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Original Article

Parametric methods for estimating survival in continuous ambulatory peritoneal dialysis patients in the presence of competing events

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ABSTRACT

Background & Aim: In many studies, the survival of patients with chronic kidney disease who are treated with peritoneal dialysis technique has been considered, while this is possible in peritoneal dialysis patients to switch to another treatment. To achieve more accurate estimation of patient survival is necessary to examine all events. The purpose of this study is to estimate the cumulative incidence function (CIF) of events using competing risks method and then calculating the survival of patients treated with peritoneal dialysis.

Methods & Materials: This study includes 417 patients with chronic kidney disease who were under peritoneal dialysis between July 1996 and December 2009 in three centers in Tehran. We achieved their survival by 13 years follow-up time. We have collected patient demographic data and clinical characteristics. CIF of death and other events was estimated using the cause-specific hazard approach and direct approach. Parametric regression model was used to adjust the effects of covariates. The data analysis was performed using the R software.

Results: In this study, the median follow-up time was 664 days. A total of 112 (26.9%) patients treated with peritoneal dialysis died before completing the study, and before the end of the study. One hundred sixty seven (40.0%) patients treated with peritoneal dialysis changed their dialysis method to hemodialysis or had renal transplantation .

Conclusion: The effective risk factors on death CIF and other competing events CIF were diabetes mellitus, albumin, creatinine, diastolic blood pressure, urea and age, creatinine, diastolic blood pressure, respectively.

Introduction

Peritoneal dialysis is a method for curing patients with kidney failure and is the second alternative to dialysis used all over the world. The number of patients who are using this kind of dialysis is approximately 15% of total. Survival is one of the criteria used to evaluate the efficacy of treatment in patients with renal failure. Survival time in dialysis patient is 7-11 years in 40-44 years old members and is 4-6 years in 60-64 years old members witch is less than healthy people. However, evidence suggests that survival of dialysis patients has improved in recent years, suggesting that the improvement of health conditions may reduce mortality (1).

Patients on peritoneal dialysis may encounter multiple possible outcomes. For example, peritoneal dialysis patients may die, be transferred to hemodialysis or undergo renal transplantation. Researchers are often interested

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in the probability of having experienced the outcome at different follow-up times. This probability is known as the cumulative incidence (CI). The common approach in the dialysis literature is to estimate the CI by the Kaplan-Meier (KM) method. In KM method, outcome is taken as the event of interest and patients experiencing the other outcomes are treating as censored in addition to those who are censored from loss to follow-up or withdrawal. The CI is then calculated by 1-KM (2).

However, the KM method was developed for cases with only one outcome. When competing risks (multiple outcomes) are present, this concept is not useful since the occurrence of one outcome changes the probability of the others. As a matter of fact, the KM method assumes that the outcomes are independent and it removes the competing risks without changing the probability of the outcome of interest (2).

Kalbfleisch and Prentice (1980) suggested an approach that accounted for the competing risks. This method is labeled the cumulative incidence function (CIF). Using this technique, the probability of any event happening is partitioned into the probabilities for each type of event (3). The main purpose of this study is to evaluate peritoneal dialysis patient survival using competing risks method.

Methods

We analyzed dialysis patient's survival in a cohort of 417 members who were under peritoneal dialysis between July 1996 and December 2009 in three centers in Tehran, Iran. We achieved their survival by 13 years follow-up time. We collected patient demographic characteristics such as age (age at admission to a treatment center), gender (male/female), clinical characteristics such as diabetes mellitus, serum albumin (g/dL), creatinine (mg/dL), urea, and diastolic blood pressure.

In peritoneal dialysis, patient time to the first event (death/exit from peritoneal dialysis) was calculated. Death and exit from peritoneal dialysis was considered as competing events. Patients who were alive and had not exit from peritoneal dialysis before 13 years follow-up were considered as lost to follow-up.

Since parametric method is more efficient than nonparametric method, in this paper, CIF is calculated using parametric method. In parametric method, there are two approaches in estimating CIF, cause-specific hazard approach and direct approach. Direct approach is superior to cause-specific hazard approach, as it can also model the independent risk factors.

