

Mortality, Hospitalization, and Quality of Life among Patients with Hepatitis C Infection on Hemodialysis

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Abstract

Background and objectives Hepatitis C virus (HCV) infection is widely prevalent among patients on hemodialysis (HD), but very rarely treated. The aim of our study is to evaluate the burdens of HCV suffered by patients on HD.

Design, setting, participants, & measurements The Dialysis Outcomes and Practice Patterns Study is an international, prospective, cohort study of patients on HD. We reviewed the HCV status of 76,689 adults enrolled between 1996 and 2015. We compared HCV-positive (HCV+) with HCV-negative (HCV-) patients for risk of mortality, hospitalization, decline in hemoglobin concentration <8.5 g/dl, and red blood cell transfusion. We also compared health-related quality of life scores using the Kidney Disease Quality of Life instrument and the Center for Epidemiologic Studies Short Depression Scale. We adjusted for age, sex, race, years on dialysis, 14 comorbid conditions (including hepatitis B infection), and serum albumin, phosphorus, and creatinine concentrations.

Results A total of 7.5% of patients were HCV+ at enrollment. Serum concentrations of alanine aminotransferase and aspartate aminotransferase were not markedly elevated in HCV+ patients on HD; the mean concentrations were only 22.6 and 21.8 U/L, respectively. Median follow-up was 1.4 years. Case-mix adjusted hazard ratios (95% confidence intervals) for HCV+ versus HCV- patients were 1.12 (1.05 to 1.20) for all-cause mortality, 5.90 (3.67 to 9.50) for hepatic-related mortality, 1.09 (1.04 to 1.13) for all-cause hospitalization, and 4.40 (3.14 to 6.15) for hepatic-related hospitalization. Quality of life measures indicated significantly worse scores for physical function, pain, vitality, mental health, depression, pruritus, and anorexia among HCV+ patients. The adjusted hazard ratio for transfusion was 1.36 (95% CI, 1.20 to 1.55) and incidence of hemoglobin concentration <8.5 g/dl was 1.12 (95% CI, 1.03 to 1.21). Only 1.5% of HCV+ patients received antiviral medication.

Conclusions HCV infection among patients on HD is associated with higher risk of death, hospitalization, and anemic complications, and worse quality of life scores. Internationally, HCV infection is almost never treated in patients on HD. Our data provide a rationale for more frequent treatment of HCV in this population.

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Introduction

Hepatitis C virus (HCV) infection is common among patients on hemodialysis (HD) worldwide, with a prevalence of 9.5% having been reported previously (1). Nosocomial HCV spread within HD facilities continues to occur, according to viral sequencing and epidemiologic evidence (2). Previous studies have reported increased mortality associated with HCV but the potential links between HCV and hospitalization, anemia, or quality of life among patients on HD remain unclear. The goal of this investigation is to study the burden of HCV infection among patients on HD enrolled in the very large, international Dialysis Outcomes and Practice Patterns Study (DOPPS) (3,4).

Materials and Methods

Patients and Data Collection

The DOPPS is an international prospective cohort study of patients on HD aged ≥ 18 years. Patients in the

DOPPS are enrolled randomly from a representative sample of dialysis facilities within each nation at the start of each study phase, as described previously (3,4).

Data from 76,689 patients on HD from Australia, Belgium, Canada, China, France, Germany, six Gulf Cooperation Council Countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates), Italy, Japan, New Zealand, Spain, Russia, Sweden, Turkey, the United Kingdom, and the United States with baseline information on HCV status were included in this study. Phase 1 of the DOPPS collected data from 1996 to 2001; phase 2 collected data from 2002 to 2004; phase 3 collected data from 2005 to 2008; phase 4 collected data from 2009 to 2011; and phase 5 collected data from 2012 to 2015. Data collection in Australia, Belgium, Canada, New Zealand, and Sweden did not begin until phase 2. Data collection in China, the Gulf Cooperation Council countries, Russia, and Turkey did not begin until phase 5. Study approval was obtained by a central institutional

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review board. Patient consent was obtained as required by national and local ethics committee regulations.

Demographic data, comorbid conditions, laboratory values, and medications were abstracted from patient records. Medication prescriptions were collected at entry and every 4 months during phases 1, 3, 4, and 5, and at entry and once yearly during phase 2. To examine the use of anti-HCV medications, we searched the prescription database for both proprietary and generic drug names of formulations of IFN and ribavirin, as well as the following new, oral agent terms: Daklinza (daclatasvir), Harvoni (ledipasvir, sofosbuvir), Incivek (telaprevir), Olysio (simeprevir), Sovaldi (sofosbuvir), Sovriad (simeprevir), Sunvepra (asunaprevir), Technivie (ombitasvir, paritaprevir), Victrelis (boceprevir), Viekira Pak (dasabuvir, ombitasvir, paritaprevir), Zepatier (ebasvir, grazoprevir). HCV status was determined on the basis of an established diagnosis of HCV infection or positive HCV serology at DOPPS enrollment. Thereafter, HCV serology was collected every 4 months in phase 1, yearly in phase 2, and monthly in phases 3–5. Mortality and hospitalization events were collected during study follow-up. Patient-reported measures were collected from self-reported questionnaires at study enrollment during each phase. Health-related quality of life was assessed using the Kidney Disease Quality of Life (KDQOL-36) instrument and summarized for the Physical Component Summary (PCS), Mental Component Summary (MCS), and Kidney Disease Burden scores (5). Responses to specific questions about pruritus and lack of appetite were analyzed separately. Self-reported depression was assessed in DOPPS phases 2–5 *via* the Center for Epidemiologic Studies Short Depression Scale (CES-D-10) (6).

Data Analyses

The primary exposure of interest was HCV status at study enrollment. Standard descriptive statistics were used to characterize the patient samples.

Models. Cox regression was used to analyze the association between HCV status and the outcomes of mortality, first hospitalization, occurrence of hemoglobin <8.5 g/dl, red blood cell transfusion, or gastrointestinal bleed during study follow-up. Models were stratified by country and phase, accounting for facility clustering using robust sandwich covariance estimators.

