo.** Describir la situación epidemiológica de los pacientes con diálisis y analizar los factores que influyen en la supervivencia de pacientes a cinco años de iniciar tratamiento sustitutivo renal en El Salvador. **Metodología.** Estudio de cohorte retrospectivo de los pacientes incluidos en el Registro Nacional de Diálisis y Trasplante Renal desde enero de 2016 hasta febrero de 2023. El seguimiento se comenzó al inicio de la diálisis, el evento de interés fue la muerte del paciente. Se utilizó el método de Kaplan-Meier para determinar la supervivencia al año y a los cinco años y la regresión de Cox con el modelo de Royston-Parmar para analizar los factores que influyen sobre la supervivencia a los cinco años. **Resultados.** El estudio incluyó 7088 pacientes, la supervivencia a uno y cinco años fue del 79,5 % (IC 95 %: 78,6-80,5) y 50,6 % (IC 95 %: 49,1-52,1) respectivamente. La regresión de Cox para la edad de inicio de tratamiento resultó en un hazard ratio de 1,02 (IC 95 %: 1,01-1,02), mientras que para el oficio de ser agricultor el hazard ratio fue 1,1 (IC 95 %: 1,01-1,18) y para la etiología hipertensiva el hazard ratio fue de 0,7 (IC 95 %: 0,64-0,78). **Conclusión.** La edad de inicio de tratamiento y el ser agricultor están asociados con una menor supervivencia a cinco años en pacientes con diálisis.

Palabras clave
Insuficiencia Renal Crónica, Diálisis, Análisis de Supervivencia.

Introduction

Chronic kidney disease (CKD) is defined as permanent damage to renal structure and function, characterized mainly by a glomerular filtration rate of less than 60 mL/min per 1.73 m^2 or the presence of markers of renal damage that persist for at least three months. When the glomerular filtration rate falls below 15 mL/min per 1.73 m^2, it is considered renal failure, and when it falls between 5 to 10 mL/min, renal replacement therapy is recommended[1-3].

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Factores que influyen en la supervivencia de pacientes con diálisis en El Salvador

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The main causes of CKD worldwide are arterial hypertension and diabetes *mellitus*; however, in the Central American and Caribbean region, another important cause of kidney disease has also been identified, which generally affects male patients engaged in agriculture and has been called Mesoamerican nephropathy.[2,4]

Globally, CKD represents a major public health problem, with a progressive increase in prevalence in the general population and an increase in the use of renal function replacement therapy, such as hemodialysis (HD), peritoneal dialysis (PD), and renal transplantation. This places a significant burden on healthcare systems. According to reports from 2022, it is estimated that more than 850 million people worldwide suffer from chronic kidney disease, with approximately 2.4 million deaths.[5]

In 2015, the prevalence of CKD was estimated at 12.6 % in El Salvador. In 2019, the CKD mortality rate in the country was 72.9 per 100 000 population, ranking as the second highest in the Americas, after Nicaragua (73.9).[6] In the country, the rate of patients on renal replacement therapy for 2018 (RRT) was 677 per million inhabitants, exceeding the regional rate for Central America and the Caribbean (392 per million inhabitants).[7]

Patients who started dialysis between 2004 and 2008 in the United States had a five-year survival rate of 39 %, in Europe 41 %, and in Japan 60 %.[8] In El Salvador, five-year survival in patients who begin renal replacement therapy is unknown, nor has research been conducted on the factors that influence mortality in these patients.

Consequently, these findings highlight the importance of analyzing the mortality associated with CKD in El Salvador. Understanding the underlying causes of survival is crucial for implementing effective preventative and management strategies.

This study aimed to describe the epidemiological situation of dialysis patients and to analyze the factors that influence the five-year survival of patients who start renal replacement therapy in El Salvador.

Methodology

The study is a retrospective dynamic cohort of patients in the National Registry of Dialysis and Renal Transplantation of El Salvador. It was implemented in 2016 and is part of the Information System for Patients with Chronic Diseases (SIEC). It is aimed at keeping track of patients receiving RRT by the Ministry of Health of El Salvador and has national coverage.[9] The start of follow-up was taken as the date of initiation of RRT up to five years of treatment; the event of interest was the death of the patient; patients who died less than 24 hours after initiation of treatment were excluded.

