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Research Article

Determinants of Overall Survival of Kidney Failure for Patients Receiving Dialysis in Saint Geberial General Hospital, Addis Ababa, Ethiopia

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ABSTRACT

Background: Chronic kidney disease (CKD) is becoming a common disease in the general population and is associated with an increased risk of mortality. The aim of this study was to investigate survival pattern and assess risk factors affecting the overall survival pattern of kidney failure patient's treated with dialysis.

Methods: The data for this study was obtained by accessing and reviewing patients' medical records and dialysis registration book of end stage renal disease (ESRD) patients registered during May 2011 to April 2016 and treated in Saint Geberial general Hospital. Kaplan-Meier estimation method and Cox proportional hazards regression models were applied.

Results: The Cox proportional hazards regression model results revealed that duration of dialysis per session, hypertension status, and infection status were the significant factors for the survival of ESRD patients.

Conclusion: Increase in duration of dialysis per session and eradicating infection over the treatment period, for kidney failure hemodialysis (HD) patients, can minimize the risk of death of kidney failure patients. In the other hand, it was found that factors, which had no significant impact on the survival of ESRD patients were age, marital status, stroke, residence, religion and weight at the baseline of the patients.

Key Words: Dialysis, Kaplan-Meier, and Cox Proportional hazards

BACKGROUND

Chronic Kidney disease (CKD) is progressive loss of kidney function over a period of months or years. Professional guidelines classified the severity of CKD in five stages in which stage 1 and 2 are ascertained by proteinuria that shows the presence of kidney damage and reduced glomerular filtration rate (GFR) as well. It has been referred by many authors that clinically significant CKD also known as 'moderate' stages to be stage 3 (GFR 30-59ml/min/1.73m^2), stage 4 (GFR 15- 29ml /min/1.73 m^2) and Stage 5 CKD which was the concern of this study, often called end-stage kidney disease or end-stage renal disease and is largely synonymous with the now outdated terms chronic renal failure and usually means the patient requires renal replacement therapy and dialysis and have GFR less than 15 ml/min/1.73 m^2 [1].

CKD constitutes a major public health problem worldwide. The worldwide prevalence of CKD was estimated as 8 to 16 %. [2] However, a recent study indicates that the incidence of kidney disease is increasing globally [3]. It has been very difficult to know the prevalence and incidence of ESRD in Africa due to lack of national registries and community based studies. ESRD has become a major health problem in sub Saharan Africa (SSA). By 2020, the burden of diabetes and cardio vascular disease (CKD) will increase in Africa alone, with concomitant increases in the prevalence of CVD and ESRD [4]. The prevalence of kidney disease was more in black race as compared to white counterparts [5]. The reason for higher prevalence among Africans is due to genetic predisposition, low socio-economic status and inequities in access to healthcare [6]. Ethiopia is one of the developing countries, in which kidney disease is a growing problem. Like many other chronic diseases, the occurrence of CKD in Ethiopia is increasing because of increased risk factors such as high blood pressure and diabetes mellitus [7]. Renal replacement therapy (RRT) is the main way or method of care for patients with ESRD. Dialysis as an alternative of RRT for long survival reduces morbidities and improves quality of life. Even if dialysis methods are useful for prolonging the life of patients, deaths remains high [8]. The use of dialysis in Ethiopia

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as a treatment strategy for ESRD dates less than a two decade. In addition, access for dialysis is limited and is a highly unaffordable for the public [9].

Survival of patient's is a key issue of the overall adequacy of treatment in most chronic diseases. Since the aim of HD is to improve the health of renal failure individuals, it would be essential to study survival time and associated risk factors of renal HD patients. Thus, assessment of survival of patients receiving HD has paramount importance. Analyses of survival of patients treated with dialysis are very important for prolonging the survival of ESRD patients.

METHODS

This section describes the data and methods used in this study to come up with the development of a survival model and estimate the probability of surviving from all the causes of death for a specified time interval calculated from the cohort of ESRD cases.

Source of Data

The source of data for this study is Saint Geberial general hospital. The data has been collected by using pretested structured questionnaire that consisted of characteristics related to demographic profiles, causes and risk factors of CKD, clinical conditions of patients at initiation and the last session of dialysis and treatments given. These are collected by reviewing patients' medical records and dialysis registration book.

Inclusion and Exclusion Criteria

Inclusion Criteria

All patients who were on maintenance hemodialysis for ESRD during the specified period were included in the study.

Exclusion Criteria

- Patients who started on hemodialysis for acute renal failure.
- Incomplete medical records

Study Design

This is a retrospective analysis of patients' clinical data on maintenance hemodialysis ESRD at Saint Geberial general hospital. The cohort is followed from 1st May 2011 to 30th April 2016 and the data was secondary since it is collected from records chart.

