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Impact of hepatitis C therapy on urinary outcomes and renal function: a prospective real-world cohort study of early kidney changes

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Abstract

Background Hepatitis C virus (HCV)–associated kidney injury can affect both the glomeruli and the renal interstitium. The aim of this single-center, prospective real-world study involving HCV patients was to assess longitudinal changes in liver and kidney parameters during HCV treatment and to examine how renal function and urine findings evolved in those with kidney manifestations prior to therapy.

Methods In total, 217 patients treated for HCV-infection were enrolled for the study. Renal abnormalities were defined as either s-creatinine above the normal limit (male > 100 µmol/l, female > 90 µmol/l), or estimated glomerular filtration rate (eGFR) below < 60 ml/min/ 1.73 m^2, or number of urine red blood cells above the normal (U–erythrocytes ≥ 20 × 10(E6)/l), or tubular proteinuria above the normal (U–α 1-microglobulin, UA1M, ≥ 12 mg/l), or glomerular proteinuria above the normal (U–albumin/creatinine ratio, UACR, in men ≥ 2.5 mg/mmol, in women ≥ 3.5 mg/mmol) levels in a spot urine test.

Results Forty patients (20%) had pretreatment kidney manifestations. Sustained virological response at 12 weeks (SVR12) was achieved in 93%, with no difference observed between patients with or without pretreatment kidney manifestations. All liver function tests improved significantly at 12 weeks. Across the study period, serum cystatin C showed a marked improvement ($p = 0.0128$), while the other filtration markers did not change significantly from pretreatment levels to one year. The tubular proteinuria marker UA1M decreased significantly from pretreatment to SVR12 and further to the one-year follow-up ($p < 0.0001$ and 0.0046, respectively). Hematuria also declined markedly from pretreatment to SVR12 ($p < 0.0001$). In contrast, no significant change was observed in the glomerular proteinuria marker, UACR.

Conclusions Successful hepatitis C eradication therapy improves kidney function assessed by serum cystatin C and reduces tubular proteinuria as well as hematuria even in patients with low grade pretreatment kidney manifestations.

Keywords Hepatitis C, Tubular proteinuria, Hematuria, Cystatin C

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Background

Hepatitis C (HCV) infection is an independent risk factor for kidney manifestations [1, 2]. HCV-related kidney damage may include a variety of histopathologic patterns, glomerular and/or interstitial lesions, and the virus can also directly contribute to kidney damage by infecting tubular epithelial and other renal cell types [3, 4]. Reported prevalence of kidney involvement among patients with HCV infection varies widely, with estimates ranging from 30 to 40%, and decreasing to approximately 4–20% when considering proteinuria alone [5–7].

Treating HCV and acquiring a sustained virological response (SVR) has shown benefit on kidney manifestations but is somewhat dependent on the extent of pretreatment kidney damage [1, 8] and comorbidities [9]. Reduced albuminuria and tubular proteinuria have been reported after successful HCV eradication therapy [10, 11]. Most clinical trials examining the reversal of kidney damage following antiviral eradication therapy have focused on patients with CKD stages 3–5. However, earlier or pre-CKD stages may represent a more effective window for intervention to prevent advanced kidney injury, and data on this earlier phase remain limited.

Aim of this single-center, prospective real-world study was to evaluate the influence of HCV treatment on the liver and renal laboratory findings longitudinally and to further examine the findings for patients with pretreatment kidney manifestations.

Methods

Patients

Two-hundred and seventeen consecutive adult patients referred for treatment of HCV at the Department of Gastroenterology at the Helsinki University Hospital in Finland between 2017 and 2018 were enrolled into the prospective observational study. The enrolled patients were followed up to one year after HCV therapy. Detailed inclusion and exclusion criteria were presented at our previous publication [12]. HCV treatment was administered according to standard clinical practice and the prevailing guidelines at the time of the study.

Study protocol

Pretreatment kidney manifestation was defined as: S-creatinine above the normal limit (male > 100 µmol/l, female > 90 µmol/l), or estimated glomerular filtration rate (eGFR) calculated according to the Chronic Kidney Disease Epidemiology Collaboration (eGFR CKD-EPI) equation below normal (< 60 ml/min/ 1.73 m^2), or number of urine red blood cells above the normal (U–erythrocytes ≥ 20 × 10(E6)/l), or tubular proteinuria above the normal (U–α 1-microglobulin, UA1M, ≥ 12 mg/l), or glomerular proteinuria above the normal (U–albumin/creatinine ratio, UACR, in men ≥ 2.5 mg/mmol, in women ≥ 3.5 mg/mmol) levels in a spot urine test. Those with any renal manifestation were referred to the Department of Nephrology for further standard examinations.

Alcohol consumption was assessed using a standard questionnaire alcohol use disorder identification test (AUDIT) [13]. The estimated time and route of HCV transmission was also evaluated based on patient interviews. Aspartate aminotransferase to platelet ratio index (APRI) was used to predict significant liver fibrosis [14]. Values < 0.5 refer to significant fibrosis to be unlikely whereas values > 1.5 refer to likely significant fibrosis. Liver fibrosis was also assessed by transient elastography (FibroScan®, Echosens, Paris, France) after a 4-hour fasting. Liver biopsy was available in 10 patients.

