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Prevalence of renal impairment and associated conditions among HCV-infected persons in the Chronic Hepatitis Cohort Study (CHeCS)

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Abstract

Background—Guidelines for the treatment of HCV-infected persons were updated in August 2015 with new recommendations for patients with renal impairment. Treatment is imperative for patients with severe, renal-associated extrahepatic manifestations of HCV infection.

Aims—We sought to describe the prevalence of these conditions among current HCV-infected patients in a population-based prospective, observational cohort study at four large US health systems.

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Disclaimer
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Methods—Data from cohort patients with chronic HCV infection during 2012 were analyzed for the period from 2006–2013. We determined the prevalence of mild-moderately impaired renal function defined as having the most recent estimated glomerular filtration rate [eGFR] <80 ml/min/1.73m^2, with severe impairment defined as eGFR<30 ml/min/1.73m^2, based on the treatment guidelines. Prevalence of extrahepatic conditions were ascertained using ICD9-codes.

Results—Among 5,772 persons the prevalence of eGFR<80 was 33% and eGFR<30 was 2%, including among patients with hepatic fibrosis. Diagnosed extrahepatic renal manifestations were rare: vasculitis- 0.2%, nephrotic syndrome- 0.3%, and cryoglobulinemia- 0.9%.

Conclusions—While the prevalence of severe renal impairment and diagnosed extrahepatic manifestations were low, mild-to-moderate renal impairment was common in HCV patients, including those with advanced liver fibrosis for whom the need for treatment is urgent.

Keywords

hepatitis C; renal disease; glomerular filtration rate; hepatic fibrosis

Introduction

Current guidelines for the treatment of hepatitis C virus (HCV)-infected persons [1] were updated in August 2015 with special considerations for patients with mild-moderate renal impairment defined as creatinine clearance (CrCl) 30 to 80 milliliters/minute (ml/min), and for those with severe renal impairment CrCl <30 ml/min, as new treatment options are becoming available for formerly hard-to-treat patients with renal impairment. Antiviral treatment is considered imperative for patients with several specific renal conditions (proteinuria, nephrotic syndrome, membranoproliferative glomerulonephritis) understood to be severe extrahepatic manifestations of chronic HCV infection, in addition to other conditions (cryoglobulinemia with end-organ manifestations e.g. vasculitis, organ transplant, advanced fibrosis or compensated cirrhosis) [1].

Previously patients with severe renal impairment from any cause were difficult to treat because the renal clearance of previously available therapies led to poor tolerability and limited treatment options. Recent analysis of data from an observational cohort found a high cure rate for sofosbuvir, a direct acting antiviral agent (DAA) with renal clearance, when used in patients with advanced kidney disease, but close monitoring during treatment was essential to detect serious adverse events [2]. Recent studies have shown treatment success with new direct acting antiviral combinations without renal clearance [3,4]; ombitasvir/paritaprevir/ritonavir plus dasabuvir is only available for patients with HCV genotype 1 and compensated cirrhosis, requires use of ribavirin in those with genotype 1A, and sustained viral response (SVR) data in dialysis patients are limited [3]. In another recent phase II/III study involving grazoprevir plus elbasvir, another DAA combination that is not cleared through the kidney, among end-stage renal disease patients with genotype 1 HCV, 75% of whom were on dialysis, 99% achieved sustained viral response to treatment with 12 weeks of treatment [4]. There is therefore a high need for studies to understand the prevalence and treatment implications of renal impairment among patients with HCV [5].

HCV infection in US dialysis patients-- a population estimated to be over 636,000 in 2012-- is five times greater than in the general population [6]. Chronic HCV infection has been associated with several types of renal disease as both a causative and a complicating factor [7–14]. Chronic HCV infection is associated with a higher incidence of primary renal cell carcinoma [15], with higher mortality among patients with chronic renal disease [16–18] and with worse outcomes after renal transplantation [19]. Recent analyses comparing a large cohort of HCV-infected veterans with in-system controls, all beginning observation with normal renal function, found that HCV infection was associated with higher cumulative incidence of decreased renal function and progressive loss of renal function [20]. An association between hypertension and hepatic fibrosis progression was also described among HCV-infected veterans [21].