Measurement of Variables

Definition of Variables

The response (dependent) variable is continuous and describes the length of treatment time in months. The explanatory (independent) variables of interest in this analysis include socio-economic, demographic, and characteristics of disease and treatment profiles.

The Response Variable

The response variable for the i^{th} individual is denoted by Y_i and it measures the length of time between the death of kidney failure patient or censoring time of kidney failure patient's and the time of start of dialysis. The gap between a defined starting point to the occurrence of a given event (in this study event is death of patient) is called survival time. In survival analysis, the outcome of interest (death in this study) is the duration of time until death occurs.

Predictor Variables

The predictor variables in survival data analysis can be categorical or continuous. In the development of the model we should also establish if the covariate is time dependent or not. Such cases affect how the covariates would be modeled in Cox proportional hazards procedure.

Description of variables included in the Analysis:

Methods for data Analysis

Survival Data Analysis

The response variable for the i^{th} individual is denoted by Y_i and it measures the length of time between the death of kidney failure patient or censoring time of kidney failure patient's and the time of start of dialysis. The gap between a defined starting point to the occurrence of a given event (in this study event is death of patient) is called survival time. The predictor variables in survival data analysis can be categorical or continuous. The censoring indicator (status) is 0 for censored observations and 1 for event, in our case death. In this study, Kaplan-Meier estimation method and Cox survival regression model was used to see the relationship between the considered independent variables and the response variable.

Descriptive Methods for the Analysis of Survival Data.

In any applied setting, a statistical analysis should begin with a thoughtful and thorough description of the data. In particular, an initial step in the analysis of a set of survival data is to present numerical or graphical summaries of the survival times in a particular group. In summarizing survival data, the most type functions applied is survivor function.

The Kaplan-Meier estimator of the survivorship function (or survival probability)

$S(t) = P(T \geq t)$ is defined as $\hat{S}_{(t)} = \Pi_{t_{(i)} \leq t}\left(\frac{n_i - d_i}{n_i}\right)^{\delta_i} = \Pi_{t(i) \leq t}\left(1 - \frac{d_i}{n_i}\right)^{\delta_i}$

With the convention that $\hat{S}_{(t)} = 1$ if $t \leq t(1)$

Where δ_i = is tie indicator.

t (1), … ,t(m) is the set of m distinct death times observed in the sample.

di is the number of death at t (i)

ni is the number of individual "at risk" right before t(i).

The Cox Proportional Hazards Regression Model

The Cox Proportional Hazard Model is a multiple regression method used to evaluate the effect of multiple covariates on the survival time. The Cox hazard function is: $\lambda(t, x, \beta) = \lambda_o(t)\, exp(\hat{\beta} x)$, where $\lambda_0(t)$ is the baseline hazard function that characterizes how the hazard function changes as a function of survival time.

(t, x, β) represents the hazard function at time t with covariates x = $(x_1, x_2, x_3, \ldots, x_p)'$,

$=(\beta_2, \beta_2, \ldots, \beta_p)'$ is a column vector of *p* regression parameters,

$e^{\hat{\beta} x}$ Characterizes how the hazard function changes as a function of subject covariates.

t *is* the failure time.

RESULT OF THE STUDY

Descriptive Survival Analysis

Table 1 show summary results about the categorical covariates included in this study. A total of 205 patients who were on dialysis for at least 30 days in Saint Geberial General hospital dialysis center were followed up for five years. The medical cards of these 205 patients were reviewed. Of these, 25.36% (52) of the patients were died and the rest 153 (74.64%) of the patients were censored at the time of the study. Only 1.95% of them were from rural area. The sample included 138 male patients of which 30(21.7%) died. Among the 67 females in the sample, 22(32.8%) were dead. The mean age at dialysis initiation was 57.81 years ranged from 16 month to 92 years old with standard deviation of 15.634 year. The mean weight of the patient's at dialysis initiation was 66.51 kg with minimum weight of 37 kg and maximum of 120 kg with standard deviation of 13.176kg

Majority of ESRD patients had clinical complication (comorbidity) at initiation of dialysis. About 83.41%, 70.24%, 72.68%, 31.21% and 13.17% of ESRD patients had diabetes, hypertension, anemic, infection, and cardiac problem respectively.

About 54% of the patients took three sessions of dialysis a week the rest of the patients (45.85%) took two sessions a week. The majority of HD patients (56.9%) had permanent catheter, 37.56% had fistula and 5.83% had graft at the time of assessment. Therefore more than half (56.9%) of the patients had a patent catheter access for HD.

