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Original Article

The Effects of Survival Predictors Before Hemodialysis Initiation is Different in Adults and the Elderly☆

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SUMMARY

Background: The aim of this study is to investigate the effects of the risk markers of sex, education, marital status, nephrology referral, and progression of comorbid conditions before hemodialysis (HD) on the survival of incident HD patients in different age groups.

Methods: A total of 7729 incident HD patients were recruited in this retrospective cohort study in 2006 and followed up to the end of 2007. Patients were divided according to their age, being classified as Adult (18–64 years), Young Elderly (65–74 years), or Old Elderly ≥ 75 years. The progressive Romano-Charlson Comorbidity Index (CCIp) was used to predict survival outcomes, CCIp = CCI_{-1}–CCI_{-3}, where CCI_{-1} and CCI_{-3} are the CCI scores in the 1st year and 3rd year before HD initiation, respectively. The Cox regression model was used to analyze the associated factors of survival.

Results: Male patients were found to have a higher risk of mortality than females in each age group. Education ≤ 6 years was an independent risk marker for mortality in the Adult group. The effect of marital status and early nephrology referral on survival was more significant in the elderly groups. The CCIp and CCI_{-3} ≥ 3 were independent risk markers for mortality in each group. The CCIp was a more valuable predictor of survival in adults than in elderly HD patients.

Conclusion: The effects of sex, education, marital status, early nephrology referral, and severity of CCI_{-3} and CCIp before HD initiation on patient survival vary in different age groups.

1. Introduction

Race, sex, and education have previously been reported to be associated with mortality in patients initiating hemodialysis (HD)[1–6], in addition to these factors, the effects of early nephrology referral and the Romano-Charlson Comorbidity Index (CCI, which is based on the International Classification of Diseases, 9th revision, Clinical Modification codes, has been widely used in the analyses of the impact of comorbidities on mortality)[7] on survival in elderly incident patients were also reported[8–11]. The progressive CCI (CCIp) was found to be a valuable predictor of survival in incident patients[12].

In the Dialysis Outcomes and Practice Patterns Study, older HD patients are less able to tolerate the initial impact of starting HD and thus have relatively higher early mortality than HD patients aged < 65 years. Even the decline in mortality during the first 180 days was substantially greater among patients aged > 65 years (53%) than in young patients (~35%)[13]. The effects of sex on survival in incident HD patients also vary in different age groups[14]. The survival advantage for black dialysis patients applied only to older adults[15]. These observations may be limited, nevertheless these facts suggest that the effect of predictive factors may differ across different age categories. Therefore, this study aims to investigate the effect of the above variables including CCIp before HD initiation on the survival of adults and elderly incident patients in Taiwan.

2. Materials and methods

2.1. Health care system and data source

The Taiwan National Health Insurance (NHI) program began on March 1, 1995. All medical institutions were obliged to submit

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standard claims documents for medical expenses on a computerized form that listed the outpatient clinic, the admission and discharge dates, the patient's identification number, sex, date of birth, and the admission diagnosis codes taken from the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM).

By the end of 2008, the Taiwan NHI program had covered 23 million enrollees, accounting for 99% of the population[16]. The claims data released by the NHI Bureau were scrambled, and permitted to be analyzed at the office of Ministry of Health and Welfare (MHW). Only the final statistical results can be carried out from the office of MHW after inspection by the staffs to reach the Act of Safety of Personal Information.

2.2. Study population and datasets

The current study recruited 7729 incident patients older than 18 years who were receiving HD (procedure codes 58001C, 58019C–58025C) for at least 3 months between January 1, 2006 and December 31, 2006. Patients who were transplanted or switched to peritoneal dialysis after starting HD were defined as the censor. An encrypted unique identification number was utilized to link information of the same patient to the database of death certificates and national household registration, managed by the MHW, to identify the date of a patient's death, education, and marital status. Patients aged 18–64 years were classified as the Adult group, < 65 years old; those aged 65–74 years, as the Young Elderly group; and those aged ≥ 75 years, as the Old Elderly group.

2.3. Dependent variables

One-year survival days were defined as the time from HD initiation to death during the 1st year of dialysis; those still alive at the end of the 1st year were defined as censored. Two-year survival days were defined as the time from HD initiation to death during 2 years of dialysis. Patients who died after December 31, 2007, were censored.

2.4. Independent variables

The patients' demographic and clinical information identified from the claims data included sex, education, marital status, referral to a nephrologists (early or late, patients who had been under a nephrologist's care for at least 4 months before HD initiation were defined as early referral[17].), CCI score and CCIp scores [1st year CCI before HD initiation (CCI_{-1}) minus 3rd year CCI before HD initiation (CCI_{-3})].

