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Original Article

Clinical characteristics and mortality in hepatitis C-positive haemodialysis patients: a population based study

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Abstract

Background. The association between hepatitis C virus (HCV) infection and clinical and laboratory measures in maintenance haemodialysis (MHD) patients are poorly understood.

Methods. We analyzed data from over 37 000 MHD patients who underwent MHD for at least 3 months in DaVita dialysis clinics across USA in July 2001.

Results. The presence of HCV infection was determined using enzyme immunoassay (EIA), which was performed in 2778 MHD patients and was positive in 363 (13%) individuals. In a multivariate logistic regression model that adjusts for case-mix and available surrogates of malnutrition-inflammation complex syndrome (MICS), the following were independent predictors of HCV infection: younger age, male gender, Black race, Hispanic ethnicity, higher haemoglobin, lower serum albumin, higher total iron binding capacity, higher creatinine, and higher serum glutamic oxaloacetic transaminase (SGOT). Among receiver operating characteristics of commonly measured laboratory values in this population, the SGOT had the highest area. An SGOT $\geq$25 u/l had an adjusted odds ratio of 4.96 (95% confidence interval: 3.75–6.57) for HCV antibody positivity (sensitivity 50%, specificity 87%). HCV EIA positivity among MHD patients younger than 65 years was associated with 40–80% higher hazard ratio of all-cause and cardiovascular death during the 2 year follow-up (July 2001 to June 2003) after adjustment for case-mix and measures of MICS.

Conclusion. HCV infection, as diagnosed by EIA, has distinct racial, age and laboratory predilections in MHD patients. HCV positivity among MHD patients younger than 65 years is associated with significantly higher cardiovascular mortality. More diligent HCV detection and treatment may improve cardiovascular survival in MHD patients.

Keywords: cardiovascular death; haemodialysis; hepatitis C; malnutrition-inflammation complex syndrome; receiver operating characteristics; SGOT

Introduction

Hepatitis C (HCV) infection is the most common cause of chronic liver disease in the world and is also common among maintenance haemodialysis (MHD) patients [1]. However, its prevalence and natural course among over a quarter of a million MHD patients in the United States is poorly defined [1]. The prevalence of HCV infection in MHD patients has been estimated to be between 5 and 40% [2,3]. Moreover, data describing the relationship between the clinical features and outcomes of HCV infection in this population are scant.

Approximately two-thirds of all MHD patients in the USA die within 5 years of the initiation of maintenance dialysis treatment, mostly due to cardiovascular (CV) disease [4]. A strong association between the elements of malnutrition-inflammation complex syndrome (MICS) and poor clinical outcome has been observed in this population [5]. Similar to MICS, HCV infection has been noted to be associated with increases in serum inflammatory cytokines such as C-reactive protein, interleukin-6, interleukin-1b and tumour necrosis factor-α [6]. There are suggestions that HCV infection is associated with markers of MICS in the MHD population, but this area remains largely unexplored [7].

Several investigations have found a relationship between HCV infection and mortality in MHD patients. Pereira *et al.* [8] showed that death from all causes in

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HCV-infected dialysis patients was 41% higher than HCV uninfected dialysis patients. Espinosa *et al*. [9] found that mortality among MHD in Spain who were anti-HCV antibody positive was 12.2 *vs* 9.2% among those negative for anti-HCV antibody. Stehman-Breen *et al*. [10] examined 200 MHD patients for HCV infection using polymerase chain reaction (PCR) testing and found that HCV PCR-positive patients were at significantly increased risk of death compared to those who were HCV PCR negative. Although a larger study from Japan of 1470 patients found an association between HCV infection and death [11], no studies have investigated the relationship between HCV infection and death from a population perspective and none have adjusted for markers of MICS, which are associated with mortality.

To better characterize the impact of HCV on short-term cardiovascular mortality and other clinical characteristics in MHD patients, we studied a large national database of MHD patients in the United States. We hypothesized that in HCV-positive patients, measures of MICS are more prevalent and in turn may be predictive of cardiovascular and all-cause mortality. We compared the all-cause and cardiovascular mortality between HCV antibody-positive and -negative patients and hypothesized that HCV-infected MHD patients have distinct demographic, clinical and laboratory characteristics that can be used to screen for HCV infection.

