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Interferon-Based Treatment of Hepatitis C Virus Infection Reduces All-Cause Mortality in Patients With End-Stage Renal Disease

An 8-Year Nationwide Cohort Study in Taiwan

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Abstract: The long-term survival of end-stage renal disease (ESRD) patients with hepatitis C virus (HCV) infection who received interferon treatment has not been extensively evaluated.

The HCV cohort was the ESRD patients with de novo HCV infection from 2004 to 2011; they were classified into treated and untreated groups according to interferon therapy records. Patients aged <20 years and those with a history of hepatitis B, kidney transplantation, or cancer were excluded. The control cohort included ESRD patients without HCV infection matched 4:1 to the HCV cohort by age, sex, and year of ESRD registration. We followed up all study participants until kidney transplantation, death, or the end of 2011, whichever came first. We assessed risk of all-cause mortality by using the multivariate Cox proportional hazard model with time-dependent covariate.

In the HCV cohort, 134 patients (6.01%) received interferon treatment. Compared with the uninfected control cohort, the treated group had a lower risk of death (hazard ratio 0.47, 95% confidence interval [CI] 0.22–0.99). The untreated group had a 2.62-fold higher risk (95% CI 1.24–5.55) of death compared with the treated group. For the HCV cohort without cirrhosis or hepatoma, the risk of death in the treated group was further markedly reduced (hazard ratio 0.17, 95% CI 0.04–0.68) compared with that in the control cohort.

For ESRD patients with HCV infection, receiving interferon treatment is associated with a survival advantage. Such an advantage is more prominent in HCV patients without cirrhosis or hepatoma.

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Abbreviations: CI = confidence interval, ESRD = end-stage renal disease, HCV = hepatitis C virus, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, KT = kidney transplant, NHIRD = National Health Insurance Research Database.

INTRODUCTION

Hepatitis C virus (HCV) infection is a critical comorbidity in patients on maintenance dialysis; its prevalence varies widely from 3% to >50% worldwide.[1,2] Dialysis-dependent patients with hepatitis C infection have impaired quality of life and significantly higher risks of morbidity and mortality.[3–5] Hemodialysis (HD)-dependent patients with active HCV infections were reported to have a higher prevalence of severe malnutrition–inflammation complex syndrome-related metabolic and physiological diseases.[4] Fabrizi et al[5] reported that anti-HCV-positive patients on dialysis had a 32% increased risk of overall mortality in a meta-analysis. Cardiovascular disease is the leading cause of death in patients with end-stage renal disease (ESRD), followed by infection.[6]

HCV infection has been suggested as an emerging risk factor for cardiovascular disease.[7,8] Interferon-based treatment of HCV infection has been reported to reduce the morbidity from cirrhosis,[9] the risk of stroke and ESRD,[10,11] and to improve the cardiovascular and renal outcomes.[12] However, the proportion of HCV-infected patients with ESRD who received interferon-based therapy is very low, <10% in a multicountries collaboration research.[13]

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The effect of antiviral treatment in improving survival of dialysis patients with HCV infection has been rarely discussed. Goodkin et al[13] reported that treated HCV patients with ESRD had a 53% lower risk of mortality than untreated HCV patients with ESRD; however, the data were statistically nonsignificant, probably because of the limited number of study cases. Under the setting of National Health Insurance (NHI) program in Taiwan, with longer follow-up durations and comprehensive variable adjustments, we investigated whether interferon-based treatment is associated with improved survival in ESRD patients with HCV infection. We hypothesize that HCV-infected dialysis patients receiving interferon-based treatment could reduce all-cause mortality.