Of the various methods available[18,19], the CCI was developed according to the ICD-9-CM codes in the claims data and has been widely used to analyze the impact of comorbidities on mortality[20]. The ICD-9-CM codes had to be recorded at least twice to be defined as comorbidity. Each comorbid condition was assigned a score of 1, 2, 3, or 6, depending on the risk of death that is associated with the particular condition. The scores were then summed to yield a total score for predicting mortality. Higher CCI scores indicated more comorbidity or a greater risk of dying[7,19].

2.5. Statistical analysis

The SAS 9.1.3 statistical software for Windows (SAS Institute Inc., Cary, NC, USA) was used for data management and analysis. Basic descriptive analysis for continuous variables (mean ± standard deviation) and for categorical variables (frequencies and percentages) was utilized to characterize patients by age. Associations between variables and age groups were examined using the Chi-square test and Student t test. Two-tailed $p < 0.05$ was considered statistically significant. Cox regression was used to assess the influence of sex, education, marital status, early referral to nephrologists, CCI_{-3} and CCIp on 2-year survival.

3. Results

3.1. Basic characteristics

Of the 7729 incident patients, 3942 were in the Adult group, 2116 in the Young Elderly group and 1671 in the Old Elderly group. 1014 (13.1%) and 1465 (19.0%) died in the 1st year and 2nd year, respectively. A total of 7.5% and 11.2% of patients in the Adult group, 15.0% and 22% in the Young Elderly group, and 23.9% and 33.5% in the Old Elderly group died in the 1st year and 2nd year, respectively (Table 1).

The number of females in each age group was larger than that of males. There were more patients with an education of > 9 years and married in the Adult group than in the Young Elderly and Old Elderly groups. The proportion of patients with early referral was 31.9% in the Adult group, 34.8% in the Young Elderly and 30.6% in the Old Elderly groups.

Congestive heart failure, cerebrovascular disease, chronic pulmonary disease, peptic ulcer, and diabetes were the five most common comorbidities in the incident patients. The number of patients with CCI ≥ 3 and the prevalence of the five most common comorbidities were found to increase with time before HD initiation in each group (Table 2). The prevalence of the five most common comorbidities, except for diabetes, was highest in the Old Elderly group and lowest in the Adult group in the first 3 years before the initiation of HD (Table 2). There were significantly more patients with CCI ≥ 3 at the 3rd year, 2nd year, and 1st year before HD initiation in the Young Elderly and Old Elderly groups ($p < 0.0001$; Table 2). The CCIp in both the Young Elderly and Old Elderly Groups were significantly higher than that in the < 65 year-old Adult group ($p < 0.0001$; Table 2).

3.2. 1- and 2-year mean survival time in different age groups

The overall 1- and 2-year mean survival time were 345.2 ± 0.7 days and 643.0 ± 2.1 days respectively, in incident patients. The 1- and 2-year survival in the Adult group patients (354.3 ± 0.7 days and 679.7 ± 2.3 days) were longer than that in the Young Elderly group (341.8 ± 1.4 days and 629.2 ± 4.27 days) and Old Elderly group (327.9 ± 1.9 days versus 573.6 ± 5.6 days; Table 1 and Fig. 1).

Patients with an education of > 9 years in the Adult group showed significantly longer 1- and 2-year survival than those in the Young Elderly and Old Elderly groups ($p = 0.001$ and $p = 0.0001$). Divorced/separated patient in the Old Elderly group had significantly shorter 1- and 2-year survival than those in the Adult and Young Elderly groups ($p = 0.004$ and $p = 0.0001$). However, the early referral effect on survival in the Old Elderly group was significantly better than that in the Adult and Young Elderly groups (Table 1).

3.3. Significant risk markers associated with 2-year survival

The sex effect on survival was not found in the Old Elderly group under univariate analysis. When all the personal variables (sex, education, marital status, timing of referral, and CCI) were used for multivariate analysis, male patients showed a higher risk of mortality than females in each group. Education ≤ 6 years was an independent risk marker for survival in the Adult group, but not in the Young Elderly and Old Elderly groups. The marital status effect

Table 1
Basic characteristics and mean survival time within 1 and 2 years of incident patients among different age groups.

