

The Association of Hepatitis C Virus Infection With the Prognosis of Chronic Hemodialysis Patients: A Retrospective Study of 3,064 Patients Between 1999 and 2010

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The prevalence of hepatitis C virus (HCV) infection is high among patients receiving chronic hemodialysis. To clarify the risk ratio of HCV infection with respect to mortality and prognosis in chronic hemodialysis patients, a retrospective longitudinal cohort study was conducted in 2010 and involved 3,064 patients receiving chronic hemodialysis at nine dialysis facilities in Hiroshima, Japan, who were recruited from 1999 to 2003. Logistic regression and Cox hazards models were used to estimate the mortality risk among hemodialysis patients. Among the patients, 422 (14.0%) were positive for HCV RNA. HCV RNA positivity was associated with death in the logistic model (adjusted odds ratio = 1.79; $P < 0.001$). However, it was not a risk factor for the reduced of survival rate in the Cox proportional hazard model (adjusted risk ratio = 1.07; $P = 0.4138$). In summary, among hemodialysis patients, HCV RNA is correlated with the mortality rate; however, it is not significantly correlated with prognosis in terms of survival time. On the other hand, diabetes and age at dialysis onset are significantly correlated with survival. Diabetes control treatment should be preferentially selected for hemodialysis patients, and antiviral therapy for HCV should be introduced based on the clinical state of the patient. **J. Med. Virol.** 87:1558–1564, 2015. © 2015 The Authors. *Journal of Medical Virology* published by Wiley Periodicals, Inc.

KEY WORDS: hemodialysis; HCV; diabetes; prognosis

INTRODUCTION

According to the World Health Organization (WHO), approximately 3% of the global population

has been exposed to the hepatitis C virus (HCV) and 130–150 million persons harbor persistent HCV infection, which has been strongly correlated with liver cancer. HCV is transmitted through exposure to contaminated blood. Hemodialysis patients are at a high risk of acquiring HCV infection because of the requirement for invasive treatment involving daily hemodialysis [Kumagai et al., 2005]. Although the number of new HCV infections in Japan is decreasing as a result of the Manual of Standard procedures for hemodialysis and nosocomial infection prevention, more than 90% of HCV infected hemodialysis patients develop chronic hepatitis. The HCV carrier rate remains higher among hemodialysis patients than among the general population. HCV carriers develop cirrhosis of the liver or hepatocellular carcinoma within 20–30 years of the initial infection [Kiyosawa et al., 1990; Seeff, 2002; Tanaka et al., 2003]. Hemodialysis patients reportedly have a high rate of death from cirrhosis of the liver or

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hepatocellular carcinoma [Espinosa et al., 2001]. On the other hand, HCV infection is associated with poor prognosis among hemodialysis patients [Fabrizi et al., 2007]. HCV infection control is very important because many patients on hemodialysis for a long time as a result of ongoing advances in medicine.

In Japan, additional public medical expenses for chronic viral hepatitis patients were initiated in 2008 and antiviral therapy is recommended. The Japanese Society for Dialysis Therapy generated clinical guidelines for the treatment of HCV infection. These guidelines stipulate that antiviral therapy should only be recommended to patients who are expected to have a good prognosis. The difference between the prognoses of hemodialysis patients with or without HCV infection and the risk ratio of HCV infection with respect to the mortality rate of hemodialysis patients were clarified, and thereby the usefulness of aggressive HCV infection management in these patients was discussed.

MATERIALS AND METHODS

Subjects

The subjects of this study were 3,096 hemodialysis patients attending nine dialysis facilities in Hiroshima, Japan from November 1999 to February 2003 who were also the subjects in our 2005 cohort study [Kumagai et al., 2005]. After excluding 32 patients (temporary dialysis: 2, missing data on the outcome: 3, missing data regarding the date of outcome: 23, missing data regarding the date of hemodialysis initiation: 3, missing data regarding HCV infection: 1), 3,064 patients were investigated in this study in October 2010 (Fig. 1). This study was conducted according to the Ethical Guidelines for Epidemiology Research in Japan and was approved by the Ethics Committee of Hiroshima University (Hiroshima Univ. Epi-294).

