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Survival Analysis of Iranian Patients Undergoing Continuous Ambulatory Peritoneal Dialysis Using Cure Model

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ABSTRACT

Background: Peritoneal dialysis is one of the most prevalent types of dialysis prescribed to the patients suffering from renal failure. Studies on the factors affecting the survival of these patients have mainly used log-rank test and Cox analysis. The present study aimed to investigate the risk factors affecting short- and long term survival of patients on continuous ambulatory peritoneal dialysis (CAPD) using cure model.

Methods: The data obtained retrospectively from 20 medical centers in Iran, between 1996 and 2009. All patients with renal failure who had been treated by CAPD and followed at least 3 months were included in the study. The STATA (11.0) software and CUREREGR module were used for survival analysis using cure model.

Results: Totally 2006 patients were included in this study. The major reasons for renal failure were hypertension (35.4%) and diabetes (33.6%). The median of survival time was 4.8 years with a 95% confidence interval of 4.3 to 5.6 years. The percentage of long-lived patients surviving was 40% (95% CI: 32%, 47%). The analysis showed that the effect of diabetes, serum albumin level, age, diastolic blood pressure, and medical center was significant on the long-term survival of the patients. In addition, in short-term survival the effects of age, albumin, and medical center were significant

Conclusions: By improving the quality of medical care in centers, nutritional status, controlling co-morbidities can help the patients on CAPD with better health and increase their short and long term survival.

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Introduction

Improvement in life expectancy is associated with lack of hypertension, diabetes, and suffering from ESRD (End Stage Renal Disease)[1]. Continuous ambulatory peritoneal dialysis (CAPD) is commonly used to care ESRD patients so that it has been reported that this method may produce better survival compared with hemodialysis[2,3]. Since 1995, CAPD has been implemented in Iran and the number of patients with this method is increasing[4,5].

A number of factors result in death of the patients including, aging, other diseases, and malnutrition. Some of studies have been conducted to determine the contribution of the factors in short- and long-term survival of the patients[6]. The majority of studies on the efficiency of treating methods, life span of the CAPD patients, and factors affecting the survival of these patients have mainly used Log-rank test and Cox analysis. Comparable to other statistical models, the survival analysis is based on specific hypotheses that should be met at data handling. Once there are a proportion of individuals with a long-term survival rate among the people in a study, then the cure models might be used in the survival analysis[7]. Most of studies that investigated the factors affecting the survival of CAPD patients have used Log-rank test and Cox risk model ([5,8-13]). Although dialysis is used mainly to maintain the patients, but not to cure them, and the patients will finally die, improvements in medical care and the quality of life of the patients have made them to experience a life comparable to the normal persons. Accordingly, using the cure model is justified to study these patients.

It might be stated that the cure model is studied for its optimal properties which may better describe the responses to the variables at different times. Therefore, providing a better clarification of the effects and of the estimated time of predicting factors to make decisions on the health of the CAPD patients would critically alter the quality of life in the patients. The model may separate the short-term survival and the long-term ones and evaluates the effects of factors involving in short- or long T term survivals[7,14,15]. In statistical point of view short-term survival consist of proportion of total patients at risks of death who eventually die and long-term survival means proportion of patients who will not die until the end of the study (we explicitly assume that length of follow-up is sufficient).

The current study aimed to investigate the survival of the patients in Iran using cure model with determining the contributing factors in either short- or long-term survival.

Methods

From 1996 to 2009, all patients with renal failure who had been treated by CAPD and followed for 3 months were included in the study. The data were obtained, retrospectively, from a total of 20 medical centers all over Iran who registered in CAPD Database.

Deaths due to CAPD were regarded as failure and patients with renal transplantation or those leaving the study were censored.

The data were subjected to survival analysis and the fitness of the cure model, using STATA (11.0) software and CUREREGR module. The effects of a number of factors on the survival of CAPD patients were evaluated including, sex, age, BMI (Body Mass Index), diabetes, medical center, cholesterol, LDL, HDL, Pth, nPCR, TG, albumin, hemoglobin, creatinine, calcium, phosphorus, and systolic/diastolic blood pressure. A 6-month-long window of time was defined for variables with multiple measurements during the follow-up period and the effect of time was included in the survival analysis.

