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Association of hepatitis C virus infection and malnutrition–inflammation complex syndrome in maintenance hemodialysis patients

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Abstract

Background. Patients undergoing maintenance hemodialysis (MHD) have a significantly higher prevalence of hepatitis C virus (HCV) infection and malnutrition–inflammation complex syndrome (MICS). In the present study of Taiwanese MHD patients, we determined the clinical characteristics and influence of HCV infection on MICS by calculation of the malnutrition–inflammation score (MIS).

Methods. This was a prospective longitudinal study performed at a single hemodialysis (HD) center in Taiwan from September 2007 through March 2008. The study enrolled 58 patients (38%) in the active HCV group and 95 patients (62%) in the non-HCV group. The two or three weekly HD sessions of all patients were followed for 7 months. The MIS was assessed using 10 components, 7 from the conventional subjective global assessment of nutrition and 3 additional elements, body mass index, serum albumin and total iron-binding capacity.

Results. HD vintage and total MIS score were greater in patients with active HCV. The active HCV group had significantly longer dialysis vintage and lower total cholesterol but higher total MIS score than the non-HCV group. The MIS 5 score, a measure of major comorbid conditions (including number of years on dialysis), was also significantly higher in the active HCV group.

Conclusion. MHD patients with active HCV infections have more severe MICS-associated metabolic and physiological disease than MHD patients without active HCV infection.

Keywords: hepatitis C virus; maintenance hemodialysis; malnutrition–inflammation complex syndrome; malnutrition–inflammation score; subjective global assessment of nutrition

Introduction

Patients undergoing maintenance hemodialysis (MHD) have a significantly higher annual incidence of hepatitis C virus (HCV) infection, ranging from 1.01 to 80.0% depending on the country [1–4]. In Taiwanese dialysis patients, the prevalence of HCV seroconversion is 15% and the annual incidence of new HCV infection is 1.36% [1, 3]. Previous studies of dialysis patients reported that persistent viremia after acute HCV infection ranged from 65.4 to 91.8% [4, 5]. The anti-HCV seroprevalence (+) is 4.4% in Taiwan and the highest anti-HCV positive rates were reported in Miaoli County, Chiayi County, Chiayi City and Yunlin county [3]. Genotype 1b is the most prevalent HCV genotype in Taiwan [1, 3] and accounts for 50–70% of all cases [6, 7].

Short-term morbidity and mortality are significantly higher in HCV-infected dialysis patients, and these patients frequently die before the development of long-term HCV complications [8–12]. Hemodialysis (HD) patients often have concomitant malnutrition–inflammation complex syndrome (MICS), a condition associated with poor short-term clinical outcome, greater mortality, greater hospitalization rate, more significant protein-energy malnutrition and decreased health-related quality of life [13–18]. HD patients infected with HCV may also have specific MICS-associated metabolic abnormalities, including endothelial dysfunction, insulin resistance, oxidative stress and inflammation [8–10, 14, 16]. Several previous studies have reported an association of the malnourished state in HD patients with the presence of HCV, but this has not been verified [8, 9, 17, 18].

The present study of Taiwanese patients undergoing MHD was conducted to determine the clinical impact of HCV infection on MICS over a 7-month period.

Materials and methods

Study population

This prospective longitudinal study was performed at the St Martin De Porres Hospital (Chiayi, Taiwan), HD center, and all patients were recruited from September 2007 to March 2008. All patients who provided informed consent were on MHD for at least 8 weeks and were >18 years. Excluded patients had clinical or laboratory evidence of active infectious disease in the month before study onset or life expectancies of 6 months (e.g. due to a terminal stage of a malignancy). A total of 212 MHD patients were initially screened, 41 patients were excluded due to the presence of an exclusion criterion and 18 additional patients were excluded due to two successive negative HCV RNA titers (inactive HCV group) after initially positive anti-HCV results. A total of 153 patients were ultimately included (Figure 1). Fifty-eight patients who were anti-HCV positive with at least one positive HCV RNA titer (HCV RNA > 50 IU/mL) in the first month and the seventh month were placed in the 'active HCV group'. Ninety-five patients with negative anti-HCV titers were categorized as the 'non-HCV group'.