The initial database contained 7321 records. Of these, 72 duplicates, 51 cases of patients who died less than 24 hours from the start of treatment, 39 records corresponding to foreign patients, 24 cases of patients who had received renal transplants, 22 records with incomplete data, and 25 cases of patients who had not received initial treatment were excluded. As a result, the final database used for analysis consisted of 7088 records.

The database initially consisted of 56 variables, of which 30 related to identification, management characteristics, and medical procedures that were not of interest for the research were eliminated, ending with 26 variables for the study.

The variables used were date of birth, sex, municipality, occupation, initial treatment, date treatment started, etiology, current treatment, arterial hypertension, diabetes *mellitus*, cancer, hepatitis B, hepatitis C, HIV/AIDS, lithiasis, hyperuricemia, lupus erythematosus, other diseases, peritoneal access, type of PD management, hemodialysis access, discharge condition, cause of death, date of death, and place of death. In addition, the variable age at treatment initiation was constructed from the date of birth and treatment initiation.

Quantitative variables were tested for normality using the Anderson-Darling test, and frequencies, proportions, and crude rates were calculated. The median and interquartile range were used as measures of central tendency and dispersion, respectively. The national and municipal prevalence rate of dialysis patients was rated using the population projections in 2023 provided by the National Statistics and Census Office,[10] and a stratified choropleth map by quartiles was prepared from the calculated rates.

The Kaplan-Meier estimator was used to calculate the overall survival rate at one and five years, and the log-rank test was used to test statistical significance.

Cox regression was initially employed for the multivariate analysis. Furthermore, this model was evaluated using the likelihood ratio, and it was determined that the model constructed predicted survival better than a model without covariates.

The predictive capacity of the model was evaluated using the Harrel concordance index, and a cut-off point of 0.6 or higher was established to consider it a good concordance. The risk proportionality analysis was

used to verify sensitivity and compliance with the proportionality assumptions, and an overall value of $p < 0.01$ was obtained.

Since the concordance index was less than 0.6 and the assumption of proportionality of exposure was not met, a Cox multivariate analysis with Royston-Parmar random effects was performed because this model fits better to complex distributions.[11,12]

The evaluation of the fit of the second model was by the likelihood ratio test, Wald test, and log-rank test. A significance level of $p < 0.01$ was obtained for all of these tests. The Harrel concordance test yielded a value that exceeded the established cut-off point.

Microsoft Excel 365 and RStudio version 4.3.0 were used for data cleaning, processing and analysis, and QGIS version 3.30.1 for geospatial analysis.

This research was conducted according to the Helsinki principles for research on human subjects, using only the information contained in existing databases, which were anonymized and coded respecting the confidentiality of the individuals.

Results

The median age of the patients was 53 years (IR: 40 to 63 years), 69.5 % of the records corresponded to males, and in 56 % of the cases, the etiology of CKD could not be identified, with arterial hypertension and diabetes *mellitus* being the main known causes. Other etiologies, such as those of congenital, glomerular, or obstructive origin, collectively accounted for 5.8 % (Table 1).

A total of 45.6 % of the patients had some comorbidity, with arterial hypertension followed by diabetes *mellitus* being the most frequent. Among the other conditions identified, which totaled 3.5 % of the records, renal lithiasis (0.5 %), cancer (0.4 %), HIV infection (0.1 %), and systemic lupus erythematosus (0.1 %) stand out. The rest of the comorbidities identified have percentages of less than 0.1 %.

When the database was extracted from the system on February 28, 2023, a total of 3997 patients were actively receiving renal replacement therapy. A prevalence of 631 dialysis patients per million inhabitants was determined, with a prevalence of 62.4 % (N: 2493) on peritoneal dialysis and 37.6 % (N: 1504) on hemodialysis. The municipalities with the highest prevalence rates are situated in proximity to bodies of water and are associated with agricultural activities (Figure 1).

Of the patients with peritoneal dialysis, 64.1 % (N: 1599) had a soft catheter, 35.8 % (N: 891) had a rigid catheter, 39.1 % (N: 976) were receiving treatment on an outpatient basis and 60.8 % (N: 1514) in hospitals; there is no data on the type of catheter and treatment modality in 0.1 % (N: 3) of the PD patients. Of the hemodialysis patients, 77.8 % (N: 1177) receive treatment by catheter, 22.1 % (N: 332) by arteriovenous fistula, and no data is recorded in 0.1 % (N: 2).

