

# Natural history of chronic hepatitis C in patients on hemodialysis: Case control study with 4-23 years of follow-up

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## Abstract

**AIM:** Hepatitis C virus (HCV) infection is very common among end-stage kidney disease patients on hemodialysis, but its natural history is not known.

**METHODS:** In this study, 189 dialysis patients (case) positive for HCV antibodies who were followed up for more than 4 years were compared with twice as many sex/age matched controls with chronic hepatitis C who were diagnosed in the same month as the case and followed up for comparable periods. The longest follow-up was 23 years in dialysis cases. The disease activities were graded into "asymptomatic" if ALT was less than 40 (35 in cases) IU/L, "low activities" if ALT was 40 (35)-79 IU/L, and "high activities" if ALT was above 80 IU/L during the last or latest 4 year period.

**RESULTS:** All 25 dialysis cases who were followed up for more than 15 years were asymptomatic and 15 of them were negative for HCV RNA. Of the 50 controls followed up for more than 15 years, 34 had high activities, and none cleared HCV RNA. There were 60 controls who were asymptomatic, but they were all positive for HCV RNA, while 22.3% of asymptomatic dialysis cases were RNA negative. No dialysis patients with chronic hepatitis C progressed to cirrhosis, whereas the disease progressed to cirrhosis in more than one quarter of the controls. These differences were highly significant ( $P < 0.0001$ ).

**CONCLUSION:** Chronic hepatitis C among hemodialysis patients is mild in disease activity, and is not progressive, perhaps due to immunological abnormalities in these patients. Hepatic C virus is frequently cleared in asymptomatic dialysis patients during a long course. A possible mechanism for viral clearance is viral particle destruction on the surface of the dialyzer membrane.

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## INTRODUCTION

Hepatitis C virus (HCV) infection is very common among patients on hemodialysis for chronic renal failure with global anti-HCV prevalence of up to 91%<sup>[1]</sup>, because of the frequent past blood transfusions and nosocomial infections<sup>[2,3]</sup>. Although

at the clinical setting, dialysis patients with HCV infection seem to have a mild disease, reports on the natural history of hepatitis C in hemodialysis patients vary<sup>[4]</sup>. Sterling *et al.*<sup>[5]</sup> compared 50 consecutive patients with end-stage renal disease and HCV infection to HCV-positive controls. Ninety-six percent of patients on dialysis had normal alanine-aminotransferase (ALT) and low necroinflammatory score on biopsy. Despite minimal biochemical evidence of disease, some dialysis patients were more likely to have bridging hepatic fibrosis. Another cohort study<sup>[6]</sup> showed that the crude relative risk of death comparing HCV positive to negative dialysis patients was not significant. However, adjustment for age, transplantation, and other factors raised the relative risk somewhat. Akpolat *et al.*<sup>[7]</sup> compared liver histology between 9 dialysis patients and 37 patients with normal renal function, and found less active and progressive chronic hepatitis C in the former. They admitted that the number of patients was too small for conclusion. Thus, more information is required on the natural history of chronic HCV infection in hemodialysis patients. This study was designed to compare end-stage kidney disease patients who were positive for HCV antibodies and control patients infected with HCV but not on dialysis.

## MATERIALS AND METHODS

At the end of 2001, 603 patients with renal failure were dialyzed with 221 consoles at Sanai Amalgamated Dialysis Center, Chiba, which consists of Sanai Memorial Hospital, Sanai Soga Hospital and Ichihara Dialysis Clinic. Of these 603 patients, 142 were tested positive for HCV antibodies. Many of these patients had chronic non-A, non-B hepatitis and were subsequently found to have HCV antibody positive. Dialysis patients commonly had cardiovascular, intracranial and other complications, and they died while on dialysis. At this center, about 55 patients on average died per year. As yet, none of these anti-HCV positive patients turned antibody negative during the observation period after 1991 when C100-3 antibody kit became available at the hospital. The antibody kit was subsequently changed to the 2<sup>nd</sup> and 3<sup>rd</sup> generation test. All dialysis patients underwent periodic blood tests that included ALT and aspartate-aminotransferase (AST) every 4 wk. In this study, 189 patients who were anti-HCV positive and followed up for more than 4 years to the end of 2001 constituted the study (case) subjects. Twenty-five patients were followed for more than 15 years (longest 23 years), 94 patients were followed for 10-15 years and 70 for 4-10 years (Table 1). Ten patients were treated with interferon<sup>[8]</sup> and they were excluded. Currently 3 patients had cirrhosis, they were positive for both HBV and HCV. They were not included. The three patients had cirrhosis when dialysis was started at this hospital.