All patients had physical examinations that documented pre-dialysis blood pressure, post-dialysis weight and body mass index. The medical chart of each patient was thoroughly reviewed by a nephrologist (H-.B.T.), and data were obtained pertaining to underlying kidney disease and other relevant comorbidities. The following dialysis parameters were determined: dialysis vintage, dialysis adequacy (Kt/V), normalized protein catabolic rate (nPCR), ultrafiltration volume, relative interdialysis weight gain and volume overload (ultrafiltration volume >5.7% of post-dialysis weight) [19]. A bicarbonate dialyzate was used and all treatments employed the Toray TR-321 HD machine and new biocompatible membranes [Toray B1-1.6H, B1-2.1H, B3-1.3A and B3-1.8A with polymethylmethacrylate; Toray TS1.8SL and Fresenius F7 with polysulfone; Gambro-170, Gambro-210 and Gambro 21L with polyamix]. Anthropometric measurements were performed while patients were undergoing HD. Body weight was determined in the first month and seventh month at 5–20 min after completion of HD.

The study was approved by the ethics committee of St Martin De Porres Hospital (Chiayi City, Taiwan) and was registered at ClinicalTrials.gov (NCT00527774).

Malnutrition–inflammation score

The malnutrition–inflammation score (MIS) was calculated from ten categories: MIS 1 (weight change), MIS 2 (dietary intake), MIS 3 (gastrointestinal symptoms), MIS 4 (functional capacity, nutritionally related functional impairment), MIS 5 (major comorbid conditions including number of years on dialysis), MIS 6 (decreased fat stores or loss of subcutaneous fat), MIS 7 (signs of muscle wasting), MIS 8 (body mass index), MIS 9 (albumin) and MIS 10 (total iron-binding capacity, TIBC) [17, 20]. Each MIS component has four severity levels ranging from 0 (normal) to 3 (very severe), so the total MIS score ranged from 0 (normal) to 30 (severely malnourished). The MIS scores of all patients were determined by the same physician at the first and the seventh month.

Laboratory measurements

Biochemical and hematological parameters were obtained from midweek pre-dialysis blood samples at the first and the seventh month. Venous blood samples were collected on the morning after an overnight fast. Plasma samples were separated from blood cells and stored at −70°C. For analysis, samples were centrifuged at 1500 *g* at 4°C for 10 min. Kt/V was calculated using Daugirdas' second formula, and nPCR was calculated using the equations of Depner [21, 22].

Serum high-sensitivity C-reactive protein (hs-CRP), ferritin, insulin and plasma intact parathyroid hormone were measured by chemiluminescent immunoassays (Immulite 2000; DPC, Los Angeles, CA). White blood cells (WBCs), hematocrit and platelets were measured by a Sysmex XT-1800i (Sysmex America Inc., Mundelein, IL). Insulin sensitivity was