Subjects and methods

Patient population

The associations between several risk factors and mortality have recently been studied in a 2 year cohort (July 1, 2001 and June 30, 2003) of all MHD patients in DaVita dialysis facilities throughout the United States [12,13]. We examined the cohort's data to obtain information pertaining to the HCV antibody status at the start of this cohort, which had been defined as occurring between July 1 and September 30, 2001. The study was approved by the Institutional Review Committees of both Harbor-UCLA and DaVita Clinical Research. Due to the nature of the proposed study, the requirement for a written consent form was exempted.

Clinical and demographic data

All repeated measures for each patient during the first 3 months of the cohort were averaged to obtain the baseline quarterly mean values. Patient's averaged post-dialysis weight and baseline height was used to calculate the body mass index (BMI = weight [kg]/height squared [m^2]). Dialysis vintage was defined as the duration of time between the first day of dialysis treatment and the first day that the patient entered the cohort. The computerized causes of death, reflecting the reported information in the Cause of Death form (Form 2746), were obtained. Cardiovascular death was defined as death due to myocardial infarction, cardiac arrest, heart failure, cerebrovascular accident and other cardiac causes.

Laboratory data and surrogates of MICS

Blood samples were drawn using uniform techniques in all DaVita dialysis clinics across the nation and were transported to the DaVita Laboratory in Deland, Florida, usually within 24 h. The HCV antibody status was examined using the third generation of HCV enzyme immunoassay (EIA version 2.0; Abbott Laboratories, Abbott Park, IL). All laboratory values were measured via automated and standardized methods in the DaVita Laboratory. Most laboratory values, including complete blood cell counts and serum levels of urea nitrogen, albumin, creatinine, ferritin and total iron binding capacity (TIBC), were measured monthly. Serum ferritin was measured quarterly. Haemoglobin was measured weekly to bi-weekly in most patients. Kt/V was used to estimate dialysis dose and normalized protein equivalent of total nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR), an estimation of daily protein intake, were measured monthly as a measure of protein intake. Most blood samples were collected pre-dialysis with the exception of the post-dialysis serum urea nitrogen to calculate urea kinetics.

Eight laboratory variables were selected as surrogates of the nutritional state and/or inflammation, together also known as MICS [5], with known association with mortality: (i) serum albumin; (ii) nPNA as an indicator of daily protein intake; (iii) serum TIBC, which has a strong association with subjective global assessment of nutrition [14]; (iv) serum ferritin, a possible inflammatory marker [15]; (v) serum creatinine, an indicator of muscle mass; (vi) peripheral white blood cell count (WBC), which correlates with serum C-reactive protein in MHD patients [16]; (vii) lymphocyte percentage, a known nutritional marker that can decrease with protein-energy malnutrition and in MHD patients [16]; and (viii) haematocrit.

Epidemiologic and statistical methods

Sensitivity (sens) was defined as the proportion of positive tests among HCV-infected MHD patients (using HCV EIA as the 'gold standard'). Specificity (spec) was the proportion of negative tests among non-HCV-infected patients. Positive predictive value (PPV) was the proportion of true HCV-infected patients among those with a positive test, and negative predictive value (NPV) was the proportion of non-HCV-infected patients among those with a negative test. Receiver operating characteristics (ROC) displayed the plot of sensitivity *vs* 1-specificity for different cutoff levels of a given screening test. Bayes' theorem [17] was applied to estimate the post-test probability (post) based on the pre-test probability (pre), i.e., the prevalence of HCV infection among all those who underwent the HCV EIA test, using the following equations:

$$\text{If the test is positive: post} = (\text{sens} * \text{pre})/[(\text{sens} * \text{pre}) + (1 - \text{spec})(1 - \text{pre})]$$

$$\text{If the test is negative: post} = [(1 - \text{sens}) * \text{pre}]/\{[\text{spec} * (1 - \text{pre})] + [(1 - \text{sens}) * \text{pre}]\}$$

In addition to standard descriptive statistics, multivariate logistic regression models were fitted to construct odds ratio of HCV infection controlling for confounding covariates.