A total of 2873 deaths were recorded in the database. Of these, 60.3 % (N: 1733) were in hospital. 39.3 % (N: 1128) of the patients died of unknown causes, 36.7 % (N: 1053) due to cardiovascular causes, 20.8 % (N: 597) due to infectious complications, 1.5 % (N: 43) due to complications related to renal disease, 0.7 % (N: 20) due to complications of the dialysis procedure, 0.5 % (N: 14) due to external cause injuries, 0.4 % (N: 12) due to discontinuation of treatment, 0.2 % (N: 5) due to neoplasms and in one patient anemia was recorded as the cause of death. 91.4 % (N: 2626) of the deaths occurred during the first five years of RRT.

The result of the Kaplan Meier analysis determined a survival of 79.5 % (CI 95 %: 78.6 - 80.5) after one year from the start of renal replacement therapy and a survival of 50.6 % (CI 95 %: 49.1 - 52.1) at five years (Figure 2).

When comparing survival by sex and initial treatment modality at five years from the start of treatment, no statistically significant difference was observed. Patients with agriculture-related trades had lower survival at five years (48.37 %; CI 95 %: 48.36 - 48.38 and 51.66 %; CI 95 %: 51.65 - 51.67) compared to those with other trades, patients with diabetic etiology also had lower survival compared to other etiologies (41.25 %; CI 95 %: 41.23 - 41.27 and 52.41 %; CI 95 %: 52.40 - 52.42), the results of the log Rank test for these variables were p value < 0.01 (Figure 3). Hypertensive etiology had higher survival compared to other etiologies (54.64 %; CI 95 %: 54.63 - 54.66 and 49.33 %; CI 95 %: 49.33 - 49.34), the difference was statistically significant ($p < 0.05$).

A hazard ratio (HR) of 1.02 ($p < 0.01$) was obtained for the variable age at treatment initiation; that is, a one-year increase in age increases the probability of death by 2 % five years after treatment initiation.

The HR for patients whose occupation was farming was 1.09, with a p-value of 0.049. It indicates that being a farmer increases the likelihood of death by 9 % five years after the commencement of treatment. The HR of patients with vascular etiology was 0.71, with a p-value < 0.01.

The exposure factor for the variable "sex" was male, resulting in an HR of 1.00. The variable "initial treatment" used hemodialysis as an exposure factor, with an HR of

Table 1. Characterization of patients in the National Registry of Dialysis and Renal Transplantation of El Salvador until February 2023.

Variable	Deceased (N:2873)			Living patients (N:4215)			Total (N 7088)	
	N	%	p-value	N	%	p-value	N	%
Gender and age								
Male	2009	69.9	0.3987	2916	69.2	0.3092	4925	69.5
Female	864	30.1	0.3987	1299	30.8	0.3092	2163	30.5
Median age	54 years (IR[a]: 42 - 63)			52 years (IR: 39 - 62)			53 years (IR: 40 - 62)	
Occupation								
Farmer	1073	37.3	<0.01	1280	30.4	<0.01	2353	33.2
Others occupations[b]	1800	62.7	<0.01	2935	69.6	<0.01	4735	66.8
Etiology								
Hypertensive	482	16.8	<0.01	1188	28.2	<0.01	1670	23.6
Diabetic	501	17.4	<0.01	538	12.8	<0.01	1039	14.7
Other causes	169	5.9	0.6733	241	5.7	0.6154	410	5.8
Not identified	1721	59.9	<0.01	2248	53.3	<0.01	3969	56.0
Comorbidities								
Arterial hypertension	1270	44.2	0.0016	1740	41.3	0.0001	3010	42.5
Diabetes Mellitus	490	17.1	0.0904	671	15.9	0.04176	1161	16.4
Others	67	2.3	<0.01	183	4.3	<0.01	250	3.5
No comorbidities	1505	52.4	0.0011	2335	55.4	<0.01	3840	54.2
Initial treatment								
Peritoneal dialysis	2261	78.7	0.6046	3302	78.3	0.5673	5563	78.5
Hemodialysis	612	21.3	0.6046	913	21.7	0.5673	1525	21.5

a. Interquartile range, b. All other professions are classified in the database.