Methods

The patient outcomes and prognoses were surveyed from the medical records of nine dialysis facilities; the date and cause of death, date of hospital changes, cause of hemodialysis, the presence or absence of diabetes, and HBs antigen (HBsAg) and HCV RNA positivity were obtained, and all data were supplied anonymously. In our 2005 study, HCV RNA positivity was determined via polymerase chain reaction (PCR) with nested primers derived from well-conserved areas within the 5'-noncoding region of the HCV genome [Okamoto et al., 1990]. HBsAg positivity was determined via passive hemagglutination (PHA) with currently available commercial kits (Mycell anti-HBs, Institute of immunology Co. Ltd., Tokyo, Japan).

Statistical Analysis

The χ^2 test was used to compare frequencies between HCV infected and uninfected patients. The

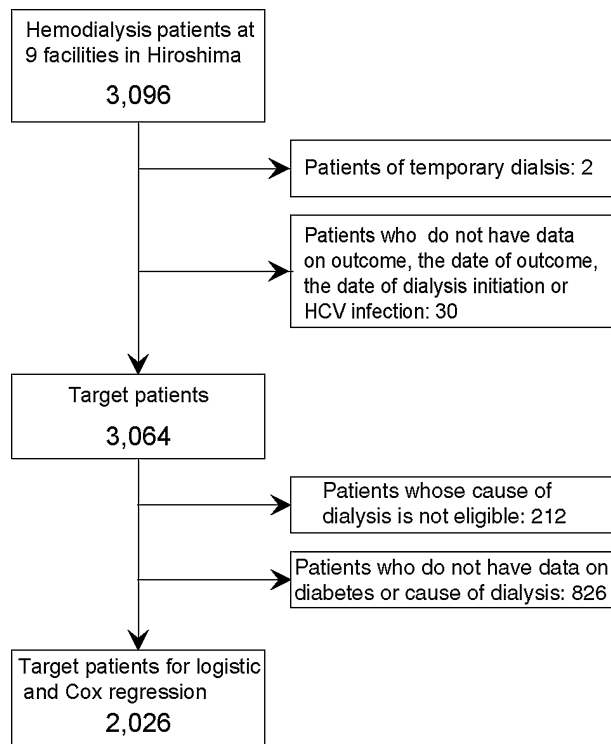


Fig. 1. Study subject. Target patients and target patients for logistic and Cox proportional hazard regression were selected as the flowchart.

log-rank test was used to compare the vital prognosis of each group according to (a) HBsAg, (b) HCV RNA, (c) diabetes, (d) cause of hemodialysis, (e) year of birth, and (f) age at onset of hemodialysis. The logistic regression model and the Cox proportional hazards model were used to estimate the mortality risk. *P*-values <0.05 were considered statistically significant. Statistical analyses were performed with a software package SPSS (version 12.0; SPSS, Inc., Chicago, IL).

RESULTS

Characteristics of Hemodialysis Patients

The subjects' background information is shown in Table I. Among the 3,064 total subjects, 1,802 (58.8%) were men and 1,262 (41.2%) were women. The average age at hemodialysis onset was 58.0 ± 15.8 years. The average duration of hemodialysis was 10.2 ± 7.5 years. Chronic glomerulonephritis was the most common cause of hemodialysis initiation (36.2%, 1,109 cases), followed by diabetic nephropathy (25.0%, 765 cases). Among the 212 cases (6.9%), the number of patients with polycystic kidney disease was highest with 70 cases (2.3%).

In addition, 947 cases, accounting for 30.9% of the total subjects, had concomitant diabetes. Additionally, 428 (14.0%) patients were HCV RNA positive and 73