Survival analyses included Kaplan–Meier and log-rank tests and Cox proportional hazard regression models, which were examined to determine whether the 2 year survival was associated with HCV infection. For each analysis, three models were examined based on the level of multivariate adjustment: (i) an unadjusted model that included mortality data; (ii) case-mix adjusted models that included age, gender, race and ethnicity, diabetes mellitus, vintage categories, entry quarter, primary insurance (Medicare, Medicaid, private/others), marriage status (married, single, divorced, widowed/other), standardized mortality ratio of the dialysis clinic during entry quarter, Kt/V (single pool), and residual renal function during the entry quarter, i.e. urinary urea clearance; and (iii) case-mix and MICS adjusted models included all of the above-mentioned covariates as well as eight surrogates of nutritional status and inflammation including BMI and eight above-mentioned laboratory values. Missing covariate data (<5%) were imputed by the mean or median of the existing values, whichever was most appropriate. All descriptive and multivariate statistics were carried out with the SAS, version 8.02 (SAS Institute, Inc., Cary, NC), and 'Stata version 7.0' (Stata Corporation, College Station, TX).

Results

The DaVita national database of all maintenance dialysis patients across the nation between July 1 and September 30, 2001, included 40 902 patients who had a unique identifier. After deletion of all patients who received peritoneal dialysis for 1 month or longer during this period and those who had inadequate or overtly missing data, the resulting database included 37 049 MHD patients. In 2778 patients (7%) the HCV antibody serology test (EIA) was documented electronically during the above-mentioned 3 month period. Among these 2778 patients, 363 (13%) had a positive HCV EIA test, while the remaining 2415 (87%) MHD patients were reported as HCV antibody negative.

Table 1 shows baseline demographic, clinical and laboratory characteristics of the entire database, as well as those with HCV EIA test results. HCV-positive patients were more likely to be men than either the HCV negative or the entire database. African Americans comprised 55% of all HCV-positive subjects, compared to less than one-third of all MHD and HCV-negative patients. Many patients with a documented HCV test had undergone dialysis for <6 months, indicating a more frequent use of HCV screening at the start of maintenance dialysis treatment. The prevalence of Medicaid insurance coverage status among HCV-positive patients was twice as high as in other groups. HCV-infected patients were a mean of 5 years younger than the average MHD patients. Diabetes mellitus was less prevalent in HCV-infected patients, but the difference lost statistical significance

Table 1. Demographic, clinical and laboratory characteristics of HCV antibody positivity in 37 049 MHD patients, including 2778 MHD patients who were tested for HCV antibody

	All MHD patients	HCV antibody tested ($n=2778$), including 1551 patients younger than 65 years		*P*-value
		HCV−	HCV+	
Number of patients	37 049	2415 (87%)	363 (13%)	n/a
Patients younger than 65 years	20 877	1277 (82%)	274 (18%)	n/a
Patients 65 years or older	16 172	1138 (93%)	89 (7%)	n/a
Gender (% female)	47	47	36	0.0001
Race (% African American)	32	31	55	<0.0001
Ethnicity (% Hispanic)	15	13	13	0.72
Diabetes (%)	45	45	39	0.02
Incident patients (% with vintage <6 months)	19	44	35	0.0005
Medicaid (%)	5	5	10	0.0009
Age (years)	60.8 ± 15.5	61.5 ± 15.8	55.7 ± 13.1	<0.0001
Post-dialysis weight (kg)	73.8 ± 19.8	75.3 ± 20.1	72.4 ± 17.3	0.01
Body mass index (kg/m^2)	26.1 ± 6.3	26.7 ± 6.4	25.2 ± 5.6	<0.0001
Kt/V (single pool)	1.54 ± 0.32	1.54 ± 0.32	1.48 ± 0.3	0.0007
nPNA or nPCR (g/kg/day)	0.99 ± 0.25	0.99 ± 0.25	1.00 ± 0.26	0.49
Serum albumin (g/dl)	3.74 ± 0.41	3.75 ± 0.40	3.66 ± 0.47	0.0003
Creatinine (mg/dl)	9.0 ± 3.4	8.8 ± 3.4	10.1 ± 3.4	<0.0001
TIBC (mg/dl)	202 ± 43	202 ± 43	222 ± 48	<0.0001
Ferritin (ng/ml)	609 ± 521	575 ± 537	545 ± 543	0.32
Iron (ng/ml)	58 ± 29	59 ± 27	73 ± 34	<0.0001
SGOT/AST (u/l)	18 ± 15	18 ± 20	34 ± 28	<0.0001
LDH (u/l)	183 ± 52	187 ± 55	199 ± 61	0.001
Intact PTH (pg/ml)	330 ± 356	338 ± 356	422 ± 423	0.0001
Calcium (mg/dl)	9.2 ± 0.7	9.2 ± 0.7	9.1 ± 0.8	0.02
Phosphorus (mg/dl)	5.7 ± 1.5	5.6 ± 1.5	5.8 ± 1.6	0.09
Blood haemoglobin (g/dl)	11.9 ± 1.3	11.9 ± 1.4	12.0 ± 1.5	0.19
WBC (×1000/HPF)	7.3 ± 2.4	7.4 ± 2.6	6.8 ± 2.4	0.0002
Lymphocyte percentage	21 ± 8	20 ± 8	23 ± 8	<0.0001

