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Original Article

Survival analysis and prognostic factors of chronic kidney disease: A case study in Batna, Algeria

Analyse de survie et facteurs pronostiques de l'insuffisance rénale chronique : Étude de cas à Batna, en Algérie

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AB S T R A C T

Introduction: Chronic kidney disease (CKD) was qualified as one of major public health issues in Algeria, and the study of risk factors for this disease is of great importance. **Methods:** Data of 247 followed up patients were recorded over the period (1987-2017) in the province of Batna in Algeria, and parametric regression models (Exponential and Weibull) were fitted to estimate survival functions by adjusting different prognostic factors. **Results:** The findings revealed that there was a minor difference between men and women in terms of survival time, for a short follow-up period, there was no difference in survival between smokers and non-smokers, but in the long term, such a difference was revealed. 75% of the deaths had an initial disease: diabetic or hypertensive nephropathy, and when adjusting this covariate into the models, women recorded a higher risk of death (thus low survival time) compared to men. **Conclusion:** These results should be taken into consideration to enhance more the national health strategy of kidney disease.

KEYWORDS: Chronic Renal Disease, Survival, Weibull, Exponential

RÉSUMÉ

Introduction : L'insuffisance rénale chronique (IRC) a été qualifiée de problème majeur de santé publique en Algérie, et l'étude des facteurs de risque de cette maladie est d'une grande importance. **Méthodes :** Les données de 247 patients ont été enregistrées sur la période (1987-2017) dans la province de Batna en Algérie, et des modèles de régression paramétriques (Exponentiel et Weibull) ont été ajustés pour estimer les fonctions de survie en ajustant différents facteurs pronostiques. **Résultats :** Les résultats ont révélé qu'il existe une légère différence entre les hommes et les femmes en termes de survie, pour une courte période de suivi, il n'y avait pas de différence de survie entre les fumeurs et les non-fumeurs, mais à long terme, une telle différence était révélée. Nous avons constaté que 75 % des décès avaient une maladie initiale : néphropathie diabétique ou hypertensive, et lors de l'ajustement de cette covariable dans les modèles, les femmes ont enregistré un risque de décès plus élevé (donc un temps de survie faible) par rapport aux hommes. **Conclusion :** Ces résultats devraient être considérés pour améliorer davantage la stratégie nationale de prise en charge de la maladie rénale.

MOTS CLÉS : Maladie rénale chronique, survie, Weibull, exponentielle

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Introduction

Chronic kidney disease (CKD) constitutes a major public health issue in Algeria. Prevalence and incidence rates are not accurate, some data consider that it affects nearly 26 000 persons, a prevalence rate of about 6 per 10000 capita, **[1],** others think there are 18,000 dialysis patients, 4,000 new cases per year **[2],** and 8000 patients need a transplant and of these 8000, only 20% have a potential family donor **[3].**

In the epidemiological analysis of the disease, several studies and research were carried out **[4]**, they attempted to estimate the effect of a specific factor on the survival of dialysis **[5]** attempted to estimate the effect of diabetes on survival of renal failure and this according to the two types of diabetes mellitus (DT1 and DT2), **[6]** worked on factors predicting coronary heart disease in chronic renal failure. In the same research field, Esteban et al. **[7]** studied the effect of smoking through cardiovascular diseases on renal function. For Ricardo *et al.*, **[8],** they are a bit beyond the traditional subject of epidemiology death risk factors of CKD by studying the quality of life for dialysis patients.

The aim of the current study was to analyze and estimate the effect of diabetes, smoking, obesity, hypertension, age, and gender on the survival and the risk of death from renal failure. We hope providing to clinicians some responses of questions such as: are diabetes and hypertension the most relevant risk factors of death? Is there any difference between men and women in terms of survival time? Do young patients and elderly have the same risk of death? To achieve these objectives, we used two regressive parametric survival models: The Exponential and the Weibull models.