MATERIALS AND METHODS

Data Source

The Longitudinal Health Insurance Database for Catastrophic Illness Patients (LHID-CIP) is maintained by National Health Research Institutes (NHRI). Taiwan National Health Insurance Administration (TNHIA) oversees the NHI program, a single-payer nationwide health insurance service, and maintains the National Health Insurance Research Database (NHIRD) for research purposes. TNHIA entrusted the maintenance of NHIRD to NHRI. By the end of 2014, >99.6% of the population of Taiwan was enrolled in the NHI,[14] and the contract rate was >93%.[14] The catastrophic injury/illness registry in Taiwan includes 31 categories of major illnesses (eg, cancer, ESRD, and hemophilia); patients with these catastrophic illnesses can apply for a catastrophic illness certificate and are exempted from copayment, thus avoiding financial hardship.[15] These applications are reviewed by specialist physicians. LHID-CIP includes detailed claims data of all patients with catastrophic illness in the NHIRD from 1997 to 2011. To ensure patient privacy, the identification number of the insurant is recoded by the TNHIA. This study was approved by the institutional review board of China Medical University Hospital, Taiwan. Diseases were identified based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study Participants

Figure 1 presents the study flow chart. We identified ESRD (ICD-9-CM 585) patients from the LHID-CIP between 1997 and 2011. ESRD patients with de novo HCV infection (first time ICD-9-CM 070.41, 070.44, 070.51, 070.54, and V02.62) between 2004 and 2011 were selected as the HCV cohort. The HCV patients <20 years and those with hepatitis B virus infection (ICD-9-CM 070.20, 070.22, 070.30, 070.32, and V02.61), cancer (ICD-9-CM 140–208), or a kidney transplant (KT) before the date of HCV diagnosis were excluded. The date of HCV diagnosis was recorded as the index date. The HCV cohort was further classified into 2 groups according to the interferon treatment records from the NHIRD: treated and untreated groups. ESRD patients without HCV, hepatitis B virus, cancer, or KT history were defined as uninfected ESRD patients. Next, the control cohort was selected through 4:1 matching of the HCV cohort by age (at 5-year stratification), sex, and year of ESRD registration. The index dates for the control cohort were assigned as the date of HCV diagnosis of their matched HCV counterparts.

Endpoint and Risk Factors

The primary endpoint in this study was all-cause mortality. All study participants were followed-up from the index date until the date of KT, death, or the end of 2011, whichever came first. Potential risk factors included the urbanization level of the residence area, renal replacement therapy (RRT) modality, and medical history. The urbanization level was modified based on the report by Liu et al,[16] and the urbanization level of all residence areas was classified into 4 levels, with level 1 representing the most urbanized areas and level 4 representing the least. RRT modality included HD and peritoneal dialysis (PD). Medical history included hypertension (HTN; ICD-9-CM 401–405), hyperlipidemia (HL; ICD-9-CM 272), diabetes mellitus (DM; ICD-9-CM 250), ischemic heart disease (IHD; ICD-9-CM 410–414), peripheral arterial disease (PAD; ICD-9-CM 440.2, 440.3, 440.8, 440.9, 443, 444.22, 444.8, 447.8, and 447.9), obesity (ICD-9-CM 278), cerebrovascular accident (CVA; ICD-9-CM 430–438), congestive heart failure (CHF; ICD-9-CM 398.91, 402.X1, 404.X1, 404.X3, 425, and 428),