Time at risk started at study enrollment and ended at the time of death, 7 days after leaving the facility because of transplant or transfer, 7 days after changing modality, loss to follow-up, or at the end of data collection.

To model the associations between HCV status and patient-reported measures, mixed models for linear outcomes and generalized estimating equation models with a logit link for binary outcomes were used, accounting for facility clustering.

Variables adjusted for as potential confounders are listed in the table footnotes for each model.

Multiple Imputation. Missing data for covariates was low (*e.g.*, <5% for the majority of covariates, <14% for all). For missing data, we used the Sequential Regression Multiple Imputation Method implemented by IVEware (Imputation and Variance Estimation Software), and analyzed using the MIAnalyze procedure in SAS/STAT v9.4 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics

Table 1 shows the characteristics of HCV-positive (HCV+) and HCV-negative (HCV-) patients at time of enrollment into the DOPPS. Among the full sample of 76,689 patients, 5762 (7.5%) were HCV+. The prevalence of HCV infection among the initial cross-sections of patients enrolled in each phase of the study varied as follows (restricted to those countries that participated in all five phases): 14.3% in phase 1, 10.7% in phase 2, 8.8% in phase 3, 6.8% in phase 4, and 8.7% in phase 5. Compared with HCV- patients, the HCV+ patients were younger; had spent more years on dialysis; more frequently had GN or vasculitis as the primary cause of ESRD; had lower prevalences of hypertension, diabetes, coronary artery disease, congestive heart failure, lung disease, cerebrovascular disease, and cancer; and had higher prevalences of hepatitis B and substance abuse. Cirrhosis was notably more common among HCV+ patients (9.9%) than HCV- patients (1.4%). Cirrhosis was present among 10.0% of HCV+ patients who were hepatitis B-negative versus 9.2% of HCV+ patients who were hepatitis B-positive; thus, cirrhosis among HCV+ patients was predominantly not because of coinfection with hepatitis B virus. Also, serum creatinine concentration was higher among HCV+ patients and platelet count was lower.

Table 1 shows that serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations were higher among HCV+ patients than HCV- patients, although mean values were still within the normal ranges. Figure 1 shows the distribution of transaminase concentrations among HCV+ patients during phase 5, the only phase when ALT and AST were measured. Most values are within the normal range or slightly elevated. Only one HCV+ patient had ALT elevation >140 U/L and only one HCV+ patient had AST elevation >100 U/L.

Mortality

Patients were followed for a median of 1.4 years. The adjusted hazard ratio (HR) for HCV+ versus HCV- patients was 1.12 (95% confidence interval [95% CI], 1.05 to 1.20) for all-cause mortality, and 5.90 (95% CI, 3.67 to 9.50) for death because of a hepatic cause (Table 2). The HRs of infectious death and of cardiovascular death did not reach statistical significance, but each showed a tendency toward higher rates in HCV+ patients.

Among the HCV+ patients, serum ALT concentration >70 U/L (greater than twice the upper limit of normal; *n*=15) was associated with significant risk of mortality compared with patients with lower ALT concentrations, with an adjusted HR of 4.30 (95% CI, 1.33 to 13.89). Comparing HCV+ patients with a value above the 90th percentile for ALT (*n*=62 with ALT>41 U/L) or AST (*n*=59 with AST>39 U/L) with a reference group consisting of patients in the 50th–75th percentiles resulted in adjusted mortality HRs of 2.41 (95% CI, 1.26 to 4.63) and 3.95 (95% CI, 2.13 to 7.33), respectively.

Hospitalization

The adjusted HR for HCV+ patients versus HCV- patients was 1.09 (95% CI, 1.04 to 1.13) for all-cause

Table 1. Patient characteristics by DOPPS region and HCV status at study enrollment (DOPPS phases 1–5, 1996–2015)

Characteristic	Overall		North America		Europe ^a		Japan		Other ^b	
	HCV+	HCV–	HCV+	HCV–	HCV+	HCV–	HCV+	HCV–	HCV+	HCV–
Patients, n	5762	70,927	1732	27,740	1846	25,526	1480	10,457	704	7204
Demographics										
Age, yr	58.5 (13.6)	62.8 (15.0)	56.1 (13.2)	62.3 (15.4)	58.9 (14.6)	64.3 (15.0)	62.3 (11.4)	62.5 (12.9)	54.8 (13.9)	59.2 (15.0)
Men, %	62.2	58.4	66.8	55.0	57.1	60.7	65.3	62.7	57.3	57.1
Black race, %	4.6 [1.1, 12.8]	1.6 [0.3, 4.6]	52.1	26.9	5.9 [1.4, 15.8]	1.4 [0.3, 4.3]	7.9 [2.2, 18.5]	3.5 [0.6, 8.4]	6.3 [2.4, 12.7]	2.3 [0.7, 4.9]
Yr on dialysis	23.3 (5.1)	25.6 (6.1)	2.1 [0.3, 5.5]	1.2 [0.2, 3.6]	23.6 (4.5)	25.5 (5.2)	20.3 (3.0)	21.1 (3.3)	23.3 (5.5)	25.1 (6.0)
Body mass index, kg/m ²	11.7	10.7	16.3	11.0	15.2	13.0	6.5	4.2	6.9	10.7
Transplant waitlisted, % ^c										
Primary cause of ESRD, %										
GN or vasculitis	32.0	21.5	14.0	12.0	31.3	20.3	50.3	44.3	37.9	27.6
Cystic/hereditary/congenital	6.4	6.4	2.8	3.9	12.4	9.5	3.0	5.4	6.6	6.9
Diabetes	25.2	32.4	35.0	42.6	14.4	22.3	29.3	32.1	20.3	29.8
Obstruction	4.0	3.5	1.4	1.8	8.6	5.9	1.2	1.2	4.0	4.7
Interstitial nephritis	3.1	3.2	2.7	1.7	5.2	5.3	1.0	1.2	2.8	4.2
Hypertension	16.1	20.1	33.9	28.9	9.7	17.7	3.3	5.4	17.1	16.8
Other cause of ESRD	12.2	10.6	8.8	6.9	16.8	15.4	11.4	9.6	10.4	8.8
Comorbidities, %										
Hypertension	75.3	82.9	86.5	87.6	75.6	82.1	63.2	73.4	79.4	86.4
Coronary artery disease	33.4	41.5	44.4	53.2	30.3	38.9	30.4	27.7	27.5	39.3
Neurologic disorder	10.3	10.1	14.0	11.8	10.6	10.3	7.5	7.6	8.5	8.7
Other cardiovascular disease	31.9	31.2	27.2	32.2	37.1	34.2	34.1	26.2	21.9	25.3
Peripheral vascular disease	20.5	25.2	21.7	29.4	23.2	28.0	18.9	13.8	14.7	20.4
Diabetes	32.0	40.1	44.8	53.3	23.4	32.6	33.9	35.7	27.3	36.9
Congestive heart failure	25.5	30.2	36.8	43.0	24.8	26.1	17.3	18.9	23.9	26.5
Lung disease	8.6	11.8	13.3	16.1	10.7	12.6	3.1	2.7	6.1	10.4
Cerebrovascular disease	13.1	16.2	15.8	18.3	12.8	16.0	12.7	13.9	10.0	14.9
Recurrent cellulitis	6.3	7.8	9.8	10.5	6.9	7.8	3.2	3.4	5.0	6.7
Cancer	9.8	12.4	9.3	12.9	11.3	15.0	11.0	8.6	3.9	7.2
Gastrointestinal bleed in last yr	6.2	5.4	8.7	7.1	5.1	5.1	6.1	4.3	4.8	3.8
Psychologic disorder	18.6	16.6	35.2	24.4	21.8	17.0	3.8	4.1	10.5	11.8
Substance abuse in last 12 mo	5.1	1.7	17.9	3.6	3.2	1.2	0.5	0.2	1.0	0.8
Cirrhosis ^d	9.9	1.4	11.7	1.6	10.1	1.5	14.4	1.3	6.3	1.0
Hepatitis B	8.4	1.8	5.7	0.9	10.5	1.8	5.6	1.9	13.8	4.3
HIV/AIDS	2.8	0.6	7.7	1.6	2.0	0.3	0.4	0.5	1.0	0.1