Survival analysis as a statistical technique have become a widespread method in different research fields, both theoretical and practical: in Unemployment analysis, **[9, 10]** ; in Insurance **[11] ;** in Clinical trials, **[12]** etc. For the application, we used the register of the CKD from the hospital of Batna in Algeria. Several R software packages were used for the application, mainly: "survival", "KMsurv", "survminer". For a reference of the application in R, see [13].

The article is organized as follows: in Section 2 we introduce the main methods and techniques of survival models, with a focus on exponential and Weibull distributions. Section 3 presents the prevalence and incidence rates of CKD in Algeria and the data used in the application of these models, which is the chronic renal failure registry of Batna, followed over the period (1987-2017) in the nephrology department of Batna hospital. Section 4 summarizes the results and the underlying discussion based on previous epidemiological and clinical studies. The article ends with a conclusion.

Material and Methods

Statistical Methods

Survival time can be defined as the time until the occurrence of an event of interest. (e.g.): the event - in biostatistics - usually takes three types: the first is the emergence of a disease, the second is the development of this disease and the last is death. *So we can say that the survival time is the time between two different states.*

Survival Function $S(t)$ and Cumulative density $F(t)$

The survival function $S(t)$, is the probability of surviving beyond the time t, it is defined as,

$$S(t) = P(X > t) = \int_t^{\infty} f(x)dx, \quad t \geq 0 \qquad (1)$$

$S(t)$, is a decreasing function, and the average survival time is expressed simply using it follows from this function, distribution function $F(t)$, which is complementary to $S(t)$,.$F(t) = 1 - S(t)$:

$$F(t) = P(X \leq t) = \int_0^t f(x)dx$$

Risk function $\lambda(t)$

This function characterizes the probability of dying in a small time interval after t, conditional on having survived up to time t (i.e. the risk of instant death to those who survived) .t

$$\lambda(t) = \lim_{h \to 0} \frac{P(t \leq X \leq t + h / X \geq t)}{h} = \frac{f(t)}{S(t)} = -\frac{S(t)'}{S(t)} - [linS(t)]' \qquad (2)$$

Parametric Models regressive Survival

We note survival time variable $\boldsymbol{T}$, and: $\boldsymbol{x_{1i}, x_{2i} \dots x_{kn}}$the observations of random variables such as: (gender, age, ...). A parametric regression model for survival time distribution, establishes a relationship between the dependent variable (output variable) $\boldsymbol{T}$ and explanatory variables (risk factors or covariates) $\boldsymbol{x_{1i}, x_{2i} \dots x_{kn}}$.The overall shape of a parametric regression model is defined as follows:

$$\ln T = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k + \sigma\mathcal{E} \qquad (3)$$

With: $\boldsymbol{\beta_0,\dots,\beta_m}$ are parameters of variables, $\boldsymbol{\sigma}$ is a real constant, and $\boldsymbol{\varepsilon}$ is a random error. In practice, the exponential model and the Weibull model are the most used, and in what follows we will study them in detail. As a result most of parametric adjustments in survival were explained as the logarithm of the survival time.

Exponential Regressive Model

The parametric regression model for the survival time $\boldsymbol{T}$ distribution given by equation **(3)** is called exponential model, if the distribution and function of the following extremes:$\boldsymbol{\sigma = 1,}$ and $\boldsymbol{\mathcal{E}}$ has the following extreme value distribution function:

$$\boldsymbol{f_{\varepsilon}(x) = e^{x-e^{x}}, -\infty < x < \infty}$$

By equivalence $\boldsymbol{T}$ follows an exponential distribution given by the density:

$$\boldsymbol{f(t) = \lambda\, exp\{-\lambda t\}, t \geq 0 \quad ; \quad \lambda = exp\{-(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k)\}}$$

Survival function for this model is given by

$$\boldsymbol{S(t) = exp\{-\lambda t\}, t \geq 0}.$$

In practice, the assumption of the exponential model is that the instantaneous rate of risk $\boldsymbol{\lambda(t)}$ is constant over time (i.e.) $\boldsymbol{\lambda(t) = \lambda, t \geq 0}$, *this assumption is not always true*. Consequently we can represent the risk of death that evolves over time, in this context, different statistical models: **Weibull, [14],** Gamma, **Cox, [15],** are developed taking into consideration this new hypothesis. In this study, we focused on the Weibull model.