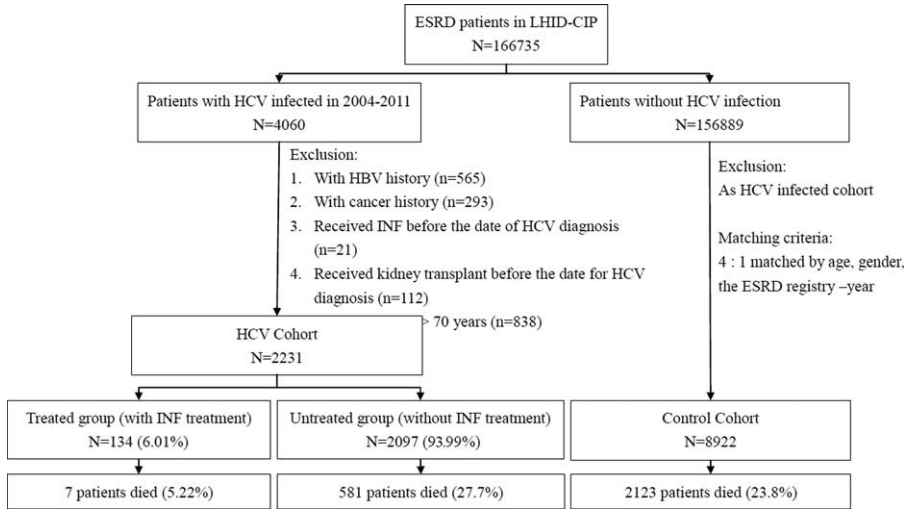

FIGURE 1. Flow chat for study subjects.

chronic pulmonary disease (COPD, ICD-9-CM 490, 491, 495, and 496), and sepsis (ICD-9-CM 038).

Statistical Analyses

The differences in categorical and continuous variables between the HCV and control cohorts were compared using the χ^2 test and *t* test, respectively. Mortality (per 1000 person-years) was calculated for the control and HCV cohorts. For HCV patients, we also compared the risk of death between the untreated and treated groups. Because the duration between the date of HCV diagnosis and treatment changed over time, we used the Cox proportional hazard regression model with time-dependent covariates to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) for death. A multivariate model was used to control the variables, which significantly differed in the crude Cox proportional hazard regression model. We further analyzed the risk of death for each HCV status and compared it with that of the control cohort stratified by follow-up durations ($\leq$3 and >3 years). Because of a close association between the severity of liver disease and all-cause mortality, we also evaluated the risk of death under different severities of liver diseases through the multivariate Cox proportional hazard regression models with time-dependent covariates. The severity of liver disease was classified based on the presence of liver cirrhosis (ICD-9-CM 571.5) with or without liver cancer (ICD-9-CM 155.0) before the endpoint. Survival rates were plotted using Kaplan–Meier analyses, and the differences among the 3 groups were compared using the log-rank test. All analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC), and all statistical significance were set at 2-sided $P < 0.05$.

RESULT

The HCV cohort included 2231 patients, and the control cohort included 8922 matched patients. In the HCV cohort, 134 patients received interferon treatment (6.01%, the treated group), and 2097 patients did not receive interferon treatment (93.99%, the untreated group). The number of men and women in the HCV cohort was almost equal; however, more men received interferon treatment than women (62.7% vs 48.6%, Table 1). The median duration between the date of HCV diagnosis and treatment in the treated group was 491 days (interquartile range 686). The mean age of patients in the HCV cohort was 55.5 years (standard deviation 9.69). Compared with the control cohort, the HCV cohort was more likely to reside in rural areas and receive HD treatment. Compared with the control cohort, the HCV cohort had a higher prevalence of DM (40.7% vs 37.3%), IHD (46.4% vs 43.9%), and sepsis (7.80% vs 6.41%) but a lower prevalence of HL (40.4% vs 43.4%).

During the study period, 2123 and 588 patients died in the control and HCV cohorts, respectively. HCV patients had 1.10-fold higher mortality than non-HCV patients in the multivariate model (95% CI 1.00–1.20, Table 2). Men had higher mortality (85.19 vs 66.88 per 1000 person-years) and a 1.30-fold risk of mortality compared with women (95% CI 1.21–1.41). The risk of death increased with age. ESRD patients with DM, obesity, CVA, CHF, and sepsis had a 1.80-, 1.54-, 1.43-, 1.28-, and 2.10-fold risk of death, respectively (95% CI 1.65–1.97, 1.08–2.19, 1.32–1.56, 1.18–1.39, and 1.88–2.35, respectively); however, patients with HL had a lower risk of death (HR 0.84, 95% CI 0.77–0.91).