Cause-specific hazard approach

In cause-specific hazard approach, overall hazard is viewed as two mutually exclusive partitions. A portion of the overall risk is referring to the risk of the interest event, and the other is associated with competing events.

$$h(t;\psi_1) + h_2(t;\psi_2)$$

The CIF for the k^{th} event is given as follows (4):

$$CIF_k(t) = \int_0^t S_1\,(t;\psi_1).\, s_2(t;\psi_2) h_k h(t;\psi_1) + h_2(u;\psi_2)du \quad k = 1,2$$

Direct approach

Dialysis patients may generally experience a series of disease events, those patients who do not experience any event can be viewed as a cured population. In this case, the distribution of recurrences can be estimated via the cure model because the cumulative probability of loco-regional recurrences is <1. This suggests that CIF_k should be modeled as an improper distribution, F(x;ψ), where F is a known function of *x* and the parameter ψ.

To parameterize the CIF, we may use the Gompertz distribution. In Gompertz distribution, an improper case of CIF occurs when $\alpha < 0$ and $|\beta| < \infty$. A simple form of CIF of the Gompertz distribution can be written as

$$F(\text{time};\alpha,\beta) = 1 - \exp[\beta\{1 - \exp(\alpha \times \text{time})\}/\alpha]$$

In these studies variances of the CI estimates were evaluated with the multivariate delta method (4). Parametric direct regression was used to adjust the effect of age, diabetes mellitus, serum albumin, creatinine, diastolic blood pressure, urea on estimated CIs of death and exit from peritoneal dialysis (5). At the end, patients' survival in peritoneal dialysis was evaluated. To estimate the parameters of the CIs Newton-Raphson method was used. The significance level was set at 0.1 and data analysis was performed using the software R (R-project, R Development Core Team, Version 2.15.0).

Results

The study involved 417 patients from three centers in Tehran. Frequency of patients according to sex, age, diabetes status, serum albumin level, creatinine level, diastolic blood pressure, systolic blood pressure, and urea levels are given in table 1. As shown in table 1 patients were mostly middle aged, but covered a wide age range, with just over one-half male. Diabetes was a common comorbidity in this study. Two hundred and forty-nine (59.7%) patients were in the normal range of serum albumin, while 160 (38.4%) patients had serum albumin level <3.5, and only 8 (1.9%) patients had serum albumin level more than normal range. Two hundred and twenty (52.8%) patients had normal creatinine level, while 197 (47.2%) patients had creatinine level more than normal.

Table 1. Patient characteristics at baseline

Characteristics	Number	Percentage
Sex		
Male	225	54.0
Female	192	46.0
Age		
Median (IQR)	52	(40–65)
Diabetes mellitus		
Yes	128	30.7
No	289	69.3
Serum albumin (g/dL)		
<3.5	160	38.4
3.5–5	249	59.7
>5	8	1.9
Creatinine (mg/dL)		
<7	220	52.8
≥7	197	47.2
Urea		
<100	26	6.2
≥100	391	93.8
Diastolic blood pressure		
<60	7	1.7
60–90	344	82.5
>90	66	15.8
Systolic blood pressure		
<90	5	1.2
90–140	294	70.5
>140	118	28.3

IQR: Interquartile range

In this study, the median follow-up time was 664 days. One hundred and twelve (26.9%) patients treated with peritoneal dialysis died before completing the study, before the end of the study 167 (40.0%) patients treated with peritoneal dialysis changed their dialysis method to hemodialysis or had renal transplantation. Thirty-eight (9.1%) patients did not experience any of these events over 13 years and were considered as cured population. One hundred (24.0%) patients who were lost to follow-up were considered as censored.

To achieve patient survival first CIF of death and exit from peritoneal dialysis was computed using cause-specific hazard approach and then using the direct approach in Gompertz distribution. Then, their survival was computed at 1, 2, 5, 13 years' time points (Figure 1).

In cause-specific hazard approach, using the Gompertz distribution parameter estimations are

