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Competing Risk Analyses of Patients with End-Stage Renal Disease

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Abstract

Introduction: Chronic kidney disease (CKD) is an important health problem that gradually leads to end-stage renal disease (ESRD). In ESRD patients, death due to other diseases or some events, such as renal transplantation (known as competing risks), would change the probability of observing the event of interest. The aim of this study was to estimate the survival of ESRD patients using competing risk analyses.

Methods: In this retrospective longitudinal study, 307 ESRD patients who were older than 20 were recruited from the dialysis and kidney transplant Centers in Kerman City, Iran, from2007 to 2011. To assess the impacts of the investigated factors on the outcome, a cause-specific hazard model and competing risk models were fitted. Also, the cumulative incidence (CI) approach and sensitivity analysis were implemented. All of the analyses were performed using Stata software, V.12.

Results: The results of competing risk models showed that age and type of dialysis were associated with death (hazard ratio (HR)=1.03, $p<0.001$ and HR=1.65, $p=0.011$, respectively). In cause specific hazard model each year increase in age was associated with a 2% increase in the risk of death. Also, the types of dialysis were associated significantly with death (HR=1.93), and the effect of the type of dialysis was estimated as HR=1.51 ($p=0.04$) when we assumed that all patients who had experienced transplantation survived for the longest survival time. For those for whom receiving the transplantation was considered as death, the HR for the type of dialysis as well as the corresponding p-values were 1.82 and 0.001, respectively.

Conclusion: Ignoring the competing risks of death due to ESRD, such as renal transplantation, in estimating the survival of these patients might lead to overestimation of the results.

Keywords: competing risk, end stage renal disease, kidney disease

1. Introduction

Chronic kidney disease (CKD) is a significant health problem throughout the world. This disorder gradually leads to end stage renal disease (ESRD) (1). The ESRD is defined as a glomerular filtration rate (GFR) lower than15 mL/min/1.73 m2 body surface area (2). The incidence and prevalence of ESRD patients have increased dramatically throughout the world during the last few decades, including in Iran (3). Per million people, the incidence and

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prevalence were 137 and 13.82, respectively, in 1997, and those numbers increased to 357 and 63.8, respectively, in 2006 (4). The last disability-adjusted life year (DALY) for ESRD in Iran in 2008was estimated to be 21500 years (5).The survival of the ESRD patients is lower than that of the general population (6). Globally, mortality rates for patients with ESRD are the lowest in Europe and Japan, but they are very high in developing countries because of the limited availability of dialysis. In the United States, the 5-year survival rate of patients who are on dialysis is approximately 30–35% (7). In ESRD patients, some factors compete in ESRD-related death, particularly renal transplantation and other diseases, such as diabetes mellitus and hypertension. In the case of competing risk data, using non-informative or independence assumption, when focusing on a cause-specific hazard model for event type A, competing risks other than A in addition to those patients who their follow up were lost would be considered as censored. Treating the events of the competing causes as censored observations will lead to a bias in the Kaplan–Meier estimate (8-10). Also competing risks refer to situations in which different types of events might occur. For example, subjects in the study might experience ESRD-related deaths or deaths due to other reasons. When a person experiences an event other than that of interest in the study, the probability of experiencing the event of interest is altered. Moreover, receiving a specified treatment (such as hemodialysis) change the probability of observing the event of interest (11, 12). The Kaplan–Meier method is the most common technique used to estimate survival rates. This method considers all patients who do not experience the event of interest to be censored, and it assumes that the censoring is non-informative or independent. This means that the probability of being censored for any subject at time t does not depend on that subject's prognosis (13). Understanding the survival estimates of these patients can be a signal of the ESRD-associated factors, because it has been proven that the rate of death and progression to ESRD can be reduced by controlling its associated factors (5). The aim of this study was to demonstrate the practicality of competing risk models and to estimate the survival of ESRD patients using competing risk analysis and to compare its results with other commonly-used approaches.