Interferon was still part of the eradication therapy in the beginning of the study, while direct-acting antivirals (DAAs) became treatment of choice during the study. The treating physician chose the treatment based on the clinical guidelines at that time. Most patients receiving DAAs were treated for a duration of 8 to 12 weeks.

Laboratory variables

Laboratory variables were analyzed at the accredited Helsinki University Hospital laboratory (HUSLAB) using standard chemical methods analogously to our previous publication [12]. Kidney function was measured by serum creatinine and serum cystatin C and estimated using three different formulas. EGFRs were calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), CKD-EPI Cystatin C equation (eGFR-EPI-cys-C) and CKD-EPI creatinine-cystatin C equation (eGFR-EPI-crea-cys-C) [15]. S-creatinine was determined with the enzymatic method of Abbott Laboratories with upper normal values 100 µmol/l in males and 90 µmol/l in females. S-cystatin C was assessed by multigent cystatin C 1P93-30 method by Abbott Laboratories and considered normal if < 1 mg/l (under 50 years of age) or < 1.2 mg/l (> 50 years of age). The cut-off for lower normal value in all eGFRs was set at 60 ml/min/ 1.73 m2.

Urine samples were collected as spot samples taken in the morning and an additional 24-h urine collection was conducted before the appointments at the Department of Nephrology. UA1M as a marker of tubular proteinuria was measured from a spot sample using the turbidimetry method of Abbott Laboratories with values < 12 mg/l considered normal. UACR as a marker for glomerular proteinuria based on a spot sample involved analyzing albumin with the method of bromocresol purple and creatinine with the enzymatic method by Abbott Laboratories with values < 2.5 mg/mmol for males and < 3.5 mg/mmol for females considered normal. A 24-h urine collection for proteinuria was considered normal with values < 100 mg/24-h. Urine hemoglobin was tested

using both dipstick test and automated phase contrast microscopy. The latter was used in addressing whether the subject had true hematuria. The hospital laboratory started using an automated microscopy analysis by the end of April 2019. The upper normal value of u – erythrocytes was 20 × 10 (E6)/l before and 10 × 10 (E6)/l after the change.

Blood complement analyses were performed using the Wieslab complement system screen method (activity percentages of serum classical, alternative and lectin pathways, S -CH100Cl, S -CH100Al, S -CH100L, respectively) and nephelometry (serum complement 3 and 4, S -C3, S -C4, respectively) by Abbott Laboratories. Complement activation products were analyzed by radial immunodiffusion (complement 4 activation product, C4d and factor B, Facb), rocket immunoelectrophoresis (complement 3 activation product, C3d) and enzyme immunological methods (factor B activation product, FacBb, membrane attack complex, SC5b-9) in the accredited laboratory of Turku University Hospital.

Table 1 Pretreatment characteristics of hepatitis C patients grouped by the presence of renal manifestation. Comparisons between those with no renal manifestation vs. with renal manifestation were not significant except for estimated duration of HCV infection and OST therapy (as shown #, ##)

Variable (unit or number of patients)	Patients *n* = 217[a]	Presence of renal manifestation before the eradication therapy	
		No *n* = 176[b]	Yes *n* = 41[c]
Age (years)*	44 (20–77)	43 (20–77)	45 (20–70)
Males *n* (%)	117 (54) (54)	97 (55)	20 (49)
Diabetes *n* (%)	12 (6)	9 (5)	3 (7)
Hypertension *n* (%)	29 (13)	21 (12)	8 (20)
Rheumatic disease *n* (%)	7 (3)	7 (4)	0 (0)
Chronic disease *n* (%)**	78 (53)	66 (55)	12 (44)
BMI (kg/m^2)***	26 (4.5)	26 (4.8)	26 (4.6)
Genotype n %			
1	91 (42)	73 (41)	18 (44)
2	23 (11)	22 (13)	1 (2)
3	102 (47)	81 (46)	21 (51)
4	1 (0.5)	0 (0)	1 (2)
Fibrosis stage *n* (%)			
F0-F1	133 (64)	110 (65)	23 (59)
F2	33 (16)	28 (16)	5 (13)
F3	11 (5)	8 (5)	3 (8)
F4	32 (15)	24 (14)	8 (21)
Estimated duration of HCV infection (years)* #	20.2 (0–44)	9.4 (0–44)	6.6 (0–41)
OST therapy *n* (%) ##	45 (21)	43 (24)	2 (5)

Information was not available for all participants, n varied between [a]146-217, [b]119-176 and [c]27-41

*mean (range)

**chronic disease includes all chronic conditions except hypertension, diabetes, rheumatic disease,

liver or kidney disease

*** mean (SD)

BMI = body mass index, OST = opioid substitution therapy

p-value 0.0433 between those with no renal manifestation vs. with renal manifestation

p-value 0.0046 between those with no renal manifestation vs. with renal manifestation

Statistical analyses

For statistical analyses, continuous variables were reported as the number of patients whose data were summarized (n), mean, standard deviation (SD), and minimum and maximum. All categorical variables were reported using frequency counts and percentages by category. Comparisons of characteristics between HCV-positive patients with or without kidney manifestations were made pretreatment, at SVR12 and one year after the treatment. Linear mixed models suitable for repeated measurements were used to study phenomenon over time and differences over time between the groups. For some variables, logarithmic transformation was applied to achieve normal distribution. In any of the statistical comparisons, two-sided tests were used at $\alpha = 0.05$ significance level. In general, missing data was not imputed. All statistical analyses and generation of all tables, and listings were performed using the SAS® (SAS Institute, North Carolina, USA) software, version 9.4.