The percentage of long-lived patients and adequacy of the length of the follow-up period was tested prior to using cure models according to Maller & Zhou[7]. This may determine if there is a considerable percentage of long-lived patients and whether the follow-up period is long enough or the significance of the long-lived patients in due to a short follow-up period. Suggested standard ranges were used to categorize the quantitative variable[11,16]. The effects of factors on short- and long-term survival were then evaluated through univariate model and the contributing factors were clarified through backward elimination in the multivariate model. Weibull parametric distribution with logistics link function was used to fit the parametric mixture cure model as it was shown to fit the data best[17].

Besides, in univariate as well as multivariate framework, scale parameter was modeled by covariates and shape parameters were considered fixed. In multivariate analysis, variables entered in both the short-term (scale parameter of Weibull distribution) and long-term (logistic link function).

The level of significance was set at $P \leq 0.05$ and the range of 0.05 to 0.10 was considered as borderline.

Results

The major reasons for renal failure were as hypertension (35.4%), diabetes (33.6%), and glomerulonephritis (7.1%) as well as polycystic kidney (3.8%) and vascular collagen disease (0.5%). Other causes constituted the remaining 19.6%. A number of 1104 (55%) out of the total patients (2006 individuals) were female aging between 15 to 100 yr [mean±SD = 50±17]. A total of 507 patients (25%) died during the study which comprised 282 female (56%) and 225 male (44%) patients. The number of death and sex were not related using Chi-squared test (*P*=0.8). For patients died during the study, the time of death varied between 91 to 2399 days after the dialysis was initiated so that the median and mean (SD) time of death were 478 and 605 (432) days, respectively. A total of 1499 (75%) patients were censored during 90 to 3960 days of follow-up period. The median of follow-up period for censored patients was 540 days with a mean (SD) censorship of 714 (554) days. Median and mean (SD) of censorship time has been extracted by filtering the data on censored patients. Figure 1 illustrates the Kaplan Meier observed curve with 95% confidence interval. The figure shows an approximate time of 7 years that the curve reached to a plateau with a survival rate of 40%, lasting by the end of the study (for 4 years), therefore, in a conservative prospective, patients who live below 7 years have short-term survival, although in dialysis survival literature survival time under 5 years or even 3 years is considered short term survival[8]. The median of survival time for all patients in the study was 4.8 years (95% CI: 4.3, 5.6). The percentage of long-lived patients surviving for more than 11 years from the study was 40% (95% CI: 32%, 47%).

Maller and Zhou method was used to study the long-term survival analysis of the patients[7] with a *P*-value of 0.01. The adequacy of the length of the work was studied to make sure that the number of living patients was not as a result of a short-term study. The hypothesis on the adequacy of the study duration was accepted at *P*=0.05 according to the proposed tables[7] which was in line with Kaplan-Meier graph in Figure 2. Therefore, the hypotheses for cure model were met.

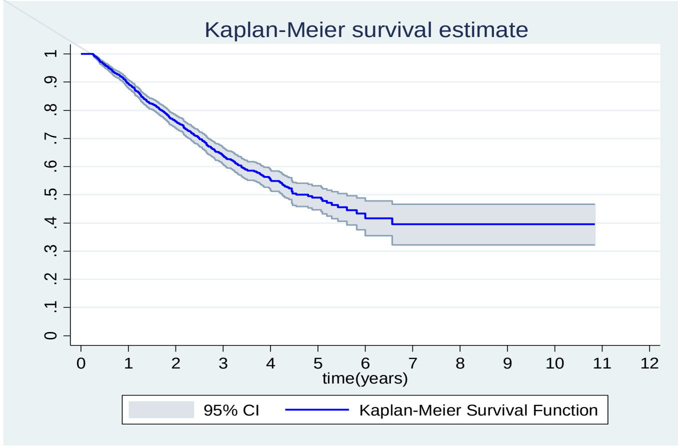

Figure 1: Overall Kaplan-Meier survival curve with 95% CI for patients on continuous ambulatory peritoneal dialysis

