Kidney Function Decline in Patients with CKD and Untreated Hepatitis C Infection

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Abstract

Background and objectives Studies evaluating the role of hepatitis C viral (HCV) infection on the progression of CKD are few and conflicting. Therefore, we evaluated the association of untreated HCV on kidney function decline in patients with stage 3–5 CKD.

Design, setting, participants, & measurements This retrospective cohort study included members of Kaiser Permanente Southern California and Kaiser Permanente Mid-Atlantic States aged ≥18 years, with incident HCV and CKD diagnoses from January 1, 2004 to December 31, 2014. We used generalized estimating equations to compare the rate of change in eGFR between those with HCV and CKD versus CKD alone, adjusting for covariates. Cox proportional hazards models compared the risk of 25% decrease in eGFR and ESKD (defined as progression to eGFR<15 ml/min per 1.73 m² on two or more occasions, at least 90 days apart) in those with HCV and CKD versus CKD alone, adjusting for covariates.

Results We identified 151,974 patients with CKD only and 1603 patients with HCV and CKD who met the study criteria. The adjusted annual decline of eGFR among patients with HCV and CKD was greater by 0.58 (95% confidence interval [95% CI], 0.31 to 0.84) ml/min per 1.73 m², compared with that in the CKD-only population (HCV and CKD, −1.61; 95% CI, −1.87 to −1.35 ml/min; CKD only, −1.04; 95% CI, −1.06 to −1.01 ml/min). Adjusted for covariates, the hazard for a 25% decline in eGFR and for ESKD were 1.87 (95% CI, 1.75 to 2.00) and 1.93 (95% CI, 1.64 to 2.27) times higher among those with HCV and CKD, respectively, compared with those with CKD only.

Conclusions Untreated HCV infection was associated with greater kidney function decline in patients with stage 3–5 CKD.


Introduction

CKD is a worldwide health problem that affects 10%–16% of adults (1,2). Hepatitis C virus (HCV) infection is a cause of some forms of CKD and infects approximately 3% of the world population (3,4). Both diseases, particularly when left untreated, cause considerable morbidity and mortality worldwide.

The role of HCV on the development and progression of CKD is controversial. Although some studies have demonstrated an association between HCV infection and developing incident CKD or ESKD (5–11), others have not (12–17). Studies to evaluate the role of HCV on the progression of CKD are scarce, and are also conflicting. An association between HCV and the progression of CKD has been demonstrated for those with certain high-risk conditions, such as diabetic nephropathy, HIV (11,18–21), and for veterans (11). However, other evidence shows lack of association between HCV infection and CKD progression (22). Lack of consensus regarding the role of HCV on CKD progression may be because of limitations of prior work, including small sample sizes, varying definitions of CKD outcomes (12), cross-sectional study design, lack of inclusion of women, lack of HCV genotypic data, and lack of consideration of HCV treatment. Successful IFN-based treatment for HCV has been shown to reduce the risk of ESKD (23), and inclusion of this covariate is important to test associations with kidney function decline.

Therefore, we evaluated decline in kidney function in patients with stage 3–5 CKD (eGFR<60 ml/min per 1.73 m²) and untreated HCV infection. Although most studies evaluate the effect of HCV infection on the development of de novo CKD and progression in patients on dialysis and patients with kidney transplant, we provide a novel perspective in a population with stage 3–5 CKD. Restricting our HCV population to untreated patients allows a natural history perspective of the combined effect of HCV and CKD on kidney function decline. New data challenge previously established end points for CKD progression used in clinical trials, demonstrating that lesser changes in eGFR over 1, 2, and 3 years are strongly associated with subsequent ESKD and mortality (24). Knowing whether HCV infection contributes to a
more rapid decline could aid the monitoring and treatment programs of patients with both CKD and HCV.

Materials and Methods

Setting
This study included patients from Kaiser Permanente Southern California (KPSC) and Kaiser Permanente Mid-Atlantic States (KPMAS; comprised of Baltimore, the District of Columbia, parts of Maryland, and northern Virginia), which collectively care for >4.7 million health plan members. At both sites, the member populations are representative of the socioeconomic and racial diversity of the area population (25). Both sites obtained data using electronic health records, which integrate medical information from all care settings. Minimal copays are a strong incentive to receive care within the system, contributing to highly complete capture of member health care utilization data.