	Adults <65 years old ($N = 3942$)					Young Elderly ($N = 2116$)					Old Elderly ($N = 1671$)				
	%	Survival time (d) (mean ± SE)		p		%	Survival time (d) (mean ± SE)		p		%	Survival time (d) (mean ± SE)		p	
		1 y	2 y	1 y	2 y		1 y	2 y	1 y	2 y		1 y	2 y	1 y	2 y
Total	100					100					100				
Sex				0.015	0.001				0.030	0.088				0.992	0.691
Male	44.1	352.8 ± 1.0	673.2 ± 3.3			43.4	339.5 ± 2.1	620.4 ± 6.7			48.2	325 ± 2.8	560 ± 8.2		
Female	55.9	356.2 ± 0.9	687.9 ± 3.2			56.6	343.6 ± 1.8	635.9 ± 5.5			51.8	330.5 ± 2.5	577.1 ± 7.6		
Education				0.001	0.000				0.701	0.192				0.922	0.810
≤ 6 y	44.1	352.6 ± 1.1	667.5 ± 3.8			43.4	341.3 ± 1.5	626.2 ± 4.8			73.1	328.3 ± 2.2	572.3 ± 6.5		
7–9 y	20.8	355.2 ± 1.5	684.5 ± 4.9			56.6	344.9 ± 4.6	651.2 ± 14.4			10.1	328.5 ± 6.1	576.3 ± 17.5		
> 9 y	35.2	355.9 ± 1.1	692.4 ± 3.5			12.7	343.0 ± 3.7	635.1 ± 11.7			16.8	325.4 ± 4.8	578.1 ± 13.9		
Marital status				0.044	0.284				0.869	0.589				0.004	0.000
Married	71.8	355.0 ± 0.8	681.5 ± 2.7			67.6	341.4 ± 1.7	629.5 ± 5.2			48.5	333.1 ± 2.5	593.1 ± 7.7		
Single	12.2	353.7 ± 2.0	682.6 ± 6.6			2.3	345.9 ± 8.3	651.8 ± 26.0			3.6	322.9 ± 9.3	511.6 ± 28.0		
Divorced/separated	8.2	353.3 ± 2.5	674.0 ± 8.5			2.6	341.0 ± 9.4	649.2 ± 25.6			1.6	313.7 ± 16.2	455.6 ± 39.3		
Widowed	7.8	350.3 ± 2.9	665.0 ± 9.5			27.5	342.5 ± 2.5	626.4 ± 8.1			46.3	323.2 ± 2.9	560.3 ± 8.5		
Early referral				0.392	0.520				0.126	0.007				0.002	0.001
Yes	31.9	354.9 ± 1.2	681.0 ± 4.3			34.8	344.9 ± 2.1	645.1 ± 7.0			30.6	336.2 ± 3.0	605.2 ± 9.7		
No	68.1	354.0 ± 0.8	678.6 ± 2.8			65.2	340.2 ± 1.7	621.7 ± 5.4			69.4	324.2 ± 2.3	561.1 ± 6.8		
Death during study period, *n* (%)		297(7.5)	440(11.2)				318(15.0)	465(22.0)				399(23.9)	560(33.5)		

Old Elderly = >75 years old; SE = standard error; Young Elderly = 65–74 years old.

on survival was more significant in the Old Elderly group. Early referral of patients in the Young Elderly group (HR 0.75; 95% CI: 0.61–0.92; $p = 0.0066$) and the Old Elderly group (HR 0.72; 95% CI: 0.59–0.88; $p = 0.0011$) demonstrated a lower risk of mortality. CCIp and $CCI_{-3} \geq 3$ were independent risk markers for survival in each group ($p < 0.005$; Table 3). For each increase in CCIp, the HR was 2.30 (95% CI: 1.89–2.8; $p < 0.0001$) in the Adult group, 1.71 (95% CI: 1.42–2.05; $p < 0.0001$) in the Young Elderly group and 1.23 (95% CI: 1.03–1.47; $p = 0.0215$) in the Old Elderly group.

4. Discussion

The 1- and 2-year survival times in the Adult groups are longer than in the Elderly groups. The effects of sex and education on survival in adult incident HD patients were more significant than in Elderly groups. Early referral is more important for Elderly groups than Adult groups. Although the score of CCI before HD initiation and CCI progressive score in the Adult group was less than in the Elderly groups, the effects of the score of CCI before HD initiation

Table 2
Five comorbid conditions and Romano-Charlson Comorbidity Index (CCI) score in incident patients.