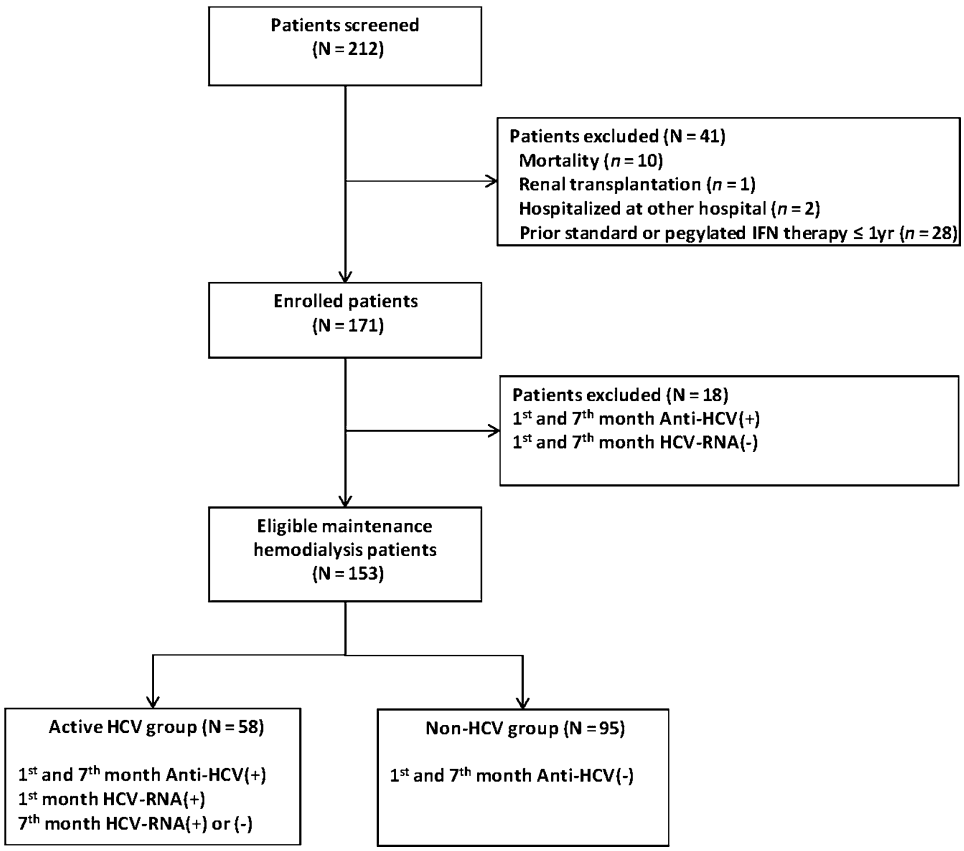

Fig. 1. Patient disposition. A total of 212 MHD patients were initially screened and 153 patients were ultimately enrolled, 58 in the active HCV group and 95 in the non-HCV group.

quantified using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) equation to measure fasting insulin and glucose (HOMA-IR = I × G/22.5), where I is insulin (μU/mL) and G is glucose (mmol/L) [IR: HOMA-index ≥ 2.5 μU/mL × mmol/L] [23]. Blood urea nitrogen, creatinine, fasting blood sugar, albumin, calcium, phosphate, glutamic-pyruvic transaminase (GPT), iron, TIBC, cholesterol and triglycerides were measured with an automated analyzer (Hitachi 7170, Tokyo, Japan). For hs-CRP, the intra-assay coefficient of variance was 8.7%, the sensitivity was 0.1 mg/L and the upper limit of detection was 150 mg/L [24]. Expected values for healthy individuals were ≤3 mg/L for hs-CRP and <40 U/L for GPT [25].

Anti-HCV antibodies were measured using a third-generation enzyme immunoassay (Abbott Laboratories, North Chicago, IL). HCV RNA was assayed qualitatively by a real-time polymerase chain reaction assay (Cobas Amplicor HCV v2.0; Roche Molecular Systems, Pleasanton, CA) at the first and the seventh month, with a detection cut-off level of 50 IU/mL.

Serum pro-inflammatory cytokines were measured with high-sensitivity interleukin (IL)-6, tumor necrosis factor (TNF)-α, adiponectin, asymmetric dimethylarginine (ADMA) immunoassay kits. These measurements were based on a solid-phase sandwich enzyme-linked immunoassay with recombinant human IL-6 (normal range: 0.03–200 pg/mL; RayBiotech, Atlanta, GA), TNF-α (normal range: 0.48–100 pg/mL; RayBiotech), adiponectin (normal range: 0.48–100 pg/mL; RayBiotech) and ADMA (normal range: 0.1–2.0 pg/mL; Immundiagnostik, Bensheim, Germany).

Statistical analysis

All data were analyzed using SAS 9.0 (SAS Institute Inc., Cary, NC). Categorical data are presented as numbers and percentages, and continuous data as means and SDs. Data with non-normal distributions are presented as medians and interquartile ranges (first quartile, third quartile). A two-sample *t*-test was performed to compare continuous data. For data with a non-normal distribution, a non-parametric Wilcoxon rank-sum test was performed. For categorical data, Pearson's chi-square test was used to compare the dispersion of contingency variables between groups. The Wilcoxon sign-rank test was used to compare HCV viral load at baseline and at the last day of follow-up. The Spearman correlation test was used to identify the correlation of HCV viral load at the last follow-up day with certain variable in patients with active HCV infection. Univariate binary logistic regression was used to identify predictors of HCV activity (probability of HCV infection) relative to certain risk factors. All statistical assessments were considered significant at $\alpha = 0.05$ for a P-value <0.05.

Results

A total of 153 subjects were included, 58 (38%) with active HCV and 95 (62%) without active HCV (Figure 1). Table 1 shows the demographic and baseline characteristics of all 153 subjects. The average age was 63.6 years (SD, 13.7) in the non-HCV group and 67.6 years (SD, 10.1) in the active HCV group.