Regressive Weibull model

The Weibull distribution has been developed by **Wallodi Weibull (1887-1979)** in 1951. For a real random variable $T \in [0, +\infty[$ follows a Weibull distribution, its survival functions: $\boldsymbol{S(t), f(t), \lambda(t)}$ are given by:

$$\begin{cases} S(t/\alpha, \beta, \kappa) = exp^{-(\alpha(t-\kappa))^{\beta}}, \forall\, t \geq \kappa \\ f(t/\alpha, \beta, \kappa) = \beta\, \alpha(\alpha(t-\kappa))^{\beta-1} exp^{-(\alpha(t-\kappa))^{\beta}}, \quad \forall\, t \geq \kappa \\ \lambda(t/\alpha, \beta) = \beta\alpha\, (t\alpha)^{\beta-1} \end{cases}$$

with:

- $\boldsymbol{\kappa}$ is a location parameter having the same dimension of $\boldsymbol{T}$, (it is assumed $\kappa = 0$).
- $\boldsymbol{\alpha}$ -caractéristique is a scale parameter of life-model.
- $\boldsymbol{\beta}$ is a shape parameter

The expected value of the Weibull distribution is. $\boldsymbol{E(T) = \alpha\Gamma(1 + \frac{1}{\beta}),}$ the Weibull distribution is the most flexible among all parametric densities family, several generalization of this distribution were developed, the main reference is the work of Lai (2014) **[16].**

Likelihood Estimation

The usual method for estimating regression parameters, $\boldsymbol{\beta_0 \dots \beta_m}$ is the Maximum Likelihood method, (Molinares, 2011). When estimating the likelihood function, each non-censored data ($\boldsymbol{\delta_i = 1}$), contributes to the likelihood via the probability density $\boldsymbol{f(t)}$, and each censored data ($\boldsymbol{\delta_i = 0}$), contributes to the likelihood via the survival function $\boldsymbol{S(t)}$. With, normalization factor $\boldsymbol{K}$, the standard form of the likelihood is given by,

$$l(t_i;\, \beta_i;\, \delta_i) = K \prod_{i=1}^{n} f(t_i;\, \beta_i)^{\delta_i} S(c_i;\, \beta_i)^{1-\delta_i} \qquad (4)$$

We work generally on the log-likelihood function, to facilitate the estimation of parameters, $\boldsymbol{\beta_k}$, $\boldsymbol{k: 0, \dots, k.}$Therefore, the equation **(4)** becomes,

$$\boldsymbol{ll(t_i;\, \beta_i;\, \delta_i) \propto \sum_{i=1}^{n} \delta_i ln\, f(t_i;\, \beta_i) + (1 - \delta_i)\, ln\, S(c_i;\, \beta_i)} \qquad (5)$$

To construct the likelihoods of these models, and as discussed above, we just replace their probability densities $\boldsymbol{f(t_i)}$ and survival functions $\boldsymbol{S(t_i)}$ in equation **(5).** The parameters $\boldsymbol{\beta_i}$ of two models will be estimated by setting the first derivatives of the log-likelihood function equals zero:

$$\frac{\partial(ll(t_i;\, \beta_i;\, \delta_i))}{\partial\, \beta_i} = 0$$

For a detailed reading of modeling and estimation of survival analysis see **[17, 18**].

DATA

Overview of causal factors of CKD and treatment methods

Chronic kidney failure (CKD) is characterized by a diseased kidney, unable to perform the tasks of filtration and disposal of blood waste, which is incumbent on it. It most often results from complications related *to hypertension* or *diabetes*. In practice, CKD is defined by a chronic and ongoing reduction (beyond 3 months) glomerular filtration flow below$15ml/mn/1,73m2$, it is the stage 5 chronic kidney disease.

Table1. Levels of kidney function in kidney failure.