We sought to describe the prevalence and severity of chronic kidney disease (CKD) and renal impairment, related comorbidities such as diabetes and hypertension [22], and hepatic fibrosis among patients observed in the Chronic Hepatitis Cohort Study (CHeCS), a population-based prospective observational cohort study at four large US health systems.

Methods

CHeCS is a population-based ‘dynamic’ multi-center observational study conducted at four large, integrated health care systems located in the United States, and represents a geographically, ethnically and clinically diverse cohort of patients with chronic hepatitis B and C [23]. The data collected are solely based on routine clinical care and thus representative of the uncontrolled health care environment of the “real world” clinical setting. Criteria for inclusion and composition of the CHeCS cohort have been summarized in a previous report [23]. Briefly, the initial cohort was created based on analysis of electronic health records (EHRs) and administrative data from over 2.3 million patients 18 years or older who had a clinical service (i.e., outpatient or inpatient, emergency department, or laboratory visit) visit provided between 2006–2013 at one of four sites: Geisinger Health System in Danville, Pennsylvania, that serves approximately 2.6 million Pennsylvania residents in 44 counties; Henry Ford Health System in Detroit, Michigan, that serves over one million southeastern Michigan residents; Kaiser Permanente-Northwest in Portland, Oregon, that serves approximately 500,000 members; and Kaiser Permanente of Honolulu, Hawaii, that serves about 220,000 persons or approximately one-sixth of Hawaii residents. The study protocol was reviewed and approved by an institutional review board at each participating site.

Confirmed cases of chronic HCV infection were identified primarily by laboratory and secondarily by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) criteria. EHR and administrative data were collected for each cohort patient and supplemented with individual chart review by trained data abstractors, who had also reviewed and verified chronic HCV infection from the EHR data. Data collected included patient demographics, medical encounters, treatment data, and laboratory, radiology, and biopsy results.

After excluding patients co-infected with hepatitis B virus or HIV, we observed all confirmed HCV-monoinfected cases with available laboratory data for renal function (serum creatinine) and calculation of FIB-4--a score calculated from liver function tests alanine aminotransferase [ALT] and aspartate aminotransferase [AST], platelet count, and patient age [9], previously validated in our cohort [24,25]. Data were censored at one year prior to the following events: sustained response to HCV therapy, patient's death, liver transplant, or loss to follow-up. Patients were observed from the latter of time from first evidence of HCV infection in the EHR or 2006, until the earlier of censoring date or 2013.

We additionally right-censored and truncated FIB-4 and creatinine data at 30 days prior to first receipt of any renal dialysis; defined as the presence of one or more of the following codes: ICD9 codes 585.6, V42.0, V56, V45.11, or E879.1; procedure codes 3993, 3995, or 5498; or CPT4 codes 90935, 90937, 90945, 90947, 90989, 90993, 90921, or 90925. The following specific renal conditions were defined by the presence of two ICD9 codes for the conditions at least 30 days apart at any time during observation: CKD (585.9, 585.1, 585.2, 585.3, 585.4, or 585.5), cryoglobulinemia (273.1 or 273.2), vasculitis (447.6), and nephrotic syndrome or membranoproliferative glomerulonephritis (581.0, 581.1, 581.2, 581.2, 581.81, 581.89, 581.9, or V13.03). Hypertension, diabetes and CKD were similarly defined by the presence of two ICD9 codes for the conditions at least 30 days apart at any point during observation, using the Healthcare Cost and Utilization Project (HCUP) Clinical Classifications Software (CCS) ICD9 categories [26].