During a mean follow-up duration of 3.22 years, the lowest mortality was observed in the treated group (26.75 per 1000 person-years), followed by the control cohort and the untreated group (72.84 and 89.29 per 1000 person-years, respectively, Table 3). After an 8-year follow-up, the survival rates in the treated group and the control cohort were ~23.20% and 4.12% higher than those in the untreated group (Figure 2, log-rank test $P < 0.0001$). In the multivariate Cox proportional hazard regression model with time-dependent covariates, the treated group had a lower risk (HR 0.47, 95% CI 0.22–0.99), whereas the untreated group had a higher risk (HR 1.14, 95% CI 1.04–1.25) than the control cohort. In the HCV cohort, the untreated group had a 2.62-fold risk of death compared with the treated group (95% CI 1.24–5.55).

Compared with the control cohort, the treated group had a lower risk of death regardless of the follow-up duration; however, a significant difference was observed only in the follow-up duration of <3 years (HR 0.34, 95% CI 0.15–0.76) (Table 3). For HCV patients, the untreated group had a 3.78-fold higher risk than the treated group (Table 3) within the follow-up duration of 3 years. For HCV patients without cirrhosis and liver cancer, the treated group had a significantly lower risk of death (HR 0.17, 95% CI 0.04–0.68) compared with the control cohort (Table 4), and the untreated group had a 6.31-fold risk of death (95% CI 1.57–25.4) compared with the treated group. For HCV patients with liver cirrhosis and liver cancer, no significant differences were observed in the risk of death for those with and without interferon treatment.

DISCUSSION

Principal Findings

An extremely low proportion (6.01%) of dialysis patients with HCV infection received antiviral treatment. The survival rates were comparable in patients on HD and PD. Interferon-based treatment was associated with a 53% lower risk of all-cause mortality in dialysis patients with HCV infection compared with the control cohort. The untreated group had a 2.62-fold risk of mortality compared with the treated group. During the mean follow-up duration of 3.22 years, the lower risk of death was more prominent in the treated group (66% reduction compared with uninfected control cohort, 3.78-fold lower than the untreated group) in the 3-year follow-up. Regarding the severity of liver disease, the survival advantages of the treated group were present mainly in HCV patients without cirrhosis and/or hepatoma (83% risk reduction compared with the uninfected control cohort, 6.31-fold lower than the untreated group); no survival advantage was noted in HCV patients with cirrhosis or liver cancer.

Comparison With the Literature

The current study provided a larger cohort (134 patients) with comprehensive adjustments for controlling variables compared with previous report by Goodkin et al.[13] Our data confirmed the lower risk of mortality in the treated group compared with both the uninfected control cohort and the untreated group. Several other studies have reported that an extremely low anti-viral treatment proportion in dialysis patients with HCV infection,[13,17] which is similar to our findings. Our data suggested that in HCV-infected ESRD patients, receiving HD or PD had similar risks of mortality; which is consistent with the report by Bose et al.[18]

Potential Explanations

Because of close associations with abundant extrahepatic manifestations, including carotid atherosclerosis,[19] stroke,[20] diabetes,[21] chronic kidney disease,[22] hypertensive cardiovascular disease,[23] ESRD,[24] and PAD,[7] HCV is suggested as a new risk

TABLE 1. Sociodemographic and Comorbid Characteristics in ESRD Cohorts With Different Hepatitis C Infection Status and Control