2. Material and Methods

We performed a retrospective, longitudinal study among all ESRD patients older than 20 who were registered from 2007 to 2011 in the dialysis or kidney transplant Centers in Kerman City (capital of the largest province in southeast Iran). The time of entry for each patient was when renal replacement therapy was initiated, such as dialysis or kidney transplant. Patients who died within three months of beginning dialysis were excluded from the study. The data that were collected included information about the cause of ESRD, demographic characteristics, and the details of renal replacement therapy. The event of interest was death, and transplantation was considered to be a competing risk. Gender, age, type of dialysis (hemodialysis and peritoneal dialysis) and blood group were considered to be independent variables. We used two different models to fit the data. In the first model, we analyzed data with the competing risk approach as explained by Fine and Gray (14). They proposed the direct use of a regression model on a cumulative incidence function. The second model that was used to fit the data was a specific hazard model. Death was considered as the main outcome, and all patients experienced other events that were considered as censored, including renal transplantation. We used a sensitivity analysis to evaluate how biased the results could become if the independent assumption were not satisfied. To ensure that we used the two worse scenarios, first, all subjects who underwent transplantation were considered to be dead, and, in the other situation, we assumed that the subjects who underwent transplantation would survive as long as the longest survival time that was observed. Then, we implemented cumulative incidence (CI) approach. This approach can be defined as complementary to Kaplan-Meier (KM), and it measures the probability of failure by time t. In the case of no competing risk, CI=1-KM. However, when competing risks exist, CI is obtained from a cause-specific hazard function that does not rely on independence assumption. To do so, for each event type (shown by c), first, we divided the number of events by the number of subjects at risk to get the hazard rate: tj, hc(tj)= mcj/ nj (where: tj = the j-th time, mcj = number of events, and nj = number of subjects at risk at the j-th time). However, to be able to experience the event at time tj, the subject must at least survive up to time tj-1. This probability is measured by S(tj-1), where S denotes the overall survival. This indicates that the probability of experiencing event type C at time tj is IC (tj) equals S(tj-1) multiply by h(tj). Then, the cumulative incidence is simply the cumulative sum of incidences (15).The two models were fitted in conjunction with the ENTER method, and the significance level was set at 0.05. All analyses were performed using Stata software, V.12.

3. Results

3.1. Characteristics of patients

We collected information of 307 ESRD patients with the mean age of 57.11±16.3. The patients were 61.6% male, and their mean (SD) age was 57.1 (16.3). Nearly 67% and 33% of the patients received hemodialysis and peritoneal dialysis, respectively. The most common blood type was type O. Among the total of 307 patients, 107 deaths

(34.9%) were recorded. In addition, 34 patients (11.1%) received transplantation. In this study, the median of follow-up was 24 months (range: 3-255) (Table 1). The results showed that the mean ± SD of time to event was 30.74 ± 33.1 months.

Table1. Characteristics of patients

Variable		n	%
Status	Death	107	34.9
	Transplantation	34	11.1
	Censored	166	54.1
Blood group	O	127	42.5
	A	87	29.1
	B	67	22.4
	AB	18	6.0
Gender	Male	189	61.6
	Female	118	38.4
Type of dialysis	Hemodialysis	202	65.8
	Peritoneal Dialysis	105	34.2

3.2. Comparison of different regression models

Statistical analysis based on the competing risk model showed that age and type of dialysis were significantly associated with death (hazard ratio (HR)=1.03, p<0.001 and HR=1.65, p=0.011, respectively). Each year increase in age was associated with a 3% increase in hazard of death. In addition, those who received peritoneal dialysis were 65% more likely to die than those received hemodialysis (p=0.01). Neither gender nor blood group had a significant effect (Table 2). The other model, i.e., the cause-specific hazard model, which considered death as an event, showed that age and the type of dialysis were associated significantly with mortality. Each year increase in age was associated with a 2% increase in the risk of death. In addition, those who received peritoneal therapy were 93% more likely to die than those who received hemodialysis (HR=1.93), but gender and blood group did not have as significant effect as the competing risk model (Table 2). Also, Table 3 shows that the probability of death among the 307 subjects in the third year was 0.39, and it increased to 0.5 (50%) in the fifth year.

Table 2. Comparison of different regression models based on significant variables

Model	Variable		HR	CI 95% for HR	p-value
Competing risk	Age		1.03	(1.02-1.04)	<0.001
	Gender (Female to male)		0.88	(0.61-1.27)	0.50
	Type of dialysis	Hemodialysis (Reference)	1	1	1
		Peritoneal Dialysis	1.65	(1.12-2.42)	0.01
	Blood group	O (Reference)	1	1	1
		A	0.9	(0.60-1.35)	0.60
		B	0.7	(0.43-1.15)	0.16
		AB	0.55	(0.20-1.53)	0.25
Cox regression (Event=Death)	Age		1.02	(1.01-1.03)	<0.001
	Gender (Female versus male)		0.87	(0.59-1.30)	0.51
	Type of dialysis	Hemodialysis (Reference)	1	1	1
		Peritoneal Dialysis	1.93	(1.26-2.96)	0.003
	Blood group	O (Reference)	1	1	1
		A	0.87	(0.55-1.36)	0.53
		B	0.78	(0.46-1.32)	0.35
		AB	0.79	(0.28-2.21)	0.6

3.3. Sensitivity analysis

In the sensitivity analysis, we assumed that all patients who had experienced transplantation survived as long as the longest survival time. In this scenario, the effect of type of dialysis was estimated as HR=1.51 (p=0.04).In the other

scenario, patients who received transplantation were considered to be dead. HR for the type of dialysis and the corresponding p-value were 1.82 and 0.001, respectively. Since the p-value of this variable in the cause-specific hazard model lies between these two p-values, if the independence assumption did not hold, the effect of the type of dialysis was the same as the cause-specific hazard model (Table 4).