Level	Description	DFG (ml/mn)
1	kidney damage	> 90
2	minimal decrease in renal function	60-89
3	Moderate decrease in kidney function	30-59
4	Severe decreased kidney function	15-29
5	ESRD	<15 or substitute treatment

(***) *According to National Kidney Foundation, and American Kidney Fund,*(AKF, 2019)

They can lead to end-stage renal disease (ESRD) and death. In most patients in Algeria, ESRD can be treated by renal transplantation and / or renal replacement therapy (hemodialysis or peritoneal dialysis). The extra-corporeal of the blood purification systems are most widely used for the treatment of terminally uremic patients (*Level 5,* showed in **Table (1**) at the beginning of the third century. In spite of their formidable success in terms of preservation of life, their technical complexities, together with their basically un-physiological characteristics, account for a very imperfect replacement of the native kidney and explain why their application remains quite a sophisticated and demanding medical exercise that requires a good technical training along with a broad knowledge in large areas of internal medicine.

Prevalence and incidence of CKD in Algeria

According to recent statistics in Algeria, there have been 26,000 dialysis patients, 4,000 new cases per year and 8000 patients needing a transplant. From the 8000 patients only 20% have household potential donor. The Algerian legislation, for now, requires a First-Degree Living-Related Donor **[2],** for the kidney transplants process, therefore, 2,000 kidney transplants have been performed since the commencement of this technique in Algeria in 1986 **[19]**. In the same context, the head of the nephrology department at the hospital Nafissa Hamoud (ex-PARNET) cited that there is a "stagnation" given the increasingly important demand **[3].**

For the statistical modeling, and due to the lack of vigorously organized databases in Algeria, we limited ourselves to use of the CKD nephrology department register of the Batna hospital.

Database Characteristics

Batna is an Algerian city located in the region of Aurès of which it is the chief town, located 435 km southeast of Algiers and 113 km southwest of Constantine. This city is the 5th largest city in the country with 290,645 inhabitants (2008 Census). The register of chronic renal failure in Batna is a personal initiation of Nephrology department executives Batna hospital, mainly by **[20].** Until 2017 there are **247** patients included in the registry of this monitoring process. In the context of this study, and view the presentation clinic, the following variables were selected: age of patient, sex , date of starting dialysis (the difference between the date of the transplant operation and actual start of dialysis), date of death (or survival time in months) (*i.e.)* the difference between the dialysis start date and the date of death or date of end of study, Body Mass Index, $BMI = \frac{Weight}{(Height)^2} * 100.$, smoking factor (Yes, No), initial disease (Diabetic nephropathy (**DN**), Hypertensive nephropathy (**HN**) and Other).

The table below describes the level and dispersion of these variables, the mean age of patients included in the

registry is 50 years, but with a standard deviation of $\boldsymbol{SD = 17.9}$ years of age, this is a sample highly dispersed.

Table2. Summary statistics of the database

1.1	VARIABLES	1.2	$\bar{X}$	1.3	SD	1.4	N (%)
1.5	AGE	1.6	50.4	1.7	17.9	1.8	-
1.9	WEIGHT	1.10	61.3	1.11	13.4	1.12	-
1.13	HEIGHT	1.14	163.2	1.15	14.6	1.16	-
1.17	BMI	1.18	24.1	1.19	13.9	1.20	-
1.21	CREATININE	1.22	105.3	1.23	37.8	1.24	-
1.25	SEX (*MEN*)	1.26	-	1.27	-	1.28	137 (55.5)
1.29	SMOKING (*YES*)	1.30	-	1.31	-	1.32	103 (58.3)
1.33	INITIALS DISEASE :	1.34		1.35		1.36	
1.37	DIABETIC NEPHROPATHY	1.38	-	1.39	-	1.40	60 (24.3)
1.41	HYPERTENSIVE NEPHROPATHY	1.42	-	1.43	-	1.44	82 (33.2)
1.45	OTHER	1.46	-	1.47	-	1.48	105 (42.5)

Source : Estimated from the Register.

Fifty five percent (55%) of patients are male (137 patients), 25% of dialysis patients are diabetic (DT1 and DT2), for the initial diseases of dialysis patients, there are 60 patients (24%) who have DN as an initial disease. 58.3% of patients are smokers, and 33% of patients have hypertensive nephropathy as initial disease.