	HCV Cohort				HCV Negative				
	Treated, N = 134		Untreated, N = 2097		All Cases, N = 2231		Control Cohorts, N = 8922		*P*
Sex	n	%	n	%	n	%	n	%	0.99
Female	50	37.3	1079	51.5	1129	50.6	4514	50.6	
Male	84	62.7	1018	48.6	1102	49.4	4408	49.4	
Age, y									0.99
20–34	9	6.72	65	3.10	74	3.32	294	3.30	
35–49	46	34.3	452	21.6	498	22.3	1992	22.3	
50–64	70	52.2	1166	55.6	1236	55.4	4944	55.4	
65+	9	6.72	414	19.7	423	19.0	1692	19.0	
Mean (SD)*	51.7	(9.91)	55.9	(9.58)	55.6	(9.65)	55.5	(9.69)	0.72
Follow-up duration, year (SD)*	1.95	(1.83)	3.10	(2.20)	3.11	(2.20)	3.25	(2.21)	0.009
Urbanization									<0.0001
1 (highest)	37	27.6	426	20.3	463	20.8	2488	27.9	
2	43	32.1	669	31.9	712	31.9	2861	32.1	
3	23	17.2	359	17.1	382	17.1	1519	17.0	
4 (lowest)	31	23.1	643	30.7	674	30.2	2054	23.0	
RRT modality									<0.0001
HD	125	93.3	1999	95.3	2124	95.2	8027	90.0	
PD	9	6.72	98	4.67	107	4.80	895	10.0	
Medical history									
HTN	111	82.8	1792	85.5	1903	85.3	7490	84.0	0.12
HL	45	33.6	857	40.9	902	40.4	3833	43.0	0.03
DM	44	32.8	864	41.2	908	40.7	3323	37.3	0.003
IHD	47	35.1	988	47.1	1035	46.4	3915	43.9	0.03
PAD	9	6.72	174	8.30	183	8.20	649	7.27	0.14
Obesity	2	1.49	20	0.95	22	0.99	91	1.02	0.89
CVA	13	9.70	491	23.4	504	22.6	1912	21.4	0.23
CHF	27	20.2	635	30.3	662	29.7	2642	29.6	0.96
COPD	19	14.2	593	28.3	612	27.4	2281	25.6	0.07
Sepsis	3	2.24	171	8.15	174	7.80	572	6.41	0.02

CHF = congestive heart failure, COPD = chronic pulmonary disease, CVA = cerebrovascular accident, DM = diabetes mellitus, ESRD = end-stage renal disease, HCV = hepatitis C virus, HD = hemodialysis, HL = hyperlipidemia, HTN = hypertension, IHD = ischemic heart disease, PD = peritoneal dialysis, PAD = peripheral arterial disease.

Chi-square test or *t-test was used comparing all HCV infection vs. controls.

factor for cardiovascular disease.[7,8] Interferon-based antiviral treatment has been associated with improvements in hepatic, cardiovascular, renal outcomes, and stroke in non-ESRD patients;[9–12] however, these factors are also the main causes of death in dialysis patients. One potential explanation for the marked reduction in the risk of death in dialysis patients is that there might be similar improvements in hepatic, cardiovascular, and neurological outcomes as observed in non-ESRD patients. Currently, no relevant reports are available yet; further investigations on whether dialysis patients could benefit from receiving antiviral treatment for hepatic, cardiovascular, or neurological outcomes are required.

Clinical Implications

Conventional key problems in HCV treatment in dialysis patients include the need to increase the sustained viral response (SVR), control the side effects, and minimize the dropout rates.[2] Conventional monotherapy achieves nearly one-third SVR;[25,26] the SVR rate of HCV-infected dialysis patients has increased to nearly 60% after combination therapy using peg-interferon and low-dose ribavirin with satisfactory tolerance,[5,27] higher than the SVR rates of the general population.[28] The proportion of dialysis patients with HCV infection receiving antiviral treatment is extremely low (<10% in the Dialysis Outcomes and Practice Patterns Study[13] and 6.1% in our study). However, in both studies, the mortality reductions by interferon use for HCV-infected ESRD patients were >50%.[13] Whether more patients should receive antiviral treatments and whether these reduced risks are a result of strict treatment indications remain unclear. Currently, the Kidney Disease: Improving Global Outcomes guideline recommends that ''the decision to treat should be based on the potential benefits and risks of therapy, including life expectancy, candidacy for kidney transplantation, and comorbidities.''[29] Further research is required to address the issue of indication for HCV treatment in dialysis patients.