Results

Altogether 217 HCV-infected patients participated in the study. Due to withdrawal of consent or loss of follow-up, the number of patients available for analyses varied at each time point. Pretreatment data is presented in Table 1 and various antiviral therapies divided by pretreatment kidney manifestation are presented in Table 2. Mean age was 44 years, 54% were male, and the mean duration of HCV infection was 20 years. Genotype 3 was the most common and the majority had either no or only minimal liver fibrosis (F0-F1). Nearly 21% were on opioid substitution therapy (OST). In total, 41 patients (20%) had pretreatment kidney manifestations, and they had significantly shorter duration of HCV infection and less patients on OST compared to those with no kidney manifestations, otherwise groups had no significant differences. Of those patients having pretreatment kidney manifestations, 46% had increased level of tubular proteinuria (UA1M), 32% had hematuria, 7% had increased serum creatinine level, 7% had hematuria and increased level of glomerular proteinuria (UACR) and finally 7% had increased level of tubular proteinuria (UA1M) and increased level of glomerular proteinuria (UACR). Those having any baseline renal manifestation were significantly

Table 2 Various antiviral therapies divided by pretreatment kidney manifestation

Antiviral therapy	HCV positive with baseline renal findings *n* = 41	HCV positive with no baseline renal findings *n* = 142	*p*-value
Interferon + ribavirin *n (%)*	2 (4.9%)	26 (18.3%)	**0.047**
Interferon + ribavirin + sofosbuvir *n (%)*	1 (2.4%)	4 (2.8%)	1.00
grazoprevir and elbasvir *n (%)*	14 (34.1%)	45 (31.7%)	0.85
grazoprevir and elbasvir + ribavirin *n (%)*	2 (4.9%)	6 (4.2%)	1.00
sofosbuvir and velpatasvir *n (%)*	18 (44.9%)	46 (32.4%)	0.20
sofosbuvir and velpatasvir + ribavirin *n (%)*	4 (9.8%)	15 (10.6%)	1.00

more often offered other than interferon + ribavirin based treatments. In other treatment modalities there were no significant differences. The majority of the patients (85%) received DAAs. Renin-angiotensin system inhibitors (RAASi) were used in only 10% of the patients and mineralocorticoid receptor antagonists (MRAs) in only 2% and no patient was using sodium-glucose co-transporter 2 (SGLT-2) inhibitors.

Longitudinal changes of kidney function, at pretreatment, at SVR12 and at one year after HCV eradication therapy grouped by pretreatment status of kidney manifestation are presented in Table 3. In the whole patient population serum cystatin C improved significantly compared to pretreatment and at one year ($p = 0.0128$). The trends for improvement were similar in patients with and without pretreatment kidney manifestations, but significant only in those with no pretreatment manifestations ($p = 0.0041$ for comparison between pretreatment and one year).

UA1M was decreased from pretreatment to SVR12 and from pretreatment to one year ($p < 0.0001$ and 0.0046, respectively) in the whole population. However, UA1M decreased significantly only in those with pretreatment kidney manifestation. Amount of hematuria was also significantly reduced from pretreatment to SVR12 ($p < 0.0001$) in the whole population. Among those with pretreatment kidney manifestation, the change was significant both in SVR12 and one year ($p < 0.0001$ and 0.0003, respectively). The reduction in hematuria was also significant at one year ($p < 0.0001$) in those without pretreatment kidney manifestation. No significant changes were observed in UACR.

Longitudinal changes of basic laboratory variables at pretreatment, SVR12 and one year after the HCV treatment also grouped by pretreatment status of kidney manifestation are presented in supplementary Table 1. SVR12 was received in 93% of the patients (145/156). The figures were 94% (31/33) and 93% (114/123), respectively, in those with pretreatment kidney manifestation and in those without (p = ns). All liver variables and APRI improved significantly during the follow-up already at SVR12.

Kidney variables, given treatments and the overall time effect from pretreatment to one year after the eradication treatment is presented in Table 4. No significant differences were found between various HCV treatments in kidney function or proteinuria. However, albeit being small changes, improvements in the amount of hematuria seemed to differ significantly between the treatment groups ($p = 0.027$).

Complement variables were investigated only among those with pretreatment renal manifestation. Activity of the classical pathway of complement between pretreatment and SVR12, activity of the lectin pathway between pretreatment and 1 year, as well as factor B activation product between pretreatment and SVR12 were significantly changed (Table 5).