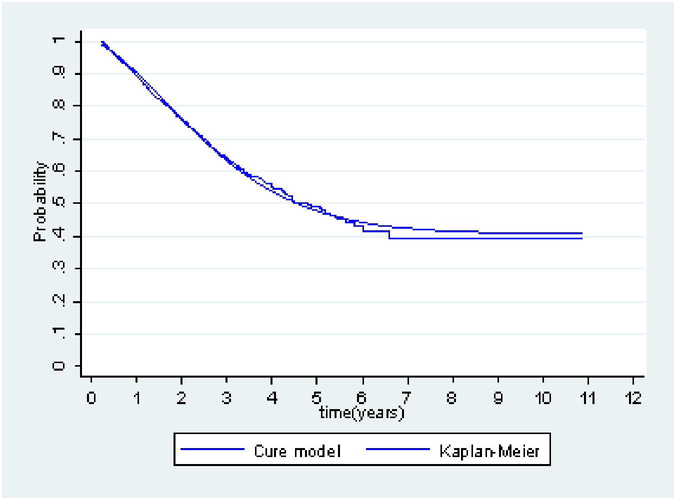

Figure 2: Overall survival curve extracted from cure model overlaid on Kaplan-Meier observed curve

Table 1 estimates the long-term patients' survival and short-term Hazard Ratio (HR) with 95% CI for studied risk factors. For example, 28% of the patients with serum albumin level lower than 3.5 g/dL were long-lived (95% CI: 21%, 36%), but the corresponding percentage for patients with albumin levels equal to or higher than 3.5 g/dL was 46% (95% CI: 26%, 63%), however, this difference is borderline (*P*=0.073). The estimated proportions of long lived patients in different categories of studied risk factors (Table 1) were extracted from logistic link function by transforming log odds ratio to probability. On the other hand, in short-term part, hazard of death for patients with low-level serum albumin is 79% greater than high-level (95% CI: 1.26, 2.52) and significant (*P*=0.001). Other risk factors in Table 1 can be interpreted as above. Moreover the effect of the medical center on long- and short-term survival was significant (*P*=0.003). It is worth mentioning that the coefficients of variables in the scale parameter of Weibull distribution for short term survival were exponentiated so the Hazard Ratios were reported in table 1 for better understanding. Shape parameter was considered fixed in all cases and almost equal to 0.45.

For constructing multivariate model, all risk factors were initially included in model and factors with *P*-values higher than 0.1 were excluded through backward elimination. The effects of diabetes, serum albumin level, age, and diastolic blood pressure on long-term survival was significant so that lower age, higher albumin level, absence of diabetes, and not low diastolic blood pressure improved the long-term survival of the patients. On the other hand, albumin and age affected the short-term survival of the patients. In addition the effects of the medical center was significant in multivariate analysis (*P*=0.005) as well as in univariate which influenced the short- and long-term survival rates.

Medical centers effect was entered in the univariate model as well as multivariate (using backward elimination) analyses as dummy variables and their effects on short-term and long term were examined by likelihood ratio test. Furthermore, medical centers have been modeled in the scale parameter of the Weibull distribution and logistic part, simultaneously, for investigating their effects on short and long term survival, respectively. However, no frailty term has been used.

Discussion

Seventy five percent of the patients were censored for whom the median time of following-up was 540 days. Median survival time was 4.8 years (95% CI: 4.3, 5.6), reaching to a plateau after 7 years. The long-term survival of the patients was estimated to be 40% (95% CI: 32%, 47%). A 160-month-long study in CAPD patients in India showed a 40% long-term survival rate[8,9]. Another study, comparing the patients in China and Canada, indicated that the 5-year survival rate in the study was higher than 60%[9].

The presence of long-lived patients among those investigated in survival analysis makes implementing the cure models more adequate[18]. At a CAPD center in Mexico, a 12-year-long study showed a 30% survival rate of the patients[19]. Most of studies have used Cox model ([5,8-13,19]), whereas improvements in medical care and, in turn, in the life of the CAPD patients, increased the chance of long-life for patients which is in contradiction to the hypotheses of Cox model. The presence of long-lived patients was statistically confirmed in the current work and, hence, the cure model was used. The model separates the short- and long-term survivals and determines their affecting factors in a single output without missing the data. In a study to clarify the factors influencing the short- and long term survival, the patients were categorized to those survived shorter than 3 years and those lived longer than 3 years. The logistic regression was used regardless of the importance of the censored data. It has also been shown that diabetes affects the 3- and 5-year survival of the patients, but not the one-year one[13]. The current data support the effect of diabetes on long-term survival. Generally, the univariate regression showed the significant effect of age, BMI, medical center, and diabetes on the long-term survival of the patients. The effects of albumin, creatinine, and calcium were in the borderline. Univariate regression of short-term survival indicated the significant effects of age, diabetes, albumin, and medical center with hemoglobin effect in the borderline. In multivariate regression, however, the effects of age, diabetes, albumin, medical center, and diastolic blood pressure on the long-term survival were significant. But, the short-term survival was affected by age, albumin, and medical center. The current findings are in accordance with several studies[5,19,20]. Interestingly, the effect of the medical center was significant in multivariate regression. Accordingly, irrespective of the personal characteristics of the patients, the medical center contributed to the survival duration. In other words, improvements in the quality of medical care may be possible for medical centers[9].