TABLE 2. Adjusted Risk of Mortality in Dialysis Patients With Respect to Hepatitis C Infection, Sociodemographics, and Comorbidities Under Cox Regression Model With Time-dependent Covariates

	PY	Death	Mortality	Crude HR (95% CI)	Adjusted HR (95% CI)
HCV					
No	29146	2123	72.84	1.00	1.00
Yes	6768	588	86.88	1.16 (1.05–1.29)**	1.10 (1.00–1.20)*
Sex					
Female	19034	1273	66.88	1.00	1.00
Male	16880	1438	85.19	1.27 (1.17–1.37)***	1.30 (1.21–1.41)***
Age†					
20–34	1555	28	18.01	1.00	1.00
35–49	9046	345	38.14	2.16 (1.47–3.17)***	2.08 (1.42–3.07)***
50–64	19533	1548	79.25	4.59 (3.16–6.67)***	3.44 (2.36–5.01)***
65+	5781	790	136.66	8.02 (5.50–11.7)***	5.26 (3.59–7.71)***
Urbanization					
1 (highest)	9701	687	70.82	1.00	1.00
2	11613	792	68.20	0.97 (0.87–1.07)	0.94 (0.85–1.04)
3	5995	500	83.41	1.18 (1.05–1.33)**	1.09 (0.97–1.22)
4 (lowest)	8605	732	85.07	1.21 (1.09–1.35)***	1.05 (0.95–1.17)
RRT modality					
HD	33045	2524	76.38	1.24 (1.07–1.44)	0.97 (0.84–1.13)
PD	2869	187	65.17	1.00	1.00
Medical history					
HTN					
No	6689	290	43.36	1.00	1.00
Yes	29225	2421	82.84	1.89 (1.68–2.14)***	1.03 (0.91–1.18)
HL					
No	22010	1468	66.70	1.00	1.00
Yes	13904	1243	89.40	1.34 (1.25–1.45)***	0.84 (0.77–0.91)***
DM					
No	24252	1217	50.18	1.00	1.00
Yes	11662	1494	128.11	2.59 (2.40–2.79)***	1.80 (1.65–1.97)***
IHD					
No	20940	1224	58.45	1.00	1.00
Yes	14974	1487	99.31	1.73 (1.60–1.86)***	1.09 (0.99–1.18)
PAD					
No	33766	2445	72.41	1.00	1.00
Yes	2148	266	123.85	1.74 (1.54–1.98)***	1.10 (0.97–1.25)
Obesity					
No	35632	2680	75.21	1.00	1.00
Yes	282	31	109.87	1.47 (1.03–2.10)	1.54 (1.08–2.19)*
CVA					
No	29074	1782	61.29	1.00	1.00
Yes	6840	929	135.82	2.26 (2.09–2.44)***	1.43 (1.32–1.56)***
CHF					
No	26079	1627	62.39	1.00	1.00
Yes	9835	1084	110.22	1.79 (1.66–1.93)***	1.28 (1.18–1.39)***
COPD					
No	26864	1896	70.58	1.00	1.00
Yes	9051	815	90.05	1.29 (1.19–1.40)***	0.96 (0.88–1.04)
Sepsis					
No	33986	2343	68.94	1.00	1.00
Yes	1928	368	190.85	2.81 (2.51–3.13)***	2.10 (1.88–2.35)***

CHF = congestive heart failure, CI = confidence interval, COPD = chronic pulmonary disease, CVA = cerebrovascular accident, DM = diabetes mellitus, HCV = chronic C hepatitis infection, HD = hemodialysis, HL = hyperlipidemia, HR = hazard ratio, HTN = hypertension. IHD = ischemic heart disease, PD = peritoneal dialysis, PAD = peripheral arterial disease, PY = person-years. Adjusted for age (continuous), sex, urbanization, RRT modality, HTN, HL, DM, IHD, PAD, obesity, CVA, CHF, COPD, and sepsis.