P-value compared HCV antibody-positive and -negative patients among those who had a documented HCV EIA test.

when adjusted for age and race (data not shown here). Among laboratory parameters, serum albumin was slightly lower but TIBC and intact parathyroid hormone (PTH) were higher in HCV-positive subjects compared to HCV-negative patients. Strikingly, serum glutamic oxaloacetic transaminase (SGOT), also known as aspartate aminotransferase (AST), was almost twice as high in HCV-positive patients as in HCV-negative subjects. Nevertheless, the mean value in HCV-positive patients was 34 u/l, which is within the 'normal' range of most commercial assays.

Using multivariate logistic regression models, the association between demographic, clinical and laboratory characteristics and the risk of HCV positivity was examined among all 2778 MHD patients who had a documented HCV EIA test result (Table 2). Younger age (<65 years) and African American race were each associated with over two times higher odds of HCV positivity. The adjusted odds of HCV infection were also 67% higher in men than women and 54% higher among Hispanic patients than other ethnic groups. Higher blood haemoglobin, higher serum creatinine, TIBC and SGOT, and lower albumin were significantly associated with higher risk of HCV infection. For each 10 u/l increase in SGOT (AST), the adjusted odds of HCV infection were increased by 16%. Table 3 shows the calculated adjusted odds ratios and sensitivity analyses for several selected cutoff levels of the SGOT after dichotomizing this laboratory value into two hypothetical groups of normal (negative test) *vs* higher than normal (positive test). The adjusted odds of HCV positivity for patients with an SGOT of 25 u/l or higher was almost five times greater than those with an SGOT below this level. While this test was only 50% sensitive in detecting HCV-positive MHD patients, its specificity was 87%. Using Bayes' theorem and assuming a pretest probability of 13% based on the prevalence of HCV infection found in this study, the post-test probability of HCV infection for those with an SGOT ≥25 u/l would be 37% and for SGOT <25 u/l only 8% (see Table 3). Figure 1 (upper and lower panels) displays the results of the above-mentioned sensitivity analyses and the comparison among the ROC area for different cutoff levels of the SGOT.

Table 4 shows the relative risk of both all-cause and cardiovascular mortality that is associated with the HCV infection at three levels of multivariate adjustment using Cox proportional hazard regression. Among the entire age range there was no crude (unadjusted) association between the HCV infection and death over 24 months of follow-up (Figure 2, upper panel). After controlling for case-mix variables, there was a 28% increase in all-cause mortality and 48% increase in cardiovascular mortality risk among HCV-positive patients. However, the statistical significance of these associations mitigated after additional controlling for the available markers of MICS. Stepwise deletion of case-mix covariates indicated that age played a major confounding role. Hence, the same associations were re-examined among MHD patients younger than 65 years only. As shown in the lower panel of Table 4, the HCV infection was associated with 41–50% higher all-cause and 68–80% higher cardiovascular death risk in this population. The lower panel of Figure 2 displays the Kaplan–Meier based cumulative proportion survival based on HCV

Table 2. Risk factors for HCV antibody positivity in 2778 MHD patients

	Odds ratio	*P*-value
Age (each 10 years younger)	1.18 (1.08–1.29)	<0.0001
Age <65 years (*vs* ≤65 years)	2.26 (1.69–3.00)	<0.0001
Male gender (*vs* female)	1.67 (1.22–2.28)	0.001
Black (*vs* other races)	2.68 (2.00–3.58)	<0.0001
Hispanic (*vs* other ethnicities)	1.54 (1.04–2.27)	0.03
Blood haemoglobin (every 1.0 g/dl increase)	1.15 (1.05–1.26)	0.004
Serum albumin (every 0.2 g/dl decrease)	1.40 (1.31–1.50)	<0.0001
TIBC (every 10 mg/dl increase)	1.17 (1.14–1.21)	<0.0001
Creatinine (every 1 mg/dl increase)	1.06 (1.01–1.12)	0.01
SGOT or AST (for each 10 u/l increase)	1.16 (1.09–1.23)	<0.0001

Odds ratios (and 95% confidence intervals) are calculated using multivariate logistic regression.