Table 3. Probability of death as estimated based on CI

Time (Month)	Number of patients at risk	Cumulative Incidence
0	307	0
12	287	0.11
24	166	0.25
36	82	0.39
48	53	0.44
60	28	0.50
72	21	0.54
108	13	0.57
252	1	0.64

Table4. Results of sensitivity analysis

Sensitivity Analysis	Variable		HR	CI 95% for HR	p-value
Those who received transplantation were considered as censored at the end of study	Age		1.03	(1.02-1.04)	<0.001
	Gender	Male (Reference)	1	1	1
		Female	0.88	(0.60-1.32)	0.56
	Type of dialysis	Hemodialysis (Reference)	1	1	1
		Peritoneal Dialysis	1.51	(1.01-2.27)	0.04
	Blood group	O (Reference)	1	1	1
		A	0.92	(0.59-1.44)	0.71
		B	0.67	(0.40-1.13)	0.13
		AB	0.47	(0.17-1.32)	0.15
Those who received transplantation were considered as died at the end of study	Age		1.01	(0.99-1.01)	0.48
	Gender	Male (Reference)	1	1	1
		Female	0.96	(0.68-1.36)	0.83
	Type of dialysis	Hemodialysis (Reference)	1	1	1
		Peritoneal Dialysis	1.82	(1.26-2.63)	0.001
	Blood group	O (Reference)	1	1	1
		A	0.87	(0.58-1.31)	0.51
		B	1	(0.65-1.54)	0.99
		AB	1.35	(0.66-2.77)	0.41

4. Discussion

The results of this study showed that the incidence of death due to ESRD was lower than that estimated when the risk of renal transplantation, as a competing event, was ignored. We also found significant associations between age and type of dialysis with the survival of patients. Based on the findings of the two models, both age and type of dialysis (peritoneal dialysis) exacerbated the death rate. In the second model, only age significantly increased the risk of death. Similar to these results, Roudbari et al. showed that death among the ESRD patients in Zahedan increased with age (6). Some studies similar to ours have been conducted in different parts of Iran. Our findings showed that the women with ESRD had a better survival rate than men, but the difference was not statistically significant. Similarly, Roudbari et al. found no association between gender and death in ESRD patients in southeast Iran (6). Also, according to a study conducted by Mousavi et al. in 2012 showed that, similar to this study, the survival of ESRD patients was not associated with gender (4). It has been proven that renal replacement therapy (RRT) can increase the survival of ESRD patients and that the role of renal transplantation is much more prominent than that of hemodialysis (4-6).

In Iran, the most prevalent type of dialysis offered to ESRD patients in renal replacement therapy (RRT) centers is hemodialysis (16). However, based on the results of our study, the type of dialysis was associated significantly with death, with people who are being treated by peritoneal dialysis having a higher risk of death than patients treated with hemodialysis. One explanation for the poor survival of patients treated with peritoneal dialysis may be higher rates of complications, such as peritonitis (7) and also the higher co-morbidities in such patients. In a study conducted by Vonesh et al., no significant difference in overall mortality was observed between patients treated with peritoneal dialysis and hemodialysis patients. In order to improve the overall model, Vonesh et al. analyzed the results separately for diabetic and non-diabetic patients. They found that the difference in survival of the patients treated with hemodialysis and those treated with peritoneal dialysis was observed only among diabetic patients (17). In our study, since the majority of patients were diabetics (nearly40%), the survival among patients treated with hemodialysis was higher than that among patients treated with peritoneal dialysis patients, i.e., 42 and 26%, respectively. In addition, a Canadian study showed the same results for end-stage renal disease treatment (18).

This study had some limitations. The most important limitation was the lack of information about some variables, such as the reason for the dialysis and the clinical backgrounds of the patients in the study. So, it is suggested that further studies with more complete information be conducted to estimate survival and its associated factors in ESRD patients.

5. Conclusions

The results indicated that ESRD has a significant death rate, which is especially high among older age groups. Also, ignoring competing risks in deaths due to ESRD, such as renal transplantation, in estimating the survival of these patients might lead to overestimation of the results. Therefore, services should be developed that can provide appropriate care and treatment of these patients. It is important to consider that for determining precise survival of these patients and obtaining more accurate interpretation, improved statistical method should be adopted.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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