TABLE I. Characteristics of study participants

	All patients	HCV RNA positive	HCV RNA negative	P-value
Total	3,064	428	2,636	
Gender				0.0003***
Men	1,802 (58.8%)	286 (66.8%)	1,516 (57.5%)	
Women	1,262 (41.2%)	142 (33.2%)	1,120 (42.5%)	
Year of birth				<0.0001***
1905–24	521 (17.0%)	45 (10.5%)	476 (18.1%)	
1925–44	1,597 (52.1%)	261 (61.0%)	1,136 (50.7%)	
1945 and above	946 (30.9%)	122 (28.5%)	824 (31.3%)	
Age at onset of hemodialysis				0.0005***
49 years or younger	904 (29.5%)	145 (33.9%)	759 (28.8%)	
50–59 years	634 (20.7%)	89 (20.8%)	545 (20.7%)	
60–69 years	723 (23.6%)	116 (27.1%)	607 (23.0%)	
70 years or older	803 (26.2%)	78 (18.2%)	725 (27.5%)	
Duration of hemodialysis				<0.0001***
5 years and below	815 (26.6%)	95 (22.2%)	720 (27.3%)	
5–10 years	971 (31.7%)	131 (30.6%)	840 (31.9%)	
10–15 years	623 (20.3%)	69 (16.1%)	554 (21.0%)	
15 years and above	655 (21.4%)	133 (31.1%)	522 (19.8%)	
Cause of hemodialysis initiation				<0.001***
Chronic glomerulonephritis	1,109 (36.2%)	147 (34.3%)	962 (36.5%)	
Diabetic nephropathy	765 (25.0%)	146 (34.1%)	619 (23.5%)	
Renal sclerosis	156 (5.1%)	16 (3.7%)	140 (5.3%)	
Other	212 (6.9%)	21 (4.9%)	191 (7.2%)	
Unknown	822 (26.8%)	98 (22.9%)	724 (27.5%)	
Diabetes				<0.0001***
No	1,908 (62.3%)	230 (53.7%)	1,678 (63.7%)	
Yes	947 (30.9%)	173 (40.4%)	774 (29.4%)	
Unknown	209 (6.8%)	25 (5.8%)	184 (7.0%)	
HBsAg				0.5620
Negative	2,991 (97.6%)	420 (98.1%)	2,571 (97.5%)	
Positive	73 (2.4%)	8 (1.9%)	65 (2.5%)	
HCV RNA				
Negative	2,636 (86.0%)			
Positive	428 (14.0%)			

Data are expressed as numbers (%). ***Parameters have significant difference ($P < 0.001$) between patients who were positive for HCV RNA or negative for HCV RNA.

(2.4%) patients were HBsAg positive; 8 (0.3%) patients were double positive.

Gender, year of birth, age at hemodialysis onset, duration of hemodialysis, cause of hemodialysis initiation, and diabetes all correlated significantly with HCV RNA positivity ($P < 0.001$); on the other hand, no significant association was observed between HBsAg and HCV RNA positivity ($P = 0.562$).

Outcome

Up to December 2010, 1,501 of 3,064 patients (49.0%) had died (Fig. 2). Death occurred significantly more frequently in HCV RNA positive patients (60.0%) than in HCV RNA negative patients (47.2%, $P < 0.001$).

The causes of death were similar to those in a 2010 reports from the Japanese Society for Dialysis

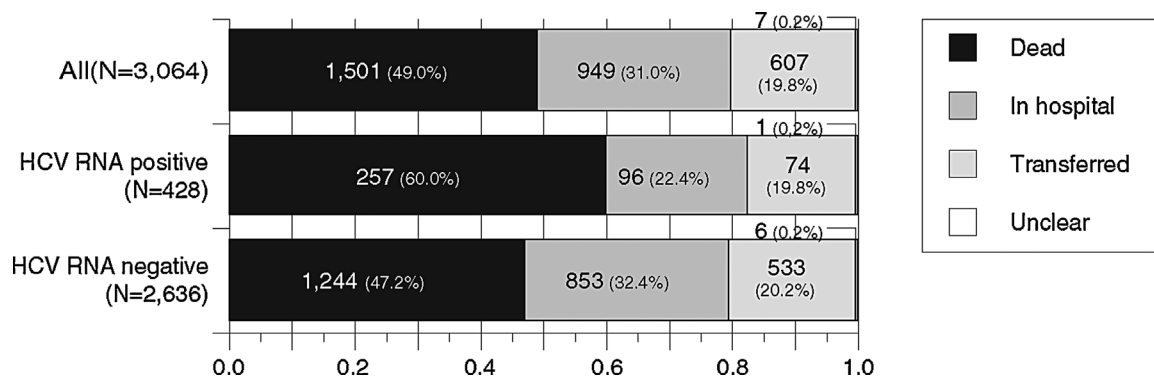


Fig. 2. Outcome according to infection status for HCV. Outcomes by all patients, HCV RNA positive patients, and HCV RNA negative patients are shown.