Table 1. (Continued)

Characteristic	Overall		North America		Europe ^a		Japan		Other ^b	
	HCV+	HCV-	HCV+	HCV-	HCV+	HCV-	HCV+	HCV-	HCV+	HCV-
Laboratory values										
Hb, g/dl	10.8 (1.7)	10.9 (1.6)	11.1 (1.7)	11.0 (1.5)	11.2 (1.7)	11.1 (1.6)	10.0 (1.4)	10.1 (1.4)	10.9 (2.0)	10.9 (1.8)
Albumin, g/dl	3.7 (0.5)	3.7 (0.5)	3.6 (0.6)	3.7 (0.5)	3.8 (0.6)	3.7 (0.6)	3.7 (0.4)	3.7 (0.5)	3.7 (0.5)	3.7 (0.5)
Ferritin, ng/ml	285 [110, 570]	330 [141, 625]	422 [200, 728]	431 [197, 757]	309 [151, 553]	327 [163, 567]	97.2 [39.0, 224.0]	95.0 [37.0, 212.0]	343 [133, 640]	393 [190, 654]
CRP, mg/l ^c	3.3 [1.0, 9.0]	5.0 [1.6, 12.0]	—	—	5.0 [3.0, 13.0]	6.4 [3.0, 15.2]	1.0 [0.5, 3.8]	1.0 [0.5, 3.3]	4.2 [2.0, 8.5]	5.3 [2.5, 14.0]
Phosphorus, mg/dl	5.4 (1.8)	5.4 (1.7)	5.5 (1.8)	5.4 (1.8)	5.2 (1.8)	5.2 (1.8)	5.5 (1.6)	5.5 (1.5)	5.6 (2.3)	5.5 (1.9)
Creatinine, mg/dl	9.4 (3.1)	8.5 (3.2)	9.1 (3.6)	8.0 (3.2)	8.7 (2.8)	8.0 (2.8)	10.2 (2.8)	10.4 (3.1)	9.8 (3.1)	9.1 (3.2)
Platelets, 10 ⁶ cells/mm ^{3d}	169 (86)	199 (87)	195 (80)	214 (76)	195 (75)	220 (78)	97.6 (81.6)	119 (101)	173 (76)	198 (74)
Bilirubin, mg/dl ^e	0.6 (2.0)	0.5 (1.6)	0.5 (0.2)	0.5 (1.1)	0.5 (1.0)	0.6 (2.2)	0.3 (0.1)	0.4 (0.6)	0.9 (3.0)	0.5 (0.4)
ALT, U/L ^f	22.6 (31.6)	16.4 (22.6)	21.4 (12.4)	16.7 (21.0)	23.8 (19.4)	18.4 (30.0)	18.7 (59.2)	11.5 (10.2)	24.8 (17.0)	16.7 (13.1)
AST, U/L ^f	21.8 (16.0)	17.3 (16.4)	23.8 (12.5)	18.4 (13.1)	21.1 (11.7)	18.3 (20.8)	19.3 (23.2)	14.7 (13.7)	23.2 (13.5)	16.3 (12.1)
Medications										
ESA prescription in last mo, %	82.4	84.0	83.3	82.9	81.9	84.3	80.8	83.6	84.7	87.5
Epoetin equivalent dose, U/wk ^g	7500 [4232, 12,695]	8279 [4600, 13,800]	12,000 [6000, 24,000]	11,500 [6000, 22,800]	7359 [4232, 12,500]	7500 [4600, 12,500]	5000 [2760, 8279]	4761 [2760, 8279]	9000 [5750, 11,500]	9199 [5980, 12,000]
ESA dose:Hb ratio, (U/wk)/(g/dl) in last 4 mo, %	45.3	1304]	2195]	2026]	1165]	1163]	812]	806]	1237]	1223]
IV iron prescription in last 4 mo, %	250 [160, 435]	250 [174, 435]	250 [200, 500]	272 [213, 625]	250 [150, 435]	250 [160, 435]	174 [160, 348]	174 [160, 348]	435 [217, 489]	254 [157, 435]

Results shown as prevalence, mean (SD), or median [interquartile range]. DOPPS, Dialysis Outcomes and Practice Patterns Study; HCV, hepatitis C virus; HCV+, hepatitis C virus-positive; HCV-, hepatitis C virus-negative; —, not measured; Hb, hemoglobin; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESA, erythropoiesis stimulating agent; IV, intravenous.