The basic demographics of the two groups were similar, except for dialysis vintage. The active HCV group had significantly longer dialysis vintage, significantly higher incidence of liver cirrhosis, significantly lower WBC count, significantly higher serum glutamic-pyruvic transaminase and serum glutamic oxaloacetic transaminase, significantly lower total cholesterol and low-density lipoprotein (LDL) and significantly higher serum ferritin (Table 1).

Table 2 shows our analysis of the risk of HCV infection by univariate binary logistic regression based on demographics, baseline characteristics, MIS score and cytokine profiles. The results indicate that the probability of active HCV infection was significantly greater in patients with longer dialysis vintage [odds ratio (OR): 1.14, 95% confidence interval (CI): 1.04–1.25, P = 0.005] but was significantly less in patients with lower total cholesterol (OR: 0.98, 95% CI: 0.98–0.99, P = 0.016). The mean dialysis vintage was 3.52 ± 3.00 years in the non-HCV group [range (min to max): 0.17–11.18 years] and was 5.33 ± 4.50 years [range (min to max): 0.17–16.57 years] in the HCV group.

Table 3 shows the results of our Spearman correlation analysis of viral load at the last follow-up day with various clinical parameters and cytokine levels in the active HCV group. The results indicate that the viral load at the last follow-up day was positively correlated with baseline viral load ($r = 0.44$, P = 0.001) and baseline serum LDL ($r = 0.283$, P = 0.038).

Table 4 shows the distribution of baseline and follow-up HCV viral load, total MIS scores and cytokine profiles of the active HCV and non-HCV groups. Only patients who were anti-HCV positive were given confirmatory measurement of HCV RNA titer. In the active HCV group, the median viral load increased from 346.4×10^6 IU/mL at baseline to 498.0×10^6 IU/mL at the last follow-up day (P = 0.005). The total MIS score and MIS score of category MIS 5 were significantly higher in the active HCV group at baseline (P = 0.034 and P = 0.006, respectively). In addition, the active HCV group had significantly higher scores in MIS 5, MIS 6 and MIS 7 at the last follow-up day (P = 0.031, P = 0.012 and P = 0.002, respectively). Median expression of IL-6 was significantly higher in the non-HCV group at baseline (P = 0.041).

Discussion

Previous methods for evaluation of the malnutrition and inflammation status of MHD patients have been limited [9, 10]. Hence, Kalantar-Zadeh *et al.* developed the MIS as a more reliable tool than IL-6 or hs-CRP to identify the extent of MICS severity [17, 18, 26]. The MIS is a comprehensive scoring system that considers prospective short-term hospitalization, mortality, nutrition, inflammation and anemia in MHD patients [18]. A previous study of HD patients reported that the presence of HCV RNA (active HCV infection), detected by molecular-based testing, is associated with certain clinical features that are suggestive of MICS [27]. Our data confirm that active HCV infection is associated with the MIS of HD patients.

In our study, the higher HCV infection rate in MHD patients who had longer dialysis vintage suggested a possible nosocomial transmission. Several previous studies have also reported nosocomial transmission HCV [1, 3]. Even though HCV is a blood-borne pathogen, several review articles have concluded that transmission may occur due to contaminated dialyzers, HD machines, hands of staff members or other shared patient items [28, 29]. However, many patients with severe chronic kidney disease are HCV carriers before the onset of HD, so the higher rate of HCV infection may be also have been due to the use of unlicensed medical practice, blood transfusions or dental procedures, as previously reported in Brazil and Japan [30–32].

In the present study, we found that total MIS score was significantly higher in the active HCV group than the non-HCV group at baseline and the last follow-up day. This suggests that HCV infection is closely associated with MICS.

Table 1. Baseline demographic and clinical characteristics of the non-HCV group and the active HCV group[a]