Therapy, the most common cause was cardiovascular diseases (430 cases, 29.2%) such as heart failure and myocardial infarction, followed by infectious disease (222 cases, 15.1%) (Fig. 3) and these causes of death were not related to HCV RNA positivity. Nevertheless the proportion of deaths from hepatic failure and HCC was higher among HCV RNA positive patients than among HCV RNA negative patients (8.7% vs. 1.6%).

Mortality and Prognosis

From the results of the logistic regression analysis shown in Table II, male gender ($P=0.008$), year of birth between 1905 and 1944 ($P<0.001$), age of 49 years or younger at hemodialysis initiation ($P=0.021$), duration of hemodialysis exceeding 5 years ($P<0.001$), diabetes ($P=0.031$), and HCV RNA positivity ($P<0.001$) were related to mortality. Regarding HBV infection, no significant correlation with mortality was found. On the contrary, the mortality risk was significantly lower among subjects with an age at dialysis onset of 70 years or older than among those aged 50–59 years and the cause of hemodialysis was not correlated with the mortality risk.

Regarding the survival duration, a univariate analysis conducted using the Kaplan–Meier method and log-rank test found that HCV RNA negative patients did not have a better prognosis than HCV RNA positive patients ($P=0.646$; Fig. 4). Patients without diabetes ($P<0.001$), with a more recent year of birth (1945–1986; $P<0.001$), cause of hemodialysis (chronic glomerulonephritis; $P<0.001$), and age at dialysis onset (younger than 49 years; $P<0.001$) had a significantly better prognosis.

Additionally, the factors associated with prognosis in a multivariate analysis of survival duration were examined using a Cox proportional hazards model

(Table II). Male gender ($P=0.001$), age of 60 years or older at dialysis onset ($P<0.001$), and diabetes ($P<0.001$) were identified as the risk factors for prognosis related to an outcome of death. Regarding HCV infection, no significant relationship with prognosis was identified ($P=0.414$).

DISCUSSION

In this study, the HCV RNA positivity rate among hemodialysis patients in Hiroshima was 14.0%, similar to the estimated prevalence of HCV among hemodialysis patients in Hiroshima in 2005 (12.9%) [Kumagai et al., 2005] and much higher than that in the overall Japanese population. The HCV carrier rates in the overall Japanese population were calculated to be 0.95% in 1995–2000 and 0.44% in 2001–2006 [Tanaka et al., 2004, 2011] and were estimated based on a database of first-time blood donors. Moreover, the reported incidence of HCV among hemodialysis patients in 2005 [Kumagai et al., 2005] was $330/10^5$ person-years, and this number was also higher than that among blood donors ($1.86/10^5$ person-years [Tanaka et al., 2008]). Although the Japanese Society for Dialysis Therapy developed a guideline for the prevention of HCV for hemodialysis patients, hemodialysis patients are considered a high risk group for HCV infection. Outside of Japan, a high risk of HCV infection has been observed among hemodialysis patients [Vallet-Pichard and Pol, 2013].

In Japan, a reported 38,055 patients were newly introduced to hemodialysis in 2012 [Nakai et al., 2014]. According to a report from the Japanese Society for Dialysis Therapy, the number of deaths among hemodialysis patients was 30,710 in 2012; therefore, the calculated cumulative number of hemodialysis patients in 2012 was 310,007. As Japan is a developed country, the number of patients with lifestyle related diseases, including those requiring