^aIncludes Belgium, Italy, France, Germany, Spain, Sweden, and United Kingdom.
^bIncludes Australia (2002–2015), China (2010–2015), Gulf Cooperation Council countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates, 2012–2015), New Zealand (2002–2015), Russia (2012–2015), and Turkey (2012–2015).

^cDOPPS phase 1 (1996–2001) only collected in the United States; also collected in all other countries in subsequent phases.
^dDOPPS phases 4 and 5 only (2009–2015), n=30,030 patients.

^eRestricted to facilities measuring CRP routinely (quarterly) for at least 75% of patients (excludes all North American facilities); not collected in DOPPS phase 1 (1996–2001).
^fDOPPS phase 5, year 2+ only (2013–2015); first nonmissing value during DOPPS phase 5 follow-up; n=6083, 7968, and 9214 for bilirubin, AST, and ALT respectively.

^gAmong patients prescribed (excludes zero doses); darbepoetin doses converted at 250:1, PEGylated epoetin β (Mircera) doses converted at 208:1, subcutaneous doses converted at 1.15:1.

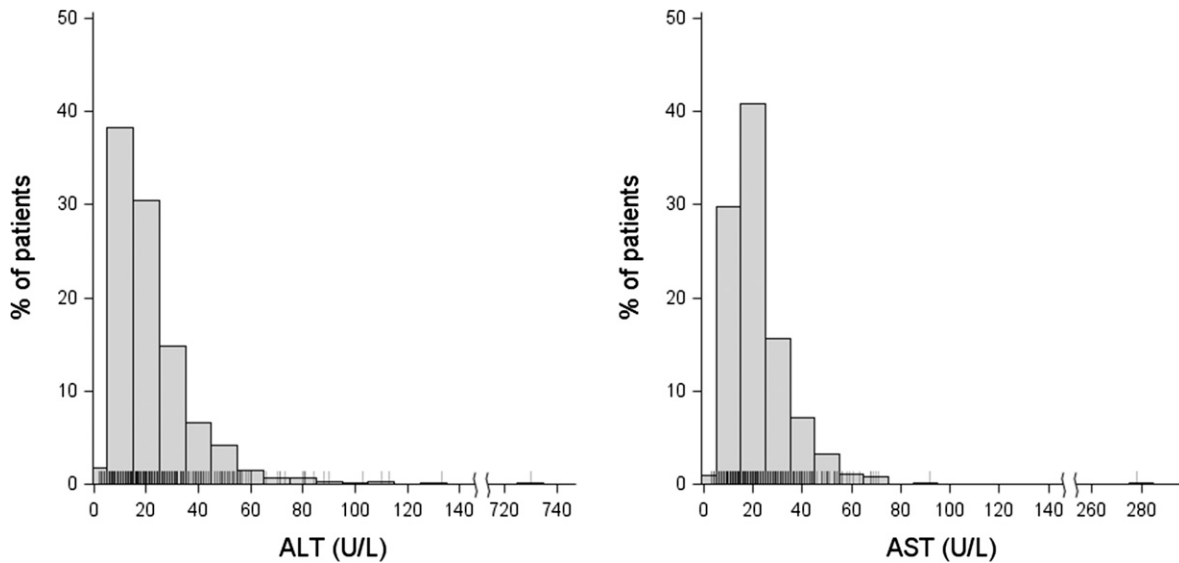


Figure 1. | ALT and AST concentrations are within normal limits or only minimally elevated among HCV+ patients (phase 5, 2012–2015). For ALT: $n=677$ patients; mean \pm SD: 23 ± 32 U/L; only one patient with ALT >140 U/L. For AST: $n=613$ patients; mean \pm SD: 22 ± 16 U/L; only one patient with AST >100 U/L. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV+, hepatitis C virus-positive.

hospitalization; 4.40 (95% CI, 3.14 to 6.15) for hepatic-related hospitalization; 1.10 (95% CI, 1.03 to 1.17) for cardiovascular hospitalization; and 1.08 (95% CI, 1.00 to 1.18) for infection-related hospitalization (Table 3).

Outcomes Associated with Anemia

Among those patients who entered the study with hemoglobin concentration ≥ 8.5 g/dl, the adjusted HR of a subsequent decline <8.5 g/dl for HCV+ patients versus HCV- patients was 1.12 (95% CI, 1.03 to 1.21), 1.36 (95% CI, 1.20 to 1.55) for blood transfusion, and 1.32 (95% CI, 1.13 to 1.54) for gastrointestinal bleeding (Table 4).

Quality of Life

The KDQOL-36 instrument was administered at entry into the DOPPS. Quality of life scores were significantly inferior for patients with HCV infection across all eight domains, on both the PCS and MCS, and also for Kidney Disease Burden score (Table 5). HCV+ patients were more likely to be moderately to extremely bothered by pruritus (rather than somewhat bothered or not at all bothered) than HCV- patients (Table 6). Similarly, HCV+ patients were significantly more likely to be moderately to extremely bothered by anorexia.