Results & Discussion

In the first step of analysis, we didn't adjust the risk factors. Results showed that the mean of survival time among the patients is 180.12 months (equivalently 15 years). By sex we found that:

- For men: **E** (*T*) = 179 months, or: 14.9 years.
- For women: **E** (*T*) = 182 months or 15.2 years.

So, in average (over the follow-up period), women are more likely to survive than men. There is a decreased regression of the survival function $\boldsymbol{S(t)}$ over the early period of the follow-up. We recorded 10 deaths in the first year of follow-up, *(i.e.)* 32% of deaths, the graph stabilize over the subsequent periods of follow-up.

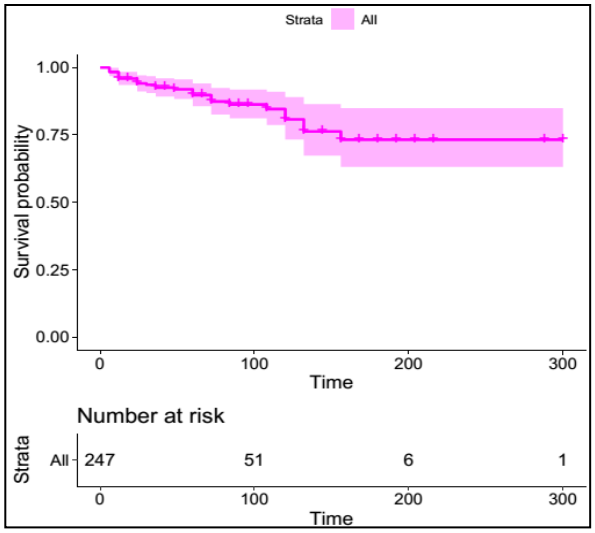

Figure 2. Graph of survival function $\boldsymbol{S(t)}$

According to the results in Table (3), a first step of analysis is to select the best model that fits well the data. To do so, two statistical information criteria were used, AIC **(**Akaike Information Criterion) **[21],** and BIC (Bayesian Information Criterion) **[22]**. The values of both criteria were almost identical for both models.

Therefore, both models have almost the same data adjustment qualities.

Table3. Estimation Results of the Exponential and Weibull models

Variables		Exponential		Weibull	
Intercepte		10.37	(1.29) **	9.49	(1.17) **
sex		0.03	-0.37	0.07	-0.3
Age		-0.04	(0.01) ***	-0.04	(0.01) **
BMI		-0.02	(0.01) **	-0.01	-0.01
Smoking		-0.56	-0.47	-0.52	-0.38
Initial disease	HNP	-1.27	-1.16	-1.09	-0.93
	DNP	-1.78	(1.03) **	-1.5	(0.85) **
	Other	-0.78	-1.06	-0.65	-0.85

Source: Elaborated by the Authors. (**) if the parameter is statistically significant

Although we observed, in descriptive analysis, a slight difference in average between men and women, we must control the difference of the survival time between men and women by using the test of $\chi 2$. In R program, the command below is used: (survdiff (survdialyse ~ sex, data = dialysebatna). The p-value is p = 0.63> 0.05. In the multivariate models, the underlying coefficient is not significant: $\beta^{sexe} = 0.03$, $\beta^{sexe} = 0.07$, for the exponential and Weibull models (respectively). Figure (3), clearly shows the indifference of the survival time between men and women, the slight difference mentioned above is observed in the long term; on the curve, almost from the interval $[150 - 200[$.