Variables Demographics	Non-HCV ($n = 95$)	Active HCV ($n = 58$)	P-value
Age at first month of dialysis[b] (years)	63.6 ± 13.7	67.6 ± 10.1	0.51
Male sex[c], *n* (%)	46 (48.4)	27 (46.6)	0.82
Age at start of HD[b]	59.9 ± 13.9	62.3 ± 10.8	0.89
Dialysis vintage (years)[d]	2.9 (0.8, 5.7)	4.1 (1.7, 8.1)	0.001*
Body mass index[b] (kg/m^2)	22.6 ± 3.6	22.5 ± 3.4	0.83
Alcohol consumption[c], *n* (%)	6 (6.3)	3 (5.2)	0.77
Smokers[c], *n* (%)	10 (10.5)	8 (13.8)	0.54
Diabetes mellitus as primary disease[c], *n* (%)	56 (58.9)	26 (44.8)	0.09
Comorbidities[c]			
Coronary artery disease, *n* (%)	26 (27.4)	10 (17.2)	0.15
Congestive heart failure, *n* (%)	14 (14.7)	10 (17.2)	0.68
Peripheral arterial occlusive disease, *n* (%)	21 (23.6)	16 (29.6)	0.42
Cerebrovascular accident, *n* (%)	14 (14.7)	8 (13.8)	0.87
Peptic ulcer disease, *n* (%)	31 (32.6)	26 (44.8)	0.13
Liver cirrhosis, *n* (%)	1(1.1)	7 (12.1)	0.005*
Cancer, *n* (%)	6 (6.3)	8 (13.8)	0.12
Hematologic data			
WBC[d] ($10^3/\mu L$)	6.9 (5.6, 8.6)	5.9 (4.7, 7.3)	0.027*
Hematocrit[b] (%)	30.1 ± 4.2	31.0 ± 4.7	0.20
Biochemical data[d]			
Albumin (g/dL)	3.6 (3.8, 4.2)	3.5 (3.8, 4.0)	0.09
BUN (mg/dL)	51.3 (62.8, 76.1)	63.5 (53.2, 73.9)	0.98
Creatinine (mg/dL)	16.2 (12.5, 20.4)	14.8 (12.3, 21.3)	0.70
FPG (mg/dL)	92.0 (76.0, 136.0)	95.5 (77.0, 134.0)	0.67
GPT (IU/L)	13.0 (11.0, 18.0)	21.0 (14.0, 37.0)	<0.001*
GOT (IU/L)	14.0 (11.0, 19.0)	19.5 (13.0, 30.0)	<0.001*
Cholesterol (mg/dL)	171.0 (149.0, 189.0)	155.0 (120.0, 177.0)	0.005*
Triglycerides (mg/dL)	125.0 (90.0, 203.0)	113.0 (83.0, 170.0)	0.20
HDL (mg/dL)	43.9 (35.1, 55.1)	41.1 (34.6, 51.5)	0.31
LDL (mg/dL)	93.2 (80.4, 113.4)	86.1 (71.0, 102.3)	0.023*
HOMA-IR (μU/mL × mmol/L)	3.04 (1.8, 8.0)	3.8 (1.4, 8.1)	0.87
Uric acid (mg/dL)	7.1 (6.4, 8.1)	7.4 (6.3, 8.4)	0.41
C-reactive protein (mg/dL)	3.6 (1.5, 9.0)	2.8 (1.6, 7.5)	0.41
hs-CRP (mg/dL)	3.6 (1.5, 9.0)	2.8 (1.6, 7.5)	0.41
Ferritin (ng/mL)	84.0 (66.0, 101.0)	94.5 (74.0, 143.0)	0.006*
TIBC (mg/dL)	244.0 (217.0, 274.0)	253.0 (232.0, 281.0)	0.18
Transferrin saturation, (%)	34.0 (28.0, 39.0)	37.5 (30.0, 48.0)	0.011*
Ca × P (mg^2/dL^2)	41.5 (32.8, 51.7)	37.6 (33.9, 48.5)	0.42
iPTH (pg/mL)	108.0 (45.6, 224.0)	105.5 (56.5, 246.0)	0.97
Dialysis parameters			
Daugirdas[d] (Kt/V^2)	2.1 (1.9, 2.4)	2.1 (1.9, 2.5)	0.57
nPCR[b] (g/kg/day)	1.2 ± 0.3	1.2 ± 0.3	0.94
ADAT score[d]	4 (4, 5)	4 (4, 5)	0.31
EPO dose[d] (index W Kg)	2.98 (1.87, 3.67)	2.45 (1.68, 3.45)	0.35
Total score of MIS[c]			
0–5	62 (65.3)	27 (46.6)	0.08
6–10	28 (29.5)	24 (41.4)	
11–15	4 (4.2)	6 (10.3)	
16–20	1 (1.0)	1 (1.7)	

[a]BUN, blood urea nitrogen; FBG, fasting blood sugar; GOT, glutamate oxaloacetate transaminase; ADAT score, Appetite and Diet Assessment Tool score; EPO, erythropoietin; MIS, malnutrition-inflammation Score; iPTH, intact parathyroid hormone.
[b]Data are presented as mean (SD) and P-values were calculated using two-sample *t*-test.
[c]Data are presented as *n* (%) and P-values were calculated using Pearson chi-square test.
[d]Data are presented as median (Q1, Q3) and P-values were calculated using Wilcoxon rank-sum test.
*$P < 0.05$.