We used estimated glomerular filtration rate (eGFR) to classify the degree of renal impairment, according to the CKD-EPI Creatinine Equation [2009]. Because AASLD guidelines are based on CrCl and not eGFR, we modified the categories of renal impairment to better reflect CrCl and to provide a more nuanced, clinically relevant description of CKD patients. We defined normal renal function as having had at the most recent follow-up time point an eGFR >80, mild impairment as an eGFR of 60–80, moderate impairment as an eGFR of 30–59, and severe impairment as an eGFR <30 ml/min/1.73m^2 [1,22, 27]. The level of hepatic fibrosis was measured via most recent FIB-4 score (calculated from AST/ALT on the same day paired with closest platelet count within 7 days) and categorized as: 'mild' if FIB-4 score was ≤ 1.6; 'mild-to-moderate' for FIB-4 > 1.6 and ≤2.55; 'moderate-to-severe' if FIB-4 ≥ 2.5 and ≤ 3.25; and severe for FIB-4 ≥ 3.25 [9, 24, 25]. We used FIB-4 score ≥ 3.25 to estimate the percentage of patients with renal impairment and hepatic fibrosis who are at high risk of complications of liver disease without treatment [1].

The differences in distribution of demographic and clinical features by level of renal impairment were analyzed by using the Pearson Chi-square test for categorical variables and Wilcoxon–Mann–Whitney rank test or the Kruskal–Wallis test for continuous variables.

Results

Of 10,889 chronic hepatitis C patients with available data, we excluded 92 (1%) who were coinfected with hepatitis B, 291 (3%) coinfected with HIV, and 1,991 (18%) patients with no serum creatinine or FIB-4 laboratory data available after 2006. We further excluded patients who had events prior to 2012 that would eliminate them from the cohort of currently

infected patients: death- 1663 (15%), liver transplant- 238 (2%), achieved SVR- 842 (8%), leaving an analysis cohort of 5,772 current patients.

Table 1 describes demographic and clinical characteristics at time of last eGFR. Most (74%) patients in the cohort were born during 1945–1964; 62% were white and 26% were black. Among 2,728 patients with available data on HCV genotype, 1,905 (70%) had HCV genotype 1 infection. Most patients (67%) had normal renal function (i.e., eGFR >80 ml/min/1.73 m^2); 23% had mild (eGFR 60–80 ml/min/1.73 m^2), 8% had moderate (eGFR 30–59 ml/min/1.73 m^2), and 2% had severe (<30 ml/min/1.73 m^2) renal impairment. Almost half (42%) of all patients were diagnosed with hypertension and a quarter (25%) with diabetes. In contrast, the prevalence of diagnosed vasculitis, nephrotic syndrome and cryoglobulinemia was low: 0.2%, 0.3% and 0.9%, respectively. Of 1,788 patients with mild-to-moderate renal impairment (30–80 ml/min/1.73 m^2), 412 (23%) had a FIB-4 score >3.25, indicative of advanced fibrosis. [1].

Table 2 describes the demographic and clinical characteristics according to degree of renal impairment; p-values refer to comparisons between the respective category of renal impairment and normal renal function (eGFR >80 ml/min/1.73 m^2). Compared to patients with normal renal function, those with severe impairment were significantly more likely to be older, to be black, to have lower annual income, to have publicly-provided insurance, to have hypertension and diabetes, and not to have received HCV treatment. Compared to those with normal renal function, patients with mild-to-moderate renal impairment (30–80 ml/min/1.73 m^2) were significantly more likely to be older, to be black, to have publicly-provided insurance, to be infected with a non-1 HCV genotype (patient with moderate impairment only), to have hypertension and diabetes (patients with moderate impairment only), and to have higher FIB-4 scores consistent with higher degrees of hepatic fibrosis. However, there were no significant differences between patients with mild impairment and those with normal renal function with respect to income, HCV genotype, diabetes, and receipt of HCV treatment.

Discussion

In this population-based “real-world” cohort of persons with chronic HCV infection we found a high prevalence of renal disease and renal-disease predisposing factors such as diabetes and hypertension. The presence of mild-moderate renal impairment was common in all hepatic fibrosis categories (on average 31%). Severe renal impairment was present, but less common in all fibrosis categories (on average 2%). Diagnosis of renal conditions considered to be severe extrahepatic manifestations of HCV infection such as cryoglobulinemia or vasculitis were rare (each less than 1%) with rates similar to those found in another recent study, which used nationally-representative hospital discharge diagnosis data [28].