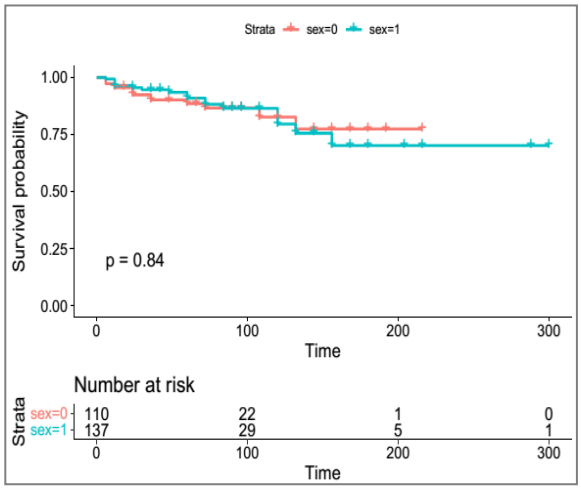

Figure 3. Plots of Survival functions $S(t)$ by sex

Smoking effect on Kidney Failure Disease

For smoking, its discriminatory effect does not clear on the first periods of follow-ups, **[0, 130],** Figure (4). However, this effect is observed on the follow-up interval **[140 - 300],** (*i.e.*). Over a short follow-up period, there was no difference in survival between smokers and non-smokers, but in the long term such a difference could be revealed (Figure 4).

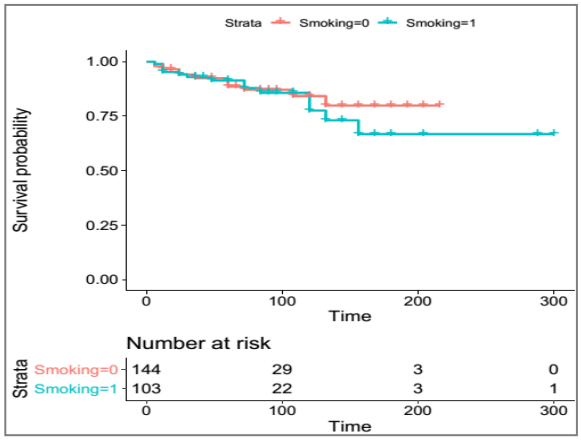

Figure 4. Plots of survival functions by smokers and non-smokers

This indifference is confirmed by the *log-rank* test which provided a $\boldsymbol{p - value = 0.58} > 0.05$. Even at the multivariate analysis, Table (3) showed that the coefficient relative for the smoking factor is not

significant for both estimated models (Exponential and Weibull).

Patient age and death risk

According to the registry data, 52% of deaths are over the age of 60, which explains that this disease will be fatal with the progression of the patient's age (*noting that this percentage is primarily estimated at the base of patients in Hemo-dialysis, those who have had a kidney transplant are not included*). However, 12.3% of deaths occur between the ages of 20 and 40, a rate that could be less if the renal transplant process was expanded using the cadaveric donor kidneys.

The multivariate estimation results showed that the age of the patient has slight effect on survival, with an estimated coefficient for the two models : $\boldsymbol{\beta^{age} = -0.04}$. In terms of the risk function, the hazard rate is = $exp^{(-0.04)} = 0.961$, which means that an increase of the age by one year yields an increase of the risk of death by 3.9 %. In other words, being young, adult or elderly does not generate a big survival benefit or risk of death for renal failure; (or to prolong or decrease the survival of a person with CKD). Recalling at this level that although people over the age of 60 constitute 52% of our study sample, this slice during modeling has no more risk of death compared to other age groups; this fact is the result of the interaction among the variables $\boldsymbol{X_i}$ when estimated the models.

In the current paper, we didn't study the genetic effect of the disease on the consistency and robustness of our model estimates, *(i.e.)* the case where the sample contains dialysis patients from the same family, at this level modeling of correlated survival data would be the appropriate choice [23].

Obesity and chronic renal disease

Regarding the overweight factor, Weisinger et al. **[24]** tried to reporte the epidemiological relationship between obesity and CKD (in particular, *nephriticrange proteinuria*). The relationship between obesity and the development of CKD is confirmed also by the study of Hall et al. [25].

Excess fat is closely associated with the development of diabetes and hypertension, two chronic diseases alone responsible for 50-60% of cases of chronic kidney failure. So, we can imagine that the relationship between obesity and CKD is an indirect one, the coefficient relating to the factor BMI is weakly significantly, $\beta^{BMI} = -0.01$. The hazard rate is = $exp^{(-0.01)} = 0.99$, so an increase of the BMI index by one unit, the risk of death increases by 1 %.