Table 3. Multivariate adjusted odds ratio and diagnostic features of seven different cutoff levels of serum SGOT (AST) concentration in relation to HCV antibody positivity in 2778 MHD patients

SGOT cutoff level	Odds ratio of HCV+	ROC area	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Post-test Probability of HCV	
							If positive test (%)	If negative test (%)
SGOT ≥20 u/l	4.33 (3.32–5.65)	0.70	66	75	28	94	28	6
SGOT ≥25 u/l	4.96 (3.75–6.57)	0.69	50	87	37	92	37	8
SGOT ≥30 u/l	4.86 (3.54–6.67)	0.65	37	93	44	91	44	9
SGOT ≥35 u/l	3.90 (2.70–5.61)	0.61	27	95	46	90	45	10
SGOT ≥40 u/l	4.04 (2.63–6.20)	0.58	20	97	48	89	50	11
SGOT ≥45 u/l	3.20 (1.98–5.16)	0.56	15	98	48	88	53	12
SGOT ≥50 u/l	3.26 (1.91–5.55)	0.55	17	99	61	89	72	11

Post test probability is estimated using Bayes' equation assuming a pre-test probability of 13% HCV infection among all MHD patients. PPV, positive predictive value; NPV, negative predictive value.

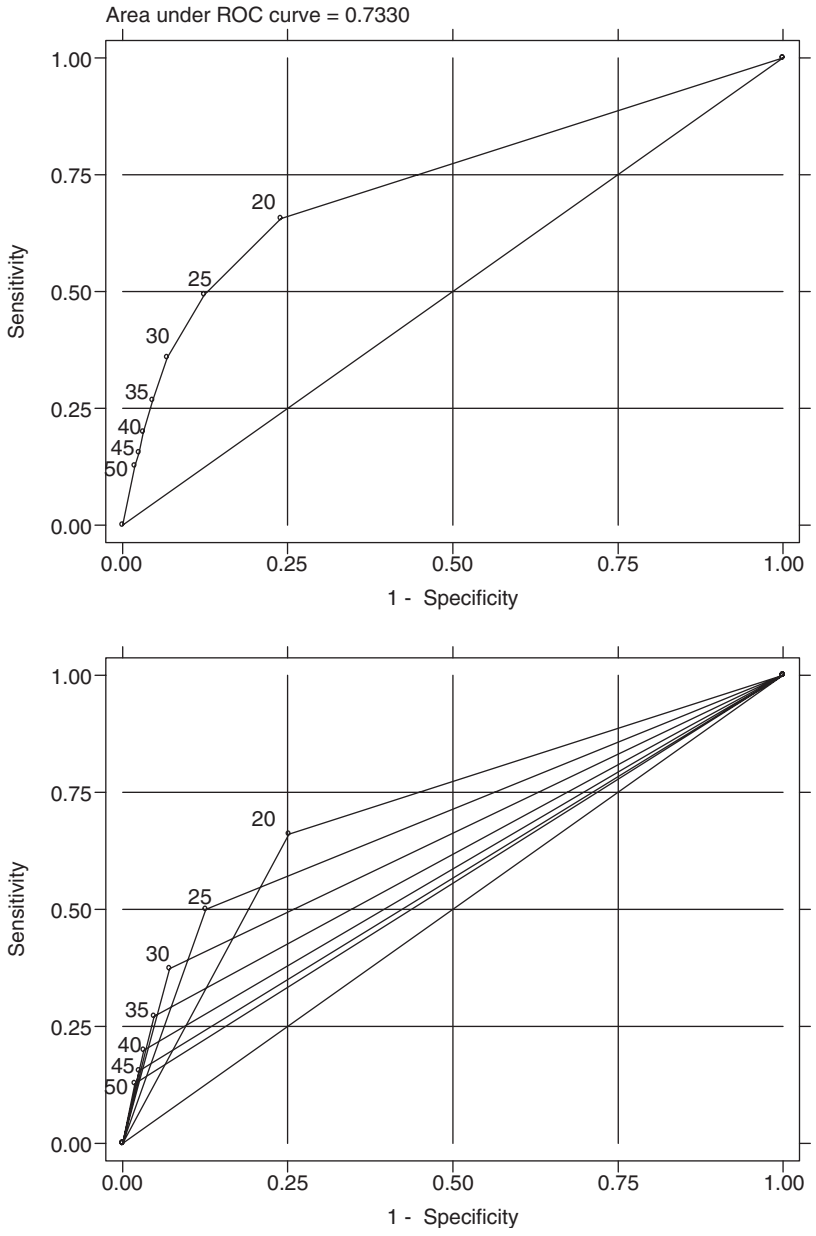

Fig. 1. Receiver operating characteristic (ROC) curve for seven cutoff levels of serum SGOT (AST) concentration for diagnosis of HCV antibody positivity in 2778 MHD patients. Upper panel, continuous ROC curve; lower panel, comparative curves.

antibody status in MHD patients younger than 65 years ($P = 0.006$).

Discussion

We have shown that in 2778 MHD patients who were selected among over 37 000 MHD patients across the United States to undergo the HCV EIA test, 13% had a positive HCV antibody. In a multivariate logistic regression model adjusting for case-mix and available surrogates of malnutrition and inflammation, younger age, male gender, African-American race, Hispanic ethnicity and lower serum albumin were independent predictors of HCV infection. The SGOT (AST) was found as the laboratory test with the strongest association with HCV antibody positivity. Moreover, HCV antibody positivity among MHD patients younger than 65 years was associated with 40–80% higher hazard ratio of all-cause and cardiovascular death during the 2 year follow-up even after adjustment for case-mix and MICS. Our analysis of HCV infection among a large group of US MHD patients with multivariate adjustment for a wide spectrum of important clinical and laboratory parameters indicates that HCV infection may be related to increased short-term cardiovascular disease and death among MHD patients.