Discussion

We found that the urinary markers UA1M and hematuria improved rapidly — already by 12 weeks after treatment — in patients with renal manifestations. Hematuria decreased following successful eradication therapy in all patients, although most changes remained within normal ranges. Liver function tests also showed substantial improvement as early as 12 weeks post-treatment, consistent with findings from previous studies.

Cystatin C, a cysteine proteinase inhibitor, has shown promise for estimating kidney function and is an ideal GFR marker as it has a constant secretion rate by all nucleated cells and it passes freely through the glomeruli [16, 17]. The diagnostic performance of CKD-EPI creatinine-cystatin C equation [14] in patients with cirrhosis was superior to conventional equations for estimating GFR [18, 19]. However, its diagnostic performance was substantially worse in subjects without cirrhosis [18]. CKD-EPI Cystatin C equation yielded less biased eGFR than serum creatinine-based formulas especially in cirrhotic patients with CKD and hence should be used preferentially in cirrhotic patients with eGFR < 60 ml/min/1.73 m^2 and in those with refractory ascites [20]. A recent publication also described that after successful HCV treatment with DAAs, the skeletal muscle mass improved and could have contributed to the increase in serum creatinine observed after HCV treatment, no change was noticed in eGFR based on cystatin C [21].

In our study most patients were not cirrhotic and eGFRs remained stable, although significant

Table 3 Longitudinal change of renal function tests at pretreatment, at SVR12 and at one year after HCV therapy grouped by the presence of renal manifestation (yes vs. no) at pretreatment

Variable	Pretreatment $n=216$[a]	SVR12 $n=175$[b]	1 year $n=142$[c]	*P*-value: Overall time effect[1] Renal manifestation Group x time interaction[2]	Pretreatment vs. SVR12/ Pretreatment vs. 1 year
eGFR CKD-EPI (≥ 60 ml/min/1.73m^2)	106 (104;108)	104 (102;107)	102 (99;105)	0.2270[1]	0.1692/0.1107
Yes	99 (93;105)	101 (95;106)	99 (93;106)	0.3885[2]	0.9247/0.6250
No	108 (106;110)	105 (103;108)	104 (100;107)		**0.0047/0.0153**
eGFR-EPI-cys-C (≥ 60 ml/min/1.73m^2)*	81 (78;84)	79 (76;81)	81 (77;84)	0.3230[1]	0.9667/0.1956
Yes	71 (64;78)	74 (67;80)	74 (67;82)	0.7589[2]	0.7182/0.4272
No	83 (80;87)	80 (77;83)	83 (79;87)		0.5946/0.1974
eGFR-EPI-crea-cys-C (≥ 60 ml/min/1.73m^2)	92 (89;94)	89 (87;91)	89 (86;92)	0.5927[1]	0.4356/0.7737
Yes	82 (76;88)	85 (79;90)	85 (78;91)	0.4673[2]	0.8486/0.6628
No	94 (92;96)	90 (88;93)	91 (88;94)		0.0509/0.9043
S-creatinine (≤ 100 µmol/l male, ≤ 90 µmol/l female)	67 (65;68)	67 (65;69)	68 (65;71)	0.6377[1]	0.4008/0.4631
Yes	72 (66;77)	70 (65;74)	69 (64;74)	0.3627[2]	0.8152/0.9556
No	65 (64;67)	67 (64;69)	67 (64;71)		**0.0235**/0.1130
S-cystatin C (< 1.0 mg/l ≤ 50 years, < 1.2 mg/l > 50 years)	1.04 (1.00;1.08)	1.01 (0.98;1.04)	0.98 (0.95;1.01)	**0.0398[1]**	0.3982/**0.0128**
Yes	1.2 (1.04;1.36)	1.1 (1.01;1.09)	1.07 (0.99;1.16)	0.9289[2]	0.6257/0.1892
No	1.00 (0.97;1.03)	0.98 (0.95;1.01)	0.95 (0.91;0.98)		0.3365/**0.0041**
Urine hematuria (< 20 E6/l)*	6 (6;7)	5 (4;6)	2 (1;4)	**< 0.0001[1]**	**< 0.0001**/0.7365
Yes	10 (7;21)	5 (3;7)	4 (1;10)	**< 0.0001[2]**	**< 0.0001/0.0003**
No	6 (6;7)	6 (4;6)	1 (1;3)		0.8833/**< 0.0001**
Urine A1M (< 12 mg/l) (< 12 mg/l)**	7.7 (6.8;8.7)	6.6. (6.1;7.2)	7.1 (6.4;7.8)	**0.0002[1]**	**< 0.0001/0.0046**
Yes	14.5 (10.6;18.4)	8.1 (6.2;10.0)	8.6 (6.3;10.9)	**< 0.0001[2]**	**< 0.0001/< 0.0001**
No	6.1 (5.8;6.3)	6.2 (5.7;6.7)	6.6 (6.0;7.2)		0.2517/0.0687
Urine ACR (< 2.5 M, < 3.5 F mg/mmol)	2.2 (0.4;4.0)	2.5 (-0.2;5.1)	1.4 (0.5;2.3)	0.7795[1]	0.4844/0.6978
Yes	7.3 (-1.6;16.3)	7.9 (-5.0;20.8)	2.7 (-0.9;6.2)	0.2456[2]	0.2982/0.2469
No	0.9 (0.8;1.0)	1.0 (0.8;1.2)	1.0 (0.7;1.3)		0.6787/0.2058