$\hat{\lambda}_{Death} = 0.0004, \hat{\lambda}_{Other\ Events} = 0.0006,$

$\hat{\alpha}_{Death} = -0.001, \hat{\alpha}_{Other\ Events} = -0.0009$

and in direct approach using the Gompertz distribution parameter estimations are

$\hat{\lambda}_{Death} = 0.0004, \hat{\lambda}_{Other\ Events} = 0.0006,$

$\hat{\alpha}_{Death} = -0.0014, \hat{\alpha}_{Other\ Events} = -0.0011$

CIF in both approaches was calculated for 13 years. This means that given patients treated with peritoneal dialysis may switch to an alternative therapy or die, probability to change therapy as the first event after 13 years is approximately 39% in both approaches and also the probability of death before switching to an alternative therapy is approximately 26% in both approaches. CIF estimate in different years have elapsed after treatment with peritoneal dialysis are given in table 2. As shown in table 2, after estimating the variance of CIFs confidence interval for CIFs was calculated. Then patient survival was calculated by $1 - CIF_{death} - CIF_{other}$ (4). As shown in table 2, patient survival after 1, 2, 3, 5 , 13 is 0.728, 0.583, 0.497, 5 , 0.344 in cause-specific hazard approach and its 0.728, 0.574, 0.483, 5 , 0.336 in direct approach. In the other word, the probability that a patient survives and does not exit from peritoneal dialysis is 34.4% in cause-specific hazard approach and its 33.6% in direct approach. Because some covariates have significant effects on CIFs and patient survival, we used parametric regression to adjust for the effect of these risk factors. Checking the assumption of proportional hazards in this regression model suggested that hazards are proportional along time in this data.

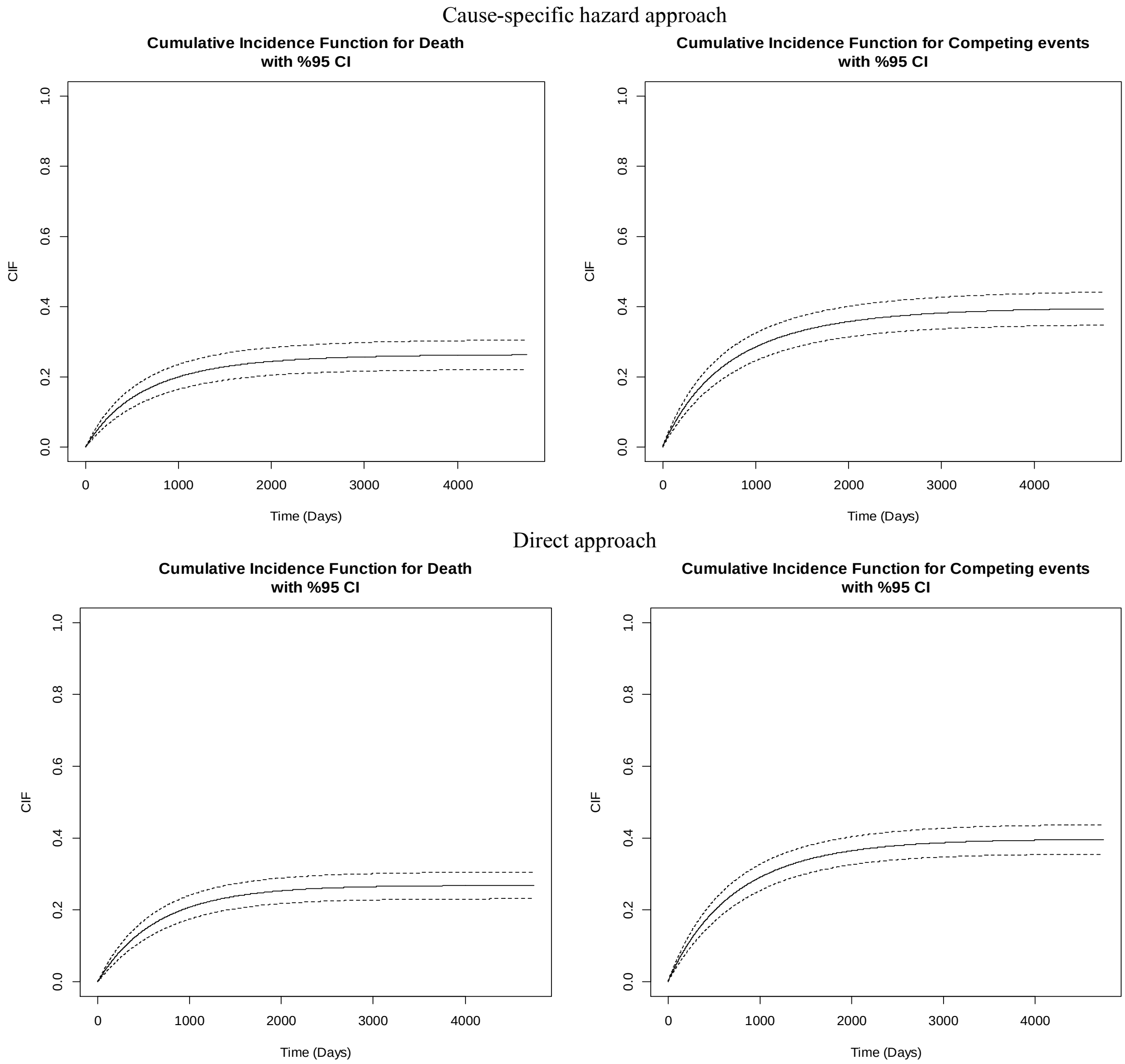

Figure 1. Comparison of cause-specific hazard and direct approaches

Table 2. Estimation of CIF of death and other competing events (95% CI) in parametric approach using Gompertz distribution