Our analysis of the ten individual items of the MIS indicated that MIS 5, MIS 6, MIS 7 and MIS 9 at the last follow-up day were significantly associated with HCV-infection and that MIS 5 was also associated with HCV infection at baseline. MIS 5 indicates disease severity of comorbidities and dialysis vintage. A previous study indicated that chronic hepatitis C is associated with more significant hepatic steatosis, Stages III–IV hepatic fibrosis and higher rate of diabetes mellitus [7]. In addition, our study demonstrated that the OR for dialysis vintage was significantly associated with HCV

Table 2. Univariate binary logistic regression of the relationship of HCV infection with demographics and clinical baseline characteristics, MIS score and cytokine profiles[a]

Variable at baseline	OR[b]	(95% CI for OR)	P-value
Age at first month of dialysis (years)	1.03	(0.99–1.06)	0.06
Age at start of dialysis (years)	1.02	(0.99–1.04)	0.28
Dialysis vintage (years)	1.14	(1.04–1.25)	0.005*
Diabetes mellitus history	0.57	(0.29–1.09)	0.09
Baseline body mass index (kg/m^2)	0.99	(0.90–1.09)	0.83
FPG (mg/dL)	0.99	(0.99–1.00)	0.37
Cholesterol (mg/dL)	0.98	(0.98–0.99)	0.016*
Triglycerides (mg/dL)	0.99	(0.99–1.00)	0.06
HDL (mg/dL)	0.98	(0.96–1.01)	0.35
LDL (mg/dL)	0.98	(0.98–1.00)	0.11
HOMA-IR (μU/mL × mmol/L)	1.01	(0.97–1.06)	0.68
hs-CRP (mg/dL)	0.99	(0.98–1.02)	0.69
Total MIS score			
0–5	(Reference)		
6–10	1.97	(0.97–4.00)	0.06
11–15	3.44	(0.90–13.20)	0.07
16–20	2.30	(0.14–38.08)	0.56
IL-6 (pg/mL)	0.99	(0.98–1.01)	0.27
TNF alpha (pg/mL)	1.02	(0.96–1.08)	0.59
Adiponectin (pg/mL)	1.00	(0.99–1.00)	0.63
ADMA (pg/mL)	0.98	(0.94–1.02)	0.33

[a]Cytokine profiles include IL-6, TNF alpha, Adiponectin and ADMA.
[b]OR (95% CI for OR) means the estimated OR with 95% confidence limits from the binary logistic regression.
*P-value < 0.05.

Table 3. Correlation of viral load on the last follow-up day with clinical and demographic variables in subjects with active HCV

Variable on last day of follow-up	r[a]	P-value
Baseline viral load	0.44	0.001*
Baseline body mass index (kg/m^2)	−0.002	0.99
FPG (mg/dL)	0.059	0.67
Cholesterol (mg/dL)	0.227	0.10
Triglycerides (mg/dL)	0.096	0.49
HDL	0.144	0.30
LDL	0.283	0.038*
HOMA-IR (μU/mL × mmol/L)	0.016	0.91
Total score of MIS	−0.053	0.70
IL-6 (pg/mL)	0.005	0.97
TNF alpha (pg/mL)	−0.055	0.69
Adiponectin (pg/mL)	−0.086	0.54
ADMA (pg/mL)	−0.126	0.43

[a]Correlation coefficient of Spearman correlation analysis.
*P-value < 0.05 from the Spearman correlation test.

infection. In particular, we found that for every 1-year increase in HD vintage, there is a 1.14-fold increased risk of HCV infection (95% CI: 1.04–1.25).