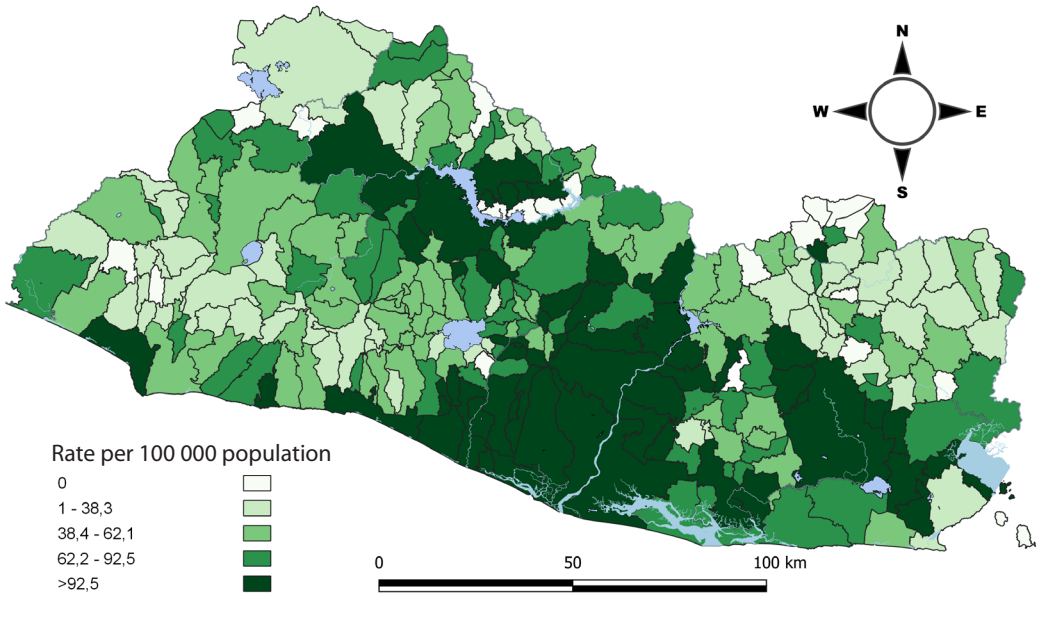

Figure 1. Prevalence of dialysis patients, El Salvador, February 2023.

0.94. The HR for diabetes etiology was 1.04. The p-values for all three variables exceeded 0.05. Figure 4 depicts the HR values and their confidence intervals.

Discussion

It was a survival study using the Kaplan Meier technique and the Royston Parmer model. Among the findings, the 5-year survival rate was higher than the unadjusted survival rate in the United States and Europe, 39 % and 41 %, respectively. However, it was lower than the 60 % survival rate in Japan. It is important to note that these mortality rates were calculated for patients who started dialysis between 2004 and 2008, so survival may vary if patients with later start dates are considered.[8]

A study conducted in Colombia with a cohort of 12 508 patients over 18 years of age showed a survival rate similar to that found in this study, with a rate of 53 % after five years of treatment.[13] Another study conducted in Indonesia, although with a smaller cohort including only patients on peritoneal dialysis, found a five year survival of 52 %.[14] Due to the low survival rate among dialysis patients, the early detection of CKD and the implementation of measures to halt its progression are deemed the most effective measures to prolong the lives of renal patients.[2]

Studies comparing treatment modalities do not suggest consistent findings.