Study Population
This retrospective cohort study included patients aged ≥18 years at the time of incident diagnoses of HCV or CKD from January 1, 2004 to December 31, 2014. An inclusion criterion was active enrollment with no membership gaps ≥45 days in the year before diagnosis date to allow for collection of baseline data. All patients were required to have at least one baseline eGFR measure (defined by the CKD Epidemiology Collaboration equation to estimate eGFR [26]), and one eGFR measurement during the follow-up period. The CKD Epidemiology Collaboration equation requires age, sex, and race to calculate eGFR. Patients who received HCV treatment before the index date were excluded from the study; patients who initiated dialysis or received a liver or kidney transplant before the index date were also excluded, as these procedures can render unreliable eGFR values (27,28). Further, patients with eGFR<15 ml/min per 1.73 m² at baseline were excluded from the ESKD analyses (described below).

CKD was identified by two occasions of eGFR<60 ml/min per 1.73 m² that are ≥90 days apart, with eGFR never returning to ≥60 ml/min per 1.73 m². Chronic HCV infection was identified by at least one positive HCV RNA, HCV genotype, or positive HCV antibody test plus one or more HCV-coded visit. For CKD, the diagnosis date was attributed to the earliest date in the series of eGFR<60 ml/min per 1.73 m². The HCV diagnosis date was attributed to the earliest date where one of the criteria above were satisfied.

Patients in the CKD-only cohort consisted of patients that were diagnosed with CKD and never received a diagnosis of HCV during the study period. Follow-up time for the CKD-only cohort started at the time of CKD diagnosis (index date), as stated above. Patients in the HCV and CKD cohort consisted of patients who were diagnosed with CKD and HCV during the study period, with either condition occurring first. For the HCV and CKD cohort, follow-up time began at the time of diagnosis of the latter of HCV or CKD (index date) (Supplemental Figure 1). When CKD was diagnosed first and HCV second, the closest eGFR value ±30 days to the time of diagnosis of HCV determined baseline eGFR, as this was the index date (Supplemental Figure 1). Patients in the HCV and CKD and CKD-only cohorts were mutually exclusive.

Outcome
Outcomes of interest included (1) rate of decline in eGFR from baseline, (2) 25% decline in eGFR (24,29,30), and (3) development of ESKD (defined as progression to eGFR<15 ml/min per 1.73 m² on two or more occasions at least 90 days apart), dialysis, or kidney transplant approval (may or may not result in actual kidney transplant). To address fluctuations related to acute illness or various inputs (31,32), we identified the median of all serum creatinine measurements taken on the same date. If there was a cluster of measurements where any two successive measurements were within 8 days of each other, we used the serum creatinine measurement taken on the median date. This median creatinine measurement was used for the eGFR calculation, such that there was no more than one eGFR measurement per week.

Follow-Up Time
Follow-up time began on the index date, defined above, and continued as long as the patient was continuously enrolled (allowing a 45-day gap for enrollment to appear in administrative databases). Follow-up time was censored at the time of initiation of HCV therapy, at the start of dialysis, actual liver or kidney transplant, death, end of the study period (December 31, 2014), or disenrollment, whichever came first. For the ESKD analyses, censoring occurred on death, disenrollment, end of the study period, actual liver transplant, or HCV treatment initiation.

Statistical Analyses
We compared the rate of change in eGFR, risk of a 25% decrease in eGFR from baseline, and risk of ESKD between patients with CKD and treatment-naïve HCV compared with those with CKD alone. To compare the estimated mean rate of change in eGFR between exposure groups, we used generalized estimating equations adjusted for potential confounding variables, including age, sex, race/ethnicity, diabetes, hypertension, acute myocardial infarction, HIV, hepatitis B virus, end-stage liver disease (ESLD), and CKD stage (see Supplemental Table 1 for detailed definitions of clinical covariates) (33). Covariates were assessed in the year before index date (baseline). Risk of a 25% decrease in eGFR and risk of ESKD were estimated using Cox proportional hazards cause-specific competing risk models adjusted for covariates as above with the exception that eGFR at baseline (i.e., closest eGFR measurement within 30 days of index date) was used in place of CKD stage (34). Death, dialysis and kidney or liver transplant were considered competing risk events for risk of a 25% change; death and liver transplant were considered competing risk events for the ESKD risk model. Log-log survival plots were used to test for assumptions of proportional hazards.
Analyses were stratified by sex, age, race, diabetes, hypertension, and CKD stage in separate models. Analyses stratifying the ESKD outcome into persistent eGFR<15 ml/min per 1.73 m² and dialysis were also performed. Three sensitivity analyses were conducted: the first used propensity score matched models to estimate risk of 25% decline in eGFR and ESKD, the second restricted analyses...
to those with positive HCV RNA as sole diagnostic criteria, and the third assessed patients with and without ESLD.