In our study, the active HCV group had higher MIS 9 (albumin level) at the 7-month follow-up (Table 4). A previous study reported by Kalantar-Zadeh *et al.* [27] indicated that each 0.1 g/dL decrease in serum albumin was associated with a 1.34-fold increased OR of active HCV (95% CI: 1.10–1.63, $P < 0.01$). In other words, serum albumin levels fall as the severity of HCV infection increases and this is usually associated with an increase in severity of cirrhosis [27]. Thus, our results can be interpreted as being analogous to the 'obesity paradox'. Our active HCV group also had higher MIS 6 decreased fat stores or loss of subcutaneous fat at the 7-month follow-up. Previous research has shown that chronic hepatitis C and end-stage renal disease are independently associated with a lower rate of obesity [7]. In particular, each 1 kg/m^2 decrease of body mass index was associated with a 1.09-fold increased OR of active HCV [27]. A partial regression leverage plot examining the basal metabolic rate (BMR) effect on MIS found no a linear relationship; low BMR has a mildly positive influence on MIS (see Table 3).

It has been reported that HCV replication disturbs the endoplasmic reticulum (ER) of hepatocytes, leading to ER stress, stimulation of ER protein degradation and decreased synthesis of albumin (MIS 9) and other proteins [33]. Muscle wasting (MIS 7) and decreased fat tissue (MIS 6)

Table 4. Viral load, MIS and cytokine levels at baseline and the last day of follow-up in the active HCV group and non-HCV group

	Baseline			Last follow-up day		
Variables	Non-HCV ($n = 95$)	Active HCV ($n = 58$)	P-value[d]	Non-HCV ($n = 95$)	Active HCV ($n = 58$)	P-value[d]
HCV viral load						
Viral load, ($\times 10^6$ IU/mL)	ND	346.4 (81.6, 1128.0)		ND	498.0 (1184.0, 1632.0)	0.005**[c]
MIS[a,b]						
Total score	4 (2, 7)	6 (3, 8)	0.034*	5 (3, 7)	6.5 (4, 10)	0.009*
MIS 1	0.08 ± 0.35	0.15 ± 0.52	0.37	0.26 ± 0.69	0.39 ± 0.86	0.36
MIS 2	0.38 ± 0.57	0.43 ± 0.53	0.42	0.29 ± 0.48	0.38 ± 0.62	0.58
MIS 3	0.08 ± 0.28	0.14 ± 0.35	0.30	0.11 ± 0.31	0.14 ± 0.39	0.75
MIS 4	0.41 ± 0.78	0.69 ± 0.98	0.06	0.51 ± 0.87	0.71 ± 0.99	0.13
MIS 5	1.12 ± 0.89	1.53 ± 0.79	0.006*	1.27 ± 0.78	1.55 ± 0.75	0.031*
MIS 6	0.35 ± 0.65	0.43 ± 0.965	0.29	0.26 ± 0.62	0.50 ± 0.73	0.012*
MIS 7	0.80 ± 0.74	1.07 ± 0.87	0.07	0.53 ± 0.71	0.98 ± 0.95	0.002*
MIS 8	0.35 ± 0.73	0.31 ± 0.68	0.81	0.31 ± 0.73	0.24 ± 0.57	0.66
MIS 9	0.66 ± 0.65	0.83 ± 0.82	0.32	0.72 ± 0.66	1.14 ± 0.76	0.001*
MIS 10	0.64 ± 0.63	0.45 ± 0.53	0.08	1.02 ± 0.69	0.89 ± 0.67	0.24
Cytokine profiles[b]						
IL-6 (pg/mL)	17.5 (11.1, 37.9)	13.8 (7.9, 26.2)	0.041*	ND		
TNF alpha (pg/mL)	2.6 (1.0, 3.1)	2.7 (1.0, 3.2)	0.72	ND		
Adiponectin (pg/mL)	269.3 (210.1, 352.2)	281.5 (244.3, 350.5)	0.25	ND		
ADAM (pg/mL)	29.7 (22.8, 34.1)	27.2 (21.4, 33.8)	0.36	ND		

ND, not done. P-value for HCV viral load is observed using Wilcoxon sign-rank test for the within-group test.
[a]Data are presented as median (Q1, Q3).
[b]Data are presented as mean ± SD.
[c]P-value for HCV viral load is observed from comparison using two-sample Wilcoxon rank-sum test.
[d]P-value (except for HCV viral load) is observed from comparison using two-sample *t*-test for the between-group test.
*P-value < 0.05 between groups.
**P-value < 0.05 of HCV viral load within groups.

due to uremic anorexia may also reflect malnutrition status. In MHD patients, HCV infection appears to negatively impact nutritional and inflammation status and may be associated with decreased survival rate [17]. Pro-inflammatory cytokines generated during HD appear to play central roles in MICS [16]. In addition, HCV-infected MHD patients have increased plasma pentosidine and GPT levels, possibly due to increased oxidative stress [34]. All of these previous findings agree with the results of the present study.