	Total ($N = 7729$)		Adult <65 years old ($N = 3942$)		Young Elderly (65–74 years old) ($N = 2116$)		Old Elderly >75 years old ($N = 1671$)		p
	n	%	*n*	%	*n*	%	*n*	%	
1st y before HD start									
CHF	2472	32.0	1066	27.0	797	37.7	609	36.4	<0.0001
CVD	1827	23.6	691	17.5	603	28.5	533	31.9	<0.0001
COPD	2115	27.4	812	20.6	639	30.2	664	39.7	<0.0001
Peptic ulcer	2726	35.3	1190	30.2	818	49.0	718	43.0	<0.0001
Diabetes	4682	60.6	2379	60.4	1414	66.8	889	53.2	<0.0001
2nd y before HD start									
CHF	1381	17.9	520	13.2	477	22.5	384	23.0	<0.0001
CVD	1444	18.7	542	13.7	484	22.9	418	25.0	<0.0001
COPD	1505	19.5	531	13.5	486	23.0	488	29.2	<0.0001
Peptic ulcer	2042	26.4	847	21.5	630	29.8	565	33.8	<0.0001
Diabetes	4373	56.6	2236	56.7	1323	62.5	814	48.7	<0.0001
3rd y before HD start									
CHF	771	10.0	270	6.8	272	12.9	229	13.7	<0.0001
CVD	1036	13.4	382	9.7	349	16.5	305	18.3	<0.0001
COPD	939	12.1	316	8.0	300	14.2	323	19.3	<0.0001
Peptic ulcer	1339	17.3	523	13.3	435	20.6	381	22.8	<0.0001
Diabetes	3956	51.2	1997	50.7	1231	58.2	718	43.0	<0.0001
CCI ≥ 3 before HD initiation									
1st y	4368	56.5	1993	50.6	1350	63.8	1025	61.3	<0.0001
2nd y	3222	41.7	1432	36.3	1024	48.4	766	45.8	<0.0001
3rd y	2070	26.8	870	22.1	708	33.5	492	29.4	<0.0001
CCI progressive score	7729	(1.3 ± 1.4)	3942	(1.2 ± 1.4)	2116	(1.4 ± 1.5)	1671	(1.5 ± 1.5)	<0.0001

The values in brackets are mean ± SD.
CCI progressive scores = 1st year CCI before HD initiation minus 3rd year CCI before HD initiation; CHF = congestive heart failure; COPD = chronic pulmonary disease; CVD = cerebrovascular disease; HD = hemodialysis.

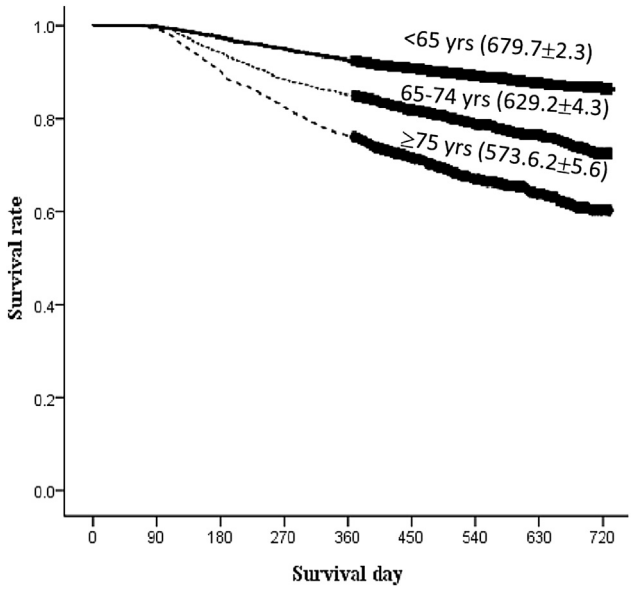

Fig. 1. Kaplan-Meier curves for the 2-year survival in incident patients. The survival time (mean ± SE) of patients ≥ 75 years old was shorter than that of patients 65–74 years old and < 65 years old.

and CCI progressive score on survival were all important in each group, especially the Adult group. These findings show that age-stratified analysis is necessary for the investigation of survival in dialysis patients.

The reason there was more females than males in both the Young Elderly and Old Elderly groups might be that pre-end stage renal disease (ESRD) males tend to advance to renal replacement therapy, all-cause mortality of males in a more rapid pace than females due to the negative effect of testosterone[21,22], and the typically poor adherence to treatment recommendations which are associated with poor clinical outcome[22]. The effect of marital status on survival being more significant in the Old Elderly group might be related to better adherence to treatment recommendations when a partner is present[23].