† Adjusted for hepatitis C status, sex, urbanization, RRT modality, HTN, HL, DM, IHD, PAD, obesity, CVA, CHF, COPD and sepsis. Mortality, per 1000 person-years.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

TABLE 3. Overall Mortality in Different HCV Status and Among Different Follow-up Durations Under Cox Regression Model With Time-dependent Covariates

HCV Status	Death	Mortality	HR (95% CI)	
Overall				
Control cohort	2123	72.84	1.00	
Treated HCV cohort	7	26.75	0.47 (0.22–0.99)*	1.00
Untreated HCV cohort	581	89.29	1.14 (1.04–1.25)**	2.62 (1.24–5.55)*
Follow-up ≤3 y				
Control cohort	1390	71.04	1.00	
Treated HCV cohort	6	29.32	0.34 (0.15–0.76)**	1.00
Untreated HCV cohort	401	91.60	1.18 (1.06–1.32)**	3.78 (1.68–8.51)**
Follow-up >3 y				
Control cohort	733	76.52	1.00	
Treated HCV cohort	1	17.53	0.29 (0.04–2.04)	1.00
Untreated HCV cohort	180	86.51	1.03 (0.87–1.21)	3.91 (0.54–28.1)

CI = confidence interval, CHF = congestive heart failure, COPD = chronic pulmonary disease, CVA = cerebrovascular accident, HCV = chronic C hepatitis infection, HR = hazard ratio. Adjusted for age (continuous), sex, urbanization, RRT modality, HTN, HL, DM, IHD, PAD, obesity, CVA, CHF, COPD, and sepsis. Mortality, per 1000 person-years.

* $P < 0.05$.

** $P < 0.01$.

The survival advantage of receiving antiviral treatments is stronger in HCV patients without cirrhosis and liver cancer; yet, it is not significant in patients with cirrhosis and liver cancer. Fabrizi et al[25] commented cirrhosis and hepatocellular carcinoma are significantly more frequent causes of death in anti-HCV-positive patients on dialysis; which may provide part of the causes for nonsignificant improvements in this group. Dialysis patients with HCV infection are more likely to develop hepatitis B and HIV coinfections and cirrhosis, anemia, and psychiatric disorders.[30] Although we excluded patients with hepatitis B, other comorbidities might still exist and could further influence the prognosis.

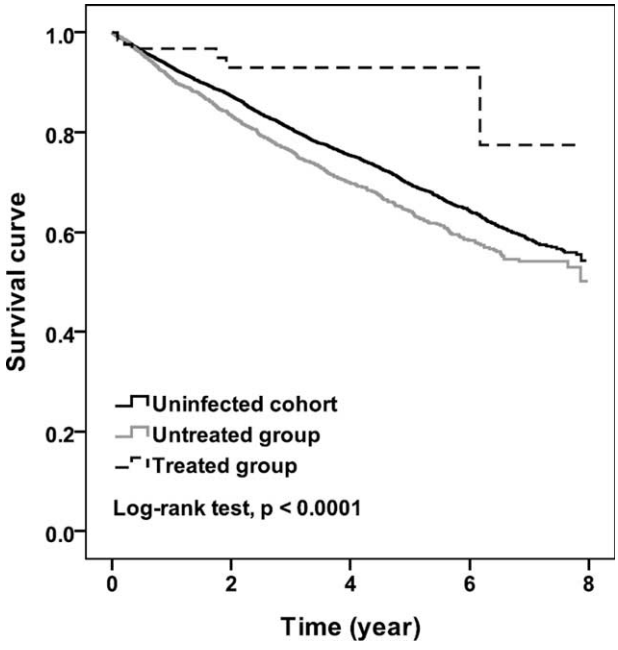

FIGURE 2. Survival curves in ESRD patients with different hepatitis C infection status and control cohort. ESRD = end-stage renal disease.