Time (years)	Cause-specific hazard approach			Direct approach		
	CIF_{Death}	CIF_{Other}	S(t)	CIF_{Death}	CIF_{Other}	S(t)
1	0.114 (0.090, 0.138)	0.158 (0.131, 0.185)	0.728	0.115 (0.092, 0.138)	0.157 (0.131, 0.183)	0.728
2	0.173 (0.140, 0.206)	0.244 (0.208, 0.280)	0.583	0.179 (0.148, 0.210)	0.247 (0.213, 0.281)	0.584
3	0.207 (0.171, 0.243)	0.296 (0.256, 0.336)	0.497	0.215 (0.181, 0.249)	0.302 (0.265, 0.339)	0.483
4	0.227 (0.189, 0.265)	0.328 (0.286, 0.370)	0.444	0.236 (0.201, 0.271)	0.335 (0.297, 0.373)	0.429
5	0.240 (0.201, 0.279)	0.350 (0.307, 0.393)	0.41	0.249 (0.214, 0.284)	0.357 (0.318, 0.396)	0.394
6	0.248 (0.208, 0.288)	0.364 (0.320, 0.408)	0.388	0.257 (0.221, 0.293)	0.371 (0.332, 0.410)	0.372
7	0.253 (0.213, 0.293)	0.374 (0.329, 0.419)	0.373	0.261 (0.225, 0.297)	0.380 (0.341,0.419)	0.359
8	0.256 (0.215, 0.297)	0.380 (0.335, 0.425)	0.364	0.264 (0.227, 0.301)	0.386 (0.346, 0.426)	0.350
9	0.259 (0.218, 0.300)	0.385 (0.340, 0.430)	0.356	0.266 (0.229, 0.303)	0.390 (0.350, 0.430)	0.344
10	0.260 (0.218, 0.302)	0.389 (0.343, 0.435)	0.351	0.267 (0.230, 0.304)	0.392 (0.352, 0.432)	0.341
11	0.261 (0.219, 0.293)	0.391 (0.345, 0.437)	0.348	0.267 (0.230, 0.304)	0.394 (0.354, 0.434)	0.339
12	0.262 (0.220, 0.304)	0.393 (0.347, 0.439)	0.345	0.268 (0.231, 0.305)	0.395 (0.354, 0.436)	0.337
13	0.262 (0.220, 0.304)	0.394 (0.347, 0.441)	0.344	0.268 (0.231, 0.305)	0.396 (0.355, 0.437)	0.336

CIF: Cumulative incidence function, CI: Confidence interval

Regression coefficients of the model and their P-value are given in tables 3 and 4. As shown in table 3, all the risk factors had a significant effect (at a $\alpha = 0.05$ level) on the CIF of death in the presence of other variables. However, as shown in table 4, three variables had not a significant effect ($P > 0.10$) on the CIF of other events and only age and diastolic blood pressure were significant at a $\alpha = 0.05$, whereas the creatinine level remained weakly significant ($P = 0.08$) but as it was a significant risk factor we kept in the model to adjust the CI estimates.

CI estimates after adjusting for the effect of underlying influential risk factors and their confidence intervals are given in table 5. We concluded that adjusting the underlying factors reduces the risk of death and increase the probability of other events. As shown in table 5, survival of patients after implementation of the underlying factors in 1, 2, 5 , 13 years are 0.735, 0.578, 5 , 0.334.

Discussion

In this study, a method of competing risks in order to achieve an accurate estimate of survival in peritoneal dialysis patient was used. Since parametric methods are more powerful and more efficient among the various techniques, we used parametric method. Survival in 13 years after adjusting covariates was 33.4% witch is approximately equal to survival in direct method, but estimated CIFs are more accurate in parametric regression. Comparison between the sexes showed that CI of death and exit from peritoneal dialysis did not have a significant difference and hence no significant difference was found between male and female survival treated with peritoneal dialysis. This result is the same as Korea and Australia studies (6, 7).