All analyses were performed as complete case analyses. Analyses were conducted with SAS (version 9.3 for Windows; SAS Institute, Cary, NC). The study protocol was reviewed and approved by the KPSC Institutional Review Board, which waived requirement for informed consent.

Results

Study Cohorts

A total of 182,164 patients with stage 3–5 CKD and no HCV, and 2549 patients with HCV and CKD were identified during the study period. Of these, 30,198 (17%) and 745 (29%) had <12 months membership, dialysis, kidney or liver transplant, HCV treatment, or fewer than one baseline and one follow-up eGFR measurement documented and were excluded from the study, respectively (Figure 1). Patients were also excluded because of the requirement of complete race, age, and sex data for the eGFR equation; 3.7% of patients with at least one serum creatinine measurement were excluded because of missing race data, and 2.6% had race imputed using the algorithm reported in the Geographically Enriched Member Socio-demographics national Kaiser Permanente datamart (35). No patients had other covariate data missing. Patients excluded because of HCV treatment differed by some variables compared with included patients (Supplemental Table 2). For the ESKD analyses, an additional 800 patients with CKD only, and 69 patients with HCV and CKD were excluded because of an eGFR <15 ml/min per 1.73 m² at baseline.

The final study cohort for the analyses of rate of eGFR decline and risk of 25% eGFR decline consisted of 151,974 patients with HCV and CKD population, 66% were diagnosed with HCV first (median time to CKD diagnosis, 1362 days), 32% were diagnosed with CKD first (median time to HCV diagnosis, 631 days), and 2% were diagnosed on the same date. Overall, the group with HCV and CKD were younger than those with CKD only and had a higher proportion of men and black and Hispanic participants (Table 1). Patients with HCV and CKD had greater prevalence of comorbidities than those with CKD only. Most patients in both cohorts had CKD stage 3 at baseline (baseline eGFR: HCV and CKD, 44; SD, 12.86; CKD only, 50; SD, 8.21) (Table 1).

The median number of follow-up eGFR measurements was somewhat higher in those with HCV and CKD (HCV and CKD median, 8; interquartile range, 4–18 versus CKD-only median, 6; interquartile range, 3–13). However, the median length of follow-up before censoring...
Comparing Rate of Change in eGFR

In unadjusted analyses, the annual decline in eGFR was greater by 2.39 ml/min per 1.73 m² in patients with HCV and CKD versus those with CKD alone. After adjustment for covariates, the decline of eGFR among patients with HCV and CKD was greater by 2.04 (95% confidence interval [95% CI], 1.75 to 2.32) ml/min per 1.73 m² compared with that in the CKD-only population (HCV and CKD, −1.61; 95% CI, −1.87 to −1.35 ml/min per 1.73 m²; CKD only, −1.04; 95% CI, −1.06 to −1.01 ml/min per 1.73 m²) (Figure 2; Supplemental Table 3).

Hazard for a 25% Decline in eGFR and ESKD

The unadjusted hazard for a 25% decline in eGFR comparing those with HCV and CKD to those with CKD alone was 2.17 (95% CI, 2.03 to 2.32) (Incidence rate [IR] in HCV and CKD, 380.5 per 100,000 person-years; IR in CKD only, 170.8 per 100,000 person-years). Adjusted for covariates, the hazard for a 25% decline in eGFR was 1.87 (95% CI, 1.75 to 2.00) times higher among those with HCV and CKD compared with those with CKD only (Table 2). Patients who were men and non-white, particularly black patients, had higher adjusted hazard of ESKD compared with women and white patients, respectively. Death, dialysis, and liver transplant during follow-up were more likely in the HCV and CKD group compared with the CKD group. Overall, 2% of patients with HCV and CKD initiated HCV treatment (Table 3).
Stratified Analyses
The adjusted hazard for a 25% decrease in eGFR comparing those with HCV and CKD with those with CKD alone differed by CKD stage; there were no other significant differences between subgroups. The adjusted hazard of ESKD between those with HCV and CKD versus CKD alone differed by diabetes, hypertension, and CKD status (Supplemental Table 4). The analyses stratifying the ESKD outcome into eGFR 15 ml/min per 1.73 m² and dialysis yielded similar results to the main ESKD analyses (Supplemental Table 4).

Sensitivity Analyses
We were able to achieve balance across all covariates in the propensity score matched model. The estimate of risk for 25% decline in eGFR and ESKD were similar to the main multivariable analyses results presented in Table 2, and do not alter conclusions (Supplemental Table 5). For sensitivity analyses among only those with positive HCV RNA as diagnostic criteria (n=1372), we also found similar results to the primary analyses (Supplemental Table 5).