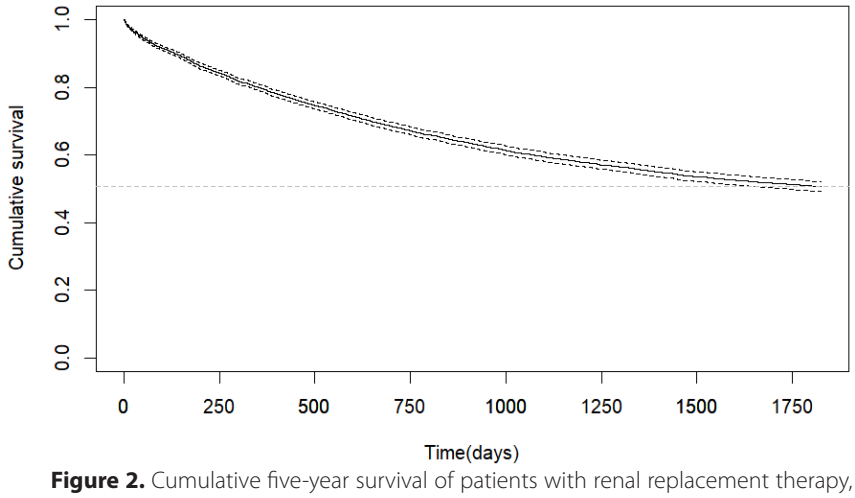

Figure 2. Cumulative five-year survival of patients with renal replacement therapy, El Salvador, February 2023.

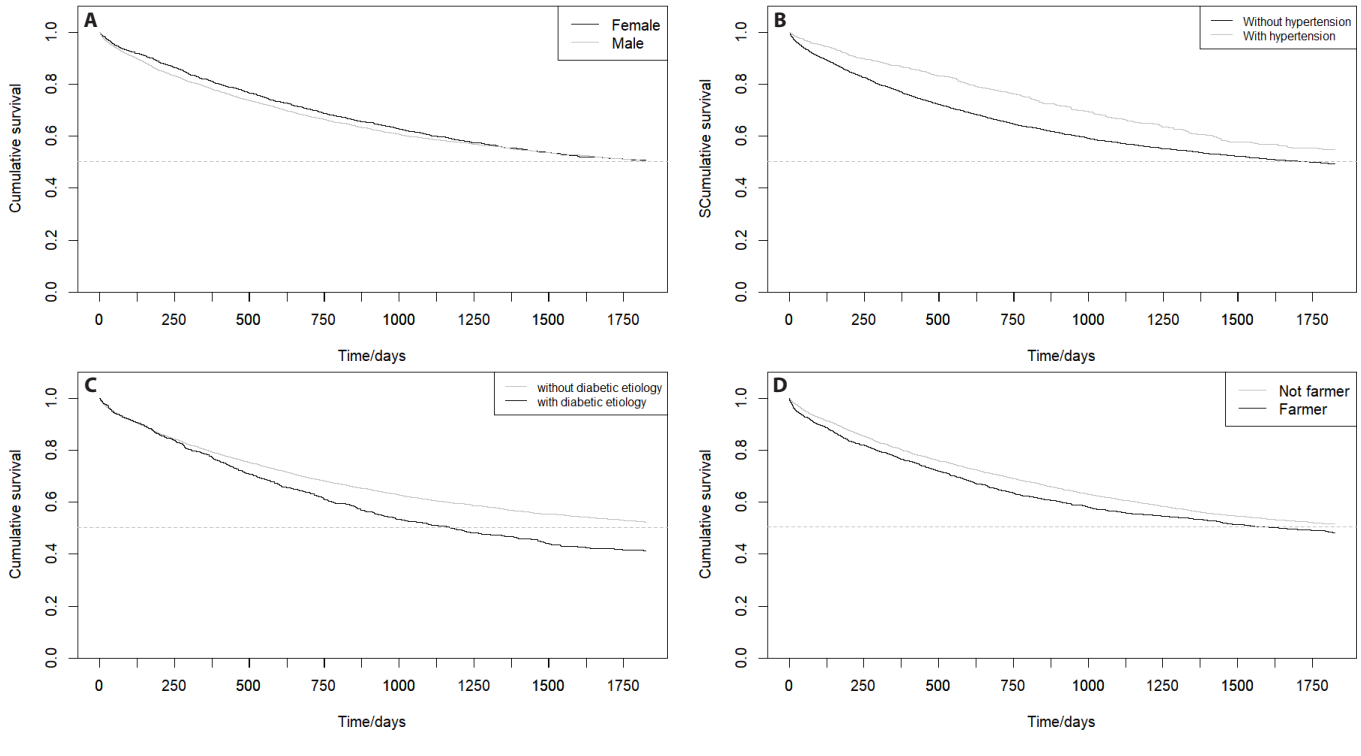

Figure 3. Cumulative five-year survival of patients with renal replacement therapy classified by sex, etiology, profession and initial treatment, El Salvador, February 2023.