Table 1: Estimates proportion of long-lived patients on continuous ambulatory peritoneal dialysis and Hazard Ratio (HR) of short-term survival probability (P) with 95% CI for different risk factors

Risk factors	Long-term Survival P (95% CI)	*P* value	Short term survival HR (95% CI)	*P* value
Age (yr)				
<55	0.56 (0.44, 0.66)	<0.001	1.00	0.012
≥55	0.25 (0.18, 0.32)		1.42 (1.08, 1.86)	
Sex				
Female	0.42 (0.34, 0.51)	0.582	1.00	0.593
Male	0.39 (0.29, 0.49)		0.94 (0.76, 1.17)	
Body mass index				
<18.5	0.50 (0.49, 0.51)	<0.001	1.00	0.001
18.5-24.9	0.42 (0.38, 0.46)		1.48 (1.03, 2.14)	
≥25	0.34 (0.26, 0.41)		1.58 (1.13, 2.21)	
Diabetes				
No	0.52 (0.43, 0.61)	<0.001	1.00	0.189
Yes	0.25 (0.16, 0.34)		1.16 (0.93, 1.46)	
Albumin (g/dL)				
≥3.5	0.46 (0.26, 0.63)	0.073	1.00	0.001
<3.5	0.28 (0.21, 0.36)		1.79 (1.26, 2.52)	
Creatinine(mg/dL)				
<7	0.29 (0.19, 0.37)	0.010	1.00	0.279
≥7	0.48 (0.39, 0.58)		0.88 (0.69, 1.11)	
Calcium (mg/dL)				
≥8.5	0.42 (0.33, 0.51)	0.080	1.00	0.386
<8.5	0.28 (0.16, 0.40)		1.11 (0.87, 1.42)	
Hemoglobin (g/dL)				
≥8	0.40 (0.32, 0.60)	0.326	1.00	0.066
<8	0.47 (0.30, 0.47)		1.36 (0.98, 1.90)	
Phosphorus (mg/dL)				
<5.5	0.36 (0.28, 0.45)	0.095	1.00	0.765
≥5.5	0.50 (0.35, 0.63)		0.95 (0.70, 1.30)	
Pth (pg/mL)				
≥300	0.48 (0.40, 0.57)	0.843	1.00	0.265
<300	0.45 (0.10, 0.75)		0.72 (0.40, 1.28)	
Triglyceride (mg/dL)				
<200	0.40 (0.32, 0.49)	0.696	1.00	0.438
≥200	0.44 (0.30, 0.57)		0.90 (0.69, 1.17)	
LDL (mg/dL)				
<100	0.39 (0.27, 0.51)	0.759	1.00	0.623
≥100	0.42 (0.27, 0.56)		0.93 (0.69, 1.25)	
HDL (mg/dL)				
<45	0.41 (0.31, 0.51)	0.757	1.00	0.254
≥45	0.45 (0.17, 0.58)		0.81 (0.57, 1.16)	
Systolic blood pressure (mmHg)				
<150	0.47 (0.40, 0.54)	0.625	1.00	0.490
≥150	0.44 (0.32, 0.55)		0.92 (0.73, 1.17)	
Diastolic blood pressure (mmHg)				
<100	0.45 (0.38, 0.52)	0.189	1.00	0.893
≥100	0.57 (0.39, 0.72)		1.03 (0.70, 1.51)	
nPCR (g/kg/day)				
≥0.9	0.46 (0.23, 0.66)	0.434	1.00	0.242
<0.9	0.55 (0.43, 0.66)		1.26 (0.85, 1.87)	

Conclusion

This study suggest by improvements in the quality of medical care in various centers, nutritional status, controlling comorbidities can help the patients on CAPD with better health experiences and improve their short- and long term survival experiences.

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Conflict of interest statement

The authors have declared that they have no competing interests.

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