The rate of decline (generalized estimating equation analyses) was faster for those with ESLD compared with those without ESLD. However, the hazard of 25% decline in eGFR and ESKD was lower in those with ESLD compared with those without. The overall message of higher risk for the HCV and CKD cohort versus CKD alone remained for all analyses. The lower hazard for patients with ESLD is likely because of higher numbers of competing risks in the cohort with ESLD (data not shown).

Discussion
We found that untreated HCV has a moderate association with kidney function decline among patients with stage 3–5 CKD. Although there is general consensus that HCV contributes to the risk of some glomerular diseases, there remains controversy regarding the role of HCV infection on the progression of CKD more broadly, with particular lack of data for those with moderate to advanced CKD (9,11,12,19,22). Our results support the hypothesis that untreated HCV contributes to kidney function decline.

Several mechanisms by which HCV worsens kidney function have been postulated. Glomerular injury may result from deposition of circulating immune complexes within the subendothelium and mesangium (36), which activate the complement system, leading to mononuclear phagocyte proliferation and the release of proteases and oxidants that alter glomerular permeability (36–38). Other research suggests that HCV triggers a cascade of local or systemic immune and inflammatory responses of the kidney through inflammatory mediators (6,39,40). Epidemiologically, patients with HCV have a five-fold increased risk in the odds of membranoproliferative GN compared with control individuals without HCV (41). Among patients with GN, HCV infection increased the rate of progression of CKD, developing ESKD, and death (42).

In our study, baseline diabetes, non-white race, and ESLD were strongly associated with greater risks of all outcomes. Prior studies have shown that decompensated liver disease, hypertension, and diabetes were associated with higher risk of CKD in patients with HCV (9); however,
few prior studies have demonstrated the increased risk of black and Hispanic race/ethnicity in this relationship. This study has several strengths. We removed the potential confounding association of HCV treatment on kidney disease progression, which was documented in 10% of our original cohort before exclusions. The racial and ethnic diversity of our study population proved important to fill existing knowledge gaps, particularly for Hispanic populations. Further, more than half of our study population are women, allowing us to contribute new

Table 2. Adjusted cause-specific hazard ratio for 25% decrease in eGFR and ESKD in patients with CKD and hepatitis C infection compared with those with CKD alone

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>25% Decline in eGFR</th>
<th>ESKD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients with 25% Decrease</td>
<td>HR^a^,b^</td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV and CKD</td>
<td>915</td>
<td>1.87</td>
</tr>
<tr>
<td>CKD only</td>
<td>65,133</td>
<td>1.00</td>
</tr>
<tr>
<td>Age, yr</td>
<td>66,048</td>
<td>1.00</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>35,529</td>
<td>1.01</td>
</tr>
<tr>
<td>Men</td>
<td>30,519</td>
<td>1.00</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>5246</td>
<td>1.01</td>
</tr>
<tr>
<td>Black</td>
<td>11,123</td>
<td>1.28</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12,613</td>
<td>1.21</td>
</tr>
<tr>
<td>Others</td>
<td>174</td>
<td>0.85</td>
</tr>
<tr>
<td>White</td>
<td>36,892</td>
<td>1.00</td>
</tr>
<tr>
<td>Baseline comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25,417</td>
<td>1.71</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42,594</td>
<td>1.24</td>
</tr>
<tr>
<td>HIV</td>
<td>250</td>
<td>1.44</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>209</td>
<td>1.16</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2082</td>
<td>1.48</td>
</tr>
<tr>
<td>ESLD</td>
<td>449</td>
<td>3.75</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>66,048</td>
<td>1.02</td>
</tr>
</tbody>
</table>

HR, hazard ratio; 95% CI, 95% confidence interval; HCV, hepatitis C virus; ESLD, end-stage liver disease.

^a^Follow-up time is censored at the time of the start of dialysis, liver/kidney transplant, HCV treatment, death, disenrollment from Kaiser Permanente health plan, or the end of the study period (December 31, 2014); ESKD analyses censored on liver transplant, HCV treatment, death, disenrollment from Kaiser Permanente health plan, or the end of the study period.

^b^Patients with baseline eGFR<15 ml/min per 1.73 m^2^ were excluded: CKD only, n=151,174; HCV and CKD, n=1534.