Initial Diseases and CKD

Figures in the register showed that 24.3% of deaths over the follow-up period have as initial disease Nephropathy Diabetic and 33.2% have Nephropathy Hypertensive (**Table 2)**. This result confirms the etiological factors of chronic renal failure. Statistically, this is established by the $\boldsymbol{\chi 2}$ test, where the $p - value = 0.0001 < 0.05$, we see clearly the difference of survival between patients with Hypertensive Nephropathy and Diabetic Nephropathy as initial diseases.

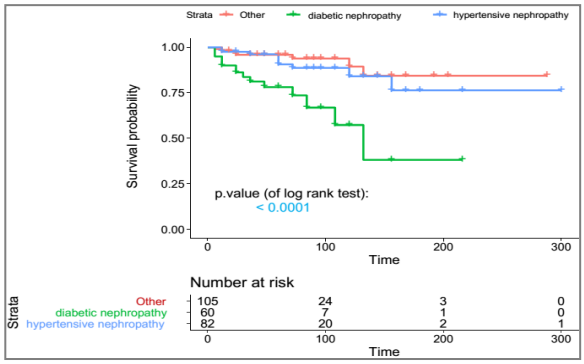

Figure 5: Plots of survival functions by the initial disease of the patient

Figure (5) illustrates the curves of survival functions of the patients whose initial disease is diabetic nephropathy, hypertensive nephropathy and unknown (Other). For the multivariate analysis in Table (3), patients whose initial disease is diabetic nephropathy have, 77% $[(1 - exp^{(-1.5)}) * 100]$; as an excess hazard rate of disease for patient.

Furthermore, we found that women whose initial diseases are: diabetic nephropathy and hypertensive nephropathy is characterized by a low survival (*thus, a high risk of death*) compared to male dialysis patients who have the same initial diseases. About diabetic nephropathy, the type of diabetes (DT1 and DT2) was not included as a discriminate variable. For this point, the study of Feigerlova *et al.* **[5]** , on diabetic nephropathy, the risk of death and decline of kidney function, have concluded that there is no difference

between DT1 and DT2 after adjustment for major risk factors.

Conclusion

The objective of this study is to estimate the effects of set of prognostic factors on survival of a sample of 247 patients with chronic failure disease followed-up over the period (1987-2017) at the nephrology department in Batna hospital, Algeria. For that, regression survival models were fitted and estimated, and a brief theoretical overview of these models were discussed including the underlying assumptions were cited in this analysis: the survival functions of the exponential model, the Weibull model and the Likelihood estimation method.

Findings displayed that 32% of deaths are recorded in the first year of follow-up, which shows that these patients arrive at the hospital in an advanced stage of the disease, a result which also confirms the insufficiency or lack of culture of the disease, diagnosis and early detection of this disease. Results showed no considerable difference between men and women in terms of survival and risk of death by this disease during the study period. For a short follow-up period, there was no difference in survival between smokers and non-smokers, but in the long run such a difference was observed.

Another result depicted that 58% of deaths had as initial disease: Nephropathy diabetic or Hypertensive, a result confirmed by the majority of clinical and epidemiological studies carried out. Thus, the Algerian government must first target hypertension and diabetes for a better management of kidney diseases. Another result shows that older people have a higher risk of death, a significant effect of obesity on survival of renal failure is also found in modeling, in the last point of our analysis.

It should be noticed that our results are limited by two contexts: a spatiotemporal context and a context of the practical difficulties encountered during the achievement of this study; the two major difficulties are, firstly, the lack of a national registry (or database) of the kidney failure chronic disease that covers also the transplants process; this national database is either a necessity and a practical requirement to conduct researches in this field. Secondly, non-collaboration and difficulties to get access to the available statistics for some hospitals. If the practical and pedagogical obstacles in this field of research in Algeria will be resolved, future studies in this field will be more precise and superior quality especially in the analysis of the quality of life of dialysis and / or transplant recipients.

Conflicts of interest

Authors do not declare any conflict of interest

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