Table 3. Effects of risk factors in estimation of CIF of death

Risk factors	β	var(β)	Z	P-value
Age	0.6540	0.046	3.06	0.0020
Diabetes mellitus (%)	0.3600	0.041	1.77	0.0760
Albumin (g/dL)	−0.5200	0.025	−3.24	0.0010
Creatinine (mg/dL)	−0.0990	0.001	−2.47	0.0130
Diastolic blood pressure	−0.0170	3.7×10^{-5}	−2.78	0.0050
Urea	−0.0007	4.6×10^{-8}	−3.37	0.0008

CIF: Cumulative incidence function

Table 4. Effects of risk factors in estimation of CIF of other competing events

Risk factors	β	var(β)	Z	P-value
Age	−0.3380	0.0310	−1.91	0.056
Diabetes mellitus (%)	−0.2940	0.0390	−1.48	0.140
Albumin (g/dL)	0.0620	0.0150	0.51	0.610
Creatinine (mg/dL)	0.0440	0.0006	1.74	0.081
Diastolic blood pressure	0.0100	2.06×10^{-5}	1.35	0.019
Urea	0.0001	1.61×10^{-8}	1.71	0.140

CIF: Cumulative incidence function

Table 5. Estimation of CIF of death and other competing events after adjusting for the effect of covariates

Time (years)	Parametric regression		
	CIF_{Death}	CIF_{Other}	S(t)
1	0.083 (0.064, 0.102)	0.182 (0.162, 0.202)	0.735
2	0.135 (0.105, 0.165)	0.287 (0.254, 0.320)	0.578
3	0.167 (0.132, 0.202)	0.350 (0.308, 0.392)	0.483
4	0.185 (0.147, 0.223)	0.389 (0.343, 0.436)	0.426
5	0.195 (0.155, 0.235)	0.414 (0.366, 0.462)	0.391
6	0.201 (0.159, 0.243)	0.430 (0.381, 0.479)	0.369
7	0.204 (0.161, 0.247)	0.441 (0.391, 0.491)	0.355
8	0.205 (0.162, 0.248)	0.448 (0.398, 0.498)	0.347
9	0.206 (0.163, 0.249)	0.452 (0.402, 0.502)	0.342
10	0.207 (0.163, 0.251)	0.455 (0.405, 0.505)	0.338
11	0.207 (0.163, 0.251)	0.457 (0.407, 0.507)	0.336
12	0.207 (0.163, 0.251)	0.459 (0.409, 0.509)	0.334
13	0.207 (0.163, 0.251)	0.459 (0.409, 0.509)	0.334

CIF: Cumulative incidence function

In addition, age had a significant effect on survival in Korea and Australia studies as the same result was obtained in the present study (6, 7). Clinical characteristics such as diabetes mellitus, serum albumin level, creatinine level, diastolic blood pressure, and urea level had a significant effect on survival, the same results was obtained in Australia, Korea, and USA (6, 8, 9).

Studies using competing risks, especially in estimating CIF in peritoneal dialysis patient are rarely found all over the world. However, using a variety of techniques in estimating CIF is abundant witch used nonparametric and semi-parametric methods, but parametric methods are rare. However, for example, Jeong and Fine in their study in 2006 used direct parametric approach in breast cancer data and consider loco-regional recurrences and death as competing events and found it works as well as nonparametric method and cause-specific hazard approach (4). Furthermore in another study in 2007, after adjustment of covariates in a parametric regression stated that parametric method for CI is an appropriate alternative to semi-parametric analysis (5).

In this study, we used the competing risks method in calculating survival and its recommended to use competing risks instead of conventional methods in survival analysis when we have competing events. The typical survival analysis rely on occurring one event and other events are considered as censored, but competing risks use more information of patients and only for those patients who there is not any information after a certain period they fall into the category of censorship. Thus, a more accurate estimate about the patients is presented.

It should be noted that the study's data were collected by review of medical records of patients as a result; there are variables beyond the control of researchers.

Conclusion

In this study age, diabetes mellitus, albumin, creatinine, diastolic blood pressure, urea had an effect on death CIF and age, creatinine, diastolic blood pressure had an effect on other competing events CIF, so these variables had an effect on patients survival. Patient's survival rate was approximately 33% which is a low survival.

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