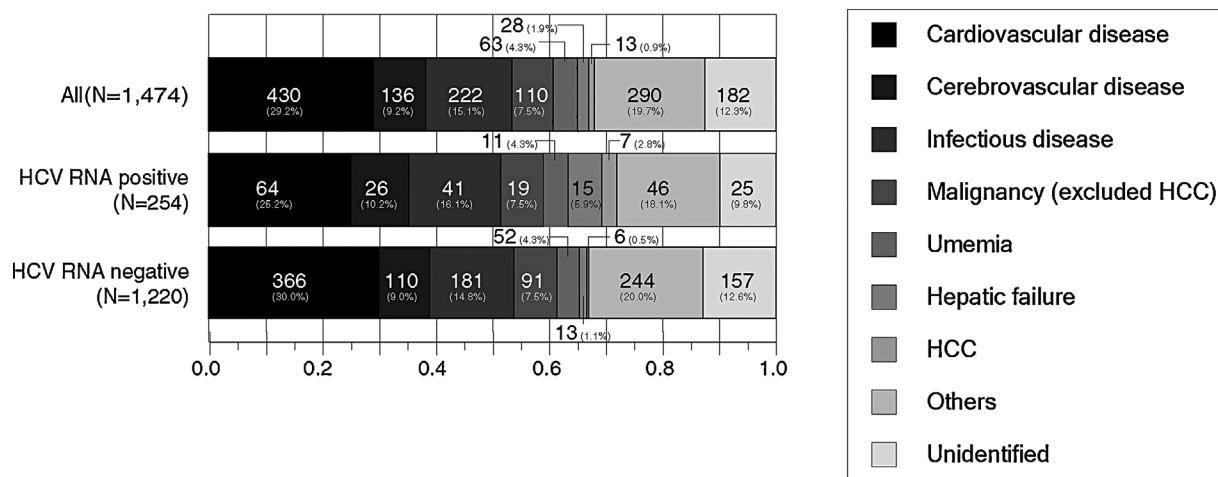


Fig. 3. Cause of death according to infection status for HCV. Among dead patients (N=1,474), cause of death by all patients, HCV RNA positive patients, and HCV RNA negative patients are shown.

TABLE II. Results of Logistic and Cox Regression Analysis for Factors of Death (N = 2,238)

	Logistic regression for mortality ^a			Cox regression for prognosis ^b		
	AOR	95%CI	P-value	ARR	95%CI	P-value
Gender						
Men	1.30	(1.07–1.57)	0.0077**	1.19	(1.05–1.34)	0.0012**
Women	1.00			1.00		
Year of birth						
1905–24	13.91	(8.58–22.71)	<0.0001***	1.04	(0.77–1.41)	0.7836
1925–44	4.78	(3.47–6.60)	<0.0001***	0.99	(0.78–1.25)	0.9150
1945 and above	1.00			1.00		
Age at onset of hemodialysis						
49 years or younger	1.48	(1.06–2.06)	0.0208*	0.29	(0.22–0.37)	<0.001***
50–59 years	1.00			1.00		
60–69 years	0.81	(0.60–1.09)	0.1668	2.08	(1.72–2.52)	<0.001***
70 years or older	0.67	(0.46–0.99)	0.0417*	4.38	(3.47–5.49)	<0.001***
Duration of hemodialysis						
5 years and below	1.00					
5–10 years	0.43	(0.34–0.56)	<0.0001***			
10–15 years	0.28	(0.21–0.38)	<0.0001***			
15 years and above	0.22	(0.15–0.31)	<0.0001***			
Cause of hemodialysis initiation						
Chronic glomerulonephritis	1.06	(0.58–1.94)	0.8584	0.93	(0.65–1.30)	0.6766
Diabetic nephropathy	1.00			1.00		
Renal sclerosis	1.08	(0.60–1.97)	0.8085	1.39	(0.99–1.92)	0.0593
Other	1.28	(0.67–2.49)	0.4562	1.23	(0.82–1.81)	0.3008
Diabetes						
No	1.00			1.00		
Yes	1.88	(1.06–3.38)	0.0314*	1.96	(1.39–2.69)	0.0002***
HBsAg						
Negative	1.00			1.00		
Positive	1.04	(0.57–1.89)	0.8870	0.88	(0.57–1.29)	0.5277
HCV RNA						
Negative	1.00			1.00		
Positive	1.79	(1.37–2.35)	<0.0001***	1.07	(0.91–1.25)	0.4138

^aR² = 0.16, model P < 0.0001, N = 2,238; AOR, adjusted odds ratio.