Non-parametric Survival Analysis

The estimates of the overall Kaplan-Meier survivor function presented in Figure 1 shows that most of the deaths occurred in the earlier months of dialysis initiation and it declined in the later months of follow up.

Cox Proportional Hazard Regression Model

Univariate Analysis

The log-rank test results presented in Table 2 show that marital status, and residence were not significant covariates for the survival of patients, however, sex, frequency of dialysis per week, hypertension, diabetes, infection, duration of dialysis per session, anemic, cardiac complication and vascular access had significant effect on the survival of the patients. Thus, those patients who were female, had three sessions of dialysis a week, and who do not have hypertension, diabetes, infection, anemic and cardiac complication, used fistula as vascular accesses had better survival experience.

Multivariable Cox Proportional Hazards Model

The estimated coefficients $\hat{\beta}$ for the covariates in the final model, their standard error, the hazard ratio corresponding to each estimated coefficient, values of the Wald statistic and 95% CI for the hazard ratio or rate are given in Table 3.

Test of Proportional Hazards Assumption

The null hypothesis is that PH assumption is not violated. Table 4 shows that the p- values of all the eight covariates (Sex, frequency

Table 1: Description of the variables.

variables	Categories
length of treatment time in months	
Patient's sex	0= Female
	1= Male
Current marital status of the patient's	0= Un-married
	1= Married
Place of residence	0=Rural
	1= Urban
Patient's age at the start of dialysis	
Frequency of dialysis per week	0= Two times per week
	1= Three time per week
Status of hypertension at initial of the dialysis	0= No
	1= Yes
Status of diabetes at initial of the dialysis	0= No
	1= Yes
Infection any time during dialysis	0= No
	1= Yes
Anemia any time during dialysis	0= No
	1= Yes
Cardiac complication	0=No
	1= Yes
Duration of dialysis per session	0= Three hour per session
	1= Three and half hour per session
	2= Four hour per session
Vascular access	0= Fistula
	1= Catheter
	2= graft

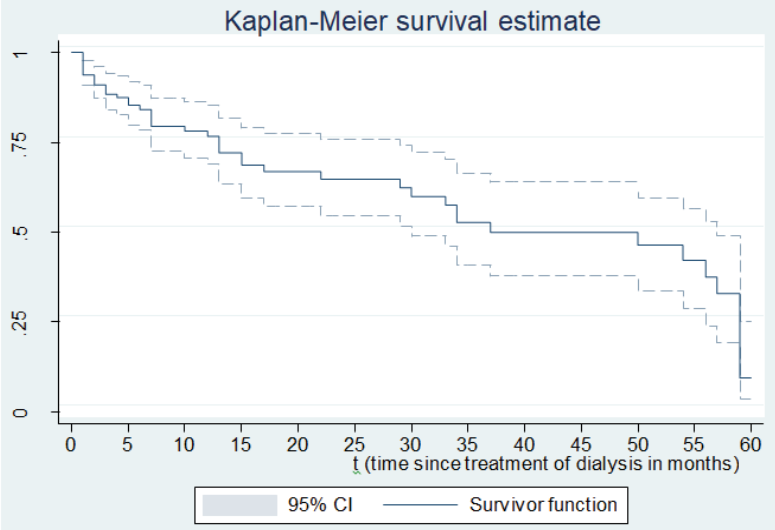

Figure1. The plot of the overall estimate of Kaplan-Meier survival function of ESRD patients treated with HD in Saint Geberial general hospital, Addis Ababa.

Table 2: Baseline Socio-demographic, comorbidity and clinical characteristics of 205 patients treated with hemodialysis for ESRD in Saint Geberial General, hospital Addis Ababa, Ethiopia.

Variable	Category	Total (%)	Number of event (%)	Censored (%)
Sex	Male	138(67.32)	30(14.63)	108(52.68)
	Female	67(32.68)	22(10.73)	45(21.95)
Residence	Urban	201(98.05)	50(24.39)	151(73.66)
	Rural	4(1.95)	2(0.98)	2(0.98)
Marital status	Married	156(76.10)	34(16.59)	122(59.51)
	Un married	49(23.90)	18(8.78)	31(15.12)
Frequency of dialysis per week	Twice per week	94(45.85)	44(21.46)	50(24.39)
	Three per week	111(54.15)	8(3.9)	103(50.24)
Hypertension	Yes	144(70.24)	50(24.39)	94(45.85)
	No	61(29.76)	2(0.98)	59(28.78)
Diabetes	Yes	171(83.41)	46(22.4)	125(60.95)
	No	34(16.59)	6(2.93)	28(13.66)
Vascular access	Catheter	116(56.59)	32(15.61)	84(40.98)
	Fistula	77(37.56)	15(7.32)	62(30.24)
	Graft	12(5.85)	5(2.44)	7(3.41)
Cardiac complication	Yes	27(13.17)	8(3.90)	19(9.27)
	No	178(86.83)	44(21.46)	134(65.37)
Duration of dialysis per session	Three hour	60(29.27)	17(8.29)	43(20.96)
	Three and half hour	121(59.02)	33(16.11)	88(42.93)
	Four hour	24(11.71)	2(0.98)	22(10.73)
	No	141(68.78)	19(9.27)	125(59.51)
	No	56(27.32)	5(2.44)	51(24.88)