The CES-D-10 questionnaire was also administered at study entry, consisting of ten questions with scores of 0–3. A total score of ≥ 10 may be considered indicative of symptoms of depression

Table 2. Mortality for HCV+ versus HCV- patients (DOPPS phases 1–5, 1996–2015)

Event	No. of Events	Crude Rate ^a	Unadjusted HR ^b (95% CI)	Adjusted HR ^c (95% CI)
All-cause mortality	15,807	139.5	1.02 (0.95 to 1.09)	1.12 (1.05 to 1.20) ^d
Cardiovascular	6790	65.8	0.97 (0.87 to 1.07)	1.10 (0.98 to 1.22)
Infection	2187	21.2	1.05 (0.88 to 1.27)	1.11 (0.91 to 1.34)
Hepatic-related ^e	113	1.1	5.88 (3.84 to 8.99) ^d	5.90 (3.67 to 9.50) ^d

$n=73,577$ patients included in all-cause models. $n=65,015$ patients included in cause-specific models as large United States dialysis organizations in DOPPS phases 4 and 5 were excluded because of differential reporting of cause of mortality. Facilities reporting zero deaths during DOPPS follow-up or having <5 cumulative patient-years of mortality follow-up were excluded. HCV+, hepatitis C virus-positive; HCV-, hepatitis C virus-negative; DOPPS, Dialysis Outcomes and Practice Patterns Study; HR, hazard ratio; 95% CI, 95% confidence interval.

^aEvents per 1000 patient years.

^bStratified by DOPPS country (United States black and nonblack patients considered as separate strata) and phase and accounting for facility clustering.

^cStratified by DOPPS country (United States black and nonblack patients considered as separate strata) and phase and accounting for facility clustering; adjusted for age, sex, time on dialysis, 13 summary comorbidities and hepatitis B infection, and albumin, phosphorus, and creatinine levels.

^d $P<0.05$.

^eIncludes hepatitis, cirrhosis, or liver failure as primary or secondary cause of death.

Table 3. Hospitalization events for HCV+ versus HCV- patients (DOPPS phases 1–5, 1996–2015)

Hospitalization Type	No. of Events	Crude Rate ^a	Unadjusted HR ^b (95% CI)	Adjusted HR ^c (95% CI)
All-cause hospitalization	38,895	626.7	1.06 (1.02 to 1.11) ^d	1.09 (1.04 to 1.13) ^d
Cardiovascular^e	14,525	187.2	1.04 (0.98 to 1.11)	1.10 (1.03 to 1.17) ^d
Stroke	2074	23.3	0.97 (0.83 to 1.13)	1.08 (0.92 to 1.27)
Myocardial infarction	2208	24.8	0.97 (0.82 to 1.15)	1.05 (0.88 to 1.25)
Infection^f	9597	116.4	1.07 (0.99 to 1.16)	1.08 (1.00 to 1.18)
Sepsis	2592	29.3	1.05 (0.89 to 1.23)	1.06 (0.90 to 1.25)
Pneumonia	2209	24.9	1.14 (0.97 to 1.33)	1.15 (0.98 to 1.35)
Hepatic-related ^g	231	2.6	5.51 (4.09 to 7.44) ^d	4.40 (3.14 to 6.15) ^d

n=71,743 patients included in all-cause models. *n*=63,377 patients included in cause-specific models as large United States dialysis organizations in DOPPS phases 4 and 5 were excluded because of differential reporting of hospitalization cause. Facilities reporting zero hospitalizations during DOPPS follow-up or having <5 cumulative patient-years of hospitalization follow-up were excluded. HCV+, hepatitis C virus-positive; HCV-, hepatitis C virus-negative; DOPPS, Dialysis Outcomes and Practice Patterns Study; HR, hazard ratio; 95% CI, 95% confidence interval.

^aFirst-hospitalization events (per 1000 patient years).

^bStratified by DOPPS country (United States black and nonblack patients considered as separate strata) and phase and accounting for facility clustering.

^cStratified by DOPPS country (United States black and nonblack patients considered as separate strata) and phase and accounting for facility clustering; adjusted for age, sex, time on dialysis, 13 summary comorbidities and hepatitis B infection, and albumin, phosphorus, and creatinine levels.

^d*P*<0.05.

^eIncludes stroke and myocardial infarction among other cardiovascular-related hospitalizations.

^fIncludes sepsis and pneumonia among other infection-related hospitalizations.

^gIncludes hospitalizations with diagnosis of viral hepatitis or ascites, or liver biopsy procedure.

(7). As shown in Table 6, the odds ratio of having a CES-D-10 score ≥ 10 (versus <10) was 1.27 (1.16 to 1.40) when comparing HCV+ patients with HCV- patients.

Prescription of HCV Antiviral Medication

Tables 7 and 8 delineate the numbers of patients treated for HCV infection by country, phase, and medication type.

Only 1.5% of patients were treated (80 of 5313 HCV+ patients with prescription data in phases 1–5). Prescription of direct acting oral agents was particularly rare. Data from 2012 to the present (phase 5 and the initial months of phase 6) reveal that only 11 patients (seven in the United States and one each in Australia, Canada, France, and Sweden) have been treated with any of the new drugs.

Table 4. Anemia-related events for HCV+ versus HCV- patients (DOPPS phases 1–5, 1996–2015)

Event	No. of Events	Crude Rate ^a	Unadjusted HR ^b (95% CI)	Adjusted HR ^c (95% CI)
Hemoglobin <8.5 g/dl ^d	8615	112.3	1.10 (1.02 to 1.19) ^e	1.12 (1.03 to 1.21) ^e
Transfusion ^f	3268	49.9	1.31 (1.15 to 1.48) ^e	1.36 (1.20 to 1.55) ^e
Gastrointestinal bleed ^g	2093	23.6	1.28 (1.10 to 1.48) ^e	1.32 (1.13 to 1.54) ^e

HCV+, hepatitis C virus-positive; HCV-, hepatitis C virus-negative; DOPPS, Dialysis Outcomes and Practice Patterns Study; HR, hazard ratio; 95% CI, 95% confidence interval.

^aFirst-events (hemoglobin <8.5 g/dl, transfusion, gastrointestinal bleed) (per 1000 patient years).

^bStratified by DOPPS country (United States black and nonblack patients considered as separate strata) and phase and accounting for facility clustering.

^cStratified by DOPPS country (United States black and nonblack patients considered as separate strata) and phase and accounting for facility clustering; adjusted for age, sex, time on dialysis, 13 summary comorbidities and hepatitis B infection, and albumin, phosphorus, and creatinine levels.