^bModel P < 0.0001, N = 2,238; ARR, adjusted risk ratio.

hemodialysis, is increasing. The number of HCV carriers among hemodialysis patients possibly remains large. This study was conducted because the clarification of disease progression in and treatment decisions for hemodialysis patients with or without HCV infection are important topics.

The reported ALT levels in hemodialysis patients with or without HCV infection are generally low, reflecting a potentially severe level of liver injury. As a result of immunodeficiency, the natural course of HCV infection among hemodialysis patients differs from that among HCV infected patients not receiving hemodialysis. Therefore, even HCV infected hemodialysis patients with low ALT levels should not be considered healthy carriers, and as the current hemodialysis control has improved and the lifespans of hemodialysis patients are consequently longer, the Japanese Society for Dialysis Therapy has recommended that HCV infected hemodialysis patients in good condition should be treated with antiviral therapies.

The high mortality of HCV carriers receiving hemodialysis was confirmed by previous medical research reports and meta-analysis [Fabrizi et al., 2007, 2010].

In Japan, a cohort study involving nearly all hemodialysis patients in Iwate [Ohsawa et al., 2011] reported that the significant risk factors associated with prognosis were age, low serum albumin level, high CRP level, complication of diabetes, and HCV antibody positivity ($P=0.043$). However, HCV antibody positivity was not a risk according to same analysis after excluding high-risk patients with additional complications such as cardiac infarction, cerebral embolism, or malignant neoplasm ($P=0.106$). On the other hand, according to the results of a logistic regression to analyze the deaths of patients within 1 year based on a survey of 3,360 hospitals conducted by the Japanese Society for Dialysis Therapy, HBsAg positivity was not correlated with death, but HCV antibody positivity was correlated with a risk of death (the relative risk of a positive outcome for anti-HCV positivity was 1.2–1.4). In this study, HCV infection was defined as HCV RNA positivity whereas the Japanese Society for Dialysis Therapy defined infection as HCV positivity; additionally, the study interval was defined as the entire follow-up after certain duration whereas the Japanese Society for Dialysis Therapy defined the interval 1 year after hemodialysis initiation. Despite the different study