of dialysis per week, diabetes, duration of dialysis per session, anemic, cardiac, infection and vascular accesses) are greater than 5% indicating that all the covariates satisfy the proportionality assumption at 0.05 level of significance, But the p-values for the covariate hypertension is 0.0323 less than 0.05, we reject the proportional hazards assumption for the covariate hypertension.

Global test results do indicate overall the proportional hazards assumption is satisfied.

Extensions of the Proportional Hazards Model

As we attempted to show in the previous sections, the proportional hazards assumption is not satisfied for the covariate hypertension. Hence, one of the ways to get sensible results is to apply stratified proportional hazards model in which the stratification is done by using the covariate hypertension as it is fixed by design.

The reference categories were those indicated in asterisk (*)

Table 3: Results of log-rank test of equality of survival distribution for the different categorical covariates.

Covariates/Factors	Chi-square	Df	p-value
Sex of the patient	5.24	1	0.0221
Residence of the patient	1.23	1	0.2678
Marital status of the patient	1.21	1	0.2715
Frequency of dialysis per week	15.07	1	0.0001
Hypertension	17.86	1	0
Diabetes	3.47	1	0.0625
Vascular access	13.14	2	0.0014
Cardiac complication	1.51	1	0.2136
Duration of dialysis per session	9.82	2	0.0074
Infection any time during dialysis	14.67	1	0.0001
Anemic any time during dialysis	6.95	1	0.0084

Table 4: Cox regression results in terms of parameter estimates and hazard ratios of the covariates.

Covariates (their categories)	B	SE	Wald X2	Sig.	Exp(B) or HR	95% CI for Exp(B)	
						Lower	Upper
Sex							
Male	-0.428	0.229	-1.22	0.22	0.652	0.328	1.298
Female (*)							
Hypertension							
Yes	2.403	8.272	3.22	0.001	11.064	2.556	47.89
No							
Frequency of dialysis per week							
Three time	-0.78	0.193	-1.85	0.065	0.458	-	-
Two time a week(*)	-	-	-	-	-	0.2	1.048
Diabetic status							
Yes	-0.4293	0.5175	-0.83	0.407	0.65	0.23608	1.795
No (*)							
Duration of dialysis per session							
Three hour a session(*)	-0.6152	0.172	-1.93	0.054	0.54	0.289	1.01
There and half hour a session							
Four hour a session	-2.456	0.788	-2.73	0.006	0.0832	0.0139	0.495
Infection status							
Yes	0.739	0.63	2.1	0.036	1.962	1.045	3.681
No (*)							
Anemic status							
Yes	0.6872	1.101	1.23	0.218	1.988	0.667	5.934
No (*)							
Cardiac complication							
Yes	-0.198	0.348	-0.47	0.638	0.819	0.3572	1.882
No (*)							
Vasular access							
Fistula	-0.9133	0.2367	-1.55	0.122	0.4001	0.1261	1.2753
Graft (*)	0.712	0.5677	0.114	0.892	1.074	0.3817	3.024
Catheter							
The reference categories were those indicated in asterisk (*)							

Table 5: Test of proportional hazards assumption.

Variable	Rho	Chi-square	Df	P value
Sex	-0.06383	0.24	1	0.6251
Frequency of dialysis per week	-0.03371	0.06	1	0.8041
Hypertension status	-0.32527	4.58	1	0.0323
Diabetes status	-0.00663	0	1	0.9537
Infection status	-0.17408	1.84	1`	0.1748
Anemic status	0.12139	1.14	1	0.286
Three and half hour	0.03304	0.06	1	0.8059
Four hour	0.16729	2.05	1	0.1525
Cardiac problem	-0.14667	1.23	1	0.2673
Fistula	-0.0219	0.03	1	0.872
Catheter	-0.08329	0.31	1	0.5529
Global test		10.6	11	0.4777

Table 6: Results of Cox Proportional Hazards Model stratified by hypertension.