^d*n*=60,319 patients; restricted to patients with baseline hemoglobin ≥ 8.5 g/dl.

^e*P*<0.05.

^f*n*=48,253 patients; excludes DOPPS phase 1 where transfusions were not included as an option on the hospitalization worksheet. In phases 2 and 3, transfusions were only ascertained on the hospitalization worksheet (as inpatient or outpatient events); in phases 4 and 5, transfusion events were additionally captured every month on the interval summary; however, dialysis units may not be aware of or record all blood transfusions that patients receive when transfusions occur in a hospital. Large United States dialysis organizations in DOPPS phases 4 and 5 did not provide transfusion events.

^g*n*=63,377 patients; large United States dialysis organizations in DOPPS phases 4 and 5 were excluded because of differential reporting of hospitalization cause. Facilities reporting zero hospitalizations during DOPPS follow-up or having <5 cumulative patient-years of hospitalization follow-up were excluded.

Table 5. Patient-reported measures for HCV+ versus HCV– patients (DOPPS phases 1–5, 1996–2015): Linear regression models

Quality of Life Measure (Higher=Better)	Outcome Mean	Unadjusted Difference (95% CI) ^a	Adjusted Difference (95% CI) ^b
KDQOL-36 Physical Component Summary^{c,d}	36.5	–1.2 (–1.5 to –0.8) ^e	–0.9 (–1.2 to –0.5) ^e
Physical functioning	41.8	–2.9 (–4.0 to –1.7) ^e	–2.8 (–3.8 to –1.7) ^e
Role-physical	38.0	–2.0 (–3.2 to –0.9) ^e	–2.1 (–3.2 to –0.9) ^e
Bodily pain	59.6	–5.6 (–6.6 to –4.6) ^e	–3.8 (–4.8 to –2.8) ^e
General health	40.9	–3.3 (–4.1 to –2.5) ^e	–2.6 (–3.5 to –1.8) ^e
KDQOL-36 Mental Component Summary^{c,d}	44.7	–1.2 (–1.6 to –0.8) ^e	–1.2 (–1.6 to –0.8) ^e
Vitality	38.8	–2.4 (–3.3 to –1.5) ^e	–2.3 (–3.2 to –1.4) ^e
Social functioning	58.3	–2.5 (–3.5 to –1.5) ^e	–1.9 (–3.0 to –0.9) ^e
Role-emotional	54.1	–2.7 (–3.9 to –1.4) ^e	–3.3 (–4.5 to –2.0) ^e
Mental health	62.8	–2.9 (–3.7 to –2.2) ^e	–2.2 (–3.0 to –1.5) ^e
KDQOL-36 Kidney Disease Burden^{c,d}	36.7	–1.8 (–2.6 to –1.0) ^e	–2.1 (–3.0 to –1.3) ^e

HCV+, hepatitis C virus-positive; HCV–, hepatitis C virus-negative; DOPPS, Dialysis Outcomes and Practice Patterns Study; 95% CI, 95% confidence interval; KDQOL-36, Kidney Disease Quality of Life instrument.

^aAdjusted for DOPPS country (United States black and nonblack patients considered separately) and phase and accounting for facility clustering.

^bAdditionally adjusted for age, sex, time on dialysis, 13 summary comorbidities and hepatitis B infection, and albumin, phosphorus, and creatinine levels.

^cParameter estimates from linear mixed models represent the modeled difference between HCV+ versus HCV– patients (*n*=44,320 patients; the models for the subscales had additional patients that did not complete all of the questions necessary to calculate the summary scores, *n*=50,771–53,576); *n*=53,596 patients completed the Kidney Disease Burden questions.

^dPhysical and mental component summary and kidney disease burden scores calculated from the KDQOL-36; Lower kidney disease burden score indicates more kidney disease burden. Parameter estimate is from a linear mixed model and represents the modeled difference between HCV+ and HCV– patients (*n*=44,320 patients).

^e*P*<0.05.

Discussion

In 1999 it was reported that HCV infection had become the most common chronic blood-borne infection in the United States (8). Guidelines from the American Association for the Study of Liver Diseases in 2015 state that evidence clearly supports the treatment of all patients infected with HCV, except those with life expectancy <12 months because of comorbid conditions (9). These guidelines further recommend that, optimally, therapy should be given early in the course of infection, before

liver fibrosis progression and advancement to complications, although the most immediate benefits will accrue to those at highest risk of hepatic complications. In the general population, HCV infection is associated with a 12-fold higher age-adjusted mortality rate (10). Between 1996 and 2010 there were >4 million hospitalizations at 500 hospitals in the United States among patients with HCV, and the rate increased during that period (11). HCV infection is also associated with inferior scores on quality of life testing (12,13). Patients who attain sustained

Table 6. Patient-reported measures for HCV+ versus HCV– patients (DOPPS phases 1–5, 1996–2015): Logistic regression models

Outcome Measure (Lower=Better)	Outcome Prevalence, %	Unadjusted Odds Ratio (95% CI) ^a	Adjusted Odds Ratio (95% CI) ^b
Depression ^c	44.1	1.28 (1.17 to 1.40) ^d	1.27 (1.16 to 1.40) ^d
Pruritus ^e	40.6	1.24 (1.16 to 1.33) ^d	1.27 (1.18 to 1.36) ^d
Lack of appetite ^f	23.2	1.25 (1.16 to 1.35) ^d	1.22 (1.12 to 1.32) ^d

HCV+, hepatitis C virus-positive; HCV–, hepatitis C virus-negative; DOPPS, Dialysis Outcomes and Practice Patterns Study; 95% CI, 95% confidence interval.

^aAdjusted for DOPPS country (United States black and nonblack patients considered separately) and phase and accounting for facility clustering.

^bAdditionally adjusted for age, sex, time on dialysis, 13 summary comorbidities and hepatitis B infection, and albumin, phosphorus, and creatinine levels.

^cOdds ratio from a logistic model for a Center for Epidemiologic Studies Short Depression Scale (CES-D-10) score ≥10 (versus <10) for HCV+ versus HCV– patients (*n*=34,035 patients); not collected in DOPPS phase 1 (1996–2001).