HCV infection is common among MHD patients, but its exact prevalence is not clear as most studies are

Table 4. Death hazard ratio for HCV antibody positivity in 2778 MHD patients (top) and 1551 MHD patients younger than 65 years (bottom)

	All-cause mortality		Cardiovascular death	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
All MHD patients ($n=2778$)				
Unadjusted	1.04 (0.83–1.30)	0.34	1.19 (0.86–1.66)	0.28
Case-mix	**1.28** (1.02–1.62)	**0.03**	**1.48** (1.05–2.08)	**0.02**
Case mix and MICS	1.16 (0.90–1.48)	0.24	1.43 (1.00–2.06)	0.05
MHD pts <65 years ($n=1551$)				
Unadjusted	**1.50** (1.12–2.00)	0.006	**1.68** (1.09–2.59)	0.02
Case-mix	**1.50** (1.11–2.03)	0.008	**1.76** (1.12–2.77)	0.01
Case mix and MICS	**1.41** (1.01–1.97)	0.04	**1.80** (1.10–2.95)	0.02

Unadjusted and case-mix and MICS adjusted hazard ratios for all cause and CV mortality are calculated using multivariate Cox regression models.

from single centre investigations or were performed before more stringent infection control measures to control HCV infection in dialysis centres were in place [1–3]. Even though the prevalence of positive HCV serology is believed to be decreasing to pre-dialysis patient population levels [9], our current study indicates a prevalence of 13% among those whose HCV antibody status was screened via the EIA in mid-2001. A selection bias might exist in choosing MHD patients for the HCV screening, especially since in our database the proportion of HCV EIA-tested patients who newly started MHD was twice as high as those who did not undergo HCV testing, i.e., 35–44% *vs* 19%, respectively (see Table 1). However, all other demographic, clinical and laboratory features, including liver enzymes, were very similar among the 2415 HCV antibody-negative patients and the rest of the 37 000 patient cohort. Moreover, when only newly started MHD patients in the main cohort were compared to the HCV-negative patients, the same similarities were observed (data not shown).