Covariates (and their category)	B	SE	Wald X2	Sig.	Exp(B) or HR	95% CI for Exp(B	
						Lower	Upper
Sex							
male	0.4428	0.353	-1.25	0.21	0.642	0.3212	1.2836
Female(*)							
Frequency of dialysis a week							
Three time	0.7285	0.4224	-1.72	0.085	0.4826	0.2108	1.1045
Two time a week(*)							
Diabetic status							
yes	0.3174	0.5223	-0.61	0..543	0.728	0.2615	2.026
No(*)							
Duration of dialysis							
There and half hour a session	-0.632	0.3191	-0.198	0.048	0.5314	0.2843	0.9933
Four hour a session	-2.409	0.8865	-2.72	0.007	0.0898	0.0158	0.5107
Three hour a session(*)							
Infection status							
yes	0.6716	0.3216	2.09	0.037	1.957	1.042	3.676
No (*)							
Anemic status							
yes	0.624	0.5624	1.11	0.267	1.866	0.6198	5.619
No (*)							
Cardiac complication							
yes	-0.111	0.4223	-0.26	0.793	0.8948	0.391	2.0477
No (*)							
Vascular access							
fistula	0.8283	0.5886	-1.41	0.157	0.4367	0.1386	1.1376
Graft(*)	0.0416	0.5294	0.08	0.937	1.042	0.369	2.9424
Catheter							

The reference categories were those indicated in asterisk (*)

DISCUSSION

The study assessed survival of ESRD patients and examined the socio-demographic, comorbidity and clinical determinants of ESRD patients. Having an infection is statistically associated with mortality of ESRD patients. In particular, after adjusting for other covariates, the hazards of death for ESRD patient's having an infection is 1.957 (almost twice) times that of ESRD patient without infection (HR=1.957, 95% CI=1.042-3.676). The 95% confidence intervals also suggest that the rates could be as low as

1.042 and as high as 3.676. That means the risk of death of ESRD patients who had infection could be as low as 1.042 times and as high as 3.676 times that of ESRD patients who do not have any infection. This finding is consistent with [10] who found that infection is the second leading cause of death among dialysis patients at the kidney disease center, Saitama university hospital in Saitama, Japan.

The result of this study revealed a negative relationship between duration of dialysis per session and hazards of death among ESRD patients. After adjusting for other covariates, the estimated coefficient is -2.094 for ESRD patients who take four hour dialysis per session and the hazards ratio is 0.0898. This indicates that the hazards of death is 91.02 % lesser for ESRD patients taking dialysis four hours in a session relative to those ESRD patients who are taking dialysis three hours in a session (HR=0.0832, 95% CI=0..139-0.495). This do suggest that the risk of death of ESRD patients who take dialysis four hour a session is lower than patients who take dialysis three hour a session. The estimated relative risk (hazard ratio) of death for ESRD patients taking dialysis three and half hours per session, as compared to those who take three hour per session, is 0.5314 (95% CI: 0.2843-0.9933). This indicates that the hazards of death is lesser by 46.86 % for those ESRD patients who are taking dialysis three and half hours in a session than those of ESRD patients who are taking dialysis three hours in a session.

This study found that diabetes was not the predictor of survival of ESRD patients. This is in contrast with the study conducted in Netherlands' [11] which demonstrated that survival among dialysis patients having diabetes mellitus is inferior to survival of ESRD patients with no diabetes. Although our univariate analyses do suggest diabetes is a significant covariate for the mortality of ESRD patients (in particular patients who do not have diabetes have beater survival than the patients having diabetes as, evidenced by the p value of log rank test 0.0625) multivariable analysis results differed from it, suggesting possible confounding or mediating roles in this link. Presence of anemia was not associated with an increased risk of mortality in our study. The results are dissimilar to that obtained by [12,13] who showed that presence of anemia is associated with reduced survival in patients with kidney disease and heart failure. This discrepancy between their study and the present study may be due to variables incorporated or considered in the models. Cardiac complication was not a statistically significant predictor of ESRD patients in this study which contrasts with the study done by [14] who found that the most common cause of death among patients under dialysis was cardiovascular disease.

CONCLUSION

The Cox regression analysis showed that duration of dialysis per session, hypertension, and infection were the major factors that affect the survival of ESRD patients. We found that kidney failure HD patients who had no infection are more likely to survive for longer time relative those of renal failure patients having infection. Duration of dialysis per session has a significant influence on the survival of ESRD patients. In particular, as the duration of dialysis per session increases the survival of the patients increase. In the other hand, it was found that factors which had no significant impact on the survival of ESRD patients were age, marital status, stroke, residence, religion and weight at the baseline of the patients.

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