One patient with renal failure started on dialysis in 1978, 11 in 1983, 5 in 1984, 4 in 1985, 8 in 1986, 13 in 1987, 18 in 1988, 14 in 1989, 21 in 1990, 24 in 1991, 22 in 1992, 14 in 1993, 18 in 1994, 10 in 1995, and 6 in 1996. There were 137 male dialysis patients whose age ranged from 21 to 75 years, averaged  $48.6 \pm 11.8$  years, and 52 females whose age ranged 24 to 83 years, averaged  $51.7 \pm 11.1$  years.

The control group consisted of anti-HCV positive patients with chronic hepatitis who were diagnosed and followed up at the Liver Center of the Chiba University Hospital. The patients who were treated with interferon and had sustained virological response were excluded. At this center, approximately 1 200 HCV positive patients were followed up at an interval of 1 to 3 mo, and about 20-30 new patients were found per month. Out of these patients, two control patients for each dialysis case were chosen who were age ( $\pm 5$  years) and sex matched, and found to be HCV positive in the same month and subsequently followed up for a similar period of time. All these patients were followed up for more than 4 years, and the disease activities were recorded in the last 4 years before death or in the latest 4 year period.

Diagnosis of cirrhosis was made on the basis of liver biopsy, imaging, blood chemistry and physical signs. Imaging findings suggestive of cirrhosis included ascites, liver surface irregularity, splenomegaly, enlarged left gastric vein, enlarged paraumbilical vein, obtuse liver edge, enlarged caudate lobe, excessively large left lobe compared to the right lobe, splenorenal or gastrosplenic shunt by ultrasound and CT, and esophago-gastric varices by endoscopy. The patients with past or currently elevated ALT in the absence of these features were diagnosed as having chronic hepatitis C.

Serum HCV RNA was measured using the branch DNA method and subsequently by Amplicor test (Nippon Roche, Tokyo). Viral load was measured twice at an interval of 2 or more years in dialysis patients to see the change in viral load. Beside the routine liver tests, 7S domain type IV collagen was measured as an indirect indicator of hepatic fibrosis in dialysis cases<sup>[9,10]</sup>.

The disease activities were graded into three categories: "asymptomatic" if ALT levels remained below 40 IU/L for the control group and below 35 IU/L for dialysis cases, the difference in the upper normal limit was due to normally low ALT and AST in dialysis patients<sup>[11,12]</sup>; "low activities" if ALT fluctuated between 35 (40 in control) and 79 IU/L; and "high activities" if ALT levels exceeded 80 IU/L during the last 4 year period.

Statistical analyses were made by the  $\chi^2$  test and ANOVA.

## RESULTS

The disease activities in these dialysis cases who were divided into three groups according to the length of dialysis (more than 15 years, 10-15 years and 4-10 years) are given in Table 1. All the 25 patients on dialysis for more than 15 years were asymptomatic, and only 3 of 50 controls were asymptomatic. The remainder of the controls all had disease activities. Of the 94 patients on dialysis for 10-15 years, 81 (85%) were asymptomatic and 6 (6.4%) had high activities. Whereas in the controls, only 26 (13.8%) of 188 were asymptomatic and 109 (58.0%) had high activities. Of the 70 patients on dialysis for 4-10 years, 58 (83%) were asymptomatic and 5 (7.1%) had high activities. The corresponding figures were 22.1% and 52.1%, respectively, in the controls. These differences were highly significant ( $P < 0.001$ ). Table 1 also lists the number of patients in parentheses in whose serum HCV RNA levels were PCR negative or below the quantifiable level by Amplicor. Of the 25 long (more than 15 years) follow-up dialysis cases, RNA was negative or below the quantifiable level in 15 (60%). However, RNA was negative in only one of 14 dialysis cases with low disease activities, the remaining 13 cases were positive. All high activities cases were positive, while none of the control patients was negative for HCV RNA.