In our investigation, as in others, the EIA was assumed as the reference standard of HCV infection. However, molecular-based assays that detect HCV RNA such as PCR and transcription mediated amplification are somewhat more sensitive diagnostic tests and may pick up additional HCV-infected patients that are EIA-negative [18]. Hence, it is likely that the true prevalence of the HCV infection in our population is higher than detected by the EIA test and that the misclassification of a small proportion of EIA-negative but HCV-infected patients may have introduced some bias towards null into our results.

Our current study indicated that HCV infection was significantly more common among younger MHD patients, especially those from minority racial and ethnic backgrounds, than the general dialysis population. Over half of HCV-infected patients in our study were African Americans. In another observational study of dialysis patients who underwent renal transplantation, HCV infection was also found to be associated with African American race [2]. This finding may be due to socio-economical constellations rather than true impact of race, as reflected by the higher prevalence of Medicaid insurance among HCV-positive subjects, even though we controlled for insurance status in our multivariate models. Another interesting finding was a significantly higher serum intact PTH among HCV-infected patients, which persisted even among African American patients. This condition may be due to the so-called 'hepatic osteodystrophy', which has been described in non-dialysis subjects with hepatitis [19].

A key finding in our study was the significantly higher short-term all-cause and cardiovascular mortality rate among the HCV-infected dialysis patients. Our original hypothesis that this association could be due to MICS in HCV-positive subjects was only partially confirmed, since serum albumin was significantly lower but TIBC was paradoxically higher in these patients compared to HCV-negative individuals. However, direct markers of inflammation such as pro-inflammatory cytokines were not available in our study. Moreover, after a very comprehensive multivariate adjustment for nine available surrogates of MICS, the association between HCV infection and mortality was mitigated in the entire study population, but persisted significantly among those younger than 65 years. Hence, we conclude that, at least among younger MHD patients, HCV is associated with poor survival and higher short-term cardiovascular death through yet-to-be-determined factors.

The association between SGOT and HCV antibody positivity, although not unexpected, appears to have some clinical utility. The relationship between hepatitis C infection and SGPT (ALT) is better described [1]. However, ALT has limited clinical utility because among the liver transaminiases, only the SGOT is routinely measured in the US dialysis population. Our analyses found that in MHD patients with an SGOT >25 or 30 u/l, i.e., upper range of normal, a strong likelihood of HCV infection coexists. The post-test probability of HCV infection is as high as 72% among those whose SGOT is >50 u/l (see Table 3). It is important to note that in our study all laboratory values, including the SGOT, were averaged values of three consecutively (monthly) measured blood tests, and not just a single measurement. Our data support