Nascimento *et al.* [32] investigated the effect of hepatitis C on two markers of systemic inflammation (hs-CRP and IL-6) and reported that the levels were not significantly different in HD patients who were HCV positive and HCV negative. In the present study, our active HCV group had a higher level of GPT at the 7-month follow-up, indicating a possible association of virus replication and liver damage. Therefore, we support the importance of monthly testing of serum transaminase level in HD patients, particularly if HCV infection is suspected [2].

HCV-infected patients usually have higher iron and ferritin levels due to hepatic inflammation. Our active HCV group had the highest ferritin level in the first month of the study, and this declined significantly during our observation period due to the cessation of intravenous iron supplementation and the administration of vitamin C (1000 mg/week) to enhance body iron utility. However, transferrin saturation remained higher in this group at the 7-month follow-up. Recent research has indicated that genes involved in iron metabolism influence iron overload and development of steatosis, but that HCV infection and host metabolic factors are the major causes of iron overload [35].

In the present study, we found no significant difference in HOMA-IR between the two groups at baseline and no significant correlation of HOMA-IR with viral load. In contrast, a recent Japanese study of MHD patients reported that HCV infection was associated with high insulin resistance (IR), high insulin concentration and independently associated with high serum glucose prevalence and high GPT, indicating an association of HCV infection and hyperinsulinemia [36]. Hsu *et al.* [37] studied patients with chronic hepatitis C and reported that higher HCV RNA levels were associated with IR in a dose-dependent manner. Adherence to overnight fasting can influence the results of the HOMA-IR test, and this may explain why our results disagree with those of these previous studies.

The inactive HCV group (anti-HCV positive/HCV RNA-negative serology), which constituted 10.5% (18/171) of our non-HCV cohort, experienced previous HCV eradication either spontaneously or after successful antiviral therapy. This percentage is similar to that reported in the study of Kalantar-Zadeh *et al.* [27], who reported an HCV clearance rate of 7.8%, would be relatively low compared with such distinctly different patient populations as children or young adults.

The recent Kidney Disease Improving Global Outcome guidelines for management of HCV in chronic kidney disease patients recommended that the decision to initiate antiviral treatment should be based on the potential benefits and risks of therapy, such as life expectancy, candidacy for kidney transplantation and presence of comorbidities [38]. We suggest that the MIS may provide a useful measure of patient status before initiation of interferon therapy and in predicting short-term clinical outcome, such as hospitalization and

mortality. However, the physiological and molecular mechanisms that underlie the MIS require further investigation.

The present study has several limitations. Firstly, our patient population was relatively small and our follow-up period was relatively brief. However, even in the 7 months of our study, we noted that patients with active HCV infection had a significant MICS. Secondly, we did not have access to patients' previous exposure to HCV, so cannot confirm the exact relationship between HD and HCV infection. Ideally, the HCV RNA titers of the 18 patients with inactive HCV infection should have been checked after an additional $\geq$3 months to exclude the possibility of undetectably low titers. It is also possible that some of the patients in our 'active HCV group' were chronic HCV patients, but our study did not aim to stratify patients into chronic and acute disease states. Thirdly, our blood sampling technique should be reviewed to examine the possibility of heparin-related attenuation of HCV infection [27]. Finally, we cannot rule out the possibility that seroconversion was nosocomial (transmitted during dialysis). However, nosocomial HCV infection control was not the subject of our study.

Conclusion

There is an urgent need to identify the most effective treatment(s) for MHD patients who have active HCV infection so that HCV can be treated promptly. The present study demonstrated that HCV infection is a strong independent predictor of MICS in Taiwanese MHD patients and that MIS can be used to evaluate the short-term clinical outcome of MHD patients with active HCV infection. We suggest simple observation for those who have spontaneous clearance of HCV at 16 weeks after the onset of acute hepatitis C so as to avoid unnecessary treatment. Careful independent validation and verification of this study and previous studies are necessary before treatment modalities can be definitely recommended for treatment of MHD patients who have active HCV infections.

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Conflict of interest statement. None declared.

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