^d*P*<0.05.

^eOdds ratio for moderately to extremely bothered by itchiness for HCV+ versus HCV– patients (*n*=52,469 patients).

^fOdds ratio for moderately to extremely bothered by lack of appetite for HCV+ versus HCV– patients (*n*=52,185 patients).

Table 7. Antiviral treatment of HCV+ patients by DOPPS country and phase (1996–2015)

Region/Country	DOPPS Phase ^a				
	1	2	3	4	5
Australia/New Zealand	—	0 (27)	0 (17)	0 (26)	1 (16)
Belgium	—	0 (43)	0 (27)	1 (31)	1 (26)
Canada	—	0 (26)	1 (29)	0 (24)	2 (31)
China	—	—	—	1 (102)	1 (58)
France	4 (112)	0 (84)	3 (66)	1 (44)	1 (6)
Gulf Cooperation Council	—	—	—	—	4 (113)
Germany	0 (32)	1 (26)	3 (25)	3 (21)	1 (41)
Italy	1 (154)	1 (139)	2 (99)	0 (76)	2 (60)
Japan	0 (498)	0 (288)	0 (276)	1 (188)	2 (208)
Russia	—	—	—	—	0 (46)
Spain	0 (152)	2 (92)	4 (74)	3 (82)	2 (84)
Sweden	—	1 (33)	1 (32)	1 (35)	2 (41)
Turkey	—	—	—	—	0 (11)
United Kingdom	0 (15)	1 (13)	0 (6)	1 (17)	0 (20)
United States	16 (618)	0 (218)	2 (136)	4 (297)	2 (252)
All DOPPS countries	21 (1581)	6 (989)	16 (787)	16 (943)	21 (1013)

Expressed as *n* treated at enrollment or during follow-up (*N* HCV+ patients at enrollment); antiviral treatment defined as IFN, ribavirin, or new oral direct Hepatitis C virus inhibitor prescription; medications collected every 4 months in DOPPS phases 1, 3–5, and once yearly in DOPPS phase 2. HCV+, hepatitis C virus-positive; DOPPS, Dialysis Outcomes and Practice Patterns Study; —, not yet joined DOPPS.
^aDOPPS phase 1 (1996–2001 in the United States, 1998–2001 in Europe/Japan); phase 2 (2002–2004); phase 3 (2005–2008); phase 4 (2009–2011); phase 5 (2012–2015).

viral response (SVR) after antiviral treatment achieve improvements in quality of life scores on various scales, including fatigue, activity, energy, work impairment, and nonwork activity impairment (14,15).

The goal of the present investigation was to study the consequences of HCV infection in patients on HD. Previous studies have reported significantly higher case-mix adjusted risks of mortality comparing HCV+ with HCV– patients on HD, with HRs ranging from 1.25 to 1.97 (16–21). However, four of these studies included <300 HCV+ patients. In contrast, the DOPPS is a very large, multinational study with more extensive adjustments for demographics, comorbid conditions, and laboratory parameters. As shown in Table 1, patients with HCV infection

are younger, less often diabetic, and have fewer cardiovascular or malignant comorbid conditions; hence, it is very important to adjust for case-mix. Our results demonstrate an adjusted mortality HR of 1.12 (95% CI, 1.05 to 1.20) associated with HCV infection and, even more strikingly, a hepatic-related mortality HR of 5.90 (95% CI, 3.67 to 9.50). It would appear misguided to assume that patients on HD do not live long enough to succumb to the liver complications of HCV infection.

Although serum transaminase concentrations were not markedly elevated among HCV+ patients, those with higher levels within the observed ranges of values were noted to have significantly higher adjusted mortality risk. Concentrations ≥ 40 U/L may merit particular concern,

Table 8. Antiviral treatment regimens by DOPPS phase (1996–2015)

Antiviral Regimen	DOPPS Phase ^a				
	1	2	3	4	5
IFN only	18	3	7	8	5
Ribavirin only	0	1	1	3	1
IFN and ribavirin	3	2	8	5	9
Oral direct HCV inhibitor only	—	—	—	—	1
Oral direct HCV inhibitor and IFN/ribavirin	—	—	—	—	5
Total prescriptions	21	6	16	16	21

Expressed as *n* treated at enrollment or during follow-up among HCV+ patients at enrollment; medications collected every 4 months in DOPPS phases 1, 3–5, and once yearly in DOPPS phase 2. DOPPS, Dialysis Outcomes and Practice Patterns Study; —, oral direct HCV inhibitors not available; HCV, hepatitis C virus.
^aDOPPS phase 1 (1996–2001 in the United States, 1998–2001 in Europe/Japan); phase 2 (2002–2004); phase 3 (2005–2008); phase 4 (2009–2011); phase 5 (2012–2015).

although this finding is preliminary because of the small sample size.

HCV infection is also associated with a significantly higher risk of hospitalization. The adjusted HR for HCV+ versus HCV– status is 1.09 (95% CI, 1.04 to 1.13) and the HR for hepatic-related hospitalization is 4.40 (95% CI, 3.14 to 6.15). Cardiovascular and infectious hospitalizations are also greater among HCV+ patients.

Cirrhosis was present among 9.9% of HCV+ patients versus 1.4% of HCV– patients, and portal hypertension, hypersplenism, or coagulopathy may contribute to bleeding or shorter red blood cell lifespan. Also, platelet counts were lower. Therefore, we decided to examine whether HCV infection is associated with gastrointestinal bleeding and/or anemic sequelae. Indeed, the HRs show higher risks of a hemoglobin concentration decline to <8.5 g/dl (HR, 1.12; 95% CI, 1.03 to 1.21), transfusion (HR, 1.36; 95% CI, 1.20 to 1.55), or gastrointestinal bleeding (HR, 1.32; 95% CI, 1.13 to 1.54) among HCV+ patients. Previous smaller studies have reported varying relationships between HCV infection and hemoglobin concentration, erythropoiesis stimulating agent (ESA) dose requirement, and intravenous iron dose requirement (22–25), but the larger DOPPS, with more comprehensive adjustment for case-mix, reveals no significant difference between the HCV+ and HCV– groups in baseline hemoglobin concentration, ESA dose, ESA dose/hemoglobin ratio, or intravenous iron dose.