Table 3. Censoring events in the analyses for 25% decline in eGFR and ESKD

<table>
<thead>
<tr>
<th>Status at the End of Follow-Up</th>
<th>Total</th>
<th>HCV and CKD</th>
<th>CKD Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>25% decline in eGFR</td>
<td>n=1603</td>
<td>n=15,1974</td>
<td>2.5 (2.2)</td>
</tr>
<tr>
<td>Mean follow-up time in years (SD)</td>
<td>1.5 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event, 25% eGFR decrease</td>
<td>66,048 (43%)</td>
<td>915 (57%)</td>
<td>65,133 (43%)</td>
</tr>
<tr>
<td>Death</td>
<td>11,110 (7%)</td>
<td>113 (7%)</td>
<td>10,997 (7%)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>551 (0.4%)</td>
<td>50 (3%)</td>
<td>501 (0.3%)</td>
</tr>
<tr>
<td>Kidney transplant</td>
<td>8 (0%)</td>
<td>0 (0%)</td>
<td>8 (0%)</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>38 (0%)</td>
<td>14 (1%)</td>
<td>24 (0%)</td>
</tr>
<tr>
<td>HCV treatment</td>
<td>28 (0%)</td>
<td>28 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Disenrollment</td>
<td>15,445 (10%)</td>
<td>138 (9%)</td>
<td>15,307 (10%)</td>
</tr>
<tr>
<td>End of study, December 31, 2014</td>
<td>60,349 (39%)</td>
<td>345 (22%)</td>
<td>60,004 (40%)</td>
</tr>
<tr>
<td>ESKD</td>
<td>n=1534</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean follow-up time in years (SD)</td>
<td>2.5 (2.3)</td>
<td>3.7 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Event, ESKD</td>
<td>5402 (4%)</td>
<td>162 (11%)</td>
<td>5240 (4%)</td>
</tr>
<tr>
<td>Death</td>
<td>29,937 (20%)</td>
<td>381 (25%)</td>
<td>29,556 (20%)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>74 (0%)</td>
<td>71 (5%)</td>
<td>3 (0%)</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>71 (0%)</td>
<td>22 (1%)</td>
<td>49 (0%)</td>
</tr>
<tr>
<td>HCV treatment</td>
<td>37 (0%)</td>
<td>37 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Disenrollment</td>
<td>21,666 (14%)</td>
<td>232 (15%)</td>
<td>21,434 (14%)</td>
</tr>
<tr>
<td>End of study December 31, 2014</td>
<td>95,521 (63%)</td>
<td>629 (41%)</td>
<td>94,892 (63%)</td>
</tr>
</tbody>
</table>

HCV, hepatitis C virus.
knowledge beyond the previous, male-dominated, large-scale studies by the Veterans Administration (11,22). Finally, to evaluate concerns of residual confounding in the main analyses, we performed stratified, propensity score-matched, and sensitivity analyses, which all supported the conclusions from the main analyses.

However, there are several potential limitations to this study. The follow-up time for the HCV and CKD population was shorter than the CKD-only population for the analyses of 25% decline and ESKD. Although this was largely driven by more frequent and faster time to the outcome events, the HCV and CKD population was also more likely to be censored before the end of the study period. If worsening CKD prompted treatment for HCV (and therefore censoring), we may underestimate decline. We may also underestimate decline due to immortality bias imposed by the 90-day requirement between first and second qualifying eGFR values to define CKD; however, the mean time between qualifying eGFR measurements was less than a year and therefore not likely to have a large effect. Finally, muscle wasting and altered creatinine metabolism can decrease creatinine generation, leading to attenuation of our findings in patients with severe HCV-associated liver disease (i.e., ESLD). In our main analyses, those with ESLD demonstrated elevated risk of kidney function decline, and more rapid decline with ESLD was seen in sensitivity analyses. Hepatorenal syndrome may play an important role in disease progression; the fact that progression may be potentially underestimated suggests a need for careful clinical observation of this high-risk group.

For HCV, delays in diagnoses and known limitations in the effectiveness of IFN-based treatments likely contributed to delays in HCV screening. As such, our results may represent the risk of kidney function decline in patients with HCV and CKD with more advanced HCV disease.

In summary, we found that untreated HCV affects kidney function decline among patients with stage 3–5 CKD over 2–3 years. As faster decline of eGFR is associated with higher risk of mortality (43), it is important to identify patients at increased risk of accelerated kidney decline. With IFN-based treatments, eradication of HCV in patients with CKD has been difficult (44–46). However, new direct-acting antiviral therapies have demonstrated excellent safety and efficacy profiles in patients with CKD (47–50). It remains to be seen whether the use of newer direct-acting HCV antivirals can mitigate the magnitude and rate of kidney function decline and progression to ESKD among patients with HCV and CKD.

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Disclosures
J.M.A. is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Kenilworth, NJ), and owns stock in the company. S.Y.T., M.H., K.B.R., and C.V.R. received research support from Merck Sharp & Dohme Corp. during the conduct of the study. C.V.R. owns <$5000 in Gilead stock shares.

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