In this study, the beneficial effect of early referral in both the Young Elderly and Old Elderly groups when compared with the Adult group supports previously reported findings[8,24], indicating that timely referral is important to improve future survival prospects of dialysis patients. It also implies that educating primary care physicians on the appropriate referral of chronic kidney disease patients, especially elderly patients, to a nephrologist is warranted. The lower prevalence of diabetes in the Old Elderly group (Table 1) might be due to their frailty and shorter life expectancy than nondiabetic people[25,26]. More diabetic patients died before 75 years of age than nondiabetic patients.

To our knowledge, this is the first study that uses a national HD dataset to compare the effect of CCI_{-3} and CCIp on survival in adult and elderly incident HD patients. This study showed that the comorbid conditions in most pre-ESRD patients were progressive before the time of HD initiation (Table 2). The increase in mortality of each increase in CCIp was higher in the Adult group (HR 2.30) than in either the Young Elderly (HR 1.71) or Old Elderly groups (HR 1.23), indicating that CCIp is more valuable as a predictor of survival in future adult dialysis patients than in old elderly dialysis patients (Tables 2 and 3).

Several limitations in the current study merit consideration. Firstly, only data from patients who survived the predialysis phase and started hemodialysis treatment were analyzed. Therefore, conclusions may not apply to the entire predialysis patient population with regard to progression to ESRD or mortality. Secondly, the diagnosis of the various comorbidities was based on claims data and ICD-9-CM codes, which may be associated with potential misclassification bias. Information on medical care, which may affect changes in survival, was not available in this study; as in all studies using administrative data sets, the key comorbid conditions contributing to additional prognostic information over and above that provided by laboratory and clinical parameters were reported[27]. Nevertheless, the current study has several strengths. Firstly, claims data from universal coverage in Taiwan allowed identification of a sample population free from selection bias and of sufficient size to document outcomes. Secondly, insurance records can be used to accurately and unambiguously analyze referral times, comorbid conditions, and survival. These records are obtained from a large collection of billing claims to the NHI and national database of death certificates and national household registration rather than data provided by nephrologists or dialysis facility staff in medical reports, which have not been validated and may be subject to recall bias.

In conclusion, the effects of sex, education, marital status, referral time to nephrologists, severity of CCI_{-3} and CCIp on the survival of adult and elderly incident HD patients were different. Nephrologists are advised to focus on the negative associations with male sex, low education, CCIp, and survival in adult incident patients. The beneficial effect of early referral on survival was more significant in patients aged ≥ 65 years compared to those aged < 65 years.

Table 3
Age stratified Cox regression for analyzing risk markers of 2-year survival (n = 7729).

Parameter	Adult <65 years old (n = 3942)				Young Elderly (n = 2116)				Old Elderly (n = 1671)			
	HR				HR				HR			
	Adjusted	95% CI		p	Adjusted	95% CI		p	Adjusted	95% CI		p
Sex (base = female)	1.49	1.21	1.83	0.0002	1.3	1.06	1.59	0.0113	1.18	0.97	1.43	0.1022
Education (base > 9 y)												
7–9 y	1.18	0.89	1.58	0.2517	0.79	0.5	1.26	0.3196	1.07	0.76	1.49	0.7122
≤ 6 y	1.65	1.30	2.09	<0.0001	1.19	0.88	1.60	0.2532	1.10	0.86	1.40	0.4594
Marital status (base = married)												
single	1.17	0.86	1.59	0.3105	0.84	0.41	1.69	0.6153	1.75	1.19	2.58	0.0046
divorced/separated	1.27	0.91	1.77	0.1529	0.79	0.4	1.54	0.4833	2.03	1.18	3.49	0.0105
widowed	1.39	1.00	1.94	0.053	1.12	0.9	1.38	0.3122	1.35	1.11	1.64	0.0023
Early referral (base = late)	0.88	0.71	1.08	0.2257	0.75	0.61	0.92	0.0066	0.72	0.59	0.88	0.0011
Severity of CCI_{-3} (base: CCI < 3)	1.28	1.21	1.35	<0.0001	1.19	1.13	1.25	<0.0001	1.15	1.09	1.21	<0.0001
CCIp	2.30	1.89	2.80	<0.0001	1.71	1.42	2.05	<0.0001	1.23	1.03	1.47	0.0215

CCI = Romano-Charlson Comorbidity Index; CCIp = CCI at 1st y minus CCI at 3rd y before HD initiation; CCI_{-3} = CCI at the 3rd y before HD initiation; HD = hemodialysis; HR = hazard rate; Old Elderly = >75 years old; Young Elderly = 65–74 years old.

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