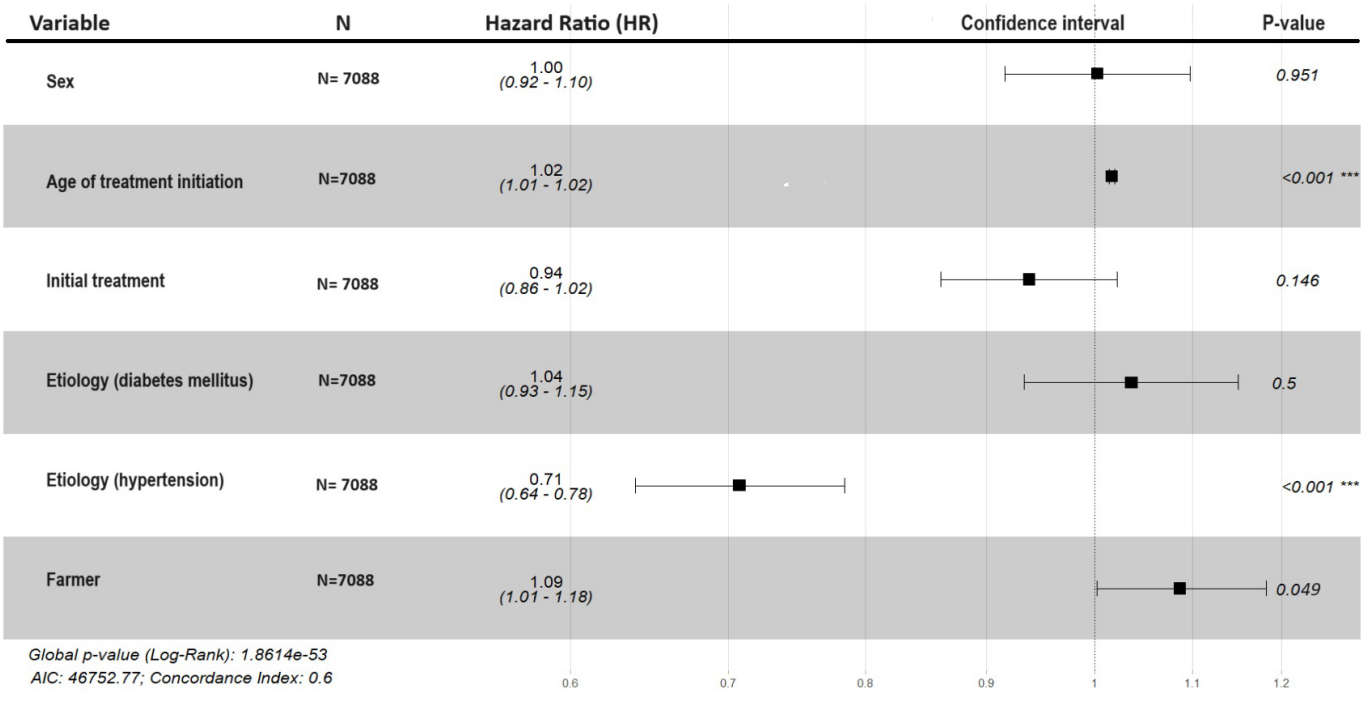

Figure 4. Cox multivariate model with Royston-Parmar random effects

While some have found greater survival in patients undergoing hemodialysis, such as the Colombian cohort study mentioned above,[13] other studies have found no significant difference between treatment modalities,[15,16] and others suggest that the differences may be related to a greater burden of comorbidities in one group or another.[15,17] For this reason, some clinical guidelines recommend leaving the treatment modality to the patient's choice, according to their needs and clinical situation.[1,2]

There were no significant differences in survival between sexes in this study; similar findings have been reported in research conducted in the United States and Europe. Even though men are at greater risk of kidney disease, there are no differences in prognosis after the onset of RRT.[18,19] The causes of this phenomenon are not entirely clear, although some research has suggested that CKD increases cardiovascular risk in women, increasing their mortality.[20]

Advanced age is an important risk factor that increases the probability of death in patients with RRT. A meta-analysis that included 12 studies comparing patients older than 65 years with those of younger age found that patients older than 65 years had a 2.80 times higher risk of death (CI 95 %: 2.45 - 3.09) and a p-value < 0.01.[21] In addition, a cohort in Brazil with 5081 hemodialysis patients found that the older the patient, the higher the risk of death.[22]