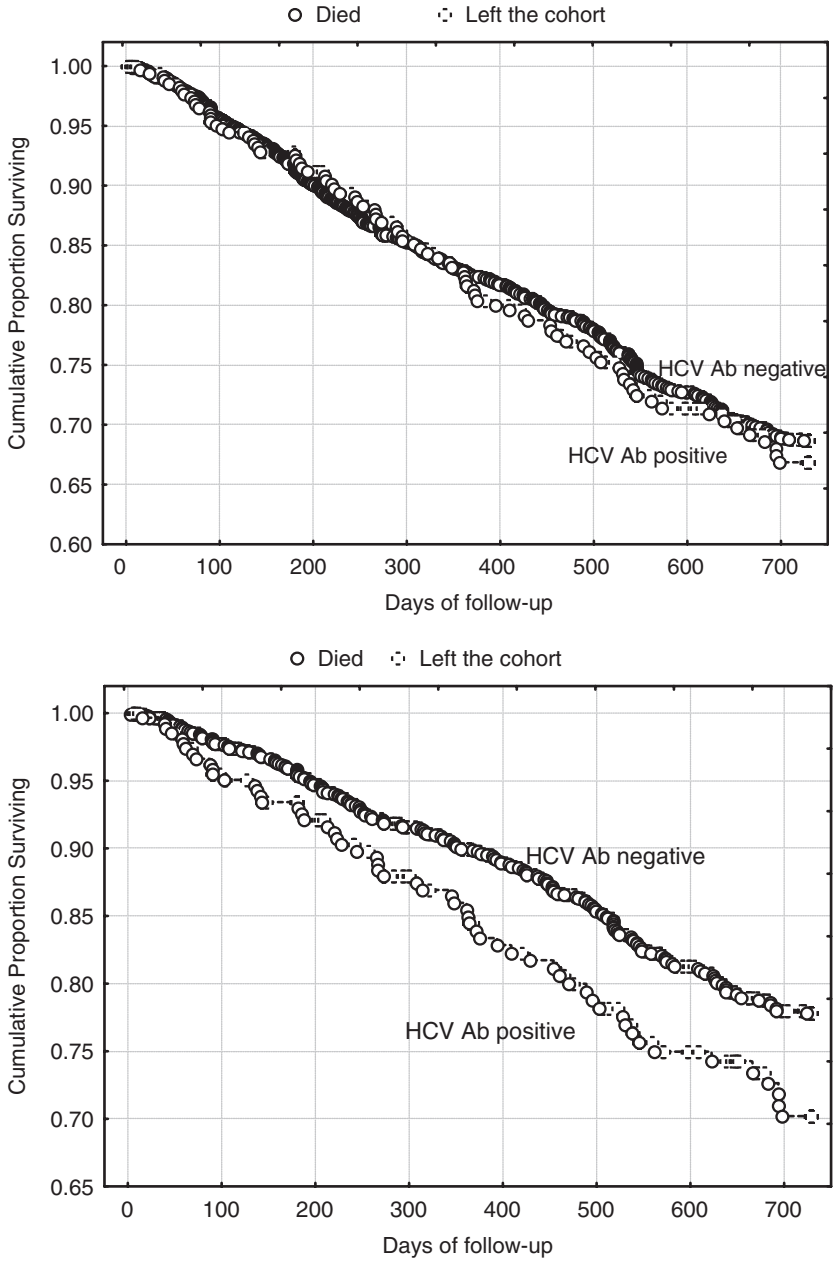

Fig. 2. Kaplan–Meier cumulative proportion of surviving patients according to HCV antibody positivity in 2778 MHD patients. Upper panel, all age groups ($n = 2775$); lower panel, MHD patients younger than 65 years ($n = 1551$).

the concept that even high 'normal' transaminases suggest a patient is at high risk for HCV infection and that normal transaminases do not exclude a diagnosis of this infection [20].

Our database lacked systematic information on the history of cardiovascular comorbidity. However, as discussed in our previous analyses of the same database [12,13], data concerning diabetes mellitus were available and adjusted for in all multivariate models. Moreover, many other covariates that were included in the models (e.g., serum albumin) are known to have strong associations with comorbid conditions. Hence, we suspect that the associations would not have been very different if additional adjustments had been made for other comorbidities. This is even more so the case in the analyses of MHD patients younger than 65 years, who usually have fewer comorbidities compared to patients over 65. Nevertheless, among these young MHD patients, HCV infection was strongly associated with a higher death rate, especially due to cardiovascular disease states. Furthermore, our adjustments are similar to past investigations, as the limited comorbidity data used in those studies usually originated from the dialysis initiation form (Form 2728), in which comorbid conditions are significantly underreported [21] and which is outdated for prevalent patients with higher vintage periods. Another limitation of our study is lack of explicit laboratory markers of inflammation such as C-reactive protein. However, we did use data on

serum ferritin and TIBC and blood WBC, lymphocyte percentage and haematocrit, which have significant association with inflammation [15]. Another limitation of our analysis is that it is based on a 2 year period of the cohort, rather than longer follow-ups over many years, and examines the data obtained during the first 3 months of the cohort. Nonetheless, our data indicate that even short-term all-cause and cardiovascular death is high in HCV-infected MHD patients. More elaborate and sensitive HCV detection tests such as molecular tests [18] were not used in our study, since such methods are substantially more costly and usually not used as screening tests. However, all laboratory measurements are performed in one single facility, and most data are means of several measures. Hence, measurement variability is minimized.

In conclusion, the demographic, clinical and laboratory features of HCV patients and their associations with mortality and cardiovascular risk found in our study have clinical utilities in the management of HCV patients. Due to the strong association of the HCV infection with death and cardiovascular disease in MHD patients, more stringent guidelines are needed to screen for HCV infection in this population. Moreover, more studies are urgently needed to verify the true prevalence of HCV infection in the 21st century among MHD patients using newer molecular testing, to better understand the natural course of HCV infection, and to evaluate the effectiveness of current and future anti-HCV treatment modalities in improving clinical outcome in young MHD patients who are at increased risk of death.

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Conflict of interest statement. Dr McAllister is an employee of DaVita, Inc. No other author declare a conflict of interest.

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