The clinical course of these 189 patients was uneventful from the point of view of liver disease. Many of these patients died from liver unrelated diseases, but the liver disease progressed to cirrhosis in none of them. The three cases of HCV positive

cirrhosis who were followed up had already had cirrhosis when they came to our hospital. All cases who were followed up for more than 15 years were asymptomatic by the end of the follow-up (Table 1). More dialysis cases who were follow-up for a shorter period of time had disease activities. Thus, chronic hepatitis C among dialysis patients seemed to slowly improve and seldom worsen. In contrast, the disease was progressive in most control patients. In the 50 control patients who were followed up for more than 15 years, the disease progressed to cirrhosis in 18 during the follow-up. In the 228 controls who were followed up for 10-15 years, cirrhosis developed in 62. In the 140 controls who were followed up for 4-10 years, 29 developed cirrhosis.

**Table 1** Clinical evaluation of dialysis (case) and control patients in recent 4 years or last 4 years before liver unrelated death

Group		Number	Disease activities		
			Asymptomatic	Low	High
Follow-up: <15 yr					
Case	Male	14(5)	14(5)	0	0 <sup>b</sup>
	Female	11(10)	11(10)	0	0 <sup>d</sup>
Control	Male	28(0)	0	8(0)	20 <sup>b</sup> (0)
	Female	22(0)	3(0)	5(0)	14 <sup>d</sup> (0)
Follow-up: 10-15 yr					
Case	Male	70(15)	58(14)	7(1)	5 <sup>b</sup> (0)
	Female	24(0)	23(10)	0	1 <sup>d</sup> (0)
Control	Male	140(0)	16(0)	29(0)	95 <sup>b</sup> (0)
	Female	48(0)	10(0)	24(0)	14 <sup>d</sup> (0)
Follow-up: 4-10 yr					
Case	Male	53(5)	41(5)	7(0)	5 <sup>b</sup> (0)
	Female	17(9)	17(9)	0	0 <sup>d</sup>
Control	Male	106(0)	24(0)	23(0)	59 <sup>b</sup> (0)
	Female	34(0)	7(0)	13(0)	14 <sup>d</sup> (0)

( ): HCV RNA, PCR negative or below quantifiable level by Amplicor <sup>b</sup> $P < 0.001$ , <sup>d</sup> $P < 0.001$  by  $\chi^2$  test.

**Table 2** Serum HCV RNA in dialysis patients in the study

Range (KIU/mL)	Group		
	Asymptomatic	Low activities	High activities
<0.5	53	2	0
0.6-100	32	2	1
101-400	48	4	1
401->850 <sup>1</sup>	21	6	9
Total	154	14	11

<sup>1</sup>Includes values above 1 000 by Amplicor Version I. Values by branched DNA method were converted to Amplicor values.  $P < 0.001$  by  $\chi^2$  test.

**Table 3** Comparison of the first and second measurements of HCV RNA at intervals longer than 2 years in dialysis patients

Change	Group		
	Asymptomatic	Low activities	High activities
Unchanged (change <50%)	44	1	2
Increased (+ >50%)	25	3	2
Decreased (- >50%)	36	5	2
Total	105	9	6

The initial serum levels of HCV RNA in 179 dialysis patients are given in Table 2. Of the 154 asymptomatic cases, the RNA

level was negative or below the quantifiable level in 53 (34.4%) and below 100 KIU/mL in 32 (20.8%), but the remaining 69 patients had RNA levels greater than 101 KIU/mL. All the 11 dialysis patients with high activities had high levels of RNA. Thus, differences among the three activity groups were significant by the  $\chi^2$  test ( $P<0.001$ ). Serum RNA could be measured twice at an interval of 2 years or longer in 120 patients. The change was less than 50% of the initial level (unchanged) in 44 (41.9%), increased by more than 50% in 25 (23.8%) and decreased by more than 50% in 36 (41.0%) (Table 3). Serum RNA clearly reflected the absence or presence of disease activities. Serum 7S fragment of type IV collagen was measured in 143 dialysis patients (Table 4). The values ranged from 1.8 to 12.0  $\mu\text{g/mL}$  with a mean of 5.59 ng/mL. The mean $\pm$ SD for the asymptomatic group was 5.05 $\pm$ 1.59 ng/mL, 6.21 $\pm$ 1.94 ng/mL for the low activities group and 6.92 $\pm$ 2.63 ng/mL for the high activity group. The differences were significant ( $P<0.05$ ) by ANOVA.