The Kaplan–Meier curve in Figure 2 reveals a wide separation among the curves of the treated group and the other 2 groups. Although Table 3 clarifies the significant survival advantage of receiving treatment within a follow-up of 3 years, only 1 death occurred in the treated group after a follow-up of >3 years. In other words, death in the treated group was markedly reduced and was much less after 3 years.

LIMITATIONS

This study has several limitations. First, obvious selection bias was present between the treated and untreated groups. Patients in the treated group were usually younger, had longer dialysis vintage, and less complicated comorbidity.[13] Hsu et al[12] used propensity score methods to minimize the bias, and Hsu et al[9] used extensive adjustment method to control for the bias. In the current study, we included extensive control variables, to adjust the bias. Second, NHIRD does not provide information regarding the SVR status, viral genotype, viral loads, lifestyle factors, and family history. Third, our study focused only on interferon-based therapy; treatment with ribavirin was not analyzed. Nevertheless, because interferon is included in both conventional monotherapy and combination therapy, we believe that this will not affect the outcomes of treated patients. Finally, this was an observational study; although ours was a nationwide study with a longer follow-up duration, the results preclude causality. An additional prospective randomized control trial is required to provide definitive results.

The major strengths of this study include the following: first, novel approaches were used to analyze the relationship between dialysis patients with HCV infection and mortality in an NHI program setting. In addition, we conducted comprehensive adjustment to control for multiple confounding factors, including COPD, ischemic stroke, IHD, and cirrhosis. Second, we divided the severity of liver disease into 2 levels (HCV infection with vs without cirrhosis/liver cancer) to identify any trends. Third, because there is a strict eligibility criterion for

TABLE 4. Risks of Mortality in HCV Patients Stratified by Severity of Hepatitis Before the End-point Under Cox Regression Model With Time-dependent Covariates

HCV Status	N	Death	Mortality	HR (95% CI)	
Without cirrhosis/liver cancer					
Uninfected cohort	8309	1851	69.36	1.00	
Treated HCV cohort	104	2	9.88	0.17 (0.04–0.68)*	1.00
Untreated HCV cohort	1591	376	75.88	1.03 (0.92–1.15)	6.31 (1.57–25.4)**
With cirrhosis/liver cancer					
Uninfected cohort	747	272	110.67	1.00	
Treated HCV cohort	30	5	84.34	0.97 (0.40–2.37)	1.00
Untreated HCV cohort	506	205	132.12	1.19 (0.99–1.43)	1.01 (0.41–2.51)

CI = confidence interval, CHF = congestive heart failure, COPD = chronic pulmonary disease, CVA = cerebrovascular accident, DM = diabetes mellitus, HCV = chronic C hepatitis infection, HL = hyperlipidemia, HR = hazard ratio, HTN = hypertension, IHD = ischemic heart disease, PAD = peripheral arterial disease. Adjusted for age (continuous), sex, urbanization, urbanization, RRT modality, HTN, HL, DM, IHD, PAD, obesity, CVA, CHF, COPD, and sepsis. Mortality, per 1000 person-years.

* $P < 0.05$.

** $P < 0.01$.

indication of HCV infection to receive interferon-based treatment; besides, the database used in this study is managed and utilized by the TNHIA for disbursing reimbursements; the data can be reasonably inferred to be both reliable and valid.

In conclusion, this nationwide cohort study showed that the proportion of treated patients among HCV-infected dialysis patients was extremely low; however, dialysis patients who received antiviral treatment were associated with significant improvements in survival, particularly patients without cirrhosis or liver cancer. The reduction in the risk of mortality in treated patients could probably be sustained over 3-year follow-up. Further prospective research is required to provide definitive evidence for the survival advantage of antiviral treatment in dialysis patients with HCV infection.

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