Data is presented as mean and 95% confidence interval (CI) for mean value or as number of patients and percentages (%). Statistically significant changes are expressed in bold

Information was not available for all participants, n varied between [a]190-216, [b]174-175 and [c]118-142, *median and 95% CI, eGFR CKD-EPI = estimated glomerular filtration rate, calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, eGFR-EPI-cys-C = estimated glomerular filtration rate, calculated using cystatin-C, eGFR-EPI crea-cys-C = estimated glomerular filtration rate, calculated using creatinine and cystatin C, A1M = urine α 1-microglobulin, albcrea = urine albumin/creatinine ratio

improvement was noticed in sole plasma cystatin C from pretreatment to one year, but only in patients without pretreatment renal abnormalities. No differences were seen between different HCV therapies regarding the impact on kidney filtration. Only 15% of the patients were treated by interferon-based therapy and the rest with DAAs. It must be noted that most kidney derangements were noticed in urine and perhaps with a longer follow-up change in kidney function could also become evident.

Urine findings and filtration markers were evaluated separately in this study. Indeed, it seemed that tubular cell damage as evaluated by UA1M was significantly reduced after successful eradication therapy. This is in line with another report studying the same biomarker. However, the patient population in that report consisted of 135 cirrhotic patients with a follow-up of 6 months [11]. Glomerular proteinuria was reduced from pretreatment phase to one year in those with pretreatment renal manifestation, albeit the change was not statistically significant in our study. Other reports showed that albuminuria was reduced after successful therapy in HCV-patients, especially without diabetes [11, 22]. In our study, hematuria

Table 4 Impact of treatment on the kidney variables, and the overall time effect between pretreatment, SVR12 and 1 year after the therapy

Variable	Treatment	Pretreatment Mean (95% CI) *n* = 190	SVR12 Mean (95% CI) *n* = 174	1 year Mean (95% CI) *n* = 118	*P*-value
Urine A1M	Sofosbuvir/Velpatasvir	8.4 (7.0;9.8)	6.7 (5.8;7.6)	6.6 (5.8;7.5)	0.0813
	Interferon	6.5 (5.5;7.5)	7.3 (5.5;9.1)	7.4 (4.6;10.0)	
	Grazoprevir/Elbasvir	7.8 (5.8;9.7)	6.3 (5.6;7.0)	7.4 (6.5;8.3)	
Urine ACR	Sofosbuvir/Velpatasvir	4.0 (-0.2;8.2)	4.0 (-1.6;9.6)	2.2 (-0.2;4.6)	0.4521
	Interferon	0.8 (0.6;1.0)	0.9 (0.6;1.2)	1.1 (0.6;1.5)	
	Grazoprevir/Elbasvir	1.0 (0.8;1.2)	1.1 (0.8;1.4)	0.9 (0.6;1.2)	
Urine hematuria*	Sofosbuvir/Velpatasvir	7 (6;8)	4 (3;5)	2 (1;4)	**0.0266**
	Interferon	5 (4;7)	8 (6;11)	4(0;9)	
	Grazoprevir/Elbasvir	7 (6;8)	6 (4;7)	2 (1;4)	
eGFR CKD-EPI	Sofosbuvir/Velpatasvir	106 (103;109)	106 (102;109)	104 (99;109)	0.4002
	Interferon	114 (110;118)	111 (105;117)	111 (104;117)	
	Grazoprevir/Elbasvir	101 (98;105)	101 (97;104)	98 (93;103)	
eGFR-EPI-cys-C	Sofosbuvir/Velpatasvir	77 (72;82)	77 (73;81)	78 (72;84)	0.1950
	Interferon	89 (81;98)	88 (79;97)	89 (77;101)	
	Grazoprevir/Elbasvir	82 (77;86)	78 (74;82)	80 (75;84)	
eGFR-EPI-crea-cys-C	Sofosbuvir/Velpatasvir	89 (85;93)	89 (85;92)	89 (83;94)	0.2820
	Interferon	100 (93;107)	97 (90;104)	98 (88;108)	
	Grazoprevir/Elbasvir	90 (86;94)	87 (83;90)	87 (83;91)	
S-creatinine	Sofosbuvir/Velpatasvir	66 (64;69)	67 (64;70)	67 (63;71)	0.2620
	Interferon	66 (62;69)	69 (62;76)	67 (62;73)	
	Grazoprevir/Elbasvir	67 (64;70)	67 (64;70)	69 (64;74)	
S-cystatin C	Sofosbuvir/Velpatasvir	1.1 (1.0;1.2)	1.0 (1.0;1.1)	1.0 (1.0;1.1)	0.2480
	Interferon	1.0 (0.9;1.1)	1.0 (0.9;1.0)	0.9 (0.8;1.0)	
	Grazoprevir/Elbasvir	1.0 (0.96;1.05)	1.0 (0.9;1.0)	1.0 (0.9;1.0)	

Data is presented as mean and 95% confidence interval (CI) for the mean values. P-value indicates treatment effect over study period (i.e. treatment x time interaction)

Statistically significant changes are expressed in bold

* continuous variable, median

was also significantly reduced, but this has not been evaluated systematically in other publications.