A study of 83 HCV+ patients in Turkey found worse MCS and PCS scores and higher depression scores among HCV+ patients (26), whereas a contradictory study of 41 HCV+ patients in Iran found that scores were better on almost all KDQOL-36 items (27). In the present study, HCV infection was clearly associated with worse patient-reported outcomes across all items and both summary scales of the KDQOL-36, and also on the CES-D-10 depression instrument, both before and after adjustment for case-mix. Pruritus and anorexia are commonly experienced by individuals with kidney or liver disease, and the data show that greater proportions of patients on HD with HCV infection are moderately to extremely bothered by these two symptoms. It is interesting to note that although itching in liver disease has classically been ascribed to the accumulation of bile salts, the serum bilirubin concentration is not elevated among HCV+ patients in the DOPPS. Recently, correlations have been reported between hepatic pruritus and the presence of lysophosphatidic acid and the enzyme responsible for its formation, autotaxin (28), but these compounds were not measured in this study.

The Kidney Disease Improving Global Outcome (KDIGO) guidelines addressing HCV in CKD were issued in 2008, when IFN and ribavirin were the only therapies approved to treat HCV (29). IFN-based therapy achieved SVR in 41% of patients on HD according to a meta-analysis; comparable or superior to the efficacy in the general population (30). However, side effects such as depression, flu-like symptoms, and anemia could be troublesome, and IFN has to be administered by subcutaneous injections for at least 6 months. The guidelines state that CKD patients accepted for kidney transplantation should be treated. Risk of mortality and allograft failure are both higher among HCV+ renal transplant recipients compared with HCV– renal transplant recipients (31). KDIGO

recommended that other patients with CKD should be evaluated on a case-by-case basis. Yet, in 2013, we found that only 1% of HCV+ patients in the DOPPS were treated, including only 3.7% of those on renal transplantation waiting lists (1). In recent years, much improved medications for HCV have become available: oral agents that only need to be taken for 12 weeks, with near-total SVR rates and minimal side effects. Nonetheless, among 980 HCV+ patients in the DOPPS between April 2012 and December 2014, only two patients worldwide were treated with any of the novel oral agents (32). Now, reviewing more recent prescription data from DOPPS phases 5 and 6 (2012 to present), we find that only 11 patients (seven in the United States and one each in Australia, Canada, France, and Sweden) have been treated with the new drugs. A phase 3 study of patients with stage 4–5 CKD and HCV infection has shown that direct antiviral therapy, in this case a combination of the oral agents grazoprevir and elbasvir, attained 99% SVR with adverse event frequencies similar to those reported on placebo (33). The new agents were found to be efficacious, safe, and well tolerated. Preliminary analysis of quality of life results showed significant improvement in the general health domain 12 weeks after treatment compared with the placebo group.

In light of the availability of safe, effective therapy, it is uncertain why patients on HD essentially remain untreated for HCV. Literature reports of treatment rates for HCV infection are rare. We are aware of a single report that mentioned that only 49 of 545 patients on HD had received IFN for HCV infection before renal transplantation (34). Treatment rates appear to be much higher in the non-CKD population—about 22%–28% in the United States and United Kingdom (35,36). In this study, only 1.5% received antiviral therapy, whereas hundreds of thousands of patients with HCV in the general population have been prescribed the new agents. It is possible that nephrologists do not recognize that HCV induces severe liver damage in patients on HD because, unlike in the general population, serum aminotransferase concentrations often remain within the normal ranges or are only slightly elevated in this setting (37–39). In this study, the mean values for ALT and AST were only 22.6 and 21.8 U/L, respectively; only one HCV+ patient had ALT elevation >140 U/L and only one HCV+ patient had AST elevation >100 U/L.

There are limitations to our study. The DOPPS only analyzes data that are routinely collected by the participating HD facilities and does not mandate special studies. Thus, we cannot report HCV RNA concentrations, HCV genotype, liver biopsy findings, or coagulation results. Also, it is possible that the associations noted between HCV status and outcomes in this observational study are partly because of unmeasured confounding factors rather than HCV infection *per se*. However, in light of the findings that HCV+ patients are younger than HCV– patients, have fewer serious comorbid conditions, and have longer dialysis vintage, it seems unlikely that HCV infection is not contributing to the deleterious outcomes and worse quality of life scores. Finally, randomized clinical trials would be needed to prove that treating HCV infection will decrease the burdens associated with the infection.

In summary, it appears erroneous to assume that HCV infection among patients on HD can be ignored because

these patients will not live long enough to develop undesirable consequences. HCV infection essentially goes untreated among patients on HD in 21 countries, yet it is associated with higher risks of mortality, hospitalization, liver complications, gastrointestinal bleeding, and anemia-related sequelae, as well as a variety of undesirable quality of life scores, including greater pain and worse vitality, depression, anorexia, and pruritus.

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Data from this manuscript have previously been published in abstract form: hepatitis C virus prevalence and clinical outcomes were reported at the meeting of the European Renal Association-European Dialysis and Transplant Association (London, England; May 29, 2015), as well as quality of life data in a separate abstract, and anemia findings were reported at the meeting of the American Society of Nephrology (San Diego, CA; November 6, 2015).

Disclosures

D.A.G. has consulted for Accelerator (Seattle, WA), ChemoCentryx, (Mountain View, CA), Omeros (Seattle, WA), Pieris (Freising, Germany), and Xenon (Burnaby, British Columbia, Canada), and is a stockholder in Cemptra (Chapel Hill, NC) and Xenon. B.B., E.K., and R.L.P. have no disclosures. M.J. has consulted for Merck (Whitehouse Station, NJ). P.M. has been an investigator and consultant for AbbVie (North Chicago, IL), Bristol Myers Squibb (New York, NY), Gilead (Foster City, CA), Janssen (Beerse, Belgium), and Merck.

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