**Table 4** Serum 7S fragment of type IV collagen in dialysis patients

Group	Number of patients	7S IV collagen (ng/mL)
Asymptomatic	118	5.05 $\pm$ 1.59 <sup>a,c</sup>
Low activities	14	6.21 $\pm$ 1.94 <sup>a</sup>
High activities	11	6.92 $\pm$ 2.63 <sup>c</sup>
Total	143	5.59

<sup>a</sup> $P<0.05$ , <sup>c</sup> $P<0.05$  by ANOVA.

## DISCUSSION

In this study, 189 dialysis patients with HCV infection were followed up for more than 4 years in comparison with 378 sex/age matched nondialysis control patients who were diagnosed as chronic hepatitis C. Disease activities were divided into three grades: asymptomatic, low activities (ALT not exceeding 80 IU/L) and high activities (ALT exceeding 80 IU/L) during the last or latest 4 year period. Of the 189 dialysis patients, 25 were followed up for more than 15 years. They all became asymptomatic after a varying period of elevated and fluctuating ALT, and 15 were HCV RNA negative. In a distinct contrast, the majority of controls who were followed up for a comparable period remained to have high activities (Table 1), and none lost HCV RNA, one quarter to one third of them progressed to cirrhosis. Serum type IV collagen 7S domain was measured in dialysis patients, and the results suggested that fibrogenetic activities increased with high disease activities. These results clearly showed that patients on hemodialysis became much better than nondialysis patients with chronic hepatitis C. No dialysis patients progressed to cirrhosis in this series.

The question is why there is such a distinct difference in the natural history of chronic hepatitis C between dialysis and nonuremic patients. It has been suggested that liver injury caused by HCV infection is mainly through immunologic processes<sup>[13]</sup> rather than the virus that is directly cytopathic<sup>[14]</sup>. It has been well established that patients with end-stage renal disease and on maintenance hemodialysis have severe immunologic abnormalities with reduced immune responsiveness<sup>[15]</sup>.

Some of our dialysis patients had a high viral load. RNA levels did not show direct correlation with disease activities, but more asymptomatic cases were RNA negative, and RNA levels tended to decrease in more patients when studied at an interval of 2 years or longer. There have been several studies on viral load in hemodialysis patients, but the results were not consistent. According to Umlauf *et al.*<sup>[16]</sup>, HCV viremia fluctuated with the time of undetectable RNA. Whereas in the

study of Fabrizi *et al.*<sup>[17]</sup>, HCV load was low and relatively stable. HCV RNA levels decreased in dialysis patients in another report<sup>[18]</sup>.

In 1996, we first described the phenomenon in which the number of HCV viral particles decreased after each dialysis procedure and restored to the previous level at the next dialysis<sup>[19]</sup>. Subsequently it was found that viral particles were adsorbed onto the dialyzer membrane and destroyed<sup>[20]</sup>. Our observations have since been confirmed. According to Furusyo *et al.*<sup>[18]</sup>, HCV RNA levels were significantly lower in 98 dialysis patients (0.4 mEq/mL) compared with 228 nonuremic patients (2.0 mEq/mL). The dialysis procedure itself might contribute to the reduction of viral load in the long run. Another possible explanation for viral load reduction in dialysis patients was coinfection with another hepatotropic virus<sup>[21]</sup>. However, our earlier study in this dialysis center, the rates of infection with hepatitis G virus<sup>[22]</sup> and TT virus<sup>[23]</sup> were very low. Yokosuka *et al.*<sup>[24]</sup> followed up 320 patients with chronic type C liver disease and found that no chronic hepatitis patients were seroconverted, seronegative conversion occurred in 2%, only in end stage cirrhotic patients with or without hepatocellular carcinoma. The difference in the temporal virus load between dialysis and non-dialysis patients was so remarkable that it required biological explanation. It is not known whether C-viruses are able to replicate in liver cells of immunologically compromised dialysis patients as in immunologically competent individuals. Hepatocytes of the dialysis patients might not have normal metabolic and synthetic capabilities under the influence of uremic state, as exemplified by very low AST and ALT levels in serum<sup>[11,12]</sup>. Replication of viral particles within hepatocytes might be reduced for the same reason. It seems that the most plausible explanation would be the negative balance between mechanical destruction of viral particles by membrane dialysis procedure and viral replication.

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