We additionally measured several complement components in patients with pretreatment renal manifestation. Activities of the classical pathway between pretreatment and SVR12, and lectin pathway between pretreatment and one year, increased, and these changes may well represent reduced complement consumption. Factor B activation product between pretreatment and SVR12 was also reduced significantly, possibly reflecting the same phenomenon. No changes, however, were noticed in serum C3, C4 or C5b-9. Some publications have reported significant increases in serum C3 and/or C4 after successful HCV therapy, even suggesting that pretreatment low C4 predicted improvement in kidney function after treatment [23, 24]. It is reasonable that complement overactivation diminishes once the chronic antigenemia associated with HCV infection has been eliminated. The role of complement activation during HCV infection may be even more diverse as in other kidney diseases there is evidence that proteinuria itself can activate complement system locally in the kidneys and complement system may also be activated in tubulointerstitial disease as well as in glomerulosclerosis locally in kidneys [25].

There are multiple strenghts in our study. It is a large, prospective patient cohort representing real-world data and having detailed assessment of kidney function as well as renal abnormalities before and after HCV therapy. The follow-up continued up to one year after the therapy far exceeding beyond SVR12. As a limitation of the study, this was an observational single center study based on the treatment guidelines valid at the time of conducting the study rather than a randomized study. Our patient population in Finland may not be generalizable to other countries as the chronic HCV prevalence has been estimated to be somewhat higher than in the other Nordics (Finland ~ 0.59% vs. others 0.16–0.27%), with people who inject drugs driving the transmission. Like the rest of Europe, genotypes 1 and 3 predominate [26]. Interferon was still part of the eradication therapy in the beginning of the study, while DAAs became treatment of choice during the study possibly affecting the post-eradication result. As always in prospective studies some patients do

Table 5 Complement variables and overall time effect between pretreatment, SVR12 and 1 year after the treatment. Investigations were performed only for the renal manifestation group

Variable (reference)	Pretreatment *n* = 37	SVR12 *n* = 19	1 year *n* = 8	*P*-value Pretreatment vs. SVR12/ Pretreatment vs. 1 year
S-C3 (0.5–1.5 g/l)	1.12 (1.03;1.22)	1.04 (1.00;1.25)	0.96 (0.85;1.27)	0.3681/0.7188
S-C4 (0.12–0.42 g/l)	0.21 (0.16;0.24)	0.17 (0.15;0.19)	0.16 (0.12;0.27)	0.7384/0.8594
S-CH100AI (> 39%)	100 (91;110)	90 (66;124)	83 (52;150)	0.0934/0.8125
S-CH100CI (> 74%)	98 (90;122)	113 (103;132)	114 (96;135)	**0.0104**/0.6875
S-CH100L (> 10%)	79 (28;103)	92 (34;118)	91 (0;134)	0.2582/**0.0313**
P-C3d (< 7 U/ml)	5.2 (4.8;6.1)	4.7 (4.1;6.1)	5.6 (2.9;9.4)	0.1392/0.8750
P-C4d (< 7 µg/ml)	2.15 (1.6;2.8)	3.4 (1.6;3.6)	2.7 (0.9;4.2)	0.0859/0.8750
P-FacB (0.1–0.4 g/l)	0.19 (0.17;0.21)	0.19 (0.16;0.22)	0.19 (0.17;0.2)	0.2324/0.75
P-FacBb (< 4 µg/ml)	1.05 (0.9;1.3)	0.9 (0.8;1.2)	0.95 (0.6;1.1)	**0.004**/0.1250
P-SC5b-9 (< 366 ng/ml)	174 (153;196)	212 (138;235)	163 (16;233)	0.9506/0.6250

Data shown as median and 95% confidence interval (CI). Statistically significant changes are expressed inbold

S = serum, P= plasma, C3 = complement 3, C4 = complement 4, CH100AI = activity of the alternative pathway of complement, CH100CI = activity of the classical pathway of complement, CH100L = activity of the lectin pathway of complement, C4d = complement 4 activation product, C3d = complement 3 activation product, FacB = factor B, FacBb = factor B activation product, SC5b-9 = membrane attack complex

not come to all preassigned visits, therefore follow-up data is limited in some patients.

Conclusions

In summary, our study provides real-life, prospective, observational data of early kidney findings in a large representative cohort of HCV-positive patients, showing that kidney function as evaluated by serum cystatin C and urine abnormalities as assessed by tubular proteinuria and hematuria seemed to improve after successful HCV treatment regardless of the used therapy. Our study indicates that early kidney changes can be improved, and the damage reversed. This further supports the early treatment of HCV patients as suggested by WHO (https://www.who.int/news-room/fact-sheets/detail/hepatitis-c).