A limitation of this observational study is that we could not ascertain how many patients were tested for specific extrahepatic manifestations of HCV and can only speculate about how many actually have the condition but are undiagnosed; these data reflect the real-world prevalence of patients diagnosed with possibly underappreciated conditions. Additionally, it

is possible that the use of two ICD9 codes over a period greater than 30 days to define the presence of diagnosed diabetes, hypertension, and specific renal conditions may have missed some cases. As severe renal impairment and hemodialysis have been associated with lower serum aminotransferase levels, such an effect would tend to lower FIB-4 values, leading to an underestimation of the prevalence of severe fibrosis and cirrhosis, among patients with very low eGFRs and those on hemodialysis. To some degree, however, this effect has been mitigated by our right-censoring FIB-4 scores at 30 days before the onset of hemodialysis. Also, since the CKD-EPI equation incorporates age, gender and ethnicity, we might expect a higher proportion of women, older people and Caucasians in the lower eGFR groups.

FIB-4 was used to measure level of hepatic fibrosis based on the strong correlation between biopsy stage and FIB-4 strata in this cohort [24, 25], although this measure may fluctuate. The use of a single measurement of most recent eGFR to define chronic renal impairment could include some patients with transient acute renal impairment. Other possible causes of kidney injury including the use of non-steroidal anti-inflammatories or angiotensin-converting enzyme inhibitors could not be assessed, but because all data were censored at one year prior to SVR the nephrotoxic effects of protease inhibitor therapy would not have influenced the analysis.

Future analyses of data from CHeCS and other cohorts may examine outcomes among patients with renal impairment, and help to determine if renal function improves after sustained virologic response given the associations between renal disease and HCV found in other studies (7–21). Clinicians treating patients with chronic HCV infection should be aware of the high prevalence of renal impairment; a substantial number of patients with renal impairment may need access to HCV treatment in the near future.

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List of abbreviations

HCV	hepatitis C virus
CDC	Centers for Disease Control and Prevention

CrCl	Creatinine clearance
Ml/min	Milliliters/minute
CKD	chronic kidney disease
SVR	sustained viral response
AST	aspartate aminotransferase
HTN	hypertension
DM	diabetes mellitus
CHeCS	Chronic Hepatitis Cohort Study
EHR	electronic health record
eGFR	estimated glomerular filtration rate

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Table 1

Demographic and clinical characteristics among 5,772 CHeCS hepatitis C viremic patients

Variables	Overall n (%)
Total	5722
Birth year	
1965 through 1984	1037 (18.0)
1955 through 1964	1978 (34.3)
1945 through 1954	2267 (39.3)
≤1944	490 (8.5)
Male	3252 (56.3)
Race	
Non-Hispanic White	3549 (61.5)
Non-Hispanic Black	1484 (25.7)
Other	739 (12.8)
Median Yearly Household Income	
<30,000	1320 (22.9)
≥30,000 and <50,000	2663 (46.1)
≥50,000 and <75,000	1313 (22.7)
≥75,000	347 (6.0)
Unknown	129 (2.2)
Insurance	
Medicaid only	722 (12.5)
Medicare or Medicare plus	1373 (23.8)
Private	3339 (57.8)
No insurance	247 (4.3)
Unknown	91 (1.6)
Genotype	
1a	1905 (33.0)
2,3,5,6	823 (14.3)
Other or unknown	3044 (52.7)
Ever received HCV treatment	2082 (36.1)
Fib4 in groups *	
<1.6	2517 (43.6)
≥1.6 and <2.5	1329 (23.0)
≥2.5 and <3.25	558 (9.7)
≥3.25 and ≤5.88	761 (13.2)
>5.88	607 (10.5)
Hypertension	2448 (42.4)
Diabetes	1463 (25.3)
Cryoglobulinemia	50 (0.9)
Vasculitis	13 (0.2)
Nephrotic syndrome	19 (0.3)