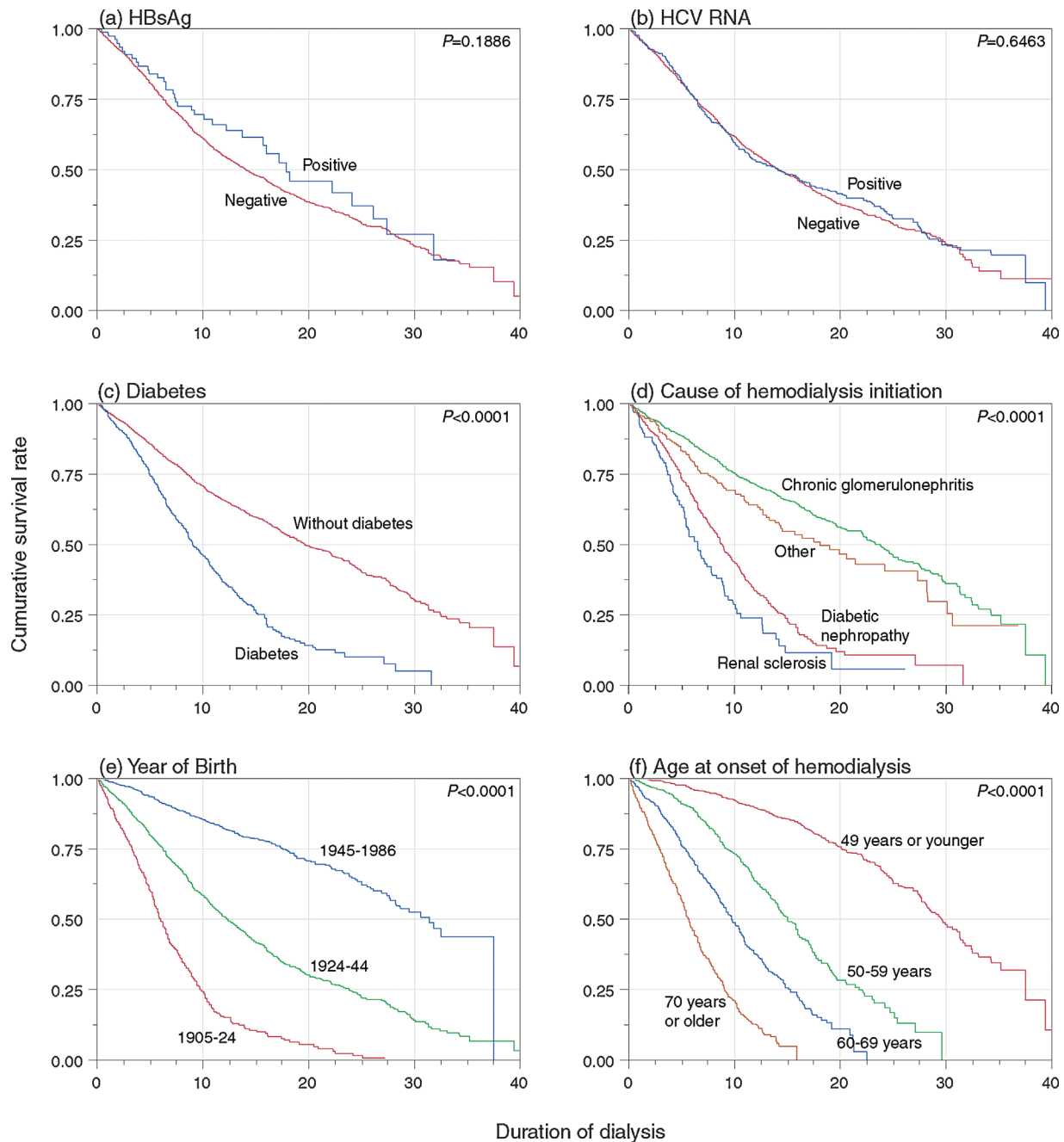


Fig. 4. Kaplan–Meier survival curve of mortality in hemodialysis patients. Survival curves of each groups classified by (a) HBs antigen, (b) HCV RNA, (c) diabetes, (d) cause of introduction of HD, (e) year of birth, (f) age at HD onset.

designs, both the logistic analysis and Cox's proportional hazard model results are in accordance with the results obtained in Iwate and by the Japanese Society for Dialysis Therapy.

We applied a logistic regression analysis to investigate the risk factors for death in hemodialysis patients and have confirmed that persistent HCV infection poses a significant risk of death after adjusting for HBsAg, Diabetes, Cause of hemodialysis, Year

of birth, and Age at onset of dialysis as in previous studies.

However, a logistic regression is a type of cross-sectional analysis that considers the risk factors for death within a specified period without considering the observed survival duration of each subject. In this study, we attempted to analyze the same subjects while considering the observed survival duration of each subject.

The Cox's hazard regression analysis results show that the risk associated with the diabetes factor is greater than that associated with the persistent HCV infection factor. In this study, the reduction in survival time caused by diabetes is considered longer than that caused by HCV infection. This result seems to conflict with several reports in which HCV infection is a risk factor for death in hemodialysis patients. However, we do not deny that persistent HCV infection is a risk factor for death in hemodialysis patients.

However, we would like to demonstrate that although HCV infection is certainly a risk factor for death, diabetes has a stronger correlation with respect to survival duration. We would like to suggest another possible treatment strategy for HCV infected hemodialysis patients.

In this study, the main causes of death among dialysis patients were cardiac disorders and infectious disease, whereas liver disease only accounted for 2.8% of deaths (hepatic failure 1.9%, hepatocellular carcinoma 0.9%). In a survival analysis, the prognostic risk factor was diabetes rather than HCV infection. This finding suggests that diabetes care should be a priority for hemodialysis patients. HCV infection is certainly a risk factor for death among hemodialysis patients. Diabetes treatment should be preferentially selected for hemodialysis patients, and the introduction of HCV antiviral therapy should be determined based on the patient's clinical state.

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