Abbreviations

APRI	the aspartate aminotransferase to platelet ratio index
AUDIT	Alcohol Use Disorder Identification Test
C3	complement 3
C4	complement 4
C4d	complement 4 activation product
C3d	complement 3 activation product
CH100AI	Complement alternative pathway activity
CH100CI	Complement classical pathway activity
CH100L	Complement lectin pathway activity
CKD-EPI	the Chronic Kidney Disease Epidemiology Collaboration equation
DAAs	direct-acting antivirals
eGFR	estimated glomerular filtration rate
FacB	complement factor B
FacBb	complement factor B activation product
HCV	hepatitis C virus
HUSLAB	Helsinki University Central Hospital laboratory
MRA	mineralocorticoid receptor antagonist
OST	opioid substitution therapy
P	plasma
RAASi	renin-angiotensin system inhibitor
S	serum
SC5b-9	membrane attack complex
SD	standard deviation
SGLT-2	sodium-glucose co-transporter 2 inhibitor
SVR12	sustained virological response at 12 weeks
UA1M	Urine α 1-microglobulin
UACR	urine albumin/creatinine ratio

Supplementary Information

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Supplementary Material 1

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Author contributions

Conceptualization and validation were performed by all authors, data curation by KK, SV, EL, methodology by all authors, writing – review & editing and accepting the final version of the manuscript by all authors.

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Data availability

Data cannot be shared publicly because of privacy of the patient participants and local legislation. Data are available from the Helsinki University HUS Ethics