Variables	Overall n (%)
Chronic kidney disease	319 (5.5)
Dialysis	25 (0.4)
eGFR *	
<30	133 (2.3)
30–80	1788 (31.2)
>80	3851 (67.3)

* Renal function categorized by latest estimated glomerular filtration rate ([eGFR] measured in ml/min/1.73m^2 [21,26]) during the period 2006–2013; all observation including eGFR censored at 30 days prior to the first receipt of dialysis

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Table 2

Prevalence of renal impairment* by demographic and clinical characteristics among 5,772 CHeCS hepatitis C viremic patients

Variables	Overall n	eGFR*<30 n (%)	eGFR* 30–80 n (%)	eGFR*>80 n (%)	p-value
Total	5722	133 (2.3)	1788 (31.2)	3851 (67.3)	
Birth year					
1965 through 1984	1037	12 (1.2)	177 (17.1)	848 (81.8)	
1955 through 1964	1978	39 (2.0)	580 (29.3)	1359 (68.7)	
1945 through 1954	2267	65 (2.9)	785 (34.6)	1417 (62.5)	
≤1944	490	17 (3.5)	246 (50.2)	227 (46.3)	<0.0001
Male	3252	73 (2.2)	859 (26.4)	2320 (71.3)	<0.0001
Race					
Non-Hispanic White	3549	27 (0.8)	1103 (31.1)	2419 (68.2)	
Non-Hispanic Black	1484	100 (6.7)	430 (29.0)	954 (64.3)	
Other	739	6 (0.8)	255 (34.5)	478 (64.7)	<0.0001
Median Yearly Household Income					
<30k	1320	56 (4.2)	402 (30.5)	862 (65.3)	
≥30k and <50k	2663	53 (2.0)	797 (29.9)	1813 (68.1)	
≥50 k and <75k	1313	14 (1.1)	429 (32.7)	870 (66.3)	
≥75k	347	4 (1.2)	121 (34.9)	222 (64.0)	
Unknown	129	6 (4.7)	39 (30.2)	84 (65.1)	<0.0001
Insurance					
Medicaid only	722	23 (3.2)	216 (29.9)	483 (66.9)	
Medicare or Medicare plus	1373	72 (5.2)	514 (37.4)	787 (57.3)	
Private	3339	30 (0.9)	974 (29.2)	2335 (69.9)	
No insurance	247	8 (3.2)	55 (22.3)	184 (74.5)	
Unknown	91	029	(31.9) 62	(68.1)	
Hypertension					
Yes	2448	114 (4.7)	853 (34.8)	1481 (60.5)	
No	3274	19 (<0.01)	935 (28.6)	2370 (72.4)	<0.0001
Diabetes					
Yes	1463	70 (4.8)	496 (33.9)	897 (61.3)	<0.0001

Variables	Overall n	eGFR*<30 n (%)	eGFR* 30–80 n (%)	eGFR*>80 n (%)	p-value
No	4259	63 (1.5)	1292 (30.3)	2954 (69.4)	
Ever received HCV treatment**	2082	34 (1.6)	637 (30.6)	1411 (67.8)	0.029
Latest Fib4					
<1.6	2517	54 (2.1)	730 (29.0)	1733 (68.9)	
≥1.6 and <2.5	1329	40 (3.0)	443 (33.3)	846 (63.7)	
≥2.5 and <3.25	558	11 (2.0)	203 (36.4)	344 (61.6)	
≥3.25 and ≤5.88	761	20 (2.6)	248 (32.6)	493 (64.8)	
>5.88	607	8 (1.3)	164 (27.0)	435 (71.7)	0.0003

*Renal function categorized by latest estimated glomerular filtration rate ([eGFR] measured in ml/min/1.73m^2 [21,26]) during the period 2006–2013; all observation including eGFR censored at 30 days prior to the first receipt of dialysis

**All treatment courses were without sustained viral response with analysis limited to currently viremic pateints