Research on the subject has linked increased mortality in this age group to a greater burden of comorbidities, physical and cognitive disability, and the decreased functional capacity of adulthood, which makes patients less resistant to the loss of amino acids and proteins that occurs during peritoneal dialysis, as well as to the insulin resistance, chronic inflammation, vascular calcification, and loss of musculoskeletal tissue that occur as a consequence of CKD.[23-25]

According to results from a study conducted in the country in 2014, hypertension and diabetes *mellitus* were the main identifiable causes of CKD, and it was not possible to identify the etiology in 50 % of cases.[26]

The Kaplan Meier analysis determined that patients with diabetic etiology had a lower survival rate; however, it was not statistically significant in the multivariate analysis, unlike other studies that have determined that CKD with diabetic etiology has a worse prognosis and a higher probability of death.[16,22] Hypertensive etiology resulted in a higher probability of survival in this study.

This result seems to indicate that there is another etiology that, in addition to causing an important proportion of CKD cases, could affect the prognosis of the patients; a possible explanation would be Mesoamerican nephropathy, a disease characterized by renal and tubulointerstitial damage that mainly affects male patients and farmers.[4,27,28] This would be congruent with the fact that during this investigation an important percentage of patients were farmers, and that a significant association

was found between being a farmer and a higher risk of mortality, there is previous evidence that indicates that this can be considered as an important risk factor in mortality related to CKD.[18,19]

Most of the patients undergoing dialysis in this study were men. This finding is consistent with other studies, such as those done in the country[26,29] in which men have been shown to have a higher prevalence of CKD.[30]

Arterial hypertension has been identified as a common comorbidity in other studies of people with CKD.[31] A study published in 2016 that analyzed ten years of data from patients with CKD in the Bajo Lempa area, El Salvador, found that 29.7 % of patients had arterial hypertension, a lower proportion than that found in this study.[29] It was expected due to the pathophysiology of chronic disease, as the kidney is one of the primary organs involved in blood pressure regulation.[1]

In 2014, the Ministry of Health of El Salvador provided care to 38.6 % of patients in RRT, resulting in a total of 1445 patients. During that time, this number has increased almost three times, becoming even higher than the SRR prevalence rate reported in that year. The Ministry of Health's rate of patients seen per million individuals is slightly lower than the prevalence of 677 patients per million individuals reported by the Central American and Caribbean Association of Nephrology and Hypertension in 2018. These findings indicate a significant increase in demand for renal care.[7,26]

In El Salvador, PD is the main method of renal replacement, unlike the world trend, where it is estimated that more than 90 % of patients are treated with HD. This data is because PD is considered the first choice in the guidelines for the care of renal patients in force in the country.[32] In Guatemala and Costa Rica PD is also the main treatment modality, while in the rest of the countries of the Central American and Caribbean region HD predominates.[7]

In a study that included databases from 20 Latin American countries and 49 European countries, the main causes of death identified were cardiovascular diseases, followed by infectious diseases and deaths of unknown causes.[33] In Colombia, a retrospective cohort of 9798 patients over 18 years of age in RRT was carried out, where the two leading causes of death were the same.[34] However, a higher percentage of deaths of unknown causes was observed.

The database used for the study was pre-built and contained only information from the Ministry of Health. It is crucial to remember that if patients receiving treatment at other facilities were included, the true prevalence of dialysis patients may be higher. Furthermore, the lack of comprehensive data or the absence of systematic data collection prevented the inclusion of certain variables in the evaluation.

It is necessary to take the findings related to the etiology of CKD with caution because this was not identified in more than 50 % of the patients. Therefore, a more comprehensive registry of the causes of CKD is necessary to yield more conclusive outcomes.

There may be other variables not collected in the database that could influence patient survival, such as nutritional status, socioeconomic status, and glomerular filtration rate at the start of renal treatment. These additional factors could have a significant impact on the results and it is important to consider them in future research to obtain a more complete understanding of the determinants of survival in patients with CKD on RRT.

Conclusions

Only half of the patients who start dialysis in El Salvador survive five years after starting treatment. Age at initiation of treatment and being a farmer are significant factors associated with a higher risk of mortality five years after initiation of renal replacement therapy, while the etiology of arterial hypertension was associated with a higher survival compared to other causes of CKD.

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