Committee (contact [kati.kaartinen@hus.fi](mailto: kati.kaartinen@hus.fi)) for researchers who meet the criteria for access to confidential data.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the STROBE statement. The study protocol was approved by the HUS Ethical Committee, decision number HUS/1264/2016. All participants gave informed consent before their participation.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Kidney Disease. Improving Global Outcomes (KDIGO) Hepatitis C Work Group. KDIGO 2022 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease. Kidney Int. 2022;102(6S):S129–205.
2. Cacoub P, Desbois A, Isnard-Bagnis C, Rocatello D, Ferri C. Hepatitis C virus infection and chronic kidney disease: time for reappraisal. J Hepatol. 2016;65(S1):S82–94.
3. Ferri C, Giuggioli D, Colaci M. Renal manifestations of hepatitis C virus. Clin Liver Dis. 2017;21:487–97. https://doi.org/10.1016/j.cld.2017.03.005. PMID: 28689588.
4. Rodrıguez-Iñigo E, Casqueiro M, Bartolome´ J, Barat A, Caramelo C, Ortiz A, et al. Hepatitis C virus RNA in kidney biopsies from infected patients with renal diseases. J Viral Hepat. 2000;7:23–9. https://doi.org/10.1046/j.1365-2893.2000.00194.x. PMID: 10718939.
5. Fabrizi F, Donato MF, Nardelli L, Tripodi F, Zanoni F, Castellano G. Hepatitis C virus infection is associated with proteinuria according to a systematic review with meta-analysis. Nefrologia (Engl Ed). 2024 Jul-Aug;44(4):486–495. https://doi.org/10.1016/j.nefroe.2024.01.021. PMID: 39216980.
6. Fabrizi F, Donato FM, Messa P. Association between hepatitis C virus and chronic kidney disease, a systematic review and meta-analysis. Ann. Hepatol. 2018;17:364–391. https://doi.org/10.5604/01.3001.0011.7382 PMID: 29735788.
7. Palazzo D, Biliotti E, Tinti F, Bachetoni A, Perinelli P, Cappoli A, et al. Glomerular and tubular kidney involvement in HCV child-a cirrhosis. EASL 2016, poster FRI-164. 2016.
8. Feng B, Eknoyan G, Guo ZS, Jadoul M, Rao HY, Zhang W, Wei L. Effect of interferon-alpha-based antiviral therapy on hepatitis C virus-associated glomerulonephritis: a meta-analysis. Nephrol Dial Transplant. 2012;27(2):640-6. https://doi.org/10.1093/ndt/gfr236. Epub 2011 May 10. PMID: 21558431.
9. Fabrizi F, Cerutti R, Dixit V, Messa P. The impact of antiviral therapy for HCV on kidney disease: a systematic review and meta-analysis. Nefrologia (Engl Ed). 2020 May-Jun;40(3):299–310. English, Spanish. https://doi.org/10.1016/j.nefro.2019.07.007. Epub 2019 Dec 6. PMID: 31813592.
10. Derbala M, Shebl FM, Rashid A, Amer A, Bener A. Microalbuminuria in hepatitis C-genotype 4: effect of pegylated interferon and ribavirin. World J Gastroenterol. 2010;16(10):1226–31. https://doi.org/10.3748/wjg.v16.i10.1226. PMID: 20222166; PMCID: PMC2839175.
11. Biliotti E, Palazzo DF, D'Alessandro M, Esvan R, Labriola R, Cappoli A, Umbro I, Volpicelli L, Bachetoni A, Villa E, Mitterhofer A, Rucci P, Taliani G. HCV cirrhotic patients treated with direct-acting antivirals: Detection of tubular dysfunction and resolution after viral clearance. Liver Int. 2021;41(1):158–67. https://doi.org/10.1111/liv.14672.
12. Kaartinen K, Vuoti S, Honkanen E, Löyttyniemi E, Singh R, Färkkilä M. Tubular cell damage may be the earliest sign of renal extrahepatic manifestation caused by Hepatitis C. PLoS ONE. 2021;16(5):e0251392. https://doi.org/10.1371/journal.pone.0251392.
13. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption–II. Addiction. 1993;88(6):791–804. https://doi.org/10.1111/j.1360-0443.1993.tb02093.x. PMID: 8329970.
14. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, Sun Y, Xuan SY. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology. 2011;53(3):726 – 36. https://doi.org/10.1002/hep.24105. PMID: 21319189.
15. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367(1):20–9. https://doi.org/10.1056/NEJMoa1114248. PMID: 22762315.
16. Dharnidharka V, Kwon C, Stevens G. Serum Cystatin C Is Superior to Serum Creatinine as a Marker of Kidney Function. Am J Kidney Dis. 2002;40(2):221–6.
17. Filler G, Bokenkamp A, Hofmann W, Le Bricon T, Martinez-Bru C, Grubb A. Cystatin C as a marker of GFR–history, indications, and future research. Clin Biochem. 2005;38(1):1–8.
18. Mindikoglu A, Dowling T, Weir M, Seliger S, Christenson R, Magder L. Performance of Chronic Kidney Disease Epidemiology Collaboration Creatinine-Cystatin C Equation for Estimating Kidney Function in Cirrhosis. Hepatology. 2014;59(4):1532–42.
19. Krones E, Fickert P, Zitta S, Neunherz S, Artinger K, Reibnegger G, Durchschein F, Wagner D, Stojakovic T, Stadlbauer V, Fauler G, Stauber R, Zollner G, Kniepeiss D, Rosenkranz A. The chronic kidney disease epidemiology collaboration equation combining creatinine and cystatin C accurately assesses renal function in patients with cirrhosis. BMC Nephrol. 2015;16:196. https://doi.org/10.1186/s12882-015-0188-0.
20. Rognant N, Lemoine S. Evaluation of renal function in patients with cirrhosis: where are we now? World J Gastroenterol. 2014;20(10):2533–41.
21. Tokuchi Y, Suda G, Kimura M, Maehara O, Kitagataya T, Ohara M, Yamada R, Shigesawa T, Suzuki K, Kawagishi N, Nakai M, Sho T, Natsuizaka M, Morikawa K, Ogawa K, Sakamoto N. Changes in the estimated renal function after hepatitis C virus eradication with direct-acting antiviral agents: Impact of changes in skeletal muscle mass. J Viral Hepat. 2021;28(5):755–63. https://doi.org/10.1111/jvh.13484.
22. Sise M, Chute D, Oppong Y, Davis M, Long J, Silva S, Rusibamayila N, Jean-Francois D, Raji S, Zhao S, Thadhani R, Chung R. Direct-acting antiviral therapy slows kidney function decline in patients with Hepatitis C virus infection and chronic kidney disease. Kidney Int. 2020;97(1):193–201. https://doi.org/10.1016/j.kint.2019.04.030.
23. Ogawa E, Furusyo N, Azuma K, Nakamuta M, Nomura H, Dohmen K, Satoh T, Kawano A, Koyanai T, Ooho A, Takahashi K, Kato M, Shimoda S, Kajiwara E, Hayashi J, Kyushu University Liver Disease Study (KULDS) Group. Elbasvir plus grazoprevir for patients with chronic hepatitis C genotype 1: A multicenter, real-world cohort study focusing on chronic kidney disease. Antiviral Res. 2018;159:143–52. https://doi.org/10.1016/j.antiviral.2018.10.003.
24. Sise M, Strohbehn I, Chute D, Corey K, Fusco D, Sabbisetti V, Waikar S, Chung R. Low Complement C4 Predicts Improvement of Kidney Function After Direct-Acting Antiviral Therapy for Hepatitis C Virus. Hepatol Commun. 2020;4(8):1206–17. https://doi.org/10.1002/hep4.1528.
25. Portilla D, Sabapathy V, Chauss D. Role of local complement activation in kidney fibrosis and repair. J Clin Invest. 2025;135(12):e188345. https://doi.org/10.1172/JCI188345. PMID: 40519169; PMCID: PMC12165786.
26. Safreed-Harmon K, Hetherington KL, Aleman S, Alho H, Dalgard O, Frisch T, Gottfredsson M, Weis N, Lazarus JV, Hep-Nordic Study Group. Policy responses to hepatitis C in the Nordic countries: Gaps and discrepant reporting in the Hep-Nordic study. PLoS ONE. 2018;13(1):e0190146. https://doi.org/10.1371/journal.pone.0190146. PMID: 29381697; PMCID: PMC5790214.

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